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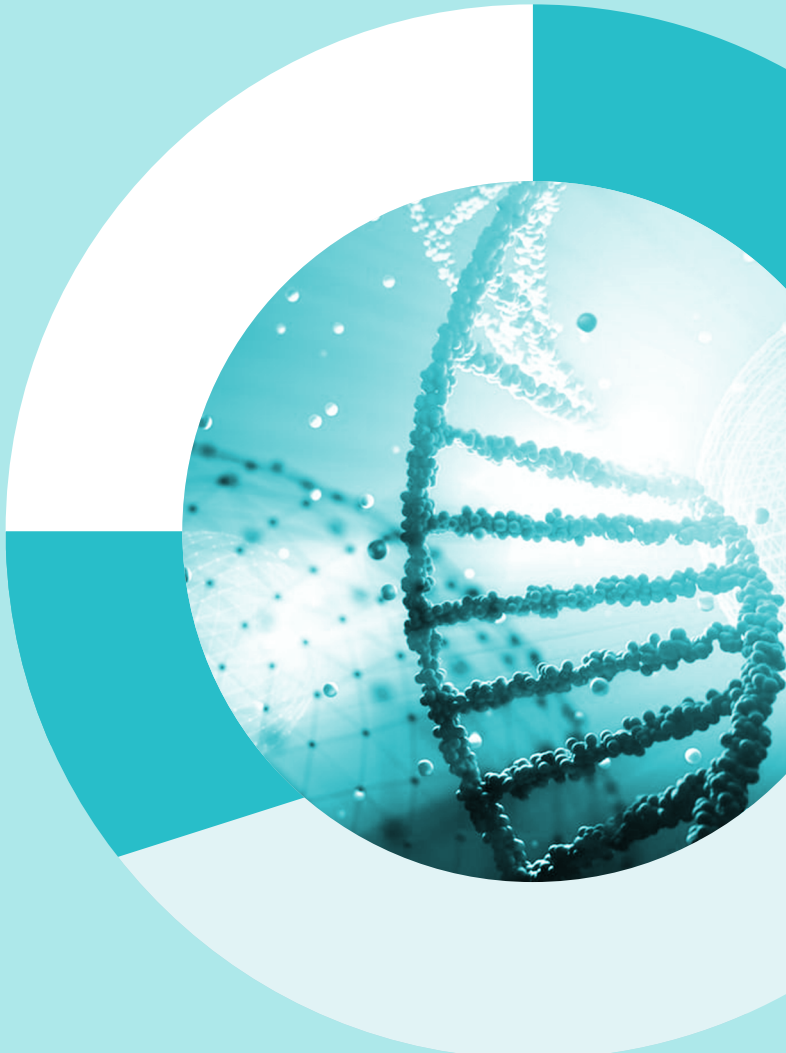

Official Journal of Cyprus Turkish Medical Association

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AIMS AND SCOPE

Cyprus Journal of Medical Sciences (Cyprus J Med Sci), the official organ of Cyprus Turkish Medical Association.

This journal is an international, open access, scientific, peer-reviewed journal in accordance with independent, unbiased, and double-blinded peer-review principles. As of 2022, the journal has become a bimonthly publication, publishing in February, April, June, and August, October and December. The journal's publication language is English. (E-ISSN:2536-507X)

The aim of the journal is to publish original research papers of the highest scientific and clinical value in all medical fields. Cyprus Journal of Medical Sciences also publishes reviews, rare case report and letters to the editors.

The target audience of the journal includes healthcare professionals physicians, and researchers who are interested or working in in all fields of medicine.

The editorial and publication process of the Cyprus Journal of Medical Sciences are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

Cyprus Journal of Medical Sciences is indexed in Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, EBSCO, J-GATE and Gale.

All manuscripts must be submitted via the online submission system, which is available at www.cyprusjmedsci.com. The journal guidelines, technical information, and the required forms are available on the journal's web page.

All expenses of the journal are covered by the Cyprus Turkish Medical Association. Potential advertisers should contact the Editorial Office. Advertisement images are published only upon the Editor-in-Chief's approval.

Statements or opinions expressed in the manuscripts published in the journal reflect the views of the author(s) and not the opinions of the Cyprus Turkish Medical Association, editors, editorial board, and/or publisher; the editors, editorial board, and publisher disclaim any responsibility or liability for such materials.

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Open access is an approach that supports interdisciplinary development and encourages collaboration between different disciplines. Therefore, Cyprus Journal of Medical Sciences contributes to the scientific publishing literature by providing more access to its articles and a more transparent review process.

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Statements or opinions stated in articles published in the journal do not reflect the views of the editors, editorial board and/or publisher; The editors, editorial board and publisher do not accept any responsibility or liability for such materials. All opinions published in the journal belong to the authors.

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Originality, high scientific quality, and citation potential are the most significant criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts that have been submitted to another journal for evaluation and rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts that have been presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

Submission Fee Policy

As of August 1, 2021, "**Cyprus Journal of Medical Sciences**" charges a submission fee of **$75** for all submitted manuscripts from the authors during only first submission. No additional fee will be charged for publication.

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**Please note that the submission fee purchase affects neither the evaluation process of the manuscript nor priority.

*The physicians who are the Cyprus Turkish Medical Association members are waived from the submission fee.

*If you are a member of the Cyprus Turkish Medical Association, you can upload your membership card photograph instead of the receipt.

PEER REVIEW PROCESS

Manuscripts submitted to Cyprus Journal of Medical Sciences will go through a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in their fields in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or by the editorial board members of the journal. The Editor in Chief is the final authority in the decision-making process for all submissions.

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ETHICAL PROCEDURES

An approval of research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013) is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement should be included that shows that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information on patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the "Materials and Methods" section of the manuscript. It is the authors' responsibility to protect the patients' anonymity carefully.

For photographs that may reveal the identity of the patients, signed consent of the patient or their legal representative should be enclosed, and the publication approval must be provided in the "Materials and Methods" section. However, the identities of the patients should be concealed in the photographs.

PLAGIARISM

Cyprus Journal of Medical Sciences is extremely sensitive about plagiarism. All submissions are screened by a similarity detection software (iThenticate by CrossCheck) at any point during the peer-review and/or production process. Even if you are the author of the phrases or sentences, the text should not have unacceptable similarity with the previously published data.

When you are discussing others' (or your own) previous work, please make sure that you cite the material correctly in every instance.

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act following COPE guidelines.

PREPRINT

Authors must provide the journal with the preprint server deposition of their article accompanying its DOI during initial submission.

Cyprus Journal of Medical Sciences does not consider preprint publications before publication. In other words, authors are allowed to present and discuss their findings on a non-commercial preprint server before submission to the journal.

If the article is published in the Cyprus Journal of Medical Sciences, it is the responsibility of the authors to update the archived preprint and link it to the published version of the article.

AUTHORSHIP

Each person listed as an author should fulfill the authorship criteria recommended by http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html). The ICMJE recommends that authorship is based on the following four criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. Also, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged on the title page of the manuscript.

Cyprus Journal of Medical Sciences requires corresponding authors to submit a signed and scanned version of the Copyright Agreement and Acknowledgement of Authorship form (available for download www.cyprusjmedsci.com) during the initial submission process to act appropriately on authorship rights and to prevent ghost or honorary

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authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without further review. As part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all the responsibility for authorship during the submission and review stages of the manuscript.

DISCLOSURE AND CONFLICTS OF INTEREST

All sources of financial support should be disclosed. All authors ought to disclose a meaningful conflict of interest in the process of forming their study. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board of the Cyprus Journal of Medical Sciences. The ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors to disclose a potential conflict of interest. The journal's Editorial Board determines cases of a potential conflict of interest of the editors, authors, or reviewers within the scope of COPE and ICMJE guidelines.

The Editorial Board of the journal handles all appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office regarding their appeals and complaints. When needed, an ombudsperson may be assigned to resolve claims that cannot be resolved internally. The Editor in Chief is the final authority in the decision-making process for all appeals and complaints.

MANUSCRIPT PREPARATION

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2019). Authors are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.cyprusjmedsci.com. Manuscripts submitted via any other medium and submissions by anyone other than one of the authors will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Authors are required to submit the following:

- Copyright Agreement and Acknowledgement of Authorship Form, and
- ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors) during the initial submission. These forms are available for download at www.icmje.org.

Preparation of the Manuscript

Title page: A separate title page should be submitted with all submissions and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, highest academic degree(s), and ORCID IDs of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number), and e-mail address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: An abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Background/Aims, Material and Methods, Results and Conclusion). Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of five keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database. (https://www.nlm.nih.gov/mesh/MBrowser.html).

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Main Points: All submissions except letters to the editor should be accompanied by 3 to 5 "main points", which should emphasize the most noteworthy results of the study and underline the principle message that is addressed to the reader. This section should be structured as itemized to give a general overview of the article. Since "Main Points" target the experts and specialists of the field, each item should be written as plain and straightforward as possible.

Language Editing Before Submission

Authors must send their manuscripts to a professional language edit service before submitting their manuscripts to the system. They need to upload the language edit certificate to the system during the submission.

You can find some useful and relevant links for language edit services below. You can also use any other Professional language editing services freely.

Enago: https://www.enago.com.tr/

Editage: https://www.editage.com/

Scribendi: https://www.scribendi.com/

Elsevier Language Editing Service: https://webshop.elsevier.com/language-editing-services/language-editing/

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. Acceptance of original papers will be based upon the originality and importance of the investigation. The main text of original articles should be structured with Introduction, Material and Methods, Results, and Discussion subheadings. An original article can be signed by maximum 6 authors unless it is a multi-center study or that it required extensive labour. Please check Table 1 for the limitations for Original Articles.

Clinical Trials

Cyprus Journal of Medical Sciences adopts the ICMJE's clinical trial registration policy, which requires that clinical trials must be registered in a publicly accessible registry that is a primary register of the WHO International Trials Registry Platform (ICTRP) or in ClinicalTrials.gov.

Instructions for the clinical trials are listed below.

- Clinical trial registry is only required for the prospective research projects that study the relationship between a health-related intervention and an outcome by assigning people.
- To have their manuscript evaluated in the journal, author should register their research to a public registry at or before the time of first patient enrollment.
- Based on most up to date ICMJE recommendations, Cyprus Journal of Medical Sciences accepts public registries that include minimum acceptable 24-item trial registration dataset.
- Authors are required to state a data sharing plan for the clinical trial registration. Please see details under "Data Sharing" section.
- For further details, please check ICMJE Clinical Trial Policy at

http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

Data Sharing

As of 1 January 2019, a data sharing statement is required for the registration of clinical trials. Authors are required to provide a data sharing statement for the articles that reports the results of a clinical trial. The data sharing statement should indicate the items below according to the ICMJE data sharing policy:

- Whether individual deidentified participant data will be shared
- What data in particular will be shared
- Whether additional, related documents will be available
- When the data will be available and for how long
- By what access criteria will be shared

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Authors are recommended to check the ICMJE data sharing examples at

http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

While submitting a clinical trial to Cyprus Journal of Medical Sciences;

- Authors are required to make registration to a publicly accessible registry according to ICMJE recommendations and the instructions above.
- The name of the registry and the registration number should be provided in the Title Page during the initial submission.
- Data sharing statement should also be stated in the Title Page even the authors do not plan to share it.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Editorial Comments: Invited brief editorial comments on selected articles are published in The Cyprus Journal of Medical Sciences. Editorials should not be longer than 1000 words excluding references. Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The subheadings of the review articles should be planned by the authors. However, each review article should include an "Introduction" and a "Conclusion" section. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, and Discussion with an unstructured abstract. Please check Table 1 for the limitations for Case Reports.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	4000	250 (Structured)	35	6	5 or total of 10 images
Review Article	5000	250	50	6	10 or total of 15 images
Case Report	1200	200	15	No tables	4 or total of 8 images
Letter to the Editor	400	No abstract	5	No tables	No media

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

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Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

Both in-text citations and the references must be prepared according to the Vancouver style.

hile citing publications, preference should be given to the latest, most up-to-date publications. Authors are responsible for the accuracy of references If an ahead-of-print publication is cited, the DOI number should be provided. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Journal Article: Yazıcı A. The efficacy of endoscopic ventilation tube insertion in pediatric populations. Cyprus J Med Sci. 2019; 4(2): 73-6.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the complete drug reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92.

Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki öğrencilerin beslenme durumları, fiziksel aktiviteleri ve beden kitle indeksleri kan lipidleri arasındaki ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

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Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar: 1(1): (24 screens). Available from: http:/ www.cdc.gov/ncidodlElD/cid.htm. (Accessed on June 5, 1996)

REVISIONS

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

Accepted manuscripts are copy-edited for grammar, punctuation, and format by professional language editors. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

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DOI: 10.4274/cjms.2021.2021-85
Cyprus J Med Sci 2022;7(3):281-282

Pleuropericardial Effusion: A Rare Onset of Rheumatoid Arthritis

Reyhan Köse Çobanoğlu

Department of Rheumatology, Aydın State Hospital, Aydın, Turkey

Dear Editor,

Pulmonary involvement is one of the most common extra-articular findings in rheumatoid arthritis (RA) where parenchymal lung disease and pleural disease are reported to be up to 79% and 50%, respectively.[1] Recent data suggests that RA-related autoimmunity may initiate in a mucosal site many years before the onset of joint symptoms, suggesting that the lung is one of these mucosal sites.[2] A 68-year-old male patient was admitted with dyspnea and chest pain that had started a week earlier. Lung sounds had decreased on the middle and lower zone of right lung on auscultation and chest X-ray revealed bilateral pulmonary effusion which was more prominent on the right lung. Pleural fluid reached a thickness of 9 cm on the right and 2 cm on the left, sub-segmental atelectasis, septal thickening and pericardial effusion were observed on chest computed tomography. Laboratory tests marked for normocytic anemia (hemoglobin: 9.0 g/dL), leukocytosis [white blood cell (WBC): 16,200/µL] and elevated acute phase reactants, erythrocyte sedimentation rate (ESR): 98 mm/h and C-reactive protein (CRP): 143 mg/dL (normal: 0–5 mg/L). Transthoracic echocardiography showed an ejection fraction of 65%, and a moderate pericardial effusion which measured 14 mm at its widest point. Sputum microscopy, sputum acido-resistant basil and sputum culture tests were negative for the exclusion of tuberculosis and other possible infections. Thoracentesis was performed and pleural fluid was exudative, pleural adenosine deiminase and mycobacterium polymerase chain reaction were negative. In pleural fluid cytology, 60% lymphocytes and 40% polymorphonuclear leukocytes were observed, and no microorganisms or malignant cells were found. ANA was positive at 1/100 titer of chromosomal dense fine speckled (DFS) pattern. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibody were positive at high titers 108.5 IU/mL (normal: 0–7 IU/mL) and 195.6 U/mL (normal: <4.5 U/mL), respectively. The patient had no previous history of arthritis. Rrheumatologic examination was unremarkable and there were no features on the hand X-ray. Methylprednisolone was initiated (0.5 mg/kg/day) and pleural and pericardial effusion improved on the control chest X-ray and echocardiography. During the one-year follow-up, the patient did not experience any joint symptoms.

RA causes joint erosions and deformities, more frequently in seropositive cases. It is crucial to diagnose and manage the disease in the "opportunity window" in order to prevent irreversible damage.[3] In recent years, growing data suggests that RA may originate from mucosal regions such as the respiratory mucosa, gastrointestinal mucosa or even the urogenital mucosa.[2] Additionally, extra-articular involvements preceding or occurring without articular manifestations, commonly as interstitial lung disease, have been reported.[4] To the best of our knowledge, this case is the first pleuropericardial effusion occurring without articular disease and with positive RA-related autoantibodies. Patients with atypical presentation and those with RF and ACPA positivity, as was the case with our patient, may develop joint findings during follow-up. However, it is an issue of debate as to whether these patients should be classified and managed as RA in the initial period with such extra-articular presentations.

Keywords: Pericardial effusion, pleural effusion, rheumatoid arthritis

ETHICS

Peer-review: Externally peer-reviewed.

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ORCID ID of the authors: R.K.Ç. 0000-0001-9017-8483.

Address for Correspondence: Reyhan Köse Çobanoğlu
E-mail: reyhan_kose@yahoo.com
ORCID ID: orcid.org/0000-0001-9017-8483

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REFERENCES

1. Demoruelle MK, Solomon JJ, Fischer A, Deane KD. The lung may play a role in the pathogenesis of rheumatoid arthritis. Int J Clin Rheumtol. 2014; 9(3): 295-309.
2. Demoruelle MK, Deane KD, Holers VM. When and where does inflammation begin in rheumatoid arthritis? Curr Opin Rheumatol. 2014; 26(1): 64-71.
3. van Nies JA, Tsonaka R, Gaujoux-Viala C, Fautrel B, van der Helm-van Mil AH. Evaluating relationships between symptom duration and persistence of rheumatoid arthritis: does a window of opportunity exist? Results on the Leiden early arthritis clinic and ESPOIR cohorts. Ann Rheum Dis. 2015; 74(5): 806-12.
4. Singh K, Al-Sadawi M, Ortega RR, Akter K, Zrodlowski T, Zmijewski C, et al. Interstitial Lung Disease as the Initial Manifestation of Rheumatoid Arthritis: A Case Report and Review of the Literature. Am J Med Case Rep. 2019; 7(12): 342-7.

REVIEW

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Therapeutic Challenges in Chronic Spontaneous Urticaria

Mehmet Ünsel

Department of Allergy and Immunology, Near East University Faculty of Medicine, Nicosia, North Cyprus

Abstract

Chronic spontaneous urticaria (CSU) involves cutaneous symptoms of swelling, redness, and itching that persist for longer than 6 weeks. These episodes can continue for months or years, with a disease duration of 1 to 5 years on average. The prevalence of CSU is estimated to be 0.5% to 1%. Frequent recurring episodes of generalized urticaria and angioedema reduce the quality of life for those patients with CSU. Treatment with second-generation antihistamines is insufficient in 36.8% of patients, even at high doses. Although omalizumab (humanized anti-immunoglobulin IgE) is also indicated for the treatment of this condition and has been used to treat patients who are unresponsive to high-dose second-generation antihistamines, omalizumab therapy is ineffective in one-third of those cases. Therefore, the current conventional treatments, including omalizumab, still do not provide adequate relief for some patients with CSU. This review discusses the therapeutic challenges, off-label drug use, and combined drug therapies in CSU patients who do not respond to the current conventional drug therapy.

Cyclosporine and methotrexate may be beneficial in the management of CSU which is unresponsive to conventional treatments. The combined use of these drugs with conventional therapies may increase the effectiveness of the treatment in difficult-to-manage cases. Methotrexate may be an effective alternative to cyclosporine for those CSU patients who cannot tolerate cyclosporine due to its high incidence of adverse effects.

Keywords: Chronic urticaria, omalizumab, cyclosporine, methotrexate, treatment

INTRODUCTION

Chronic spontaneous urticaria (CSU) involves cutaneous symptoms of swelling, redness, and itching that persist for longer than 6 weeks. These episodes can continue for months or years, with a disease duration of 1 to 5 years on average. The prevalence of CSU in the population is estimated to be 0.5% to 1%, and it is more common in women. Although onset can occur at any age, it is more common between 20 and 40 years of age.[1] Therefore, it is generally a serious health problem for adults. In a substantial proportion of patients (33%–67%), urticaria is accompanied by angioedema. Frequently recurring episodes of generalized urticaria and angioedema impair the quality of life in patients with CSU.[1]

Treatment of Chronic Urticaria

The recommended first-line treatment for CSU is second-generation antihistamines. Antihistamines are effective, inexpensive, and can be taken up to 4 times a day. However, a proportion of CSU patients do not respond to standard or high-dose antihistamines. A meta-analysis of responses to antihistamine therapy in CSU showed that 38.6% of patients responded at standard doses and 63.2% of those who were unresponsive to the standard dose responded after up-dosing.[2]

For those patients who do not respond to antihistamine up-dosing, omalizumab (humanized anti-immunoglobulin IgE) is added to the treatment at a standard dose of 300 mg subcutaneously every 4 weeks.[3] Despite the favorable safety profile of omalizumab, at the standard dose, it is also ineffective in approximately one-third of patients.[4] For this reason, the search continues for new monoclonal anti-IgE antibodies which may be more effective in those CSU patients who do not respond to the available treatments.

Ligelizumab is another humanized recombinant monoclonal anti-IgE antibody, like omalizumab. However, as it has a 50-fold higher IgE binding capacity than omalizumab, ligelizumab more potently suppresses IgE-mediated mast cell degranulation.[5] In a phase 2b trial of ligelizumab by Maurer et al.[6], patients received 3 different doses of ligelizumab (24 mg, 72 mg, and 240 mg) and omalizumab 300 mg at 4-week intervals.

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ORCID IDs of the authors: M.Ü. 0000-0003-2152-3786.

Address for Correspondence: Mehmet Ünsel
E-mail: unselmehmet@yahoo.com
ORCID ID: orcid.org/0000-0003-2152-3786

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At the end of 12 weeks, a complete response was observed in 30%, 44%, and 40% (respectively) of those patients treated with ligelizumab and 26% of the patients treated with omalizumab. Although the frequency of adverse events was similar to that with a placebo and omalizumab, injection site reactions and injection site erythema were more common in those patients who received 72 mg and 240 mg ligelizumab. The efficacy of omalizumab was lower in that study than in many previous studies. In placebo-controlled phase III trials, 43%–48% of CSU patients who received omalizumab 300 mg every 4 weeks showed a complete response.[7-9] The results of the phase III studies were later supported by real-life studies of omalizumab at standard doses (300 mg every 4 weeks). Complete response rates of 47.2% and 55.6% were reported in two different real-life studies of omalizumab.[10,11] According to the results of the real-life studies[10,11] and phase III trials,[7-9] ligelizumab seems to have similar effectiveness to omalizumab in CSU. Head-to-head studies with large patient samples are needed to clarify whether ligelizumab will be more effective than omalizumab.

Off-Label Treatments for Chronic Urticaria

Other than second-generation antihistamines and omalizumab, no new drugs have been indicated for the treatment of chronic urticaria. Phase trials of ligelizumab are ongoing. There is a lack of consensus on how to treat those patients who do not respond to current conventional treatments due to the lower effectiveness and less favorable safety profiles of other drugs. However, there are a few articles about off-label drug use for CSU in the literature.[11-15] As described above, the four-tier treatment algorithm proposed in the EAACI/GA²LEN/EDF/WAO International Guideline on CSU recommends second-generation antihistamine (a single daily dose as a first-line therapy and up to 4 doses/day as a second-line therapy), followed by a combination of second-generation antihistamine and omalizumab as a third-line therapy. If these approaches fail, a combination of second-generation antihistamine and cyclosporine is recommended as a fourth-line therapy. Cyclosporine is the only drug recommended in the guideline for off-label use due to low-quality evidence supporting the efficacy of sulfasalazine, methotrexate, interferon, plasmapheresis, phototherapy, intravenous immunoglobulins, and other treatment options.[3] There are literature data indicating that cyclosporine (3 mg/kg/day and 1–5 mg/kg/day) is effective in patients with antihistamine-refractory CSU,[12,13] but there has been little research into the effectiveness and safety of cyclosporine in those patients who are unresponsive to omalizumab and high-dose second-generation antihistamine.[11] Cyclosporine is believed to act by directly suppressing mast cell mediator release.[16,17] In a study by Kessel and Toubi[12], 120 patients who did not respond to second-generation antihistamines were started on 3 mg/kg/day cyclosporine and 20 (16.6%) of these patients discontinued treatment because of severe adverse effects (severe headache, peripheral neuropathy, abdominal pain and/or diarrhea). Of the 100 patients who received 3 months of cyclosporine treatment, complete response was observed in 30 patients (30%) and moderate response in 32 patients (32%). A review investigating the effectiveness of cyclosporine in a similar patient group showed that cyclosporine at low (2 to <4 mg/kg/day) and moderate (4–5 mg/kg/day) doses was effective for chronic urticaria unresponsive to antihistamine. One or more adverse events (headache, gastrointestinal symptoms, infection, hypertension, paresthesia, abnormal serum creatinine, and/or hirsutism) were observed in 23% of those taking low-dose cyclosporine and 57% of those taking moderate-dose cyclosporine.[13] In a retrospective study, 12 patients who did not respond to omalizumab and high-dose second-generation antihistamine were treated off-label with 2.5 mg/kg/day cyclosporine.[11] Six of these patients responded to cyclosporine; one of those patients used cyclosporine and omalizumab, one used cyclosporine and twice daily antihistamine, and four patients used cyclosporine alone. The other six patients terminated treatment due to nonresponse and/or severe adverse effects. Three of the patients (25%) did not respond to cyclosporine and five patients (41.6%) discontinued treatment because of severe adverse effects despite receiving low-dose (2.5 mg/kg/day) therapy. The high rate of cyclosporine-related adverse effects (hypertension, hyperlipidemia, hirsutism, gingival hypertrophy) was consistent with previous clinical studies.[12,13] In summary, cyclosporine may be effective in some CSU patients who do not respond to the current conventional drug treatments, including omalizumab, and can be used off-label for the treatment of CSU with careful patient selection and close monitoring for adverse effects.

As with other drugs, cyclosporine is not sufficient to treat all CSU patients because of its serious adverse effects and/or lack of effectiveness. In the literature, there have been a few promising studies with small patient series suggesting that methotrexate is useful and safe in antihistamine-refractory or steroid-dependent chronic urticaria[14,15] but again, there are few studies on the effectiveness and safety of methotrexate in those patients who are unresponsive to omalizumab and high-dose second-generation antihistamine.[18] In a retrospective study by Sagi et al.[14], 15 mg methotrexate was administered orally or intramuscularly once a week to eight chronic urticaria patients unresponsive to high-dose antihistamine therapy. Seven of these eight patients showed a complete response with methotrexate, while the other was unresponsive. One of the seven patients who responded completely with methotrexate did so after the dose was increased to 25 mg. One patient showed a slight elevation in liver function test results during treatment which normalized when the methotrexate dosage was decreased. Methotrexate was effective within the first 4 weeks. Perez et al.[15] retrospectively evaluated the efficacy of methotrexate in 10 chronic urticaria and two isolated angioedema patients. All patients included in that study were unresponsive to at least two of the following: antihistamine, azathioprine, colchicine, montelukast, sulfasalazine, doxepin, dapsone, intravenous immunoglobulin, and cyclosporine. Of the 10 patients with chronic urticaria, nine were unresponsive to cyclosporine treatment. The patients were given 5–25 mg methotrexate once a week. Under methotrexate therapy, urticaria symptoms regressed with no change in steroid dose in three patients, urticaria symptoms regressed with reduced steroid dose in four patients, urticaria resolved with steroid cessation in one patient, and nonresponse was observed in two patients. While one of the two patients with angioedema was unresponsive to methotrexate, both angioedema severity and steroid dose decreased in the other patient. Methotrexate was well-tolerated by all patients, with mild adverse effects such as hair thinning and fatigue reported. In another retrospective study, subcutaneous methotrexate 15 mg/week was administered to 10 patients who did not respond to high-dose second-generation antihistamine and omalizumab and/or cyclosporine.[18] Four of the patients had been previously treated with cyclosporine. The mean duration of methotrexate therapy was 5.1 months (1.5–9 months). Of these 10 patients, methotrexate monotherapy or combined therapy resulted in complete response in six (60%), a well-controlled response in one (10%), partial response in one (10%), and nonresponse in two patients (20%). Methotrexate was administered as monotherapy to four patients (40%) and given as part of combination therapy in the other six

patients (60%). Of the six patients who received combination therapy, three received second-generation antihistamine and methotrexate, two received omalizumab and methotrexate, and one received second-generation antihistamine, omalizumab, and methotrexate. There was a slight elevation in liver function tests in one patient (10%) who was also unresponsive to methotrexate therapy. Another patient discontinued treatment because she experienced a burning sensation in the stomach, exacerbation of preexisting gastroesophageal reflux, vomiting, and diarrhea. Despite encouraging results from small studies suggesting methotrexate may be safe and effective in CSU,[14,15,18] methotrexate was found to have no benefit over the placebo according to a meta-analysis that included 104 patients in two placebo-controlled studies investigating the effectiveness of combined antihistamine and methotrexate in antihistamine-resistant CSU.[19]

Despite methotrexate having adverse effects and contradictory results, cyclosporine or methotrexate may be off-label treatment options for those CSU patients who do not respond to monoclonal antibody therapy and high-dose second-generation antihistamines.

The literature contains mostly monotherapy drug studies in CSU. Few studies have examined responses to combined therapy.[11,20] However, in real life, these drugs are used in combination to treat chronic urticaria. Cyclosporine or methotrexate can be used as monotherapies or in combination with omalizumab and second-generation antihistamines. In a clinical trial including 21 CSU patients who were nonresponsive to omalizumab (300 mg every 4 weeks) and cyclosporine (3 mg/kg/day), after 4 months of receiving the drugs in combination the response rate increased to 76.1% with no increase in adverse effects.[20] In another retrospective study, 126 patients in a chronic urticaria drug trial were treated with omalizumab (300 mg every 4 weeks), second-generation antihistamine (1–4 doses/day), cyclosporine (2.5 mg/kg/day), and methotrexate (15 mg/week) alone or in combination on a case-by-case basis (omalizumab monotherapy in 70.6%, combined therapy in 25.4%, and cyclosporine or methotrexate monotherapy in 4% of patients), and complete response was reported in 77.8% of these patients, well-controlled response in 18.3%, partial response in 3.2%, and nonresponse in 0.8% of the patients.[11] This study provided evidence that combined drug use may be much more effective than monotherapy in CSU.

CONCLUSION

Methotrexate, either as monotherapy or in combination with second-generation antihistamine and/or omalizumab, seems to be a beneficial treatment option for patients with chronic urticaria refractory to omalizumab with second-generation antihistamine treatment. In those patients who partially respond to omalizumab and second-generation antihistamine treatment, methotrexate can be added to the existing treatment regimen. In those patients unresponsive to omalizumab, methotrexate can be administered either in combination with second-generation antihistamine or as monotherapy, depending on treatment response. Methotrexate can be effective as monotherapy or combination therapy even in patients who are unresponsive to omalizumab and cyclosporine. Moreover, since methotrexate has a much better safety profile than cyclosporine, methotrexate offers an alternative to cyclosporine for those patients unresponsive to omalizumab and second-generation antihistamine. Further studies with larger patient series and more real-life data are necessary to corroborate these findings.

MAIN POINTS

- CSU is characterized by episodes of skin redness, swelling, and itching which last for more than 6 weeks. CSU can last for many years, with its average duration being 1–5 years, and it affects between 0.5% and 1% of the population.
- At present, second-generation antihistamines and omalizumab (humanized anti-immunoglobulin IgE) are widely used in the treatment of CSU.
- For those patients who do not respond to antihistamine up-dosing, omalizumab (300 mg every 4 weeks, subcutaneous) is added to the treatment.
- Omalizumab is ineffective in one-third of patients treated at the standard dosage.
- Cyclosporine or methotrexate can be used in combination with omalizumab and second-generation antihistamines or as a monotherapy.

ETHICS

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DISCLOSURES

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REFERENCES

1. Maurer M, Weller K, Bindslev-Jensen C, Giménez-Arnau A, Bousquet PJ, Bousquet J, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA²LEN task force report. Allergy. 2011; 66(3): 317-30.
2. Guillén-Aguinaga S, Jáuregui Presa I, Aguinaga-Ontoso E, Guillén-Grima F, Ferrer M. Updosing nonsedating antihistamines in patients with chronic spontaneous urticaria: a systematic review and meta-analysis. Br J Dermatol. 2016; 175(6): 1153-65.
3. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy. 2018; 73(7): 1393-414.
4. Bérard F, Ferrier Le Bouedec MC, Bouillet L, Reguiai Z, Barbaud A, Cambazard F, et al. Omalizumab in patients with chronic spontaneous urticaria nonresponsive to H1-antihistamine treatment: results of the phase IV open-label SUNRISE study. Br J Dermatol. 2019; 180(1): 56-66.
5. Arm JP, Bottoli I, Skerjanec A, Floch D, Groenewegen A, Maahs S, et al. Pharmacokinetics, pharmacodynamics and safety of QGE031 (ligelizumab), a novel high-affinity anti-IgE antibody, in atopic subjects. Clin Exp Allergy. 2014; 44(11): 1371-85.
6. Maurer M, Giménez-Arnau AM, Sussman G, Metz M, Baker DR, Bauer A, et al. Ligelizumab for Chronic Spontaneous Urticaria. N Engl J Med. 2019; 381(14): 1321-32.
7. Kaplan A, Ledford D, Ashby M, Canvin J, Zazzali JL, Conner E, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. J Allergy Clin Immunol. 2013; 132(1): 101-9.
8. Saini SS, Bindslev-Jensen C, Maurer M, Grob JJ, Bülbül Baskan E, Bradley MS, et al. Efficacy and Safety of Omalizumab in Patients with Chronic Idiopathic/Spontaneous Urticaria who Remain Symptomatic on H1 Antihistamines: A Randomized, Placebo-Controlled Study. J Invest Dermatol. 2015; 135(3): 925.

9. Maurer M, Rosén K, Hsieh HJ, Saini S, Grattan C, Gimenéz-Arnau A, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med. 2013; 368(10): 924-35.

10. Salman A, Ergun T, Gimenez-Arnau AM. Real-life data on the effectiveness and safety of omalizumab in monotherapy or combined for chronic spontaneous urticaria: a retrospective cohort study. J Dermatolog Treat. 2020; 31(2): 204-9.

11. Unsel M. Efficacy of drug therapies in antihistamine refractory chronic spontaneous urticaria: Real life data. Asian Pac J Allergy Immunol. 2021; 21.

12. Kessel A, Toubi E. Cyclosporine-A in severe chronic urticaria: the option for long-term therapy. Allergy. 2010; 65(11): 1478-82.

13. Kulthanan K, Chaweekulrat P, Komoltri C, Hunnangkul S, Tuchinda P, Chularojanamontri L, et al. Cyclosporine for Chronic Spontaneous Urticaria: A Meta-Analysis and Systematic Review. Allergy Clin Immunol Pract. 2018; 6(2): 586-99.

14. Sagi L, Solomon M, Baum S, Lyakhovitsky A, Trau H, Barzilai A. Evidence for methotrexate as a useful treatment for steroid-dependent chronic urticaria. Acta Derm Venereol. 2011; 91(3): 303-6.

15. Perez A, Woods A, Grattan CE. Methotrexate: a useful steroid-sparing agent in recalcitrant chronic urticaria. Br J Dermatol. 2010; 162(1): 191-4.

16. Stellato C, de Paulis A, Ciccarelli A, Cirillo R, Patella V, Casolaro V, et al. Anti-inflammatory effect of cyclosporin A on human skin mast cells. J Invest Dermatol. 1992; 98(5): 800-4.

17. Harrison CA, Bastan R, Peirce MJ, Munday MR, Peachell PT. Role of calcineurin in the regulation of human lung mast cell and basophil function by cyclosporine and FK506. Br J Pharmacol. 2007; 150(4): 509-18.

18. Unsel M. Safety of Methotrexate in Chronic Urticaria Unresponsive to Omalizumab. Iran J Allergy Asthma Immunol. 2021; 20(4): 500-4.

19. Patil AD, Bingewar G, Goldust M. Efficacy of methotrexate as add on therapy to H1 antihistamine in difficult to treat chronic urticaria: A systematic review and meta-analysis of randomized clinical trials. Dermatol Ther. 2020 ;33(6): e14077.

20. Sánchez J, Alvarez L, Cardona R. Cyclosporine and omalizumab together: A new option for chronic refractory urticaria. J Allergy Clin Immunol Pract. 2020; 8(6): 2101-3.

REVIEW

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Therapeutic Interventions Implemented During the First Year of the COVID-19 Pandemic: A Systematic Review of Evidence

Özen Aşut, Şanda Çalı

Department of Public Health, Near East University Faculty of Medicine, Nicosia, North Cyprus

Abstract

The aim of this study was to review the knowledge and evidence on the therapeutic effectiveness of some agents currently utilized for treating coronavirus disease-2019 (COVID-19).

The literature search was performed using the databases PubMed, Scopus, Google Scholar, and the Cochrane Library. The publications identified were screened to select cohort studies, randomised controlled trials, meta-analyses, narrative and systematic reviews. End points displaying the results of epidemiological and statistical methods were evaluated to specify the strength of evidence.

Eleven randomised controlled trials, a controlled trial, five cohort studies, four reviews, two systematic reviews, a systematic review-meta-analysis, and a meta-analysis were included. These 25 studies covered treatments with antimalarials, anticoagulation, antivirals, corticosteroids, interferons, monoclonal antibodies, and convalescent plasma. The outcomes assessed included all-cause and in-hospital mortality, death or mechanical ventilation within 28 days, mean or median day to viral clearance, median and day-28 recovery time, and improvement in oxygen support class.

The results showed evidence for the efficacy of remdesivir and corticosteroids in critically ill patients. Only corticosteroids showed efficacy regarding reduced mortality. Favipiravir, anticoagulation, interferons and monoclonal antibodies were agents with weaker evidence of therapeutic efficacy.

The key findings of this review highlight evidence regarding the efficacy of remdesivir and corticosteroids for hospitalised patients.

Keywords: COVID-19, coronavirus disease 2019, therapeutic alternatives, antivirals, remdesivir, favipiravir, corticosteroids, immunomodulators

INTRODUCTION

Coronavirus disease-2019 (COVID-19) was officially announced by the World Health Organisation (WHO) on December 31, 2019,[1] and declared a global pandemic by the WHO on March 11, 2020.[2,3] COVID-19 is predominantly self-limited while up to 20% will progress to severe disease. Early treatment to prevent disease progression and complications is pronounced currently as an urgent need.[4-8]

Antimalarial medications, chloroquine and hydroxychloroquine were among the first drugs introduced for treatment and prophylaxis.[9,10] Although countries continued keeping these drugs in their treatment protocols, the WHO cautioned against administering these unproven treatments.[11-14]

Basically, therapeutics for COVID-19 fall into three categories: Antiviral, immune-based, and adjunctive therapies. Some antiviral medications,

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ORCID IDs of the authors: Ö.A. 0000-0002-9604-4037; Ş.Ç. 0000-0001-9929-2637.

Address for Correspondence: Özen Aşut
E-mail: ozen.asut@neu.edu.tr
ORCID ID: orcid.org/0000-0002-9604-4037

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antibiotics and immuno-therapeutics have been introduced for COVID-19 based on the experiences of previous coronavirus diseases and in-vitro findings.[15-19] The therapeutics investigated in trials include ivermectin,[16,17] melatonin,[18,20] and monoclonal antibodies.[15,19]

The National Institutes of Health (NIH) COVID-19 Treatment Guidelines panel has outlined evidence-based statements on primary therapeutics for COVID-19 according to the available research.[17,21,22]

Antiviral medications including remdesivir and favipiravir; immunomodulators such as interferons, corticosteroids, monoclonal antibodies, and anticoagulation and convalescent plasmas are the subjects of this review as well as research on some therapeutics under investigation with insufficient or no evidence to highlight the multidimensional progress on this issue. There are more than 60 thousand COVID-19 publications available on PubMed. It is important that the choice of therapeutic agents by the medical professionals should rely on the best possible evidence currently available.[23]

Objective of the study

The aim of this study was to establish the current knowledge and evidence on the therapeutic efficacy of some prominent agents utilized in the treatment of COVID-19 through a review of the existing evidence-based medical literature universally. Since information on this issue is evolving rapidly, the content within this review intends to serve as a reference for the information available at the time of publication.

Methods

Information Sources and Criteria of Eligibility

The literature search was performed as recommended for systematic reviews[24] through the databases PubMed, Scopus, Google Scholar and the Cochrane Library, only in English, using the keywords COVID-19 therapy and treatment. Additional studies were identified through other means (such as Medscape, references of articles, and press releases).

Article Search

There was no time limit set regarding the study period and publication dates. Starting on 20 June, 2020, an online search was performed until November 10, 2020. Newly appearing articles and other data were covered by continuing the literature search until January 30, 2021.

Study Selection and Recruitment of Articles

The publications identified were screened by the researchers based on title and abstract in order to find the relevant articles. Cohort studies, randomised controlled trials, meta-analyses, narrative and systematic reviews were recruited into the study list. Pre-print articles, case reports and case series other than those in the review studies were excluded.

Subsequently, 59 full articles were assessed in order to eliminate any articles with study types and content other than those in the inclusion criteria and to select those articles containing a strength of evidence. Some articles were excluded due to the insufficient quality of the research methods, analyses of the data or interpretation of the findings (Figure 1).

Data Collection Process

Data were collected using a data extraction form which covered the following features of the articles: The database, journal name and issue, authors and title; time, setting and the universe of studies; the number of participants, the number of studies (for reviews); and the aim, type, methods, results and outcomes of the studies. The data extraction and assessment were carried out by the two researchers independently. Decisions were made after discussion and by consensus based on the evidence.

Data Items

Data items included the following variables:

Participants: COVID-19 patient groups of differing ages and severity (mild, moderate, severe), hospitalised and non-hospitalised patients, need of oxygen supplementation

Interventions: Therapies applied in COVID-19: Pharmacotherapeutics such as antivirals, chloroquine and hydroxychloquine, anticoagulation, monoclonal antibodies, interferons, convalescent plasma, corticosteroids etc.

Comparisons: Therapies applied to control groups: Usual care, antivirals (lopinavir/ritonavir, oseltamivir, umifenovir), antibiotics and placebos.

Outcomes: 28-day all-cause mortality, in-hospital mortality, death or mechanical ventilation (MV) within 28 days, lethality, improvement of radiologic findings, days to viral clearance, mean or median days to viral clearance, recovery at day 28, time to recovery measured as discharge from hospital, improvement in oxygen support class, organ-support free days, improvement and clinical recovery rate, and median recovery time.

Study design: Cohort studies, randomised controlled trials, meta-analyses, narrative and systematic reviews.

Funding sources: Studies with conflicts of interest

Risk of Bias in Individual Studies

Assessment of the risk of bias included methods of randomisation, treatment allocation and blinding. The novel and urgent nature of COVID-19 therapeutic interventions resulted in weaknesses in preventing bias, as a lack of controls, randomisation or blinding were declared in the method sections of the studies and these were used in assessing the strength of the evidence.

Summary Measures

Principal summary measures included hazard ratios, relative risks, odds ratios, their confidence intervals, risk differences, lethality, other epidemiological measures, statistical tests and their *p* values.

Limitations

Since COVID-19 has a short history of only one year, the results of the studies selected have limitations due to the infection's novel nature, time restrictions, low participant sizes, the lack of sufficient previous experience, and the uncertain nature of future advances. Furthermore, the rapid progress in the treatment of COVID-19 limits the comprehensiveness of a review due to the time needed to finalise studies.

The fact that only English publications have been covered in this study may be considered a bias regarding publication language.

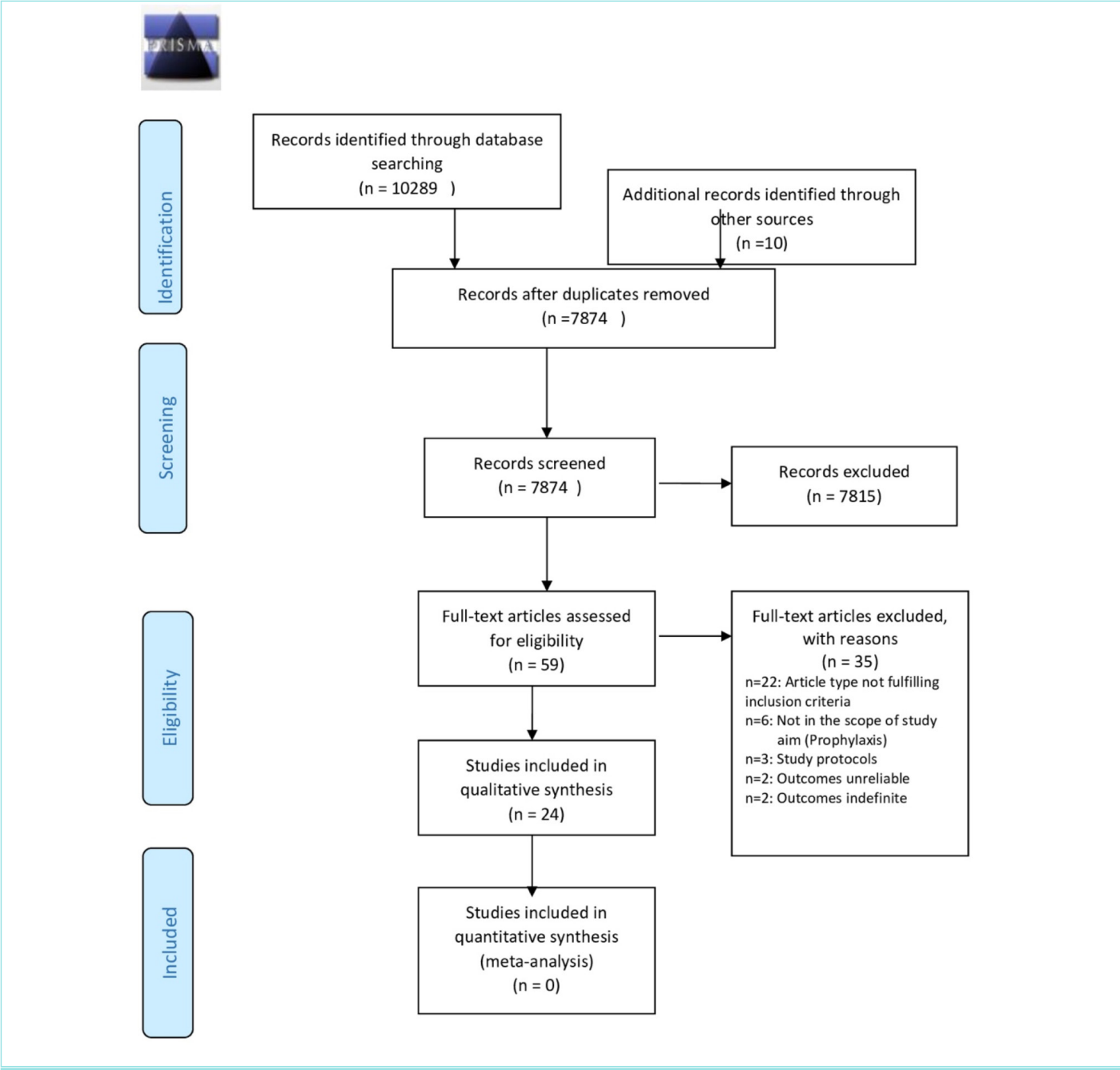

Figure 1. Prisma flow diagram of the search results.

Results

In this study, the selection of the research articles was based on the quality of the evidence in the studies. The number of studies screened, assessed and included are displayed in the flow diagram (Figure 1).

Randomised controlled trials, systematic reviews and meta-analyses comprised 15 of the total 25 studies selected. Eleven randomised controlled trials, one controlled trial, five cohort studies, four reviews, two systematic reviews, one systematic review and meta-analysis, and one meta-analysis were included. Some preliminary research other than these was also covered in the main text of the article, although not included in the tables.

The studies reviewed were conducted in the following countries: China, the Netherlands, Italy, France, the United States of America (USA), Columbia, Iran, Mexico, Denmark, the United Kingdom (UK), Korea, Singapore, India, Greece, Germany, Spain, Japan, Hong Kong, Taiwan, Australia, Brazil, Canada, New Zealand, Ireland and Thailand. The details of the publications selected are presented in Tables 1–5. The contents of the articles are presented under the headings relevant to the therapeutic agents.

Prophylactic Dose/Treatment-Dose Anticoagulation

Increased venous and arterial thromboembolic events have been reported previously. In a cohort study of 2773 patients, the association

of treatment dose anticoagulation (AC) and in-hospital survival was investigated. The mortality rate of the intervention group was significantly lower than the control group among patients who required MV (Table 1) ($p<0.001$).[25]

On the other hand, the results of an interim analysis released on January 28, 2021, based on three international randomised open-label trials on the use of anticoagulation from 17 countries revealed contrasting findings to this cohort study. Accelerating COVID-19 therapeutic interventions and vaccines (ACTIV-4a) conducted at 60 international sites), Randomised embedded multi-factorial adaptive platform trial at 290 international sites (REMAP-CAP) and Antithrombotic therapy to ameliorate complications of COVID-19 (ATTACC at 58 international sites) compared the effectiveness of therapeutic and prophylactic doses of anticoagulation in reducing the need for organ-support. The intervention was heparin treatment versus usual care pharmacologic venous thromboembolism (VTE) prophylaxis. The enrolment of severe state patients requiring intensive care unit (ICU)-level care were paused after an interim analysis demonstrated that therapeutic heparin did not improve organ-support free days at day 21. However, therapeutic dose anticoagulation treatment was superior to usual care pharmacologic VTE prophylaxis for moderate state patients (hospitalised, not on ICU organ support).[26]

Currently, the NIH COVID-19 Treatment Guidelines Panel recommends prophylactic dose anticoagulation for hospitalised patients.[27]

Chloroquine-Hydroxychloroquine

A study on the association of hydroxychloroquine use and intubation or death revealed no significant association between hydroxychloroquine use and intubation or death (Table 1).[28]

A randomised controlled trial (RCT) of 150 patients investigated virus elimination by high dose hydroxychloroquine, which showed no significant difference from the current standard care (Table 1).[29]

A systematic review by Hernandez et al.[30] disclosed further data on hydroxychloroquine or chloroquine use in COVID-19 (Table 1). Four randomised controlled trials and 10 cohort studies assessed its treatment effects. The evidence on the benefits and harms of hydroxychloroquine or chloroquine were depicted as very weak and conflicting.[30]

In a later update of the systematic review, five new randomised trials and 4 cohort studies revealed no new evidence regarding its therapeutic efficacy (Table 1).[31] In addition, there was now a low strength of evidence that hydroxychloroquine had positive effect on all-cause mortality and the need for MV.[31] In the RECOVERY trial, an RCT comparing a range of treatments with usual care in hospitalised patients, the primary outcome was 28-day mortality. The enrolment of patients in the hydroxychloroquine group was closed after an analysis determined a lack of efficacy (Table 1).[32] Furthermore, a randomised study from Brazil revealed increased lethality with higher doses of chloroquine (Table 1).[33] The large SOLIDARITY-WHO and ORCHID-NIH trials were prematurely discontinued, with press releases announcing a lack of efficacy.[31]

Convalescent Plasma

The efficacy and safety of convalescent plasma has been appraised as uncertain due to a lack of RCTs.[34]

The data from several small observational studies demonstrated improvements of symptoms (Table 2).[35-38] The strength of evidence is assessed as very low.

Convalescent plasma is under investigation in 11 studies registered in clinical trials (a total of 1106 patients). The ongoing trials are taking place in China, Italy, the USA, Columbia and Iran.[36]

Monoclonal antibodies-Bamlanivimab and Tocilizumab

Monoclonal antibodies are biotherapeutics for passive immunotherapy against viral infections similar to convalescent plasma. In animal models, there is evidence that antibody therapy may reduce viral load.[19,39-43]

Bamlanivimab

Bamlanivimab, one of the monoclonal antibodies, was studied in a phase II RCT for treating ambulatory mild or moderate COVID-19 patients. Patients were randomised for treatment by one of three doses, or a placebo. The 2800 mg dose resulted in a significant decrease of viral load in the intervention group.[41] In addition, bamlanivimab demonstrated a lower relative risk of hospitalisation (Table 2).[41]

The NIH Guidelines Panel announced in its February 11, 2021, update that bamlanivimab and the combination of casirivimab and imdevimab are available through the FDA's emergency use authorisations (EUAs) for the treatment of mild to moderate outpatients at high risk of progressing to severe disease and/or hospitalisation.[17,40]

Tocilizumab

Non-randomised studies have suggested mortality benefit with tocilizumab, a humanized monoclonal antibody in COVID-19 patients.[15]

In a randomised clinical trial studying the effect of early tocilizumab administration, hospitalised patients with severe COVID-19 requiring oxygen but not ICU-level care were investigated. The trial was stopped early after initial analyses showed no evidence of improvement in primary outcomes.[43]

In the STOP-COVID study of the USA, the treatment of critically ill patients with tocilizumab was investigated by time to death and 30-day mortality. Tocilizumab treated patients had a lower risk of death compared to the others (Table 2).[42] In contrast to the findings from STOP-COVID and multiple observational studies, none of the tocilizumab RCTs reported mortality benefit at 28 or 30 days, and only two of these trials reported outcomes meeting predefined thresholds for efficacy (Table 2).[23]

An update of NIH Panel on February 11, 2021 pointed out that there is insufficient evidence to recommend either for or against the use of tocilizumab or sarilumab for patients within 24 hours of ICU, requiring MV or NIV. For patients not requiring ICU-level care, the panel recommended against the use of these agents except in a clinical trial.17

Interferons

Interferons are cytokines with antiviral properties. Hence, they have been suggested as a potential treatment for COVID-19 due to their antiviral activity.[44] Interferon studies covered in this review include one cohort study, one RCT and the preliminary results of an ongoing RCT.

Table 1. Trials on therapeutic measures utilized in COVID-19: Insufficient or conflicting evidence, needing further investigations; or evidence for no therapeutic efficacy (anticoagulation, hydroxychloroquine or chloroquine)

Title of article and authors	Type of research	Participants/number of studies	Country - region	Intervention-Treatment and primary end point	Outcome/Results
Association of treatment dose anticoagulation with in-hospital survival among hospitalised patients with COVID-19. **Paranjpe I et al.** [25]	Cohort study	2773 hospitalised patients **786** patients received anticoagulation (AC) therapy **395** of patients requiring mechanical ventilation	New York (NY) city, USA	Treatment dose anticoagulation therapy (AC) (oral, sc, iv)	**1.Overall: In- hospital mortality** Treatment group: 22.5% (median survival 21 days) Control group: 22.8% (median survival 14 days) **2. Patients requiring mechanical ventilation (395 patients)** **In-hospital mortality:** Treatment group: **29.1%** (median survival 21 days) **Control group: 62.7**% (median survival of 9 days) Longer duration of AC treatment associated with a reduced risk of mortality Adjusted **HR: 0.86 per day** (95% **confidence interval** [CI] 0.82−0.89, p<0.001)
Observational study of hydroxychloroquine in hospitalised patients with COVID-19. **Geleris J et al.** [28]	Cohort study	1376 hospitalised COVID-19 patients	NY city, USA	HydroxychloroquineDay1:600 mg × 2 400 mg/day for a median of 5 days **End points:** Death or intubation Median follow -up 22.5 days	25.1% reached one endpoint: 180 intubated patients, of whom 66 died 166 deaths without intubation No significant association between treated and untreated groups **Hazard ratio: 1.04, 95% CI 0.82 − 1.32**
Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. **Tang W et al.** [29]	Randomised controlled trial (RCT) 11-29 Feb. 2020	150 mild to moderate patients in 16 governmen-tal COVID-19 treatment centers	China 3 provinces: Hubei, Henan and Anhui	Hydroxychloroquine 1200 mg/ day for 3 days 800 mg/day up to 2 weeks **Primary outcome**: Negative seroconversion in 28 days	**No significant difference from current standard of care** regarding virus elimination No deaths Adverse events more in trial group
Hydroxychloroquine or chloroquine for treatment or prophylaxis of COVID-19. A living systematic review. **Hernandez AV et al.**[30]	Systematic review Evidence through 1 July 2020	4 RCTs, 10 cohort studies, 9 case series assessed treatment effects, no study on prophylaxis	-	Hydroxychloro-quine or chloroquine **Outcomes:** All-cause mortality Severe disease Virologic clearance	Evidence conflicting and insufficient on: all-cause mortality, progression to severe disease, clinical symptoms and upper respiratory virologic clearance with antigen testing
Update Alert 2: Hydroxychloroquine or chloroquine for the treatment or prophylaxis of COVID-19. **Hernandez AV et al.**[31]	Letter (Update of living systematic review) Evidence through 1 Aug. 2020	5 RCTs 4 Cohort studies Placebo or standard care controlled	-	Chloroquine Hydroxychloroquine **Outcomes:** All-cause mortality Need for mechanical ventilation Reductions in hospitalization	No new evidence regarding chloroquine therapy **Low strength of evidence** from RCTs and cohort studies that HCQ has **no positive effect on all-cause mortality** **and need for mechanical ventilation** No benefit or reductions in hospitalization **Low strength of evidence** for "no positive effect" on intubation or death and discharge from the hospital
Effect of hydroxychloroquine in hospitalised patients with COVID-19 **The RECOVERY Collaborative Group.**[32]	Randomised controlled, open-label platform trial	Hospitalised COVID-19 patients 1561 hydroxy chloroquine (HCQ) 3155 usual care		HCQ 800mg twice: Day 1 400mg-twice for 9 days **Primary outcome** Death within 28 days	**Death within 28 days:** No significant difference between trial and control groups 421 patients (27.0%) in the HCQ group 790 (25.0%) in the usual-care group **Rate ratio: 1.09;** 95% CI **0.97 to 1.23,** p=0.15 **Discharge from hospital alive** in 28 days: 59.6% for HCQvs. 62.9% for usual care; rate ratio, 0.90; 95% CI, 0.83 to 0.98 HCQ group had a **higher frequency of invasive mechanical ventilation or death:** 30.7% vs. 26.9%; risk ratio **1.14;** 95% CI, 1.03 to 1.27

Table 1. Continued

Title of article and authors	Type of research	Participants/number of studies	Country - region	Intervention-Treatment and primary end point	Outcome/Results
Effects of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalised with severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection: A randomised clinical trial. **Borba MGS et al.**[33]	Randomised double blind trial	440 adult hospitalised patients receiving cephtriaxone and oseltamivir: 81 were randomised as 40: 41 patients	Brazil	Chloroquine diphosphate 450mg versus 600mg **End points:** Primary: Lethality by day 13 Secondary: Lethality by day 28	Results: Low dose lethality 11/73 :**15.1%** **High dose** chloroquine diphosphate**:** Increased lethality for patients: **27.2%** **Lethality odds ratio: 3.6** (95% CI: **1.2 to10.6**)

AC: anticoagulation, AOR: adjusted odds ratio, ARDS: acute respiratory distress syndrome, CI: confidence Interval, COVID-19: coronavirus disease-2019
EUA: emergency use authorization, DA: Food and Drug Administration, HCQ: hydroxychloroquine, HR: hazard ratio, IDSA: Infectious Diseases Society of America, NIH: National Institutes of Health, NIV: non-invasive ventilation, MV: mechanical ventilation, OR: odds ratio, RCT: randomised controlled trial, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, VTE: venous thromboembolism.

Interferon Beta-1b

The first interferon RCT was a phase 2 clinical trial utilising interferon beta-1b for therapy (Table 3).[45] In the trial group, hospitalised patients were randomised into triple therapy (interferon beta-1b, lopinavir/ritonavir, and ribavirin) or double therapy (lopinavir/ritonavir and ribavirin). The control group received only lopinavir/ritonavir therapy. The median time to negative nasopharyngeal swab was 7 days in the total combination therapy group and 12 days in the control group (hazard ratio: 4.37, p=0.001). Further analyses revealed that the shortening of the time to viral clearance was due to the effect of the interferon beta1b group.[45]

Interferon Alfa-2b

A cohort study investigated the efficacy of nebulized interferon alfa 2b among 77 hospitalised patients. Three patient groups received either umifenovir, interferon alfa 2b or both agents. The end point was viral clearance. Interferon accelerated viral clearance by 7 days.[46] However, this study had limitations and a low strength of evidence (Table 3).

Interferon Beta-1a

The results of an RCT from the UK evaluating the effects of inhaled interferon beta-1a among hospitalised patients was reported on July 20, 2020 (Table 3).[47] Compared to the control group, the intervention group patients were more likely to recover by day 28 [odds ratio (OR): 3.86, p=0.017]. In addition, the intervention group had decreased odds of developing severe disease.[47]

The interferon studies covered in this review have several limitations including low patient size (total 305) and display a low strength of evidence.

Remdesivir

Remdesivir is an antiviral known to have inhibitory activity against SARS-CoV and MERS-CoV. *In vitro* studies revealed the efficacy of remdesivir in inhibiting SARS-CoV-2 as well.

The therapeutic effectiveness of remdesivir was investigated in a multicentre randomised, controlled trial covering 10 countries with 1063 hospitalised patients. The primary outcome was the time to recovery (Table 4).[48]

The final report was published in October, 2020.[48,49] Patients in the remdesivir group had a shorter time to recovery (median 10 days, compared with 15 days; rate ratio for recovery 1.29; p<0.001).[49] Those patients who received remdesivir were found more likely to have clinical improvement on day 15 (OR: 1.5) (Table 4).[49] The strength of evidence was appraised as high for this study.

A double-blind controlled trial of 237 patients from China found no significant differences in favour of the trial group (Table 4).[50]

In a multinational cohort study of 53 hospitalised severely ill patients, remdesivir therapy improved the oxygen support class in 68% of the patients and 47% were discharged. Of those receiving MV, 57% were extubated. The overall mortality rate and mortality among MV patients were lower than previously reported (Table 4).[51]

A multi-country RCT of 397 patients with severe disease but without the need for MV were randomised into therapy with remdesivir to receive either 5 or 10-day treatments. There was no significant difference between the two groups on day 14 regarding clinical improvement as assessed on an ordinal scale (Table 4).[52]

Remdesivir has been approved by the FDA for use among hospitalised COVID-19 patients and endorsed globally.[8]

The remdesivir studies in this review cover some earlier and later research. Three RCTs and one cohort study included 1749 hospitalised cases covering multiple countries. The results have consistently manifested the efficacy of remdesivir, as shown by the assessments of relevant studies with moderate to high strengths of evidence.

Table 2. Trials on therapeutic measures utilized in COVID-19: Insufficient evidence of therapeutic efficacy, needing further investigations: Convalescent plasma and monoclonal antibodies

No	Journal name and date	Title of article and authors	Type of research	Participants/ number of studies	Country - region	Intervention-Treatment and primary end point	Outcome/Results
1	Transfusion and Apheresis Science Published June, 2020	Treatment for emerging viruses: Convalescent plasma and COVID-19. **Brown BL et al.** [35]	Review Case series	9 patients in 3 case series	China	Convalescent plasma of 1 dose 200 mL with neutralizing antibody titers >1:640	Improved oxygenation Reduced inflammation and C- reactive protein Viral load undetectable in 7 of 9 patients **Limitation:** Study type No controls
2	HemaSphere Published June, 2020	The emerging role of convalescent plasma in the treatment of COVID-19. **Psaltopoulou T et al.** [36] **Ye M et al.** [37] **Shen C et al.** [38]	Narrative Review 6 case series April 2020	34 patients in 6 case studies	China	Convalescent plasma plus other therapies: Antiviral agents such as L/R, umifenovir (Arbidol) and levofloxacin, methyl prednisolone	Reported to suppress viremia and restore coagulation factors Improvement of radiologic findings reported [37] Viral load negative in 12 days, in 5 patients [38] Risks: Transfusion related acute lung injury, antibody dependent enhancement **Limitations:** No information on other outcomes No control groups
3	N Engl J Med **2020** Epub 28 October, 2020	SARS-CoV-2 Neutralizing antibody LY-CoV555 in outpatients with COVID-19. **Chen P et al.** [41]	RCT Phase 2	452 Mild or moderate non-hospitalised COVID-19 patients		Bamlanivimab In one of three doses (700 mg, 2800 mg, or 7000 mg) or placebo **Primary outcome**: Change in viral load on day 11	2800 mg dose resulted in a **significant decrease of viral load** in the intervention group on day 11 (Interim analysis, Sep5, 2020) Bamlanivimab demonstrated a lower relative risk of hospitalisation: **RR: 0.26;** 95% CI: 0.09 to 0.75 **Hospitalization or visit to an emergency department**: **Intervention** group: **1.6%** Placebo group: **6.3%** **Limitation:** Phase 2 trial
4	JAMA Internal Medicine Published online Oct 20, 2020	Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. **Gupta et al. for the STOP-COVID investigators** [42]	Cohort study	Total 3924 patients 433 (11%) intervention group **-younger population**	USA 68 sites	Tocilizumab Given in 2 days of ICU admission **Outcome:** Death at day 27	39.3% of total patients died at 27 days Tocilizumab treated group had a lower risk of death: 27.5% versus 37.1% **Hazard ratio 0.71** (95% CI: 0.56 to 0.92) Risk difference: **9.6%** (95% CI, 3.1% to 16.0%) **Limitation:** Age bias between groups
5	JAMA Internal Medicine Published Oct. 20, 2020	Time to re-assess Tocilizumab's role in COVID-19 pneumonia. **Parr JB** [23]	Editorial Review- 1 Study retrospective cohort 4 Studies randomised controlled trials	Number of patients/sites 3924 68 126 24 450 67 131 9 389 69	**USA** **Italy** Multicountry **COVAC-TA** (Canada, Denmark , France, Germany, Italy, Netherlands, Spain, UK, US) **France** Multicountry **EMPACTA** Trial (Brazil, Kenya, Peru, US, Mexico, S. Africa)	**Tocilizumab** **Primary outcomes**: Mortality at day 28 or day 30 Survival without non-invasive ventilation (NIV) or mechanical ventilation (MV) by day 14 Death or mechanical ventilation at day 28	**1 Retrospective cohort- USA study** Threshold for efficacy of Tocilizumab met: **27.5% versus 37.1%**Risk difference **9.6**% (95% **CI: 3.1 to 16.0%**) **4 Randomised controlled trials** Threshold for efficacy of Tocilizumab for the first two primary outcomes not met in any of the 4 studies Threshold for efficacy of Tocilizumab for **survival without NIV or MV by day 14 met** for the France study : **HR 0.58 (95% CI 0.33 to 1.00)** Threshold for efficacy of Tocilizumab for **death or mechanical ventilation at day 28** met in EMPACTA Trial **HR 0.56 (95% CI 0.32–0.97)** Reduced need for mechanical ventilation **Mortality at day 28 or 30: No effect:** 10.4% vs 8.6%, ARD 2.0%, (95% CI, -5.2 to 7.8)

AC: anticoagulation, AOR: adjusted odds ratio, ARDS: acute respiratory distress syndrome, CI: confidence Interval, COVID-19: coronavirus disease-2019
EUA: emergency use authorization, DA: Food and Drug Administration, HCQ: hydroxychloroquine, HR: hazard ratio, IDSA: Infectious Diseases Society of America, NIH: National Institutes of Health, NIV: non-invasive ventilation, MV: mechanical ventilation, OR: odds ratio, RCT: randomised controlled trial, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, VTE: venous thromboembolism.

Favipiravir

In the light of *in vitro* studies, research in China, Japan, and Russia have introduced favipiravir as a promising agent with its advantage of being an oral formulation utilized on an outpatient basis.[53] Recently, treatment guidelines from multiple countries have included favipiravir in their treatment protocols.[53,54]

The studies on favipiravir treatment covered in this review include a controlled trial and a review of observational studies.

An early controlled trial published in March 2020 announced that favipiravir treatment resulted in a shorter viral clearance time compared to lopinavir/ritonavir treatment ($p<0.001$). Favipiravir treatment was associated with significant improvement rates in chest imaging (91.43% vs. 62.22%, $p=0.004$). (Table 4).[53] The study was non-randomised and open-label. The strength of evidence is accordingly evaluated as low.

A recent review of observational favipiravir interventions has highlighted its therapeutic effectiveness in terms of recovery rates and clinical improvements among mild to moderate patients. The findings demonstrated high recovery rates at days 7 and 14 for both mild and moderate cases in one study. Clinical improvement was reported for 66.7% overall in another study. The Japan observational registry revealed similar results for mild and moderate COVID-19 cases (Table 4).[54] However, although the number of patients is high, the quality of evidence is appraised as very low due to study type and the lack of control groups.

A pre-print publication regarding favipiravir efficacy should be mentioned, even though the study is not within the inclusion criteria of our review. In this prospective randomised controlled, open-label multicentre trial involving 240 patients with mostly moderate COVID-19 from China, the therapeutic effectiveness of favipiravir *versus* umifenovir was studied. The clinical recovery rate on day 7 was significantly higher ($p=0.019$) for the favipiravir group (71.4%) than the umifenovir group (55.8%). However, there was no difference between the groups regarding ICU admission and all-cause mortality.[55]

Favipiravir is widely used across many highly populated communities of middle income countries in Asia. However, more RCTs are mandatory for higher evidence-based results.

Corticosteroids

Corticosteroids were not advised for COVID-19 treatment unless needed for other conditions according to WHO, US CDC and IDSA early recommendations.[2,39]

The approach for treating patients with COVID-19 changed dramatically when the results of the UK-based RECOVERY trial were reported in June, 2020. This was an RCT of 6425 patients receiving dexamethasone or usual care. Treatment with dexamethasone reduced mortality by one-third in those patients receiving MV (rate ratio: 0.64) and by one-fifth in patients receiving oxygen (rate ratio: 0.82) compared with usual care. However, there was no benefit for those patients not receiving respiratory support (Table 5).[56]

The WHO REACT Working group studied the results of the current data on corticosteroid therapy on COVID-19 in a meta-analysis. A total of 1703 patients were randomised in seven trials for a prospective meta-analysis (Table 5).[57]

There were 222 deaths in the trial group and 425 deaths in the control group; 28-day all-cause mortality was lower among those patients receiving corticosteroids (OR=0.66, $p<0.001$). The association was similar for dexamethasone and hydrocortisone suggesting a general benefit for glucocorticoids.[57]

Following this, a systematic literature search and meta-analysis of RCTs and observational studies on adults was performed from December, 2019 to October, 2020 comprising a total of 20,197 patients in 37 retrospective observational studies and five RCTs. The findings confirmed the previous findings. The primary outcomes were short-term mortality (including 28-day, 30-day) and the secondary outcomes were MV, length of hospital stay, and secondary infections. The findings have confirmed a beneficial effect of corticosteroids on short-term mortality and a reduction in the need for MV. The overall risk estimate was 0.72, suggesting a beneficial effect of steroid use on the mortality of patients hospitalised with moderate or severe respiratory failure. Fewer patients required MV in the corticosteroids group [relative risk (RR): 0.71] (Table 5).[58]

The relevant research indicated in this review highlighted the efficacy of corticosteroids in reducing mortality among critically ill patients requiring oxygen. The trials on this topic cover more than 28 thousand (28,325) patients and the results indicate high evidence. Corticosteroids are the only therapeutics which are currently shown to be effective in reducing mortality in COVID-19.

The details of the presented articles of this review are illustrated in tables: Table 1,[25,28-33] Table 2,[23,35-38,41-42] Table 3,[45-47,59] Table 4,[48-54] and Table 5.[56-58]

Discussion

New findings from recent research draw attention to the urgent need for new approaches and agents for managing COVID-19, including in mild and moderate cases. A prospective cohort study with patients recovering from COVID-19 displayed evidence of ventricular dysfunction and signs of myocardial inflammation in 78% of the patients.[60,61] In addition, post-mortem research has shown inflammation is ongoing in the heart muscle weeks after recovery. These findings may be precursors of a considerable burden of heart failure in the coming years.[62]

In this review, we aimed to contribute to the collection and dissemination of the new evidence for COVID-19 therapy regarding all forms of the disease. We shall discuss our findings together with expert opinions and global statements about this issue.

A considerable number of studies on the therapeutic efficacy of various treatments for COVID-19 have weaknesses regarding the study sample and research methods utilized. Currently, evidence comes mostly from those studies conducted among hospitalised patients, while more research is essential for the therapy of mild and moderate forms.[8,53]

The results of studies in this review show evidence for the efficacy of the antiviral remdesivir and also corticosteroids. The efficacy of therapeutic dose anticoagulation has been demonstrated among

Table 3. Trials on therapeutic measures utilized in COVID-19: Insufficient or conflicting evidence, needing further investigations; or evidence for no therapeutic efficacy: Interferons and antivirals

No	Journal name and date	Title of article and authors	Type of research	Participants/ number of studies	Country - region	Intervention-Treatment and primary end point	Outcome/Results
1	The Lancet Published online May 8, 2020	Triple combination of interferon beta-1b, lopinavir-ritonavir and ribavirin in the treatment of patients hospitalised with COVID-19: An open-label, randomised, phase 2 trial. **Hung IFN et al.**[45]	Randomised controlled trial (RCT) Phase 2 trial	127 patients: **Trial group** 86: Disease onset <7 days **52** patients Disease onset ≥7days **34** patients **Control group** **41** patients	Hong Kong 6 hospitals	**Combination therapy** Trial group -Lopinavir-ritonavir -**ribavirin** -**interferon beta-1b** 8 million units every other day up to 7 days (1-3 times) **Control group** Lopinavir-ritonavir **Outcome: Median time to negative nasopharyngeal and all specimen swab**	**Time (days) to negative nasopharyngeal swab**: Combination therapy group (All trial group) vs. all control group: Significantly shorter median time from therapy to negative swab: **7 days (5−11days) vs 12 days (8−15 days) p=0.0010** **Hazard ratio: 4.37**(95% CI: 1.86−10.24) **Interferon group** (52) patients vs. control: 6.5 (4.0−8.0) vs 12.5 (8.0−14.8), **p<0.0001** Ribavirin group (34 patients) vs. control: 10.5 (8.0-12.3) vs. 12.0 (8.0-17.0), p=0.10 **Conclusion:** Early triple therapy was safe and superior to control in shortening virus shedding, relieving symptoms and facilitating discharge of patients **Limitations:** Open-label study, low number of patients, phase 2 study
2	Frontiers in Immunology Published May 16, 2020	Interferon alfa-2b treatment for COVID-19. **Zhou Q et al.**[46]	Cohort study Jan16 – Feb 20, 2020	77 COVID-19 patients	Wuhan China	3 groups: 1.Umifenovir 200mg 2.Interferon α2b 5mU 3.Interferon α2b + Umifenovir **End point**: Mean days to viral clearance	**End point:** Mean days to viral clearance Umifenovir : 27.9 days, Interferon α2b: 21.1 days, Interferon α2b + Umifenovir : **20.3 days** **p= 0.002** Interferon accelerated viral clearance by **7 days** and reduced elevated blood levels for inflammatory markers IL-6 and CRP **Limitations**: Age and comorbidity differences between the intervention and control groups, low patient size
3	Press release July 20, 2020	Synairgen announces positive results from trial of SNG001 in hospitalised COVID-19 patients **Synairgen**[47]	Double blind placebo- controlled trial March 30- May 27, 2020	101 non-ventilated patients	UK 9 hospitals	Interferon beta 1a (inhaled) -14 days **End point**: Recovery at day 28 Odds of developing severe disease	**Recovery at day 28 : OR= 3.86** (95% CI: 1.27−11.75) , p=0.017 Decreased odds of developing severe disease: **OR=0.21** (95% CI: 0.04−0.97) p=0.046 **Limitations:** Pre-publication, low patient size, conflict of interest
4	The New England Journal of Medicine Published Mar. 18, 2020	A trial of lopinavir-ritonavir in adults hospitalised with severe COVID-19. **Cao Bet al.**[59]	RCT Jan 18-Feb 3, 2020	199 hospitalised patients:	Wuhan, China	Lopinavir-ritonavir versus standard care	No benefit beyond standard care

AC: anticoagulation, AOR: adjusted odds ratio, ARDS: acute respiratory distress syndrome, CI: confidence Interval, COVID-19: coronavirus disease-2019
EUA: emergency use authorization, DA: Food and Drug Administration, HCQ: hydroxychloroquine, HR: hazard ratio, IDSA: Infectious Diseases Society of America, NIH: National Institutes of Health, NIV: non-invasive ventilation, MV: mechanical ventilation, OR: odds ratio, RCT: randomised controlled trial, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, VTE: venous thromboembolism.

Table 4. Trials on therapeutic measures utilized in COVID-19 with promising evidence of efficacy: Antivirals

No	Journal name and date	Title of article and authors	Type of research	Participants/ number of studies	Country - region	Intervention-Treatment and primary end point	Outcome/Results
1	The New England Journal of Medicine Published May 22, 2020	Remdesivir for the treatment of COVID-19 - Preliminary Report **Beigel JH et al.**[48]	RCT Feb 21-April 19, 2020 Double blind, placebo- controlled trial	1063 hospitalised COVID-19 patients	Trial sites/ patients USA 45 Denmark 8 UK 5 Greece 4 Germany 3 Korea 2 Mexico 2 Spain 2 Japan 1 Singapore 1	Remdesivir 200 mg iv-day 1 100 mg-days 2-10 **Primary outcome**: Time to recovery (discharge from hospital) **Key secondary outcome**: Clinical status at day 15, as assessed on an eight-category ordinal scale	Time to recovery shortened by remdesivir **Median recovery time:** **Remdesivir 11 days** (95% CI: 9–12) **Placebo 15 days** (95% CI: 13–19) (Rate ratio for recovery, 1.32, 95% CI: 1.12 to 1.55) **p <0.001**
2	The New England Journal of Medicine Published Oct. 8, 2020	Remdesivir for the treatment of COVID-19 — Final Report **Beigel JH et al.**[49]	RCT Feb 21-Apr 19, 2020 Double blind, placebo- controlled trial	1062 COVID-19 patients in 60 sites & 13 subsites in USA	Trial sites /patients USA 45 Denmark 8 UK 5 Greece 4 Germany3 Korea 2 Mexico 2 Spain 2 Japan 1 Singapore 1	Remdesivir 200 mg iv-day 1 100 mg-days 2-10 Total 1062 patients Remdesivir-541 Placebo- 521 **Primary outcome**: Time to recovery **Secondary outcome**: Clinical status at day 15 as assessed on an eight-category ordinal scale	Patients completing the study: Trial group 391 Control group 340 Time to recovery shortened by remdesivir: **Median recovery time** **Remdesivir group 10 days (95% CI: 9–11)** **Placebo group 15 days (95% CI: 13–18)** **Rate ratio for recovery: 1.29**(95% CI: **1.12–1.49), p<0.001** **Clinical improvement on day 15 better in therapy group:** **OR 1.5, 95% CI: 1.2 to 1.9** The Kaplan–Meier **estimates of mortality: By day 15**: Remdesivir group 6.7% placebo group 11.9% (hazard ratio, 0.55; 95% CI: 0.36 to 0.83) **By day 29**: Remdesivir group 11.4%, placebo group15.2% (hazard ratio, 0.73; 95% CI: 0.52 to 1.03)
3	The Lancet Published online April 29, 2020	Remdesivir in adults with severe COVID-19. **Wang Y et al.**[50]	RCT Double blind, placebo controlled Feb 6- March 12, 2020	237 severe hospitalized patients (2:1 ratio) 158 intervention, 79 controls	Hubei China Multicenter- 10 hospitals	200 mg day1 100 mg days 2-10, infusion Concomitant use of lopinavir-ritonavir, interferon, cortico-steroid in all patients **Primary end point:** Clinical improvement in 28 days based on 6-point ordinal scale or discharge from hospital	Faster time to clinical improvement, although not significant: **Hazard ratio: 1.52** (95% **CI: 0.95 to 2.43**) **Limitations:** Concomitant use of multiple other drugs, small patient size
4	The New England Journal of Medicine Published April 10, 2020	Compassionate use of remdesivir for patients with severe COVID-19. **Grein J et al.**[51]	Cohort study Jan 25-March 30, 2020	61 hospitalised patients with severe COVID-19 (defined as oxygen saturation of ≤94% or need of oxygen support)	22 patients from USA, 21 from European countries 1 Canada 9 Japan **Total 53 patients evaluated**	Remdesivir iv 200 mg on day 1-100 mg for 9 days **Outcome:** Improvement in oxygen support class Median follow up: 18 days	36 patients **(68%)** had **improvement in oxygen support class** **Worsening in 15%** 17 of 30 (**57%**) receiving mechanical ventilation were extubated 25 patients (47%) discharged Overall mortality **13%** (7 patients) **Mortality 18%** (6/34) among patients under invasive ventilation **Limitation:** No control group, low patient size

Table 4. Continued

No	Journal name and date	Title of article and authors	Type of research	Participants/ number of studies	Country - region	Intervention-Treatment and primary end point	Outcome/Results
5	The New England Journal of Medicine Published May 27, 2020	Remdesivir for 5 or 10 days in patients with severe COVID-19. **Goldman JD et al.**[52]	RCT March 2020 Phase 3 trial	397 hospitalised COVID-19 patients	Trial sites: USA Italy S.Korea Singapore Spain Germany Hong Kong Taiwan	Remdesivir 200 mg on day 1 and 100 mg subsequently **End point:** Clinical status on day 14 assessed on an ordinal scale	Patients not needing mechanical ventilation received remdesivir for 5 or 10 days No significant difference between 5 and 10- day therapies regarding clinical improvement based on clinical status on day14 **Limitation:** No placebo group
6	Engineering Published March18, 2020	Experimental treatment with favipiravir for COVID-19: An open-label control study. **Cai Q et al.**[53]	Controlled trial Jan 30-Feb14, 2020	Treatment group: 35 patients received Favipiravir and interferon alfa Control group: 45 patients received Lopinavir/ Ritonavir (LPV/ RTV) and interferon alfa	Shenzhen, China People's hospital	**Favipiravir** 1600 mg x 2 on day 1 600 mg x 2 on 2-14 days **LPV/RTV** 400/100 mg x 2 on 1-14 days **End points:** Viral clearance time Chest CT improvement	Favipiravir group had **shorter viral clearance time:** Median (interquartile range, IQR: 4 (2.5–9) days vs. 11 (8–13) days **p< 0.001** Significant improvement rate in chest imaging (CT) (**91.43% vs. 62.22%) p=0.004** Higher improvement rates of chest CT for viral clearance within 7 days of treatment Multivariable Cox regression: Favipiravir treatment was significantly associated with faster viral clearance (**p=0.026**) **Limitations:** Non-randomised and open -label trial Low patient number
7	International Journal of Infectious Diseases Published Oct. 29, 2020	Role of favipiravir in COVID-19. **Joshi S et al.**[54]	Review of favipiravir interventions **Limitations:** Observa-tional studies, No control groups	Mild to moderate COVID-19 patients	China Thailand Japan	Favipiravir 1800×2 on day 1 800×2 up to 14 days **Outcome:** Clinical recovery or improvement	**1.Clinical recovery rates** (Doi Y et al) **Outcome at day 7** Mild patients:73.8%, Moderate patients: 66.6% **Outcome at day 14** Mild:87.8%, Moderate:84.5% **2.Clinical improvement rates** (Rattanaumpawan et al) Overall:66.7% , patients not needing oxygen supply: 92.5% **3.Clinical improvement rates** (Japan observational registry-2158 cases) Mild:73.8%, moderate:66.6%,severe 40.1%

AC: anticoagulation, AOR: adjusted odds ratio, ARDS: acute respiratory distress syndrome, CI: confidence Interval, COVID-19: coronavirus disease-2019
EUA: emergency use authorization, DA: Food and Drug Administration, HCQ: hydroxychloroquine, HR: hazard ratio, IDSA: Infectious Diseases Society of America, NIH: National Institutes of Health, NIV: non-invasive ventilation, MV: mechanical ventilation, OR: odds ratio, RCT: randomised controlled trial, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, VTE: venous thromboembolism.

Table 5. Trials on therapeutic measures utilized in COVID-19 with evidence for efficacy on mortality of severely ill patients: Corticosteroids

No	Journal name and date	Title of article and authors	Type of research	Participants/ number of studies	Country - region	Intervention- Treatment and primary end point	Outcome/Results
1	RECOVERY Trial Press release June 16, 2020 JAMA Oct 6, 2020	Corticosteroids in COVID-19 ARDS. Evidence and hope during the pandemic. Editorial. **Prescott HC et al.**[56]	Open – label randomised controlled trial **Limitation:** Open-label study	6425 patients Trial 2104 patients: Dexametha-sone Control 4321 patients: Usual care	United Kingdom	Dexamethasone 6 mg /day for 10 days **Primary outcome:** Mortality in trial and control groups	**Mortality rates** Mechanical ventilation patients: **Trial Control** 29.3% 41.4 % **Rate ratio 0.64** (95%CI 0.51 to 0.81) Patients needing oxygen supply: **Trial Control** 23.3% 26.2% **Rate ratio 0.82** (95% CI 0.72 to 0.94) No benefit observed for patients not receiving oxygen support (rate ratio 1.19, 95% CI 0.91 to 1.55)
2	The Journal of the American Medical Association (JAMA) Published online Sep 2, 2020	Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19-A meta-analysis. **The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group**[57]	Prospective meta-analysis Feb 26-June 9, 2020 Final follow-up July 6, 2020	7 trials: RECOVERY, REMAP-CAP, CoDEX, CAPE COVID +3other 1703 patients randomised Corticosteroid **678** patients Usual care or placebo: **1025** patients	Australia Brazil Canada China Denmark France Ireland Netherlands New Zealand Spain UK USA	**Corticosteroid groups included dexamethasone at low and high doses:** low-dose hydrocortisone, and high-dose methyl-prednisolone compared with others who received usual care or placebo Critically ill patients End point: Mortality at 28 days	**Total 647 patients died** **222** deaths among 678 patients randomised to corticosteroids **425 deaths** among 1025 patients randomised to usual care or placebo **28-day all-cause mortality** was lower among patients who received corticosteroids compared with those who received usual care or placebo **Summary odds ratio= 0.66** (95% CI 0.53-0.82) **p<0.001** Based on a fixed-effect meta-analysis, patients receiving systemic corticosteroids were **34% less likely to die over 28 days**
3	Critical Care (Crit Care) December 2020	Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. **Van Paassen J et al.**[58]	A systematic literature review and meta-analysis of RCTS and observational studies December 2019 to October 2020	Effect of corticosteroids Total **20197** patients in **44 studies:** 37 retrospective observational studies 5 RCTs **Hospitalised** (28 studies) **or ICU admitted** patients (15 studies)	31 studies conducted in China, 11 in Europe, 5 in North America, 2 in South America and 1 multi-continent	**Corticosteroids** **Primary outcome:** Short-term mortality (including 28-day, 30-day) **Secondary outcomes:** Need of mechanical ventilation, Length of hospital stay, Secondary infection	**Outcomes:** Confirmation of a beneficial effect of corticosteroids **on short-term mortality** and a reduction in need for mechanical ventilation **Overall risk estimate (OR): 0.72** (95%CI 0.57–0.87), suggesting a beneficial effect on mortality in patients hospitalized with moderate or severe respiratory failure Fewer patients required mechanical ventilation in the corticosteroids group **RR= 0.71** (95% CI 0.54–0.97)

AC: anticoagulation, AOR: adjusted odds ratio, ARDS: acute respiratory distress syndrome, CI: confidence Interval, COVID-19: coronavirus disease-2019
EUA: emergency use authorization, DA: Food and Drug Administration, HCQ: hydroxychloroquine, HR: hazard ratio, IDSA: Infectious Diseases Society of America, NIH: National Institutes of Health, NIV: non-invasive ventilation, MV: mechanical ventilation, OR: odds ratio, RCT: randomised controlled trial, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, VTE: venous thromboembolism.

moderately ill, but not severely ill, patients in preliminary research.[26] However, these studies have yet to be finalised before general consideration for use in this group. Weak therapeutic evidence exists for favipiravir, interferons alfa-2b, beta-1b and beta-1a; convalescent plasma and monoclonal antibodies, this needs further research.[41,45-47] Bamlanimivab deserves special mention with emerging data of promising efficacy. Bamlanivimab and the combination of casirivimab and imdevimab are currently recommended for mild to moderate COVID-19 at high risk or progressing to severe disease and/or hospitalisation.[17]

Dexamethasone and other corticosteroids comprised the only drug group demonstrating reductions in mortality among hospitalised patients requiring MV or high-flow oxygen. Dexamethasone was also effective in decreasing the number of people requiring oxygen.[56-58] Accordingly, the NIH Treatment Guidelines Panel recommends the use of corticosteroids for patients in need of oxygen supplementation.[22]

Remdesivir exhibited high evidence of efficacy for the therapy of COVID-19.[48-52] Even though the NIH Panel does not recommend for or against the use of remdesivir in hospitalised patients not requiring oxygen, remdesivir remains the only drug approved by the FDA for use among hospitalised patients.[22] The use of remdesivir for mild to moderate COVID-19 cases is a subject of medical research currently and remains a challenge for the medical community with the disadvantage of its route of administration. Favipiravir was found to be effective for the treatment of mild to moderate COVID-19 cases in observational studies and one controlled trial covered in this study.

Remdesivir and favipiravir have been currently included in multiple COVID-19 treatment guidelines globally.[8] Japan, Russia, Saudi Arabia, Thailand, Kenya and four states from India have recommended the use of favipiravir oral therapy in mild to moderate COVID-19 in their treatment guidelines.[53,54] Around 27 favipiravir studies including RCTs are ongoing in China, Japan, Italy, the USA, the UK, Canada, Egypt, Thailand, France and Iran.[60] The results of these studies will highlight the efficacy of this antiviral with more evidence, which is convenient for use on an outpatient basis.

Antiviral medications other than remdesivir were not seen to have sufficient evidence for COVID-19 therapy. The Solidarity trial in 30 countries, sponsored by the WHO, assessed hydroxychloroquine, interferon, lopinavir/ritonavir, and remdesivir in hospitalised patients. None of these drugs, nor tocilizumab, showed an effect on mortality.[23,39,63]

No evidence for the use of chloroquine and hydroxychloroquine has been identified among the current research available. Conversely, weak evidence has been announced by some studies against the use of these agents.[31]

CONCLUSION

The data based on sound research on all aspects of COVID-19 is mounting rapidly. The findings of the latest research on COVID-19 therapy point to the necessity of considering the results of ongoing larger trials and providing instant knowledge to health professionals. Progress in this area is vital since it may be influential in preventing later consequences, sequellae and deaths from COVID-19 among the growing patient population.

The findings demonstrated in this review may be of assistance for medical practitioners in order to highlight the therapeutics with the best current evidence to assist in their decisions on treatment approaches for COVID-19.

MAIN POINTS

- While there is currently no globally approved treatment for COVID-19, multiple agents are under trial for the treatment COVID-19; yet a discrepancy exists between high income and other countries of the world regarding the drugs preferred.
- This study presents an overview of the mostly evidence-based global research on this issue, with randomised controlled trials, systematic reviews and meta-analyses comprising 15 out of the total 25 studies included.
- The results show sufficient evidence for the efficacy of remdesivir and corticosteroids based on international research, with reduced mortality demonstrated only for corticosteroids.
- Favipiravir, anticoagulation, interferons and monoclonal antibodies were agents with promising but weaker evidence of therapeutic efficacy and so need further investigations.
- The inclusion of favipiravir studies may be a reminder to global researchers to review the evidence about this agent as well, since it has been prescribed widely in a number of countries worldwide.

ETHICS

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Authorship Contributions

Concept: Ö.A., Ş.Ç., Design: Ö.A., Ş.Ç., Data Collection and/or Processing: Ö.A., Ş.Ç., Analysis and/or Interpretation: Ö.A., Ş.Ç., Literature Search: Ö.A., Ş.Ç., Writing: Ö.A., Critical Review: Ş.Ç.

DISCLOSURES

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REFERENCES

1. World Health Organisation. Emergencies preparedness, response. Pneumonia of unknown cause – China. Available from: https://www.who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en/ (Accessed on May, 5 2020).
2. Tobaiqy M, Qashqary M, Al-Dahery S, Mujallad A, Hershan AA, Kamal MA, et al. Therapeutic management of patients with COVID-19: a systematic review. Infect Prev Pract. 2020; 2(3): 100061.
3. World Health Organisation. Available from: www.who.int.
4. CDC COVID-19 Response Team. Characteristics of Health Care Personnel with

COVID-19 - United States, February 12-April 9, 2020. MMWR Morb Mortal Wkly Rep. 2020; 69(15): 477-81.

5. Harapan H, Itoh N, Yufika A, Winardi W, Keam S, Te H, et al. Coronavirus disease 2019 (COVID-19): A literature review. J Infect Public Health. 2020; 13(5): 667-73.
6. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel Coronavirus-infected pneumonia in Wuhan,China. JAMA. 2020; 323(11): 1061-9. Erratum in: JAMA. 2021; 325(11): 1113.
7. Suleyman G, Fadel RA, Malette KM, Hammond C, Abdulla H, Entz A, et al. Clinical characteristics and morbidity associated with coronavirus disease 2019 in a series of patients in metropolitan Detroit. JAMA Netw Open. 2020; 3(6): e2012270.
8. Kim PS, Read SW, Fauci AS. Therapy for early COVID-19: A critical need. JAMA. 2020; 324(21): 2149-50.
9. Tahiri Joutei Hassani R, Bennis A.. Hdroxychloroquine as antiviral prophylaxis for exposed caregivers to COVID-19: An urgent appraisal is needed. J Infect Public Health. 2020; 13(6): 865-7.
10. Chatterjee P, Anand T, Singh KJ, Rasaily R, Singh R, Das S, et al. Healthcare workers & SARS-CoV-2 infection in India: A case-control investigation in the time of COVID-19. Indian J Med Res. 2020; 151(5): 459-67.
11. Gupta N, Agrawal S, Ish P. Chloroquine in COVID-19: the evidence. Monaldi Arch Chest Dis. 2020; 90(1).
12. Ferner RE, Aronson JK. Chloroquine and hydroxychloroquine in COVID-19. BMJ. 2020; 369: m1432.
13. McEniery CM, Fisk M, Miles K, Kaloyirou F, Hubsch A, Smith J, et al. ChemoPROphyLaxIs with hydroxychloroquine For covId-19 infeCtious disease (PROLIFIC) to prevent COVID-19 infection in frontline healthcare workers: A structured summary of a study protocol for a randomised controlled trial. Trials. 2020; 21(1):604. Erratum in: Trials. 2020; 21(1): 641.
14. World Health Organisation. WHO discontinues hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19. (2020). Retrieved from: https://www.who.int/news/item/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19 (Accessed on 20 Aug 2020).
15. Berardicurti O, Ruscitti P, Ursini F, D'Andrea S, Ciaffi J, Meliconi R, et al. Mortality in tocilizumab-treated patients with COVID-19: a systematic review and meta-analysis. Clin Exp Rheumatol. 2020; 38(6): 1247-54.
16. Sharun K, Dhama K, Patel SK, Pathak M, Tiwari R, Singh BR, et al. Ivermectin, a new candidate therapeutic against SARS-CoV-2/COVID-19. Ann Clin Microbiol Antimicrob. 2020; 19(1): 23.
17. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. What's New. Retrieved from: https://www.covid19treatmentguidelines.nih.gov/whats-new/ Last Updated: February 11, 2021. (Accessed on 18 Feb 2021).
18. Zhang R, Wang X, Ni L, Di X, Ma B, Niu S, et al. COVID-19: Melatonin as a potential adjuvant treatment. Life Sci. 2020; 250: 117583.
19. Shanmugaraj B, Siriwattananon K, Wangkanont K, Phoolcharoen W. Perspectives on monoclonal antibody therapy as potential therapeutic intervention for Coronavirus disease-19 (COVID- 19). Asian Pac J Allergy Immunol. 2020; 38(1): 10-8.
20. García IG, Rodriguez-Rubio M, Mariblanca AR, de Soto LM, García LD, Villatoro JM, et al. A randomised multicenter clinical trial to evaluate the efficacy of melatonin in the prophylaxis of SARS-CoV-2 infection in high-risk contacts (MeCOVID Trial): A structured summary of a study protocol for a randomised controlled trial. Trials. 2020; 21(1): 466.
21. The COVID-19 Treatment Guidelines. Immunomodulators under evaluation for the treatment of COVID-19. Last updated: November 3, 2020. Retrieved from: https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/immunomodulators/
22. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Last updated: November 3, 2020. Retrieved from: https://www.covid19treatmentguidelines.nih.gov/ (Accessed on 1 December 2020).
23. Parr JB. Time to reassess Tocilizumab's role in COVID-19 pneumonia. JAMA Intern Med. 2021; 181(1): 12-5.
24. Bramer WM, Rethlefsen ML, Kleijnen J, Franco OH. Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. Syst Rev. 2017;6(1): 245.
25. Paranjpe I, Fuster V, Lala A, Russak AJ, Glicksberg BS, Levin MA, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol. 2020; 76(1): 122-4.
26. ATTACC, ACTIV-4a & REMAP-CAP Multiplatform RCT. Results of interim analysis. Release date: Jan 28 2021. Retrieved from: https://nhlbi-connects.org/documents/mpRCT%20Interim%20Presentation.pdf (Accessed on Feb 26, 2021).
27. 27. NIH COVID-19 Treatment Guidelines. Antithrombotic therapy in patients with COVID-19. Last Updated: February 11, 2021. Retrieved from: https://www.covid19treatmentguidelines.nih.gov/antithrombotic-therapy/ Accessed 26 Feb 2021. (Accessed on 26 Feb 2021).
28. Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med. 2020; 382(25): 2411-8.
29. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ. 2020;369: m1849.
30. Hernandez AV, Roman YM, Pasupuleti V, Barboza JJ, White CM. Hydroxychloroquine or chloroquine for treatment or prophylaxis of COVID-19: A living systematic review. Ann Intern Med. 2020; 173(4): 287-96.
31. Hernandez AV, Roman YM, Pasupuleti V, Barboza JJ, White CM. Update Alert 2: Hydroxychloroquine or chloroquine for the treatment or prophylaxis of COVID-19. Ann Intern Med. 2020; 173(7): W128-9.
32. RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L, Bell JL, Staplin N, et al. Effect of Hydroxychloroquine in hospitalised patients with COVID-19. N Engl J Med. 2020; 383(21): 2030-40.
33. Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et al.

Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. JAMA Netw Open. 2020; 3(4): e208857.

34. Frellick M. NIH Panel counters FDA: No solid data on plasma for COVID-19. Retrieved from: https://www.medscape.com/viewarticle/935058#vp_3 September 02, 2020. (Accessed on 10 Oct 2020).

35. Brown BL, McCullough J. Treatment for emerging viruses: Convalescent plasma and COVID-19. Transfus Apher Sci. 2020; 59(3): 102790.

36. Psaltopoulou T, Sergentanis TN, Pappa V, Politou M, Terpos E, Tsiodras S, et al. The emerging role of convalescent plasma in the treatment of COVID-19. HemaSphere. 2020; 4(3): e409.

37. Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. J Med Virol. 2020; 92(10): 1890-901.

38. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et.al. Treatment of 5 critically Ill patients with COVID-19 with convalescent plasma. JAMA. 2020; 323(16): 1582-9.

39. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. IDSA. Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/ (Accessed on Nov 27, 2020).

40. U.S. Food and Drug Administration. Letter of FDA Emergency Use Authorization to Eli Lilly and Company dated November 10, 2020. In: Phillips C, Eli Lilly and Company, 2020. Available at: https://www.fda.gov/media/143602/download (Accessed on 2 December 2020).

41. Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with COVID-19. N Engl J Med. 2021; 384(3): 229-37.

42. Gupta S, Wang W, Hayek SS, Chan L, Mathews KS, Melamed ML, et al. Association between early treatment with tocilizumab and mortality among critically Ill patients with COVID-19. JAMA Intern Med. 2021; 181(1): 41-51.

43. Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: A randomized clinical trial. JAMA Intern Med. 2021; 181(1): 24-31.

44. Interferons (Alfa, Beta). Last Updated: August 27, 2020. Retrieved from: https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/immunomodulators/interferons/#:~:text=Interferons%20are%20a%20family%20of,and%20in%20vivo%20antiviral%20properties. (Accessed on Nov 18, 2020).

45. Hung IF, Lung KC, Tso EY, Liu R, Chung TW, Chu MY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet. 2020; 395(10238): 1695-704.

46. Zhou Q, Chen V, Shannon CP, Wei XS, Xiang X, Wang X, et al. Interferon-α2b treatment for COVID-19. Front Immunol. 2020; 11: 1061. Erratum in: Front Immunol. 2020; 11: 615275.

47. Synairgen announces positive results from trial of SNG001 in hospitalised COVID-19 patients. Available from: https://www.synairgen.com/wp-content/uploads/2020/07/200720-Synairgen-announces-positive-results-from-trial-of-SNG001-in-hospitalised-COVID-19-patients.pd. (Accessed on November 20, 2020).

48. Beigel JH, Tomashek KM, Dodd LE. Remdesivir for the treatment of COVID-19 - Preliminary Report. Reply. N Engl J Med. 2020; 383(10): 994.

49. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of COVID-19 - Final Report. N Engl J Med. 2020; 383(19): 1813-26.

50. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020; 395(10236): 1569-78. Erratum in: Lancet. 2020; 395(10238): 1694.

51. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe COVID-19. N Engl J Med. 2020; 382(24): 2327-36.

52. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 Days in patients with severe COVID-19. N Engl J Med. 2020; 383(19): 1827-37.

53. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental treatment with favipiravir for COVID-19: An Open-label control study. Engineering (Beijing). 2020; 6(10): 1192-8.

54. Joshi S, Parkar J, Ansari A, Vora A, Talwar D, Tiwaskar M, et al. Role of favipiravir in the treatment of COVID-19. Int J Infect Dis. 2021; 102: 501-8.

55. Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, et al. Favipiravir versus Arbidol for COVID-19: A randomized clinical trial. [Preprint] medRxiv. 2020.

56. Prescott HC, Rice TW. Corticosteroids in COVID-19 ARDS: Evidence and hope during the pandemic. JAMA. 2020; 324(13): 1292-5.

57. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, et al. Association between administration of systemic corticosteroids and mortality among critically Ill patients with COVID-19: A meta-analysis. JAMA. 2020; 324(13): 1330-41.

58. van Paassen J, Vos JS, Hoekstra EM, Neumann KMI, Boot PC, Arbous SM. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. Crit Care. 2020; 24(1): 696.

59. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. N Engl J Med. 2020; 382(19): 1787-99.

60. Stiles S. COVID-19: Are there far-reaching cardiac complications? Available from: https://www.medscape.org/viewarticle/938664?nlid=138212_2681&src=wnl_cmemp_201120_mscpedu_fmed&uac=66188AY&impID=2688515&faf=1 (Accessed on Nov 20, 2020).

61. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020; 5(11): 1265-73.

62. Lindner D, Fitzek A, Bräuninger H, Aleshcheva G, Edler C, Meissner K, et al. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. JAMA Cardiol. 2020; 5(11): 1281-5.

63. Mc Namara D. IDSA Updates COVID Guidelines for Antibodies, Antivirals, Other Drugs. Nov 23, 2020. Retrieved from: https://www.medscape.com/viewarticle/941479?nlid=138431_2049&src=WNL_mdplsnews_201_mscpedit_imed&uac=66188AY&spon=18&impID=2702740&faf=1 (Accessed on Nov 28, 2020).

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Evaluation of Platelet Large Cell Ratio (PLCR) Results in Patients with Preeclampsia and HELLP

Berna Şermin Kılıç, Nil Atakul

Department of Obstetrics and Gynecology, İstanbul Training and Research Hospital, İstanbul, Turkey

Abstract

BACKGROUND/AIMS: Preeclampsia is a multi-systemic syndrome that often occurs after the 20th week of pregnancy. It is one of the main causes of maternal morbidity and mortality in the obstetric population. There is still a debate about whether hemolysis, elevated liver enzyme levels, and low platelet levels (HELLP) is a form of severe preeclampsia or a separate disease. We aimed to find a relationship between platelet large cell ratio (PLCR) and preeclampsia in our study, and try to assess whether this parameter could be used as marker for early diagnosis.

MATERIALS AND METHODS: This retrospective cohort study included 86 preeclampsia and 50 normotensive patients who were admitted to İstanbul Training and Research Hospital between January 2018 and December 2019. Complete blood count values from preeclampsia and normotensive pregnancies were measured using an automated hematological analyzer (XN 3000, Sysmex Corp., Kobe, Japan) at their first entry to the emergency service department. The PLCR value was calculated using data from full blood count analysis. Hemogram and biochemistry results were compared in the preeclampsia and control groups from the patient records.

RESULTS: No statistically significant difference was found among the body mass index (BMI), PLCR, hemoglobin (Hg), hematocrit (Hct) and platelet values of the preeclampsia and control group pregnant women. The PLCR values showed a statistically significant positive correlation with alanine transaminase, aspartate aminotransferase, urea, and lactate dehydrogenase values ($p<0.05$) in the preeclampsia patients. The PLCR value showed the highest statistically significant negative correlation with the platelet count and a positive correlation with the creatinine level ($p<0.01$).

CONCLUSION: Our study supports the belief that HELLP syndrome develops with different mechanisms and adaptive responses from preeclampsia, the underlying enhanced inflammatory response has been demonstrated. Our findings support the belief that anti-inflammatory treatment method could be applied along with appropriate preventive and therapeutic options in those patients with HELLP syndrome.

Keywords: Blood platelets, pre-eclampsia, pregnancy

INTRODUCTION

Preeclampsia is a multi-systemic, pregnancy-specific syndrome characterized by hypertension and proteinuria, which often occurs after the 20th week of pregnancy.[1] Preeclampsia is one of the most important health problems which cause maternal morbidity and mortality. It occurs in 3%–8% of pregnancies.[2] Although the exact pathogenesis of preeclampsia is unknown, placental vascular inadequate perfusion, maternal endothelium damage and increased vascular permeability are thought to contribute to the pathophysiology of this disease.[3] Preeclampsia, which can be described as a common inflammatory process that develops due to endothelial damage; platelets that come into contact with the damaged endothelium activate the coagulation system, which leads to both an increase in consumption and bone marrow production of platelets. Increased thrombopoiesis produces larger and younger

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ORCID IDs of the authors: B.Ş.K. 0000-0002-0103-0709; N.A. 0000-0003-3874-8797.

Address for Correspondence: Berna Şermin Kılıç
E-mail: berna_doctor@hotmail.com
ORCID ID: orcid.org/0000-0002-0103-0709

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platelets rather than older platelets, and these platelets are more enzymatic and metabolically active.[4] As a result, the bone marrow releases larger young platelets resulting in increased platelet indexes such as average platelet volume (MPV), platelet distribution width (PDW) and PLCR. Hemolysis, elevated liver enzyme levels, and low platelet levels (HELLP) syndrome is a serious complication of pregnancy with hemolysis, high liver enzymes and low platelets. It occurs in 0.2%–0.6% of all pregnancies. HELLP occurs in 10%–20% of severe preeclampsia and often leads to negative maternal and perinatal consequences.[5]

There is still a debate about whether HELLP is a form of severe preeclampsia or a separate disease. Laboratory findings and clinical presentations differ in preeclampsia and HELLP syndrome. Preeclampsia is associated with an increase in platelet function. Thus, platelets contribute to the formation of micro-thrombosis in the placenta and exacerbate vascular dysfunction seen in preeclampsia. Therefore, platelet activation markers may be more sensitive to an early suspicion of potential preeclampsia than the number of platelets, which can vary during normal pregnancy as a result of preeclampsia.[6]

Various studies have shown that platelets are decreased significantly in women with preeclampsia, and MPV is increased significantly.[7] The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are inflammatory markers used to predict the diagnosis and severity of preeclampsia.[8]

PLCR values are novel parameters that have recently been studied in patients with preeclampsia. In a study involving 219 patients with preeclampsia,[9] PLCR values were found to be higher in those patients with severe preeclampsia compared to patients with mild preeclampsia, and they stated that thrombocyte markers could be used to predict the prognosis of preeclampsia.

PLCR is an indicator of larger platelets (>12 fL) shown as a percentage. The normal percentage range is 15%–35%. It is also used to monitor platelet activity.[10]

In our study, we aimed to determine the prognostic and diagnostic importance of PLCR, a systemic inflammatory response marker easily detected in peripheral blood, in preeclampsia and HELLP syndrome.

MATERIALS AND METHODS

Eighty-six preeclampsia and 50 normotensive pregnant patients were admitted to İstanbul Training and Research Hospital Obstetrics and Gynecology Emergency Department between January 2018 and December 2019 and these inpatients were examined retrospectively.

Those patients with blood pressure, measured at least twice with an interval of six hours, above or equal to 140 mmHg in systolic and 90 mmHg in diastolic, and with 300 mg or more of proteinuria in 24-hour urine were included in the mild preeclampsia group. Blood pressure (above 160/110 mmHg), Oliguria (less than 400 mL in 24 hours), headache, visual impairment, pain in the epigastric and upper right quadrant, pulmonary edema, cyanosis, more than 3 gr/24-hour urine or 3+ proteinuria in spot urine sample, thrombocytopenia (<100,000/mm^3), and patients with impaired liver function were included in the severe preeclampsia group. HELLP syndrome was defined as hemolysis, high liver enzymes and low platelets.

The small for gestational age (SGA) is defined as a birth weight below the 10th percentile for the gestational week.

Those patients with hypertension <20 gestational weeks (GWs) or before pregnancy, kidney disease, diabetes mellitus, cardiovascular, neurological disease, a history of drug use, the presence of any infection, fetal anomaly, in utero fetal death, hematological or immunological diseases were excluded from this study.

Those patients with HELLP, eclampsia, associated coagulopathy, bleeding, acute renal failure, hepatic insufficiency, unregulated hypertension, pulmonary hypertension, pulmonary edema, hemodynamic instability, or the need for mechanical ventilation were followed up in the intensive care unit for close monitoring.

Blood samples were taken from preeclampsia and normotensive patients at the first entrance to the emergency room and analyzed with an automated hematologic analyzer (XN 3000, Sysmex Corp., Kobe, Japan). PLCR was calculated using data from the complete blood count analysis. The hemogram and biochemistry results were examined retrospectively in the preeclampsia and control group from the patient records. The mean PLCR values of the two patient groups were compared.

Statistical analysis

The R-version for statistical analysis 2.15.3 program (R Core Team, 2013) was used. The normal distribution conformity of quantitative data was evaluated by the Shapiro–Wilk test and graphical examination. Independent samples t-test was used in comparisons between two groups of quantitative variables with normal distribution, and Mann–Whitney U test was used in comparisons between two groups of quantitative variables which did not show normal distribution. Pearson correlation analysis was used to determine the level of relationship between the quantitative variables of the preeclampsia and control group pregnant women. Statistical significance was considered as $p<0.05$. The statistical analysis of the PLCR values of the preeclampsia women who were admitted to the intensive care unit or had SGA fetuses was performed using the Chi-square test.

Permission and approval of İstanbul Training and Research Hospital Ethics Committee were obtained for our study (decision no: 2072, date: 06/12/2019). Since our study was retrospective, written consent could not be obtained from the patients.

Results

In our study, 86 preeclampsia and 50 normotensive pregnant patients were analyzed. Of the 86 preeclampsia patients, 44 patients were admitted to the intensive care unit and 42 patients were followed up in cesarean section or normal labor postpartum delivery rooms. SGA fetus was detected in 26 (30%) of the preeclampsia pregnancies.

As shown in Table 1, the age of the preeclampsia patients was statistically higher than the normotensive patients ($p<0.05$). There was no statistically significant difference found between the Body Mass Index (BMI), PLCR, hemoglobin (Hg), hematocrit (Hct), or platelet values of the preeclampsia and normotensive patients. The gestational week of the preeclampsia patients was statistically lower than the control group ($p<0.05$). The urea, creatinine, alanine transaminase (ALT) and aspartate transaminase (AST) values of the preeclampsia patients were statistically significantly higher ($p<0.05$) than the control group.

Table 2 shows the correlation of the preeclampsia patients' laboratory and clinical data with each other. The GW and BMI values did not show a statistically significant correlation with any laboratory values. The platelet values show a statistically significant high positive correlation with PLCR, ALT, AST, and lactate dehydrogenase (LDH) values ($p<0.01$). The ALT values show a statistically significant high positive correlation with AST, urea, and LDH values ($p<0.01$). The AST values show a statistically significant high positive correlation with ALT, urea, and LDH values ($p<0.01$).

The PLCR values show a statistically significant high positive correlation with ALT, AST, urea, and LDH values ($p<0.05$). The PLCR value showed the highest statistically significant correlation with platelet count negatively and with creatinine level positively ($p<0.01$).

The PLCR values of the preeclampsia patients admitted to the intensive care unit were not statistically significantly different from those patients monitored in postpartum delivery room ($p=0.444$).

There was no statistically significant difference found in the PLCR values between the preeclampsia patients with SGA fetus or the women with appropriate for gestational age (AGA) fetuses using chi-square analysis ($p=0.162$).

DISCUSSION

Preeclampsia pathogenesis consists of two consecutive stages. In the first stage, genetic factors, immunological maladaptation or primary trophoblast defect primarily cause placentation problems. In the second stage, abnormal cytokine released from the placenta, oxidative stress and the release of free radicals, the stimulation of leucocytes and macrophages, the activation of the complement system and apoptosis and the release of micro-particles into the maternal circulation cause widespread endothelial damage. Widespread endothelium damage also leads to the emergence of the maternal presentation of preeclampsia. Vascular damage is caused by the interaction of macrophages, T-lymphocytes, activated complement and the coagulation system and platelets.[11]

In HELLP syndrome, the inflammatory reaction is more severe, and the inflammation mostly attacks the liver and clotting system. Clinical symptoms usually appear before laboratory findings. However, in some cases, HELLP syndrome may present with viral syndrome-like symptoms or weakness.[12]

HELLP syndrome, considered a complication of preeclampsia, is characterized by pronounced endothelial cell damage to the liver. Hepatic ischemia can cause inflammation, subcapsular hematomas and intraparenchymal hemorrhage. Liver rupture is a rare but serious and life-threatening complication.[13]

Hemolysis in microangiopathic blood dissemination, one of the most important features of the disease, reflects the damage of the vascular endothelium. The decreased number of platelets in HELLP syndrome indicates increased consumption. Platelets are activated and adhere to the damaged vessel endothelium, resulting in an increased platelet turnover with a shorter half-life. The diagnosis of hemolysis is supported by the high concentration of LDH and the presence of non-conjugate bilirubin. The elevation of liver enzymes may reflect a hemolytic process due to liver involvement. The elevation of AST and ALT levels is mostly due to liver damage. Thrombocytopenia (platelet<100,000/mL) is definitely seen in HELLP.[13]

Maternal manifestations of HELLP syndrome can be explained by systemic inflammatory reaction including; hypertension, proteinuria, intravascular coagulation, low platelet count, and hemolysis endothelial cell dysfunction.[14] In our study, we found that PLRC values did not differ between the preeclampsia and normotensive patients (Table 1) and correlated with the HELLP syndrome criteria (Table 2). We did not find any correlation between PLCR values in preeclampsia patients and with those patients who had SGA fetuses or with patients who were admitted to the intensive care unit, showing preeclampsia severity. Although an inflammatory process plays a role SGA fetus, it occurs due to chronic vascular insufficiency. We conclude that the significant difference of PLCR values in HELLP syndrome may be explained by the acute nature of the disease.

Our findings suggest that HELLP has a different etiopathogenesis than preeclampsia. Our study also supports the belief that HELLP syndrome is mainly an inflammatory process.

In another report,[15] supporting our study, plasma levels of Interleukin-6 (IL-6) and IL-1Ra were found to be increased significantly during HELLP compared to preeclampsia and normotensive pregnancies. During HELLP acute flare, median GSTA1-1 levels were found to be significantly higher than preeclampsia and normal pregnancies.[15] Those studies have concluded that these findings are associated with a more intense inflammation of HELLP syndrome. In addition, prednisone therapy in patients during HELLP syndrome has been shown to decrease the increase in plasma levels of cytokine IL-6.[15] Corticosteroids have been reported to have an endothelial stabilizing effect in patients with HELLP syndrome. With gene expression measurement (HELLP - healthy), it has been showed that there was an up-regulation of IL-10, IL-6 receptor and TGF-b3 in HELLP placentas.[16]

Table 1. Analysis of preeclampsia and control pregnant patient data

	Preeclampsia (n=86)	Control (n=50)	p-value
Age (years)	31.2	27.3	**0.01**
BMI (kg/m²)	28.8	30.4	0.08
PLCR	32.1	33.9	0.13
GH (weeks)	34.8	36.3	**0.01**
Hg (g/dL)	11.2	11.5	0.428
HCT (%)	33.9	35.3	0.96
PLT (k/L)	213	225	0.48
Urea	66	11	**0.01**
Creatinine	77	0.8	**0.01**
ALT (IU/L)	64.9	17.2	**0.01**
AST (IU/L)	83.6	12.3	**0.01**
LDH (U/L)	389		
Uric acid	5.3		

Significant p-values are shown in bold.
GH: gestational week, BMI: body mass index, PLCR: platelet large cell ratio, PLT: platelet, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, n: number.

Table 2. Correlation of clinical and laboratory data of preeclampsia patients

GH (weeks)	1	2	3	4	5	6	7	8	9
BMI (kg/m^2)	0.17								
PLT (K/L)	-0.15	0.27							
PLCR	0.25	-0.28*	-0.46**						
ALT (IU/L)	-0.04	-0.09	-0.46**	0.33*					
AST (IU/L)	-0.05	-0.16	-0.49**	0.33*	0.92**				
UREA (mg/dL)	0.06	0.09	-0.29	0.33*	0.51**	0.54**			
LDH (U/L)	0.03	-0.16	-0.47**	0.32*	0.82**	0.93**	0.56**		
Creatinine (mg/dL)	0.05	-0.11	-0.25	0.47**	0.35*	0.42**	0.67**	0.50**	
Uric Acid (mg/dL)	0.08	0.26	-0.01	0.19	0.10	0.04	0.49**	0.07	0.48**

*Statistically significant correlation (0.05 level) (2-tailed), **statistically significant correlation (0.01 level) (2-tailed).
GH: gestational week, BMI: body mass index, PLCR: platelet large cell ratio, PLT: platelet, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase.

Although the cause of tissue damage in HELLP syndrome is multifactorial. It can be said that factors from aberrant inflammatory response to abnormal placentation have an important role.

HELLP is seen as a more severe variant of preeclampsia. However, several studies[17] suggest that this may be a separate disease: differences in placental gene expression and maternal polymorphic alleles related to inflammatory responses confirm this hypothesis.

In our study, we found the highest statistically significant correlation of PLCR values with platelet count and creatinine level. We assume that platelet count and creatinine levels are the most important laboratory parameters in the progression of preeclampsia to HELLP syndrome.

Our study supports the belief that HELLP syndrome develops with different mechanisms and adaptive responses from preeclampsia, and the underlying increased inflammatory response was shown in our study. Our findings also support the belief that anti-inflammatory treatment methods might be applied with appropriate preventive and therapeutic options, especially in patients with HELLP syndrome.

CONCLUSION

We are the first to show that complete blood parameters are simple, inexpensive and rapidly achievable tests in daily practice and they could be used to determine the risk of progression to HELLP syndrome in patients with preeclampsia. Our results support the hypothesis that the innate immune system contributes to maternal susceptibility to HELLP syndrome. Therefore, the identification of the components of the maternal innate inflammatory system that predispose patients to hypertensive disorders of pregnancy merits further investigation.

Although there are only a limited number of studies examining PLCR values in preeclampsia patients, a limitation of our study is the lack of exclusion of other inflammatory conditions which might cause higher or lower PLCR values in some patients. However, due to the large sample size of our study, we assume that this effect is negligible.

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MAIN POINTS

- PLCR values can be used to determine the risk of progression to HELLP syndrome.
- Enhanced inflammatory response has been demonstrated in HELLP syndrome.
- Anti-inflammatory treatment methods can be a therapeutic option in those patients with HELLP syndrome.

ETHICS

Ethics Committee Approval: İstanbul Training and Research Hospital Ethics Committee approved this study (decision no: 2072, date: 06/12/2019).

Informed Consent: Since this study was retrospective, written consent could not be obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.Ş.K., Design: B.Ş.K., Supervision: B.Ş.K., Data Collection and/or Processing: B.Ş.K., N.A., Analysis and/or Interpretation: N.A., Literature Search: N.A., Writing: B.Ş.K, Critical Review: B.Ş.K.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Stamilio DM, Sehdev HM, Morgan MA, Propert K, Macones GA. Can antenatal clinical and biochemical markers predict the development of severe preeclampsia? Am J Obstet Gynecol. 2000; 182(3): 589-94.
2. Walker JJ. Pre-eclampsia. Lancet. 2000; 356(9237): 1260-5.
3. Burton GJ, Woods AW, Jauniaux E, Kingdom JC. Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. Placenta. 2009; 30(6): 473-82.
4. Juan P, Stefano G, Antonella S, Albana C. Platelets in pregnancy. J Prenat Med. 2011; 5(4): 90-2.

5. Stella CL, Malik KM, Sibai BM. HELLP syndrome: an atypical presentation. Am J Obstet Gynecol. 2008; 198(5): e6-8.

6. Holthe MR, Staff AC, Berge LN, Lyberg T. Different levels of platelet activation in preeclamptic, normotensive pregnant, and nonpregnant women. Am J Obstet Gynecol. 2004; 190(4): 1128-34.

7. Tzur T, Sheiner E. Is there an association between platelet count during the first trimester and preeclampsia or other obstetric complications later in pregnancy? Hypertens Pregnancy. 2013; 32(1): 74-82.

8. Serin S, Avcı F, Ercan O, Köstü B, Bakacak M, Kıran H. Is neutrophil/lymphocyte ratio a useful marker to predict the severity of pre-eclampsia? Pregnancy Hypertens. 2016; 6(1): 22-5.

9. Tesfay F, Negash M, Alemu J, Yahya M, Teklu G, Yibrah M, et al. Role of platelet parameters in early detection and prediction of severity of preeclampsia: A comparative cross-sectional study at Ayder comprehensive specialized and Mekelle general hospitals, Mekelle, Tigray, Ethiopia. PLoS One. 2019; 14(11): e0225536.

10. Hong H, Xiao W, Maitta RW. Steady increment of immature platelet fraction is suppressed by irradiation in single-donor platelet components during storage. PLoS One. 2014; 9(1): e85465.

11. Zhou Y, McMaster M, Woo K, Janatpour M, Perry J, Karpanen T, et al. Vascular endothelial growth factor ligands and receptors that regulate human cytotrophoblast survival are dysregulated in severe preeclampsia and hemolysis, elevated liver enzymes, and low platelets syndrome. Am J Pathol. 2002; 160(4): 1405-23.

12. Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. Obstet Gynecol. 2004; 103(5 Pt 1): 981-91.

13. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013; 122(5): 1122-31.

14. Delmis J. Hipertenzija i trudnoća [Hypertension in pregnancy]. Lijec Vjesn. 2006; 128(11-12): 357-68.

15. van Runnard Heimel PJ, Kavelaars A, Heijnen CJ, Peters WH, Huisjes AJ, Franx A, et al. HELLP syndrome is associated with an increased inflammatory response, which may be inhibited by administration of prednisolone. Hypertens Pregnancy. 2008; 27(3): 253-65.

16. Tranquilli AL, Landi B, Corradetti A, Giannubilo SR, Sartini D, Pozzi V, et al. Inflammatory cytokines patterns in the placenta of pregnancies complicated by HELLP (hemolysis, elevated liver enzyme, and low platelet) syndrome. Cytokine. 2007; 40(2): 82-8.

17. Haram K, Mortensen JH, Nagy B. Genetic aspects of preeclampsia and the HELLP syndrome. J Pregnancy. 2014; 2014: 910751.

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Comparison of Intubation Difficulty in Patients with and Without Obstructive Sleep Apnoea Syndrome

Ülkü İnce, Hanife Karakaya Kabukçu

Department of Anesthesiology and Reanimation, Akdeniz University Faculty of Medicine, Antalya, Turkey

Abstract

BACKGROUND/AIMS: Obstructive sleep apnoea syndrome (OSAS) is a medical disease in which the upper respiratory tract is repeatedly blocked during sleep. Difficult intubation is more common among OSAS patients compared to the average population. Airway safety is also of importance for anaesthesia management. The prediction of difficult intubation may prevent many complications which can develop when attempting to establish the patency of the airway.

MATERIAL AND METHODS: Patients who were going to undergo ear-nose-throat operations were allocated into two groups, including 209 patients without OSAS (Group 1) and 113 patients with OSAS (Group 2). The neck circumference, the inter-incisor distance, the sterno-mental (SM) and the thyro-mental (TM) distances were measured; the Mallampati (MP) and the Cormack-Lehane (CL) tests were performed and recorded. It was evaluated whether these tests could be used as predictive markers for difficult intubation or not.

RESULTS: A neck circumference of above 40 cm, an inter-incisor distance lower than 4 cm, and MP and CL grades of 3 or 4 were found to be associated with difficult intubation. No association was found between difficult intubation and TM or SM. The rate of intubation difficulty was higher in the OSAS group.

CONCLUSION: We found that a short inter-incisor distance, a large neck circumference and a high Mallampati and CL degree were related to difficult intubation and OSAS. In line with these results, we concluded that OSAS is associated with intubation difficulty. We consider that pre-specifying these tests could reduce airway-related complication risks.

Keywords: Difficult intubation, obstructive sleep apnoea syndrome, anaesthesia

INTRODUCTION

Obstructive sleep apnoea syndrome (OSAS) is characterized by persistent and recurrent obstruction of the upper airways during sleep.[1] A recent epidemiological study in adults showed that 49.7% of men and 23.4% of women have moderate to severe OSAS defined as an apnoea-hypopnoea index (AHI) ≥15/hour.[2]

One study found a relationship between difficult intubation and OSAS and its severity.[3] The degree of difficulty in providing airway patency is parallel to hypoxic brain damage and the death risk. Therefore, airway control is significant in anaesthesia management in OSAS patients. The prediction of difficult intubation allows for changes in the anaesthesia method, the preparation of auxiliary instruments and allows for the presence of an experienced specialist, hence reducing the complication risks.

An ample amount of tests have been defined for this purpose, including the Mallampati (MP) and Cormack-Lehane (CL) tests, the sterno-mental (SM) distance, the thyro-mental (TM) distance, the inter-incisor distance and neck circumference measurements.

The goal of this study was to assess intubation difficulty in patients with and without OSAS, as well as to establish intubation difficulty predicting tests.

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ORCID IDs of the authors: Ü.İ. 0000-0001-5517-1489; H.K.K. 0000-0002-9626-139X.

Address for Correspondence: Ülkü İnce
E-mail: uuulkuuu@hotmail.com
ORCID ID: orcid.org/0000-0001-5517-1489

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MATERIALS AND METHODS

This study was conducted with Akdeniz University Clinical Research Ethics Committee's approval (ethics committee approval number: 70904504/141, date: 18.03.2015). ASA 1 or 2 patients aged 17–70 years who would undergo one or more of septoplasties, conchaplasty, uvulo-palato-pharyngoplasty (UPPP), tympanoplasty, functional endoscopic sinus surgery, septorhinoplasty, mastoidectomy or tongue root resection due to any reasons were included in this study. The patients were informed about the study, and written consent was obtained from them prior to the study. The operations were performed by the same surgical team and the same anaesthesia team. Those patients without OSAS were classified as Group 1 (n=209), and those with OSAS were classified as Group 2 (n=113).

The inter-incisor distance, neck circumference, and thyro-mental and sterno-mental distances were measured and recorded. The oro-pharyngeal structures were evaluated and recorded according to the Modified Mallampati classification. This was performed when the patients were seated, their mouths were opened entirely, and their tongues were fully extended out. Sterno-mental and thyro-mental distance measurements were made with the head in full extension. The sterno-mental distance was defined as the distance between the highest end of the sternum and the end of the mandible; The thyro-mental distance was defined as the distance between the thyroid cartilage and the end of the mandible. The distance between the upper and lower incisors with the patient's mouth wide open was measured as the inter-incisor distance.

After full muscle relaxation following anaesthesia induction, the patient's head was positioned at extension at the atlanto-occipital joint and the upper cervical spine. The neck was placed in flexion from the inferior cervical spine, and intubation was performed. Laryngoscopy was performed using Macintosh 3 or 4 blades, and the appearance was evaluated and recorded according to the Cormack-Lehane classification. Intubation was defined as "easy" if intubation could be achieved at the first attempt with direct laryngoscopy and as "difficult" when an instrument and/or position change and/or tracheal pressure was required after laryngoscopy.

Statistical Analysis

Categorical variables were expressed as frequency and percentage. Constant variables with a normal distribution were expressed as mean and standard deviation. Variables that did not fit the normal distribution were expressed as median and minimum-maximum**.** The Chi-square test was used in the analysis of the data. Data were analysed using IBM SPSS Statistics 18© (IBM Corp., Chicago, IL, USA) Copyright SPSS Inc.1989, 2010 software.

RESULTS

Of a total of 322 patients, 92 (28.6%) were females, and 230 (71.4%) were males (Table 1). The male ratio was found to be significantly higher in Group 2 compared to Group 1 (p=0.00). The demographic characteristics of the patients are summarized in Table 2.

A significant difference was determined between the groups concerning intubation difficulty (p<0.01). The rate of difficult intubation was higher in the OSAS group (Table 3). Three of the patients with difficult intubation had a history of difficult intubation, while easily intubated patients did not have this history.

A relationship was determined between a neck circumference of over 40 cm and difficult intubation (p<0.01) (Table 4). The neck circumference was found to be over 40 cm in 84.8% of the patients in the OSAS group, and there was a significant difference between the OSAS group and the group without OSAS (p<0.01).

A significant association was found between the inter-incisor distance being smaller than 4 cm (p<0.01) (Table 4). The percentage of patients whose inter-incisor distance was 4 cm or below was 26.5% in the OSAS group, while this rate was 17.2% in the group without OSAS. A significant difference was determined between the groups (p<0.05).

No correlation was seen between the sterno-mental and thyro-mental distances and difficult intubation (p=0.40 and 0.23, respectively).

A significant association was determined between Mallampati 3 or 4 and difficult intubation (p<0.01) (Table 5). In our study, while the rate of Mallampati 3 or 4 was 31.0% in the OSAS group, this rate was 7.2% in the group without OSAS, and this difference was statistically significant (p<0.01).

A significant difference was determined between Cormack-Lehane grade of 3 or 4 and difficult intubation (p<0.01) (Table 5). In our study, while the rate of Cormack-Lehane grades of 3 or 4 was 34.8% in the OSAS group, this rate was 12.8% in the group without OSAS, and this difference was statistically significant (p<0.01).

DISCUSSION

Airway control is essential in the anaesthesia management of OSAS patients**.** Many studies have found a link between OSAS and difficulty in intubating. Hiremath et al.[3] evaluated 15 patients with intubation difficulty and 15 control patients regarding clinical, polysomnography and radiology parameters in their prospective, case-controlled study investigating the relationship between OSAS severity and difficult intubation and they revealed a significant relationship between them. In that study, the Apnoea-hypopnea Index (AHI) was found to

Table 1. Gender differences between groups

	Gender		Total (n, %)
	Female (n, %)	Male (n, %)	
Group 1	79 (37.8%)	130 (62.2%)	209 (100%)
Group 2	13 (11.5%)	100 (88.5%)	113 (100%)
Total	92 (28.6%)	230 (71.4%)	322 (100%)

OSAS: obstructive sleep apnoea syndrome, Group 1: patients without OSAS, Group 2: patients with OSAS, n: number of the patients.

Table 2. Quantitative differences between groups

	Group 1 (n=209) (mean ± SD)	Group 2 (n=113) (mean ± SD)
Weight (kg)	74.2±14.7	88.5±13.4
Height (cm)	171±9.0	173.5±8.3
BMI	25.5±4.3	29.4±4.1
Age	34.5±12.0	45.1±8.8

OSAS: obstructive sleep apnoea syndrome, Group 1: patients without OSAS, Group 2: patients with OSAS BMI: Body Mass Index, *p<0.05 was accepted as statistically significant. n: number of patients, SD: standard deviation.

be significantly higher in the difficult intubation group (patients with CL grade 4 were recorded as "difficult intubation" by the anaesthetist) compared to the control group; AHI was found to be greater than 10 in eight patients in the difficult intubation group and in two patients in the control group ($p<0.03$). In their retrospective study, Siyam and Benhamou[4] reported that intubation was more difficult in 36 OSAS patients than in the control group, and no significant association was found between OSAS severity and intubation difficulty. In another retrospective study,[5] 90 patients who had undergone UPPP surgery were included, and the rate of difficult intubation was found to be higher in the OSAS group than in the control group. In the same study, the patients were divided into three groups according to their AHI values and those with AHI of <40 were classified as the "mild OSAS" group, those with AHI of 40–70 were classified as the "moderate OSAS" group, and those with AHI of >70 were classified as the "severe OSAS" group. The incidence of difficult intubation was found to be higher only in those patients whose AHI was >40. We also found the rate of intubation difficulty to be higher in the OSAS group ($p<0.01$).

Hiremath et al.[3] found those OSAS patients who had demonstrated intubation difficulty to be associated with an increased neck circumference. A short and large neck has been reported in the literature to be among the risk factors for intubation difficulty.[6-7] Acer et al.[8] found the threshold value of neck circumference to be 360 mm, and its sensitivity was found to be 94.74% and specificity to be 42.68% compared to the risky CL test group in their study conducted with 227 patients. Kandemir et al.[9] found the neck length and the circumference to be statistically significant in the prediction of intubation difficulty, and a 43.7% sensitivity, a 66% selectivity and a 50% positive predictive value were obtained for a neck circumference of 40.75 cm and above. In our study, we found a significant association between difficult intubation and a neck circumference of more than 40 cm, similar to the literature, and the rate of patients with a neck circumference of over 40 cm was found to be higher in the OSAS group compared to the non-OSAS group.

The inter-incisor distance which is measured with the mouth fully opened was previously evaluated by Wison et al.[10]. The authors showed that the inter-incisor distance is shorter in those patients with difficult laryngoscopy. A risk score was formed for the prediction of difficult laryngoscopy. The likelihood of mandibular protrusion was suggested to be related to increased risk in those patients whose inter-incisor distance was smaller than 5 cm (approximately three fingers width). We discovered a link between a smaller than 4 cm inter-incisor distance and problematic intubation, with the OSAS group having a greater rate of patients with an inter-incisor distance smaller than 4 cm.

Patil et al.[11] reported that a smaller than 6 cm distance between the lower border of the mandible and thyroid prominence with the neck in full extension was a predictor of difficult intubation. Frerk[12] found a smaller than 7 cm TM distance to be significant, and Karkouti et al.[13] found a smaller than 7.75 cm TM distance to be significant for difficult intubation. In their study conducted with 350 patients, Savva[6] concluded that the TM distance is not sensitive and specific enough and cannot be used as a single criterion in predicting difficult intubation. The authors found that the TM distance was smaller than 6.40 cm in patients with difficult intubation, similar to the study results of Kandemir et al.[9]. The TM distance, problematic intubation, and OSAS were not found to be associated in our study. The number of patients was smaller than ours in the studies of Frerk, Karkouti and Kandemir et al.'s[9-13], and the rate of OSAS patients was higher in our study, and differences may have arisen from this. Lohom et al.[14] reported that sensitivity decreased by 25% when measuring the TM and the SM distances together with the Mallampati test; however, the selectivity and the positive predictive value reached as high as 100%. Savva[6], as a result of their study with 350 patients, suggested using the SM distance as the only objective indicator for difficult intubation. At the same time, when the SM distance was less than 12.5 cm, they found a sensitivity of 82.4%, selectivity of 88.6% and a positive predictive value of 26.9%. Al Ramadhani et al.[15] accepted the threshold value of the SM distance to be 13.5 cm or less. We did not find an association between the SM distance and difficult intubation and OSAS. This may have resulted from the higher number of OSAS patients in our study.

The patients with CL grades 3 or 4 were accepted as difficult intubation in the study of Kandemir et al.[9]. Furthermore, the Mallampati-thyromental distance combination was the test that demonstrated the highest selectivity and positive predictive value for predicting difficult

Table 3. Assessment of groups concerning intubation difficulty

	Intubation		Total
	Easy	Difficult	
Group 1 (n, %)	173 (82.8%)	36 (17.2%)	209 (100%)
Group 2 (n, %)	67 (59.3%)	46 (40.7%)	113 (100%)
Total (n, %)	240 (74.5%)	82 (25.5%)	322 (100%)

OSAS: obstructive sleep apnoea syndrome, Group 1: patients without OSAS, Group 2: patients with OSAS. n: number of patients.

Table 4. The association between intubation difficulty and neck circumference and inter-incisor distance

		Intubation		Total (n, %)
		Easy (n, %)	Difficult (n, %)	
Neck circumference	≤40 cm	119 (50.0%)	13 (16.2%)	132 (41.5%)
	>40 cm	119 (50.0%)	67 (83.8%)	186 (58.5%)
Total		238 (100%)	80 (100%)	318 (100%)
Inter-incisor distance	≤4 cm	40 (16.7%)	26 (31.7%)	66 (20.5%)
	>4 cm	200 (83.3%)	56 (68.3%)	256 (79.5%)
Total		240 (100%)	82 (100%)	322 (100%)

n: number of the patients.

Table 5. The association between intubation difficulty and Mallampati and Cormack-Lehan

		Intubation		Total (n, %)
		Easy (n, %)	Difficult (n, %)	
Mallampati	1–2	218 (90.8%)	54 (65.9%)	272 (84.5%)
	3–4	22 (9.2%)	28 (34.1%)	50 (15.5%)
Total		240 (100%)	82 (100%)	318 (100%)
Cormack-Lehane	1–2	216 (91.9%)	34 (42.5%)	250 (79.4%)
	3–4	19 (8.1%)	46 (57.5%)	65 (20.6%)
Total		235 (100%)	80 (100%)	315 (100%)

n: number of the patients.

intubation. Both OSAS and difficult intubation were found to be related to a higher Mallampati score in the study of Hiremath et al.[3]. We also found a significant association between Mallampati grades of 3 and 4 and difficult intubation. Additionally, the rate of Mallampati grades of 3 and 4 was significantly higher in the OSAS group.

Shiga et al.[16] conducted a meta-analysis of 35 studies comparing intubation tests with the CL test, and they found difficult intubation at a rate of 5.8% as a result of their meta-analysis.

Lohom et al.[14] compared intubation tests and CL tests in 212 cases and found the difficult intubation rate to be 9%. Kandemir et al.[9] found the difficult intubation incidence to be 7.9% in their study that accepted CL grade 3 and 4 patients as their difficult intubation criteria. We also determined a significant relationship between CL 3–4 and difficult intubation (p=0.00). The rate of CL 3–4 was higher in the OSAS group.

The limitations of this study include its small sample size and recruitment from a single centre

We determined an association between intubation difficulty and OSAS and a shorter than 4 cm inter-incisor distance, a neck circumference of over 40 cm, and Mallampati grades of 3–4, and CL grades of 3–4. We consider that these parameters may be helpful in the prediction of difficult intubation. In line with these results, we concluded that OSAS is associated with intubation difficulty. We suggest that further studies be conducted on the subject.

CONCLUSION

We found that a short inter-incisor distance, a large neck circumference and a high Mallampati and CL degree were related to difficult intubation and OSAS. In line with these results, we concluded that OSAS is associated with intubation difficulty. We consider that pre-specifying these tests could reduce airway-related complication risks.

MAIN POINTS

- Difficult intubation is more common among OSAS patients compared to the average population.
- Prediction of difficult intubation may prevent many complications that can develop when attempting to establish the patency of the airway.
- Patients who were going to undergo ear-nose-throat operations were allocated to two groups so as to include 209 patients without OSAS (Group 1) and 113 patients with OSAS (Group 2).
- A neck circumference of over 40 cm, an inter-incisor distance lower than 4 cm, and MP and CL grades of 3 or 4 were found to be associated with difficult intubation
- The rate of difficult intubation was found to be significantly higher in Group 2.

ETHICS

Ethics Committee Approval: Ethics approval was obtained from the Akdeniz University Clinical Reserch Ethics Committee (decision number: 70904504/141, date: 18.03.2015).

Informed Consent: Written informed consent was obtained from all patients included in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ü.İ., H.K.K., Design: Ü.İ., H.K.K., Data Collection and/or Processing: Ü.İ., H.K.K., Analysis and/or Interpretation: Ü.İ., H.K.K., Literature Search: Ü.İ., H.K.K., Writing: Ü.İ., H.K.K., Critical Review: Ü.İ., H.K.K.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. White DP. Sleep-related breathing disorder. 2. Pathophysiology of obstructive sleep apnoea. Thorax. 1995; 50(7): 797-804.
2. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med. 2015; 3(4): 310-8.
3. Hiremath AS, Hillman DR, James AL, Noffsinger WJ, Platt PR, Singer SL. Relationship between difficult tracheal intubation and obstructive sleep apnoea. Br J Anaesth. 1998; 80(5): 606-11.
4. Siyam MA, Benhamou D. Difficult endotracheal intubation in patients with sleep apnea syndrome. Anesth Analg. 2002; 95(4): 1098-102.
5. Kim JA, Lee JJ. Preoperative predictors of difficult intubation in patients with obstructive sleep apnea syndrome. Can J Anaesth. 2006; 53(4): 393-7.
6. Savva D. Prediction of difficult tracheal intubation. Br J Anaesth. 1994; 73(2): 149-53.
7. Randell T. Prediction of difficult intubation. Acta Anaesthesiol Scand. 1996; 40(8 Pt 2): 1016-23.
8. Acer N, Akkaya A, Tuğay BU, Öztürk A. A Comparison of Cormeck-Lehane and Mallampati tests with Mandibular and Neck Measurements for predicting Difficult Intubation. Balkan Med J. 2011; 28: 157-63.
9. Kandemir T, Şavlı S, Ünver S, Kandemir E. Sensitivity of the Combination of Mallampati Scores with Anthropometric Measurements and the Presence of Malignancy to Predict Difficult Intubation. Turk J Anaesthesiol Reanim. 2015; 43(1): 7-12.
10. Wilson ME, Spiegelhalter D, Robertson JA, Lesser P. Predicting difficult intubation. Br J Anaesth. 1988; 61(2): 211-6.
11. Patil VU, Stehling LC, Zaunder HL. Predicting the difficulty of intubation utilizing an intubation guide. Vol. 10. Chicago: Year Book Medical Publishers; 1983. pp. 32.
12. Frerk CM. Predicting difficult intubation. Anaesthesia. 1991; 46(12): 1005-8.
13. Karkouti K, Rose DK, Ferris LE, Wigglesworth DF, Meisami-Fard T, Lee H. Inter-observer reliability of ten tests used for predicting difficult tracheal intubation. Can J Anaesth. 1996; 43(6): 554-9.
14. Lohom G, Ronayne M, Cunningham AJ. Prediction of difficult tracheal intubation. Eur J Anaesthesiol 2003; 20(1): 31-6.
15. Al Ramadhani S, Mohamed LA, Rocke DA, Gouws E. Sternomental distance as the sole predictor of difficult laryngoscopy in obstetric anaesthesia. Br J Anaesth. 1996; 77(3): 312-6.
16. Shiga T, Wajima Z, Inoue T, Sakamoto A. Predicting difficult intubation in apparently normal patients: a meta-analysis of bedside screening test performance. Anesthesiology. 2005; 103(2): 429-37.

ORIGINAL ARTICLE

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The COVID-19 Vaccine Knowledge and Attitude Scale: A Methodological Study

Kemal Elyeli, Hatice Bebiş

Department of Public Health Nursing Near East University Faculty of Nursing, Nicosia, North Cyprus

Abstract

BACKGROUND/AIMS: The coronavirus disease-2019 (COVID-19) virus has spread to many countries in a short time since its emergence in December 2019 and it has been declared as a pandemic. It is important to wear a mask and comply with physical distance rules to protect against COVID-19. However, the COVID-19 vaccine is important for breaking the infection chain. This study was a methodological type of validity and reliability study on the COVID-19 Vaccine Knowledge and Attitude Scale conducted in the Northern Cyprus between October 2020 and January 2021.

MATERIALS AND METHODS: The COVID-19 Vaccine Knowledge and Attitude Scale was produced via two different studies (a cross-sectional study and a methodological study). The first study was the cross-sectional (n=396) study. This study's results were used for the first draft candidate scale, 50 items, with the literature. In this study, it was aimed to evaluate the validity and reliability of the COVID-19 Vaccine Knowledge and Attitude Scale. The study population consisted of individuals who were over the age of 18 years living in Northern Cyprus, who could speak Turkish, used social media platforms, and had a smart phone or a computer. In this study,firstly, the researchers evaluated the first candidate scale (n=50 items) and then this was reduced to 25 items. According to the literature, the study sample size (25x10) should be at least 250 participants. In this study, sampling selection was achieved via a Convenience Sampling method and 477 participants who met the study criteria and agreed to participate in this study as a volunteer took part. Also, in this study, confirmatory factor analysis (CFA)was performed with a different sample (n=120).The data was collected via Google Form (age, gender, eight socio-demographic questions and the COVID-19 Vaccine Knowledge and Attitude Scale) on internet platforms. SPSS were used for the statistical evaluation of the study. The Content Validity Index method was used for the content validity of the scale. Kaiser–Meyer–Olkin (KMO) and Bartlett's tests were applied to evaluate the sampling adequacy and suitability for factor analysis. Pearson correlation analysis was used for item analysis and the Cronbach alpha reliability coefficient was used to test internal consistency. Subsequently, approximately 2 weeks later, the scale was reapplied to the participants (n=85) to test-retest reliability using the paired dependent sample t-test.No statistically significant difference was found($p>0.05$).The results are shown as mean ± standard deviation, number(n) and percentage (%). Aconfidence interval (CI) of 95% and $p<0.05$ were accepted as statistical significance. The IBM SPSS V22 (IBM Corp., Armonk, NY, USA) Amosprogram was used for CFA.

RESULTS: Content and construct validity of the items were evaluated (n=477). The 16-item scale had a KMO test result of 0.808 and a Bartlett's test result of 2,308,179. In the determination of the invariance of the scale with respect to time (n=85), there was no statistical difference ($p>0.05$).

Cronbach's alpha coefficients were calculated for the whole scale and its factors (total scale $\alpha=0.68$, Factor 1 "perceived severity" $\alpha=0.81$, Factor 2. "perceived barriers" $\alpha=0.782$ and Factor 3 "perceived benefits" $\alpha=0.70$). CFA was also evaluated with a different sample (n=120). According to these results; the Degrees of Freedom (DF) value was found to be 101 ($p<0.001$), the Root mean square error approximate value (RMSEA) was

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ORCID IDs of the authors: K.E. 0000-0001-7666-4282; H.B. 0000-0001-6217-9753.

Address for Correspondence: Kemal Elyeli
E-mail: kemal.elyeli@neu.edu.tr
ORCID ID: orcid.org/0000-0001-7666-4282

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0.08, the Goodness of Fit Index (GFI) value was 0.89; the Normalized Fit Index (NFI) value was 0.62 and the Comparative Fit Index (CFI) value was 0.67.

CONCLUSION: The scale was considered a valid and reliable instrument. However, it is recommended to test it in other groups in order to increase its reliability criteria.

Keywords: COVID-19 vaccine, validity-reliability, scale development

INTRODUCTION

The coronavirus disease-2019 (COVID-19) virus spread very rapidly and turned into a long-term pandemic. The rate of morbidity and mortality (3.4%) of the virus causes fear and panic in society, causes economic losses, and psychological and social problems.[1,2] The virus causes serious health problems and death in all age groups, but especially for those who are elderly, have chronic diseases, or have immune system problems. The virus also creates a heavy burden on the health system.[3,4]

There is no specific treatment for the virus to date, so prevention has become even more essential.[2] It is aimed to gain both individual and social immunity with the vaccines developed.[5] In the world, seven different vaccines have been developed so far.[6] Their level of protection ranges from 40% to 90% and it is predicted that they will protect for at least six months.[7] However, there are various problems and concerns about obtaining the vaccines, their application, their side effects, and the preventiveness of these vaccines.[8] In some sections of society, these concerns remain even for vaccines developed many years ago (measles, polio, rubella, etc.), and this leads to "anti-vaccination"or "vaccine-hesitancy" attitudes.[9,10]

Health belief is defined as the individuals' beliefs and attitudes towards health behaviors.[11] If a person thinks that a disease has fatal or dangerous health consequences (perceived severity) and believes that the current method of protection/treatment will protect/cure them (perceivedbenefits), they will seek health care. However, the same person may also experience some difficulties (perceivedbarriers) in accessing the treatment.[12] Valid, reliable measuring tools are needed to determine the community's knowledge regarding the vaccine, and the associatedperceived barriers, perceived severity and perceived benefits.

This study was conducted as a methodological study to determine the validity of the newly developed "COVID-19 Vaccine Knowledge and Attitude Scale".

MATERIALS AND METHODS

This study was a methodological type of validity and reliability study conducted in Northern Cyprus between October 2020 and January 2021.

Population

The study population consisted of individuals over the age of 18 years living in the Northern Cyprus, who could speak Turkish, used social media platforms, and had a smart phone or a computer.

Sampling

In this study, the first candidate scale with 50 items was produced from the first study which was a cross-sectional (n=396) study[13] and subsequently, it was reduced to 25 items. According to the literature,[14-18] the sample size should be at least 5–10 times of the number of scale items. In this study, the second candidate scale was 25 items, and so the study sample size was calculated to be at least 250 participants.

In this study, sample selection was achieved with a Convenience Sampling Method and 477 participant who met the study criteria and agreed to take part as volunteers were enrolled in this study. Subsequently, approximately 2 weeks later, the scale was applied to 85 participants again to test-retest its reliability. The confirmatory factor analysis (CFA) was performed with a different sample of 120 (Figure 1).

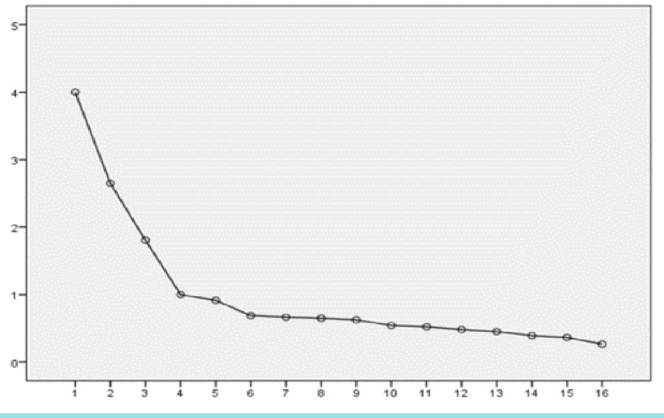

Figure 1. Steps of this research.

Data Collection

The data was collected via Google Form (age, gender, eight socio-demographic questions and the COVID-19 Vaccine Knowledge and Attitude Scale) on internet platforms.

Ethical Aspects of the Study

Ethics committee approval for this study was obtained from Near East University Scientific Research Ethics Committee (decision number: 2020/85, date: 26.11.2020), and written informed consent was obtained from all participants before the study.

Inclusion/Exclusion Criteria

Those who could read and understand Turkish and who volunteered to participate in this study were included, and those who could not access the internet via their computer or smart phone were excluded from this study.

Limitations of the Study

The research data was collected with the participants' self-declaration and applies only to this sample group. It cannot be generalized to other groups.

Data Collection Tools

Socio-demographic Questionnaire

It consists of eight questions that investigate the age, gender, and educational status of the individuals, and the COVID-19 transmission status and chronic disease history of themselves and their family.

COVID-19 Vaccine Knowledge and Attitude Scale

COVID-19 Vaccine Knowledge and Attitude Scale was developed by the researchers. The final version consists of16 items inthreesub-scales. All scale items were calculated positively and the sub-scales can used individually. There is no cut-off point of the scale. High scores obtained indicate that the participant has a high level of "severity" (five items= 1;2;3;4;5),"barriers" (seven items= 6;7;8;9;10;11;12), and "benefits" (four items= 13;14;15;16) perception regarding COVID-19 Vaccine Knowledge and Attitude. The scale was a Likert type scale. Items were evaluated as1=Strongly Disagree, 2=Disagree, 3=Neutral, 4=Agree, and 5=Strongly Agree. It takes about 10 minutes to complete the scale.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences software version 21.0 (IBM SPSS Corp., Armonk, NY, USA).While testing the reliability of the scale, the Content Validity Index (CVI) was used to evaluate the Content Validity, and exploratory factor analysis was used to evaluate the Construct Validity. Kaiser–Meyer–Olkin (KMO) and Bartlett's tests were applied to evaluate the sampling adequacy and suitability for factor analysis. Pearson correlation analysis was used for item analysis and the Cronbach alpha reliability coefficient was used to test internal consistency. Test-retest reliability was evaluated via the paired dependent t-test. The results are shown as mean ± standard deviation, number (n) and percentage (%). Confidence interval (CI) 95% and $p<0.05$ were accepted as statistical significance. The Amos SPSS V22 (IBM Corp, Armonk, NY, USA) was used for CFA.

RESULTS

The Study Participants Sociodemographic Characteristics

The average age of the participants was 23±39.3 years, 67.1% (n=320) were women, and 81.8% (n=390) were university graduates. It was determined that 27.9% of the participants (n=133) had a family member infected with the COVID-19 virus, and 5% (n=24) lost one of their family members due to COVID-19. In addition, it was determined that 9% (n=43) of the participants had been infected with COVID-19.

COVID-19 Vaccine Knowledge and Attitude Scale Validity Assessment

Content Validity Index Analysis

The first draft of this scale (50-item scale) was prepared on the basis of a health belief model, according to the results of a literature review and before the Cross-Sectional type study (n=396) results. Following this, the first draft scale items (50-item scale) were evaluated independently by the researchers, and they reached a consensus on the second draft scale (25-item draft scale).

The second candidate scale (25 items) and its items were evaluated by expert researchers (n=5) according to the CVI. CVI evaluation for each item was as follows: 1 = the item is not relevant, 2 = the item is not relevant and a major change is required to become relevant, 3 = the item is relevant but a minor change is required, 4 = the item is very relevant. Those itemsassessed as 3 or 4 were considered sufficient in terms of Item Contend Validity and remained in the draft scale. At this stage, five items were removed from the scale; so that the third draft scale (20-item scale) was created. The evaluation of the experts for this scale was found to be CVI= 80%–90%.

Construct Validity Analysis

According to the results of the first analysis (n=477), four items with Eigenvalues <1 were removed from the draft scale. Statistical evaluation was continued with the remaining fourth draft scale (16-item scale).

In the Table 1, KMO and Bartlett tests were used for exploratory factor analysis on the data obtained from the fourth draft scale (16-item scale). KMO was found to be 0.808, and the Bartlett test result was found to be 2308.1 ($p<0.001$) (Table 1).

Table 1. Distribution of factor analysis of the scale

Kaiser–Mayer–Olkin (KMO) sample measurement value adequacy		**0.808**
Bartlett's test	**Chi-square**	2308.179
	SD	120
	Sig	0.001

SD: standard deviation, Sig: significance.

The Varimax orthogonal rotation method was used to rotate the factor loadings matrix and explain the factor variances with fewer variables in a maximum way. An Eigenvalue of 1 was accepted to determine the number of factor items. A Scree Plot diagram was used to determine the number of factors. According to the Scree Plot diagram, the last point before falling below a nEigenvalue of 1determines the number of factors.[19]

It was determined that among the scale items included in the analysis, those with an Eigenvalue >1 explained 51.55% of the total variance. The variance ratio explained by the first factor with an Eigenvalue of 4.00 was 25.00%; the variance ratio explained by the second factor with an Eigenvalue of 2.64 was 16.55%; the variance ratio explained by the third factor with an Eigenvalue of 1.80 was 11.28%. The total variance ratio explained in the scale was found to be 51.55%.

When the Scree Plot graph was examined, it was determined that a sharp decline continued until the fourth point, and after the fourth point, the slope of the line became horizontal (Figure 2). When the dot intervals up to the fourth point were counted, it was determined that it was three, and this suggests that a useful model for these data may have three factors. Accordingly, the first factor is perceived severity, the second factor is perceived barriers, and the third factor is perceived benefits (Table 1).

COVID-19 Vaccine Knowledge and Attitude Scale Reliability Analysis

Reliability is the degree to which the items of the measurement tool are consistent with each other, the degree to which their results are free of random errors.[11] Internal Consistency Cronbach Alpha, Spearman and Guttman Coefficients, Item analysis, and test-retest confidence analyses were used to determine the reliability of the scale developed.

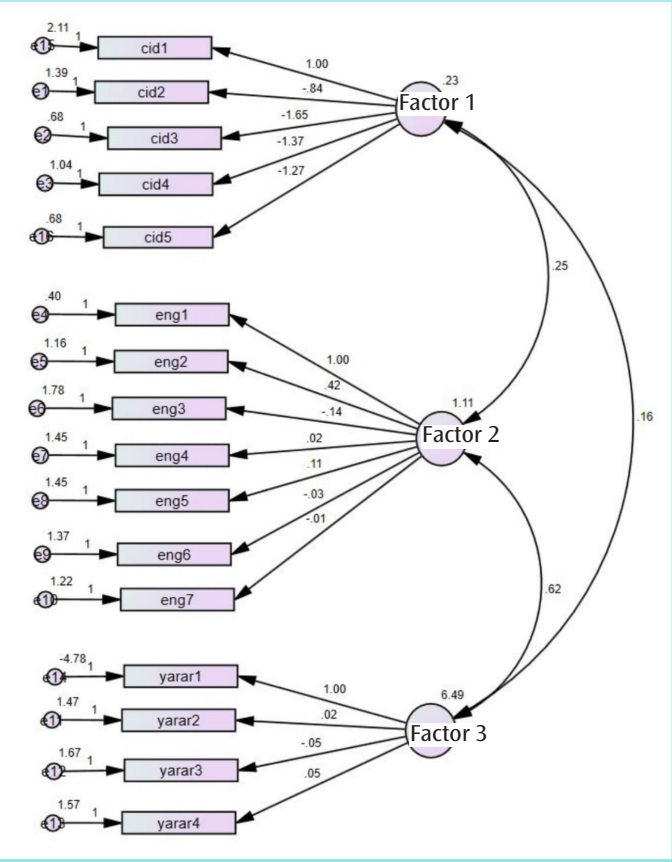

Figure 2. Scree plot of Eigenvalue.

Internal Consistency Reliability (Cronbach Alpha) Analysis

Cronbach's alpha coefficient, one of the methods of testing the internal consistency reliability in Likert-type scales, was calculated for the whole scale and its sub-scales (Table 2). The Scale Total Cronbach alpha value was α = 0.68, Factor 1/perceived severity Cronbach Alpha value was α=0.81, Factor 2/perceived barriers Cronbach Alpha value was α=0.78 and Factor 3/perceived benefits Cronbach Alpha value was determined to be α=0.70. A Cronbach alpha item deleted test was performed, but it was determined that the Cronbach alpha value did not increase if any items were removed.

Determination of Spearman-Brown and Guttman Values Analysis

As can be seen in Table 3, the split-half reliability coefficients obtained by dividing the scale items into two equivalent halves were calculated. Accordingly, the Spearman value (Equal-length Spearman–Brown) was found to be S=0.349, and the Guttman value (Guttman split-half) was G=0.347.

Table 2. Internal consistency distribution of the scale

Cronbach α coefficients	n	Cronbach α coefficients
Total	477	0.68
Factor 1: severity	477	0.81
Factor 2: barriers	477	0.78
Factor 3: benefits	477	0.70

n: number.

Table 3. Internal consistency of the scale Spearman and Guttman coefficients

Coefficients	Number	Point
Spearman–Brown	477	0.349
Guttman	477	0.347

Item Correlation Analysis

Correlation Analysis

In Table 4, "Pearson-moment correlation analysis" was performed to determine the relationship between the scale score and factor scores. A correlation was found between Factor 1-perceivedseverityand Factor 2-perceivedbarriers (r=0.310), Factor 3-perceived benefits (r=1.000), and the scale total score (r=0.816) (p<0.001). A correlation was found between Factor 2-PerceivedBarriersand the scale total score (0.782), Factor 1-Perceived Severity (r=-0.105), Factor 3-Perceived Benefits (r=1.000) (*p*<0.001). A correlation was found between Factor 3-Perceived Benefits and the overall score of the scale (r=0.697), Factor 1-PerceivedSeverity (r=1.00), and Factor 2-PerceivedBarriers (r=-0.108) (*p*<0.001).

Item Loads of Factors Analysis

In cases where the Eigenvalue was below 0.40, the relevant item was removed from the scale. The factor loads are shown in Table 5.

The factor loads of the items in the first factor vary between 0.522 and 0.807, the factor loads of the substances in the second factor vary between 0.459 and 0.713, and the factor loads of the substances in the third factor vary between 0.472 and 0.721.

Test-Retest Analysis

In Table 6, to determine the relationship between the overall and sub-scales of the scale, the test was applied to a group of the study participants (n=85) again. Subsequently, the data was analyzed with the paired dependent sample t-test. There was no statistically significant difference between either the total mean point of the scale (pre-test=52.28±4.30, post-test=45.95±5.08) and the mean points of Factors 1, 2 and 3 between the pre-test and post-test (p>0.05).

Confirmatory Factor Analysis

The CFA performed in the AMOS SPSS version 22 (IBM Corp, Armonk, NY, USA) statistical program examined the relationship between the different participants (n=120) and the factors and co-variance values (Figure 2).

The structure examined contains five items for severity sub-scale, seven items for barrierssub-scale, and four items for benefits sub-scale. The results of the CFA are shown in Figure 3. According to these results, the Degrees of Freedom (DF) value was found to be 101 (p<0.001),the root mean square error of approximation (RMSEA) value was found to be 0.08, the Goodness of Fit Indices value (GFI) was 0.89, the Normed Fit Index (NFI) value was 0.62, and the Comparative Fit Index value (CFI) was 0.67.

DISCUSSION

The COVID-19 virus affected billions of lives shortly after its emergence and caused many deaths worldwide. There have been more than three million deaths from COVID-19 worldwide to date, and the number of

Table 4. Correlation of scale total score and factor scores

Variables	Total point		Severity		Barriers		Benefits	
	r	p-value	r	p-value	r	p-value	r	p-value
Total point	**	**	0.816	**0.001**	0.782	**0.001**	0.697	**0.001**
Severity	0.816	**0.001**	**	**	0.310	0.001	1.000	**0.001**
Barriers	0.782	**0.001**	-0.105	**0.001**	**	**	1.000	**0.001**
Benefits	0.697	**0.001**	1.00	**0.001**	-0.108	0.001	**	**

r=Pearson's correlation test

Table 5.Item load distribution of factors

Factor groups	Factor weight
Factor 1	0.807–0.639
Factor 2	0.713–0.459
Factor 3	0.721–0.472

deaths due to the virus in Northern Cyprus has exceeded 30.[20,21] In this study, 5% of the participants had lost a family member due to COVID-19, and approximately 10% had been infected with COVID-19 (Table 1). The data in this study are similar to the literature.

In the literature, it is stated that draft scale questions in scale development studies be created by scanning the literature or by qualitative interviews.[22-24] In this study, the literature was reviewed and the first draft scale (50-item draft scale) was created using cross-sectional study data conducted with a different sample group in the first step of the research as part of the scale development study.[23] In this study, firstly, the researchers evaluated the first candidate scale (50 items) and then the second draft candidate scale was created by reducing the number of items to 25.

Validity is the conformity of the measurement tool to the feature required to be measured and the degree of measurement of the feature it intends to measure.[25] A developed measurement tool is expected to meet validity. Validity is evaluated as content validity and construct validity.[26] Testing the content validity of a scale is carried out to determine whether the newly developed scale measures the concept that it is intended to measure and whether it contains unrelated concepts.[27] The scale was presented to experts in this field in order to eliminate items that are not related to the condition to be measured. The scale was edited in line with the comments and assessments of these experts. In the literature, it is stated that the number of experts to be consulted to test the content validity can vary between 5 and 40.[25,28-30] The purpose of the validity test is to evaluate the draft scale items by determining whether the draft items represent the behaviors to be measured. This second draft scale (25-item scale) was presented to experts (n=5) to test its content validity. As a result of the evaluations of the experts, five items scoring below three were removed from the scale, and it was determined that the CVI value of the scale was above 80%. The research was then carried out with the third draft scale (20items).

The construct validity determines to what extent the items in the scale accurately measure what it is intended to measure.[31] The test of construct validity is done by using the factor analysis method and scoring the answers given to the items in the measurement tool. As a result of this analysis, items with low factor loads are excluded from the scale. Factor analysis is continued until an appropriate result is reached, which includes a sufficient number of items to measure the desired area.[32,33] With the KMO test and Bartlett's tests, data on the scale are tested to ensure their suitability for factor analysis. The lower limit of KMO testing is 0.50, and factor analysis should not be continued in case of the result being lower than this value. The KMO result is expected to be above 0.70 and close to 1 to perform a good factor analysis.[20,25,34] In this study, the Kalmogrow–Simirnow test was used to determine the normality distribution of the data. Accordingly, whether or not the sample size was sufficient to develop a scale was tested with the KMO test and Bartlett's test among the exploratory tests. As a result of these tests, it was determined that the items were sufficient to develop the scale. The KMO coefficient of the study (0.808) and Bartlett's test (2308.179) were found to be sufficient for analysis (Table 1).

Among principal component analysis, the Varimax Rotation method is one of the most used methods to determine the factor structure of a scale.[32] In this study, Varimax rotation was used and the factor structure of the scale was determined. In the literature, the value of factor load is used to explain the relationship between items and the factor and when deciding on the substances to be included in the scale. The lower limit specified for the factor load value is 0.30, and load values between 0.30 and 0.59 are considered to be medium and values 0.60 and above are considered high. It is recommended that values above 0.40 should be taken as the factor load value.[26,32] In this study, four items with a factor load below 0.40 were excluded from the scale. Thus, the number of items on the scale decreased to n=16 items (the fourth draft of the scale).

Table 6. Test/Re-test analysis results of COVID-19 Vaccine Knowledge and Attitude Scale and sub-scales

Scale total and sub-scale	Pre-test			Post-test			Statistic	
	Min	Max	Mean ± SD	Min	Max	Mean ± SD	t-test	p-value
Factor 1	11.00	23.00	17.49±2.47	8.00	23.00	16.06±3.45	-0.136	0.140
Factor 2	13.00	31.00	21.21±3.86	9.00	31.00	17.04±4.31	0.134	0.144
Factor 3	8.00	20.00	13.57±2.41	8.00	20.00	12.84±2.17	-0.224	0.014
Total	41.00	64.00	52.28±4.30	38.00	64.00	45.95±5.08	-0.144	0.116

t-test: for paired two dependent sample.
COVID-19: coronavirus disease-2019, Min: minimum, Max: maximum, SD: standard deviation.

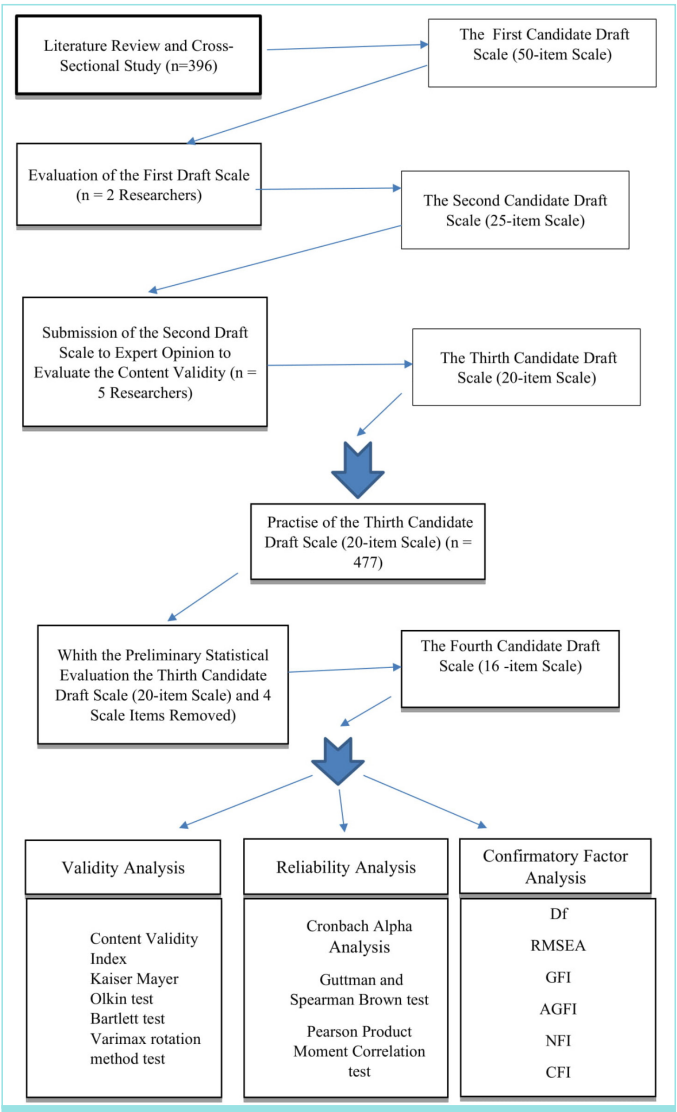

Figure 3. Confirmatory factor analysis.

As a result of factor analysis, the higher variance rates mean a stronger factor structure. However, it is not possible to reach a high variance rate in many areas; variance rates varying between 40% and 60% are considered ideal.[31] In this study, the total variance explained after factor analysis was determined to be 51.55%. This scale is within acceptable limits in terms of the exploratory factor load value.

The Scree Plot graph is used to determine the number of factors.[34] In this graph, the vertical axis expresses Eigenvalues and the horizontal axis expresses factors. Points giving a steep slope in the graph are included in the study. Points giving a superficial, flat slope are not included in the study. A horizontal line is drawn from the point where the graph shows a horizontal slope, and the distances between the points above this line are accepted as a scale.[35] In the literature, it is recommended to take the opinions and comments of experts in the naming of the sub-scales.[36] In this study, according to the factor analysis, the three factors were named as the perceived severity sub-scale, the perceived barriers sub-scale and the perceived benefits sub-scale.

The consistency of all the items in the measurement tool and the degree to which the measurement results are free from random errors is called Reliability. A test accepted as valid should also be reliable.[25,26] Internal consistency, split-half, test-retest, and factor analysis methods are used in the reliability analysis of a developed scale.

Internal consistency is determined by calculating the Cronbach alpha coefficient.[37] Internal consistency is the reliability method that indicates the items included in the measurement tool can measure the variable that is desired to be measured. A high Cronbach alpha coefficient means that the items in that scale are consistent with each other.[38] In the literature, it is reported that a scale is reliable if the Cronbach alpha coefficient is in the range of 0.60–0.70, while values between 0.70–1.00 are considered as high reliability.[26] In this study, the total scale the Cronbach's alpha value of the scale was found to be α=0.68. This value was considered as meaning the reliability of the scale was within acceptable limits. Removing any item from the scale while evaluating Cronbach alpha may increase the Cronbach alpha value.[39] However, in this study, it was determined that the Cronbach alpha value did not increase with the deletion of any item. For the Cronbach alpha value of the sub-scales, the perceived severity sub-scale with α=0.81, the perceived barriers sub-scale with α=0.78, and the perceived benefits sub-scale with α=0.70, were determined, and it was considered a reliable measurement tool.

In determining the internal consistency of the scale, in addition to the Cronbach alpha coefficient, the split-half method is used and the Guttman and Spearman–Brown reliability coefficients are calculated.[40] When calculating the internal reliability coefficient using the division in half method, the coefficient value should be at least 0.70.[29] In this study, the Spearman–Brown value of the scale was calculated to be S=0.349 and the Guttman value as G=0.347. The Spearman–Brown and Guttman values were found to be low in this study.

Testing consistency-against-time is another scale of reliability. The scale is applied to part of the same sampling group after 2 to 4 weeks, and the mean scores between the two measurements are compared.[25,26] In this study, the relationship between the overall and sub-scale of the scale was evaluated in the test-retest method with a group of the study participants (n=85), and there was no statistically significant difference between them ($p>0.05$). This result was evaluated as a consistent measurement of the scale against time.

Item analysis is carried out to test whether the items in the whole or sub-scales of the measurement tool are significantly included in the whole or sub-scales of the scale. In item analysis, the variance of each scale item and the variance of the total scale score are compared with Pearson-moment correlation analysis, and the relationship between them is examined.[40] If the items of the scale are of equal weight and in the form of independent units, it is expected that the correlation coefficient between each item and the total value will be high, and the item-total correlation results will also show statistical significance.[25,34,20] In this study, there was a statistically significant relationship between all items in the scale and the total score according to the results of Pearson-moments correlation analysis calculated to determine item-total correlations ($p<0.05$). As a result of the Pearson-moment correlation analysis performed for the item-total correlations of the sub-scales, a significant correlation was found between the perceived severity, perceived barriers,perceived benefits items, and their sub-scales total score ($p<0.05$).These results

indicate that the items in the scale are distinctive in terms of the properties they measure.

CFA is a frequently used analysis method in developing a new measurement tool, the evaluation of the psychometric properties of the measuring instrument, examining the effectiveness of the method, determining whether the validity of the measurement tool created varies according to time, population and groups, and determining the correlation between measurement errors.[41] CFAof the scale developed in this study was carried out with a different sample (n=120) (Figure 3).

In the CFA, if the RMSEA value is less than 0.08 and the Goodness of Fit Indices value (GFI) is above 0.90, it indicates that the scale has a "good" fit.[42] If the Normed Fit Index (NFI) value is above 0.90 and the Comparative Fit Index value (CFI) is equal to 0.95, it means that the scale has a "perfect" fit.[33] According to this study's results, the degrees of freedom (DF) value was found to be 101. RMSEA value was found to be 0.08, the Goodness of Fit Indices value (GFI) was 0.89, the Normed Fit Index (NFI) value was 0.62, and the Comparative Fit Index value (CFI) was 0.67. In line with these data, it was found that the CFA of the scale was within the reference values given.

CONCLUSION

The COVID-19 Vaccine Knowledge and Attitude Scale, which was analyzed for validity and confidence in this study, is a valid and reliable tool. However, it is recommended to test it in other groups in order to increase its reliability criteria.

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MAIN POINTS

- This is the first scale regarding COVID-19 Vaccine Knowledge and Attitudes in the literature.
- This scale may help to plan health education in the future regarding a community' sperceived fears, barriers and benefits with respect to the COVID-19 vaccine.
- As this scale is validate and reliable, it might be implemented in different studies in a standardized way.

ETHICS

Ethics Committee Approval: Ethics committee approval for this study was obtained from Near East University Scientific Research Ethics Committee (decision number: 2020/85, date: 26.11.2020).

Informed Consent: Written informed consent was obtained from all participants before the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: K.E., H.B., Design: K.E., H.B., Data Collection and/or Processing: K.E., H.B., Analysis and/or Interpretation: K.E., H.B., Literature Search: K.E., H.B., Writing: K.E., H.B., Critical Review:K.E., H.B.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Ji Y, Ma Z, Peppelenbosch MP, Pan Q. Potential association between COVID-19 mortality and health-care resource availability. Lancet Glob Health. 2020; 8(4): e480.
2. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical–therapeutic staging proposal. J Heart Lung Transplant. 2020; 39(5): 405-7.
3. Song F, Shi N, Shan F, Zhang Z, Shen J, Lu H, et al. Emerging 2019 novel coronavirus (2019-nCoV) pneumonia. Radiology. 2020; 295(1): 210-7.
4. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020; 382(8): 727-33.
5. RIVM. COVID-19 (novel coronavirus) no date. (cited 2021 February 7) Available from: URL: https://www.rivm.nl/en/novel-coronavirus-covid-19.
6. Yiğit T, Oktay BÖ, Özdemir CN, Moustafa Paşa S. Aşı karşıtlığı ve fikri gelişimi. Journal of Social and Humanities Sciences Research. 2020; 7(53): 1244-61.
7. Thanh Le T, Andreadakis Z, Kumar A, Gómez Román R, Tollefsen S, Saville M, et al. The COVID-19 vaccine development landscape. Nat Rev Drug Discov. 2020; 19(5): 305-6.
8. Lipsitch M, Dean NE. Understanding COVID-19 vaccine efficacy. Science. 2020; 370(6518): 763-5.
9. Riad A, Pokorná A, Attia S, Klugarová J, Koščík M, Klugar M. Prevalence of COVID-19 vaccine side effects among healthcare workers in the Czech Republic. J Clin Med. 2021; 10(7): 1428.
10. WHO. COVID-19 vaccines 2021 (cited 2021 April 20) Available from: URL: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines
11. Gözüm S, Çapik C. Sağlık davranışlarının geliştirilmesinde bir rehber: Sağlık İnanç Modeli. DEUHYO ED. 2014 ;7(3): 230-7.
12. Green EC, Murphy EM, Gryboski K. The Health Belief Model. The Wiley Encyclopedia of Health Psychology. 2020: 211-4.
13. Elyeli K, Bebiş H. Yetişkinlerin COVID-19 pandemisi ve COVID-19 aşısı ile ilgili bilgi tutum ve davranışları ile COVID-19 anksiyete düzeyi arasındaki ilişkinin belirlenmesi. JBACHS. 2021.
14. Özüdoğru HY, Kan A, Uslu L, Yaman E. Yerel halkın suriyelilere yönelik tutum ölçeği geliştirme çalışması. Sosyal Politika Çalışmaları Dergisi. 2018; 18: 115-40.
15. Tahtalıoğlu H, Özgür H. Türkiye'de akademisyenlerin idari görevlerine dair "cam tavan" algısı ölçeği geliştirme. Ömer Halisdemir Üniversitesi İktisadi ve İdari Bilimler Fakültesi Dergisi. 2020; 13(4): 809-23.
16. Çalışkan A. Kriz yönetimi: bir ölçek geliştirme çalışması. Türk Sosyal Bilimler Araştırmaları Dergisi. 2020; 5(2): 106-20.
17. Canaslan A, Güçlü N. Teacher's Learning Agility: Scale Development Study. Kastamonu Education Journal. 2020; 28(5): 2071-83.
18. Chang SC, Yeh HC, Kuo YL. Scale development and model validation for the process of exercise engagement for people with prediabetes. J Korean Acad Nurs. 2020; 50(2): 298-312.
19. Mair P. Factor analysis. In: Modern Psychometrics with R. 2018. Cham: Springer. 2018. pp.17-61.

20. WHO. Weekly operational update on COVID-19 2020 Available from: URL: https://www.who.int/publications/m/item/weekly-update-on-covid-19---15-april-2020 (Accessed on April 15, 2021).

21. Ministery of Health. COVID-19 general situation Available from: URL. https://saglik.gov.ct.tr/COVID-19-GENEL-DURUM Accessed on April 15, 2021).

22. Liu Y, Yao Y, Fan DXF. Evaluating tourism market regulation from tourists' perspective: scale development and validation. Journal of Travel Research. 2020; 59(6): 975-92.

23. Karahan BÜ. Okumaya yönelik tutum ölçeği: Ölçek geliştirme çalışması. Kastamonu Eğitim Dergisi. 2018; 26(1): 67-73.

24. Kılıç S. Cronbach's alpha reliability coefficient. Psychiatry and Behavioral Sciences. 2016; 6(1): 47-8.

25. Tavşancıl E. Tutumların ölçülmesi ve SPSS ile veri analizi. Nobel Akademik Yayıncılık, Ankara. 2010.

26. Gözüm S, Aksayan S. Kültürlerarası ölçek uyarlaması için rehber II: ölçek uyarlama aşamaları ve dil uyarlaması. HEMAR-G. 2003; 5 (1): 3-14.

27. Aksoy B. Hemşirelik öğrencilerinde mesleki risk algısı: Bir ölçek geliştirme çalışması. T.C. Trakya Üniversitesi Sağlık Bilimleri Enstitüsü Hemşirelik Anabilim Dalı Yüksek Lisans Programı, Yüksek Lisans Tezi. 2016.

28. Çalışkan C. Afet okuryazarlığı ölçek geliştirme çalışması. Hacettepe Üniversitesi Sağlik Bilimleri Enstitüsü, Doktora Tezi. 2020.

29. Çavmak D, Atalay E, Söyler S. Hemşirelikte kariyer sorunları: bir ölçek geliştirme çalışması. İşletme Araştırmaları Dergisi. 2019; 11(3): 1897-910.

30. Karakoç AG, Dönmez L. Ölçek geliştirme çalışmalarında temel ilkeler. Tıp Eğitimi Dünyası. 2014; 13(40): 39-49.

31. Karagöz Y. SPSS 21.1 uygulamalı biyoistatistik Tıp, eczacılık, diş hekimliği ve sağlık bilimleri için. Nobel Akademik Yayıncılık: Ankara; 2014. pp. 650-703.

32. Çokluk Ö, Şekercioğlu G, Büyüköztürk Ş. Sosyal bilimler için çok değişkenli istatistik: SPSS ve LISREL uygulamaları. Pegem Akademi Yayıncılık: Ankara; 2012.

33. Tavşancıl E. Tutumların ölçülmesi ve SPSS ile veri analizi, Nobel Yayın Dağıtım, 3. Baskı. İstanbul. 2006.

34. Watson JC. Establishing evidence for internal structure using exploratory factor analysis. Measurement and Evaluation in Counseling and Development. 2017; 50(4): 232-8.

35. Şahin MG, Öztürk NB. Eğitim alanında ölçek geliştirme süreci: bir içerik analizi çalışması. Kastamonu Eğitim Dergisi. 2018; 26(1): 191-9.

36. Erkuş A. Psikolojide ölçme ve ölçek geliştirme. Ankara: Pegem Akademi Yayınları. 2012. and Evaluation in Counseling and Development. 2017; 50(4): 232-8.

37. Gollagi SG, Kotagi V, Pareek PK. Reliability test (cronbach alpha test) for variables selection in secure SDLC. Journal of Advancement in Parallel Computing. 2020; 3(1): 1-7.

38. Amirrudin M, Nasution K, Supahar S. Effect of variability on cronbach alpha reliability in research practice. Jurnal Matematika, Statistika & Komputasi. 2021; 17(2): 223-30.

39. Bonett DG, Wright TA. Cronbach's alpha reliability: Interval estimation, hypothesis testing, and sample size planning. Journal of Organizational Behavior. 2015 ; 36(1): 3-15.

40. de Vet HCW, Mokkink LB, Mosmuller DG, Terwee CB. Spearman–Brown prophecy formula and Cronbach's alpha: different faces of reliability and opportunities for new applications. Journal of Clinical Epidemiology. 2017; 85: 45-9.

41. Ergül B, Yılmaz V. COVID-19 salgını süresince aile içi ilişkilerin doğrulayıcı faktör analizi ile incelenmesi. IBAD Sosyal Bilimler Dergisi. 2020: 38-51.

42. Akyüz HE. Yapı geçerliliği için doğrulayıcı faktör analizi: Uygulamalı bir çalışma. BEÜ Fen Bilimleri Dergisi. 2018; 7(2): 186-98.

Appendix 1. COVID-19 Vaccine Knowledge and Attitude Scale

		Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
1	COVID-19 Vaccines protect against COVID-19 disease.					
2	Those with chronic diseases should get the COVID-19 vaccine.					
3	The elderly need to get the COVID-19 vaccine.					
4	Everyone should get the COVID-19 vaccine.					
5	COVID-19 vaccines cause mild COVID-19 disease.					
6	COVID-19 vaccines can have serious side effects.					
7	COVID-19 vaccines have just been developed, they are not safe yet.					
8	COVID-19 vaccines with low protection are used in developing countries.					
9	Even if serious side effects of COVID-19 vaccines are seen, they are hidden from society.					
10	The positive news in the press about COVID-19 vaccines is exaggerated as advertising.					
11	Highly protective COVID-19 vaccines are applied in developed countries.					
12	It is impossible for everyone to get the vaccine in sufficient dosage and frequency.					
13	Children should also get the COVID-19 vaccine.					
14	Young people should also get the COVID-19 vaccine.					
15	Even if the virulence of the COVID-19 virus decreases, it is necessary to be vaccinated.					
16	Someone recovering from COVID-19 disease should still get the COVID-19vaccine.					

Appendix 2. COVID-19 Vaccine Knowledge and Attitude Scale in Turkish [COVID-19 Aşısı Bilgi ve Tutum Ölçeği]

		Kesinlikle Katılmıyorum	Katılmıyorum	Kararsızım	Katılıyorum	Kesinlikle Katılıyorum
1	COVID-19 aşıları, COVID-19 hastalığından korur.					
2	Kronik hastalığı olanlarCOVID-19 aşısı yaptırmalıdır.					
3	Yaşlıların COVID-19 aşısını yaptırması gerekir.					
4	COVID-19 aşısını herkes yaptırmalıdır.					
5	COVID-19 aşıları hastalığı hafif geçirmeyi sağlar.					
6	COVID-19 aşılarının ciddi yan etkileri olabilir.					
7	COVID-19 aşıları yeni geliştirildi, henüz güvenli değiller.					
8	Koruyuculuğu düşük COVID-19 aşıları, gelişmekte olan ülkelerde uygulanır.					
9	COVID-19 aşılarının ciddi yan etkileri görülse bile toplumdan gizlenir.					
10	COVID-19 aşıları ilgili basında çıkan olumlu haberler abartılı ve reklamdır.					
11	Koruyuculuğu yüksek COVID-19 aşıları, gelişmiş ülkelerde uygulanır.					
12	Herkesin yeterli doz ve sıklıkta aşı yaptırması imkansızdır.					
13	COVID-19 aşısını çocuklar da yaptırmalıdır.					
14	COVID-19 aşısını gençler de yaptırmalıdır.					
15	COVID-19 virüsünün hastalık yapma gücü azalsa bile, aşılanmak gerekir.					
16	COVID-19 hastalığından iyileşen biri, yinede COVID-19 aşısı yaptırmalıdır.					

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Health Workers' Depression, Anxiety, Stress, and Compassion Levels During the COVID-19 Outbreak

Alev Yıldırım Keskin[1], Sibel Şentürk[2]

[1]Department of Nursing, Aksehir Kadir Yallagoz Health School, Selçuk University, Konya, Turkey
[2]Department of Nursing, Bucak Health School, Burdur Mehmet Akif Ersoy University, Burdur, Turkey

Abstract

BACKGROUND/AIMS: Healthcare professionals should be evaluated for depression, anxiety and stress during and after the epidemic, and the necessary education, training and psychological support should be provided so that they can provide quality health care and maintain their compassion. This study examined health workers' depression, anxiety, stress, and compassion levels during the coronavirus disease-2019 (COVID-19) outbreak.

MATERIAL AND METHODS: This descriptive and cross-sectional study was conducted using 234 health personnel who provided care to COVID-19 patients. The data were gathered using the Information Request Form, Depression, Anxiety and Stress Scale - 21 Items (DASS-21), and Compassion Scale (CS).

RESULTS: The participants' average total score of DASS-21 was 38.28±13.95 and their average CS score was 93.34±11.77. There was a strong, negative, and significant correlation between the DASS-21 sub-dimensions of depression, anxiety, and stress and the CS sub-dimensions of indifference, separation, and disengagement (p=0.000).

CONCLUSION: This study determined that health workers experienced depression, anxiety, and stress during the COVID-19 outbreak and their CS remained high.

Keywords: COVID-19, health worker, depression, anxiety, stress, compassion

INTRODUCTION

There have been many pandemics in the world over the last twenty years.[1,2] Having first appeared in the Wuhan-Hubei Province, China in December 2019, coronavirus disease-2019 (COVID-19) spread all over the world. It quickly threatened people's lives and caused a huge panic.[3,4] The World Health Organization (WHO) named this coronavirus, which was identified on January 12, 2020, 2019-nCoV.[5] On February 11, 2020, the WHO concluded that COVID-19 is a virus which causes serious acute respiratory disease, and declared a pandemic status.[6] Since that declaration, it is estimated that the world has seen more than 122,992,844 million confirmed COVID-19 cases, with more than 2,711,071 deaths.[7] There have been a total of 3,035,338 cases, 30,178 deaths, and 1644 serious patients in Turkey to date since March 10, 2020 when the first case was seen here.[8] Health workers represent the most at-risk group during pandemics.[9] Health workers are motivated to be compassionate when witnessing the physical and emotional suffering of their patients. However, prolonged exposure to such situations can cause compassion fatigue, leading to desensitization toward patients who are in serious emotional and physical pain.[10] In the literature, compassion fatigue is also described as the physical, emotional, and psychological impact of helping others — often through experiences of stress or trauma.[10-12] When examining the literature, it is evident that health personnel slowly start to exhibit adverse psychological signs from having to risk their lives and show compassion towards their

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ORCID IDs of the authors: A.Y.K. 0000-0003-0981-5364; S.Ş. 0000-0002-5634-174X.

Address for Correspondence: Alev Yıldırım Keskin
E-mail: alevyildirim@selcuk.edu.tr; ayiles@hotmail.com
ORCID ID: orcid.org/0000-0003-0981-5364

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patients constantly. However, due to the overwhelming trauma during pandemics, these effects manifest rapidly and can evolve into symptoms of anxiety, depression, and stress that can have life-long effects.[11-13]

The fact that COVID-19 spreads easily from person to person, and shows high morbidity and mortality rates maximizes an individual's danger perceptions.[14,15] The increasing number of cases and lack of equipment leads to pressure and anxiety in health workers.[16] In addition to facing these critical situations, health workers who are directly dealing with COVID-19 patients' diagnoses, treatment, and care are at greater risk of psychological distress.[17,18] Health workers are at risk of infection despite employing the necessary protective measures against the spread of COVID-19, such as wearing masks, face shields, goggles, glasses, protective clothing, proper handwashing techniques, and maintaining social distancing.[3,4] The established literature emphasizes that mental and physical burnout in health workers may result from an increasing number of suspected cases, the high risk of infection, increased workloads, the lack of medicines and vaccines to combat COVID-19, a lack of sufficient social and psychological support, fatigue, psychological disorders, and obsessions.[17-20] Moreover, it is reported that the fear and anxiety levels of health workers are higher due to the infectious and fatal nature of COVID-19, especially when treatment is delayed.[17,21] During the COVID-19 pandemic period, the psychological status of healthcare professionals who have to work more and are under more stress has been investigated in various studies.[4,17,18,21] However, in the literature, there are a limited number of studies on the depression, anxiety and stress levels of healthcare workers regarding the COVID-19 epidemic.[11-13] No studies have been found that examine depression, anxiety, stress and compassion levels together. This study was conducted to determine the levels of depression, anxiety, stress and compassion of healthcare professionals during the COVID-19 pandemic process. It is thought that it will contribute to the literature in maintaining their physical and psychological health and in taking the necessary precautions in high-risk environments by strengthening preparations.

Study Questions

1. What are health workers' depression, anxiety, stress, and compassion levels?
2. What are the factors which affect health workers' depression, anxiety, stress, ancompassion levels?
3. Is there a correlation between health workers' compassion levels and their depression, anxiety, and stress levels?

MATERIALS AND METHODS

Study Type

This is a cross-sectional and descriptive study.

Study Population and Sample

The population of the study consisted of health personnel who provided care to COVID-19 patients in a state hospital in the interior of Anatolia region. The sample of this study consisted of 234 health workers who agreed to join the study between June 10 and July 10, 2020.

Data Collection

The data were collected using the Information Request Form which was designed by the researchers to be in line with the relevant literature, the Depression Anxiety Stress Scale-21 (DASS-21), and the Compassion Scale (CS). Before starting this study, pre-implementation was conducted with five health personnel and the questionnaire form was also finalized. Due to the COVID-19 outbreak, the questionnaire form was shared and completed online on three different health platforms after contacting healthcare personnel managers. Before we initiated this study, the health personnel were informed about the study aim and their informed consent was obtained. Data collection for each participant took approximately 10–15 minutes.

Information Request Form

The Information Request Form was designed by reviewing the relevant literature[4,17-19,21] and includes 15 questions: eight regarding the health personnel's socio-demographic characteristics (age, gender, employment duration, educational level, marital status, department where they work, position at the hospital, and number of children), and seven regarding the changes which occur as a result of contact with COVID-19 patients.

Depression Anxiety Stress Scale-21 (DASS-21)

The Depression Anxiety Stress Scale-21 (DASS-21), developed by Lovibond and Lovibond[22], contains 42 items. Subsequently, Henry and Crawford[23] developed a 21-item shorter version. The Turkish adaptation of the scale was designed by Yılmaz et al.[24]. The DASS-21 which was used in this study included a total of 21 items: seven items each for the depression, anxiety and stress subscales. The responses were rated on a 4-point Likert scale as follows: (0) Did not apply to me at all; (1) Applied to me to some degree, or some of the time; (2) Applied to me to a considerable degree, or a good part of the time; (3) Applied to me very much, or most of the time. The higher the total scores are, the higher the levels of depression, anxiety, and stress experienced by the participants are. In this study, the Cronbach's alpha value was 0.94.

Compassion Scale (CS)

The CS was developed by Pommier[25] and the Turkish validity and reliability tests were performed by Akdeniz and Deniz Engin[26]. It contains 24 items. It is rated on a 5-point Likert scale with the following ratings: 1=Never, 2=Rarely, 3=Sometimes, 4=Often, and 5=Always. There are six subscales of the CS: kindness (items 6, 8, 16, 24), indifference (items 2, 12, 14, 18), common humanity (items 11, 15, 17, 20), disengagement (items 1, 7, 19, 23), mindfulness (items 4, 9, 13, 21), and separation (items 3, 5, 10, 22). The indifference, separation, and disengagement sub-dimensions of the scale are scored reversely. The average total score is calculated with this scoring. However, when the subscales are scored separately, it is not necessary to reverse the score. The lowest possible score is 24, while the highest is 120; higher total scores indicate higher compassion levels. In the study by Akdeniz and Deniz Engin[26], the Cronbach's alpha value was found to be 0.85. In this study, the Cronbach's alpha value was 0.88.

Statistical Analysis

The data were processed using the IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Armonk, NY, USA) program. Descriptive statistics were calculated and the Kolmogorov–Smirnov test was performed to determine whether the data followed a normal distribution. In the statistical analysis, the numbers, percentages, standard deviation, frequency, average, minimum, and maximum values were analyzed to assess the health workers' socio-demographic

characteristics. For paired comparisons, the Independent t-test was used; while for the comparisons of more than two groups, the One-Way ANOVA test was used. For correlation analyses, if the data did not follow a normal distribution, the Pearson correlation analysis was used. Results were considered significant for $p<0.05$.

Ethical Consideration

The ethical suitability of the research was approved by the Medicine Faculty Non-Interventional Ethics Council of Selçuk University (protocol number: 2020/255) and the Scientific Research Platform of the Ministry of Health of Turkey (protocol number: 2020-05-07T11_53_50). Additionally, verbal approval was obtained from the health platforms on which the study was carried out. The participants were informed of the study-aim, study-length, and questionnaire forms via the link and their informed consent was obtained after it was explained that participation was voluntary.

Limitations of the Study

Among the limitations of this study; only those healthcare professionals who were providing care for COVID-19 patients participates. Also, there are a limited number of online platforms to reach out to individuals on. Therefore, the findings may not be generalizable to all health workers in Turkey. The lack of face-to-face interviews with the healthcare workers is another study limitation as it can reduce the effective answering of the questions.

RESULTS

It was found that 70.5% of the participant health workers were aged ≥26 years, 84.2% of them were female, 45.3% of them had an employment duration of 1–5 years, 28.6% of them worked in emergency rooms, and 79.1% of them were employed as nurses/medical assistants (Table 1).

When the distribution of the health workers in our study was investigated according to changes during the COVID-19 period, it was seen that 70.9% of the participants had close and/or direct contact with COVID-19 diagnosed patients. We found that those health workers' who came into close and/or direct contact with COVID-19 diagnosed patients exhibited the most physiological symptoms such as fatigue (41.9%), sleeplessness (33.8%), weakness and sweating (26.1%). Furthermore, these health workers experienced the most psychological symptoms, such as worry (56.4%), stress (48.3%) and fear (43.2%). Among the most important social changes experienced by the healthcare professionals were agreeing with the following: social life is becoming more important (53.8%), and nature is important (46.6%). 64.1% of the health workers who came into close and/or direct contact with COVID-19 diagnosed patients were worried that they may spread the disease to their family members; 60.7% of them often prayed; and 59.0% of them realized that good health is the most important thing in life (Table 2).

The health workers' average total score on the DASS-21 scale was 38.28±13.95 and the stress subscale average score was 13.79±5.63. The average CS total score was found to be 93.34±11.77 and the disengagement subscale average score was 16.76±2.58. The DASS-21 and the CS sub-dimensions are listed in Table 3.

The participant health workers' depression, anxiety, and stress levels were investigated. We found that 34.7% of the participants experienced moderate levels of anxiety, 38.4% of the participants exhibited normal levels of depression, and 62.4% of the participants experienced normal levels of stress (Table 4).

The average total scores obtained from the DASS-21 Scale, the depression subscale, and the stress subscale from those aged between 18 and 21 years (14.00±8.90) were found to be higher than those aged ≥26 years (11.92±4.52). The average scores on the CS-separation subscale differed in terms of age, gender, experience, and the department where they were employed. The average scores on the CS-separation subscale was detected to be higher in women (16.31±2.80). As the health workers' experience increased, the average scores on the CS-separation subscale decreased (15.83±3.25) (Table 5).

We found that the health workers' average scores on the CS-mindfulness subscale differed according to the department where they worked, and their average score on the CS-disengagement subscale differed according to their professional experience. In Table 5, the comparison

Table 1. Distribution of health workers in terms of socio-demographic characteristics (n=234)

Socio-demographic characteristics	n	%
Age		
18–21 years	4	1.7
22–25 years	65	27.8
≥26 years	165	70.5
Gender		
Female	197	84.2
Male	37	15.8
Educational status		
Medical vocational high school	20	8.6
Associate degree	19	8.1
Graduate degree	164	70.1
Master/doctorate degree	31	13.2
Marital status		
Married	131	56.0
Single	103	44.0
Number of children		
0	123	52.6
1–2 children	98	41.9
≥3 children	13	5.5
Employment duration		
1–5 years	106	45.3
6–10 years	41	17.5
≥11 years	87	37.2
Department where they worked		
Emergency room	67	28.6
Intensive care	32	13.7
Polyclinics	20	8.6
Service	53	22.6
Operation room/delivery room	27	11.5
Radiology	10	4.3
Others	25	10.7
Position at hospital		
Doctor/dentist	10	4.2
Hospital manager	3	1.3
Nurse/medical assistant	185	79.1
Technician/technical personnel	36	15.4

n: number.

Table 2. Distribution of health workers according to changes during the COVID-19 pandemic period (n=234)

Changes during COVID-19 Pandemics	n	%
Being in close and/or direct contact with COVID-19 diagnosed patients		
Yes	166	70.9
No	68	29.1
Physiological changes due to being in close and/or direct contact with COVID-19 diagnosed patients*		
Sleeplessness	79	33.8
Fatigue	98	41.9
Weakness	61	26.1
Lack of appetite	34	14.5
Increased appetite	11	4.7
Palpitation	30	12.8
Chest tightness	29	12.4
Pain	29	12.4
Sweating	61	26.1
Psychological changes due to being in close and/or direct contact with COVID-19 diagnosed patients COVID-19*		
Anxiety	132	56.4
Fear	101	43.2
Helplessness	36	15.4
Hopelessness	40	17.1
Depression	30	12.8
Worry	66	28.2
Stress	113	48.3
Feeling of security	36	15.4
Anger	33	14.1
Compassion	58	24.8
Social changes due to being in close and/or direct contact with COVID-19 diagnosed patients COVID-19*		
I understood and appreciated more and more that Social life is important.	126	53.8
Friendship and sincerity are valuable.	103	44.0
Team mentality is significant.	102	43.6
Nature is important.	109	46.6
Domestic and familial changes due to being in close and/or direct contact with COVID-19 diagnosed patients COVID-19*		
I feared that I may spread the disease to my family members.	150	64.1
Family members feared that I may get infected.	110	47.0
My love and passion for my family members increased.	98	41.9
I contacted my spouse and children only on phone calls.	21	9.0
I felt that family was important and valuable.	95	40.6
Spiritual changes due to being in close and/or direct contact with COVID-19 diagnosed patients COVID-19*		
I often prayed.	142	60.7
I read the Koran.	35	15.0
I often gave thanks.	121	51.7
I performed ritual prayers.	44	18.8
Changes in professional life due to being in close and/or direct contact with COVID-19 diagnosed patients COVID-19*		
I understood that my job is important.	80	34.2
I understood that good health is the most important thing in life.	138	59.0
I felt stronger in my job.	73	31.2
I felt weaker in my job.	20	8.6

*Percentages were calculated over "n" value since more than one option was selected.
COVID-19: coronavirus disease-2019, n: number.

of the health workers' scores between the DASS-21 and CS are shown in terms of some descriptive characteristics. There was a significant difference between the DASS-21 (depression and stress subscales) and sociodemographic characteristics (age), respectively (p=0.025; p=0.007). There was also a significant difference between the DASS-21 Scale total scores and age (p=0.035). As for CS, a statistically significant difference was found between the separation subscale and socio-demographic characteristics of age (p=0.000), professional experience (p=0.000) and the department they work in (p=0.086). In addition, while there was a positive and strong relationship between the CS-mindfulness subscale and the department they worked in (p=0.042), a significant difference (p=0.026) was found between the CS-separation subscale and professional experience. A statistically significant difference was found between gender and the CS-well-being subscale and the separation subscale (p=0.042; p=0.023) (Table 5).

When the health workers' DASS-21 and CS scores were assessed using correlation analysis, it was noted that there was a significant, negative, and strong correlation between the DASS-21-depression subscale and the CS-indifference, CS-separation and CS-disengagement subscales (p<0.01). A significant, negative, and strong correlation was found between the DASS-21 anxiety subscale and the CS-indifference, CS-separation, and CS-disengagement subscales (p<0.01). A significant, negative, and strong correlation was detected between the DASS-21 stress subscale and the CS-indifference, CS-separation, and CS-disengagement subscales (p<0.01) (Table 6).

DISCUSSION

When health workers are combatting global pandemics, they experience anxiety, fear/worry, stress, and depression. Psycho-physiological symptoms and post-traumatic stress symptoms are also seen during these periods. It is known that factors such as being isolated and being in contact with high risk/sick people are common causes of trauma; this trauma negatively affects the health workers' psychological health.[19]

Our study results revealed that the health workers' compassion levels were very high and they experienced depression, anxiety, and stress during the pandemic. In a study by Guo et al.[3] regarding the psychological effects of COVID-19 on health workers in China, it was identified that 4%–98% of the health workers had moderate to high levels of anxiety, 13%–47% of them had depression, and 10%–57% of them experienced recurrent worry/panic. In a study by Lai et al.[21], where psychologically correlated factors among 1257 health workers exposed to coronavirus were investigated, it was seen that the majority of the health workers suffered from depression (50.4%), anxiety (44.6%),

Table 3. Descriptive characteristics related to the DASS-21 and CS scores (n=234)

DASS-21 subscales	Min-max/n	X ± SD	Cronbach Alpha
Depression	7–28	12.39±4.88	0.86
Anxiety	7–28	12.09±5.28	0.90
Stress	7–28	13.79±5.63	0.92
DASS-21 Total	**21-84**	**38.28±13.95**	**0.94**
CA and subscales			
Kindness	4–20	16.18±3.69	0.89
Indifference	4–20	16.46±2.67	0.61
Common humanity	4–20	15.35±3.40	0.75
Separation	4–20	16.24±2.81	0.66
Mindfulness	4–20	16.24±3.52	0.84
Disengagement	4–20	16.76±2.58	0.58
CS total	**49–112**	**93.34±11.77**	**0.88**

Min: minimum, Max: maximum, X: arithmetic mean, SD: standard deviation, n: number.

Table 4. Distribution of health workers' depression, anxiety, and stress levels (n=234)

DASS-21						
	Depression		Anxiety		Stress	
Level	**n**	**%**	**n**	**%**	**n**	**%**
Normal	90	38.4	56	23.9	146	62.4
Mild	57	20.6	38	16.2	37	15.8
Moderate	73	31.3	81	34.7	40	17.1
High	12	8.8	32	13.6	11	4.7
Excessive	2	0.9	27	11.6	0	0.0

DASS-21: Depression, Anxiety and Stress Scale - 21 Items (DASS-21), n: number.

sleeplessness (34%), and distress (34.0%). A study by Tan et al.[27] aimed to understand the psychological effects of the COVID-19 pandemic on 470 health workers in Singapore using the DASS-21. They reported that the scores varied from 2.45 to 3.82. According to their results, 14.5% of these workers were anxious, 8.9% of them were depressed, 6.6% of them were stressed, and 7.7% of them suffered from clinical anxiety; doctors and nurses experienced depression, stress, and anxiety the most. It is known that the perceived risks associated with pandemics are dependent on the individuals' awareness and knowledge regarding pandemics.[3] In line with this study's results, we are of the opinion that poor access to psychological support, insufficient medical information, lack of knowledge regarding pandemics, low levels of personal protective measures, and poor education on infection control played a critical role in elevating the trauma level of clinical nurses. Consequently, we believe that it will be beneficial if health workers' stress, anxiety, and depression levels are determined; it will also assist health workers if people's awareness and knowledge regarding health workers' anxiety, depression, stress, and correlating factors are raised.

In the current study, we discovered that as the health workers' age increased, the level of their DASS-21-depression and stress subscales decreased. In previous studies carried out during pandemics, it was reported that stress levels are higher among younger health workers.[3,19] This is in line with the findings of our study. Therefore, we believe that younger health workers may experience higher levels of fear, anxiety, and stress because factors such as their family responsibilities may be more pressing; they may be afraid of spreading the disease to their spouses, children, or to those with whom they live. They may also experience higher levels of fear, anxiety, and stress because they may be professionally less experienced. Moreover, the long and arduous working-hours of health personnel during pandemic periods may make their immune systems vulnerable, and consequently, increase their anxiety and stress levels. Therefore, psychological intervention teams should be established in hospitals and other pandemic settings to support health workers. Health workers actively working in the field should be encouraged to receive help from these teams.

According to the relevant literature, there are results that indicate high compassion levels in health workers.[28,29] It is emphasized that health workers exhibiting high compassion levels are unable to maintain these levels for a long time. Compassion fatigue symptoms as well as physical, psychological, and social symptoms such as depression, anxiety, stress, headaches, anger, and discomfort may occur as a result.[10,28,30] Our results led us to conclude that the working conditions of our participants must have been arranged very well, as the participant health workers did not display compassion fatigue. Even when subjected to difficult and intense working conditions, they revealed high compassion levels. Measures taken for health workers by the Turkish government during this pandemic include the provision of protective equipment (gloves, masks, face shields, goggles, glasses, disinfectants, gowns), education aimed at maintaining social distance, health protocols, social isolation and facilities to achieve this (hostels, hotels, apartment accommodation), the rearrangement of working-hours, increased salaries, and assistance in maintaining domestic/familial communication. These measures also

Table 5. Comparison of health workers' scores obtained from DASS-21 and CS in terms of some descriptive characteristics

	DASS-21				CS subscales						
Variables	**Depression**	**Anxiety**	**Stress**	**DASS-21 total**	**Kindness**	**Indifference**	**Common humanity**	**Disengagement**	**Mindfulness**	**Separation**	**CS total**
Age											
18–21 years	14.00±8.90	16.75±7.45	19.25±2.87	50.00±14.89	18.50±1.73	16.50±2.51	17.25±2.21	15.50±2.38	18.00±2.30	15.75±3.50	99.25±9.94
22–25 years	13.47±5.33	11.92±5.23	14.89±6.41	40.29±14.98	16.06±3.76	16.58±2.59	15.47±3.46	16.72±2.80	15.64±3.55	17.15±2.59	93.93±12.59
≥26 years	11.92±4.52	12.05±5.23	13.22±5.23	37.20±13.36	16.17±3.69	16.41±2.72	15.26±3.40	16.07±2.81	15.81±3.52	16.63±2.55	92.96±11.50
Test statistics	0.190	0.511	0.082	0.213	0.244	0.623	0.367	0.903	0.455	0.349	0.769
*p***	**0.025**	0.523	**0.007 a>b>c**	**0.035**	0.708	0.685	0.382	**0.000**	0.785	0.386	0.341
	a>b>c			**a>b>c**				**b>c>a**			
Gender											
Female	12.63±5.04	12.14±5.40	13.96±5.72	38.74±14.30	16.39±3.55	16.43±2.74	15.47±3.35	16.31±2.80	15.98±3.43	16.78±2.65	93.85±11.37
Male	11.10±3.70	11.86±4.63	12.86±5.11	35.83±11.76	15.05±4.24	16.59±2.30	14.72±3.65	15.83±2.87	14.83±3.84	16.64±2.21	90.62±13.60
Test statistics	0.049	0.508	0.207	0.286	0.268	0.842	0.386	0.218	0.346	0.732	0.630
*p**	0.080	0.070	0.277	0.246	**0.042***	0.742	0.221	**0.023**	0.069	0.766	0.125
								a>b			
Professional experience											
1–5 years	12.89±5.17	12.46±5.32	14.66±6.07	40.01±14.33	16.04±3.69	16.55±2.68	15.43±3.36	16.54±2.54	15.72±3.57	17.03±2.52	93.83±12.15
6–10 years	11.63±4.13	11.85±4.73	12.90±4.60	36.39±11.56	16.85±2.88	16.56±2.43	15.75±2.73	16.29±2.41	16.36±2.53	17.29±2.07	95.97±9.19
≥11 years	12.13±4.82	11.77±5.50	13.14±5.42	37.05±14.39	16.03±4.01	16.29±2.79	15.08±3.73	15.85±3.25	15.63±3.85	16.18±2.78	91.50±12.21
Test statistics	0.629	0.956	0.101	0.734	0.014	0.676	0.037	0.107	0.001	0.154	0.035
*p***	0.264	0.360	0.058	0.132	0.977	0.514	0.496	**0.000**	0.890	**0.026**	0.193
								a>b>c		**b>a>c**	
Department where they worked											
Emergency room	12.39±4.88	13.62±5.88	15.28±5.70	42.77±14.69	16.34±3.56	16.80±2.13	15.85±2.97	16.55±2.64	16.17±3.24	16.58±2.75	94.41±11.72
Intensive care	12.56±4.58	11.56±4.68	13.37±5.41	37.50±13.31	16.71±2.95	16.50±2.72	15.09±2.92	15.68±3.45	15.93±2.68	17.15±2.37	94.41±11.72
Polyclinics	12.40±5.56	11.90±6.16	13.15±6.12	37.45±16.28	15.85±4.06	15.50±3.54	15.05±3.17	15.80±3.53	15.25±3.72	16.30±3.71	90.15±11.05
Clinics	11.40±4.45	11.73±4.68	13.49±4.62	36.71±11.86	15.81±3.75	16.67±2.57	14.81±3.62	15.96±2.65	15.09±3.91	16.90±2.21	92.39±12.80
Operation room	13.07±5.04	10.81±4.50	14.18±6.59	38.07±14.63	16.33±4.35	16.33±2.77	14.85±3.89	16.51±2.72	15.92±3.81	16.88±2.25	93.14±12.05
Radiology	10.56±4.02	11.04±4.89	11.48±5.10	33.08±12.07	16.50±3.71	16.80±2.09	16.30±2.79	17.00±1.82	16.40±3.30	17.01±1.91	95.60±9.46
Test statistics	0.650	0.183	0.123	0.957	0.284	0.026	0.927	0.188	0.290	0.394	0.194
*p***	0.504	0.800	0.964	0.876	0.070	0.888	0.105	**0.086**	**0.042**	0.658	0.105
								f>a>e>d>c>b	f>a>b>e>c>d		

*Independent t-test, **One-Way ANOVA test.
DASS-21: Depression, Anxiety and Stress Scale - 21 Items (DASS-21), CS: Compassion Scale, n: number.

Table 6. Correlation analyses of health workers' scores of DASS-21 and CS

Compassion Scale	DASS-21							
	Depression		Anxiety		Stress		DASS-21 total	
	r	p	r	p	r	p	r	p
Kindness	-0.009	0.894	0.061	0.351	0.018	0.790	-0.033	0.612
Indifference	-0.181	**0.005****	0.238	**0.000****	0.194	**0.003****	-0.232	**0.000****
Common humanity	-0.032	0.632	0.027	0.681	0.006	0.923	-0.024	0.717
Disengagement	-0.245	**0.000****	0.286	**0.000****	0.238	**0.000****	-0.290	0.000**
Mindfulness	-0.006	0.925	0.062	0.342	0.054	0.415	-0.047	0.470
Separation	-0.231	**0.000****	0.282	**0.000****	0.240	**0.000****	-0.284	0.000**
CS total	-0.056	0.391	0.125	0.055	0.078	0.234	-0.099	0.132

**p<0.01, significant values are shown in bold.
DASS-21: Depression, Anxiety and Stress Scale - 21 Items (DASS-21), CS: Compassion Scale, n: number.

included psychological support, guidance, and counseling against fear and anxiety.[8]

Education and training aimed at combatting compassion fatigue is essential to achieve high quality care in hospitals, to promote patient and employee satisfaction, to maintain professional commitment, and to enhance team collaboration. Similar to our results, a study by Polat and Erdem[28] investigating the correlation between compassion fatigue and the quality of life among health workers found a significant difference between compassion fatigue and the socio-demographic characteristics of age, gender, position, administrative function, employment duration, and the institution where the participants worked. The study by Kılıç et al.[29] regarding nurses also reported that CS scores were statistically significant and high among those who worked in the same department, were in the profession for 1–5 years, and those who thought of quitting the nursing profession. From these findings, we inferred that higher age, longer employment duration, and more experience may cause compassion fatigue. It was identified that a positive correlation existed between the CS-mindfulness subscale and the department where the health workers worked; a negative correlation was found between the CS-separation subscale and professional experience. Furthermore, a negative correlation existed between the CS-kindness and CS-disengagement subscale and gender. [29] The study by Kişmir and İrge[31] concurred with our study. Therefore, we concluded that the health workers who displayed high levels of awareness and consciousness, were pleased to work at their relevant departments, worked peacefully, and had high levels of empathy may suffer compassion fatigue if the current pandemic conditions continue.

Similar to our findings, Çınar and Aslan[32] argued that compassion driven behaviors produced positive health outcomes. There was a negative correlation for compassion with regards to depression and stress. It is essential to manage the factors which affect compassion levels so that professional burnout does not lead to undesired disorders such as anxiety, stress, and depression. The close correlation between compassion and well-being generates an expectation that compassionate people should show low levels of anxiety and stress. These results lead us to conclude that as health workers' stress, anxiety, and depression levels decrease, their indifference, disengagement, and separation issues increase.

Healthcare workers were found to exhibit high levels of affection, moderate depression, and suffer from anxiety and stress. The constant empathy of healthcare professionals for the trauma, pain, stress, anxiety, and depression of their patients resulted in compassion fatigue. In order to increase the quality of care and professional satisfaction of healthcare professionals, it is necessary to protect their physical and psychological health and to prevent compassion fatigue. Therefore, there is a clear need for ancillary clinical and political strategies to be planned to support healthcare professionals throughout the COVID-19 pandemic. The necessary education, training and psychological support should be given to alleviate their anxiety and stress; this will also improve their health physically, psychologically and socially.

Implications for Nursing Practice

This study discussed the depression, anxiety, stress and compassion levels of health workers who work closely with COVID-19 patients in Turkey. According to our findings, these health workers exhibited depression, anxiety, stress and showed high levels of compassion. In light of these results, (i) health workers who risk their lives to the detriment of their health at clinics during pandemics should be supported physically, psychologically and; (ii) their stress, anxiety, depression and compassion levels should be periodically assessed and any necessary precautions should be taken; (iii) the difficulties, stress, anxiety, and worry that health workers face during pandemics should be evaluated so that they can be supported by psychological support experts; (iv) all necessary protective measures and equipment must be provided to health workers who are a high risk group during the pandemic period in our country; and education and training via mass media should be held.

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MAIN POINTS

- Healthcare professionals are among the occupational groups that experienced the most difficulties during the COVID-19 pandemic.
- Healthcare workers experience anxiety, depression and stress during the pandemic.
- During the pandemic, it could be seen that the healthcare workers' compassion levels are quite high, but if precautions are not taken, it may cause compassion fatigue.

ETHICS

Ethics Committee Approval: Ethics committee approval was obtained from the Medicine Faculty Non-Interventional Ethics Council of Selçuk University (protocol number: 2020/255) and Scientific Research Platform of Ministry of Health of Turkey (protocol number: 2020-05-07T11_53_50).

Informed Consent: Informed consent was obtained after it was explained that participation was voluntary.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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DISCLOSURES

Conflict of Interest: The authors have no conflicts of interest to declare.

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REFERENCES

1. Tang L, Pan L, Yuan L, Zha L. Prevalence and related factors of post-traumatic stress disorder among medical staff members exposed to H7N9 patients. Int J Nurs Sci. 2016; 4(1): 63-7.
2. Paladino L, Sharpe RP, Galwankar SC, Sholevar F, Marchionni C, Papadimos TJ, et al. American college of academic international medicine (ACAIM). Reflections on the ebola public health emergency of international concern, Part 2: The unseen epidemic of posttraumatic stress among health-care personnel and survivors of the 2014-2016 ebola outbreak. J Glob Infect Dis. 2017; 9(2): 45-50.
3. Guo J, Liao L, Wang B, Li X, Guo L, Tong Z, et al. Psychological effects of COVID-19 on hospital staff: A national cross-sectional survey of China mainland. The Lancet Psychiatry. 2020; 1-20.
4. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020; 323(11): 1061-9.
5. Wang J, Wang Z. Strengths, weaknesses, opportunities and threats (swot) analysis of China's prevention and control strategy for the COVID-19 epidemic. Int J Environ Res Public Health. 2020; 17(7): 2235.
6. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, et al. Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin. bioRxiv. 2020.
7. World Health Organizations (WHO) announces COVID-19 outbreak a pandemic. (2020). Available from: URL: http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic. (Accessed on March 22, 2021)
8. Republic of Turkey Ministry of Health. Available from: URL: https://covid19bilgi.saglik.gov.tr/tr/. (Accessed on March 22, 2021)
9. Tuncay EF, Koyuncu E, Özel Ş. A revıew of protective and risk factors affecting health of health workers in pandemics. Ankara Med J. 2020; (2):488-501.
10. Sorenson C, Bolick B, Wright K, Hamilton R. Understanding compassion fatigue in healthcare providers: A review of current literature. J Nurs Scholarsh. 2016; 48(5): 456–65.
11. Cabello RI, Meneses-Echaves JF, Serrano-Ripoll MJ, Fraile-Navarro D, Roque MAF, Moreno GP, et al. Impact of viral epidemic outbreaks on mental health of healthcare workers: A rapid systematic review. [Preprint] (BMJ). 2020. DOI: doi.org/10.1101/2020.04.02.20048892
12. Kavaklı M, Ak M, Uğuz F, Türkmen OO. The mediating role of self-compassion in the relationship between perceived COVID-19 threat and death anxiety. Turkish J Clinical Psychatry. 2020; 23 (Supp 1): 15-23.
13. Huang Y, Zhao N. Generalized anxiety disorder, depressive symptoms and sleep quality during COVID-19 outbreak in China: a web-based cross-sectional survey. Psychiatry Res. 2020; 288: 112954.
14. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel corona virus infected pneumonia. N Engl J Med. 2020; 382(13): 1199-207.
15. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. N Engl J Med. 2020; 382(10): 970-1.
16. Wang W, Tang J, Wei F. Updated understanding of the out break of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. J Med Virol. 2020; 92(4): 441-7.
17. Sethi BA, Sethi A, Ali S, Aamir HS. Impact of coronavirus disease (COVID-19) pandemic on health professionals. Pak J Med Sci. 2020; 36(COVID19-S4): S6-11.
18. Ornell F, Halpern SC, Kessler FHP, Narvaez JCM. The impact of the COVID-19 pandemic on the mental health of healthcare professionals. Cad Saude Publica. 2020; 36(4): e00063520.
19. Kang L, Li Y, Hu S, Chen M, Yang C, Yang BX, et al. The mental health of medical workers in Wuhan, China dealing with the 2019 novel coronavirus. Lancet Psychiatry. 2020; 7(3): e14.
20. Ramaci T, Barattucci M, Ledda C, Rapisarda V. Social stigma during COVID-19 and its impact on HCWs outcomes. Sustainability. 2020; 12(19): 3834.
21. Lai J, Ma S, Wang Y, Cai Z, Hu J, Wei N, et al. Factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019. JAMA Netw Open. 2020; 3(3): e203976.
22. Lovibond PF, Lovibond SH. The structure of negative emotional states: comparison of the depression anxiety stress scales (DASS) with the beck depression and anxiety inventories. Behav Res Ther. 1995; 33(3): 335-43.
23. Henry JD, Crawford JR. The short-form version of the depression anxiety stress scales (DASS- 21): construct validity and normative data in a large non-clinical sample. Br J Clin Psychol. 2005; 44(Pt 2): 227-39.
24. Yılmaz Ö, Boz H, Arslan A. The Validity and reliability of depressıon stress and anxıety scale (DASS21). Research of Financial Economic and Social Studies. 2017; 2(2): 78-91.
25. Pommier EA. The compassion scale. Dissertation abstracts international section A. Humanities and Social Sciences. 2010; 72: 1174.
26. Akdeniz S, Deniz Engin M. The Turkish adaptation of the Compassion Scale: A validity and reliability study. The Journal of Happiness and Well-Being. 2016; 4(1): 50-61.
27. Tan BYQ, Chew NWS, Lee GKH, Jing M, Goh Y, Yeo LLL, Zhang K, et al. Psychological Impact of the COVID-19 Pandemic on Health Care Workers in Singapore. Ann Intern Med. 2020; 173(4): 317-20.
28. Polat FN, Erdem R. The relationship between the level of compassion fatigue and quality of professıonal life: The case of medical professionals, masters's thesıs. Journal of Süleyman Demirel University Institute of Social Sciences. 2017; 1(26): 291-312.
29. Kılıç D, Bakan BA, Aslan G, Uçar F. An ınvestigation of the relationship between ethical sensitivity and compassion fatigue in nurses working

in oncology units and intensive care units. Journal of Adnan Menderes University Health Sciences Faculty. 2020; 4(1): 20-9.

30. Dikmen Y, Aydın Y. Compassion tiredness in nurses: what? how? what to do? J Hum Rhythm. 2016; 2(1):13-21.

31. Kişmir Ş, İrge NT. The ımpact of compassion fatigue level on employees motivation and job satisfaction: An Application on Non-Physician Healthcare Workers and A Public-Private Hospital Comparison. Research Studies Anatolia Journal. 2020; 3(1): 1-18.

32. Çınar F, Aslan EF. Measuring the compassion levels of operating theater nurses: Turkish validity and reliability research. Kocaeli Med J. 2018; 7(3): 222-9.

ORIGINAL ARTICLE

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Factors in Relation with in-Hospital Mortality in Geriatric Patients with COVID-19

Emine Emektar[1], Filiz Koç[2], Emine Fırat Göktaş[2], Seda Dağar[1], Hüseyin Uzunosmanoğlu[1]

[1]Keçiören Training and Research Hospital, Department of Emergency Medicine, Ankara, Turkey
[2]Keçiören Training and Research Hospital, Department of Infectious diseases, Ankara, Turkey

Abstract

BACKGROUND/AIMS: The World Health Organization has designated a severe acute respiratory syndrome as coronavirus-2 (SARS-CoV-2) infection. It is caused by a new coronavirus novel coronavirus disease-2019 (COVID-19), which was initially diagnosed in December, 2019 in Wuhan, China. SARS-CoV-2 infection particularly affects the geriatric age group, with a more severe progress rate of the disease. This study aimed to define the clinical characteristics of geriatric individuals with COVID-19 and investigate the in-hospital mortality rate and its predictors.

MATERIALS AND METHODS: This was a descriptive and retrospective research. This research covered all individuals over the age of 60 who were admitted to hospital with a COVID-19 diagnosis. The demographics, physical examination findings, vital signs, hospital outcomes, comorbidities, and laboratory results of these patients were assessed. The main results were the discovery of the hospital mortality rate and its determinants.

RESULTS: A total of 168 elderly individuals with positive polymerase chain reaction (PCR) test findings were included in this research. 51.8 percent of the patients were female, with a median age of 67 years. The patients in our research had an in-hospital death rate of 10.7%. We found that high troponin and fibrinogen and low oxygen saturation at the time of admission had a negative effect on survival.

CONCLUSION: High troponin and fibrinogen levels, as well as low oxygen saturation levels at the time of admission, were found to be the most important predictors of in-hospital death in elderly COVID-19 patients according to our study results. We believe that it would be beneficial to monitor other parameters not only at the time of admission, but also during the hospitalization period of the patients.

Keywords: COVID-19, geriatric, mortality

INTRODUCTION

The World Health Organization (WHO) dubbed novel coronavirus disease-2019 (COVID-19), which causes a severe acute respiratory syndrome, as coronavirus 2 (SARS-CoV-2) infection. It was first diagnosed in Wuhan, China, in December 2019. Shortness of breath, myalgia, tiredness, dry cough, and fever are the primary clinical signs of this disease, which is extremely infectious. COVID-19 spread swiftly throughout China and other nations around the world since the first recorded case in Wuhan, China, in late 2019 [1,2]. The WHO labeled it as a pandemic on March 11, 2020, after a number of people died as a result of it.[1,2]

SARS-CoV-2 infection particularly touches the geriatric age group, who experience a more serious progress of the disease.[3,4] Early statistical data from China regarding the case-mortality rates of patients aged >60 years indicated that the rate was 3.6% in patients aged 60–69 years, 8% in patients aged 70–79 years, and 14.8% in individuals aged >80 years, which shows that the elderly are more vulnerable to COVID-19.[5] To the best of our knowledge, there have been few studies in the literature that have focused on the clinical features of senior COVID-19 patients, and their risk factors for death are still being investigated. Studies conducted by Chinese researchers on geriatric patients have shown that dyspnea

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ORCID IDs of the authors: E.E. 0000-0002-6056- 4401; F.K. 0000-0001-9469-1153; E.F.G. 0000-0003-0453-829X; S.D. 0000-0002-7874-382X; H.U. 0000-0002-4370-1283.

Address for Correspondence: Emine Emektar
E-mail: emineakinci@yahoo.com
ORCID ID: orcid.org/0000-0002-6056- 4401

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at presentation, complications, including acute respiratory distress syndrome (ARDS), and comorbidities, including chronic obstructive pulmonary disease and cardiovascular disease, are some of the factors that result in poor outcomes.[6,7]

There are limited studies on this subject in Turkey. This study intended to identify the clinical features of geriatric patients who have COVID-19 and explore the in-hospital mortality rate and its predictors.

MATERIALS AND METHODS

This descriptive retrospective research was carried out in a tertiary-care training and research hospital. The study protocol was approved by the local ethics committee before implementation (no: 2012-KAEK-15/2149, date: 22/07/2020).

Study Population

Included in the study were hospitalized patients aged ≥60 years who had positive results from a polymerase chain reaction (PCR) test between March 21, 2020 and July 1, 2020. Since the first case of COVID-19 in Turkey, our hospital has conducted the hospitalization, examination, and treatment of patients in accordance with the Ministry of Health's national COVID-19 standards.[8] Patients with incomplete data and those with negative PCR test results who were followed up with a pre-diagnosis of COVID-19 were excluded from this study. The required laboratory tests [ferritin, fibrinogen, D-dimer, partial thromboplastin time (PTT), prothrombin time (PT), erythrocyte sedimentation rate, C-reactive protein (CRP), routine biochemical tests, and complete blood count) and imaging tests (posterior-anterior chest radiography and/or low-dose chest computed tomography without contrast] were performed based on the results of physical examinations.

Reverse transcriptase PCR (RT-PCR) testing on nasopharyngeal swabs using techniques approved by Turkey's reference network of SARS-CoV-2 confirmed the diagnosis of COVID-19. The hospital outcomes, the patients' physical examination findings, vital signs, length of hospitalization, complaints at admission, demographic data, comorbidities, and their laboratory results were obtained from the hospital management system and patient files using retrospective scanning. The patients were also divided into two groups based on their in-hospital mortality: those who survived (survivors) and those who did not survive (non-survivors). The impact of the factors that were statistically significant in univariate analysis on mortality were investigated using multivariate logistic regression analysis.

Statistical Analysis

The data analysis was performed using IBM SPSS 20.0 (IBM Corp., Chicago, IL, USA) statistical software. The normal distribution of discrete and continuous numerical variables was investigated using the Kolmogorov–Smirnov test. Descriptive statistics are presented as medians and interquartile ranges (IQR: 25–75) for discrete and continuous numerical variables and as case numbers and percentages (%) for categorical variables. The categorical and continuous variables were evaluated using the Chi-square and Mann–Whitney U tests, respectively. Univariate tests were used to assess mortality predictors, and variables that were statistically significant ($p \leq 0.2$) were included in the regression model of multivariate logistic. The correlation of those parameters that were significant in univariate tests was evaluated using the Spearman correlation test. Multivariate regression pattern fit was evaluated using the Hosmer–Lemeshow test. In addition, $p<0.05$ was considered statistically significant.

RESULTS

This research included 168 geriatric individuals who had positive PCR test results. The median age of these patients was 67 years, and 51.8 percent of them were female. The most common comorbidity was hypertension (60.1%). The most common complaint was cough and/or sputum (49.4%), and 85.7% of patients had pneumonia. The average stay in the hospital was ten days. Tables 1 and 2 show the patients' demographics and laboratory results, respectively.

When the patients' characteristics were compared according to in-hospital mortality (non-survivor/survivor), there were statistically significant differences regarding age, hypertension, heart rate, oxygen saturation, and dyspnea ($p<0.05$ for all) (Table 3). Furthermore, a comparison of the laboratory results of the survivors and non-survivors showed that the values for CRP, ferritin, D-dimer, fibrinogen, PT, urea, aspartate transaminase (AST), and troponin were higher in the non-survivors ($p<0.05$ for all values) (Table 4).

The effects of the factors in Tables 3 and 4 on mortality were investigated using multivariate logistic regression analysis, in addition to the other variables. As there was a correlation of the values for urea, creatinine, D-dimer, fibrinogen, and heart rate with body temperature, the model did not contain the PTT and PT values of all patients. The multivariate model included hypertension, body temperature, oxygen saturation, troponin, AST, urea, fibrinogen, and CRP data, as well as age and gender, with $p \leq 0.2$ from Table 3. After the Hosmer–Lemeshow test was used to determine if the model was a good fit, it was discovered that high troponin and fibrinogen levels, as well as low oxygen saturation at the time of admission, had unfavorable effects on survival (Table 5).

DISCUSSION

In this research, which investigated the factors affecting geriatric COVID-19 patients and their in-hospital mortality, two important results were found. First, the in-hospital mortality rate of the study's patients was 10.7%, and those who did not survive were older, more frequently referred to the hospital due to dyspnea, and had low oxygen saturation and higher CRP, ferritin, D-dimer, fibrinogen, PT, urea, AST, and troponin values. Second, the most prominent predictors of in-hospital mortality in geriatric COVID-19 patients were high troponin and fibrinogen and low oxygen saturation at admission.

COVID-19 has a particularly negative impact on the aged population in terms of illness prevalence, severity, and death rates. In studies of hospitalized COVID-19 patients in all age groups, the median age ranged from 49 to 56 years.[9-11] A study conducted in China reported that the rates of hospitalization due to COVID-19 diagnosis increased with age.[12] Old age is also linked to a higher risk of death.[5,13], and studies in China and Italy have shown that mortality increases as age increases.[5,14] In our study, the median age of patients who did not survive was higher, similar to results in the literature, but there was no gender difference. This higher median age may have been a result of the curfew restriction applied to the elderly in Turkey for the majority of the study period.

One of the mechanisms explaining the high incidence seen in elderly COVID-19 patients may be increased viral shedding. As older patients have higher peak viral loads, they are more likely to spread the virus.

Table 1. Socio-demographic data of patients (n=168)	
Age, years, median (IQR: 25–75)	**67 (63–73)**
Sex, n (%)	
Female	87 (51.8%)
Male	81 (48.5%)
Current smoker, n (%)	20 (11.9%)
Comorbidity, n (%)	
Hypertension	101 (60.1%)
Diabetes mellitus	79 (47%)
Congestive heart failure/coronary artery disease	30 (17.9%)
Chronic lung disease	23 (13.7%)
Malignancy	7 (4.2%)
Chronic renal disease	11 (6.5%)
Other diseases	41 (24.14%)
Vital signs, median (IQR: 25–75)	
Respiratory rate	15 (14–18)
Saturation	92 (90–95)
Pulse	80 (73.2–88)
Fever (temperature)	37.2 (36.5–38.0)
***Complaints of patients, n (%)**	
Without complaint	23 (13.7%)
Cough/sputum	83 (49.4%)
Fever	73 (43.5%)
Dyspnea	48 (28.6%)
Myalgia/fatigue	73 (43.5)
Sore throat	18 (10.7%)
Diarrhea	9 (5.4%)
Nausea or vomiting	15 (8.9%)
Headache	13 (7.7%)
Anosmia	8 (4.8%)
Pneumonia severity, n (%)	
Without pneumonia	24 (14.3%)
Mild	96 (57.1%)
Moderate/severe	48 (28.6%)
Bilateral infiltration in thorax CT, n (%)	72 (42.9%)
Day from disease onset to hospital admission, median (IQR: 25–75)	2 (1–4)
Treatment, n (%)	
Nasal oxygen	50 (29.8%)
High flow oxygen	20 (11.9%)
Non-invasive ventilation	17 (10.1%)
Invasive ventilation	20 (11.9%)
Medical treatments, n (%)	
Chloroquine	168 (100%)
Azithromycin	72 (42.9%)
Favipravir	65 (38.7%)
Oseltamivir	27 (16.1%)
Immune plasma	14 (8.3%)
Enoxaparin treatment dose	53(31.5%)
Enoxaparin prophylaxis	102 (60.7%)
Antibiotics	53 (31.5%)
Plasma	14 (8.3%)
Tocilizumab	8 (4.8%)
Prognosis	
Healed and discharged	150 (89.3%)
Death	18 (10.7%)
Intensive care unit, n (%)	32 (19%)
Length of stay of ICU, median (IQR: 25–75)	7.5 (4–26.7)
Length of stay of hospital, median (IQR: 25–75)	10 (7–13)

*Some patients may have had more than one complaint.
IQR: interquartile range, CT: computed tomography, ICU: intensive care unit, n: number.

Table 2. Laboratory results of all geriatric patients	
Parameters, median (IQR: 25–75)	
Hemoglobin	13.5 (12.6–14.4)
White blood cell	6000 (4700–7350)
Neutrophil	3795(268–5252)
Lymphocyte	1315 (980–1857.5)
Platelet	192 (160.2–239.7)
Neutrophil lymphocyte ratio	2.94 (1.89–4.89)
Platelet lymphocyte ratio	147.5 (103.1–209.9)
C-reactive protein	17.6 (7.6–49.50)
Sedimentation	37 (23–55)
Ferritin	165.8 (81.3–299.2)
D-dimer	550 (390–1020)
Fibrinogen	165.8 (81.3–301.9)
Prothrombin time	11.3 (10.5–11.9)
Partial thromboplastin time	24 (21.7–27.1)
Urea	36.4 (27.8–44.3)
Creatinine	0.97 (0.83–1.13)
Aspartate aminotransferase	27.5 (19–36)
Alanine aminotransferase	21 (15–31.7)
Lactate dehydrogenase	233 (198–279)
Troponin	6.05 (3.82–15.24)

IQR: interquartile range.

The cause of increased viral loads in the elderly is not entirely clear, but it may be the result of the effects of aging on both airway patency and the immune system.[15]

Cough, fever, and dyspnea were the most prevalent symptoms in the research, in that order. The novel coronavirus is mostly responsible for lung infections. Reduced airway clearance, lung reserve, and defensive barriers, as well as muscle atrophy, produce changes in the physiological activities of the respiratory system in the aged.[3] Lung infections were more prevalent in COVID-19-infected senior individuals than in young patients, and the disease had a more severe course in geriatric patients. In our study, 85.7% of the patients showed relevant findings on thorax imaging, and 28.6% had moderate-to-severe pneumonia. In addition, those patients who did not survive presented with lower oxygen saturation levels, which can be a predictor of mortality.

Biochemical monitoring of COVID-19 patients using *in vitro* diagnostic tests is imperative for assessing the diagnosis, progression, and severity of the disease and for monitoring its treatment. The human angiotensin-

Table 3. A comparison of the patient characteristics regarding in hospital mortality (survivor/non-survivor)			
	Survivor (n=150)	**Dead (n=18)**	**p-value**
Age, years, median (IQR: 25–75)	67 (62–72)	72 (68–81.5)	0.005
Sex, n (%)			
Male	71 (47.3%)	10 (55.6%)	0.509
Female	79 (52.7%)	8 (44.4%)	
Comorbidity, n (%)			
Hypertension	86 (57.3%)	15 (83.3%)	0.033
Diabetes mellitus	69 (46%)	10 (55.6%)	0.443
Congestive heart failure/coronary artery disease	26 (17.3%)	4 (22.2%)	0.533*
Chronic lung disease	20 (13.3%)	3 (16.7%)	0.717*
Chronic renal disease	8 (5.3%)	3 (16.7%)	0.099
Vital signs, median (IQR: 25–75)			
Pulse	84.5 (72–95.2)	95 (79.5–98)	0.012
Saturation	93 (90–95)	88.5 (85–92)	<0.001
Fever (temperature)	37.1 (36.5–38)	37.9 (37.1-38.2)	0.071
Complaint of patients', n (%)			
Fever	63 (42%)	10 (55.6%)	0.273
Cough/sputum	72 (48%)	11 (61.1%)	0.293
Dyspnea	38 (25.3%)	10 (55.6%)	0.007
Fatigue /myalgia	65 (43.3%)	8 (44.4%)	0.928
Diarrhea	8 (5.3%)	1 (5.6%)	0.968*
Presence of pneumonia, n (%)	127 (84.7%)	17 (94.4%)	0.475
Bilateral infiltration in thorax CT, n (%)	65 (43.3%)	7 (38.9%)	0.719
Day from disease onset to hospital admission, median (IQR: 25–75)	2 (1–3)	3 (1–5)	0.376

*Fisher exact test.
IQR: interquartile range, CT: computed tomography, n: number.

Table 4. Comparisons of laboratory findings			
	Survivor (n=150)	**Dead (n=18)**	**p-value**
Hemoglobin	13.5 (12.6–14.4)	13.7 (12.3–14.4)	0.994
White blood cell	6000 (4700–7200)	6300 (4625–10,350)	0.547
Neutrophil	3765 (2715–5132)	4000 (2370–8077.5)	0.462
Lymphocyte	1335 (980–1812.5)	1245 (932.5–2027)	0.843
Platelet	192.5 (163–239.2)	173(132–254.7)	0.433
Neutrophil lymphocyte ratio	2.81 (1.81–4.58)	3.5 (2.01–7.06)	0.204
Platelet lymphocyte ratio	150.2 (103.8–210)	134 (82.6–200)	0.214
C-reactive protein	16.1 (7.06–35.4)	74.9 (29.6–173.1)	<0.01
Sedimentation	37 (23–54)	45 (24–63.2)	0.531
Ferritin	160 (77.6–272.3)	295 (100.3-576.2)	0.020
D-dimer	520 (390–942.5)	1045 (505–2350)	0.005
Fibrinogen	160 (77.6–272.3)	295.7 (100.3–576.2)	0.030
Prothrombin time	11.2 (10.5–11.9)	11.8 (11.3–12.9)	0.005
Partial thromboplastin time	23.8 (21.8–26.3)	26.3 (21.3–34.2)	0.099
Urea	36.4 (27.8–42.8)	41.7 (33.6–83.8)	0.013
Creatinine	0.97 (0.82–1.12)	1.05 (0.89–1.55)	0.133
Aspartate aminotransferase	26 (134.2)	38 (24.2–69.2)	0,012
Alanine aminotransferase	20 (15–31)	23.5 (14.7–41.7)	0.322
Lactate dehydrogenase	228 (198–277.5)	243 (201.7–394.2)	0.312
Troponin	5.99 (3.51–11.9)	24.6 (5.2–76)	0.001

n: number.

converting enzyme 2 (ACE2) cell surface receptor is bound by this new coronavirus. Although the disease mainly affects the lower respiratory tract, the virus can also bind to other organs. High ACE2 expression has been detected in bladder urothelial cells, the ileum and esophageal epithelium, kidney proximal tubule cells, myocardial cells, and type II alveolar cells, indicating that these organs and tissues are targets of SARS-CoV-2.[16,17] Our study found that patients who did not survive had higher levels of urea, and those with chronic kidney disease also had a higher mortality rate. Studies have shown that the blood urea nitrogen and creatinine levels in patients who were followed up due to COVID-19 infection were generally high, and their glomerular filtration rates were <60 mL/min/1.73 m^2. During the patients' hospitalizations, proteinuria and hematuria were also observed, as was increased creatinine.[18] Hence, the kidney functions of COVID-19 patients may be affected, primarily by the presence of an existing disease or multi-organ dysfunction.

It is believed that SARS-CoV-2 can infect the liver bile duct endothelial cells and result in inflammatory damage to the liver. Studies have shown a general increase in liver enzymes. However, it was found that there is no direct relationship between the increase in enzymes and the disease's severity. Although the cause of liver damage in COVID-19 is not fully understood, it is suggested that the elevation in liver enzymes is caused by cytokine storm syndrome and drug-induced liver damage.[19] CRP is an acute phase reactant which is synthesized in the liver and increases during inflammation due to infection or tissue damage. In the vast majority of COVID-19 patients, it was found to be high, and it is associated with the disease's severity.[17,20] It is also believed to be an early marker for sepsis and mortality. A retrospective study by Luo et al.[20] suggested that CRP levels, particularly at the time of admission, may be important in grading disease severity. Although those patients in our study who did not survive had elevated AST and CRP levels, no significant results were achieved in the model we established. We believe that the changes in these acute phase reactants during follow-up, rather than their levels at presentation, may be significant for mortality.

Ferritin, a protein involved in iron storage, increases in COVID-19 as a result of the activation of macrophages and hepatocytes. The stimulation of macrophages and hepatocytes causes ferritin, a protein implicated in iron storage, to rise in COVID-19. High blood ferritin levels and a life-threatening hyper-inflammation maintained by a cytokine storm define COVID-19 hyperferritinemic syndromes and systemic inflammatory response, which finally results in multi-organ failure.[21] In a study of patients hospitalized due to COVID-19, the level of ferritin in the blood was shown to be associated with the severity of the condition.[22] Our study also found higher ferritin levels in those patients who did not survive. Also, the troponin levels of the patients who did not survive were elevated at the time of hospital admission; this was another mortality predictor, as the regression model demonstrates.

COVID-19 can cause serious inflammatory events which can increase thrombosis and myocardial infarction. In elderly individuals with COVID-19 pneumonia, cardiac problems such as myocardial infarction, arrhythmia, and/or worsening/novel heart failure are prevalent.[22,23]

COVID-19 individuals have been shown to have a coagulation problem predisposition. Hence, coagulation tests are important in diagnosing and evaluating disseminated intravascular coagulation (DIC), which is a serious complication in COVID-19 patients. The levels of PT, fibrinogen, and D-dimer are the prominent markers linked to disease severity. It was observed that levels of fibrinogen and D-dimer are significantly higher in geriatric intensive care patients and patients with severe pneumonia.[17,23] In our study, those patients who did not survive had higher PT, D-dimer, and fibrinogen levels at the time of admission than those who survived. A study of 225 patients reported that 6.4% of those who did not survive had elevated DIC and fibrinogen levels.[24] As a statistically significant positive correlation was observed between fibrinogen and D-dimer in our study model, when only fibrinogen was included in the mortality model, a high level of fibrinogen at the time of admission was shown to be another mortality predictor. The literature emphasizes the importance in hospitalized patients of sequential follow-up of D-dimer levels, rather than the D-dimer value at the time of admission. In a review published by Mucha et al.[25] D-dimer, fibrinogen, PT, and PTT follow-up were recommended every 48 hours for venous thromboembolism (VTE) prophylaxis in patients hospitalized due to COVID-19. Furthermore, they recommended a VTE ultrasound in individuals with level of D-dimer ≥3.0 µg/mL.

Table 5. Multivariate regression model to predict 28-day mortality

	Wald	p-value	Odds ratio	(95% CI)
Age	3.448	0.063	1.106	0.99–1.23
Gender	1.419	0.234	0.362	0.07–1.92
Hypertension	0.015	0.903	1.117	0.18–6.62
Temperature	0.396	0.529	0.972	0.89–1.06
Saturation	9.756	0.002	0.612	0.45–0.83
Troponin	5.044	0.025	1.012	1.01–1.02
Aspartate aminotransferase	2.326	0.127	1.021	0.99–1.04
Urea	0.728	0.393	1.01	0.98–1.03
Fibrinogen	6.251	0.012	1.008	1.02–1.03
C-reactive protein	0.015	0.901	0.999	0.98–1.01

CI: confidence interval.

Chronic diseases in the elderly are a common problem in the field of global public health. Dai et al.[26] showed that the older patients with COVID-19 exhibited a relatively higher proportion of comorbidities than non-elderly patients. Compared with geriatric patients with a single disease, the hospitalization rates and fatality rates of patients with comorbidities are higher, and the clinical prognosis is significantly poorer.[27] D-dimer and fibrinogen can be influenced by other clinical conditions associated with additional fibrin formation, including old age, malignancies and infections. In our study, D-dimer and fibrinogen levels may have increased due to both COVID-19 disease and other accompanying comorbid diseases.

Although COVID-19 does not yet have a particular medication, studies are ongoing. Various therapies are being used to treat the disease. Since the first case in Turkey, guidelines and treatment regimens have been recommended by the Ministry of Health.[8] Patients in our hospital receive standard treatment in accordance with the ministry's guidelines. We believe that the application of these standard treatments had no effect on mortality. In our research, elevated troponin levels reflected myocardial injury in the COVID-19 patients. Due to fibrinogen's negative effects on atherogenesis, inflammation, platelet activity, coagulation, and plasma viscosity, high fibrinogen levels may increase cardiovascular risk.[28] Although the regulation of anticoagulant cure in patients with COVID-19 was made according to the D-dimer levels of the patients at the time we conducted our study in our country, these treatments can be started earlier and closely monitored, especially in elderly patients

with high fibrinogen and troponin levels. It was determined that seriously sick older individuals with COVID-19 who received early HFNC had a better prognosis than those who received HFNC later.[29] Similarly, we suggest that non-invasive or invasive oxygen treatment could be considered early in this disease process.

There are certain limitations to our research. Firstly, because of the study's retrospective format, all laboratory tests, including those for interleukin 6 (IL-6), IL-2, IL-10, and interferon levels, had not been performed in all of the patients. Therefore, the roles of those tests in predicting in-hospital mortality could not be investigated. Secondly, the patients' laboratory test results during their hospitalizations were not examined. Thirdly, because of the Ministry of Health guidelines for COVID-19, there were slight differences in the processes regarding the hospitalization, examination, and treatment of the patients over the course of the pandemic. During the period just after the first case was detected, patients were hospitalized and followed up even if they were asymptomatic; however, the indications for hospitalization were changed during the following periods, which may have caused a difference in our results. We did not investigate the background characteristics of the patients or the features of the disease. The baseline characteristics and co-morbidities of the patients when they were admitted to the hospital may have influenced the course of the disease. Also, since our study is a descriptive study, our results may include some bias due to the lack of statistical testing.

This study investigated the factors affecting geriatric COVID-19 patients and their in-hospital mortality. The rate of mortality for geriatric COVID-19 patients was found to be 10.7%. In addition, laboratory tests were especially important for monitoring the recovery rates, severity, mortality, and treatment of COVID-19 patients. Those patients who did not survive tended to be older, have numerous pneumonia symptoms, and show higher levels of CRP, ferritin, D-dimer, fibrinogen, PT, urea, AST, and troponin. The most prominent predictors for in-hospital mortality in geriatric COVID-19 individuals were high troponin and fibrinogen and low oxygen saturation levels at the beginning of hospitalization. We believe that it would be beneficial to monitor other parameters during the patients' hospitalization periods rather than only at the beginning of hospitalization.

CONCLUSION

This study investigated the factors affecting geriatric COVID-19 patients and their in-hospital mortality. The rate of mortality for geriatric COVID-19 patients was found to be 10.7%. In addition, laboratory tests were especially important for monitoring the recovery rates, severity, mortality, and treatment of COVID-19 patients. Those patients who did not survive tended to be older, have numerous pneumonia symptoms, and show higher levels of CRP, ferritin, D-dimer, fibrinogen, PT, urea, AST, and troponin. The most prominent predictors for in-hospital mortality in geriatric COVID-19 individuals were high troponin and fibrinogen and low oxygen saturation levels at the beginning of hospitalization. We believe that it would be beneficial to monitor other parameters during the patients' hospitalization periods rather than only at the beginning of hospitalization.

MAIN POINTS

- COVID-19 particularly affects the geriatric age group who experience a more severe course of the disease.
- The in-hospital mortality rate of the study's patients was 10.7% for COVID-19 geriatric patients.
- High troponin and fibrinogen levels, as well as poor oxygen saturation upon admission, were the most important predictors of in-hospital death in elderly COVID-19 patients.

ETHICS

Ethics Committee Approval: Ethics committee approval for this study was obtained from Ankara Keçiören Training and Research Hospital Ethics Committee (decision no: 2012-KAEK-15/2149, date: 22/07/2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.E., Design: E.E., E.F.G., Data Collection and/or Processing: E.F.G., Supervision: F.K., Analysis and/or Interpretation: E.F.G., S.D., Literature Search: S.D., H.U., Writing: E.E., S.D., H.U., Critical Review: E.E., H.U.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Park SE. Epidemiology, virology, and clinical features of severe acute respiratory syndrome -coronavirus-2 (SARS-CoV-2; Coronavirus Disease-19). Clin Exp Pediatr. 2020; 63(4): 119-24.
2. Lai CC, Wang CY, Wang YH, Hsueh SC, Ko WC, Hsueh PR. Global epidemiology of coronavirus disease 2019 (COVID-19): disease incidence, daily cumulative index, mortality, and their association with country healthcare resources and economic status. Int J Antimicrob Agents. 2020; 55(4): 105946.
3. Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. J Infect. 2020; 80(6): e14-8.
4. Wang L, He W, Yu X, Hu D, Bao M, Liu H, et al. Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. J Infect. 2020; 80 (6): 639-45.
5. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020; 323(13): 1239-42.
6. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020; 8(5): 475-81.
7. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020; 382(18): 1708-20.

8. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available from: URL: https://www.covid19treatmentguidelines.nih.gov/

9. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020; 323(11): 1061-9. Erratum in: JAMA. 2021; 325(11): 1113.

10. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395(10223): 497-506.

11. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395(10223): 507-13.

12. Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis. 2020; 20 (6): 669-77.

13. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020; 323(20): 2052-9.

14. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA. 2020; 323(18): 1775-6. Erratum in: JAMA. 2020; 323(16): 1619.

15. Smorenberg A, Peters EJ, van Daele P, Nossent EJ, Muller M. How does SARS-CoV-2 targets the elderly patients? A review on potential mechanisms increasing disease severity. Eur J Intern Med. 2021; 83: 1-5.

16. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020; 382(13): 1199-207.

17. Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE, Tan GB, et al. Hematologic parameters in patients with COVID-19 infection. Am J Hematol. 2020; 95(6): E131-4.

18. Henry BM, Lippi G. Chronic kidney disease is associated with severe coronavirus disease 2019 (COVID-19) infection. Int Urol Nephrol. 2020; 52(6): 1193-4.

19. Guan GW, Gao L, Wang JW, Wen XJ, Mao TH, Peng SW, et al. [Exploring the mechanism of liver enzyme abnormalities in patients with novel coronavirus-infected pneumonia]. Zhonghua Gan Zang Bing Za Zhi. 2020; 28(2): 100-6.

20. Luo X, Zhou W, Yan X, Guo T, Wang B, Xia H, et al. Prognostic value of C-reactive protein in patients with Coronavirus 19. Clin Infect Dis. 2020; 71(16): 2174-9.

21. Zhang Y, Cao W, Xiao M, Li YJ, Yang Y, Zhao J, et al. [Clinical and coagulation characteristics of 7 patients with critical COVID-2019 pneumonia and acro-ischemia]. Zhonghua Xue Ye Xue Za Zhi. 2020; 41(0): E006.

22. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395(10229): 1054-62.

23. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020; 5(7): 811- 8.

24. Deng Y, Liu W, Liu K, Fang YY, Shang J, Zhou L, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 in Wuhan, China: a retrospective study. Chin Med J (Engl). 2020; 133(11): 1261-7.

25. Mucha SR, Dugar S, McCrae K, Joseph D, Bartholomew J, Sacha GL, et al. Coagulopathy in COVID-19: Manifestations and management. Cleve Clin J Med. 2020; 87(8): 461-8.

26. Dai SP, Zhao X, Wu JH. Effects of Comorbidities on the Elderly Patients with COVID-19: Clinical Characteristics of Elderly Patients Infected with COVID-19 from Sichuan, China. J Nutr Health Aging. 2021; 25(1): 18-24.

27. Zhang K K, Zhu M L, Liu X H, et al. Investigation of multimorbidity and geriatric syndromes in the elder people in Beijing communities. Chin J Integr Med. 2016; 36(5): 419-21.

28. Sui J, Noubouossie DF, Gandotra S, Cao L. Elevated plasma fibrinogen is associated with Excessive Inflammation and Disease Severity in COVID-19 Patients. Front Cell Infect Microbiol. 2021; 11: 734005.

29. Lagier JC, Amrane S, Mailhe M, Gainnier M, Arlotto S, Gentile S, et al. High-flow oxygen therapy in elderly patients infected with SARS-CoV2 with a contraindication for transfer to an intensive care unit: A preliminary report. Int J Infect Dis. 2021; 108: 1-3.

ORIGINAL ARTICLE

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Preventive Measures for COVID-19 Infection and the Attitudes of Individuals: A Sample in Turkey

Fahriye Oflaz[1], Fatma Atkan[2]

[1]Koç University School of Nursing, Istanbul, Turkey
[2]Koç University Graduate School of Health Sciences, Istanbul, Turkey

Abstract

BACKGROUND/AIMS: This study aimed to determine the knowledge and beliefs of individuals regarding coronavirus disease-2019 (COVID-19) and its transmission pathways, their sources of information, their practice status of preventive measures and related factors.

MATERIALS AND METHODS: One thousand and four hundred and forty-four people completed a questionnaire between March 22, 2020, and April 6, 2020. The 12-question questionnaire consisted of questions regarding socio-demographics, information sources, the beliefs of the participants, and their practices to prevent the transmission of COVID-19. The data were analyzed using chi-square, t-test and One-Way ANOVA for comparisons.

RESULTS: The participants had sufficient knowledge about COVID-19 and its preventive measures. They were using social media platforms, official websites, and the TV news to obtain information about COVID-19. The rates of belief in the recommended measure and practicing these measures, such as keeping social distance, hand-washing, staying at home, avoiding public transportation and using disinfectants were quite common. Data showed that women, people living in cities, healthcare workers, and regular commuters believed in the measures more, however, their level of anxiety and seeing themselves and their environment as being risk were higher as well.

CONCLUSION: Despite all the positive results regarding COVID-19 and its preventive measures, the fact that it has spread rapidly indicates the need for more studies to continuously evaluate what is changing in this process as time passes.

Keywords: COVID-19, preventive measures, demography, society attitudes

INTRODUCTION

The coronavirus disease-2019 (COVID-19) is a respiratory disease caused by a new coronavirus. It first appeared in Wuhan, China in December 2019. The disease is highly infectious, and its main clinical symptoms include fever, dry cough, fatigue, myalgia, and dyspnea. It is also characterized by acute respiratory distress syndrome, septic shock, difficult-to-tackle metabolic acidosis, and bleeding and coagulation dysfunction.[1-3] The World Health Organization (WHO) declared an international public health emergency on January 30, 2020, urging all countries to cooperate to prevent the fast spread of COVID-19.[4,5] Following this, it was declared a pandemic on March 11, 2020.[6]

What has happened from the beginning and during the pandemic has shown that the management of the outbreak depends primarily on people's compliance with and their implementation level of the recommended measures. Strict infection control measures are the primary intervention to minimize the spread of the virus in both healthcare settings and the community.[7,8]

One of the main components of the studies regarding the prevention of transmission and spread in the pandemic is the ability of individuals in the society to carry out measures as recommended. Although the biological characteristics of COVID-19, such as the genetic type,

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ORCID IDs of the authors: F.O. 0000-0002-3878-028X; F.A. 0000-0002-9583-5638.

Address for Correspondence: Fahriye Oflaz
E-mail: foflaz@ku.edu.tr
ORCID ID: orcid.org/0000-0002-3878-028X

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structural and chemical features are very important to treat the disease, to be able manage the pandemic, this information should be usable and should be understood by lay-people. Managing the anxieties, fears and conceptual misconceptions of individuals in the community -at the local and/or wider public level- is as important as treating patients individually. As stated in the Health Belief Model, health behaviors are greatly influenced by people's knowledge, perception and attitudes.[5,9,10]

Lessons learned from the SARS epidemic in China, in 2003, showed that knowledge and attitudes towards infectious diseases can make it difficult to prevent the spread of the disease.[5,11,12] The awareness of individuals in the community to cope with highly contagious respiratory diseases plays a vital role in limiting the spread of infection, especially in middle and low-income countries whose health systems do not have the capacity to respond well to epidemics.[7,13]

Observing/following what human behavior is and how it evolves during the pandemic will make it easier to manage the unseen part of this pandemic now and in the future. The situations which direct the movements of the crowd as well as individuals should be investigated in detail and these movements or tendencies should be directed so as to facilitate the fight against COVID-19. With this in mind, this study aimed to reveal people's knowledge and beliefs about the coronavirus infection and the preventive measures, and their sources of information, as well as to determine the level of implementation of the recommended preventive measures.

In this context, when the literature is reviewed, although the countries of the studies were different for severe acute respiratory syndrome (SARS) and COVID-19, the researchers generally found that individuals in the society have a high level of knowledge. Also, in these studies, the usage of social media as a source of information was prominent but the belief that an individual's compliance with the recommended measures would be protective was found to be low. Additionally, it was also stated that individuals approached some measures that are frequently found on social media in a positive way but are actually ineffective in preventing transmission. The differences such as gender, socio-cultural features, age, education level and economic status were also shown as significant variables in terms of believing in and complying with the recommended preventive measures.[5,7,14,15]

In studies related to healthcare professionals, it has been stated that the level of knowledge about the pandemic, attitudes towards precautions, risk perception and anxiety varied according to their occupational groups, age and gender, and as to whether the healthcare professionals also used social media as a source of information.[16-18] There were no studies addressing this subject in Turkey.

This study aimed to investigate the source of information obtained by individuals, how this information guided their behaviors, their thoughts and beliefs regarding these new situations and their practice of preventive measures, and also the relationship of their sociodemographic characteristics with these variables. We believe that an understanding of these features would contribute to the sustainability of the preventative measures in the long term and would guide any further measures to be taken in the future. The answers to the following questions were sought:

1. What are the beliefs related to preventive measures against coronavirus transmission and what are their related factors?
2. What are individuals' thoughts about becoming infected or feeling at risk and the related factors with these variables?
3. What are the opinions about the implementation of precautions stated to be protective against contagion and becoming sick and what are their related factors?

MATERIALS AND METHODS

Type of Research

This study was planned as a descriptive and correlational research.

The Population and the Sample

In calculating the sample size, a 95% confidence interval and 0.05 error were considered. In cases where the number of the population is not known exactly, when p=0.05 (q=0.05 d= 0.03) is selected from the standard table and considering the estimated number of the population as 100 million, the determined number was 1067. The inclusion criteria for this study were as follows; being voluntary, being able to understand Turkish and being at least 18 years of age. There were no specific exclusion criteria. Those questionnaires which were not completed entirely and those questionnaires filled in by individuals under 18 years old were excluded from the evaluation.

Data Collection

The data were collected through a digital questionnaire prepared by the researchers using the online Qualtrics System. In the beginning part of the questionnaire, participants read the Informed Consent Form to learn about the purpose and the content of the research, its duration, confidentiality, and the participation criteria, and those who gave approval were expected to complete the survey. No fee was paid to the subjects participating in this study. The questionnaire was delivered to individuals and groups via social media and e-mail using the snowball method. A total of 1528 entries were made to the digital survey between March 22, 2020, and April 6, 2020. When those questionnaires that were not answered properly, those that were left incomplete and those which did not meet the inclusion criteria were eliminated, the sample group consisted of 1444 people.

The Data Collection Form consists of 12 questions which investigate the sociodemographic characteristics of the participants, the individuals they live with, the presence of any diagnosed chronic diseases, and the information sources they follow. In addition, their feelings and thoughts about the coronavirus infection, and their level of belief in the efficacy of preventive measures for the transmission of coronavirus were also asked. The participants were asked to rate their level of belief regarding the preventive measures by answering "it does not protect" for 0 points to "it fully protects" for 10 points, and the statements about the level/adequacy for the recommended preventive measures and their state of knowing as "not enough" for 1 point to "excellent/fully sufficient" for 10 points. The internal consistency coefficient of these questions was calculated to be 0.83.

Statistical Analysis

The data of this study were analyzed using the IBM Statistical Package for Social Science (SPSS) version 26.0 (SPSS IBM Corp, Armonk, NY, USA). The independent variables of this study were age, gender, educational status, marital status, profession, economic status, people living together, chronic disease status and sources of information. The

dependent variables were the individuals' feelings and thoughts about coronavirus infection and their belief scores for practices which will prevent coronavirus transmission. Percentages, and arithmetic means from descriptive statistics in the analysis of data were calculated. The chi-square, t-test and One-Way ANOVA were used for comparisons.

RESULTS

The average age of the participants was 39.43±13.45 years (18–77) (median: 39 years), 80% (n=1,147) were female, 50.8% (n=727) were married and 50% (n=719) were found to have a regular job with a salary. 90.5% of the participants (n=1302) had a university or higher education level and 59.1% (n=847) stated that their income was equivalent to their expense. In addition, 20.5% (n=291) were healthcare workers, 21.7% (n=307) are academicians, 21.3% (n=301) were white collar workers, 511.6% (n=167) were students, and 86.6% (n=1245) were living in cities. 30.1% (n=426) of the participants stated that they work from home and 27% (n=384) still commute to work. The rate of those living alone was 12.9% (n=185). 72.1% of the participants (n=979) stated that they do not have any diagnosed disease and 21.1% (n=287) stated that they take regular medication. The age groups of the participants and the sources of information are displayed in Table 1. Comparing the information sources with age, it was observed that there was a statistical difference between the average age of those who follow scientific publications and sites (38.03±13.24 years) and those who follow the TV news (43.99±13.29 years). The TV followers were significantly older than the scientific sites followers (F=12.802; p=0.001). The participants were asked to rate their beliefs regarding the efficacy of the measures that were frequently shared on social media and the TV news for the purpose of coronavirus prevention. They mostly marked hand-washing, social distancing and ventilating houses etc. as 8 or more, but they gave an average of 5 points to wearing a mask (Table 1).

The comparison of the self-evaluation scores of the participants regarding their belief in the protectiveness of the measures taken and their practices in terms of their gender is shown in Table 2. Although the scores regarding their beliefs in the protectiveness of measures and self-evaluation were generally higher in women, it was observed that the women had higher levels of stress than the men did, and they got lower scores on reassuring themselves than the men.

Table 3 displays the beliefs and the preventative measure implementation levels according to age groups in general. The level of believing that using vitamins, ventilating items and warm weather will protect, and generally believing in measures seems to increase with age. Although the risk perception is lower in the 18–29 age group compared to other groups, their ability to focus their attention on another subject and to reassure themselves appears to be low.

Table 4 displays the differences between the education levels in terms of having belief in the measures and self-evaluations. In general, there was no difference among the educational levels in terms of the individuals' beliefs in the efficacy of measures, but their belief increased as the education level decreased in terms of those practices for which the protection is not clear. Those who had primary education level considered the level of implementation of the measures in the society to be insufficient compared with those with postgraduate education. In terms of hand-washing levels, the high school group gave themselves higher scores than the graduate group. In addition, considering themselves at risk was lower in the university group than in the other groups and their belief that they would recover was higher.

Belief in using alcoholic disinfectants was lower among those living in the village compared to the other groups. Belief in the protection of sunny weather was lower among those living in the inner city. While the level of knowledge about the coronavirus was higher among those living in the inner city; those living in the village rated their level of taking preventive measures with lower scores (Table 5). In the group working from home, the belief that not getting on public transportation would protect them was higher, and the belief that ventilating the house/items would protect them was lower. The level of practicing preventive measures, such as hand-washing and exercising adequately were found to be lower in the group that said that they commute to work. However, in this group, feeling at risk and worrying about themselves and their

Table 1. Age, the source of information and the mean scores of believing in the efficacy of the preventive measures

Age	**n**	**%**
18–29	384	30.1
30–39	266	20.8
40–49	254	19.9
50–59	294	23.0
60–77	79	6.2
Information resources*		
Social media (Facebook, LinkedIn, Twitter, WhatsApp, Instagram)	1108	77.0
Scientific publications and websites (WHO, Ministry of Health)	1088	75.6
TV News	1101	76.5
Health professional acquaintances	637	44.3
Newspapers	387	26.9
YouTube	312	21.7
Ekşi sözlük web site (eksisozluk.com)	80	5.6
Other	45	3.1
Belief in the proposed precautions (min: 1 – max: 10)	**n**	**Mean ± SD**
Social distancing	1326	9.18±1.48
Staying at home	1429	8.80±1.80
Hand-washing	1430	8.76±1.53
Not using public transportation	1412	8.60±2.19
Ventilating the house/rooms	1425	8.32±1.94
Drinking water	1426	8.10±2.17
Using alcohol disinfectant	1401	7.68±2.41
Having COVID-19 test - PCR	1372	7.19±2.72
Warm-sunny weather	1402	6.84±2.70
Taking vitamin supplements	1387	6.10±2.80
Being under the 30 years old	1310	6.03±2.96
Wearing gloves	1382	5.98±2.89
Wearing mask	1394	5.67±2.79
Taking some medicines talked about by mess media in advance	1221	2.98±2.45

*Multiple answers, min: minimum, max: maximum, WHO: World Health Organization, COVID-19: coronavirus disease-2019, PCR: polymerase chain reaction, n: number.

Table 2. The comparisons of gender with believing in the efficacy of preventive measures related to COVID-19 and self-evaluation scores

Belief in the precautions	Male (mean ± SD)	Female (mean ± SD)	t-test	p-value
Social distancing	9.01±1.44	9.22±1.49	-1.971	0.049
Hand-washing	8.52±1.61	8.82±1.50	-2.970	0.003
Staying at home	8.46±2.01	8.88±1.73	-3.194	0.002
Not using public transportation	8.27±2.32	8.69±2.15	-2.824	0.005
Ventilating the house/items	7.92±2.08	8.42±1.89	-3.853	0.001
Drinking water	7.60±2.26	8.24±2.12	-4.450	0.001
Wearing gloves	5.56±2.88	6.09±2.88	-2.695	0.007
Taking vitamin supplements	5.50±2.87	6.17±2.76	-3.563	0.001
Wearing mask	4.94±2.75	5.86±2.77	-4.895	0.001
Self-evaluation				
Efficacy of hand-washing	8.82±1.51	9.23±1.14	-4.115	0.001
Efficacy of general fulfillment of proposed measures	8.01±1.59	8.50±1.58	-4.629	0.001
Knowledge about coronavirus symptoms	7.90±1.95	8.35±1.72	-3.476	0.001
Efficacy of knowing where to apply if infected	7.73±2.55	8.32±2.24	-3.521	0.001
Efficacy of applying healthy nutrition measures at home	7.95±1.86	8.38±1.82	-3.545	0.001
Worrying about catching coronavirus infection	5.47±2.68	6.21±2.62	-4126	0.001
Concern about family members catching the coronavirus	6.52±2.77	7.56±2.61	-5.555	0.001
Efficacy of being able to concentrate on the other issues other than coronavirus	6.92±2.46	6.33±2.50	3.506	0.001
Efficacy of being able to relax at home	7.33 ±2.20	6.87±2.38	2.882	0.001

COVID-19: coronavirus disease-2019, SD: standard deviation.

Table 3. The comparisons of age with believing in the efficacy of preventive measures related to COVID-19 and self-evaluation scores

Believing in the precautions	18–29 Mean ± SD	30–39 Mean ± SD	40–49 Mean ± SD	50–59 Mean ± SD	60–77 Mean ± SD	F#	p-value
Taking vitamin supplement	5.67±2.84[6]	5.88±2.85	6.17±2.74	6.32±2.77[6]	6.10±2.81	2.541	0.038
Ventilating the house	7.87±2.24[2]	7.59±2.27	7.91±2.25	8.18±2.06	8.31±2.25[2]	3.123	.014
Warm-sunny weather	6.11±2.91[4]	6.53±2.69	6.78±2.72	7.65±2.20	7.96±2.21	18.20	.001
Being under the 30 years old	6.19±2.99[7]	5.30±3.05[7]	6.25±2.71	6.28±2.96	6.11±2.94	4.670	.001
Self-evaluation							
Efficacy of faith in the proposed measures	6.70±2.33	6.56±2.35[1]	7.13±2.24[1]	7.06±2.22	7.31±2.17	3.757	.005
Efficacy of implementing precautions in the immediate environment	6.77±2.35[3]	7.03±2.30	7.39±2.08[3]	7.40±2.01	7.44±2.05	5.074	.001
Efficacy of applying healthy nutrition measures at home	7.76±2.27[4]	8.27±1.70	8.70±1.48	8.50±1.57	8.50±1.68	12.41	.001
Efficacy of exercising at home	4.42±2.98[4]	4.96±2.95	5.53±2.97	5.58±2.72	5.61±2.64	9.173	.001
Worrying about catching coronavirus infection	5.93±2.71	6.36±2.59[5]	6.11±2.76	6.04±2.43	5.29±2.70[5]	14.13	.001
Efficacy of being able to concentrate on the other issues	6.25±2.66[6]	6.02±2.58	6.60±2.36	6.79±2.23	7.17±2.22[6]	5.758	.001
Efficacy of being able to relax at home	6.43±2.57[4]	6.61±2.29	7.54±2.17	7.28±2.06	7.81±2.08	14.67	.001
Feeling at risk	5.29±2.85[3]	5.84 ±2.73	6.25±2.88[3]	5.89±2.55	5.92±2.77	4.833	.001
Believing I would recover, if I become infected	5.27±2.81[7]	5.98±2.59[7]	6.02±2.62	5.81±2.32	5.65±2.66	4.343	.002

One-Way ANOVA post hoc: *TUKEY*

[1]40–49 significantly higher than 30–39, [2]18–29 significantly lower than 60–77, [3]18–29 significantly lower than 40–49, [4]18–29 significantly lower than other groups,[5]30–39 significantly higher than 60–77, [6]18–29 significantly lower than 50–59,[7]18–29 significantly lower than 30–39.

COVID-19: coronavirus disease-2019, SD: standard deviation.

Table 4. The comparisons of education level with believing in the efficacy of preventive measures related to COVID-19 and self-evaluation scores

Believing in precautions	Primary (mean ± SD)	High School (mean ± SD)	University (mean ± SD)	Graduate (mean ± SD)	F#	p-value
Using alcohol disinfectants	8.60±2.41	8.13±2.24	7.68±2.37	7.52±2.53	2.738	0.042
Ventilating the house	9.19±1.66	8.94±1.74[1]	8.33±1.90*	8.08±2.04*	7.247	0.001
Ventilating items	8.59±2.85	8.49±2.16*	8.03±2.06*	7.59±2.39[2]	6.903	0.001
Warm-sunny weather	7.54±2.50	7.65±2.68[1]	6.83±2.69*	6.62±2.69*	4.615	0.003
Drinking water	9.09±1.41	8.74±1.81[1]	8.12±2.13*	7.86±2.32*	6.426	0.001
Having COVID-19 test-PCR	7.70±3.37	8.34±2.23*	7.87±2.68*	7.32±2.93[2]	5.281	0.001
Self-evaluation						
Efficacy of fulfillment of precautions in the society	2.45±2.28[3]	3.49±2.26	3.56±2.10	3.76±1.92*	2.981	0.030
Efficacy of hand-washing	9.04±1.46	9.36±1.06[1]	9.18±1.21*	9.01±1.30*	3.028	0.029
Feeling at risk	6.05±3.11	6.30±2.78	5.67±2.79[4]	6.23±2.74	4.526	0.004
Believing I would recover, if become infected	5.00±3.08	5.24±2.77	5.87±2.62[5]	5.59±2.50	3.036	0.028

#One-Way ANOVA, Post hoc: TUKEY.
[1]High-school group significantly higher university and graduate group,[2]Graduate group significantly lower than university and high school group,[3]Primary school group significantly lower than graduate group,[4]University group lower than other groups,[5]University group higher than other groups.
COVID-19: coronavirus disease-2019, SD: standard deviation, PCR: polymerase chain reaction.

Table 5. The comparisons of the residential location and the type of work of the participants with regards to believing in the efficacy of preventive measures related to COVID-19 and self-evaluation scores

Believing the precautions	Inner city (mean ± SD)	County (mean ± SD)	Village (mean ± SD)	F#	p-value
Using alcohol disinfectants	7.70±2.40	7.71±2.39	6.17±2.60[1]	3.373	0.035
Warm-Sunny weather	6.75±2.73[2]	7.49±2.47	7.40±2.22	5.652	0.004
Self-evaluation					
Knowledge about coronavirus infection	7.71±1.78[3]	7.39±2.06	6.94±178	3.523	0.030
Efficacy of implementing precautions	8.29±1.79	8.44±1.68	6.82±2.21[1]	6.355	0.002
	Working from home	**Commuting to work**	**Not working**		
Self-evaluation					
Knowing where to apply if infected	7.82±2.50[1]	8.50±2.11	8.28±2.28	9.501	0.001
Efficacy of general implementation of proposed measures	8.47±1.43	8.10±1.75[5]	8.52±1.57	8.923	0.001
Efficacy of implementation of precautions in the society	7.35±2.03	6.95±2.22[3]	7.06±2.32	3.655	0.026
Efficacy of hand-washing	9.17±1.09	9.02±1.36[4]	9.22±1.24	4.866	0.041
Efficacy of applying healthy nutrition measures at home	8.48±1.63[2]	8.19±1.88	8.20±1.94	3.553	0.029
Efficacy of exercising at home	5.45±2.94	4.44±2.88[5]	5.14±2.90	12.195	0.001
Efficacy of sleeping	7.56±2.44[1]	6.89±2.53	6.91±2.57	10.026	0.001
Worrying about catching coronavirus infection	5.87±2.67	6.63±2.66[5]	5.85±2.59	11.686	0.001
Concern about family members catching the coronavirus	7.16±2.80	7.73±2.59[5]	7.31±2.58	4.906	0.008
Efficacy of being able to concentrate on the other issues other than coronavirus	6.52±2.49	6.03±2.52[5]	6.62±2.46	6.832	0.001
Feeling at risk	5.56±2.59	7.32 ±2.71[5]	5.19±2.65	78.842	0.001
Believing I would recover, if infected	5.75±2.57	6.03 ±2.56[4]	5.54±2.65	3.984	0.019

#One-Way ANOVA Post hoc:TUKEY
[1]Village group significantly lower than other groups, [2]Inner city group lower than county group, [3]Inner city group higher than other groups.
[1]Working at home group different from the other groups, [2]Working at home group different from not working group, [3]Working outside group different from working at home group, [4]Working outside group different from not working group, [5]Working outside group different from the other groups.
COVID-19: coronavirus disease-2019, SD: standard deviation.

Table 6. The comparisons of the occupation with regards to believing in the efficacy of preventive measures related to COVID-19 and self-evaluation scores

Believing in the precautions	Academics (mean ± SD)	Unclassified jobs (mean ± SD)	Health professionals (mean ± SD)	Students (mean ± SD)	Psychosocial professionals (mean ± SD)	F#	p-value
Hand-washing	8.81±1.63	8.57±1.68*	8.97±1.31[1]	8.63±1.50*	8.55±1.48*	3.046	0.010
Wearing mask	5.83±2.76	5.16±2.63*	6.44±2.75[1]	5.22±2.74*	4.85±2.55*	10.04	0.001
Ventilating house/room	8.45±1.88*	8.15±2.02	8.41±1.88*	8.11±2.01	7.94±1.88[3]	3.045	0.010
Drinking water	8.21±2.09	7.79±2.34*	8.32±2.00[1]	7.97±2.26*	7.63±2.41*	4.780	0.001
Warm-sunny weather	7.30±2.48*	6.97±2.56*	6.84±2.58*	5.76±3.02	5.61±2.87[4]	13.73	0.001
Wearing gloves	6.06±2.75	5.65±2.79*	6.00±2.98	6.30±3.00[2]	5.47±2.72*	2.816	0.015
Taking the medicines published by media	3.41±2.60*	3.10±2.54*	2.93±2.47*	2.28±2.07	2.16±1.67[4]	6194	0.001
Being younger than 30	6.16±2.90	5.74±3.06	6.40±2.67[1]	6.40±2.85	5.40±3.14*	3.002	0.011
Self-evaluation							
Knowledge about coronavirus infection	7.72±1.84	7.44±1.91*	7.54±1.59	7.96±1.72[1]	7.71±1.81	2.827	0.015
Knowing where to apply if infected	8.28±2.26*	7.44±2.66*	8.17±2.25*	8.94±1.68[1]	8.41±2.25	14.41	0.001
Efficacy of general implemnetation of proposed measures	8.49±1.45	8.16±1.77*	8.32±1.59	8.57±1.50[1]	8.41±1.64	2.478	0.030
Efficacy of implementation of precautions of my immediate environment	7.18±2.16	7.37±2.08*	7.58±1.91*	7.01±2.18[1]	6.78±2.47	3.128	0.008
Efficacy of hand-washing	9.24±1.14	9.06±1.27*	8.88±1.39*	9.26±1.18[1]	9.03±1.29	2.428	0.033
Efficacy of general implementation of precautions at home	8.47±1.45*	8.18±1.74	7.96±2.03	8.45±1.64*	7.83±2.24[2]	4.494	0.001
Efficacy of applying healthy nutrition measures at home	8.72±1.42[5]	8.29±1.69	7.89±2.06	8.24±1.94	7.60±2.43	9.230	0.001
Efficacy of exercising at home	5.56±2.67[5]	5.15 ±3.00	4.52 ±2.99	4.55 ± 2.97	4.62 ±2.95	5.655	0.001
Worrying about catching coronavirus infection	6.00±2.55	5.89±2.69	5.64±2.42	6.70±2.73[1]	5.48±2.58	5.794	0.001
Concern about family members catching coronavirus	7.16±2.65*	7.19±2.74*	6.96±2.83*	7.88±2.46[1]	7.96±2.19	5.666	0.001
Efficacy of being able to relax at home	7.02±2.31*	6.96±2.40*	7.16±2.20*	6.75±2.30	6.48±2.54[2]	3.463	0.004
Feeling at risk	5.78 ± 2.62	5.75 ±2.75	5.20 ±2.34	7.21±2.86[1]	4.58± 2.60	23.16	0.001

#One-Way ANOVA Post hoc:*TUKEY*.
[1]Health professionals significantly different from other groups,[2]Students significantly different from general workers and psychosocial professionals,[3]Psychosocial professionals significantly different from health professionals and academicians,[4]Psychosocial professionals significantly different from health professionals, general workers and academicians,[5]Academicians significantly different from other groups.
COVID-19: coronavirus disease-2019, SD: standard deviation.

family were higher. Again, in this group, being able to pay attention to issues other than coronavirus was found to be lower than in the other groups (Table 5).

While healthcare professionals' levels of belief that hand-washing, wearing masks, consuming plenty of fluids and being younger than 30 would protect them was significantly higher than the other groups, the levels of belief in the protection of sunny weather, ventilation measures and those medicines mentioned in the media were found to be lower than the other groups. Students relied more on using gloves than the other groups (Table 6). Healthcare professionals rated their knowledge about the disease and where to apply if they become sick to be higher. In addition, their level of taking precautions, hand-washing, and the worry of becoming sick and seeing themselves at risk were higher than the other groups as well. While the academic group found themselves to be good in terms of exercise and nutrition, the students rated themselves more negatively in terms of sleeping, being able to relax despite the pandemic, and implementing measures for their homes and belongings (Table 6).

DISCUSSION

Knowledge, attitudes and concerns of individuals about this disease affect the implementation of preventive measures. In our study, most of

the participants were women, university graduates, and were living in cities. They considered their level of knowledge about the coronavirus infection, its transmission pathways and the precautions against it to be sufficient in general. When asked to give a score between 1 and 10 regarding the protectiveness of the proposed measures, such as measures related to hand-washing, staying at home, not using public transportation and social distancing, they gave high scores. However, the score of their belief in the protectiveness of wearing a mask was only 5.

Other studies have also shown that individuals have a high level of knowledge regarding coronavirus and its transmission pathways and its related measures.[5,7,15,18,19] In some studies about the SARS epidemic, it was found that individuals achieved high scores in implementing the recommended precautions, their anxiety levels were low, and their risk perceptions varied.[19-21] Similarly, Vartti et al.[14] stated that although Finnish people had a high level of knowledge and worry about SARS, their individual attitudes were insufficient to comply with the measures and their beliefs about the effectiveness of individual measures were low. In relation to the SARS epidemic, Lau et al.[19] also stated that their participants had higher scores on implementations such as wearing masks, frequent hand-washing, disinfection measures at home, using public transportation and not going to public places at the beginning, but the scores of these measures decreased in the second phase of the study. Their results suggest that the participants had the correct information about the ways of transmission, but the decrease in their beliefs about the effectiveness of the practices as time passes may be related to the decrease in panic and anxiety feelings experienced by them.

In this study, it was determined that women had higher scores of beliefs in and implementation of the preventive measures and their levels of concern about contamination were higher than for men. Additionally, they gave lower scores regarding relaxing despite the pandemic than men. The level of education seems to make a difference in transmission prevention perceptions, such as warm weather conditions and the ventilation of the items, for which there is no evidence of being effective in preventing contamination. It was observed that as the education level decreased, the score regarding belief in such ineffective practices increased. Considering themselves to be at risk was lower among university graduates, and the belief that they would recover was higher in this group. Those individuals with higher education might have thought that they have sufficient information and that was enough to keep the disease under control. Although this finding indicates that people who have received university education have an optimistic approach, it is a finding that should be taken into consideration as this type of approach may reduce the level of precautions taken.

The findings of this present study reveal that there is a significant relationship between being a man and believing in measures against COVID-19 and also applying these measures. Zhong et al.[5] and Lau et al.[19] also found that men had lower scores than females in implementing the recommended measures. Previous studies also noted that men would tend to show more risky behaviors than women.[22,23]

In our study, when the individuals were evaluated in terms of where they live, the scores given regarding effective methods did not change according to their place of residence. However, for those living in the village, the score of believing that sunny and warm weather would protect them was higher, and the score of believing in the preventiveness of alcoholic disinfectants was lower. Those people living in cities had higher scores regarding taking preventive measures. Studies in the literature also support our findings about the low level of knowledge of those individuals living in rural areas compared to those living in cities.[5,7] Our findings suggest that people living in cities may be at an advantage in terms of faster and easier access to correct information sources, and this was reflected in their implementation of recommended measures. For this reason, while planning information and training on the coronavirus infection and its preventative measures, it should be aimed at reaching those individuals living in rural areas as well. In the group working from home, belief that they would be protected by not getting on public transportation was higher. In the group commuting to work, the level of implementing preventive measures, the level of adequate hand-washing and the level of exercise were found to be low. Meanwhile, the score of seeing oneself as being at risk, and worrying about themselves and their family was also higher in this same group. Again, in this group, the score for being able to concentrate on issues other than coronavirus was found to be lower than for other individuals. Considering that half of the individuals participating in our study have a job that they regularly commute to, it is possible that they are at high risk in terms of contacting infected individuals and transmitting the virus to those in their environment. In addition, since they were in the work environment on a daily basis, it was possible that their level of implementation of the recommended measures may not be sufficient.

The scores of believing that hand-washing, masks, consuming fluids and being younger would protect them from the coronavirus infection, and their level of knowledge regarding the disease and where to apply if infected, and their implementation levels of precautions such as hand-washing were significantly higher in the health professionals than in the other groups. The students trusted using gloves more than the other groups. This finding supports the idea that healthcare professionals have sufficient knowledge regarding infection control measures, hygiene principles and coronavirus disease knowledge and experience as expected in terms of their professional characteristics. Bhagavathula et al.[17], contrary to the findings of our study, in their study on healthcare professionals, concluded that healthcare workers had insufficient knowledge of COVID-19 and its precautions, but their risk perception was higher. In our study group, the knowledge level in health professionals seemed sufficient, but the level of worrying about their risk of becoming infected and worrying about transmitting the virus to their family members was also higher. Similar to our study, there are studies showing that there is a high concern among health professionals in terms of catching the infection and transmitting it to their close family members.[24,25]

This high concern of healthcare professionals can be attributed to the uncertainties and unknown features related to this new pandemic, which is due to the lack of comprehensive and accurate information.[16] It is important to address this issue by incorporating it into outbreak management strategies, as health professionals' concerns can negatively affect their effectiveness during an outbreak. Making sure that adequate protective measures are taken can give health professionals a sense of personal safety. Good infection control guidelines, equipment and psychological support should be provided; intensive education campaigns and management support should be established to reduce the concerns of healthcare workers during pandemics. In this study, it was found that students evaluated themselves more negatively

regarding sleeping, being able to relax, and implementing measures related to their home and their belongings. Interruptions occurred in their education as students are one of the vulnerable groups during the pandemic. This finding may indicate that they may need more support in terms of maintaining their physical and mental health.

In our study, it was seen that the participants mostly followed internet-based official institutions and scientific publications, social media platforms and the TV news. In addition, the rate of obtaining information from healthcare professionals they know was quite high. The fact that the individuals participating in our study were young or middle-aged explains why technology and media tools usage as news sources was high. McFadden et al.'s[18] findings coincide with the findings of our study. In their study, the participants chose health professionals as the most reliable source of information and social media as the least trusted source of information. In a study on the SARS epidemic, it was concluded that the participants mostly received information from communication tools such as television, newspaper and radio respectively.[19] Vartti et al.[14], in the SARS process, also found that the society trusts doctors more, but used the internet as a source of information. These results show the importance of the correct use of social media and media communication tools such as television and the importance of facilitating access to accurate information in order to inform the public about the disease and its prevention methods. In this process, media tools such as mobile applications and television should be used by policy makers to better inform the public.

The strength of our study lies in its large sample recruited during the early stages of the coronavirus outbreak.

Due to limited access to the internet and online health resources, especially for older adults and people who live in rural areas, there is a greater risk of having poor knowledge, negative attitudes, and inappropriate preventive practices regarding the coronavirus infection.

Study Limitations

This study also had some limitations. First, this study was conducted via the internet. For this reason, we could not reach those people who have no access to the internet. Furthermore, the timing was at the beginning of the pandemic. These issues may limit the generalization of our results.

Conclusion

It was concluded that the participants had sufficient knowledge regarding the coronavirus infection, its transmission pathways and precautions, and they mostly tried to obtain information from social media platforms, official web sites and the TV news. The rates of believing and implementing measures such as social distancing, hand-washing, staying at home, not using public transportation, and using alcohol disinfectants were high. It was found that women, those who live in cities, those who are health professionals, and those who regularly commute to work believe in the recommended measures more, but their levels of anxiety and considering themselves and their environment to be at risk were higher. Despite all these positive results, the rapid spread of the coronavirus infection shows that there is a need for further studies to evaluate what is changing during this pandemic relating to these factors as time passes.

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MAIN POINTS

- Strict infection control measures are the primary intervention to minimize the spread of the virus.
- People mostly used social media platforms, official websites, and the TV news to obtain information regarding COVID-19.
- The most common preventive measures among people included maintaining social distancing, hand-washing, staying at home, avoiding public transport and using disinfectants.
- Women, people living in cities, healthcare workers, and regular commuters believed in the recommended preventive measures for COVID-19 infection more, however, their level of anxiety and seeing themselves and their environment as being at risk were higher.
- Despite the positive attitudes and the knowledge of people, the rapid spread of the coronavirus infection implies that there is a need for further studies to evaluate changes as time passes during this pandemic process.

ETHICS

Ethics Committee Approval: Ethics committee approval was obtained from the Social Sciences Ethics Committee of the Koç University (approval code: 2020.203.IRB3.083) and research permission was obtained from the Ministry of Health (2020-05-25T17_23_48).

Informed Consent: Online written informed consent was obtained from the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.O., Design: F.O., Data Collection and/or Processing: F.O., F.A., Analysis and/or Interpretation: F.O., F.A., Writing: F.O., F.A.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention. [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China]. Zhonghua Liu Xing Bing Xue Za Zhi. 2020; 41(2): 145-51.
2. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395: 507-13.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395: 497–506.

4. World Health Organization. 2019-nCoV outbreak is an emergency of international concern. 2020. Available from: URL: http://www.euro.who.int/en/health-topics/emergencies/pages/news/news/2020/01/2019-ncov-outbreak-is-an-emergency-of-international-concern (Accessed on April 24, 2020).

5. Zhong BL, Luo W, Li HM, Zhang QQ, Liu XG, Li WT, et al. Knowledge, attitudes, and practices towards COVID-19 among Chinese residents during the rapid rise period of the COVID-19 outbreak: a quick online cross-sectional survey. Int J Biol Sci. 2020; 16(10): 1745-52.

6. World Health Organization. Coronavirus disease (COVID-2019) situation reports. 2020. Available from: URL: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. (Accessed on April 24, 2020).

7. Abdelhafiz AS, Mohammed Z, Ibrahim ME, Ziady HH, Alorabi M, Ayyad M, et al. Knowledge, Perceptions, and Attitude of Egyptians Towards the Novel Coronavirus Disease (COVID-19). J Community Health. 2020; 45(5): 881-90.

8. Li JY, You Z, Wang Q, Zhou ZJ, Qiu Y, Luo R, et al. The epidemic of 2019-novel-coronavirus (2019-nCoV) pneumonia and insights for emerging infectious diseases in the future. Microbes Infect. 2020; 22(2): 80-5.

9. Ajilore K, Atakiti I, Onyenankeya K. College students' knowledge, attitudes and adherence to public service announcements on Ebola in Nigeria: Suggestions for improving future Ebola prevention education programmes. Health Education Journal. 2017; 76(6): 648-60.

10. Tachfouti N, Slama K, Berraho M, Nejjari C. The impact of knowledge and attitudes on adherence to tuberculosis treatment: a case-control study in a Moroccan region. Pan Afr Med J. 2012; 12: 52.

11. Hung LS. The SARS epidemic in Hong Kong: what lessons have we learned? J R Soc Med. 2003; 96(8): 374-8.

12. Tao N. An analysis on reasons of SARS-induced psychological panic among students. Journal of Anhui Institute of Education. 2003; 21: 78-9.

13. Egypitan PM. Egypt's coronavirus figures still within range. Retrieved (April 17, 2020), 2020; 4. Available from: URL: https://www.egypttoday.com/Article/2/83291/PM-Egypt%E2%80%99s-coronavirus-figures-still-within-range

14. Vartti AM, Oenema A, Schreck M, Uutela A, de Zwart O, Brug J, et al. SARS knowledge, perceptions, and behaviors: a comparison between Finns and the Dutch during the SARS outbreak in 2003. Int J Behav Med. 2009; 16(1): 41–8.

15. Geldsetzer P. Use of Rapid Online Surveys to Assess People's Perceptions During Infectious Disease Outbreaks: A Cross-sectional Survey on COVID-19. J Med Internet Res. 2020; 22(4): e18790.

16. Alsubaie S, Hani Temsah M, Al-Eyadhy AA, Gossady I, Hasan GM, Al-Rabiaah A, et al. Middle East Respiratory Syndrome Coronavirus epidemic impact on healthcare workers' risk perceptions, work and personal lives. J Infect Dev Ctries. 2019; 13(10): 920-6.

17. Bhagavathula A, Aldhaleei WA, Rahmani J, Mahabadi MA, Bandari DK. Knowledge and Perceptions of COVID-19 among Health Care Workers: Cross-sectional Study. JMIR Public Health Surveill. 2020; 6(2): e19160.

18. McFadden SM, Malik AA, Aguolu OG, Willebrand KS, Omer SB. Perceptions of the adult US population regarding the novel coronavirus outbreak. PLoS One. 2020; 15(4): e0231808.

19. Lau JT, Yang X, Tsui H, Kim JH. Monitoring community responses to the SARS epidemic in Hong Kong: from day 10 to day 62. J Epidemiol Commun Health. 2003; 57(11): 864-70.

20. Lee-Baggley D, DeLongis A, Voorhoeave P, Greenglass E. Coping with the threat of severe acute respiratory syndrome: Role of threat appraisals and coping responses in health behaviors. Asian J Soc Psychol. 2004; 7(1): 9-23.

21. Leung GM, Lam TH, Ho LM, Ho SY, Chan BH, Wong IO, et al. The impact of community psychological responses on outbreak control for severe acute respiratory syndrome in Hong Kong. J Epidemiol Community Health. 2003; 57(11): 857-63.

22. Pawlowski B, Atwal R, Dunbar RIM. Sex Differences in Everyday Risk-Taking Behavior in Humans. Evolutionary Psychology. 2008; 6(1): 29-42.

23. Cobey KD, Stulp G, Laan F, Buunk AP, Pollet TV. Sex differences in risk taking behavior among Dutch cyclists. Evol Psychol. 2013; 11(2): 350-64.

24. Abolfotouh MA, AlQarni AA, Al-Ghamdi SM, Salam M, Al-Assiri MH, Balkhy HH. An assessment of the level of concern among hospital-based health-care workers regarding MERS outbreaks in Saudi Arabia. BMC Infect Dis. 2017; 17(1): 4.

25. Nour MO, Babilghith AO, Natto HA, Al-Amin FO, Alawneh SM. Knowledge, attitude and practices of healthcare providers towards MERS-CoV infection at Makkah hospitals, KSA. Int Res J Med Sci. 2015; 3(4): 103-12.

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The Prevalence of *Helicobacter pylori* in Northern Cyprus: A Retrospective Study

Özgur Sirkeci[1], Emel Erkuş Sirkeci[2], Turgay Ulaş[3]

[1]Department of Internal Medicine, Near East University Hospital, Lefkosa, North Cyprus
[2]Department of Emergency, Near East University Hospital, Lefkosa, North Cyprus
[3]Department of Hematology, Near East University Hospital, Lefkosa, North Cyprus

Abstract

BACKGROUND/AIMS: The aim of this study was to evaluate *Helicobacter pylori (H. pylori)* prevalence in Northern Cyprus.

MATERIALS AND METHODS: From December 2012 to April 2018, we retrospectively enrolled 1226 patients aged over 18 with *H. pylori* positivity who presented at outpatient clinics with dyspeptic complaints. Age, gender and ethnicities were evaluated from the data of patients

RESULTS: *H. pylori* positivity was detected in 286 of the 1226 patients (23.3%). The female positivity rate was 21% (147/693) and the male positivity rate was 26% (139/533). *H. pylori* positivity was found in 119 of 599 (19.8%) patients in the citizen of TRNC (The Turkish Republic of Northern Cyprus) and 148 of 571 patients (25.6%) in citizen of TR (The Turkish Republic).

CONCLUSION: *H. pylori* is a still common infection, although with decreasing frequency. Despite the fact that TRNC is an eastern Mediterranean country, the prevalence of *H. pylori* in TRNC is much lower than other Southeast Mediterranean countries.

Keywords: *Helicobacter pylori*, prevalence, Cyprus

INTRODUCTION

Helicobacter pylori (H. pylori) is the main cause of gastric ulcer, duodenal ulcer, and non-ulcer dyspepsia.[1] It is also an important risk factor for stomach cancer.[2] Worldwide, more than 50% of the population is infected with *H. pylori*. It is more commonly found in developing countries[3] due to risk factors including low socioeconomic levels, poor hygiene conditions, and overcrowding.[4] Both non-invasive and invasive tests can be used for *H. pylori* diagnosis. The most commonly used non-invasive tests are the urea breath test, the stool antigen test, and serology. The invasive tests are histology and the campylobacter-like organism (CLO) test. The urea breath testing and stool antigen testing are favored due to their easy implementation and reasonable cost.[5] *H. pylori* is highly prevalent throughout the world, although its prevalence is declining. In a nationwide study in Australia with 1355 participants, the infection prevalence varied between 5%–32% with a higher prevalence in low-socioeconomic cities.[6] In Europe, it is more common in eastern European countries than in western European countries.[7,8] In a study in Denmark, the average prevalence of *H. pylori* infection was determined to be 20%.[9] The seroprevalence in Israel was determined to be 45%[10] and the Turkey *Helicobacter pylori* Prevalence (TURHEP) study designed in Turkey in 2003 found the prevalence of *H. pylori* to be 82.5% in the population over the age of 18 years of age.[11] However, no research study had been performed in Northern Cyprus regarding the prevalence of *H. pylori* to date. As previously mentioned, there is a high prevalence of *H. pylori* in Turkey and other southeastern Mediterranean countries. Therefore, the aim of this study was to determine the prevalence of *H. pylori* in Northern Cyprus.

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ORCID IDs of the authors: Ö.S. 0000-0001-9048-5096 24; E.E.S. 0000-0003-2743-7619 26; T.U. 0000-0001-9332-663X.

Address for Correspondence: Özgur Sirkeci
E-mail: ozgursirkeci@hotmail.com
ORCID ID: orcid.org/0000-0001-9048-5096 24

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MATERIALS AND METHODS

Patients over 18 years of age who were admitted to the gastroenterology and internal medicine department with dyspeptic complaints from December 2012 to April 2018 and evaluated for *H. pylori* infection were included in this study. In a total of 1226 patients, *H. pylori* serology was detected using the stool antigen and urea breath test results from the hospital database. The results for post-eradication control were not included in this study. The files of the patients who were evaluated for *H. pylori* infection were examined and H. pylori test results were noted in terms of age, sex, and ethnicity. The patients were divided into age groups of 18–30, 30–40, 40–50, 50–60, and over 60 years of age. The patients were also divided by ethnicity as Turkish Republic of North Cyprus (TRNC) citizens, Turkish Republic (TR) citizens, and those from Middle Eastern countries. Ethics committee approval was received from the Ethics Committee of Scientific Research (31.05.2018-58/578).

Statistical Analysis

The data were analyzed using the Statistical Package for Social Science software version 24.0 (IBM Corp., Armonk, NY, USA). The frequencies for the age groups, sex, and ethnicity were calculated. The data were expressed as percentiles and numbers.

RESULTS

H. pylori positivity was detected in 286 of 1226 patients (23.3%) with 147 of the 693 (21%) females showing *H. pylori* positivity and 139 of 533 males (26%). One hundred and nineteen (19.8%) of the 599 TRNC citizenship patients were *H. pylori* positive. For the TR citizens, 148 (25.6%) out of 571 patients were *H. pylori* positive and 12 (36.4%) out of the 33 patients from Middle Eastern countries were *H. pylori* positive. When *H. pylori* positivity was examined according to age, 133 out of 517 patients were aged 18–30 (25.8%), 48 out of 206 patients were 30–40 years of age (25.8%), 39 out of 170 patients were 40–50 years of age (22.9%), 40 out of 176 patients were 50–60 years of age (22.7%), and 26 out of 159 patients were 60 years of age or older (16.4%). When the distribution of *H. pylori* positivity was examined according to age and ethnicity the 18- to 30-year-old TRNC patients had statistically significantly lower *H. pylori* positivity ($p<0.05$).

DISCUSSION

To the best of our knowledge, this is the first prevalence study performed on *H. pylori* in TRNC. The primary findings of this study were that Cypriot Turks have a lower *H. pylori* positivity compared to citizens of Turkey and Middle Eastern countries.

H. pylori is the most common chronic infection in the world. Its prevalence varies between countries and populations due to social and economic features. Its prevalence is much more common in developing countries but this is decreasing. In Japan, *H. pylori* prevalence in individuals born before 1950 is over 90%, while those born after 2000 are at a 2% level.[12] In 1992, the prevalence of *H. pylori* in Taiwan was 54.4%, but in a recent study, its prevalence in asymptomatic patients was 21.2% and 37.9% in patients with dyspepsia.[13] A Turkish study conducted with a pediatric population compared the years 2002–2003 and 2012–2013 and found that the prevalence of infection decreased from 48% to 23%.[14]

The current study is the first study concerning the prevalence of H. pylori infection in Northern Cyprus and it found a very low prevalence compared to the surrounding countries. The disease is more common in developing countries than in developed countries. In European countries, the prevalence is 20%–40%, and in Belgium, *H. pylori* prevalence is 11%.[15] However, the infection prevalence in developing countries is extremely high. For example, *H. pylori* prevalence is 79% in Kazakhstan, 95%–100% in Indonesia and 88.3% in Serbia. Recent prevalence studies show 41% of asymptomatic patients from the United Arab Emirates are infected and 44.5% of the asymptomatic population are infected with *H. pylori* in northern Iran.[16,17] A recent prevalence study from Jordan showed very high seropositivity (88.6%).[18] According to the TURHEP study carried out in Turkey in 2003, the prevalence of *H. pylori* infection was found to be 82.5%. In addition, *H. pylori* prevalence is over 80% in southeast Mediterranean countries.[19] The current study found H. pylori frequency to be 23.3%. Although Cyprus is an eastern Mediterranean country, the prevalence of the disease is quite low in comparison to its geographic region and is similar to European countries. This may be attributed to a stable socio-cultural structure, high education level, better hygiene conditions, and a lack of overcrowding in the population.

In a study conducted by Perez-Perez et al.[20], the prevalence of *H. pylori* in Turks living in Germany was 30.4%, which was a lower prevalence in Turkey. In our study, *H. pylori* prevalence was 19.8% among Cypriot patients and 25.6% among Turkish patients who were born in Turkey but lived in Cyprus. Compared with the studies performed in Turkey, both Cypriot and Turkish patients who lived in Cyprus had a lower prevalence. It could be suggested that these results are related to the non-crowded population of Cyprus and that Turks living there enjoy a better socio-cultural structure.

When disease frequency was evaluated according to age, the lowest frequency of *H. pylori* infection was for those over 60 years and the infection was most commonly detected between 30–40 years of age. Our results are compatible with previously published results. Meyer et al.[21] stated that this may be related to a spontaneous remission of infection through aging. However, in a study from Armenia, *H. pylori* seropositivity was most commonly detected in patents over 60 years old.[22] This may be related to a lack of evaluation and treatment of *H. pylori* in dyspeptic patients. We detected the lowest prevalence in individuals over 60 years of age and believe that this was related to a spontaneous remission of infection through aging and the successful evaluation and treatment of *H. pylori* in Northern Cyprus in recent years.

Our study was a retrospective study and we only evaluated age, gender, and ethnicity. Also, we only evaluated dyspeptic patients. These were the limitations of our study. Prospective studies on this subject may be planned to evaluate an asymptomatic population with more demographic features.

H. pylori is still a common infection but with a decreasing frequency. Despite the fact that TRNC is an eastern Mediterranean country, the prevalence of *H. pylori* in TRNC is much lower than in other southeastern Mediterranean countries. More cohort studies are needed which include quality of life and education levels in both dyspeptic and asymptomatic populations.

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MAIN POINTS

- *H. pylori* is a still common infection, but with decreasing frequency all over the world. Worldwide, more than 50% of the population is infected with *H. pylori*.
- *H. pylori* is commonly found in developing countries due to risk factors including low socioeconomic levels, poor hygiene conditions, and overcrowding.
- Despite the fact that TRNC is an eastern Mediterranean country, the prevalence of *H. pylori* in TRNC is much lower than in other southeastern Mediterranean countries.

ETHICS

Ethics Committee Approval: Ethics committee approval was received from the Near East University Ethics Committee of Scientific Research. (date and number: 31.05.2018-58/578)

Informed Consent: Informed consent was not taken because this was a retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.S., T.U., Design: Ö.S., T.U., E.E.S., Supervision: Ö.S., T.U., Data Collection and/or Processing: Ö.S., T.U., Analysis and/or Interpretation: T.U., E.E.S., Literature Search: Ö.S., E.E.S., Writing: Ö.S., T.U. E.E.S., Critical Reviews: T.U., E.E.S.

DISCLOSURES

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REFERENCES

1. Sachs G, Scott DR, Wen Y. Gastric infection by Helicobacter pylori. Curr Gastroenterol Rep. 2011; 13(6): 540-6.
2. Infection with Helicobacter pylori. IARC Monogr Eval Carcinog Risks Hum. 1994; 61: 177-240.
3. Hunt RH, Xiao SD, Megraud F, Leon-Barua R, Bazzoli F, van der Merwe S, et al. Helicobacter pylori in developing countries. World Gastroenterology Organisation Global Guideline. J Gastrointestin Liver Dis. 2011; 20(3): 299-304.
4. Zhong C, Li KN, Bi JW, Wang BC. Sodium intake, salt taste and gastric cancer risk according to Helicobacter pylori infection, smoking, histological type and tumor site in China. Asian Pac J Cancer Prev. 2012; 13(6): 2481-4.
5. Mentis A, Lehours P, Mégraud F. Epidemiology and Diagnosis of Helicobacter pylori infection. Helicobacter. 2015; 20 Suppl 1: 1-7.
6. Pandeya N, Whiteman DC; Australian Cancer Study. Prevalence and determinants of Helicobacter pylori sero-positivity in the Australian adult community. J Gastroenterol Hepatol. 2011; 26(8): 1283-9.
7. Wex T, Venerito M, Kreutzer J, Götze T, Kandulski A, Malfertheiner P. Serological prevalence of Helicobacter pylori infection in Saxony-Anhalt, Germany, in 2010. Clin Vaccine Immunol. 2011; 18(12):2109-12.
8. Miendje Deyi VY, Vanderpas J, Bontems P, Van den Borre C, De Koster E, Cadranel S, et al. Marching cohort of Helicobacter pylori infection over two decades (1988-2007): combined effects of secular trend and population migration. Epidemiol Infect. 2011; 139(4): 572-80.
9. Dahlerup S, Andersen RC, Nielsen BS, Schjødt I, Christensen LA, Gerdes LU, et al. First-time urea breath tests performed at home by 36,629 patients: a study of Helicobacter pylori prevalence in primary care. Helicobacter. 2011; 16(6): 468-74.
10. Muhsen K, Cohen D, Spungin-Bialik A, Shohat T. Seroprevalence, correlates and trends of Helicobacter pylori infection in the Israeli population. Epidemiol Infect. 2011; 140(7): 1207-14.
11. Özaydın AN, Çalı Ş, Türkyılmaz AS, Hancıoğlu A. Marmara Sağlık Eğitim ve Araştırma Vakfı, 2007. TURHEP Türkiye *Helicobakter pylori* Prevalans Araştırması 2003 (TURHEP Turkey *Helicobacter pylori* Prevalence Survey 2003), İstanbul.
12. Inoue M. Changing epidemiology of Helicobacter pylori in Japan. Gastric Cancer. 2017; 20(Supll 1): 3-7.
13. Chen MJ, Fang YJ, Wu MS, Chen CC, Chen YN, Yu CC, et al. Application of Helicobacter pylori stool antigen test to survey the updated prevalence of Helicobacter pylori infection in Taiwan. J Gastroenterol Hepatol. 2020; 35(2): 233-40.
14. Yaman A, Kuloğlu Z, Kahveci A, Sayıcı U, Ensari A, Kansu A. Change of Helicobacter pylori prevalence in a decade among children undergoing endoscopy. Turk J Pediatr. 2016; 58(6): 579-82.
15. O'Connor A, O'Moráin C. Helicobacter pylori infection in Europe: current perspectives. Expert Rev Gastroenterol Hepatol. 2013; 7(6): 541-8.
16. Khoder G, Muhammad JS, Mahmoud I, Soliman SSM, Burucoa C. Prevalence of Helicobacter pylori and Its Associated Factors among Healthy Asymptomatic Residents in the United Arab Emirates. Pathogens. 2019; 8(2): 44.
17. Maleki I, Mohammadpour M, Zarrinpour N, Khabazi M, Mohammadpour RA. Prevalence of Helicobacter pylori infection in Sari Northern Iran; a population based study. Gastroenterol Hepatol Bed Bench. 2019; 12(1): 31-7.
18. Obaidat MM, Roess AA. First nationwide seroepidemiology and risk factors report of Helicobater pylori in Jordan. Helicobacter. 2019; 24(3): e12572.
19. Eshraghian A. Epidemiology of Helicobacter pylori infection among the healthy population in Iran and countries of the Eastern Mediterranean Region: a systematic review of prevalence and risk factors. World J Gastroenterol. 2014; 20(46): 17618-25.
20. Perez-Perez GI, Rothenbacher D, Brenner H. Epidemiology of Helicobacter pylori infection. Helicobacter. 2004; 9 Suppl 1: 1-6.
21. Meyer B, Werth B, Beglinger C, Dill S, Drewe J, Vischer WA, et al. Helicobacter pylori infection in healthy people: a dynamic process? Gut. 1991; 32(4): 347-50.
22. Gemilyan M, Hakobyan G, Benejat L, Allushi B, Melik-Nubaryan D, Mangoyan H, et al. Prevalence of Helicobacter pylori infection and antibiotic resistance profile in Armenia. Gut Pathog. 2019; 11: 28.

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Prevalence of *Helicobacter pylori* Infection in Pediatric Patients With Celiac Disease

Zeynep Civelek[1], Nafiye Urgancı[2], Merve Usta[2], M. Banu Özgüven[3]

[1]Department of Pediatrics, University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital, İstanbul, Turkey
[2]Division of Pediatric Gastroenterology, University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital, İstanbul, Turkey
[3]Department of Pathology, University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital, İstanbul, Turkey

Abstract

BACKGROUND/AIMS: Celiac disease (CD) has been reported to be associated with chronic gastritis and immunological disorders. The aim of the study was to determine the association between *Helicobacter pylori (H. pylori)* infection and CD in children.

MATERIALS AND METHODS: Two hundred and two patients with CD aged from 6 months to 17 years (mean: 7.12±4.64), and 209 age- and sex-matched children without CD were screened for *H. pylori* infection.

RESULTS: Endoscopic appearance revealed significant differences between those patients with CD and the controls both in the antrum and the corpus ($p<0.001$). Those patients with CD had more frequent superficial gastritis than the control group. Panmucosal gastritis was common in the *H. pylori*-positive patients with CD. Lymphoid aggregates were significantly higher in the *H. pylori*-positive and *H. pylori*-negative patients with CD ($p<0.001$).

CONCLUSIONS: The prevalence of *H. pylori* infection was not different between those pediatric patients with CD or without CD.

Keywords: Celiac disease, children, *H. pylori*, infection, endoscopy

INTRODUCTION

Celiac disease (CD) is an immune-mediated disease characterized by malabsorption due to villous atrophy of the proximal small intestine triggered by gluten. The prevalence of CD in Turkey has been reported to be 0.47%.[1]

It has been reported that 70-80% of adults and 30%–56.6% of children in Turkey are infected with *Helicobacter pylori (H. pylori)*.[2] As *H. pylori* is the leading cause of chronic gastritis (more than 90%),[3] it is speculated that the prevalence of *H. pylori* in patients with CD might be high. The autoimmune response against *H. pylori* can be a factor in the development of CD in patients infected with this bacterium.[4]

There are studies reporting no significant change in the prevalence of *H. pylori* in patients with CD when compared with the normal population and also no relationship between *H. pylori* and the natural course of CD.[5-11] An increased prevalence of *H. pylori* in those patients with CD has been established in some studies,[12] and a decreased prevalence in others.[13-15] In this study, the prevalence of *H. pylori* infection in pediatric patients with CD was determined and compared with the prevalence in children without CD.

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ORCID IDs of the authors: Z.C. 0000-0001-8483-3752; N.U. 0000-0003-4854-507X; M.U. 0000-0002-5086-6270; M.B.Ö. 0000-0002-3540-4772.

Address for Correspondence: Nafiye Urgancı
E-mail: nafiyeurganci@yahoo.com
ORCID ID: orcid.org/0000-0003-4854-507X

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MATERIALS AND METHODS

A total of 202 children with diagnosed CD and followed up between 2000 and 2015 at a division of pediatric gastroenterology were evaluated prospectively and compared with 209 controls who were recruited from children who had diagnostic upper gastrointestinal endoscopy for complaints such as abdominal pain, weight loss, growth retardation after CD had been excluded. The control group consisted of patients who were thought to have organic abdominal pain due to the fact that they had morning hunger pains, especially those who woke up during the night, and who had undergone endoscopy.

The diagnosis of CD was based on the criteria declared by ESPGHAN.[16] The diagnosis was made only histopathologically. The modified Marsh classification was used for grading the histopathological changes of the small intestinal biopsies.[17]

Endoscopic Evaluation

Endoscopy was performed with an Olympus Q260 or Olympus GIF P30 (Olympus, Tokyo, Japan). Intravenous (0.1 mg/kg) or rectal (0.5 mg/kg) midazolam was given 30 minutes before the endoscopy for sedation. The biopsy specimens were taken from four sites (the body, antrum, esophagus, and the duodenal bulb), and they were fixed in 10% formalin, paraffin-embedded sections stained with hematoxylin and eosin. Two blinded pathologists evaluated the biopsy specimens.

Visual analogue scales according to the updated Sydney scoring system on a four-point scale (0=normal/absent, 1=mild, 2=moderate and 3=marked)[18] was used for the scoring of *H. pylori* density.

Written informed consent was obtained from the parents before the procedures. The study was approved by the Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (number: 1100, date: 10.23.2018).

Statistical Analysis

Statistical analyses were performed by the IBM SPSS Statistics 22 (IBM Corp, Armonk, NY). All results are expressed as the mean ± standard deviation. The analysis was conducted using Fisher's exact test, the chi-square test and Continuity (Yates) correction. P-values of <0.05 were considered statistically significant.

RESULTS

The mean age of the patients with CD was 7.12±4.64 years (range: 6 months–17 years), and 44.5% of them were male. The mean age of the controls was 7.12±4.64 years and 50% of them were male. The characteristics of the study participants are shown in Table 1.

Significant correlation was only observed between patients with diarrhea and short stature at admission and the presence of *H. pylori* (p=0.027, p=0.025, respectively).

Endoscopic appearance was significantly different between those patients with CD and the controls both in the antrum and the corpus (p<0.001). Superficial gastritis was more common in those patients with CD than in the control group in the antrum and the corpus. Nodularity was more frequent in the control group in the antrum and the corpus than in the patient group. Comparison of the endoscopic findings between patients regarding whether they had CD or not are shown in Table 2. When the endoscopic appearance of the antrum and the corpus were compared, no significant difference was obtained in those patients with CD according to the presence of *H. pylori* (p>0.05), whereas a significant difference was observed in the histopathological findings between these patients (p<0.001). The *H. pylori*-positive patients with CD and the controls had more panmucosal gastritis than the *H. pylori*-negative ones. The lymphoid aggregates differed significantly between those patients with CD and the controls (p<0.001). No significant difference was observed between the *H. pylori*-positive and *H. pylori*-negative patients with CD according to the Marsh classification (p=0.09) and gluten free diet (GFD) (p=0.42).

There was significant difference seen in macroscopic appearance both in the antrum and the corpus, and the histopathology in the antrum between the *H. pylori*-positive patients with CD and the controls (p<0.001). Nodularity in the corpus and the antrum was low and superficial gastritis was high in the *H. pylori*-positive patients with CD. No significant difference was observed in the *H. pylori*-positive patients and the controls in terms of lymphoid aggregates in the antrum (p=0.22) (Table 3), but lymphoid aggregates were significantly higher in the corpus of patients with CD than in the controls (p=0.001).

There was no significant difference in antral appearance between the *H. pylori*-negative patients with CD and the *H. pylori*-negative controls (p>0.05), but a histopathological difference was observed between these

Table 1. The clinical characteristics of the patients and the controls

	Patients with CD (n=202)	Controls (n=209)
Age (years) mean ± SD	7.12±4.64	7.7±2.8
Male/female	0.80 (90/112)	1.00 (105/104)
Duration of disease (years), mean ± SD	8.05±3.6	
Clinical presentation, n (%)		
Short stature	96 (47.5%)	
Low weight gain	94 (46.5%)	
Diarrhea	67 (33.2%)	
Abdominal distension	38 (18.8%)	
Abdominal pain	18 (8.9%)	
Weight (<3rd percentile)	91 (45%)	
Height (<3rd percentile)	91 (45%)	
Compliance with GFD, n (%)		
Compliant	148/202 (73.3%)	
Non-compliant	36/202 (17.8%)	
EMA		
Negative	43 (22.9%)	
Positive	145 (77.1%)	
Marsh Score		
1	6 (3%)	
2	8 (4%)	
3a	51 (25.2%)	
3b	62 (30.7%)	
3c	75 (37.1%)	

CD: Celiac disease, SD: standard deviation, GFD: gluten free diet, EMA: epithelial membrane antigen, n: number.

groups (p<0.001) in both the antrum and the corpus. *H. pylori*-negative patients with CD had higher superficial gastritis in the antrum and the corpus than the *H. pylori*-negative controls. Lymphoid aggregates were significantly higher in the antrum of these patients than the controls (p=0.002) (Table 3).

In addition to nonspecific findings in the duodenum of the control group, no histopathological findings were detected except lymphocytic, plasmacytic PNL and duodenitis.

Discussion

The exact mechanism of gastrointestinal diseases such as gastritis, peptic ulceration and atrophic gastritis in patients with CD is unknown.[7] It has been proposed that *H. pylori* infection may affect the development of gluten-associated enteropathy by triggering and modulating the inflammation and immune responses in the small intestine,[7,13,14] and the pH and status of the gastric mucosa can play a key role in the digestion of gluten.[15]

Table 2. Endoscopic findings of the patients and the controls

	Patients with CD (n=202)	Controls (n=209)	p-value
Endoscopic findings			
Antrum			
Nonspecific histology	29 (14.4%)	66 (31.5%)	0.0001
Superficial gastritis	114 (56.4%)	50 (23.9%)	0.0001
Panmucosal gastritis	59 (29.2%)	93 (44.5%)	0.0001
Corpus			
Nonspecific histology	53 (26.2%)	75 (35.8%)	0.04
Superficial gastritis	104 (51.4%)	76 (36.3%)	0.002
Panmucosal gastritis	45 (22.2%)	58 (27.7%)	0.21
Macroscopic appearance			
Antrum			
Normal	147 (72.7%)	121 (57.9%)	0.001
Hyperemic	38 (18.8%)	36 (17.9%)	0.70
Nodular	17 (8.4%)	52 (24.9%)	0.0001
Corpus			
Normal	159 (78.5%)	121(57.9%)	0.0001
Hyperemic	32 (16%)	36 (17.2%)	0.79
Nodular	11 (5.5%)	52 (24.9%)	0.0001
H. pylori			
Antrum			
Positive	133 (65.8%)	135 (64.6%)	0.83
Negative	69 (34.2%)	74 (35.4%)	
Corpus			
Positive	107 (52.9%)	120 (57.4%)	0.37
Negative	95 (47.1%)	89 (42.6%)	
Lymphoid aggregates			
Positive	49 (24.2%)	29 (13.9%)	0.008
Negative	153 (75.8%)	180 (86.1%)	

p<0.05 is statistically significant.
CD: Celiac disease, n: number.

Aydogdu et al.[8] reported the possible association between CD and *H. pylori* gastritis, and stated that no effect was observed in the clinical presentation of the disease, except for abdominal distension. Luzza et al.[5] observed that recurrent abdominal pain is the only distinctive symptom between *H. pylori*-positive and *H. pylori*-negative patients and a 3-month course of GFD improved all of the symptoms in these patients whether they had *H. pylori* or not. In our study, no relationship was determined between presence of *H. pylori* and gastrointestinal symptoms in those patients with CD. In contrast with the literature, we observed that prevalence of *H. pylori* was higher in those patients with growth retardation and lower in patients with diarrhea.

Borghini et al.[9] excluded the correlation between CD and *H. pylori* infection by specific antibodies detected in gastric biopsy cultures. In the study conducted by Diamanti et al.[7], no significant difference was observed in terms of histopathology and endoscopic findings between those patients with CD and those without, but there was a higher prevalence of *H. pylori* in patients with chronic gastritis in both groups. We observed a low prevalence of nodular appearance in both the antrum and the corpus in *H. pylori*-positive patients with CD. When compared with the controls, superficial gastritis was high and panmucosal gastritis was low in patients with CD independent of their *H. pylori* status. In contrast, Luzza et al.[5] reported higher antral nodularity in both *H. pylori*-positive patients with CD and controls in comparison to *H. pylori*-negative ones, and they also stated that the prevalence of *H. pylori* did not increase in those patients with CD and that clinical and pathological signs could not be related with *H. pylori*. Similarly, Crabtree et al.[6] reported that gastritis in patients with CD is mostly related with *H. pylori,* but this was not significantly different from the normal population.

It has been stated that the prevalence of *H. pylori* was low among CD patients compared with controls, and it is estimated to be between 4% and 35%,[13-15] due to the effect of antigenicity of gliadin on the gastric acids. CD can develop at any age.[19,20] It is questionable if the presence of *H. pylori* is protective against the development of CD.[21,22] It has also been proposed that the presence of *H. pylori* can be associated with less severe villous atrophy.[21,23]

The mechanism of protection of *H. pylori* against CD is unknown. The association between *H. pylori* and a decreased the risks of allergies, atopic diseases and other inflammatory disorders has been reported,[24-26] indicating the involvement of both local and systemic regulatory T-regulatory lymphocytes in the gastric mucosa in those patients with *H. pylori*.[27,28] Lebwohl et al.[15] stated that those patients without *H. pylori* and gastric T-regulatory cells may not reduce immune responses to gluten and *H. pylori* may affect ingested gluten by modifying gastric pH or its proteases[29] and decrease its immunogenicity. Lucero et al.[30] mentioned that *H. pylori* infection rates were not different among participants whether they had CD or not, but patients with CD who had infection with *cagA*+ strains had milder histological damage, suggesting that *cagA*+ H. pylori may be protective against CD progression.

Luzza et al.[5] reported that the rate of *H. pylori* positivity was similar among children whether they were given treatment or not, whereas Ciacci et al.[13] observed that the *H. pylori* infection was significantly lower in untreated adult patients with CD than in the treated patients and the controls. Increased *H. pylori* prevalence in the treated patients can be explained by GFD-induced changes in the intestinal environment and/or the host immuno-response. In our study, no significant difference

Table 3. Comparison of endoscopic and histopatological findings between the patients and the controls

Patients with CD					controls				
	H. pylori (+)		H. pylori (-)		H. pylori (+)		H. pylori (-)		p-value
	Antrum	Corpus	Antrum	Corpus	Antrum	Corpus	Antrum	Corpus	
Normal mucosa	84 (63.3%)	77 (71.9%)	47 (68.3%)	70 (73.2%)	63 (46.7%)	60 (50%)	58 (78.4%)	61 (68.5%)	0.71
Hyperemia	30 (22.8%)	18 (17.2%)	17 (24.4%)	22 (23.2%)	25 (18.5%)	18 (15%)	11 (14.9%)	18 (20.2%)	0.54
Nodularity	19 (13.9%)	12 (10.9%)	5 (7.3%)	3 (3.6%)	47 (34.8%)	42 (35%)	5 (6.8%)	10 (11.2%)	<0.001
Nonspecific	3 (2.5%)	5 (4.7%)	25 (36.6%)	48 (50%)	7 (5.2%)	11 (9.2%)	59 (79.7%)	63 (70.8%)	0.81
Superficial gastritis	77 (58.2%)	60 (56.3%)	37 (53.7%)	44 (46.4%)	39 (28.9%)	60 (50%)	11 (14.9%)	16 (18%)	<0.001
Panmucosal gastritis	52 (39.2%)	42 (39.1%)	7 (9.8%)	3 (3.6%)	89 (65.9%)	49 (40.8%)	4 (5.4%)	10 (11.2%)	<0.001
Lymphoid aggregates	35 (26.6%)	42 (39.1%)	13 (19.5%)	7 (7.1%)	27 (20%)	24 (20%)	2 (2.7%)	5 (5.6%)	<0.001

$p<0.05$ is statistically significant.
CD: Celiac disease

was observed in *H. pylori* prevalence between those patients who were compliant with GFDs and those who were not.

CONCLUSION

In conclusion, no significant correlation was established between CD and *H. pylori* infection in our study. We observed that *H. pylori* increases the rate of gastritis in pediatric patients with CD, but this difference was not significant when compared with those children without CD. As stated in the literature in recent years, we believe that it would be more enlightening to perform immunological studies of T-regulatory cells and their associated cytokines, both in the serum and in the tissue, in those patients with HP gastritis and CD, in order to explain the etiopathogenesis.

MAIN POINTS

- The association between *H. pylori* and the natural course of CD is controversial.
- *H. pylori* increases the rate of gastritis in pediatric patients with CD.
- No significant difference was observed in the prevalence of *H. pylori* infections between those pediatric patients with CD or without.

ETHICS

Ethics Committee Approval: The study was approved by the Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (number: 1100, date: 10.23.2018).

Informed Consent: Written informed consent was obtained from the parents before the procedures.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.U., Design: N.U., Data Collection and/or Processing: Z.C., Analysis and/or Interpretation: B.Ö., Literature Search: Z.C., N.U., M.U., M.B.Ö., Writing: N.U., Critical Review: N.U., M.U.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Dalgic B, Sari S, Basturk B, Ensari A, Egritas O, Bukulmez A, et al. Turkish Celiac Study Group. Prevalence of celiac disease in healthy Turkish school children. Am J Gastroenterol. 2011; 106(8): 1512-7.
2. Yilmaz E, Doğan Y, Gürgöze MK, Unal S. Seroprevalence of Helicobacter pylori infection among children and their parents in eastern Turkey. J Paediatr Child Health. 2002; 38(2): 183-6.
3. Dixon MF. Campylobacter pylori and chronic gastritis. In: Rathbone BJ, Heatley RV, eds. Campylobacter pylori and gastroduodenal disease. Oxford: Blackwell Scientific Publications, 1989: 106-16.
4. Ramakrishnan K, Salinas RC. Peptic ulcer disease. Am Fam Physician. 2007; 76(7): 1005-12.
5. Luzza F, Mancuso M, Imeneo M, Mesuraca L, Contaldo A, Giancotti L, et al. Helicobacter pylori infection in children with celiac disease: prevalence and clinicopathologic features. J Pediatr Gastroenterol Nutr. 1999; 28(2): 143-6.
6. Crabtree JE, O'Mahony S, Wyatt JI, Heatley RV, Vestey JP, Howdle PD, et al. Helicobacter pylori serology in patients with coeliac disease and dermatitis herpetiformis. J Clin Pathol. 1992; 45(7): 597-600.
7. Diamanti A, Maino C, Niveloni S, Pedreira S, Vazquez H, Smecuol E, et al. Characterization of gastric mucosal lesions in patients with celiac disease: a prospective controlled study. Am J Gastroenterol. 1999; 94(5): 1313-9.

8. Aydogdu S, Cakir M.,Yuksekkaya HA, Tumgor G, Baran M, Arikan C, et al. Helicobacter pylori infection in children with celiac disease. Scand J Gastroenterol. 2008; 43(9): 1088-93.
9. Borghini R, Donato G, Marino M, Casale R, Picarelli A. Culture of gastric biopsies in celiac disease and its relationship with gastritis and Helicobacter pylori infection. Dig Liver Dis. 2018; 50(1): 97-100.
10. Basyigit S, Unsal O, Uzman M, Sapmaz F, Dogan OC, Kefeli A, et al. Relationship between Helicobacter pylori infection and celiac disease: a cross-sectional study and a brief review of the literature. Prz Gastroenterol. 2017; 12(1): 49-54.
11. Jozefczuk J, Bancerz B, Walkowiak M, Glapa A, Nowak J, Piescikowska J, et al. Prevalence of Helicobacter pylori infection in pediatric celiac disease. Eur Rev Med Pharmacol Sci. 2015; 19(11): 2031-5.
12. Konturek PC, Karczewska E, Dieterich W, Hahn EG, Schuppan D. Increased prevalence of Helicobacter pylori infection in patients with celiac disease. Am J Gastroenterol. 2000; 95(12): 3682-3.
13. Ciacci C, Squillante A, Rendina D, Limauro S, Bencivenga C, Labanca F, et al. Helicobacter pylori infection and peptic disease in coeliac disease. Eur J Gastroenterol Hepatol. 2000; 12(12): 1283-7.
14. Rostami Nejad M, Rostami K, Yamaoka Y, Mashayekhi R, Molaei M, Dabiri H, et al. Clinical and histological presentation of Helicobacter pylori and gluten related gastroenteropathy. Arch Iran Med. 2011; 14(2): 115-8.
15. Lebwohl B, Blaser MJ, Ludvigsson JF, Green PH, Rundle A, Sonnenberg A, et al. Decreased risk of celiac disease in patients with Helicobacter pylori colonization. Am J Epidemiol. 2013; 178(12): 1721-30.
16. Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr. 2012; 54(1): 136-60.
17. Rostami K, Kerckhaert J, Tiemessen R, von Blomberg BM, Meijer JW, Mulder CJ. Sensitivity of antiendomysium and antigliadin antibodies in untreated celiac disease: disappointing in clinical practice. Am J Gastroenterol. 1999; 94(4): 888-94.
18. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol. 1996; 20(10): 1161-81.
19. McColl KE. Clinical practice. Helicobacter pylori infection. N Engl J Med. 2010; 362(17): 1597-604.
20. Catassi C, Kryszak D, Bhatti B, Sturgeon C, Helzlsouer K, Clipp SL, et al. Natural history of celiac disease autoimmunity in a USA cohort followed since 1974. Ann Med. 2010; 42(7): 530-8.
21. Narang M, Puri AS, Sachdeva S, Singh J, Kumar A, Saran RK. Celiac disease and Helicobacter pylori infection in children: Is there any Association? J Gastroenterol Hepatol. 2017; 32(6): 1178-82.
22. Maxim R, Plesa A, Stanciu C, Girleanu I, Moraru E, Trifan A. Helicobacter pylori prevalence and risk factors among children with celiac disease. Turk J Gastroenterol. 2019; 30(3): 284-9.
23. Villanacci V, Bassotti G, Liserre B, Lanzini A, Lanzarotto F, Genta RM. Helicobacter pylori infection in patients with celiac disease. Am J Gastroenterol. 2006; 101(8): 1880-5.
24. Chen Y, Blaser MJ. Inverse associations of Helicobacter pylori with asthma and allergy. Arch Intern Med. 2007; 167(8): 821-7.
25. Chen Y, Blaser MJ. Helicobacter pylori colonization is inversely associated with childhood asthma. J Infect Dis. 2008; 198(4): 553-60.
26. Arnold IC, Dehzad N, Reuter S, Martin H, Becher B, Taube C, et al. Helicobacter pylori infection prevents allergic asthma in mouse models through the induction of regulatory T cells. J Clin Invest. 2011; 121(8): 3088-93.
27. Robinson K, Kenefeck R, Pidgeon EL, Shakib S, Patel S, Polson RJ, et al. Helicobacter pylori-induced peptic ulcer disease is associated with inadequate regulatory T cell responses. Gut. 2008; 57(10): 1375-85.
28. Wang SK, Zhu HF, He BS, Zhang ZY, Chen ZT, Wang ZZ, et al. CagA+ H pylori infection is associated with polarization of T helper cell immune responses in gastric carcinogenesis. World J Gastroenterol. 2007; 13(21): 2923-31.
29. McColl KE. Clinical practice. Helicobacter pylori infection. N Engl J Med. 2010; 362(17): 1597-604.
30. Lucero Y, Oyarzún A, O'Ryan M, Quera R, Espinosa N, Valenzuela R, et al. Helicobacter pylori cagA+ Is Associated with Milder Duodenal Histological Changes in Chilean Celiac Patients. Front Cell Infect Microbiol. 2017; 7: 376.

ORIGINAL ARTICLE

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The Effect of Problematic Internet Use and Social-Appearance Anxiety on the Smartphone Addiction of Adolescents

Özlem Şensoy[1], Dijle Ayar[2]

[1]Pediatric Nursing Department, School of Nursing, İstanbul University, İstanbul, Turkey
[2]Pediatric Nursing Department, Faculty of Health Sciences, Alanya Alaaddin Keykubat University, Antalya, Turkey

Abstract

BACKGROUND/AIMS: According to the World Health Organization, the use of technological tools, such as the internet, computers, and smartphones, is increasing every day all over the world. The widespread use of the Internet and technological devices among children today shows the risks which children carry in terms of problematic internet use and smartphone addiction. This study examined the effects of problematic internet use and social-appearance anxiety on the smartphone addiction of adolescents.

MATERIALS AND METHODS: The study was designed to collect descriptive, correlational, predictive, and cross-sectional data on 700 adolescents. The data were collected using the Problematic Internet Use Scale, the Social-Appearance Anxiety Scale, and the Smartphone Addiction Scale. Numbers, percentage analysis, and correlation and regression analyses were employed to evaluate the data.

RESULTS: A strong positive relationship was found between adolescents' problematic internet use and their smartphone addiction ($r=0.651$, $p<0.001$), while a moderate positive relationship was observed between social-appearance anxiety and smartphone addiction ($r=0.454$, $p<0.001$). Of the variables identifying smartphone addiction, 48% were associated with problematic internet use and social-appearance anxiety.

CONCLUSION: This study determined that adolescents with high problematic internet use and high social-appearance anxiety were more likely to have smartphone addiction. This study found that 48% of smartphone addiction was explained by problematic internet use and social-appearance anxiety.

Keywords: Pediatric nursing, adolescents, problematic internet use, social-appearance anxiety, smartphone addiction

INTRODUCTION

According to the World Health Organization (WHO), 2016, the use of technological tools, such as the internet, computers, and smartphones, is increasing every day all over the world.[1] The Household Use of Information Technology Survey (2019)[2] conducted in Turkey revealed that the rate of computer and internet use among individuals in the 16-year-old age group was 81.8%, with 87.9% of households having internet access and 96.8% of the population were determined to have a mobile phone or smartphone.[3]

The widespread use of the internet and technological devices among children today shows the risks which children carry in terms of problematic internet use.[4,5] Problematic internet use, which is seen as a social problem throughout the world, is defined as the use of the internet to the extent that it affects daily life adversely and the individual's inability to control their use of the internet.[6] Although problematic internet use can be seen at any age, adolescents are among the most important at risk groups.[7] Adolescents are also accepted as a group that promptly adopts new technologies and the social media

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ORCID IDs of the authors: Ö.Ş. 0000-0001-7709-7021; D.A. 0000-0001-5196-2355.

Address for Correspondence: Dijle Ayar
E-mail: dijleozer87@gmail.com
ORCID ID: orcid.org/0000-0001-5196-2355

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tools that these technologies introduce, and yet are more vulnerable to their potential adverse effects. In adolescence, when physical and psychological changes occur, the emergence of behaviors such as problematic internet use will adversely affect the development of adolescents.[8]

Problematic internet use affects the development and social life of adolescents negatively, as well as their psychological health. This situation may harm both the school life and family life of adolescents. Therefore, determining and preventing problematic internet-use related factors in adolescents is emphasized to be important to the individual and society. Adolescents tend to meet their socialization needs especially on the internet.[9] Some studies emphasized that adolescents, who especially have social-appearance anxiety, make use of the internet for socialization in this period of their lives when peer interaction and making friends are important.[10,11] Studies in the literature emphasize that there is a significant relationship between problematic internet use and social-appearance anxiety.[12-14] Interest in, liking, and attention to the sharing of adolescents who have high social-appearance anxiety leads to increased popularity among friends, which, in turn, escalates the internet usage of adolescents each day, resulting in problematic internet use.[15]

Social-appearance anxiety is the tension and anxiety experienced by the individual when their physical appearance is evaluated by others.[16] In their meta-analysis study on social-appearance anxiety and internet use in adolescents, Prizant-Passal et al.[17] found that adolescents with high social-appearance anxiety used the internet because they felt comfortable and secure in the internet environment and that the internet provided privacy of identity. As social-appearance anxiety increases in adolescents, the use of the internet gradually increases and this causes problematic internet use, and the use of the internet via smartphones today also causes an increase in smartphone addiction. There is limited research in the literature investigating the effects of internet addiction and social-appearance anxiety on smartphone addiction.[18] For this reason, this study examined the effects of problematic internet use and social-appearance anxiety on smartphone addiction in adolescents.

MATERIALS AND METHODS

Participants and Procedures

This study was a descriptive, correlational, predictive, and cross-sectional study of high school students. The study was conducted between January 2019 and June 2019 on students attending nineth, 10th, and 11th grades in three high schools selected using the simple random-sampling method among high schools affiliated to the Fatih District National Education Directorate of İstanbul Provincial Directorate of National Education. The sample size of the study was calculated to be 615 adolescents on the GPOWER version 3.0.1 (Heinrich-Heine-Universität, Düsseldorf, Germany) statistical software package based on regression analysis using the Type 1 error of 0.01, the Type 2 error of 0.01 (99% power), and the moderate effect size of 0.15. However, to better understand the relationship between the variables, 730 adolescents who agreed to participate in this study, who had parental consent, and who met the inclusion criteria were included in this study. However, 700 adolescents were included in the study as the data forms of 30 adolescents could not be obtained during the data collection process.

Inclusion Criteria

a) adolescents between 14 and 18 years of age; b) they or their parents had a smartphone; c) they had internet access at home or at school; and d) they agreed to participate voluntarily in this study, and their parents gave written consent.

Exclusion Criteria

a) they did not have access to the internet from home or school; b) they did not use a smartphone; c) they had special learning difficulties; d) they wished to withdraw from the study at some stage; and e) they could not obtain parental consent. Table 1 provides information about their demographic variables.

Data Collection

The data were collected during classes at the high schools. Participants were asked to fill out the survey forms anonymously after informed consent was obtained by the researchers. Volunteer participants took part in the study, and they were free to leave the study at any point. The data were collected from each class in a separate lesson (each lesson was 40 minutes). The scales were administered by the researcher in the classroom during a lesson with the permission of the teacher.

Instruments

The Descriptive Information Form was designed by the researchers in accordance with the literature.[10] It consists of items requesting socio-demographic information about the participants-age, gender, grade, parents' education level, monthly income level, and internet and smartphone use.

The Problematic Internet Use Scale–Adolescent Form (PIUS–A)

The Problematic Internet Use Scale–Adolescent Form (PIUS–A) was developed by Ceyhan & Ceyhan[19] to assess the problematic internet use of high school students. The scale consists of 27 items to be scored as "not appropriate at all" (1 point), "barely appropriate" (2 points), "slightly appropriate" (3 points), "reasonably appropriate" (4 points), and "fully appropriate" (5 points). The possible scores range from 27 to 135. Higher scores obtained on the scale indicate excessive and unhealthy problematic internet use. The overall internal consistency coefficient of the scale was reported to be 0.93,[19] and Cronbach's alpha value of the scale was determined to be 0.92, thus, this scale was judged to be a valid and reliable instrument to identify problematic internet use of high school students in the Turkish population. In this study, the Cronbach alpha value of the scale was determined to be 0.920.

The Social-Appearance Anxiety Scale (SAAS)

The Social-Appearance Anxiety Scale (SAAS) was developed by Hart et al.[20] to measure the social-appearance anxiety of individuals. The validity and reliability of the scale were conducted by Doğan.[21] It consists of 16 items and only one sub-dimension. Each item on the scale is scored as 1=not appropriate at all, 2=inappropriate, 3=slightly appropriate, 4=appropriate, and 5=fully appropriate. Higher scores obtained from this scale indicate more pronounced social-appearance anxiety. SAAS is a self-reporting scale developed to measure emotional, cognitive, and behavioral concerns that individuals experience about their appearance. The KMO value of the scale was reported to be 0.94. The factor loadings of the scale varied from 0.34 to 0.78. The fit indices were the Root Mean Square Error of Approximation is a Parsimony-Adjusted Index (RMSEA)=0.066; Comparative Fit Index (CFI)=0.95; Incremental Fit Index (IFI)=0.95, Normed Fit Index (NFI)=0.93, and Goodness-of-Fit Index (GFI)=0.93 (χ^2=311.89, p<0.001).[21] The Cronbach's alpha coefficient of the scale was 0.91. The scale was judged to be a valid and

reliable scale for use in adolescents. The Cronbach's alpha value of the scale in this study was determined to be 0.940.

The Smartphone Addiction Scale (SAS)

The Smartphone Addiction Scale was developed by Şar et al.[22] to determine the level of smartphone addiction among adolescents. It consists of 30 items and four sub-dimensions. It has a 5-point Likert-type structure scored as "strongly agree" (5 points), "agree" (4 points), "neutral" (3 points), "disagree" (2 points), and "strongly disagree" (1 point). The factor loadings of the scale varied between 0.44 and 0.81. The KMO value of the scale was 0.947, χ^2=4,919.85, and p=0.000. The Cronbach's alpha value of the scale was 0.96. The Model Fit Indices of the scale were RMSEA=0.075, CFI=0.97, NFI=0.96, and NNFI=0.97. As a result of the analysis, the scale was concluded to be a valid and reliable scale.[22] In this study, The Cronbach's alpha value of the scale was found to be 0.942.

Compliance With Ethical Standards

Approval of the authors who developed the scales used in this study was obtained by e-mail. At the outset, Ethics Committee approval was obtained from the Dokuz Eylül University Non-Interventional Research Ethics Committee (protocol no: 4293-GOA, date: 01.11.2018, issue: 2018/28-17). Following approval by the Ethics Committee, permission for the research was granted by the Provincial Directorate of National Education of the İstanbul Governorship. Before the study, the parents were informed about the study content in a meeting at the school. Information forms about the study aim and content were mailed to those parents who did not attend the meeting. Only those students whose parents gave written consent were included in this study.

Evaluation of data

The research data were analyzed using the IBM SPSS Statistics version 24 (IBM Corp, Armonk, NY, USA). Numbers, percentages, and mean values were used to evaluate the descriptive information of the adolescents. The Shapiro–Wilk test was used to confirm that the scale data fit the normal distribution. The relationship between problematic internet use and smartphone addiction, and the relationship between social-appearance anxiety and smartphone addiction were evaluated using a Pearson's correlation analysis. The effect of problematic internet use and social-appearance anxiety on smartphone addiction was evaluated with multiple regression analysis. The multi-collinearity test was employed to determine whether variables would be included in the model. In multi-collinearity tests, the VIF value should be less than 10, the tolerance value should be greater than 0.2, and the condition index value should be less than 15. The variables in this study were included in the model as they were found to meet the desired criteria. The significance level was accepted as p<0.001.

RESULTS

Table 1 reports the sample characteristics. As a result of the correlation analysis conducted in this study, a significant, strong, and positive correlation was determined between the mean of the total PIUS-A scores of adolescents and the mean of the total smartphone addiction scores (r=0.651, p<0.001). Additionally, there was a moderately significant positive correlation between the mean of the total SAAS-A scores of the adolescents and the mean of the total smartphone addiction scores (r=0.454, p<0.001) (Table 2).

Three models were established considering the relationship between the study variables and smartphone addiction. Multiple regression analysis was used to evaluate the models.

In Model 1, the PIUS-A was identified as explaining 45% of smartphone addiction (p<0.001). A strong positive relationship was found between

Table 1. Adolescent characteristics

	Mean	SD
Mean age	15.67	1.02
	n	%
Adolescents' age		
14	68	9.7
15	282	40.3
16	188	26.9
17	145	20.7
18	17	2.4
Gender		
Female	302	43.1
Male	398	56.9
Student's class		
9th class	338	48.3
10th class	193	27.6
11th class	169	24.1
Mother's education level		
Primary	193	27.6
Middle	156	22.3
High school	211	30.1
University	140	20.0
Father's education level		
Primary	111	15.9
Middle	169	24.1
High school	233	33.3
University	187	26.7
Perception of income		
Low	68	9.7
Middle	562	80.3
High	70	10.0
Weekly internet usage		
<5 hours per week	445	63.6
5–14 hours per week	224	32.0
15–39 hours per week	10	1.4
>40 hours per week	21	3.0
Internet usage purposes		
Studying	130	18.6
Watching movies	137	19.6
Chatting	109	15.6
Using social media sites	211	30.1
Online games	113	16.1

SD: standard deviation, n: number.

problematic internet use and smartphone addiction (β=0.669, p<0.001).

In Model 2, the mean total scores obtained from the SAAS-A were determined to explain 21% of smartphone addiction (p<0.001). A moderate positive relationship was identified between social-appearance anxiety and smartphone addiction (β=0.454, p<0.001).

In Model 3, the mean total scores obtained from the scales relating to PIUS-A and SAAS-A were included in the model. Taken together, these variables explained 48% of smartphone addiction. According to this model, the variables that affected the smartphone addiction of the adolescents mostly were determined to be the problematic internet use of adolescents (β=0.581) and social-appearance anxiety (β=0.204), respectively (p<0.001) (Table 3).

DISCUSSION

The findings of this study indicated the effects of adolescents' problematic internet use and social-appearance anxiety on smartphone addiction. Three models were created to explore the relationships between the study variables and smartphone addiction.

Model 1 showed that problematic internet use in adolescents explained 47% of smartphone addiction. The use of smartphones is highly preferred among adolescents, as it provides easy access to the internet at any time and in any place via a portable device.[23-25] The fact that internet and smartphone use allow for social interaction also encourages adolescents to use it frequently.[26] Similar to our study, there are studies in the literature showing a significant relationship between problematic internet use and smartphone addiction.[10,27,28] In a study conducted in Japan (Ministry of Internal Affairs and Communications) on the internet use of 38,630 adolescents, 59.7% of adolescents were found to access the internet via their smartphones and that they also preferred smartphones especially as they allowed internet access whenever and wherever they wanted.[29] Studies in the literature supported the findings determined in Model 1 in our study that adolescents with a high level of problematic internet use report their smartphone addiction to be at a high level.[18,27,29]

Table 2. The relation of adolescents' smartphone addiction levels with their problematic internet use and social appearance anxiety levels

	1	2	3
1. Smartphone addiction	1.0		
2. Problematic internet use	0.669*	1.0	
3. Social-appearance anxiety	0.454*	0.431*	1.0

*p<0.001.

Table 3. The predictive status of problematic internet use and social-appearance anxiety levels of the adolescent on their smartphone addiction levels

	Model 1 β	Model 2 β	Model 3 β
PIUS–A	0.669*		0.581*
SAAS-A		0.454*	0.204*
R	0.669	0.454	0.694
R^2	0.448	0.207	0.481
F	565.540	181.671	323.467
p-value	<0.001	<0.001	<0.001
DW	1.766	1.829	1.796

*p<0.001, DW: Durbin–Watson, PIUS–A: Problematic Internet Use Scale-Adolescent, SAAS–A: Social-Appearance Anxiety Scale–Adolescent Form.

Model 2 indicated that the increase in the mean SAAS-A score of adolescents led to an increase in smartphone addiction by 0.454 times and that the mean of the total SAAS-A scores explained 21% of the total smartphone addiction. Similar to our study, Doğan and Tosun[11] determined that as the level of social anxiety increased in high school students, smartphone addiction increased as well. In the study of Wang et al.[30], individuals who were concerned about establishing a face-to-face relationship were determined to use smartphones as an avoidance behavior. In a study on 443 adolescents aged between 14 and 18, Emirtekin et al. [31] found that 19% of adolescents' smartphone addiction was explained by social-appearance anxiety.

In Model 3, on the other hand, both problematic internet use and social-appearance anxiety in adolescents were determined to affect smartphone addiction. Various studies show that adolescents are highly prone to smartphone and internet use, particularly because smartphones provide easy access to the internet and anonymity among adolescents with social-appearance concerns.[17] Adolescents with pronounced social-appearance anxiety feel more confident and more comfortable on the internet, and can interact with other individuals more easily, compared to face-to-face interaction.[17,32] In their meta-analysis study, Prizant-Passal et al.[17] found that individuals with high social-appearance anxiety had higher problematic internet use and smartphone addiction. In particular, adolescents with high social-appearance anxiety prefer to socialize on the internet, especially with smartphones, because they can mask their identities and photographs on the internet, and they are highly unlikely to receive criticism of their images, which is what they worry about. Adolescents with high social-appearance anxiety have more online communication than face-to-face communication.[11] In their study with 319 university students, Demirci et al.[33] found that adolescents with high social-appearance anxiety had higher levels of smartphone addiction and that these two variables were mutually influential. In other words, adolescents who were smartphone addicts were identified as those who experience high social-appearance anxiety. In their study with 381 university students, Hawi and Samaha[34] found that students with a high level of smartphone addiction had higher levels of social-appearance anxiety compared to those students without smartphone addiction.

In the literature, there was no study investigating the effect of both PIUS and social-appearance anxiety of adolescents together with regards to smartphone addiction. The strength of our study was that it had a large sample size (n=700) and that the sample was made up of the most delicate age group in terms of smartphone use. Also, addressing social-appearance anxiety in adolescents in our study was very important in terms of preventing problems that may adversely affect the future health of adolescents, such as eating behavior disorders, anxiety, depression and addiction.[35]

Schools are the most appropriate places for health education and screening programs to promote and maintain health. Adolescents are open to the information provided at school and are more willing to participate in existing programs and activities with their peers. The duties and responsibilities of school nurses in Turkey involve the provision of accurate health information to students and the organization of training

programs in order for adolescents to acquire positive attitudes towards health education. Accordingly, the school nurse should plan training programs on the conscious use of technology for students. In addition, with these awareness training interventions, the school nurse should draw attention to the effects of technological devices on adolescents resulting from their inappropriate use. Early recognition and treatment of adolescent's smartphone addictions is crucial given the negative consequences of untreated addiction on adolescent development.

In this study, the high social-appearance anxiety of adolescents was found to significantly affect smartphone addiction. Social-appearance anxiety is another important issue that the school nurse should pay attention to. Enhancing the self-confidence of adolescents who particularly have high social-appearance anxiety and helping them to be aware of their strengths is among the important responsibilities of the school nurse. The school nurse should also follow the times when adolescents are online and when they quit, encourage them to spend more time with their family and friends, and direct them towards social activities (e.g. sports, cinema, etc.) which they are/may be interested in instead of online games.

Limitations and Suggestions for Future Research

This study has several limitations. The primary limitation of our study is the cross-sectional nature of the work, which prevents the establishment of causal relationships. The present study was limited in that we did not collect data on all the variables that could be related to PIUS-A and SAS, such as prior family or individual mental health history. This study determined that adolescents with high problematic internet use and high social-appearance anxiety were more likely to have a smartphone addiction. This study found that 48% of smartphone addiction was explained by problematic internet use and social-appearance anxiety.

CONCLUSION

In future studies, we recommend that some of the sociodemographic characteristics of adolescents, such as their past mental health history and familial features, should be taken into consideration and the effects of these variables on smartphone addiction should be investigated. In addition, issues such as internet addiction and smartphone addiction should be addressed in detail in schools, and adolescents should be provided with counseling services on these issues.

MAIN POINTS

- This study found that 48% of smartphone addiction was explained by problematic internet use and social-appearance anxiety.
- This study determined that adolescents with high problematic internet use and high social-appearance anxiety were more likely to have a smartphone addiction.
- The early recognition and treatment of adolescent's smartphone addiction are crucial given the negative consequences of untreated addictions on adolescent development.

ETHICS

Ethics Committee Approval: The Ethics Committee approval was obtained from the Dokuz Eylül University Non-Interventional Research Ethics Committee (protocol no: 4293-GOA, date: 01.11.2018, issue: 2018/28-17). Following approval by the Ethics Committee, permission for the research was granted by the Provincial Directorate of National Education of Istanbul Governorship.

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.Ş., D.A., Design: Ö.Ş., D.A., Data Collection and/or Processing: Ö.Ş., D.A., Analysis and/or Interpretation: Ö.Ş., D.A., Literature Search: Ö.Ş., D.A., Writing: Ö.Ş., D.A., Critical Review: D.A.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. World Health Organization. Internet users by region and country, 2010-2016. (2016). URL: https://www.itu.int/en/ITU-D/Statistics/Pages/stat/treemap.aspx
2. Turkish Statistical Institute. (2019). Information and communication technology (ICT) usage survey on households and individuals. Available from: http://www.tuik.gov.tr/PreHaberBultenleri.do?id=30574
3. Turkish Statistical Institute. (2015). Household Information Technology Use Survey. available from: URL: http://www.tuik.gov.tr/PreHaberBultenleri.do?id=18660
4. Sırakaya M, Seferoğlu, SS. Çocukların çevrim-içi ortamlarda karşılaştıkları riskler ve güvenli internet kullanımı, In: Akkoyunlu B, İşman A, Odabaşı HF, editors. Eğitim teknolojileri okumaları, 1. Baskı. Ankara: Pegem Akademi; 2018. pp. 185-202.
5. Prievara DK, Piko BF, Luszczynska A. Problematic internet use, social needs, and social support among youth. International Journal of Mental Health and Addiction. 2019; 17(4): 1008-19.
6. Lim Y, Nam SJ. Exploring factors related to problematic ınternet use in childhood and adolescence. International Journal of Mental Health and Addiction. 2020; 18(4): 891-903.
7. Haug S, Castro RP, Kwon M, Filler A, Kowatsch T, Schaub MP. Smartphone use and smartphone addiction among young people in Switzerland. J Behav Addict. 2015; 4(4): 299-307.
8. Çelikkaleli Ö, Ata R, Avcı R. Investigation of problematic internet usage in middle adolescence stage in terms of demographic variables. Journal of Computer and Education Research. 2018; 6(12): 123-41.
9. Akar F. Purposes and characteristics of internet use of adolescents. Pegem Eğitim ve Öğretim Dergisi. 2017; 7(2): 257-86.
10. Ayar D, Bektas M, Bektas I, Akdeniz Kudubes A, Selekoglu Ok Y, Sal Altan S, et al. The effect of adolescents' internet addiction on smartphone addiction. J Addict Nurs. 2017; 28(4): 210-4.
11. Doğan U, Çolak TS. Self-concealment, social network sites usage, social appearance anxiety, loneliness of high school students: a model testing. Journal of Education and Training Studies. 2016; 4(6): 176-83.
12. Durak HY. Investigation of nomophobia and smartphone addiction predictors among adolescents in Turkey: Demographic variables and academic performance. The Social Science Journal. 2019; 56(4): 492-517.

13. Şahan M, Çapan BE. The role of interpersonal cognitive distortions and social anxiety in adolescents' problematic internet use. Ege Eğitim Dergisi. 2017; 18(2): 887-913.

14. Tras Z, Öztemel K, Baltacı UB. Role of problematic internet use, sense of belonging and social appearance anxiety in facebook use intensity of university students. International Education Studies. 2019; 12(8): 1-10.

15. Kartol A, Peker A. The investigation of predictors of fear of missing out (fomo) in adolescents. OPUS Uluslararası Toplum Araştırmaları Dergisi, 2020; 15(21): 454-74.

16. Amil O, Bozgeyikli H. Investigating the relationship between social appearance anxiety and loneliness of Turkish University Youth. Journal of Studies in Social Sciences. 2019; 11(1): 68-96.

17. Prizant-Passal S, Shechner T, Aderka IM. Social anxiety and internet use - A meta-analysis: What do we know? What are we missing? Comput Human Behav. 2015; 62: 221-9.

18. Choi SW, Kim DJ, Choi JS, Ahn H, Choi EJ, Song WY, et al. Comparison of risk and protective factors associated with smartphone addiction and internet addiction. J Behav Addict. 2015; 4(4): 308-14.

19. Ceyhan A, Ceyhan E. The validity and reliability study of problematic internet use scale for adolescents. Journal of Dependence. 2014; 15(2): 56-64.

20. Hart TA, Flora DB, Palyo SA, Fresco DM, Holle C, Heimberg RG. Development and examination of the social appearance anxiety scale. Assessment. 2008; 15(1): 48-59.

21. Doğan T. An Investigation of the psychometric properties of the social appearance anxiety scale in an adolescent sample. Elementary Education Online. 2011; 10(1): 12-9.

22. Şar AH, Ayas T, Horzum MB. Developing the Smart Phone Addiction Scale and its validity and reliability study. Online Journal Of Technology Addiction & Cyberbullying, 2015; 2(1): 1-17.

23. Jeong YJ, Suh B, Gweon G. Is smartphone addiction different from Internet addiction? comparison of addiction-risk factors among adolescents. Behaviour & Information Technology. 2020; 39(5): 578-93.

24. Nie, J., Zhang, W, Liu Y. Exploring depression, self-esteem and verbal fluency with different degrees of internet addiction among Chinese college students. Compr Psychiatry. 2017; 72: 114-20.

25. Tateno M, Teo AR, Ukai W, Kanazawa J, Katsuki R, Kubo H, et al. Internet addiction, smartphone addiction, and hikikomori trait in japanese young adult: social isolation and social network. Front Psychiatry. 2019; 10: 455.

26. Tsitsika AK, Andrie EK, Psaltopoulou T, Tzavara CK, Sergentanis TN, Ntanasis-Stathopoulos I, et al. Association between problematic internet use, socio-demographic variables and obesity among Eur adolescents. Eur J Public Health. 2016; 26(4): 617-22.

27. Ben-Yehuda L, Greenberg L, Weinstein A. Internet addiction by using the smartphone-relationships between internet addiction, frequency of smartphone use and the state of mind of male and female students. J Reward Defic Syndr Addict Sci. 2016; 2(1): 22-7.

28. Yayan EH, Dağ YS, Düken ME, Ulutaş A. Investigation of relationship between smartphone addiction and internet addiction in working children in industry. Journal of Human Sciences. 2019; 16(1): 143-54.

29. Skarupova K, Ólafsson K, Blinka L. The effect of smartphone use on trends in European adolescents' excessive Internet use. Behaviour & Information Technology. 2016; 35(1): 68-74.

30. Wang JL, Wang HZ, Gaskin J, Wang LH. The role of stress and motivation in problematic smartphone use among college students. Computers in Human Behavior. 2015; 53: 181-8.

31. Emirtekin E, Balta S, Sural İ, Kircaburun K, Griffiths MD, Billieux J. The role of childhood emotional maltreatment and body image dissatisfaction in problematic smartphone use among adolescents. Psychiatry Res. 2019; 271: 634-9.

32. Weinstein A, Dorani D, Elhadif R, Bukovza Y, Yarmulnik A, Dannon P. Internet addiction is associated with social anxiety in young adults. Ann Clin Psychiatry. 2015; 27(1): 4-9.

33. Demirci K, Akgönül M, Akpinar A. Relationship of smartphone use severity with sleep quality, depression, and anxiety in university students. J Behav Addict. 2015; 4(2): 85-92.

34. Hawi NS, Samaha M. Relationships among smartphone addiction, anxiety, and family relations. Behaviour & Information Technology. 2017; 36(10): 1046-52.

35. Yaman Ç. Physical and physiological correlates of social physique anxiety in college students. Universal Journal of Educational Research. 2017; 5(3): 334-7.

ORIGINAL ARTICLE

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The Use of Internet for Allergic Diseases: Which One is the First Step: Specialists or Google?

Nilüfer Galip[1], Mehmet Ünsel[2]

[1]Department of Pediatrics, Divison of Pediatric Allergy and Clinical Immunology, University of Kyrenia, Kyrenia, North Cyprus
[2]Department of Internal Medicine, Division of Allergy and Immunology, Near East University, Nicosia, North Cyprus

Abstract

BACKGROUND/AIMS: Allergic diseases are one of the most common health problems worldwide affecting all ages and a popular topic on the internet. The aim of this study was to determine the tendency of internet use by those patients with allergic diseases and the parents of children with allergies.

MATERIALS AND METHODS: A cross-sectional observational study was conducted in two parts for pediatric and adult allergic patients, in two tertiary care academic hospitals in Northern Cyprus. Participants were recruited from adult patients and the parents of allergic children attending the outpatient clinics and the assessment of participants perspectives on internet use were evaluated by a written questionnaire.

RESULTS: Four hundred and fifty-two participants; 259 adults and 193 parents of pediatric patients were enrolled into the study. The only statistically significant parameter for the relation with internet use is the "age of patients". In the adult group; younger patients (below the age 35) used internet sources more frequently. In the pediatric group "age of disease onset" was analyzed with cut-off points of 6 months of age and 12 months of age, with both of them having statistically significant p-values of 0.003 and 0.000 respectively. The type of allergic disease had no association with internet use in either group.

CONCLUSION: This study reported the only statistically significant factor associated with internet use is age for adult patients and age of onset for pediatric allergies. We would like to highlight the need for evidence-based online information for parents especially for the allergies concerning the first year of life.

Keywords: Allergies, e-health, digital health, internet use, Googling

INTRODUCTION

The use of internet sources for several health issues has grown tremendously in the last decades. The internet has become popular as a first-line reference to access information easily and quickly even in health issues. Approximately 35% of Americans use the internet to access information,[1] and this frequency can be up to 72% in different sources.[2] However, information on the web about health issues may not be accurate and its usefulness in health-related problems is controversial.

In the last 20 years, the usage of the internet has grown exponentially worldwide,[3] and the effect of internet and social networks on "health" is a topic of growing interest. Information services supporting the self-management of chronic diseases may help patients to improve their knowledge about these diseases or to help them with preventive measures.

Allergic diseases are one of the most common health problems worldwide, affecting all ages. Worldwide, between 10% and 30 % of the population suffer from allergic rhinitis. Adverse drug reactions may

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ORCID IDs of the authors: N.G. 0000-0002-6982-2083; M.Ü. 0000-0003-2152-3786.

Address for Correspondence: Nilüfer Galip
E-mail: dr_ngalip@yahoo.com
ORCID ID: orcid.org/0000-0002-6982-2083

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affect up to 10% of the world's population and affect up to 20% of all hospitalized patients.[4] A study of 38,480 children (infant to 18 years) indicated that 8% have a food allergy.[5] Therefore, it is not surprising for allergies to be one of the most popular topics on the internet.

Therefore, the aim of this study was to determine the tendency of internet use by those individuals with allergic diseases and the parents of children with allergies.

MATERIALS AND METHODS

A cross-sectional observational study was conducted in two sections for pediatric and adult allergic patients in two tertiary care academic hospitals in Kyrenia and Nicosia, Northern Cyprus. Participants were recruited from February to June 2019, including all patients and parents of allergic children attending the outpatient clinics who agreed to be involved in this study. The assessment of the parents of children with allergies and the adult allergic patients' perspectives on internet use were evaluated by a written questionnaire of 7 multiple choice questions and a form to investigate the demographic characteristics of the study population. Three of the multiple-choice questions were about the information sources that they use regarding allergic diseases and the final four questions were about their internet sources. The participants gave written informed consent by filling out the questionnaire themselves. The study protocol was approved by the Ethics Committee of the University of Kyrenia with reference number 2021/01-003 and date: 31.03.2021.

Statistical Analysis

The data were statistically analyzed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics (frequencies, mean, ± standard deviation values), chi-square test, and independent samples t-test were used and $p<0.05$ was considered statistically significant.

Results

Four hundred and fifty-two patients (259 adult patients and 193 parents of pediatric patients) were enrolled in this study. The demographical characteristics of the study population are given in Table 1 for the adults and in Table 2 for the pediatric participants.

The first question was designed to determine the frequency of obtaining information from other sources rather than allergy specialists. Most of the participants stated that they try to obtain information about their health concerns from other sources before they come to an allergy clinic with 70.2% and 81.8% for pediatric and adult participants respectively. The question about the sources of information revealed that the adult participants mostly used web sources (36.5%), while the parents of pediatric patients stated that their first-line source is pediatricians (40.8%). The use of web sources as a first-line reference source was extremely low in parents (6.2%) compared to adult patients. The most preferred web sources were those web pages written by specialists with similar ratios both in the adult patients and the parents of children. In both the adult and child groups, approximately half of the participants said that they prefer to research general information related to their disease and almost one third of the participants stated that they research treatment methods. 60.8% in the pediatric group and 63.4% in the adult group expressed views that web-based sources are helpful. The detailed questions about internet use and the distribution of answers are given in Table 3.

Table 1. Demographical characteristics of adult patients

	Adults (n=259)		
Age (min–max, median, ± SD) (years)	18–79, 35, ±11.6		
Age onset (min–max, median, ± SD) (year)	2–76, 30 ±13.8		
Gender (M/F)	102/157		
Diagnosis (%)			
Asthma	24.2		
Rhinitis	72.4		
Eczema	6.2		
Anaphylaxis	3.2		
Food allergy	1.2		
Drug allergy	2.7		
Urticaria/angioedema	32.3		
Employment (employed/non-employed) (%)	91.5/8.5		
Education level (primary/secondary/graduate) (%)	14.7/21.9/63.4		
Income (low/middle/high) (%)	21.1/39.2/29.7/10		
Family history of allergies (%)	**Mother**	**Father**	**Siblings**
Asthma	12	3.5	7
Rhinitis	18.6	12.8	17.9
Eczema	2.7	2.7	3.9

min: minimum, max: maximum, SD: standard deviation, M: male, F: female, n: number.

Table 2. Demographical characteristics of pediatric patients

	Pediatric (n=193)	
Age (min–max, median, ± SD) (months)	1–216, 53, ± 53.2	
Age Onset (min–max, median, ± SD) (months)	1–198, 24, SD ± 58.5	
Gender (M/F)	80/113	
Diagnosis (%)		
Asthma	30.2	
Rhinitis	20.3	
Food allergy	2.6	
Allergic proctocolitis	17.7	
Urticaria/anaphylaxis	3.1	
Eczema	11.5	
Asthma + rhinitis	14.6	
Age	**Mother**	**Father**
Employment (employed/unemployed) (%)	24-49/35/SD ±5.1 67/33	24-63/39/SD±6.1 97.8/2.2
Education level (primary/secondary/graduate) (%)	6.2/24.7/69.1	10.2/22.2/67.6
Income (very low/low/middle/high) (%)	24.3/32.4/29.4/14	9.9/34.1/34.6/21.4
Family history of allergies	**Mother**	**Father**	**Siblings**
Asthma	24.7	10	31.6
Rhinitis	65.8	66.7	57.9
Eczema	23.3	23.3	10.5

min: minimum, max: maximum, SD: standard deviation, M: male, F: female, n: number.

Table 3. Distribution of answers to questions

Questions	Pediatric (n=193)	Adult (n=259)
Did you try to get information from any other sources about your/your child's allergic disease before you attended the allergy clinic?		
Yes/no (%)	70.2/29.8	81.8/14.4
What were your sources for obtaining information about your/your child's allergic disease?		
General practitioner for adults/ Pediatrician for children	40.8	12.4
Allergy specialist	29.1	27.9
Friends, family members, people around with similar problems	9.1	16.4
Web sources	21	36.5
Others	-	6.9
What is your first-line source of information?		
General practitioner for adults/ Pediatrician for children	44.5	19.2
Allergy specialist	43.5	43.7
Friends, family members, people around with similar problems	5.8	5.7
Web sources	6.2	31.4
Are you using Google or similar search engines to get information about your/ your child's allergic diseases?		
Yes/no	82.8/17.2	74.1/25.9
What kind of web sites do you prefer to read about your/your child's allergic diseases?		
Web-sites written by specialist allergists	52.2	53.8
Discussion forums	29.1	32.1
Newspapers/magazines	7	7.7
Social media (Facebook/ Instagram etc.)	11.5	6.4
What kind of information do you read from internet sources about your/your child's allergic diseases?		
General information about the course of the disease/symptom	50.3	49.2
Information about treatment methods	31.8	32.7
Disease specific diets	11.5	4.9
Alternative medicine	6.4	13.1
Did internet resources help you?		
Yes	23.7	23
Partly	60.8	63.4
No	15.5	13.6

Table 4. Relation of demographical characteristics with internet use

Factors related with internet use	p-value (adults)	p-value (pediatric)
Gender	0.91	0.81
Age	0.05*	0.003 and 0.000**
Education (graduate vs. others)	0.63	0.54
Employment	0.09	0.14
Income	0.26	0.13

*Age cut-off point for adult patients is taken as 35 years of age, **For pediatric patients onset age of the disease is taken in two cut-off points, 12 months and 6 months of age.

When the factors associated with internet use are examined (Table 4), the only statistically significant parameter is the age of patients. In the adult group of allergic patients, the younger patients used internet sources more frequently and its analysis is statistically significant with a cut-off age of 35 years old. In the pediatric group, the "age of disease onset" was analyzed to reveal cut-off points of 6 months of age and 12 months of age, with both of them being statistically significant with p-values of 0.003 and 0.000 respectively. However, the type of allergic disease had no association with internet usage either in the adult patients or the parents according to this study.

DISCUSSION

The current study demonstrated that patients with allergies or the parents of children with allergic diseases tend to research health information online, which is similar to many other health issues.

The use of the internet, in other words, the "World Wide Web" for several health issues and medical purposes has been increasing worldwide in recent years. Several medical topics have been the subject of internet research including cancer, developmental disabilities, vaccines etc. A new term that we have come across in the last decade is Dr. Google. Dr. Google is the de facto second opinion for Americans according to many surveys.[6] A study from Austria showed a rate of 21% in terms of internet use in the parents of children before attending a general pediatric outpatient clinic due to an acute illness.[7] In another study by the same author, this rate was given as 94.4%.[8] A study from Nigeria showed a level of 40% internet search in the parents of children with orofacial cleft with a majority of 80% of these using Google.[9] Nevertheless, it is still unknown in which areas that internet usage is more needed or more useful regarding different health issues.

When we evaluate the studies about internet use in terms of allergic diseases, there are few studies from developed countries.[10-12] We thought our study can be a pioneering study to reveal the deficiency and the need in the field of internet sources about both adult and childhood allergic diseases. We have not encountered any other studies investigating this issue in the literature to date.

A study from Ireland revealed the high demand for web-based information relating to allergic diseases in Ireland.[11] This study also evaluated and compared the searches regarding allergies in the years 2015 and 2019 and concluded with two dramatic outcomes. Firstly, over 60% of websites promoted nonevidence-based diagnostics, and secondly, Government-funded Department of Health websites did not feature in the top five results for "allergy testing", "food allergy" or "food intolerance" in either 2015 or 2019.[11] In current study, unlike the study

in Ireland, the participants stated that they mostly prefer to obtain information from web pages written by experts.

Another study from the United States of America (USA) investigating the educational quality of videos on YouTube about food allergy concluded that the videos frequently recommend controversial diagnostics and commonly identify non-IgE mediated reactions.[10] They underlined the fact that there is a need for high-quality educational videos on food allergy.[10] These striking results from several countries made us think how important it is for reliable sites with evidence based information to provide knowledge in the native language for each country.

We did not question whether the information obtained from internet sources had an effect on the follow-up or treatment process of the allergic diseases in our study. However, there are a large number of studies questioning this issue specific to other diseases in the literature.[7,13,14] In early 2019, the World Health Organization stated vaccine hesitancy to be one of the most severe threats to global health. It is fueled by nonevidence-based misinformation spread by celebrities and politicians via the internet.[15] Similarly, allergic conditions are susceptible to misinformation, non-validated testing procedures and personalized treatment methods that are not supported by evidence-based literature.[16]

In a study evaluating the role of health information sources in decision making with Hispanic mothers during their child's first 1000 days, Criss et al.[13] stated the trusted information sources in their study to be healthcare providers (doctors, nurses, nutritionists), but the participants in all different groups mentioned the need to use other sources such as the internet and family members for immediate information.[13] This study mentioned the importance for healthcare workers to be aware of the health information environment of their patients and provide easy to read, printed handouts or lists of trustworthy internet sources.[17] In another review by Stukus[16], the author underlined the importance for medical professionals to be aware of their patients' need to obtain information online and recommended medical professionals to spend time searching information online from a patient perspective and suggested that this could help to better understand their patients' needs.[16]

Allergic diseases in early infancy are usually very challenging for new mothers. The most striking result of our study is the relationship between disease onset and internet use, which was statistically shown to be higher for the mothers of younger children. One of the studies evaluating the accuracy of online discussion forums used by mothers for common childhood aliments revealed that the most common health topics listed are bowel movements (e.g., constipation, diarrhea, abnormal color), reflux, gas, vomiting, rash and eczema.[14] These symptoms appear to be so similar with the symptoms of allergic diseases usually seen in early infancy. The study concluded that nearly half of the health-related advice provided in online discussion forums is accurate but there is also incorrect advice available and these sources are not verified through evidence-based resources.[14] In our study, the rate of parents using discussion forums was 29.1%, and these were the second most preferred internet resource after those web-sites written by experts.

There are also some studies evaluating the "Googling" habits of people according to their different types of allergic diseases.[12,18] Kornafeld et al.[12] reported the search interest and search volume on anaphylaxis in their study. They found similar trends worldwide and in the USA. The top three topics were anaphylaxis, anaphylactic shock and food allergies. They also analyzed search interests on anaphylaxis by country and the top three countries showing the highest activity of "Googling" were Austria, New Zealand and the United Kingdom (UK). In that study, the researchers reported on the risk of misinformation regarding anaphylaxis caused by search engines and social media and concluded that high quality information is obligatory to be presented to the public by healthcare professionals.[12] Another study evaluating the Google trends regarding rhinitis and related topics in European countries revealed that significant spikes in Google searches were found with the increased awareness of this disease. There were differences in the searches between countries but similarities between different regions of the same country so their findings call for uniform nomenclature or self-management guidelines for each country.[18]

The limitations of this study are that the allergic diseases were not classified according to their severity and the effect of internet use on the follow-up and treatment of the disease were not investigated.

CONCLUSION

Patients with allergies or the parents of children with allergic diseases tend to research health information online in a similar way to many other health issues. This study reported the only statistically significant factor associated with this tendency is age for adult patients and onset age of the disease for pediatric allergies. We clearly demonstrated that the frequency of parents' internet usage is increasing as the onset age of the allergic disease gets younger. There are other studies in the literature which support this finding, reporting that the rate of online research is higher in new mothers. Despite the fact that the type of allergic disease has no relation to internet usage according to our study, we would like to underline the need for evidence-based online information on food allergy and atopic dermatitis, which are the most common allergic diseases in the first year of life.

MAIN POINTS

- Most of the participants stated that they try to obtain information regarding their health concerns from other sources before they come to an allergy clinic with 70.2% and 81.8% for pediatric and adult participants respectively.
- The most preferred web sources were those web pages written by specialists.
- Adult patients mostly used web sources (36.5%), while the parents of pediatric patients stated that their first-line source for allergies is a pediatrician (40.8%).
- This study reported the only statistically significant factor associated with internet use for allergies is "age" for adult patients and "onset age of the disease" for pediatric allergies.
- According to this study, there is a clear need for evidence-based online information on food allergy and atopic dermatitis, which are the most common allergic diseases in the first year of life.

ETHICS

Ethics Committee Approval: The study protocol was approved by Institutional Ethics Committee with reference number 2021/01-003 and

date 31.03.2021.

Informed Consent: The participants gave written informed consent by filling out the questionnaire themselves.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.G., Design: N.G., Data Collection and/or Processing: N.G., M.Ü., Analysis and/or Interpretation: N.G., M.Ü., Literature Search: N.G., M.Ü., Writing: N.G., M.Ü.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. McMullan M. Patients using the Internet to obtain health information: how this affects the patient-health professional relationship. Patient Educ Couns. 2006; 63(1-2): 24-8.
2. Pew Internet Project. Susannah Fox. The social life of health information. 2014: (3 screens). Available from: URL: http://www.pewresearch.org/fact-tank/2014/01/15/The-Social-Life-of-Health-Information/ (Accessed on Feb 6, 2018)
3. International Telecominications Union. Statistics. (2 screens). Available from: URL: https://www.itu.int/en/ITU-D/Statistics/Pages/stat/default.aspx (Accessed on Feb 6, 2021)
4. American Academy of Allergy Asthma and Immunology. Allergy Statistics. Available from: URL: https://www.aaaai.org/About/News/For-Media/Allergy-Statistics (Accessed on April 4, 2021).
5. Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics. 2011; 128(1): e9-17.
6. Fox S. After Dr Google: peer-to-peer health care. Pediatrics. 2013; 131 Suppl 4: S224-5.
7. Sebelefsky C, Voitl J, Karner D, Klein F, Voitl P, Böck A. Internet use of parents before attending a general pediatric outpatient clinic: does it change their information level and assessment of acute diseases? BMC Pediatr. 2016; 16: 129.
8. Sebelefsky C, Karner D, Voitl J, Klein F, Voitl P, Böck A. Internet health seeking behaviour of parents attending a general paediatric outpatient clinic: A cross-sectional observational study. J Telemed Telecare. 2015; 21(7): 400-7.
9. Adekunle AA, James O, Adeyemo WL. Health Information Seeking Through Social Media and Search Engines by Parents of Children With Orofacial Cleft in Nigeria. Cleft Palate Craniofac J. 2020; 57(4): 444-7.
10. Reddy K, Kearns M, Alvarez-Arango S, Carrillo-Martin I, Cuervo-Pardo N, Cuervo-Pardo L, et al. YouTube and food allergy: An appraisal of the educational quality of information. Pediatr Allergy Immunol. 2018; 29(4): 410-6.
11. King C, Judge C, Byrne A, Conlon N. Googling Allergy in Ireland: Content Analysis. J Med Internet Res. 2020; 22(5): e16763.
12. Kornafeld A, Gonzalez-Estrada A, Dimov V. 'Googling' anaphylaxis. Curr Opin Allergy Clin Immunol. 2019; 19(5): 432-8.
13. Criss S, Woo Baidal JA, Goldman RE, Perkins M, Cunningham C, Taveras EM. The Role of Health Information Sources in Decision-Making Among Hispanic Mothers During Their Children's First 1000 Days of Life. Matern Child Health J. 2015; 19(11): 2536-43.
14. Farrell A. Accuracy of online discussion forums on common childhood ailments. J Med Libr Assoc. 2018; 106(4): 455-63.
15. World Health Organization. Ten threats to global health in 2019. Available from: URL: https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019 (Accessed on Jun 2, 2021)
16. Stukus DR. How Dr Google Is Impacting Parental Medical Decision Making. Immunol Allergy Clin North Am. 2019; 39(4): 583-91.
17. Buultjens M, Robinson P, Milgrom J. Online resources for new mothers: opportunities and challenges for perinatal health professionals. J Perinat Educ. 2012; 21(2): 99-111.
18. Bousquet J, Agache I, Anto JM, Bergmann KC, Bachert C, Annesi-Maesano I, et al. Google Trends terms reporting rhinitis and related topics differ in European countries. Allergy. 2017; 72(8): 1261-6.

ORIGINAL ARTICLE

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Correlation of Trends in the Incidence of Selected Infectious Diseases with Healthcare Expenditures: An Ecological Study

Seda Behlül[1,2], Macide Artaç Özdal[2]

[1]Department of Health Management, Near East University Faculty of Health Sciences, Nicosia, North Cyprus
[2]Department of Health Management, European University of Lefke, Faculty of Health Sciences, Lefke, North Cyprus

Abstract

BACKGROUND/AIMS: Although progress has been made in the prevention and treatment of infectious diseases, they continue to represent global public health problems, leading to the deaths of millions of people. This study aimed to evaluate the correlation between the trends in the incidence of human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), syphilis, tuberculosis and Hepatitis B and the changes in health expenditure between 2007 and 2016 in Northern Cyprus.

MATERIALS AND METHODS: The incidences of particular infectious diseases over time were examined using the serial measure method. The area under the curve (AUC) line was calculated to determine the frequency of infectious disease occurrence. P-values less than 0.05 were accepted as significant.

RESULTS: The AUC value for Hepatitis B was the highest, followed by syphilis, tuberculosis and AIDS (AUC=2482.50 for Hepatitis B, AUC=149.07 for syphilis, AUC=99.66 for tuberculosis and AUC= 72.82 for AIDS). There was a significant reduction in the incidence of tuberculosis and syphilis during the study period (r= -0.702; F=7.792; p=0.024 for tuberculosis) and (r= -0.663; F=6.263; p=0.037 for syphilis). There was a statistically significant negative correlation between the trends in health expenditure and tuberculosis (r= -0.829; F=11.404; p=0.010; r^2=0.588) and syphilis (r= -0.755; F=10,583; p=0.012; r^2 =0.467).

CONCLUSION: The reducing trend in the incidence of tuberculosis and syphilis corresponding to in-creasing health expenditure suggests the need for health policies to sufficiently fund preventive measures against infectious diseases, particularly hepatitis B.

Keywords: Area under the curve, health expenditures, epidemiology, infectious diseases, serial measure-ment method

INTRODUCTION

The variety and number of infectious diseases observed in a region or country are among the most crucial indicators of the health status of that country. Despite progress in prevention and diagnostic methods, infectious diseases are still a major challenge in terms of global infection control.[1,2] There is varied evidence on the impact of social, economic and behavioral conditions on the epidemiology of diseases around the world.[3,4] For example, the rates of human immunodeficiency virus (HIV), syphilis and Hepatitis B are higher in low- and middle-income countries compared to high income regions.[5]

The pathogens causing infectious diseases can be transmitted to the human body indirectly or through direct contact, such as from human to human or from water, food, or non-human vectors to humans.[6] In order to determine the current situation regarding the impact of infectious

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ORCID IDs of the authors: S.B. 0000-0003-0324-5380; M.A.Ö. 0000-0002-9334-2485.

Address for Correspondence: Seda Behlül
E-mail: seda.behlul@neu.edu.tr
ORCID ID: orcid.org/0000-0003-0324-5380

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diseases, legal regulations have been established to ensure that countries report statistics correctly. Nations have introduced regulations that make the reporting of infectious diseases, such as tuberculosis (TB), Acquired Immunodeficiency Syndrome (AIDS), Hepatitis B, syphilis and others, obligatory. According to figures provided by the World Health Organization (WHO) in 2017, there were 940,000 deaths from AIDS, 1.4 million deaths due to TB and 208,000 deaths associated with Hepatitis B.[2] In a study conducted in the European Union and the European Economic Area, the ranking of selected infectious diseases according to the annual Disability Adjusted Life Years (DALYs) per 100,000 population was determined. The results showed that the highest was influenza, second was TB, and third was HIV, followed by Hepatitis B and syphilis.[7]

Hepatitis B, a viral infection which can cause both acute and chronic diseases, is an important global public health problem. It has been estimated that 325 million people worldwide are chronic carriers of this disease. Hepatitis B can be transmitted during labor or through exposure to infected blood. The virus can spread through the blood or other bodily fluids of an infected person. It is also a significant occupational hazard for healthcare workers. The chronic infection that it causes in the liver may lead to more serious problems, such as cirrhosis of the liver and liver cancer. Hepatitis B, however, can be prevented by safe and effective vaccines, with a 95% effectiveness in preventing Hepatitis B infections.[8] Syphilis is a sexually transmitted disease (STD) that has primary, secondary, latent and tertiary stages.[9] It is among the notifiable diseases because its incidence is increasing around the world.[10] With the increase in the severity of the disease, syphilis can cause serious problems such as central nervous system and cardiovascular system diseases.[11]

Syphilis is a major public health problem that has significant potential to cause adverse outcomes. One of the major concerns related to syphilis is that, similar to other sexually transmitted diseases, it is also associated with HIV and leads to adverse health outcomes.[12] People with syphilis infections are more likely to be infected with HIV.[11]

TB is considered to be a major public health threat.[13] In the WHO declaration in 2016, the elimination of the TB epidemic is one of the sustainable development goals. TB originates from bacteria that primarily affect the lungs. It can be treated and prevented. In addition, people with HIV, malnutrition, diabetes, tobacco users and people with weakened immune systems are at increased risk of developing this disease.[14] HIV infection is identified as the strongest risk factor for TB, meaning that there is a high likelihood of TB in HIV positive individuals. About a quarter of the world's population has hidden TB.[15]

HIV/AIDS can be regarded as a major global health problem as it leads to many opportunistic infections by increasing the susceptibility of patients to many other infectious diseases. Drug addicts, sex workers, prison inmates and others living in closed environments are among the populations at high risk of HIV transmission. Unsafe injections with HIV contaminated needles, non-sterile medical procedures, and unsafe sexual intercourse are all associated with an increased risk of HIV infections.[16]

Particular infectious diseases have adverse impacts on the social and economic welfare of societies.[17] The health status of populations can be affected by various factors, including ecological balance, demographic and cultural structure, and natural resources. Ecosystem and climate changes, population growth, migration, substance abuse, microbiological changes, and lack of public health programs can increase infectious diseases, thus leading to poor health. Poverty is a crucial factor affecting the transmission of various infectious diseases and the health outcomes of infectious diseases represent one of the most important indicators of poverty, thus increasing the prevalence and severity of poverty.[18]

Within the scope of preventive health services, various screening tests are performed for the early diagnosis of diseases. The health expenditure allocated for these services has an important place in general health expenditures. In the literature, it has been determined that those expenditures made for the purpose of detecting STDs have an impact on the incidence in the population.[19] Therefore, an accurate determination of disease burdens can lead to an increase in health expenditures in preventive health care or public health practices and a decrease in the incidence of these diseases in the future. This situation has a positive impact on the health and financial situation of a society.[20-22] Similarly, a reduction in expenditure on infection prevention and control programs in European Countries has had a negative impact on the health level of the population, particularly in terms of preventing the diagnosis of diseases such as TB and HIV.[23]

Uncontrolled population growth causes various public health concerns in societies. In particular, the high prices for accommodation in crowded populations, high costs or inadequate healthcare services, and the lack of sufficient manpower are factors that can increase the burdens on healthcare services. To meet the needs for shelter and food, unprotected and risky sexual practices are also increasing the risk of infectious diseases, mainly HIV/AIDS, syphilis, Hepatitis B and TB.[24] In crowded living conditions, inadequate nutrition, increased use of alcohol and substances, increasing sexual and physical violence and discrimination make the diagnosis and treatment of diseases such as HIV and TB more difficult, leading to the rapid progress of such diseases. Therefore, this leads to negative impacts on the health of societies.[25,24]

HIV/AIDS, syphilis, TB, Hepatitis B, Hepatitis C, and Gonorrhea are among the infectious diseases that are reported by State Hospitals and Health Centers in Northern Cyprus. HIV/AIDS, syphilis, TB and Hepatitis B are infectious diseases whose recordings are obligatory and are the most frequently seen notifiable infections in the country. Although progress has been made in the prevention and treatment of these infectious diseases, they continue to represent global public health problems, leading to the deaths of millions of people. The main aim of this study was to evaluate the trends in the major notifiable infectious diseases, namely HIV/AIDS, syphilis, TB and Hepatitis B, in Northern Cyprus. This study further aimed to evaluate the correlation between the trends in particular infectious diseases and any changes in health expenditure.

MATERIALS AND METHODS

An ecological study design was employed to study the trends in the incidence of the selected notifiable infectious diseases, including AIDS, syphilis, TB and Hepatitis B. Data on the cases diagnosed with the particular infectious diseases reported between 2007 and 2016 were collected from reports published by the Prime Ministry, State Planning Organization (SPO).[26] The incidences of these infectious diseases were calculated based on the total population (at risk population) living in Northern Cyprus. The total population numbers for Northern Cyprus between 2007 and 2016 were also collected from the records of the SPO (excluding military personnel and non-residents).

Permission to collect and analyze the data was obtained from the SPO. The study methodology was approved by the university's Ethics Committee of European University of Lefke with reference number ÜEK/63/02/07/2021/03 and date 06.07.2021.

Statistical Analysis

In this study, the data were analyzed using the IBM Statistical Package for Social Science (SPSS) software version 23.0 (IBM Corp., Armonk, NY, USA) and MedCalc Package Programs version 18.11 (1993-2019 MedCalc Software bvba). Trends in the incidence of AIDS, Hepatitis B, syphilis and TB between 2007 and 2016 were assessed using descriptive analysis. Using the MedCalc package program, the incidences of particular infectious diseases over time were examined using the serial measure method. The area under the curve (AUC) was calculated, which allowed for the determination of the frequency of the disease within a certain period of time. For this purpose, the AUC line was calculated to determine the frequency of infectious disease occurrence.[27]

The correlation between the incidence of infectious diseases and health expenditures was investigated by regression and correlation analysis. The functional structure of the relationship between the diseases and health expenditures is explained using the linear regression model. P-value <0.05 was accepted as significant.

RESULTS

This study includes four notifiable diseases. The descriptive statistics on the incidence of the selected infectious diseases are shown in Table 1. The mean incidence between 2007 and 2016 for Hepatitis B was greater compared to other infectious diseases, with 277.91±29.30 cases per 100,000 population diagnosed with Hepatitis B. The mean incidence for AIDS was the least, with 8.48±3.18 cases per 100,000 population.

The trends and frequency of the infectious diseases observed in the study period were determined based on the AUC line. The AUC graphs show fluctuations for the 10-year period for each of the diseases studied. For Hepatitis B infection, in the ten-year period, the lowest value was determined in 2011 and the highest value in 2016 (Figure 1a). For syphilis and TB infections, in the ten-year period, the lowest incidence was determined in 2016 and the highest value in 2007 (Figures 1b and Figure 1c). AIDS was found to have its highest value in 2015 and lowest in 2009 (Figure 1d).

The status of these studied diseases in the population over the 10-year period are shown in Figure 1. The AUC graphs show in which time period the highest and lowest values of incidence occurred. When the changes in the incidence of each infectious disease between the years of 2007 and 2016 were compared, there were significant decreases in the incidence trends of TB and syphilis during the study period (r= -0.702; p=0.024 for TB and r= -0,663; p=0.037 for syphilis) (Table 2). There were no significant changes in the incidence of Hepatitis B and AIDS (p=0.409 for Hepatitis B and p=0.154 for AIDS).

In the regression model used to study the correlation between the changes in health expenditure and the selected notifiable infectious diseases, a statistically significant correlation was found between the health expenditure with TB (p=0.010) and health expenditure with syphilis (p=0.012) (Table 3). There was no significant relationship between health expenditure and AIDS or Hepatitis B (p-value >0.05). Since there were significant correlations between health expenditure and syphilis and TB, the trends in health expenditures and the incidence of syphilis and TB were studied for the period between 2007 and 2016. A correlation model for the relationship between health expenditure and the selected notifiable infectious diseases was studied by checking the incidence of each infectious disease. When allowing for the incidence of the other infectious diseases studied, there were still significant negative correlations between health expenditure with syphilis and TB (r=-0.683, p<0.05 for Syphilis and r=-0.767, p<0.01 for TB). However, a positive correlation was found between TB and syphilis (r=0.961, p<0.01) (Table 4). According to these results, Hepatitis B was determined to have had an important disease in the population. The AUC value of Hepatitis B was the highest among the studied diseases, followed by syphilis, TB and AIDS respectively (AUC=2,482.50 for Hepatitis B, AUC=149.07 for syphilis, AUC=99.66 for TB and AUC= 72.82 for AIDS) (Table 5).

The health expenditures in North Cyprus increased in Turkish Lira from 183 million TL ($140 million) to 321 million TL ($125 million) between 2007 and 2016. The median and mean health expenditures in the study period were 210 million TL and 226 million ± 467 million TL, respectively (1 USD = 1.3 TL, Inflation rate % = 9.4 in 2007), (1 USD = 3.02 TL, inflation rate % = 10.19 in 2016). Figures 2a and 2b show the correlation between health expenditure and the incidence of syphilis and TB. In the period between 2007 and 2016, as the health expenditure increased, there was a significant decline in the incidence of syphilis and TB (r^2=0.467 and r^2=0.588). First, last, minimum, maximum and AUC values of the infectious diseases are included in this table. The AUC graphs are used to compare the incidence of the cases in the society and show their importance for the society. According to this, Hepatitis B was seen to be the most important disease in the time period examined (Figure 3).

The trends in health expenditure and infectious diseases are shown in Figure 4. While the infectious disease rates changed per 100,000 population per year, health expenditure increased between 2007 and 2014, decreased between 2014 and 2015 and increased again between 2015 and 2016.

DISCUSSION

Main Findings of This Study

Both the health expenditure and the population of the Turkish Republic of Northern Cyprus (TRNC) increased every year between 2007 and 2016. The selected infectious diseases, namely Hepatitis B, TB, AIDS and syphilis, which are defined as notifiable diseases, were studied in terms of the changes in their incidence and the correlation between their incidence rates and health expenditures. The most commonly observed notifiable infectious disease in the study period was reported to be Hepatitis B, however there was no significant change in its trends or its incidence. The trends in the incidence of syphilis and the TB incidence

Table 1. The mean incidence of infectious diseases, namely Hepatitis B, Syphilis, Tuberculosis and AIDS observed between the years of 2007 and 2016

Variable	Median	Mean ± SD	Minimum	Maximum
Hepatitis B	286.89	277.91±29.30	221.83	320.56
Tuberculosis	10.65	11.06±3.68	4.12	17.82
AIDS	8.07	8.48±3.18	4.19	12.67
Syphilis	15.90	16.71±5.06	8.84	27.25

AIDS: acquired immunodeficiency syndrome, SD: standard deviation.

rate showed a significant decrease during the study period (2007 and 2016). The analysis of the correlation between the changes in health expenditures and trends in the incidence of infectious diseases showed that there were significant correlations between health expenditures and syphilis and TB. There was a significant decrease in the incidence of TB and syphilis as health expenditures increased. There was also a significant positive correlation between TB and syphilis incidence.

Explanation and Comparison With Existing Literature

The present study revealed that Hepatitis B had the greatest incidence during the 10-year study period, with no significant decline in its incidence during these years. This may indicate that the population is not sufficiently vaccinated to reduce the incidence of this disease and there is a crucial need to develop policies and interventions to increase

Table 2. Comparison of the changes in incidence of the infectious diseases, namely Hepatitis B, Syphilis, Tuberculosis and AIDS

Diseases	r	B0	B	F	p-value	95% CI	
						Lower	Upper
Hepatitis B	0.295	-5457.318	2.851	0.760	0.409	-4.691	10.393
Tuberculosis	-0.702	1732.06	-0.856	7.792	0.024	-1.562	-149
AIDS	0.487	-1022.56	0.513	2.483	0.154	-238	1.263
Syphilis	-0.663	2245.90	-1.108	6.263	0.037	-761	0.031

p<0.05 was accepted as significant.
AIDS: acquired immunodeficiency syndrome, CI: confidence interval.

Table 3. The Comparison of the correlation between health expenditure and infectious diseases, namely Hepatitis B, Syphilis, Tuberculosis and AIDS observed between the years of 2007 and 2016

Diseases	r	B0	B	F	p-value	95% CI	
						Lower	Upper
Hepatitis B	0.360	$6.63x10^8$	5752772	1.194	0.306	-6387884.215	-4054471949
Tuberculosis	-0.829	$4.577x10^9$	$-9.878x10^8$	11.404	0.010	-163675862	-30846102.3
AIDS	0.612	$8.037x10^8$	$7.054x10^8$	4.683	0.060	-.5845508.865	184161747.1
Syphilis	-0.755	$5.476x10^9$	$-1.158x10^9$	10.583	0.012	-63120685.2	23857422.03

p<0.05 was accepted as significant.
AIDS: acquired immunodeficiency syndrome, CI: confidence interval.

Table 4. The results of the correlation analysis between health expenditure and the incidence of infectious diseases, namely Hepatitis B, Syphilis, Tuberculosis and AIDS observed between the years 2007 and 2016

	Health Expenditure (95% CI)	Hepatitis B (95%CI)	Syphilis (95% CI)	Tuberculosis (95% CI)
Hepatitis B	0.360 (L: -0.348 U: 0.807)			
Syphilis	-0.683* (L: -0.918 U: -0.094)	0.203 (L: -0.489 U: 0.738)		
Tuberculosis	-0.767** (L: -0.042 U: -0.265)	0.046 (L: -0.601 U: 0.656)	0.961** (L: 0.839 U: 0.991)	
AIDS/HIV	0.608 (L: -0.036 U: 0.895)	0.463 (L: -0.235 U: 0.846)	-0.023 (L: -0.643 U: 0.615)	-0.145 (L: -0.710 U: 0.553)

*p<0.05, ** p<0.01 was accepted as significant.
AIDS: acquired immunodeficiency syndrome, HIV: human immunodeficiency virus, CI: confidence interval.

Table 5. The AUC values of the trends in the incidence of infectious diseases, namely Hepatitis B, Syphilis, Tuberculosis and AIDS observed between the years of 2007 and 2016

Variables	First	Last	Min	Max	AUC
Hepatitis B	303.92	289.27	221.83	320.56	2482.50
Syphilis	17.81	4.12	4.12	17.81	99.66
Tuberculosis	27.24	8.83	8.83	27.24	149.07
AIDS	12.22	11.78	4.19	12.67	72.82

Area under curve (baseline = 0).
AUC: area under the curve, AIDS: acquired immunodeficiency syndrome, Min: minimum, Max: maximum.

the coverage of Hepatitis B vaccinations in the region.[28] There was a decreasing trend in the incidence of tuberculosis in the study period. Although there is no data regarding tuberculosis in Northern Cyprus, there is data regarding tuberculosis incidence, treatment and control in the Southern part of the country, which is home to the officially recognized government which joined the European Union (EU) in 2004. There is evidence that surveillance systems and control measures are adequately implemented in this region and this has helped to reduce the number of tuberculosis cases, particularly in the Cyprus born population.[29] However, the increase in migration to Cyprus is reflected

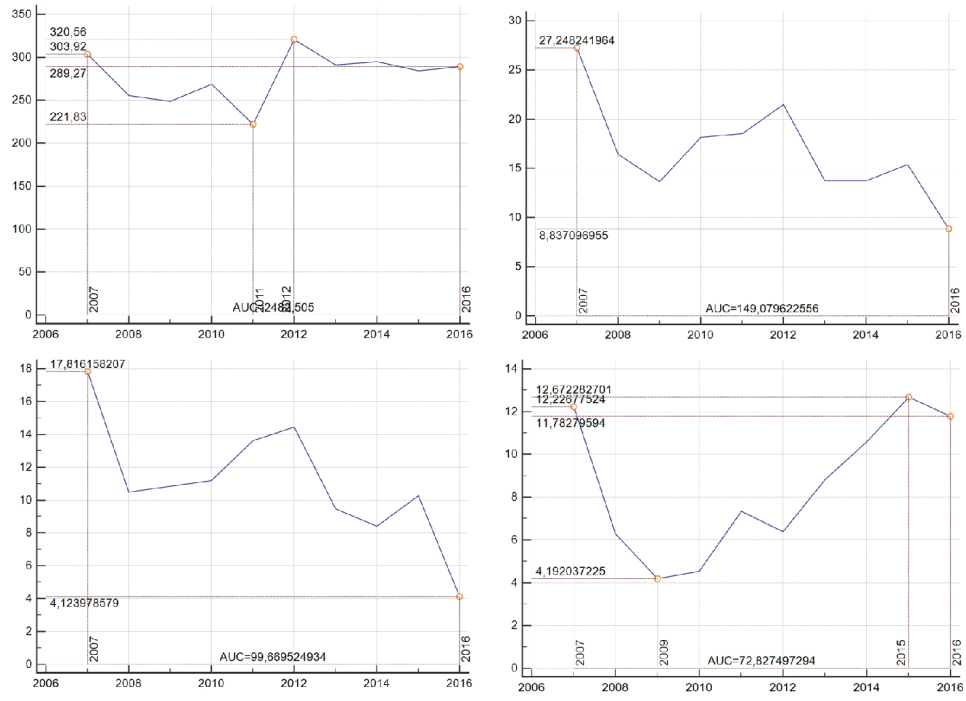

Figure 1. The trends in the incidence of Hepatitis B, Syphilis, Tuberculosis and AIDS between the years of 2007 and 2016 shown as the area under the AUC line.

a) The trends in the incidence of Hepatitis B infection between 2007 and 2016, **b)** The trends in the incidence of Syphilis infections between 2007 and 2016, **c)** The trends in the incidence of Tuberculosis infection between 2007 and 2016, **d)** The trends in the incidence of AIDS infections between 2007 and 2016.

AUC: area under the curve, AIDS: acquired immunodeficiency syndrome.

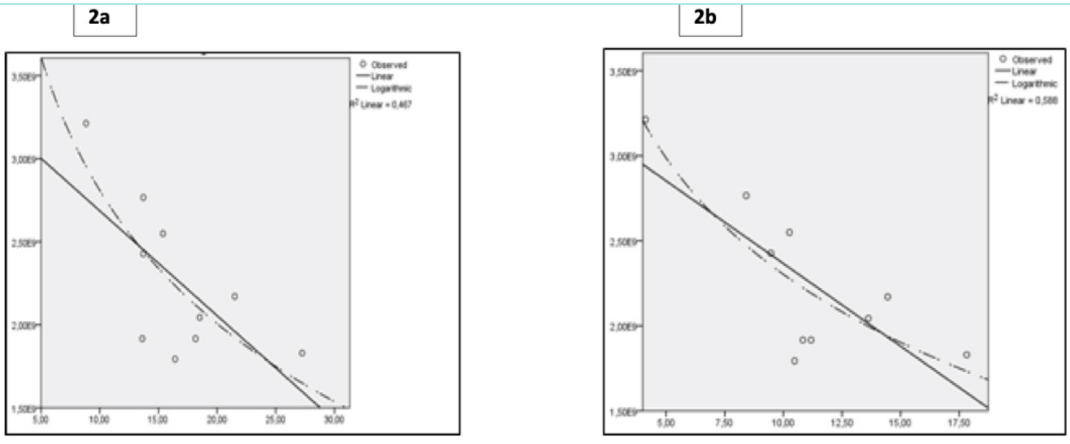

Figure 2. The correlation between trends in health expenditure and trends in the incidence of the infectious diseases, namely syphilis and tuberculosis between the years of 2007 and 2016.

a) The correlation between the trends in health expenditure and syphilis between the years of 2007 and 2016, **b)** The correlation between the trends in health expenditure and tuberculosis between the years of 2007 and 2016.

in the increased incidence of tuberculosis, particularly among the foreign-born population.[30] This was not reflected in the trends shown in our study. This is likely because cases seen in migrants are managed by the healthcare services in Southern Cyprus and the decrease in the recording of TB cases in Northern Cyprus is more representative of the decreases in the Cyprus born population.[29] Therefore, this may show that cases involving residents in the country cannot be detected and this may lead to a significant threat to life for the whole population as a result of the risk of transmission to healthy people.

The study also showed that there was a significant decrease in the incidence of syphilis in the country. Syphilis infection rates are strongly correlated with sexual activities and the prevalence of AIDS.[12] AIDS is not widely prevalent in the country and this study also showed that the 10-year incidence of the disease was low. In addition, the country has policies for screening groups that are sexually active and provides treatment for sexually transmitted diseases.[31] These may explain why the syphilis incident rate has reduced.

The correlation analysis between the trends in health expenditure and the incidence of notifiable infectious diseases showed that the incidence of TB and syphilis decreased in tandem with the increase in the health expenditure. There is broad evidence that supports the importance of healthcare expenditure, particularly spending on public health and prevention services to control STDs.[32,21] The evidence regarding TB shows that although spending on treatment of TB has an impact on the reduction of its incidence to a certain extent,[33] public health and social service spending play the most important role in controlling the incidence of this disease among populations.[34,35] Although there are limited data regarding the trends in health expenditures allocated to public health services and policies for the prevention of infectious diseases in Northern Cyprus, the amount of health expenditure allocated to public health services,[25] and the enhancement in the vaccination program against tuberculosis may explain this association.[36] In a general study on STDs, it was also shown that incidence control is not associated with the level of healthcare expenditures.[32] It is therefore important to further investigate this association between the incidences of infectious diseases, especially by allowing for other factors, such as public health spending, social service spending etc.

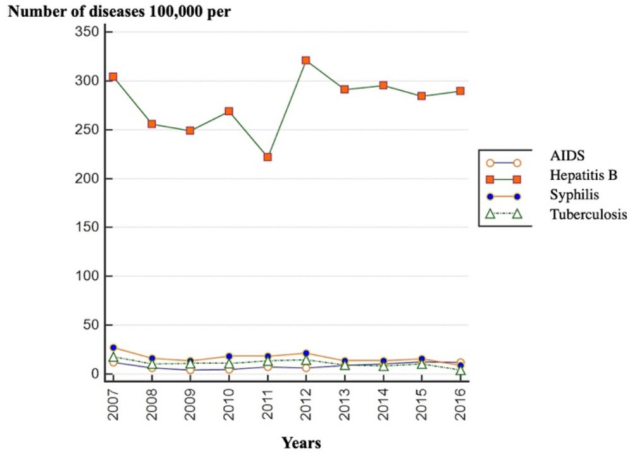

Figure 3. The trends in the number of infectious diseases, namely Hepatitis B, Tuberculosis, Syphilis, AIDS/HIV per 100,000 population observed between the years of 2007 and 2016.

AIDS: acquired immunodeficiency syndrome, HIV: human immunodeficiency virus

Strengths and Weaknesses of the Study

This study is the first study to evaluate trends in selected important infectious diseases in Northern Cyprus, which have largely not been represented in studies discussing the health status and health problems in Southern Cyprus, which is the officially recognized part of the country supported by many international healthcare organizations. Due to political reasons, many important health problems have not been sufficiently treated in the country and it is important to provide evidence and support those parties who are influential in enhancing public health in the region. This study, therefore, carries crucial importance in providing guidance for the control of infectious diseases in the region. Another strength of this study is that it uses the AUC method to study the frequency of infectious diseases in the population, rather than for the evaluation of diagnostic performance. Hence, this study provides evidence supporting the use of this method

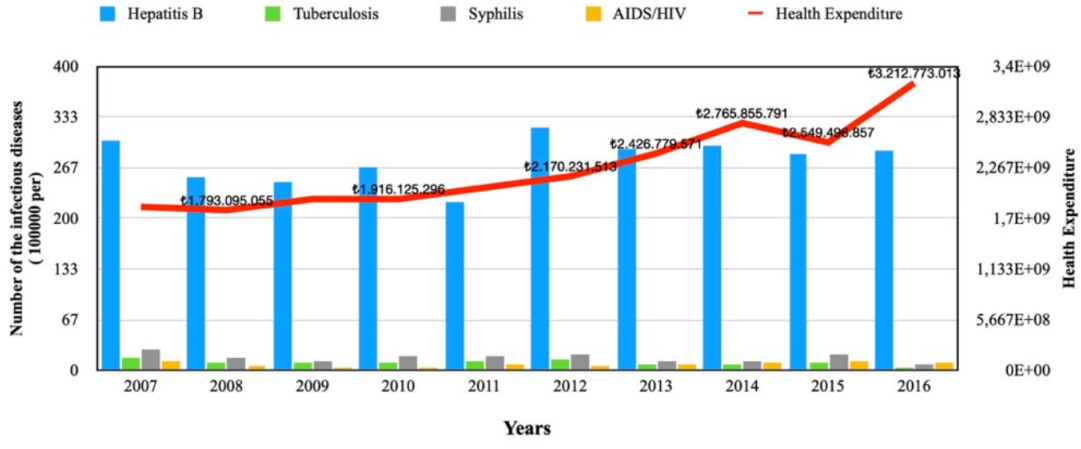

Figure 4. The trends in the incidence of infectious diseases, namely Hepatitis B, Tuberculosis, Syphilis, AIDS/HIV and health expenditure observed between the years of 2007 and 2016.

AIDS: acquired immunodeficiency syndrome, HIV: human immunodeficiency virus

for different purposes and this approach can act as a guide for researchers performing studies in the field of epidemiology. Ecological data were used in this study, which are collective data representing the whole population, but not individuals. When resources for collecting data are limited, this approach is advantageous as it can be used to quickly and economically to collect data about the health status of a population. However, ecological data provides information for the total population, and the findings may not be applicable for all individuals. This renders studies using ecological data prone to ecological fallacy, which assumes that individuals in a population all have similar characteristics. Another limitation of this study is that the data on the incidence of infectious diseases were collected from the vital registration system of Northern Cyprus, which is a developing region. In developing regions, vital registration systems may not be accurately recorded, particularly as they may not take international recording standards into consideration. For example, the disease records may not be based on the International Coding System of Diseases, e.g. ICD-10. This may also reduce the accuracy of the findings obtained using vital statistics data to evaluate trends in infectious diseases.

Infectious diseases represent a significant threat to public health, particularly in developing countries, which makes it essential to investigate their distribution in different regions in order to provide guidance for their prevention and control. This study focused on the incidence of four notifiable infectious diseases in Northern Cyprus, namely Hepatitis B, TB, HIV/AIDS and syphilis, and evaluated the trends in their incidence as well as the correlation of their incidence with healthcare expenditure. Hepatitis B was shown to be the most prevalent condition in the region with trends indicating a decline between 2007 and 2016. TB and syphilis were shown to have reduced incidences and these trends were associated with increases in health expenditures. Policies must be developed to effectively treat Hepatitis B cases and take preventive measures in order to reduce the transmission of this infection within the population. Although TB, HIV/AIDS and syphilis were not shown be a significant threat to public health in the population, the reduced incidence observed could be as a result of the migrant population using healthcare services other than those in Northern Cyprus or due to the poor detection rates of cases. Therefore, it is necessary to continually improve healthcare services and public health spending for the control and prevention of these diseases.

CONCLUSION

Infectious diseases, namely HIV/AIDS, TB, syphilis and Hepatitis B have been important public health problems that require targeted interventions for their control and this warrants studies on the trends in incidence of these diseases that have been classified as notifiable diseases. The incidence of Hepatitis B was the highest among the other diseases studied, although with no increase in the incidence between 2007 and 2016. TB was the only notifiable disease studied, which showed significant reduction in incidence in the specified study period. These incidence rates are providing important implications for developing measures for improving the management of the Hepatitis B vaccinations and continuing the prevention measures taken against TB. Further studies must be conducted to assess the rates of infectious diseases and the association between the rates of diseases and other factors such as, public health spending, social service spending and others.

MAIN POINTS

- This study used the serial measure method to study the trends in AIDS, Hepatitis B, syphilis and tuberculosis between 2007 and 2016 in Northern Cyprus.
- There was a significant reduction in the incidence of tuberculosis and syphilis during the study period.
- This study also reports a negative correlation in the trends in health expenditure and tuberculosis and syphilis.

ETHICS

Ethics Committee Approval: The study methodology was also approved by the European University of Lefke Ethics Committee with the number and date ÜEK/63/02/07/2021/03.

Informed Consent: Informed consent is not warranted in this study as the data used in the study was ecological data, not including information on individual patients. The consent for the use of data from the State Planning Organization of Turkish Republic of Northern Cyprus (TRNC).

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.B., M.A.Ö., Design: S.B., M.A.Ö., Data Collection and/or Processing: S.B., M.A.Ö., Analysis and/or Interpretation: S.B., M.A.Ö., Literature Search: S.B., M.A.Ö., Writing: S.B., M.A.Ö., Critical Review: S.B., M.A.Ö.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Unemo M, Bradshaw CS, Hocking JS, de Vries HJC, Francis SC, Mabey D, et al. Sexually transmitted infections: challenges ahead. Lancet Infect Dis. 2017; 17(8): e235-79.
2. World Health Organization. (2017) Global Hepatitis Report 2017. World Health Organization. Available from: URL: https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/ [Accessed on 26th May 2021].
3. Peeling RW, Mabey D, Kamb ML, Chen XS, Radolf JD, Benzaken AS. Syphilis. Nat Rev Dis Primers. 2017; 3: 17073.
4. Frew PM, Parker K, Vo L, Haley D, O'Leary A, Diallo DD, et al. Socioecological factors influencing women's HIV risk in the United States: qualitative findings from the women's HIV SeroIncidence study (HPTN 064). BMC Public Health. 2016; 16(1): 803.
5. Degenhardt L, Peacock A, Colledge S, Leung J, Grebely J, Vickerman P, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. Lancet Global Health. 2017; 5(12): e1192-207.
6. Ellwanger JH, de Lima Kaminski V, Chies JAB. Emerging infectious disease prevention: Where should we invest our resources and efforts? Journal of Infection and Public Health. 2019; 12(3): 313-6.

7. Cassini A, Colzani E, Pini A, Mangen MJ, Plass D, McDonald SA, et al. Impact of infectious diseases on population health using incidence-based disability-adjusted life years (DALYs): results from the Burden of Communicable Diseases in Europe study, European Union and European Economic Area countries, 2009 to 2013. Euro Surveill. 2018; 23(16): 17-00454.
8. World Health Organization. (2020a) Hepatitis B 2020 factsheet. Available from: URL: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b (Accessed on 26th May 2021).
9. Kojima N, Klausner JD. An update on the global epidemiology of syphilis. Curr Epidemiol Rep. 2018; 5(1): 24-38.
10. Forrestel AK, Kovarik CL, Katz KA. Sexually Acquired Syphilis. Part 1: Historical aspects, microbiology, epidemiology, and clinical manifestations. J Am Acad Dermatol. 2019; 82(1): 1-14.
11. Totten S, MacLean R, Payne E. Infectious syphilis in Canada: 2003-2012. Can Commun Dis Rep. 2015; 41(2): 30-4.
12. Lang R, Read R, Krentz HB, Ramazani S, Peng M, Gratrix J, et al. Increasing incidence of syphilis among patients engaged in HIV care in Alberta, Canada: a retrospective clinic-based cohort study. BMC Infect Dis. 2018; 18(1): 125.
13. Semu M, Fenta TG, Medhin G, Assefa D. Effectiveness of isoniazid preventative therapy in reducing incidence of active tuberculosis among people living with HIV/AIDS in public health facilities of Addis Ababa, Ethiopia: a historical cohort study. BMC Infect Dis. 2017; 17(1): 5.
14. World Health Organization (2020b) Tuberculosis 2020 factsheet. Available from: URL: https://www.who.int/news-room/fact-sheets/detail/tuberculosis (Accessed on 26th May 2021).
15. Davy-Mendez T, Shiau R, Okada RC, Moss NJ, Huang S, Murgai N, et al. Combining surveillance systems to investigate local trends in tuberculosis-HIV co-infection. AIDS Care. 2019; 31(10): 1311-8.
16. World Health Organization (2020c) HIV/AIDS 2018/factsheet. Available from: URL: https://www.who.int/news-room/fact-sheets/detail/hiv-aids. (Accessed on 26th May 2021).
17. Jin Y, Austin L, Vijaykumar S, Jun H, Nowak G. Communicating about infectious disease threats: Insights from public health information officers. Public Relations Review. 2019; 45(1): 167-77.
18. Adhikari SR, Sapkota VP, Khan M, Maskay NM. A study of the relationship between infectious diseases and health economics: some evidences from Nepal. Asian Pac J Trop Dis. 2016; 6(6): 437-42.
19. Chesson HW, Ludovic JA, Berruti AA, Gift TL. Methods for Sexually Transmitted Disease Prevention Programs to Estimate the Health and Medical Cost Impact of Changes in Their Budget. Sex Transm Dis. 2018; 45(1): 2-7.
20. Chesson HW, Harrison P, Scotton CR, Varghese B. Does funding for HIV and sexually transmitted disease prevention matter? Evidence from panel data. Eval Rev. 2005; 29(1): 3-23.
21. Gallet CA. The impact of public health spending on California STD rates. International Advances in Economic Research. 2017; 23(2): 149-59.
22. Owusu-Edusei Jr, Chesson HW, Gift TL, Tao G, Mahajan R, Ocfemia MC, et al. The estimated direct medical cost of selected sexually transmitted infections in the United States, 2008. Sex Transm Dis. 2013; 40(3): 197-201.
23. O'Riordan M, Fitzpatrick F. The impact of economic recession on infection prevention and control. J Hosp Infect. 2015; 89(4): 340-5.
24. Grief SN, Miller JP. Infectious disease issues in underserved populations. Prim Care. 2017; 44(1): 67-85.
25. Kral AH, Bluthenthal RN, Lorvick J, Gee L, Bacchetti P, Edlin BR. Sexual transmission of HIV-1 among injection drug users in San Francisco, USA: risk-factor analysis. Lancet. 2001; 357(9266): 1397-401.
26. State Planning Organization (2017). Available from: URL: http://www.devplan.org/Frame-tr.html (Accessed on April 24, 2019).
27. Gulkesen KH, Koksal IT, Bilge U, Saka O. Comparison of methods for prediction of prostate cancer in Turkish men with PSA levels of 0-10 ng/mL. J BUON. 2010; 15(3): 537-42.
28. de Castro Rocha DFN, da Cunha Rosa LR, de Almeida Silva C, de Oliveira BR, Martins TLS, Martins RM B, et al. Epidemiology of HIV, syphilis, and hepatitis B and C among manual cane cutters in low-income regions of Brazil. BMC Infect Dis. 2018; 18(1): 546.
29. Voniatis C, Migliori GB, Voniatis M, Georgiou A, D'Ambrosio L, Centis R, et al. Tuberculosis elimination: dream or reality? The case of Cyprus. Eur Respir J. 2014; 44(2): 543-6.
30. Petrou P. Battling Tuberculosis beyond antibiotics. Value Health Reg Issues. 2017; 13: 79-81.
31. Turkish Republic of Northern Cyprus, Republican Assembly. 7/2000 Nightclubs and similar Entertainment Places Laws. 2000.
32. Cheeks MA, Fransua M, Stringer HG Jr, Silva S, Relf M. A Quality improvement project to increase early detection of syphilis infection or re-infection in HIV-infected men who have sex with men. J Assoc Nurses AIDS Care. 2016; 27(2): 143-52.
33. Dye C, Lönnroth K, Jaramillo E, Williams BG, Raviglione M. Trends in tuberculosis incidence and their determinants in 134 countries. Bull World Health Organ. 2009; 87(9): 683-91.
34. Jiang WX, Long Q, Lucas H, Dong D, Chen JY, Xiang L, et al. Impact of an innovative financing and payment model on tuberculosis patients' financial burden: is tuberculosis care more affordable for the poor? Infect Dis Poverty. 2019; 8(1):21.
35. Talbert-Slagle KM, Canavan ME, Rogan EM, Curry LA, Brandley EH. State variation in HIV/AIDS health outcomes: the effect of spending on social services and public health. AIDS. 2016; 30(4): 657-63.
36. TRNC Functional Institutional Review. TEPAV, TRNC Premiership, 2012. [Online] Available from: URL: https://www.tepav.org.tr/upload/files/1455090622-3.KKTC_Devleti_Fonksiyonel___Kurumsal_Gozden_Gecirme_Calismasi___ANA_RAPOR.pdf (Accessed on May 26, 2021).

ORIGINAL ARTICLE

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The Effects of the Violence Tendency Levels of Nursing Students on Their Attitudes Towards Homosexual Individuals

Nurdan Aymelek Çakıl[1], Hilal Seki Öz[2], Yasemin Ceyhan[3]

[1]Department of Nursing Women's Health, Kırşehir Ahi Evran University Faculty of Health Sciences, Kırşehir, Turkey
[2]Department of Psychiatric Nursing, Kırşehir Ahi Evran University Faculty of Health Sciences, Kırşehir, Turkey
[3]Department of Internal Diseases Nursing, Kırşehir Ahi Evran University Faculty of Health Sciences, Kırşehir, Turkey

Abstract

BACKGROUND/AIMS: Nurses' attitudes towards homosexuality are an important factor affecting the quality of care given to homosexual individuals. Therefore, attitudes towards homosexual individuals and the variables affecting these attitudes should be investigated in the undergraduate period of nursing students. This study was conducted to determine the effects of the violence tendency levels of nursing students on their attitudes towards homosexual individuals.

MATERIAL AND METHODS: This study used a cross-sectional and descriptive design. It was conducted with 502 nursing students at a state university. The data were collected using a student information form, the Hudson and Ricketts Homophobia Scale (HRHS) and the Violence Tendency Scale (VTS).

RESULTS: The mean HRHS score of the students was 94.25±22.23, and their mean VTS score was 37.82±8.25. It was found that the students' attitudes towards homosexuals were related to their academic year, number of siblings, the region they lived in, and whether they live with their parents or not. Additionally, it was determined that the students' level of tendency towards violence was low, and low levels of violence tendency were related to higher levels of education of the mother ($p<0.05$). There was no significant relationship between the students' violence tendency levels and their homophobia levels ($R2=0.001$).

CONCLUSION: It was determined that the nursing students' level of tendency towards violence was low, but their attitudes towards homosexuals were negative. Their level of tendency towards violence did not explain their attitude towards homosexuals significantly. These results showed that there are different factors affecting nursing students' homophobic attitudes.

Keywords: Nursing students, tendency towards violence, homophobia, attitudes

INTRODUCTION

Sexual identity is a concept that defines the sexual orientation of an individual regardless of gender, not only by physiological and biological characteristics, but also by the individual's emotions, thoughts and desires. A discrepancy between what would be expected of an individual's physiology and their sexual orientation is expressed by various concepts.[1] The most common discrepancies are lesbian, gay, bisexual and transgender (LGBT). Homosexuality is a general expression that includes all of these concepts.[2] The reason for the occurrence of this condition, which is also called homosexuality, is not fully known. While some studies define these orientations as psychological

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ORCID IDs of the authors: N.A.Ç. 0000-0002-5765-7359; H.S.Ö. 0000-0003-2228-9805; Y.C. 0000-0002-2100-5324.

Address for Correspondence: Nurdan Aymelek Çakıl
E-mail: nurdanaymelek@gmail.com
ORCID ID: orcid.org/0000-0002-5765-7359

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disturbances, others emphasize that the underlying cause of such an orientation is not fully known.[2,3] Among the situations that could cause homosexuality, nutritional, genetic, hormonal, developmental, social and cultural effects are mentioned.[2] However, there is no scientifically proven finding.

The differentiation of sexual orientation is incompatible with the habits brought by social culture, whether or not there is any psychological disorder. For this reason, homophobic behaviors against homosexual individuals are observed in society. Homophobia is a negative attitude towards individuals with different sexual orientations.[4] Social norms suggest that men and women should be romantically attracted to their opposite sex. If this is not the case, unfair and violent approaches such as the exclusion, rejection or humiliation of the person are encountered.[5] Violence may be psychological as well as physical. Those who practice violence engage in deliberate behavior, with the aim of direct harm or damage to the individual they are opposed to. It was reported that deaths due to violence rank fourth among individuals aged 15–44 in the world, while it is 2.28 per hundred thousand in all age groups in Turkey.[6] It is inevitable that homophobic and transphobic violence will be directly proportional to the rate of violence in the general population.[7,8] Homosexuals are in a group with a high probability of being exposed to violence due to the perspective of society, and studies have supported this view.[9,10]

Homosexual individuals face different forms of violence such as being neglected by society as well as physical and psychological violence. These negative attitudes and behaviors lead to the deterioration in the health of homosexual individuals over time.[11,12] Like all people in the world, homosexuals have the right to receive fair and quality health care. Health services should be provided equally to everyone, regardless of the individual, their race or language. All occupational groups are expected to act in accordance with professional awareness in the provision of health services. In particular, nursing is an important profession among health care providers as it interacts most with the patients. Unconditional admission, holistic care and humanitarianism are at the core of the profession of nursing. With this understanding, every individual who wants to receive health services should be welcomed equally. In line with the roles of the profession of nursing, nurses are expected to display their advocacy, caregiver, therapeutic and rehabilitative roles towards homosexual individuals when necessary.[13] The finding in some studies that nursing students' levels of tendency towards violence are low shows that nurses comply with professional ethics and morals.[14-18] However, some studies have also reported that health workers have negative attitudes towards homosexual individuals.[19-21]

It is extremely important in undergraduate education to train nurses to enhance their professional understanding by teaching them the roles and responsibilities of the profession of nursing. However, the influence of social culture in the formation of these targeted outcomes should not be ignored. The occupational awareness of individuals who have been raised according to the accepted norms of sexual identity and sexual orientation in their society may also be affected accordingly. Although there are studies examining the views of nursing students towards homosexual individuals,[19-21] there is insufficient information on the effect of any possible violent tendencies on their homophobic points of view.[22] Therefore, this study was conducted to determine the impact of nursing students' levels of tendency towards violence on their attitudes towards homosexuals. Thus, knowing about the levels of tendency towards violence and homophobia among nursing students, who are the nurses of the future, will be possible, and how much the concept of tendency towards violence can explain negative attitudes towards homosexual individuals will be determined. According to these results, the differences in gender and gender roles will be emphasized in the course content of the students. This will contribute to making the right decisions and planning appropriate care for patients with different sexual orientations in the process of providing nursing care.

In this context, the research questions of the study were determined as follows:

1. What are the attitudes of nursing students towards homosexuals?
2. What is the violence tendency level of nursing students?
3. How do nursing students' violence tendency levels affect their attitudes towards homosexuals?

MATERIALS AND METHODS

Objective and Methods

With this cross-sectional and descriptive study, it was aimed to determine the effect of nursing students' violence tendency levels on their attitudes towards homosexuals.

Population and Sample

The population of this study was determined to be 806 nursing students in their first to fourth years of study at the Health Sciences Faculty of a state university in Turkey between November and December in 2020. Five hundred and two students who voluntarily agreed to participate in the study and were selected by a purposive sampling method participated in this study. The results of the power analysis conducted using the G*Power 3.1 (Heinrich-Heine-Universität, Düsseldorf, Germany) program showed the power of the study conducted with 502 participants to be 95% with type-1 error, setting alpha at 0.05.

Data Collection Tools

The data were collected using the Student Information Form prepared by the researchers, the Violence Tendency Scale and the Attitudes towards Homosexuality Scale.

Student Information Form

This form was prepared by the researchers using the literature. It consists of 14 questions about the students' gender, academic year, income perceptions, regions of residence, cohabitation situations, whether or not their parents were alive, levels of education of their parents, parental employment statuses, families' attitudes, presence of people with different sexual orientations around them and their statuses of being friends with those people.[1,4,5,14,18,19]

Violence Tendency Scale (VTS)

The Violence Tendency Scale was developed by Göka, Bayat and Türkçapar in 1995, in a study conducted on behalf of the Turkish Ministry of National Education to measure the violence tendencies of secondary school students. Later, the scale was re-evaluated, its validity was tested, and it was used in the research of the Turkish Prime Ministry Family Research Institution on "violence in the family and in the social

field" (1998). The reliability coefficient of the scale was found to be 0.87 in this study. It is a four-point Likert-type scale consisting of 20 items. For each item, the response options range from (1) not at all suitable to (4) very suitable. Higher scores on the scale indicate higher levels of tendency towards aggression and violence. Violence tendency was categorized according to the scores obtained from the scale. Scores of 1–20 are evaluated as "very low", 21–40 points are evaluated as "low", 41–60 points are evaluated as "high", and 61–80 points are evaluated as "very high" tendency towards violence.[23] In this study, the Cronbach's alpha reliability coefficient of the scale was found to be 0.83.

Hudson and Ricketts Homophobia Scale (HRHS)

It is a 25-item, six-point Likert-type scale developed by Hudson and Ricketts to measure attitudes towards homosexual individuals in 1980. The scale was adapted to Turkish by Sakalli and Uğurlu[24] and the number of items in the scale was reduced to 24 in 2001. Items 5, 6, 8, 10, 11, 13, 17, 18, 21, 22 and 23 in the scale are inversely scored. A single total score is taken from this scale, and higher scores indicate increased negative attitudes towards homosexuals. In Sakallı and Uğurlu's[24] study, the Cronbach's alpha internal consistency coefficient of the scale was found to be 0.94. In this study, the Cronbach's alpha coefficient of the scale was found to be 0.88.

Data Collection

After obtaining the necessary preliminary permissions for the study, the implementation of the study was carried out online between November and December 2020, the data were collected according to the principles of the Declaration of Helsinki. Each participant was informed with an informed consent form, and their consent was obtained.

Statistical Analysis

The SPSS version 22 (IBM Corp, Armonk, NY, USA) program was used for data analysis. Frequencies, percentages and means were used as the descriptive statistics of the data. The normality of the distribution of the data was checked with Shapiro–Wilk test, and it was found that the data showed a normal distribution ($p>0.05$). Therefore, for the statistical analyses, the significance test of the difference between the two means, one-way analysis of variance (ANOVA) and Tukey's HSD analysis were used. In the comparison of the categorical variables, gender, academic year, number of siblings and region were analyzed as the independent variables, and the total scores of the participants on Violence Tendency Scale (VTS) and Hudson and Ricketts Homophobia Scale (HRHS) were analyzed as the dependent variables. The relationship between the dependent variables was tested by Pearson's correlation analysis. Simple linear regression analysis was used to determine the impact of tendency towards violence on attitudes towards homosexuals. The level of statistical significance was accepted as $p<0.05$.

Ethical Aspects of Research

This research was carried out in accordance with the principles of the Declaration of Helsinki, and written consent was obtained from the students who voluntarily agreed to participate in the study. Institutional permission was obtained from the Department of Nursing at the Faculty of Health Sciences where the study was conducted, and approval was obtained from the Kırşehir Ahi Evran University Non-Invasive Ethics Committee with the decision dated 24.11.2020 and numbered 2020-17/128.

RESULTS

The distributions of the HRHS and VTS scores of the students based on their personal data are given in Table 1. The mean HRHS score of the participants was determined to be 95.50 (94.25±22.23), and their mean VTS score was determined to be 36.00 (37.82±8.25). It was observed that there was a statistically significant relationship between the participants' mean HRHS scores and their academic year, number of siblings, the region they lived in and whether their parents were alive. It was determined that there was a statistically significant relationship between the students' mean VTS scores and the level of education of their mothers and whether their parents were alive.

Table 2 shows the distributions of the participants HRHS and VTS scores according to the social environment characteristics of the participants. There was no statistically significant relationship between the participants' social environment characteristics and their VTS scores ($p<0.001$). A statistically significant relationship was determined between the participants' mean HRHS scores and the presence of a homosexual person in their immediate environment and their desire to be friends with the homosexual person. It was observed that the participants who said, "I am friends with homosexuals" had a more positive attitude towards homosexual individuals than those who said they were indecisive about the question or not friends with any homosexuals.

Table 3 shows the effect of tendency towards violence on their points of view regarding homosexual individuals. It was determined that 66.3% of the participants had a low tendency towards violence, and 31.9% had a high tendency towards violence. No significant relationship was found between the participants' tendency towards violence and their points of view regarding homosexuals ($p>0.05$).

DISCUSSION

Negative and discriminatory attitudes towards homosexual individuals who receive care from the health system are an important problem affecting the right to health of such individuals. Additionally, homosexual individuals encounter discriminatory attitudes in their interactions with health care professionals, and their negative experiences lead them to avoid seeking care when they need it again.[25,26] For this reason, it is important to investigate the attitudes of nurses and variables that affect these attitudes during their student years, as nursing students will provide continuous health care services to homosexual individuals.

In this study, it was determined that the participants' attitudes towards homosexual individuals were negative according to their HRHS mean scores, and there was a significant relationship of their HRHS scores with regards to their academic year, their number of siblings, their region of residence and whether or not their parents were alive. In a study conducted with 335 nursing students, it was discovered that variables such as gender and parental education levels affected attitudes towards homosexuals.[4] In another study, it was determined that gender, academic year, family structure and socio-economic status were correlated with the nursing students' perspectives regarding homosexuals and their willingness to provide care to these individuals.[22] In a study conducted with nursing students in Korea, it was established that 92% of students had negative attitudes towards homosexuals.[27] In other studies that were conducted with nursing students, it has been observed that the students had negative attitudes towards homosexuals.[28-30] The findings of this study were compatible with the literature. As homosexuality

Table 1. Distributions of the students' homophobic attitudes and violence tendencies based on their personal information (n=502)

Characteristic	n (%)	HRHS ($\bar{X} \pm SD$)	Test	VTS ($\bar{X} \pm SD$)	Test
Academic year					
1st	120 (23.9)	93.55±23.38	F=1.334 p=0.034*	37.13±7.99	F=1.115 p=0.292
2nd	133 (26.5)	86.93±23.25		39.29±8.04	
3rd	121 (24.1)	100.51±18.52		36.04±7.87	
4th	128 (25.5)	96.59±21.25		38.16±8.85	
Gender					
Female	359 (71.5)	91.96±22.46	F=3.271 p=0.071	36.91±7.82	F=2.050 p=0.153
Male	143 (28.5)	100.00±20.61		40.11±8.85	
Number of siblings					
Only child	13 (2.6)	84.23±21.30	F=1.456 p=0.008*	37.07±5.75	F=1.130 p=0.272
1 sibling	78 (15.5)	88.84±27.76		38.44±8.50	
2–3 siblings	273 (54.4)	94.11±21.76		37.57±8.38	
4 or more siblings	138 (27.5)	98.52±22.36		38.02±8.09	
Birth order in family					
First born	157 (31.3)	94.56±21.05	F=0.903 p=0.717	37.52±7.88	F=1.107 p=0.303
Middle sibling	185 (36.9)	95.68±22.71		38.40±8.69	
Last born	160 (31.9)	92.28±22.77		37.46±8.08	
Region of residence					
1. Aegean region	35 (7.0)	90.85±23.99	F=1.448 p=0.009*	38.00±7.11	F=0.864 p=0.713
2. Marmara region	18 (3.6)	92.22±16.75		38.16±7.83	
3. Black Sea region	31 (6.2)	104.45±20.45		36.93±5.18	
4. Central Anatolia region	253 (50.4)	96.10±20.37		37.43±7.93	
5. Eastern Anatolia region	18 (3.6)	107.05±20.58		43.00±2.01	
6. Southeastern Anatolia region	46 (9.2)	93.52±27.04		37.43±8.31	
7. Mediterranean region	101 (20.1)	86.05±22.71		38.21±9.23	
Cohabitation status					
With both parents	447 (89.0)	95.26±22.03	F=0.953 p=0.600	37.78±8.08	F=1.256 p=0.137
With mother	29 (5.8)	82.31±21.26		34.44±7.08	
With father	8 (1.6)	87.75±25.70		44.50±8.43	
Other	18 (3.6)	91.11±22.54		41.38±11.19	
Whether parents are alive or not					
Both alive	471 (93.8)	94.90±22.22	F=1.571 p=0.002*	37.77±8.19	F=1.828 p=0.002*
Only mother is alive	22 (4.4)	81.72±17.79		36.45±8.63	
Only father is alive	9 (1.8)	90.44±25.16		44.00±8.39	
Parents' employment status					
Both working	54 (10.8)	90.98±22.80	F=0.925 p=0.668	36.48±7.22	F=1.101 p=0.312
Only the father is working	363 (72.3)	95.38±21.81		38.18±8.29	
Only the mother is working	11 (2.2)	80.18±21.93		35.36±9.01	
Neither of them is working	74 (14.7)	93.17±23.30		37.40±8.57	
Mother's level of education					
Uneducated	48 (9.6)	104.47±21.01	F=1.230 p=0.095	38.54±8.96	F=1.523 p=0.022*
Elementary school	274 (54.6)	95.87±21.33		37.36±7.65	
Secondary school	148 (29.5)	89.19±23.73		37.90±8.47	
Higher education	32 (6.4)	88.37±17.13		40.31±10.59	
Father's level of education					
Uneducated	4 (0.8)	84.50±19.46	F=1.018 p=0.443	49.25±6.18	F=0.849 p=0.739
Elementary school	204 (40.6)	99.00±20.50		37.44±7.46	
Secondary school	196 (39.0)	91.78±22.72		37.02±8.29	
Higher education	98 (19.5)	89.68±23.20		39.76±9.20	

Table 1. Continued

Characteristic	n (%)	HRHS ($X^- \pm SD$)	Test	VTS ($X^- \pm SD$)	Test
Income					
Income less than expenses	99 (19.7)	93.82±24.74	F=1.131 p=0.215	38.41±8.09	F=0.943 p=0.576
Income equals expenses	324 (64.5)	94.61±21.58		37.34±8.21	
Income more than expenses	79 (15.7)	93.27±21.75		39.06±8.53	
Family's attitude					
Loving/tolerant	338 (67.3)	95.77±21.85	F=1.077 p=0.313	37.06±8.14	F=0.804 p=0.806
Repressive/authoritarian	89 (17.7)	91.22±23.89		40.88±8.34	
Irrelevant/unconcerned	19 (3.8)	97.10±15.47		42.47±7.66	
Democratic	56 (11.2)	88.89±22.82		35.98±7.32	

*p<0.05, HRHS: Hudson and Ricketts Homophobia Scale, VTS: Violence Tendency Scale, SD: standard deviation, n: number.

Table 2. Hudson and Ricketts Homophobia Scale and Violence Tendency Scale Score distributions based on social environment characteristics (n=502)

Characteristic	n (%)	HRHS ($X^- \pm SD$)	VTS ($X^- \pm SD$)
The presence of homosexual individuals around			
Present	87 (17.3)	78.52±22.31	39.65±9.03
Absent	415 (82.7)	97.54±20.77	37.44±8.03
		F=2.252 p=0.000*	F=0.993 p=0.488
The desire to become friends with homosexual individuals			
Yes **	203 (40.4)	75.79±17.31	38.14 ±8.41
No	130 (25.9)	115.73±11.49	38.94±8.68
Indecisive	169 (33.7)	100.10±14.47	36.62±7.60
		F=3.314 p=0.000*	F=1.041 p=0.405

*p<0.001, **Significant group in Tukey's HSD analysis.
HRHS: Hudson and Ricketts Homophobia Scale,VTS: Violence Tendency Scale, SD: standard deviation, n: number.

Table 3. The effect of tendency towards violence on perspectives regarding homosexual individuals (n=502)

Students' tendency towards violence	n (%)	HRHS (X ± SD)	β/r	R^2	F	p-value
Very low	2 (0.4)	68.50±41.71				
Low	333 (66.3)	94.54±21.52				
High	160 (31.9)	93.72±23.39	0.034	0.001	1.071	0.361
Very high	7 (1.4)	99.42±24.06				

β: beta value, R^2: regression square, HRHS: Hudson and Ricketts Homophobia Scale, SD: standard deviation, n: number.

is perceived as taboo by society in Turkey, and as nursing students are a part of society, they often have the same perception regarding homosexuals.[31] This negative attitude gets stronger, especially with the prevalence of the traditional perspective, and so discrimination against homosexuality increases in rural areas.[32] In this study, it was observed that the attitudes of the participants differed significantly based on the regions they lived in and the number of their siblings. It may be stated that differences in eastern and western cultures in Turkey affect both the number of children a family has and their attitude towards homosexuality. As the number of siblings increases, the family structure becomes more traditional, and this traditional perspective makes the family members' attitudes towards homosexuality more negative. The differences found in this study in the participants' attitudes towards homosexuality based on their academic year was thought to be due to the courses the students took in nursing education. It may be argued that this situation is related to the internalization of the information that supports the humanitarian and holistic perspective provided in the curriculum.

In this study, the participants' mean VTS score was 37.82±8.25, and 66.3% of them had a low level of tendency towards violence. It was determined that the mean VTS scores were related to whether the parents of the participants were alive and the education levels of their mothers. In one study, the gender-related perceptions and violent tendencies of nursing students were investigated, the mean VTS score of the participants was found to be 38.86±9.33, and a significant relationship was found between the students' tendencies towards violence and their income status.[33] In another study, it was found that the students' tendencies towards violence were low, their mean

VTS score was 38.79±9.32, and the mean VTS score was associated with their academic year, gender, smoking and alcohol usage status and their status of exposure to violence. It was determined that the students' experiences such as resorting to or being subjected to violence increased their tendency towards violence.[17] In the literature, it is seen that the tendencies of nursing students towards violence are at a low level, and the findings in our study were compatible with the literature. Considering that the profession of nursing is based on the concept of providing help (altruism) and that students aim to help and heal people while choosing the profession of nursing, it may be stated that the low tendency of the participants of this study towards violence was an expected result. In this study, it was determined that for those students with high tendencies towards violence, the loss of one of the parents and the education level of the mother made a significant difference. In another study, it was reported that tendency towards violence is related to the family environment in which students grow up, and most students had been exposed to violence within their families.[34] In another study conducted with university students, it was stated that 49.4% of those students with a tendency towards violence mimicked violence from their families.[35] In line with these studies, it may be stated that variables such as the loss of one of the parents or the education level of the mother, which make a difference in the tendency of individuals towards violence, may cause changes in the family environment, increase the child's exposure to violence in the family due to increased responsibilities and stress, and this situation may affect the students' tendency towards violence.

It was determined that the mean HRHS scores of the participants of this study were related to the presence of homosexuals around them and their status of wanting to be friends with homosexuals. It was seen that those students who said, "I am friends with homosexuals" had a more positive attitude towards homosexual individuals than those who said they were indecisive about this question or not friends with homosexuals. In a study conducted with midwifery students, it was reported that the students' attitudes towards homosexual individuals changed positively after getting to know and becoming friends with a homosexual individual.[36] Similarly, in studies conducted with nursing students, it was determined that having a homosexual person around them or getting to know a homosexual person positively affected the nursing students' attitudes towards homosexual individuals.[4,22,37] In a study investigating the discrimination and prejudice levels of nursing students, it was shown that those who were not friends with homosexuals had more negative attitudes towards lesbians.[30] It may be stated that the experiences of students, such as getting to know a homosexual person or making homosexual friends, contribute to their overcoming prejudices against homosexual individuals by spending time together and sharing, and students who say "I am friends with a homosexual person" have positive attitudes towards homosexual individuals with an approach that is less judgmental and more respectful of sexual identities, especially due to their flexible perspective.

In this study, no significant relationship was identified between the participants' tendency towards violence and their points of views regarding homosexuals. The literature review conducted in this study revealed no other study examining attitudes towards homosexuals and the tendency towards violence together. In Turkey, attitudes towards homosexuality in the social structure continue to be negative, and it can be observed that this situation stems from the gender perception and patriarchal structure of society, and negative judgments against homosexuality are transferred from generation to generation through social learning.[38] Another important factor affecting attitudes towards homosexuals is the individual's perception of gender, and as this perception sets in, the individual's attitude towards homosexual individuals becomes more negative. A statistically significant relationship was found between nursing students' gender perception scores and violence tendency scores.[33,39] The relationship between the perception of gender and tendency towards violence is structured and maintained by the patriarchal system as a goal and product of the masculine social structure in the context of the construction of masculinity and male violence.[40] The reason for the lack of a significant relationship in this study between the participants' tendency towards violence and their negative perspectives regarding homosexuality may be the fact that 71.5% of the participants were women, the profession of nursing is built with a philosophy of helping people, and the male participants in the study had a perspective that left their patriarchal stereotypes behind, preferring nursing, which is a female dominated profession.

In this study, it was determined that the attitudes of the nursing students towards homosexuals were negative, and there was a relationship between their negative attitudes and their academic year, their number of siblings, their region of residence and their cohabitation statuses. It was also observed that the students' levels of tendency towards violence were low, and there was a relationship between their levels of tendency towards violence and whether their parents were alive and the education levels of their mothers. It was seen that the levels of the tendency of the nursing students towards violence did not explain their attitudes towards homosexual individuals. In line with these results, since it is thought that the homophobic attitudes of nursing students may be related to their region and their culture, further studies examining cultural variables are recommended. Additionally, it is recommended to increase the number of educational and social environments that will enable students to recognize their homophobic prejudices, respect personal choices and gain an empathetic perspective, add course contents to prevent homophobia in nursing education into the nursing curriculum and integrate more examples of empathy, self-knowledge and anger management into nursing courses.

Limitations of the Study

Although 62% of the population was reached in this study, the fact that it was conducted in a single faculty is among the limitations of this study. Additionally, obtaining the data online may be considered another limitation.

MAIN POINTS

- Negative myths and attitudes may negatively impact the care provided to homosexuals.
- With our study, the participating nursing students had the opportunity to notice their feelings towards homosexual individuals.
- With this study, the attitudes of the nursing students were evaluated, and the results showed that the tendency towards violence, which has become a stereotype, is not actually significant on homophobic attitudes.
- Educational and social activities should be planned to change negative perceptions and attitudes and create awareness among nursing students about differences.

ETHICS

Ethics Committee Approval: Ethics committe approval was obtained from Kırşehir Ahi Evran University Medical Faculty Non-Invasive Research Ethics Committee with the decision dated 2020-17/128 and dated 24.11.2020.

Informed Consent: Each participant was informed with an informed consent form, and their consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.A.Ç., H.S.Ö., Design: N.A.Ç., H.S.Ö., Data Collection and/or Processing: N.A.Ç., H.S.Ö., Y.C., Analysis and Interpretation: N.A.Ç., H.S.Ö., Writing: N.A.Ç., H.S.Ö., Y.C., Critical revision: N.A.Ç., H.S.Ö., Y.C.

DISCLOSURES

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REFERENCES

1. McConaghy N, Hadzi-Pavlovic D, Stevens C, Manicavasagar V, Buhrich N, Vollmer-Conna U. Fraternal birth order and ratio of heterosexual/homosexual feelings in women and men. J Homosex. 2006; 51(4): 161-74.
2. American Psychological Association (APA) 2008. Answers to your questions for a better understanding of sexual orientation and homosexuality. Available from: URL: http://www.apa.org/topics/lgbt/orientation.pdf. (Accessed on February 2021).
3. Özsungur B. Cinsel kimlik gelişimi ve cinsel kimlik bozukluğunda psikososyal değişkenler: Gözden geçirme. Çocuk ve Gençlik Ruh Sağlığı Dergisi. 2010; 17(3): 163-74.
4. Yüksel R, Arslantaş H, Eskin M, Kızılkaya M. Hemşire öğrencilerin eşcinsel bireylere yönelik tutumlarını etkileyen faktörler. Yeni Symposium. 2020; 58(1): 18-25.
5. Sakallı N. Pictures of male homosexuals in the heads of Turkish college students: the effects of sex difference and social contact on stereotyping. J Homosex. 2002; 43(2): 111-26.
6. World Health Organization (WHO). Global Status Report on Violence Prevention 2014. Available from: URL: https://www.who.int/publications/i/item/WHO-NMH-NVI-14.2 (Accessed on February 2021).
7. Human Rigth Watch, 2020 World Report. Available from: URL: https://www.hrw.org/sites/default/files/world_report_download/hrw_world_report_2020_0.pdf (Accessed on February 2021).
8. Smith DE. Homophobic and transphobic violence against youth: The Jamaican context. International Journal of Adolescence and Youth. 2018; 23(2): 250-8.
9. Dworkin SH, Huso Yİ. LGBT identity, violence, and social justice: The psychological is political. Int J Adv Couns. 2003; 25(4): 269-79.
10. Meyer D. Evaluating the severity of hate-motivated violence: Intersectional differences among LGBT hate crime victims. Sociology. 2010; 44(5): 980-95.
11. Almedia J, Johnson RM, Corliss HL, Molnar BE, Azrael D. Emotional distress among LGBT youth: the influence of perceived discrimination based on sexual orientation. J Youth Adolesc. 2009; 38(7): 1001-14.
12. Russell ST, Fish JN. Mental health in lesbian, gay, bisexual, and transgender (LGBT) youth. Annu Rev Clin Psychol. 2016; 12: 465-87.
13. Shattell M, Chinn PL. Nursing silent on LGBTQ health: Rebel nurses provide hope. Arch Psychiatr Nursing. 2014; 28(1): 76-7.
14. Yüksel A, Engin E, Öztürk Turgut E. Hemşirelik öğrencilerinin şiddet eğilimlerinin incelenmesi. Uluslararası Sosyal Araştırmalar Dergisi. 2015; 8(41): 834-40.
15. Top FÜ, Çınarsoy K, Alagöz H, Aydın Pekdemir E, Kaya B. Sağlık bilimleri fakültesi öğrencilerinin şiddet eğilimleri ve problem çözme yetenekleri. IV. Ulusal Psikiyatri Hemşireliği Kongresi (Uluslararası Katılımlı) Kongre Kitabı. 2010.p.167.
16. Özgür G, Öztürk E, Moradi D. Hemşire öğrencilerin aile içi şiddet konusundaki görüşleri. III. Ulusal Psikiyatri Hemşireliği Kongresi (Uluslararası Katılımlı) Kongre Kitabı. 2009.p.150.
17. Tosunöz İK, Öztunç G, Eskimez Z, Yeşil Demirci P. Hemşirelik öğrencilerinin şiddet eğilimlerinin belirlenmesi. Cukurova Med J. 2019; 44(2): 471-8.
18. Şahin T. Lisansüstü eğitim alan öğrencilerin eşcinsel bireylere yönelik tutumlarının incelenmesi. Ege Üniversitesi Sağlık Bilimleri Enstitüsü, Yüksek Lisans Tezi. 2020.
19. Akdaş Mitrani AT. Eşcinsellere yönelik olumsuz tutumlar: Meslek grupları ve ilişkili özellikler. Turkish Journal of Forensic Sciences. 2008; 7(4): 23-30.
20. Çabuk FD. Tıp öğrencileri ve hekimlerin eşcinsellik hakkındaki tutumları ve gey ve lezbiyenlerin sağlık hizmeti deneyimleri. Gazi Üniversitesi Tıp Fakültesi, Uzmanlık Tezi. 2010.
21. Yıldırım Y. Lezbiyen ve biseksüel kadınların cinsel sağlık ve üreme sağlığı hizmetleri ile ilgili görüş ve deneyimleri. Mersin Üniversitesi Sağlık Bilimleri Enstitüsü, Yüksek Lisans Tezi. 2018.
22. Sadıç E, Beydağ KD. Hemşirelik öğrencilerinin lezbiyen ve geylere yönelik tutumları ve etkileyen faktörler. Hemşirelik Bilimi Dergisi. 2018; 1(2): 5-13.
23. Başbakanlık Aile Araştırma Kurumu Başkanlığı. Aile İçinde ve Toplumsal Alanda Şiddet. Başbakanlık Aile Araştırma Kurumu Başkanlığı Yayınları. Bilim Serisi. Ankara; 1998. Yayın No:113.
24. Sakalli N, Uğurlu O. Effects of social contact with homosexuals on heterosexual Turkish university students' attitudes towards homosexuality. J Homosex. 2001; 42(1): 53-62.
25. Dinkel S, Patzel B, McGuire MJ, Rolfs E, Purcell K. Measures of homophobia among nursing students and faculty: a Midwestern perspective. Int J Nurs Scholarsh. 2007; 4: Article24. Erratum in: Int J Nurs Educ Scholarsh. 2007; 4: Article 24.
26. Lim FA, Hsu R. Nursing Students' attitudes toward lesbian, gay, bisexual, and transgender persons: An integrative review. Nurs Educ Perspect. 2016; 37(3): 144-52.
27. Kwak HW, Kim MY, Kim MY. Severity and influencing factors of homophobia in Korean nursing students. Int J Environ Res Public Health. 2019; 16(23): 4692.
28. Bilgic D, Daglar G, Sabancioguları S, Ozkan SA. Attitudes of midwifery and nursing students in a Turkish university toward lesbians and gay men and opinions about healthcare approaches. Nurse Educ Pract. 2018; 29: 179-84.

29. Gönenç IM, Senturk Erenel A. Determining homophobic attitudes of nursing students in Turkey and the factors affecting them. Clin Exp Health Sci. 2019; 9: 21-8.

30. Unlu H, Beduk T, Duyan V. The attitudes of the undergraduate nursing students towards lesbian women and gay men. J Clin Nurs. 2016; 25(23-24): 3697-706.

31. Bostanci Daştan N. The attitudes of nursing students towards lesbians and gay males in Turkey. Int J Nurs Pract. 2015; 21(4): 376-82.

32. Pinto D, Nogueira C. Portuguese nursing students' attitudes towards lesbians: From prejudice to recommendations for change. Trends in Psychology/Temas em Psicologia. 2016; 24(3): 805-14.

33. Özpulat F. Hemşirelik öğrencilerinin şiddet eğilimleri ile toplumsal cinsiyet algıları arasındaki ilişki. Başkent Üniversitesi Sağlık Bilimleri Fakültesi Dergisi. 2017; 2(2): 151-61.

34. Yagiz R, Sevil Ü, Guner Ö. The effect of university students' violence tendency on their attitude towards domestic violence and the factors affecting domestic violence attitudes. J Inj Violence Res. 2020; 12(1): 39-46.

35. Okour AM, Hijazi HH. Domestic violence and family dysfunction as risk factor for violent behavior among university students in North Jordan. J Fam Violence. 2009; 24(6): 361-6.

36. Mete A, Özerdoğan N. Ebelik bölümü öğrencilerinin lezbiyen, gay, biseksüel, transseksüel (LGBT) hakkında bilgi, görüş ve tutumlarının değerlendirilmesi. STED/Sürekli Tıp Eğitimi Dergisi. 2019; 28(3): 163-71.

37. Rowniak SR. Factors related to homophobia among nursing students. J Homosex. 2015; 62(9): 1228-40.

38. Duyan V, Tuncay T, Sevin Ç, Erbay E. Sosyal hizmet öğrencilerinin eşcinselliğe yönelik tutumları: Bir atölye eğitiminin etkileri. Toplum ve Sosyal Hizmet. 2011; 22: 7-18.

39. Kul Uçtu A, Karahan N. Sağlık yüksekokulu öğrencilerinin cinsiyet rolleri, toplumsal cinsiyet algısı ve şiddet eğilimleri arasındaki ilişkinin incelenmesi. Itobiad: Journal of the Human & Social Science Researches. 2016; 5(8): 2882-905.

40. Çelik G. "Erkekler (de) ağlar!": Toplumsal cinsiyet rolleri bağlamında erkeklik inşası ve şiddet döngüsü. Fen Dergisi. 2016; 8(2): 1-12.

ORIGINAL ARTICLE

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The Relationship Between Mental Workload and Fatigue in Emergency Department Nurses

Khalamala Ibrahim Salih Barzani[1], Ümran Dal Yılmaz[2]

[1]Ble General Hospital, Erbil, Iraq
[2]Near East University Faculty of Nursing, Nicosia, North Cyprus

Abstract

BACKGROUND/AIMS: Workload is main factor affecting fatigue. Fatigue is one of the most important issues in work environments which causes reduce the quality of work, increases errors and accidents.

The aim of the study is determination of the relationship between mental workload and fatigue in emergency department nurses.

MATERIALS AND METHODS: In this cross-sectional descriptive-analytic study, the relationship between mental workload and fatigue in nurses who are working in Ble, Mergasor and Ashti General three hospitals in the emergency department were investigated. Total 65 voluntary nurses were composed the sample of the study. Data collection tools consisted of three demographic characteristics, fatigue (CIS20R) and mental workload (NASA-TLX) questionnaires. Data were gathered between December 2018 and January 2019, after the ethics committee approval. Descriptive statistics, correlation coefficient and One-way ANOVA tests were used in analysis of the data.

RESULTS: In the present study, despite the lack of a statistically significant relation between the mental workload and fatigue, different degrees of mental workload and fatigue were found among the nurses of the emergency department'

CONCLUSION: Mental workload and fatigue can negatively affect the nurses' satisfaction and their performance, and consequently affect the implication of nursing process or in other word the provision of safe care for patients negatively.

It is recommended that implement comprehensive, systematic and continuous education programs to increase the level of tolerance and resilience of emergency department nurses.

Keywords: Mental workload, fatigue, nurses, emergency department

INTRODUCTION

Fatigue is one of the most important issues in work environments. Fatigue is a very complex concept that includes psychological and physiological factors. Fatigue is associated with a reduced capacity and motivation to work. Although fatigue may have different causes, it affects performance and motivation quite similarly and reduces mental and physical performance.[1] When an individual is tired, their normal behavior might change and they may make a small error. At the same time, fatigue interacts with physical, mental and emotional performance, causing a significant decrease in energy and leading to weakness.[1,2] In general, fatigue causes blurred feelings, reduced physical activity, disrupts the balance of the nervous system and reduces work efficiency. Fatigue can also be effective in developing or exacerbating various disorders, including mental illness, cardiovascular disease, slowness of the mind, weakness, memory loss, muscle aches, forgetfulness and imbalance.[3]

Workload is one of the main factors affecting fatigue. Workload can be defined as the demand on the operator to achieve a certain level of

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ORCID IDs of the authors: K.I.S.B. 0000-0003-4519-813X; Ü.D.Y. 0000-0002-9482-6983.

Address for Correspondence: Ümran Dal Yılmaz
E-mail: umrandal65@gmail.com; umran.dal@neu.edu.tr
ORCID ID: orcid.org/0000-0002-9482-6983

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performance or the overall amount of work that must be done by a person or group of people in a given time interval. Workload and long working-hours are the main factors in fatigue. The overall concept of workload originates from a range of human factors and is essentially related to the mental abilities of the individual.[3-5] Mental workload refers to the portion of operator information processing capacity or resources that are actually required to meet the system's demands. Mental workload may be viewed as the difference between the capacities of the information processing system that are required for task performance to satisfy performance expectations and the capacity available at any given time.[1-4,6]

Individuals working in occupations with a high workload might have to struggle with decreased performance, memory loss, damage to their thinking process, irritability, and decreased learning due to fatigue and inappropriate scheduling.[6] Due to the critical nature of the job and the necessity of the safety of the patients, the relationship between work-related fatigue and error is very important in individuals who work in hospitals. Nurses are subject to extreme mental workloads because they are always making important decisions which have a direct effect on people's lives.[6,7]

Nursing is believed to be at the forefront of stressful hospital and medical careers.[8] In a 2010 study, the Canadian Association of Nurses found that nurses experience significant levels of fatigue.[9] Nursing, especially in emergency departments, is by nature a stressful profession, as it is highly complex, active, and dynamic.[5,9,10] Emergency departments are difficult places to work due to their demanding working conditions, heavy workloads, psychological stress, lack of resources, and inadequate support.[5,10,11] Nurses in emergency departments report increasing role overload because of critical staff shortages, time constraints, focus on the survival of the patients and increased patient numbers and acuity, the presence of stressors, possible conflicts with their team, and the deficiencies of the facilities. Such overload could compromise staff satisfaction with their working environment, which might lead to more dissatisfaction.[5,12,13] All of these factors have adverse effects on the nature of the nursing job by compromising decision making, creativity, and problem-solving ability, all of which are essential aspects of patient care in the health care system.[14]

Therefore, given the criticality of the tasks of nurses in the emergency department and the need for high accuracy and alertness during the care of patients with special conditions, the researchers decided to conduct this study aimed at determining the relationship between mental workload and fatigue.

The research questions included were the following:

- What is the rate of fatigue and its dimensions among emergency department nurses?
- What is the rate of mental workload and its dimensions among emergency department nurses?
- What is the relationship between mental workload and the fatigue dimensions in emergency department nurses?
- What is the relationship between mental workload and the demographic characteristics of emergency department nurses?
- What is the relationship between fatigue and the demographic characteristics of emergency department nurses?
- The aim of this study was to determine the relationship between mental workload and fatigue in emergency department nurses.

MATERIALS AND METHODS

Study Design: The research design was a cross-sectional and descriptive-analytic study.

Study Setting: The study was performed on nurses who were working in Ble, Mergasor and Ashti General, in the emergency department, in Iraq. The data were gathered between December 2018 and January 2019.

Sample Selection: The study population comprised 65 nurses employed in the emergency departments of three hospitals. All of the nurses filled out a questionnaire and all of the nurses voluntarily took part in this study.

Data collection tool: The study data were collected using a questionnaire based on a literature review.[2-18] The questionnaire contained three sections. The first section consisted of questions regarding the nurses' demographic characteristics. The other two sections were the The Checklist Individual Strength Questionnaire 20R (CIS20R) and National Aeronautics and Space Administration - Task Load Index (NASA-TLX) Scale.

- The CIS20R questionnaire was used to assess fatigue. This questionnaire consists of 20 questions containing four factors, namely: mental fatigue, concentration, motivation and physical activity. The mental fatigue factor includes eight questions (numbers: 1, 4, 6, 9, 12, 14, 16, and 20); the concentration factor includes five questions (3, 8, 11, 13 and 19); the motivation factor includes four questions (2, 5, 15 and 18); and finally, the physical activity factor includes three questions (7, 10, and 17). Each of these factors is assessed through a 6-point scale. According to the CIS questionnaire, the overall fatigue scores can be in a range from 20 up to 120. The higher the total is, the higher the overall fatigue is. The CIS is a 20-item fatigue questionnaire developed by the Dutch research team of Vercoulen in 1994. The questionnaire has been translated into multiple languages including Turkish. Ergin and Yıldırım[15] found that the internal consistency reliability of the CIS-T was Cronbach's α=0.87 and the interclass correlation coefficient reliability was r=0.92. The item-discriminant validity ranged from r=0.10 to 0.63.[15] The reliability and validity of the CIS20R questionnaire were evaluated by Habibi et al.[3] for emergency service personnel in Iran. They obtained a reliability of 0.86 for this questionnaire.

- The NASA-TLX workload index is used to assess mental workload; this scale is one of the most well-known tools for assessing the mental workload from an individual perspective. NASA-TLX uses a visual scale of 0 to 100 divided into 10 units. Six subscales of mental needs, physical needs, time requirements, performance, effort and frustration are evaluated. Each subscale is defined in the questionnaire and the subjects are asked to study the definitions before answering the questions. The minimum score of each subscale is zero and the maximum score is 100, which the respondent determines, based on the score attributed to each individual subscale. The mean of the subscales is reported as the amount of work load, which is a number between 0 and 100. Average scores below 50 are acceptable and scores above 50

are considered unacceptable. The NASA-TLX is a widely used, subjective, multidimensional assessment tool which rates the perceived workload in order to assess a task, system, or team's effectiveness or other aspects of performance. It was developed by the Human Performance Group at NASA's Ames Research Center over a three-year development cycle which included more than 40 laboratory simulations.[16]

The face validity and reliability of the NASA-TLX method was confirmed (α=0.897) for intensive care unit (ICU) nurses in Iran. According to these results, it was suggested that the NASA-TLX method and the performance obstacles and facilitators questionnaire to assess the workload of ICU nurses can be used.[17]

Data Collection

The nurses were informed about the study. The nurses were required to complete the questionnaire while they were at work in the emergency department. The implementation of the data collection forms lasted about 30 minutes.

Ethical Aspect

Ethics committee approval was obtained from the Near East University (approval number: 678, date: 22.11.2018) and written permission was obtained from the General Health Directorate of Erbil. Verbal/written consent was obtained from the nurses before distributing the questionnaire.

Statistical Analysis

Statistical analysis was carried out using the SPSS 21.0 limited version of the Statistical Package for the Social Sciences (IBM Corp., Armonk, NY, USA) by applying descriptive analysis and normality tests. Normal distribution was analyzed with the Kolmogorov–Smirnov test. The relationship between variables was evaluated with Pearson correlation analysis. One-Way ANOVA was used to compare variables of more than two characteristics. The Levene test was used to assess the homogeneity of variances. In this study, $P<0.05$ was accepted as the statistical significance level.

RESULTS

The mean age of the participants was 28.95 years. 50.8% of the participants had 1–3 years of working experience. 52.3% of the participants were male. The majority of the nurses had a degree (64.6%).

The subjective feeling of fatigue score (23.41±12.27) and reduction of motivation score (7.04±4.38) obtained the highest and lowest rates respectively. Total fatigue was estimated to be 53.79±18.42.

The performance score (62.69±14.73) and the temporal demand score (45±16.65) obtained the highest and lowest rates respectively. The total mental workload was estimated to be 55.26±6.98.

Based on the Spearman correlation coefficient, there was no significant relationship between the mental workload and fatigue dimensions in the emergency department nurses.

Eta's statistical index showed a very weak correlation between the variables of gender, level of education and hospital workplace, with the mean scores of mental workload among the emergency department nurses. Also, based on the Pearson correlation test results, there was no statistically significant correlation between age and years of working in the emergency department with the mean scores of mental workloads.

Based on the above table, it shows a very weak correlation between the variables of gender, level of education and hospital workplace, with the mean scores of fatigue among the emergency department nurses. Also, based on the Pearson correlation test results, there was no statistically significant correlation between age and years of working in the emergency department with the mean scores of fatigues.

DISCUSSION

The focus of the present study was to determine the relationship between mental workload and fatigue in emergency department nurses. This study was conducted on 65 nurses with varying gender, levels of education and hospital workplaces. The majority of the nurses had a degree (64.6%). In relation to the dominance of males in the sample of

Table 1. Descriptive characteristics of the nurses (n=65)

Variables		Frequency (n)	Percent (%)
Age (mean: 28.95)	≤25	6	9.2
	26–30	44	67.7
	≥31	15	23.1
Years working in emergency department (mean: 3.51)	1–3	33	50.8
	4–6	26	40
	7–9	6	9.2
Gender	Male	34	52.3
	Female	31	47.7
Level of education	Preparatory of nursing	15	23.1
	Diploma	42	64.6
	Bachelor	8	12.3
Workplace hospital	Ble General Hospital	25	38.4
	Ashti General Hospital	20	30.8
	Mergasur General Hospital	20	30.8

n: number.

Table 2. Mean scores of Checklist Individual Strength (CIS) and its dimensions among emergency department nurses (n=65)

CIS and its dimensions	Mean ± SD (min)
CIS-Subjective feeling of fatigue	23.41±12.27
CIS-Reduction of concentration	15.41±5.24
CIS-Reduction of motivation	7.04±4.38
CIS-Reduction of physical activity	7.89±5.39
CIS total score	53.79±18.42

SD: standard deviation, n: number.

Table 3. Mean scores of mental workload and its dimensions among emergency department nurses (n=65)

Mental workload and its dimensions	Mean ± SD (min)
Mental demand	60±13.11
Physical demand	58.84±12.83
Temporal demand	45±16.65
Performance	62.69±14.73
Effort	53.53±14.29
Frustration	51.53±18.15
Mental workload total score	**55.26±6.98**

SD: standard deviation, n: number.

this study, it can be stated that the reason for this may be related to the nature of the emergency department and the need for more male staff in these units (Table 1). Johnston et al.[5] stated in their review article that research on emergency department nurses frequently reported different demographic profiles from other nursing populations, with a greater proportion of male staff, more advanced qualifications and longer clinical experience. However, this was culturally specific as data from Taiwan, China, Brazil and Iran primarily included female nurse staff populations limited.[5]

The results of the present study showed that total fatigue was 53.79±18.42. Also, in the present study, the subjective feeling of fatigue score (23.41±12.27) was the highest rate (Table 2). Based on the results of the present study, it is concluded that the mean of the overall fatigue score is in the medium range. These results are consistent with the results of Motamedzade et al.[18] (the total mean of their fatigue score was 58.40±11.90). Among the fatigue dimensions, mental fatigue had the highest mean in comparison with the other dimensions. However, in the study of Teixeira et al.[19], 42% of the participants had severe fatigue. Additionally, in the study of Guntupalli et al.[20], 20.8% had severe fatigue.

Other studies have mentioned many reasons for fatigue in nurses, including severe illness, patients' death, high workloads, role ambiguity, frequent exposure to stressful situations and occupational stress, organizational positions such as authority, social support, autonomy and workload.[11,18,21,22]

Several studies have indicated that factors, including shift-work and long-term work, play a role in nurses' subjective feelings of fatigue.[23,24] The results of the Kagamiyama and Yano[24] study revealed rotating shift-work was one of the important factors in the high degree of subjective fatigue among nurses, due to the fact that after a night-shift, they have a disrupted sleep rhythm which can cause the subjective feeling of fatigue in nurses.

The effects of long working-hours has been an important issue for those researchers involved in ergonomics studies over the past few decades.[23,25] Nursing shortages have been associated with increased nurse workloads. In his study, Bae[25] found that 15.6% of hospital nurses in two American states worked more than 40 hours per week. Studies have shown that there is a relationship between long hours of work and cumulative fatigue.[24,26,27] Long hours of work increased the exposure to psychological and physical demands and may induce fatigue and stress in the affected workers.[28] The results of one study showed that

Table 4. The relationship between mental workload and the fatigue dimensions in emergency department nurses (n=65)

	Subjective feeling of fatigue		Reduction of concentration		Reduction of motivation		Reduction of physical activity		CIS total score	
Mental workload	**p**	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**	**r**
	0.82	-0.87	0.317	0.12	0.58	0.06	0.62	-0.05	0.82	-0.02

Spearman correlation coefficient, CIS: Checklist Individual Strength Questionaire, n: number.

Table 5. The relationship between mental workload and the demographic characteristics of emergency department nurses (n=65)

	Pearson's chi-squared test				Eta test		
	Age		Years of working in emergency department		Gender	Level of education	Hospital
Mental workload	r	p	r	p	r	r	r
	0.13-	0.26	0.02	0.83	0.03	0.16	0.17

n: number.

Table 6. The relationship between fatigue and the demographic characteristics of emergency department nurses (n=65)

	Pearson's chi-squared test				Eta test		
	Age		Years of working in emergency department		Gender	Level of education	Hospital
Mental workload	**r**	**p**	**r**	**p**	**r**	**r**	**r**
	0.07	0.57	0.11	0.37	0.10	0.07	0.08

n: number.

the average percentage of feelings of subjective fatigue "before going to work" increased with the increase in the length of weekly working-hours.[27] Therefore, improving each of these factors can help reduce the pressure and mental fatigue of nurses. The mental workload is the amount of effort that the mind makes while discharging our duty. Activities that require concentration, control measures and speed of action usually increase the mental and physical load significantly in those who perform them.[29]

Nowadays, the intense competition for scarce resources in the health system makes a quantitative and qualitative measurement of the nurses' workload necessary. In hospital emergency departments, the staff and especially nurses bear the burden of a heavy workload due to the fact that it is the frontline department in a hospital and they face cases that often have severe and acute medical conditions. This heavy workload and urgent patient care have a major impact on the nurses' performance.[12,14,21]

The results of the present study showed that the performance score (62.69±14.73) and mental demand score (60±13.11) were at higher rates than the others dimensions. The total mental workload score was 55.26±6.98 (Table 3).

High performance pressure in comparison to the other dimensions of the workload in the current study indicates that the emergency department nurses are not satisfied with their performance in carrying out their assigned tasks in line with their determined purpose. The results of previous studies have shown that solutions such as an appropriate association between nursing managers and nursing staff could have a positive effect on nurses' performance and their efficiency.[30,31] In the present study, the high mental stress also indicates the severity, complexity, and the need to have great accuracy in performing the assigned tasks in the emergency department. In previous studies, it was found that the doctors' and nurses' highest workload in the emergency department was related to mental or psychological stress.[30-33]

The results of the present study showed no significant relationship between the mental workload and fatigue dimensions in emergency department nurses (Table 4).

In the present study, there is no correlation between the level of fatigue and its dimensions with the mental workload in nurses. Our result was not consistent with the results of Van Bogaert et al.[32] In their study, it was determined that workload, as a major component of the health service, plays a decisive role in undesirable consequences such as emotional exhaustion, depersonalization, and burnout.

Workload is one of several predictors of fatigue, and mental workload is associated with all of the dimensions of fatigue, which includes both the mental and physical ones, so it can be said that high and low workloads are associated with fatigue.[33,34]

In the present study, the lack of a significant correlation between the level of fatigue and mental workload among emergency department nurses may be due to the difference in measurement instruments used, especially the fatigue measurement instrument.

The evaluation tool for fatigue in the current study was more specialized and included more dimensions of fatigue than those instruments used in other studies. Therefore, the type of assessment tools used may explain the differences in outcomes.

It should be mentioned that in the Barbosa et al.[34] study that a significant correlation was not found between these two variables among doctors. Moreover, in the Bakhshi et al.[35] study, there was no significant association between mental workload and fatigue among the nurses.

The results of the present study revealed a very weak correlation between the variables of gender, level of education and hospital workplace with the mean scores of mental workload and fatigue among emergency department nurses. Also, there was no statistical correlation between age and years of working in the emergency department with their mean scores of mental workload and fatigue based on a Person correlation test (Tables 5 and 6).

CONCLUSION

In the present study, despite the lack of a statistically significant relation between the mental workload and fatigue, different degrees of mental workload and fatigue were found among the nurses of the emergency department.

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MAIN POINTS

- Mental workload and fatigue can negatively affect the satisfaction and performance of emergency department nurses, and consequently negatively affect the implementation of the nursing process, or in other words, the provision of safe care for patients.
- It is important to implement comprehensive, systematic and continuous education programs to increase the levels of tolerance and resilience of emergency department nurses.
- It is recommended that future researchers investigate the practical experiences of nurses in emergency departments regarding those factors affecting the level of mental workload or fatigue.

ETHICS

Ethics Committee Approval: Ethics committee approval was received for this study from Near East University (approval number: 678, date: 22.11.2018).

Informed Consent: Given by the nurses who participated in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: K.I.S., Ü.D.Y, Design: K.I.S., Ü.D.Y., Supervision: Ü.D.Y., Data Collection and/or Processing: K.I.S, Analysis and/or Interpretation: K.I.S., Literature Review: K.I.S., Ü.D.Y., Writing: K.I.S., Ü.D.Y.; Critical Review: Ü.D.Y.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Zhao C, Zheng C, Zhao M, Liu J. Physiological assessment of driving mental fatigue using wavelet packet energy and random forests. Am J Biomed Sci. 2010; 2(3): 262-74.
2. Coetzee SK, Klopper HC. Compassion fatigue within nursing practice: a concept analysis. Nurs Health Sci. 2010; 12(2): 235-43.
3. Habibi E, Parvari R, Khodarahmi B, Dehghan HA, Hosseini M. Assessment of the relationship between work schedule and fatigue among the emergency personnel of Isfahan, Iran using the check list individual strength standard method. J Health Serv Res Policy. 2011; 7(6): 1288-96.
4. Hernández Arellano JL, Ibarra Mejía G, Serratos Pérez JN, García Alcaraz JL, Brunette MJ. Construction of a survey to assess workload and fatigue among AMT operators in Mexico. Work. 2012; 41 (Suppl 1): 1790-6.
5. Johnston A, Abraham L, Greenslade J, Thom O, Carlstrom E, Wallis M, et al. Review article: Staff perception of the emergency department working environment: Integrative review of the literature. Emerg Med Australas. 2016; 28(1): 7-26.
6. Graham AT. Academic staff performance and workload in higher education in the UK: The conceptual dichotomy. Journal of Further and Higher Education. 2015; 39(5): 665-79.
7. Powell AC, Savin S, Savva N. Physician workload and hospital reimbursement: Overworked physicians generate less revenue per patient. Manufacturing & Service Operations Management. 2012; 14(4): 512-28.
8. Nantsupawat A, Nantsupawat R, Kunaviktikul W, Turale S, Poghosyan L. Nurse Burnout, Nurse-Reported Quality of Care, and Patient Outcomes in Thai Hospitals. J Nurs Scholarsh. 2016; 48(1): 83-90.
9. Canadian Nurses Association (2010). Nurse fatigue and patient safety. Available from: URL: https://kipdf.com/nurse-fatigue-and-patient-safety_5ac4d8e11723dd77b2b5007e.html
10. Hunsaker S, Chen HC, Maughan D, Heaston S. Factors that influence the development of compassion fatigue, burnout, and compassion satisfaction in emergency department nurses. J Nurs Scholarsh. 2015; 47(2): 186-94.
11. Tao H, Ellenbecker CH, Wang Y, Li Y. Examining perception of job satisfaction and intention to leave among ICU nurses in China. International Journal of Nursing Sciences. 2015; 2(2): 140-8.
12. Habibi E, Soury S, Vardanjani HR, Khodarahmi B, Dehghan H, Hosseini M, et al. A survey of the relationship between work schedule and its effect on the fatigue of rescue personnel in Isfahan with a standard method of CIS202. J Educ Health Promot. 2015; 4: 98.
13. Dall'Ora C, Griffiths P, Ball J, Simon M, Aiken LH. Association of 12 h shifts and nurses' job satisfaction, burnout and intention to leave: findings from a cross-sectional study of 12 European countries. BMJ Open. 2015; 5(9): e008331.
14. Starc J. Stress Factors among Nurses at the Primary and Secondary Level of Public Sector Health Care: The Case of Slovenia. Open Access Maced J Med Sci. 2018; 6(2): 416-22.
15. Ergin G, Yildirim Y. A validity and reliability study of the Turkish Checklist Individual Strength (CIS) questionnaire in musculoskeletal physical therapy patients. Physiother Theory Pract. 2012; 28(8): 624-32.
16. Hart SG, Staveland LE. Development of NASA-TLX (Task Load Index): Results of empirical and theoretical research. Advances in Psychology. 1988; 52: 139-83.
17. Mohammadi M, Mazloumi A , Seraji JN, Zeraati H. Designing questionnaire of assessing mental workload and determine its validity and reliability among ICUs nurses in one of the TUMS's hospitals**.** Journal of School of Public Health and Institute of Public Health Research. 2013; 11(2): 87-96**.**
18. Motamedzade M, Abbasinia M, Parvari R, Oliaie M, Karimi S, Mohammadi P. Mental workload and its association with fatigue in operating room personnel of Hamadan hospitals, Iran, 2016. Journal of Occupational Health and Epidemiology. 2017; 6(2): 98-105.
19. Teixeira C, Ribeiro O, Fonseca AM, Carvalho AS. Burnout in intensive care units - a consideration of the possible prevalence and frequency of new risk factors: a descriptive correlational multicentre study. BMC Anesthesiol. 2013; 13(1): 38.
20. Guntupalli KK, Wachtel S, Mallampalli A, Surani S. Burnout in the intensive care unit professionals. Indian J Crit Care Med. 2014; 18(3): 139-43.
21. Hooper C, Craig J, Janvrin DR, Wetsel MA, Reimels E. Compassion satisfaction, burnout, and compassion fatigue among emergency nurses compared with nurses in other selected inpatient specialties. J Emerg Nurs. 2010; 36(5): 420-7.
22. Myhren H, Ekeberg O, Stokland O. Job satisfaction and burnout among intensive care unit nurses and physicians. Crit Care Res Pract. 2013; 2013: 786176.
23. Caruso CC. Negative impacts of shiftwork and long work hours. Rehabil Nurs. 2014; 39(1): 16-25.
24. Kagamiyama H, Yano R. Relationship between subjective fatigue, physical activity, and sleep indices in nurses working 16-hour night shifts in a rotating two-shift system. J Rural Med. 2018; 13(1): 26-32.
25. Bae SH. Presence of nurse mandatory overtime regulations and nurse and patient outcomes. Nurs Econ. 2013; 31(2): 59-68, 89; quiz 69.
26. Bannai A, Tamakoshi A. The association between long working hours and health: a systematic review of epidemiological evidence. Scand J Work Environ Health. 2014; 40(1): 5-18.
27. Park J, Kim Y, Chung HK, Hisanaga N. Long working hours and subjective fatigue symptoms. Ind Health. 2001; 39(3): 250-4.
28. Salve UR. Relationship of duration of work exposure and feeling of subjective fatigue: A case study on jewelry manufacturing workers in India. Int J Env Health Eng. 2017; 6(1): 1.
29. Hoonakker P, Carayon P, Gurses A, Brown R, McGuire K, Khunlertkit A, et al. Measuring workload of ICU nurses with a questionnaire survey: the NASA Task Load Index (TLX). IIE Trans Healthc Syst Eng. 2011; 1(2): 131-43.
30. Rouhi G, Hosseini SA, Anaraki HR, Mollaie E, Nasiri H. Distribution of workload and efficacy of nursing staff in internal medicine ward in a selected hospital of Golestan University of Medical Sciences. J Res Dev Nurs Midw. 2013; 9(2): 65-73.
31. van den Oetelaar WF, van Stel HF, van Rhenen W, Stellato RK, Grolman W. Balancing nurses' workload in hospital wards: study protocol of developing a method to manage workload. BMJ Open. 2016; 6(11): e012148.
32. Van Bogaert P, Clarke S, Willems R, Mondelaers M. Nurse practice environment, workload, burnout, job outcomes, and quality of care in psychiatric hospitals: a structural equation model approach. J Adv Nurs. 2013; 69(7): 1515-24.
33. Fan J, Smith AP. The impact of workload and fatigue on performance. Communications in Computer and Information Science. 2017; 726: 90-105.
34. Barbosa FT, Leão BA, Tavares GM, Santos JG. Burnout syndrome and weekly workload of on-call physicians: cross-sectional study. Sao Paulo Med J. 2012; 130(5): 282-8.
35. Bakhshi E, Mazloumi A, Hoseini SM. Relationship between mental fatigue and mental workload among nurses. Zahedan Journal of Research in Medical Sciences. 2019; 21(1): e83082

ORIGINAL ARTICLE

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The Comparison of the Differentiation Potential of Periodontal Ligament and Dental Pulp Mesenchymal Stem Cells in the Inflammatory Synovium Microenvironment

Deniz Genç[1], Burcu Günaydın[2], Serhat Sezgin[3], Akın Aladağ[3], Emine Figen Tarhan[4]

[1]Department of Pediatric Health and Disease Nursing, Muğla Sıtkı Koçman University Faculty of Health Sciences, Muğla, Turkey
[2]Department of Histology and Embryology, Muğla Sıtkı Koçman University Institute of Health Sciences, Muğla, Turkey
[3]Muğla Sıtkı Koçman University Faculty of Dentistry, Muğla, Turkey
[4]Department of Rheumatology, Muğla Sıtkı Koçman University Faculty of Medicine, Muğla, Turkey

Abstract

BACKGROUND/AIMS: Dental mesenchymal stem cells are easily accessible sources for mesenchymal stem cells (MSCs) and can rapidly proliferate in culture conditions. Rheumatoid arthritis (RA) is a chronic and multi-systemic autoimmune inflammatory disease that results in cartilage damage. The present study aimed to investigate the regenerative potential of dental MSCs in the synovial fluid microenvironment of patients with RA.

MATERIALS AND METHODS: Synovial fluid samples (8-10 mL/patient) were collected from patients with RA (age; 48–67 years). Dental pulp (DP) and periodontal ligament (PL) tissues were collected from healthy individuals, and the tissues were enzymatically digested in 3 mg/mL collagenase type I. MSCs were cultured in Dulbecco's Modified Eagle Medium (DMEM). The cells were cultured in the presence and absence of the synovial fluid samples of the patients with RA and subjected to flow cytometry analysis for cell surface expressions of positive markers for chondrogenesis (CD49e) and an osteogenic marker (alkaline phosphatase; ALP). The differentiation capacity of MSCs was evaluated with osteogenic or chondrogenic stimulation media and analyzed by staining the cells with Alizarin Red or Alcian Blue, respectively.

RESULTS: The cytokines interleukin (IL)-1β (61.1±9.8) and IL-6 (2386.7±397.4) were significantly higher in the end-stage RA-SF samples, compared to the early-stage RA-SF samples (IL-1β:35.2±4.8, IL-6:561.3±197.6) ($p<0.05$, $p<0.001$, respectively). DP-MSCs were significantly differentiated to osteocytes and formed calcium deposits cultured with end-stage RA-SF samples, whereas PL-MSCs were differentiated to osteocytes in limited levels, and low concentrations of calcium deposits were observed. Chondrocytes were observed in DP and PL-MSCs, and cartilage formation was observed only in DP-MSCs when cultured with end-stage RA-SF samples. The neutralization of IL-1β or IL-6 tended to decrease osteogenic marker expressions of DP-MSCs cultured in the presence of end-stage RA-SF samples.

CONCLUSION: The present study showed the differentiation potential of DP-MSCs into osteogenic and chondrogenic lineage in the inflammatory microenvironment of SF. DP-MSCs may be candidates for tissue regeneration, especially in patients with RA with bone or cartilage erosions.

Keywords: Mesenchymal stem cells, synovial fluid, dental pulp

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ORCID IDs of the authors: D.G. 0000-0003-0351-2805; B.G. 0000-0002-2451-7907; S.S. 0000-0001-7899-8171; A.A. 0000-0002-0058-905X; E.F.T. 0000-0002-2592-1741.

Address for Correspondence: Deniz Genç
E-mail: denizgenc@mu.edu.tr
ORCID ID: orcid.org/0000-0003-0351-2805

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INTRODUCTION

Distinct types of cells have been described in the oral cavity, and most of them share different characteristics from commonly used bone marrow or adipose tissue mesenchymal stem cells (MSCs). Thus, each source of MSCs may contribute to variable differentiation capacity in a different inflammatory environment[1]. The therapeutic potentials of MSCs have been explored to date in various degenerative and inflammatory disorders, such as Crohn's disease, rheumatoid arthritis (RA), diabetic nephropathy and allergic diseases[2]. The effects of MSCs in regulating inflammation and tissue regeneration are multifaceted, but it is generally thought that these cells have a strong anti-inflammatory and regenerative potential in the inflammatory microenvironment[3]. Recent studies have demonstrated that MSCs, when exposed to an inflammatory environment, have a local and systemic immunoregulatory effect through the release of various mediators, including many metabolites, exosomes, growth factors, and chemokines. Studies have shown that MSCs isolated from different sources could represent variable immunoregulatory and regenerative responses according to the inflammatory niche[4].

RA is a chronic inflammatory disease which has destructive effects on joint cartilage and subchondral bone. RA is divided into four specific stages: i) early stage: join pain and stiffness, (ii) moderate-stage: inflammation in the synovium causing damage to the joint cartilage, (iii) severe: damage in the cartilage and bones and (iv) end-stage: no longer any inflammation in the joints, bone erosions and mobility loss[5]. Differentiation of naive T cells into Th1 or Th17 cells contributes to synovitis. The pro-inflammatory cytokines interleukin (IL)1β and tumor necrosis factor α (TNF-α) are the two main mediators in the initial phase of RA. In addition, IL-6, IL-8, IL-15, IL-17 and interferon-γ (IFN-γ) produced in the joints have progressive effects and cause joint destruction in RA[6]. These cytokines in the synovial fluid (SF) may vary in the different stages of RA. While TNF-α, IFN-γ and IL-6 are predominantly secreted in the early stage of RA, they tend to decrease in the later stages[7]. Nowadays, non-steroidal anti-inflammatory agents, corticosteroids and disease-modifying anti-rheumatic drugs are used in RA[8]; however, most of these medications have side effects, such as loss in bone density or susceptibility to infections[9]. Therefore, new therapeutic options are required which target inflammatory responses and tissue regeneration without side effects.

In previous studies, MSCs have shown promising trends for clinical application in RA. The MSCs used are mostly isolated from bone marrow, adipose tissue or the umbilical cord. In the present study, we evaluated the differentiation potential of dental pulp and periodontal ligament MSCs in the synovial fluids of different stages of patients with RA to investigate whether they can be new cellular candidates for tissue damage.

MATERIALS AND METHODS

Study Population

This study was approved by the Muğla Sıtkı Koçman University Clinical Ethics Committee with reference number 02/IV, 30.01.2020. Six patients with RA (aged between 48 and 67 years old) with synovial fluid aspiration participated in the present study. The patients had bone or cartilage erosions (end-stage RA). The patients were included in this study according to their ACR and EULAR diagnostic criteria for RA, and the additional inclusion criteria for the present study were as follows: 1) patients with RA without comorbidity, 2) positive for rheumatoid factor and 3) Elevated C-Reactive Protein (CRP) values. The minimum number of patients for statistical analyses was determined using G-power analysis. The total number of patients was calculated to be n=6 with the parameters as follows: α-err probability was 0.05 and power (1-β err probability) was 0.80. The demographic data of the patients and healthy individuals for dental tissue collection are given in Tables 1 and 2, respectively.

Dental Pulp and Periodontal Ligament MSCs Isolation

Tissues were obtained from four healthy individuals who applied to the Muğla Sıtkı Koçman University Faculty of Dentistry. The isolation of MSCs from the dental tissues was performed as described before[10]. In brief, dental pulp and periodontal ligament tissues were mechanically fragmented into 1x1 mm^2 pieces and enzymatically digested in collagenase type I solution (3 mg/mL) in phosphate buffer solution (PBS, pH=7.4) (Thermofisher, US) for 45 minutes at 37°C. The tissue fragments were passed through a 70-micron filter and washed twice with DMEM-Low Glucose 1.0 g/L (Pan Biotech, Germany) supplemented with 10% fetal bovine serum (FBS, Pan Biotech, Germany) and 1% Penicillin/Streptomycin (100 U/mL, 100 µg/mL) (Thermofisher, US) and thereafter referred to as "complete DMEM," and centrifuged at 1200 rpm for five

Table 1. Demographic data of RA patients and healthy individuals

	Rheumatoid arthritis	Healthy subjects
Male/Female	1/5	3/5
Age (years)	48–67	26–42
Duration of illness over 3 years (number of patients)	3	None
Bone or cartilage erosions	3	NA
Treatment		
Infliximab	1	None
Adalumimab	1	None
Methotrexate	2	None
Corticosteroid	3	None
Duration of illness under 3 years (number of patients)	3	None
Bone or cartilage erosions	0	NA
Treatment		
Hydroxychloroquine sulfate	1	None
Methotrexate	2	None
Corticosteroid	2	None
ANA (positive)	100%	NA
RF (IU/mL)	34.55±23.52	NA

ANA: anti-nuclear antibody, RF: rheumatoid factor, NA: not applicable.

Table 2. Data of healthy individuals for dental pulp and periodontal ligament tissue collection

Male/Female	**3/5**
Age (years)	**26–42**
Dental pulp tissues (number of healthy subjects)	4
Periodontal ligament tissues (number of healthy subjects)	4
Inflammatory or genetic diseases (number of healthy subjects)	0
Abscess or microbial contamination (number of healthy subjects)	0

minutes. Cell pellet (3000 cells/cm^2) was transferred to a T25 flask and incubated in 5 mL of complete DMEM until it reached 70%–80% confluence approximately for 10 days. MSCs were cultured until the third passage by transferring cells to T75 flasks containing 3,000 cells/cm^2 in 10 mL of complete DMEM. The third passage cells were analyzed for positive cell surface markers of CD29, CD90 and CD105, and negative markers of HLA-DR, CD3 and CD28, by staining the cells with anti-CD29 (APC), anti-CD90 (PerCp), anti-CD105 (FITC), anti-HLA-DR (APC, anti-CD3 (PerCp), and anti-CD28 (PE), respectively. All antibodies were purchased from BD Biosciences, US. Analysis was performed via flow cytometry (BD Accuri C6 Plus), and the data were recorded as mean fluorescence index (MFI) %.

Cytokine Analysis of SF Samples

The cytokine profiles were analyzed from 50µL of each SF sample using the CBA Th1/Th2/Th17 kit (BD Biosciences, US) via flow cytometry. The analysis was performed as described in the kit protocol and as described previously[11]. In brief, standard beads were prepared with serial dilutions (1:2, 1:4, 1:8, 1:16, 1:32, 1:64, 1:128, and 1:256) in 12x75 mL in standard tubes. The standard curve was obtained via flow cytometry. SF samples were diluted in 1:5 with assay diluent in the CBA kit. The dilution factor was calculated for each of the samples. The pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, IFN-γ, IL-17) were analyzed with BD Accuri C6 plus software. Data were recorded as pg/mL.

Culture Conditions

The culture conditions were determined as described previously[12] with some modifications. DP-MSCs or PL-MSCs (5x10^4 cells/cm^2) were cultured in six well-plates (Corning®, US) for two separate analyses, one of the culture plates was used for osteogenic or chondrogenic differentiation analysis, and one of the culture plates was used for cell surface marker analysis (5x10^4 cells/cm^2). DP-MSCs or PL-MSCs in the third passage were cultured with each of the fresh synovial fluid samples with osteogenic or chondrogenic stimulation medium (1:1 v/v) at 37°C and 5% CO_2 incubation for three weeks for the osteogenesis or chondrogenesis, using osteogenic or chondrogenic differentiation kits (StemPro™, Thermofisher, US). After the culture period, adherent cells were washed with PBS, and fixation was done with 10% formaldehyde solution. Osteogenic differentiation potential was evaluated by staining the cells with Alizarin Red (Sigma-Aldrich, Germany), and chondrogenic differentiation was evaluated by staining the cells with Alcian Blue (Sigma-Aldrich, Germany). Complete DMEM was used as a negative control medium, and osteogenic differentiation or chondrogenic differentiation media were used as positive control media[10].

The results of the samples of the patients with RA were evaluated by comparing the calcium deposits or cartilage formation in the negative and positive control media.

Cell Surface Marker Analysis for Osteogenic or Chondrogenic Differentiation

At the end of the culture period, the adherent cells were trypsinized with 0.25% Trypsin EDTA solution and subjected to cell surface markers for osteogenic or chondrogenic differentiation by staining cells with anti-ALP (Alexa Fluor 488) or anti-CD49e (PE), respectively, and analyzed via flow cytometry as described before[13]. The cell population was gated for CD90+ cells and these cells were analyzed for ALP or CD49e expressions as MFI%.

Additionally, a neutralization assay was performed to determine whether the high expressed cytokines affect the differentiation potential of DP-MSCs in the osteogenic or chondrogenic lineage. 5 mM anti-IL-6 neutralizing antibody (eBioscience, US) or 5 mM anti-IL-1β antibody (Invivogen, France) were added in the end-stage patients with RA-SF and the samples were cultured with DP-MSCs, and cultured for 21 days with the osteogenic or chondrogenic stimulation medium (1:1 v/v) for 21 days at 37°C in 5% CO_2 incubation. The cells were trypsinized and subjected to flow cytometry analysis for cell surface expressions of CD49e or ALP in the CD90+ cell population.

Statistical Analysis

Statistical analyses were performed using one-way analysis of variance (ANOVA) with the GraphPad Prism 9.0 software. Data were presented as mean ± standard deviation. The Mann−Whitney U test was performed to investigate the difference between two sample data. $P<0.05$ was considered significant.

RESULTS

Characterization of DP-and PL-MSCs

The MSCs isolated from the dental pulp and periodontal ligament tissues formed fibroblast-like colonies in passage 0 (P0), P1, P2 and P3. The third passage cells expressed the positive cell surface markers of CD29, CD90 and CD105 over 95% and lacked the expression of the negative markers of HLA-DR, CD3 or CD28 (Figure 1).

Cytokine Levels in the SF Samples

The levels of secreted cytokines were analyzed for the evaluation of inflammatory microenvironment in the different stages of the patients with RA. The end-stage RA-SF samples showed significantly high levels of IL-1β (61.1±9.8) and IL-6 (2386.7±397.4), compared to the early-stage RA-SF samples (IL-1β: 35.2±4.8, IL-6: 561.3±197.6) ($p<0.05$, $p<0.001$, respectively). TNF-α, IL-17 and IFN-γ levels were slightly higher (TNF-α: 981.6±182.3, IL-17: 17.9±2.6, IFN-γ: 92.5±12.8) in the early-stage patients' RA-SF samples compared to the end-stage patients with RA (TNF-α: 648.3±212.9, IL-17: 12.1±3.2, IFN-γ: 96.7±27.3), but no significance was observed between the two groups ($p>0.05$) as shown in Figure 2.

The Osteogenic and Chondrogenic Differentiation Potential of DP-MSCs Increased in the SF Samples of End-Stage Patients With RA

The cultured DP-MSCs with end-stage RA-SF samples showed a high expression of ALP in the CD90+ cell population (59.1±5.3), while PL-MSCs expressed a low expression of the osteogenic marker (19.5±7.2). The low expression of ALP was significant in DP-MSCs cultured with the early-stage RA-SF samples (18.7±4.2) in comparison to the end-stage RA-SF samples and DP-MSCs cultured with osteogenic medium (51.1±3.8) ($p<0.005$). The chondrogenic marker expression was significantly higher in DP-MSCs cultured with the end-stage RA-SF samples (39.2±2.5) when compared to those in the early-stage patients with RA (19.7±3.2) ($p<0.01$). Additionally, DP-MSCs cultured with the SF samples of the end-stage patients with RA formed osteogenic colonies and calcium deposits to a greater extent compared to the PL-MSCs. Cartilage formation was observed in DP-MSCs cultured with the SF samples of the end-stage patients with RA, while sparse colonies of chondrocytes were observed in DP-MSCs cultured with the early-stage patients' RA-SF samples. Also, chondrocytes were observed in DP-MSCs or PL-MSCs cultured with

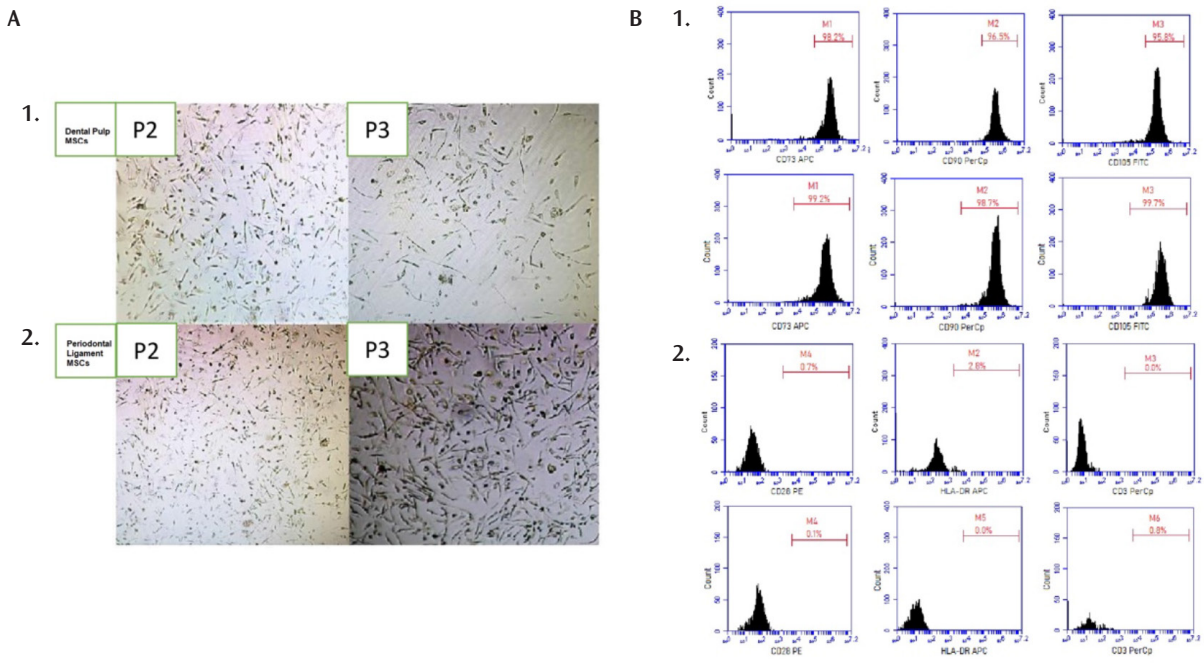

Figure 1. Characterization of MSCs. **A)** The fibroblast-like colony formation of A1) DP-MSCs or A2) PL-MSCs in the second and third passages. **B)** The cell surface markers for MSCs B1) DP-MSCs or B2) PL-MSCs expressed positive markers (CD73, CD90, CD105) over 95%, and lack the expression of hematopoietic markers.

PL-MSCs: mesenchymal stem cells derived from human placenta, DP-MSCs: mesenchymal stem cells from the exfoliated decidu-ous teeth dental pulp

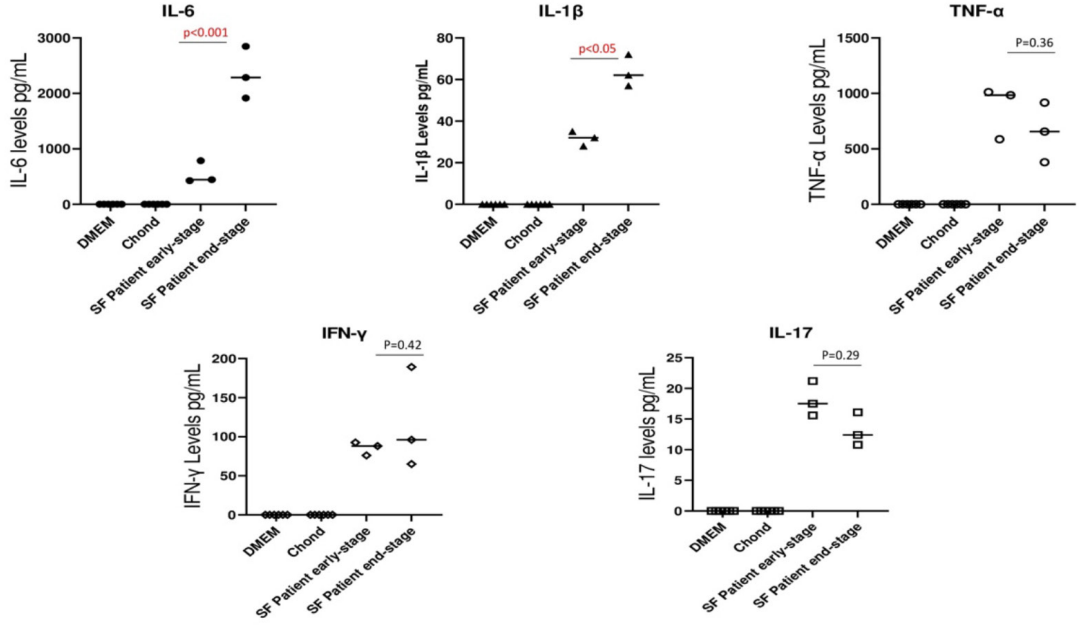

Figure 2. Cytokine levels of SF samples of RA patients. IL-1β and IL-6 levels were significantly high in the end-stage RA-SF samples compared to the early-stage patients ($p<0.05$ and $p<0.001$, respectively). TNF-α, IFN-γ and IL-17 levels were closer in the end-stage and the early-stage RA-SF samples, and no significant difference was observed ($p>0.05$).

RA: rheumatoid arthritis, RA-SF: rheumatoid arthritis synovial fibroblasts, TNF-α: tumor necrosis factor-alpha, IFN-γ: cytokine interferon-gamma, IL: interleukin

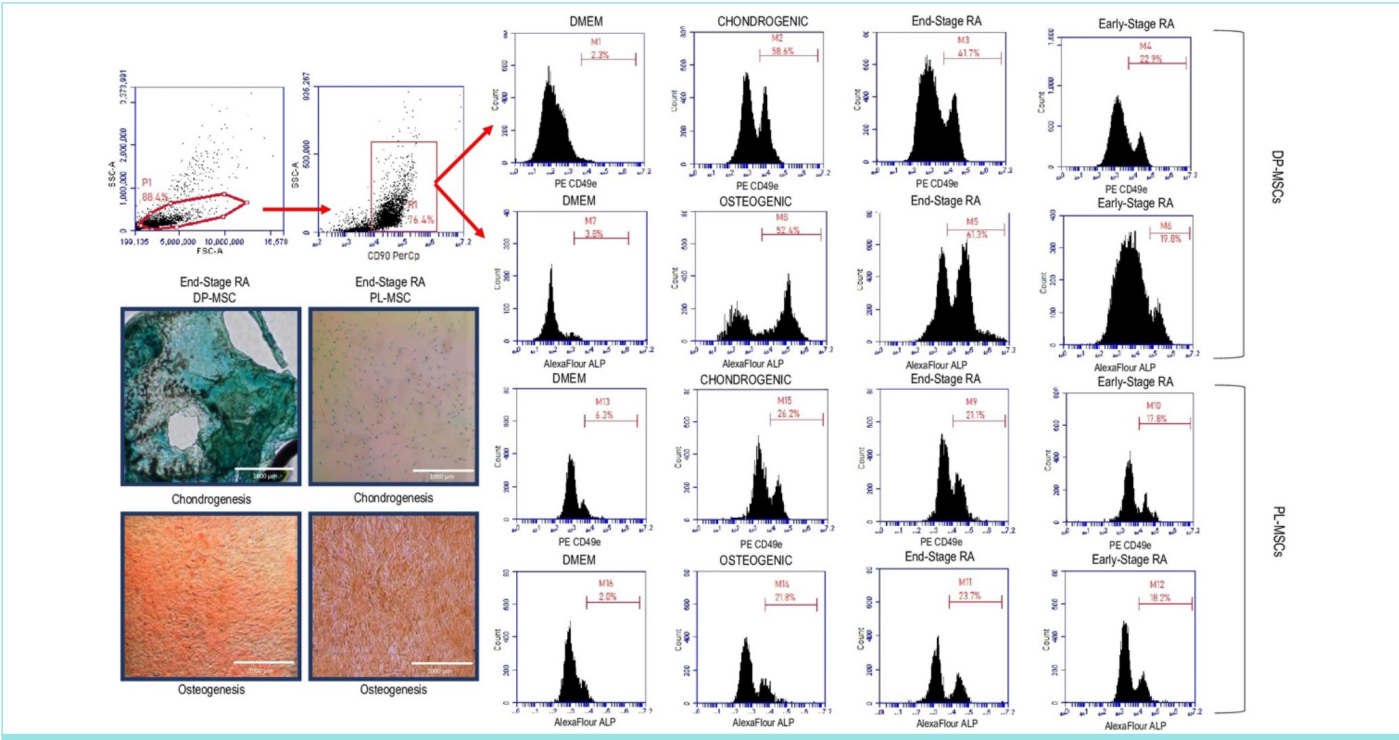

Figure 3. The analysis of the differentiation potential of DP- and PL-MSCs. Gating strategy for positive cell surface markers of DP- or PL-MSCs. CD90+ cells were gated from the total cell population to analyze the CD49e or ALP ratio in DP- or PL-MSCs from 21-day of cultured cells. Positive cell surface markers of chondrogenic (CD49e) or osteogenic (ALP) differentiation of MSCs. The differentiation potential of DP- or PL-MSCs cultured with end-stage RA-SF samples. DP-MSCs showed cartilage formation and tight clusters with high intensity of calcium deposits, while PL-MSCs showed sparse colonies of chondrocytes and looser clusters of osteogenic colonies.

PL-MSCs: mesenchymal stem cells derived from human placenta, DP-MSCs: mesenchymal stem cells from the exfoliated decidu-ous teeth dental pulp, RA-SF: rheumatoid arthritis synovial fibroblasts

the SF samples of the early-stage RA patients, but the chondrogenic differentiation marker of CD49e was significantly higher in DP-MSCs (39.2±2.5) compared to those in the PL-MSCs (25.7±3.8) ($p<0.05$). As a result, DP-MSCs fully participated in the osteogenic and chondrogenic differentiation process with high expression of osteogenic and chondrogenic markers and formed osteogenic colonies and cartilage, while PL-MSCs weakly differentiated into osteogenic or chondrogenic lineage in the end-stage and early-stage RA-SF microenvironments (Figures 3 and 4).

The Neutralization of IL-1b Tended to Downregulate the Osteogenic Differentiation of DP-MSCs

To evaluate the effects of cytokine profiles on the osteogenic or chondrogenic differentiation potential of DP-MSCs in which ALP or CD49e expressions were observed in cells cultured with end-stage RA-SF, we performed neutralization assays for the highly secreted cytokines IL-1β and IL-6.

The osteogenic marker expression tended to decrease with the neutralization of IL-1β in DP-MSCs (48.6±3.9) when compared with un-neutralized cultures (57.7±2.7) ($p>0.05$), and the neutralization of IL-6 tended to decrease the ALP expression of DP-MSCs (49.3±2.8), but no significant change was observed compared to un-neutralized cultures ($p>0.05$).

The chondrogenic marker expression of DP-MSCs slightly reduced with the neutralization of IL-1β (54.4±1.7) or IL-6 (46.7±3.1), but no significant difference was observed when compared with un-neutralized cultures ($p>0.05$) as shown in Figure 5.

DISCUSSION

MSCs are adult stromal cells which can be isolated from bone, adipose tissue, umbilical cord, placenta or dental tissues. These cells have the capacity to differentiate into a variety of tissue types, including cartilage, tendon, fat and muscle[14]. In addition to their multiple differentiation capacity, MSCs are candidates for the cellular treatment of many inflammatory diseases, with the anti-inflammatory responses they generate in inflammatory conditions[15,16]. In addition to suppressing inflammation, their use in damaged tissue regeneration has been shown in previous studies[17-19]. In the present study, we investigated the differentiation capacity of periodontal ligament and dental pulp MSCs in the synovial fluid microenvironment aspirated from two distinct stages of patients with RA to investigate the cellular therapeutic benefits of these cells in cartilage or bone damage in RA.

MSCs can develop variable anti-inflammatory or regenerative responses depending on the source from which they are isolated and the inflammatory conditions in which they are found. In previous studies, it has been reported that umbilical cord MSCs (UC-MSCs) support M2 macrophage differentiation to a greater extent compared to bone marrow MSCs, thus exhibiting a high regulatory effect on immune responses[20]. In a study conducted on bone regeneration, it was shown that, unlike BM-MSCs, UC-MSCs were persistent in implants for up to

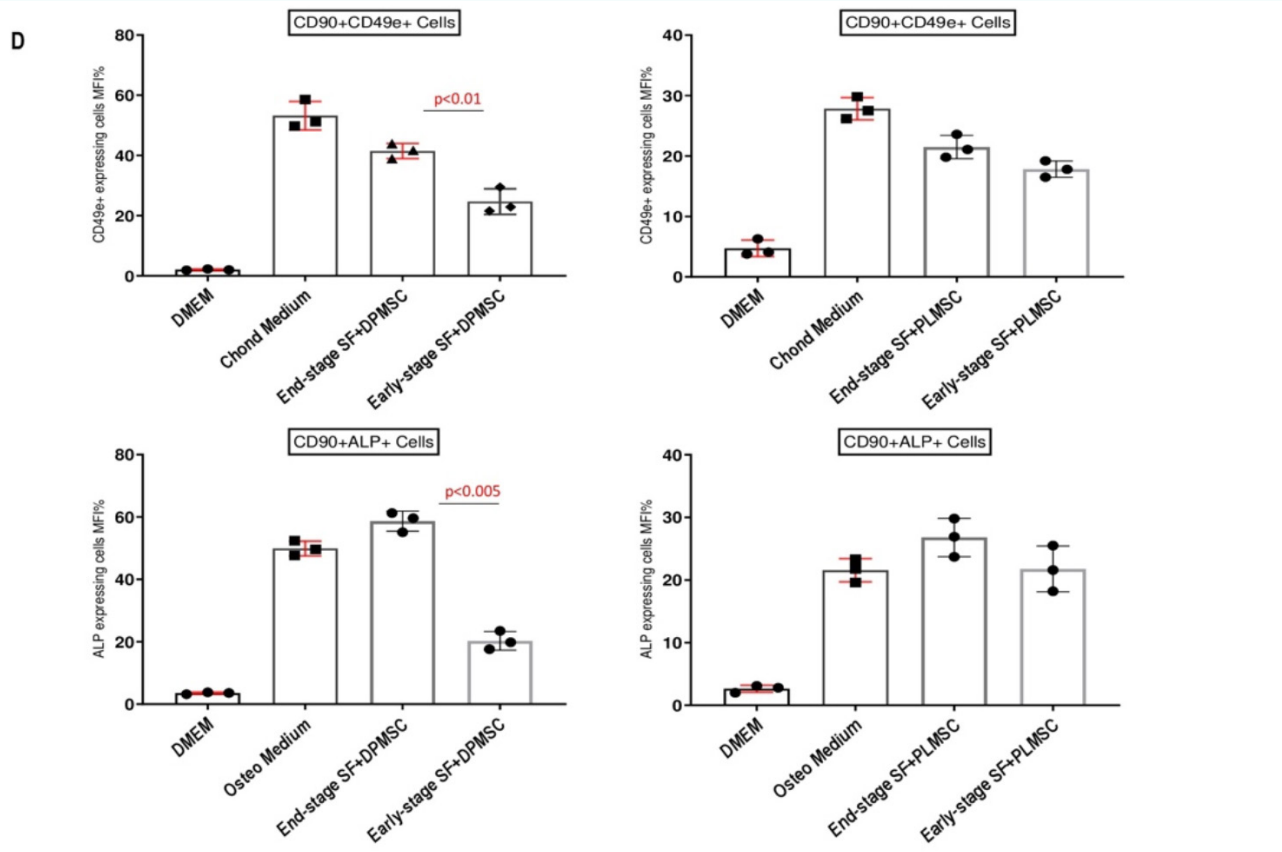

Figure 4. The statistical analysis of cell surface markers for osteogenic or chondrogenic differentiation of DP- and PL-MSCs. The ratio of chondrogenic and osteogenic differentiation markers (CD49e and ALP) in the flow cytometry analysis were significantly high in DP-MSCs cultured with the end-stage RA-SF samples, compared to the early-stage RA-SF samples (CD49e: $p<0.01$, ALP: $p<0.005$).

PL-MSCs: mesenchymal stem cells derived from human placenta, DP-MSCs: mesenchymal stem cells from the exfoliated decidu-ous teeth dental pulp, RA-SF: rheumatoid arthritis synovial fibroblasts

three weeks and achieved bone formation in the local injured site. However, unlike BM-MSCs, UC-MSCs activated the host cells for bone regeneration, highlighting the effects of the microenvironment in determining cell differentiation and response[20,21]. Studies conducted to date have demonstrated the protective effects of intraperitoneally injected MSCs against joint destruction in collagen-induced arthritis (CIA) in RA and similar inflammatory arthritis models. In one of these studies, it was reported that after intravenous injection of bone marrow or UC-MSCs, recovery occurred in 3–6 months and this effect was achieved by increasing the Treg cell population[22]. In addition, it has been shown that locally applied MSCs are more effective than systemic application in tissue regeneration in RA cartilage damage.

In the current study, we found that the cytokine profiles of patients with RA change the differentiation potential of PL-MSCs and DP-MSCs towards chondrogenesis or osteogenesis. DP-MSCs differentiate to osteogenic colonies and expressed a high ratio of ALP in the SF samples of the end-stage patients with RA with high levels of IL-1β and IL-6. PL-MSCs showed slight osteogenic differentiation potential in the same inflammatory niche. These data indicate the variable differentiation potentials of PL-MSCs and DP-MSCs in the inflammatory microenvironment of RA-SF. Also, these results demonstrate that DP-MSCs are a more suitable source for MSCs for cartilage and bone repair in the RA-SF microenvironment since RA is an inflammatory disease characterized by cartilage and bone damage. Additionally, the differentiation potential of MSCs may change with the origin of the source and due to the presence of progenitor cells of different types[23]. Although the mechanisms that determine the osteogenic behavior of adipose tissue MSCs and bone marrow MSCs are complex, their differentiation potential is entirely dependent on the inflammatory cytokines secreted in the damaged tissue. In one study, BM-MSCs were shown to downregulate osteogenic differentiation in an environment with inflammatory cytokines, such as IL-6 and TNF-α[24]. In contrast, IL-6 was shown to support the differentiation of BM-MSCs towards osteogenesis and was mentioned as a central mediator of bone homeostasis, and it was shown to positively affect skeletogenesis and bone formation[25]. In another study, it was concluded that IL-1β activates osteogenic differentiation of BM-MSCs with the activation of the BMP/Smad pathway[26]. However, contrasting results have been reported for the effects of IL-1β on the osteogenic differentiation capacity of murine BM-MSCs. In a previous study, IL-1β or TNF-α stimulation of bone marrow MSCs inhibited the osteogenic differentiation potential *in vitro*[27]. These results in the previous studies indicate that the differentiation potential of MSCs may be influenced by distinct inflammatory conditions or the source of the MSCs. We, therefore, conducted neutralization assays for the highly secreted IL-1β and IL-6 cytokines, which were at the same time prominent cytokines in RA. Although statistically significant change was not observed, the slight downregulation of osteogenic and

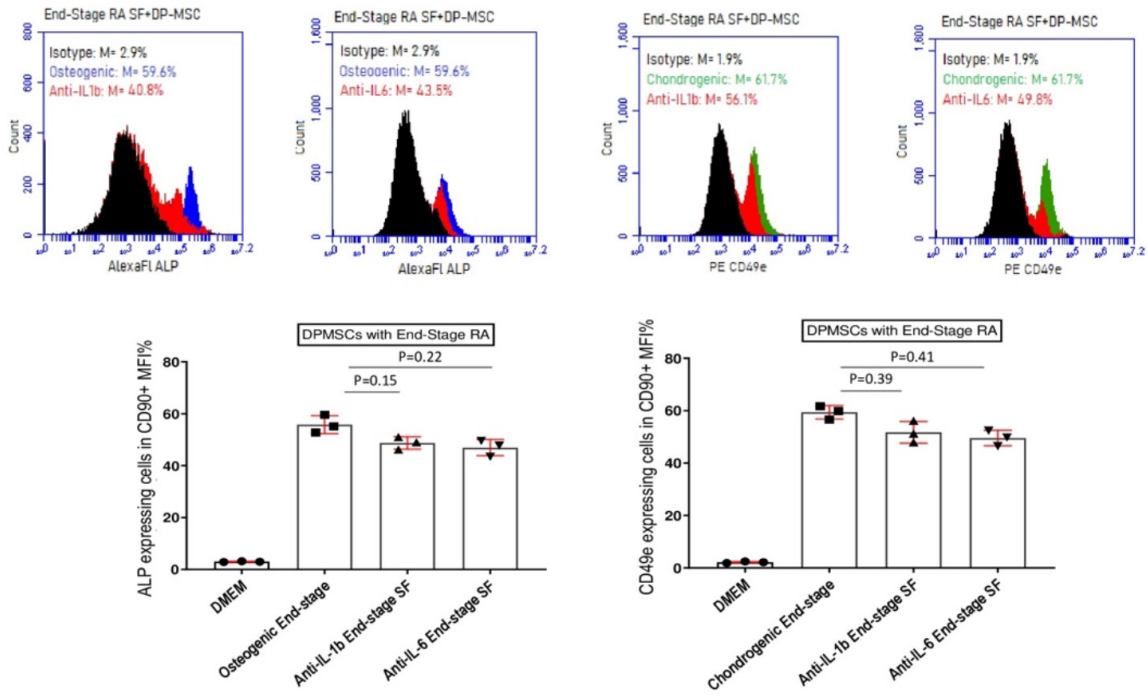

Figure 5. Neutralization of IL-1β and IL-6 in end-stage RA-SF samples cultured with DP-MSCs. The neutralization of IL-1β and IL-6 tended to decrease the CD49e or ALP expression ratio of CD90+ cell population in the 21 days of the culture period.

IL: interleukin, RA-SF: rheumatoid arthritis synovial fibroblasts

chondrogenic markers in DP-MSCs due to neutralization of IL-1β or IL-6 suggests that these cytokines may also be important in DP-MSCs differentiation potential.

CONCLUSION

The present study shows that the DP-MSCs can differentiate towards osteogenic cells in the end-stage RA-SF microenvironment, but the osteogenic or chondrogenic differentiation potential of PL-MSCs is limited in the RA-SF niche. There may be other inflammatory factors, such as exosomes, inflammatory molecules or proteins, which play a role in the differentiation process. Thus, further analysis can be performed to highlight the differentiation mechanisms in DP-MSCs or PL-MSCs. In addition, DP-MSCs may be used for damaged tissue regeneration in patients with RA with bone or cartilage erosions, and for this purpose, further *in vivo* studies can be performed.

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MAIN POINTS

- Dental pulp mesenchymal stem cells can differentiate both into osteocytes or cartilage in the inflammatory synovial fluid microenvironment.
- Periodontal ligament mesenchymal stem cells can differentiate into chondrocytes in the inflammatory microenvironment of synovial fluid.
- Dental pulp mesenchymal stem cells can be a candidate for bone or cartilage repair in rheumatoid arthritis.

ETHICS

Ethics Committee Approval: This study was approved by Muğla Sıtkı Koçman University Clinical Research Ethics Committee with the number of 02/IV, 30.01.2020.

Informed Consent: All participants gave informed consent to participate.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.G., Design: D.G., Data Collection and/or Processing: S.S., A.A., E.F.T., Analysis and/or Interpretation: D.G., B.G., Literature Search: D.G., B.G., S.S., A.A., E.F.T., Writing: D.G.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Sharpe PT. Dental mesenchymal stem cells. Development. 2016; 143(13): 2273-80.
2. Shi Y, Wang Y, Li Q, Liu K, Hou J, Shao C, et al. Immunoregulatory mechanisms of mesenchymal stem and stromal cells in inflammatory diseases. Nat Rev Nephrol. 2018; 14(8): 493-507.

3. Ballini A, Scacco S, Coletti D, Pluchino S, Tatullo M. Mesenchymal Stem Cells as Promoters, Enhancers, and Playmakers of the Translational Regenerative Medicine. Stem Cells Int. 2017; 2017: 3292810.

4. Rivera-Cruz CM, Shearer JJ, Figueiredo Neto M, Figueiredo ML. The Immunomodulatory Effects of Mesenchymal Stem Cell Polarization within the Tumor Microenvironment Niche. Stem Cells Int. 2017; 2017: 4015039.

5. Guo Q, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone Res. 2018; 6: 15.

6. Lettesjö H, Nordström E, Ström H, Nilsson B, Glinghammar B, Dahlstedt L, et al. Synovial fluid cytokines in patients with rheumatoid arthritis or other arthritic lesions. Scand J Immunol. 1998; 48(3): 286-92.

7. Ridgley LA, Anderson AE, Pratt AG. What are the dominant cytokines in early rheumatoid arthritis? Curr Opin Rheumatol. 2018; 30(2): 207-14.

8. Köhler BM, Günther J, Kaudewitz D, Lorenz HM. Current Therapeutic Options in the Treatment of Rheumatoid Arthritis. J Clin Med. 2019; 8(7): 938.

9. Barnes PJ. Corticosteroids: the drugs to beat. Eur J Pharmacol. 2006; 533(1-3): 2-14.

10. Yildirim S, Zibandeh N, Genc D, Ozcan EM, Goker K, Akkoc T. The Comparison of the Immunologic Properties of Stem Cells Isolated from Human Exfoliated Deciduous Teeth, Dental Pulp, and Dental Follicles. Stem Cells Int. 2016; 2016: 4682875.

11. Dăcălescu A, Zlei M, Aanei C, Ungureanu D, Tepeluş M, Burcoveanu C, et al. Flow cytometry-based quantification of cytokine levels in AML patients plasma and cell culture supernatants. Rev Med Chir Soc Med Nat Iasi. 2008; 112(1): 196-202.

12. Grässel S, Stöckl S, Jenei-Lanzl Z. Isolation, culture, and osteogenic/chondrogenic differentiation of bone marrow-derived mesenchymal stem cells. Methods Mol Biol. 2012; 879: 203-67.

13. Arpornmaeklong P, Brown SE, Wang Z, Krebsbach PH. Phenotypic characterization, osteoblastic differentiation, and bone regeneration capacity of human embryonic stem cell-derived mesenchymal stem cells. Stem Cells Dev. 2009; 18(7): 955-68.

14. Newman RE, Yoo D, LeRoux MA, Danilkovitch-Miagkova A. Treatment of inflammatory diseases with mesenchymal stem cells. Inflamm Allergy Drug Targets. 2009; 8(2): 110-23.

15. Regmi S, Pathak S, Kim JO, Yong CS, Jeong JH. Mesenchymal stem cell therapy for the treatment of inflammatory diseases: Challenges, opportunities, and future perspectives. Eur J Cell Biol. 2019; 98(5-8): 151041.

16. Poggi A, Zocchi MR. Immunomodulatory Properties of Mesenchymal Stromal Cells: Still Unresolved "Yin and Yang". Curr Stem Cell Res Ther. 2019; 14(4): 344-50.

17. Zhai Q, Dong J, Zhang X, He X, Fei D, Jin Y, et al. Mesenchymal Stem Cells Enhance Therapeutic Effect and Prevent Adverse Gastrointestinal Reaction of Methotrexate Treatment in Collagen-Induced Arthritis. Stem Cells Int. 2021; 2021: 8850820.

18. Liu J, Feng B, Xu Y, Zhu J, Feng X, Chen W, et al. Immunomodulatory effect of mesenchymal stem cells in chemical-induced liver injury: a high-dimensional analysis. Stem Cell Res Ther. 2019; 10(1): 262.

19. Fan XL, Zhang Z, Ma CY, Fu QL. Mesenchymal stem cells for inflammatory airway disorders: promises and challenges. Biosci Rep. 2019; 39(1): BSR20182160.

20. Tesarova L, Jaresova K, Simara P, Koutna I. Umbilical Cord-Derived Mesenchymal Stem Cells Are Able to Use bFGF Treatment and Represent a Superb Tool for Immunosuppressive Clinical Applications. Int J Mol Sci. 2020; 21(15): 5366.

21. Todeschi MR, El Backly R, Capelli C, Daga A, Patrone E, Introna M, et al. Transplanted Umbilical Cord Mesenchymal Stem Cells Modify the In Vivo Microenvironment Enhancing Angiogenesis and Leading to Bone Regeneration. Stem Cells Dev. 2015; 24(13): 1570-81.

22. Ansboro S, Roelofs AJ, De Bari C. Mesenchymal stem cells for the management of rheumatoid arthritis: immune modulation, repair or both? Curr Opin Rheumatol. 2017; 29(2): 201-7.

23. Musina RA, Bekchanova ES, Belyavskii AV, Sukhikh GT. Differentiation potential of mesenchymal stem cells of different origin. Bull Exp Biol Med. 2006; 141(1): 147-51.

24. Deshpande S, James AW, Blough J, Donneys A, Wang SC, Cederna PS, et al. Reconciling the effects of inflammatory cytokines on mesenchymal cell osteogenic differentiation. J Surg Res. 2013; 185(1): 278-85.

25. Rezaee F, Rellick SL, Piedimonte G, Akers SM, O'Leary HA, Martin K, et al. Neurotrophins regulate bone marrow stromal cell IL-6 expression through the MAPK pathway. PLoS One. 2010; 5(3): e9690.

26. Wang H, Ni Z, Yang J, Li M, Liu L, Pan X, et al. IL-1β promotes osteogenic differentiation of mouse bone marrow mesenchymal stem cells via the BMP/Smad pathway within a certain concentration range. Exp Ther Med. 2020; 20(4): 3001-8.

27. Lacey DC, Simmons PJ, Graves SE, Hamilton JA. Proinflammatory cytokines inhibit osteogenic differentiation from stem cells: implications for bone repair during inflammation. Osteoarthritis Cartilage. 2009; 17(6): 735-42.

ORIGINAL ARTICLE

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Effects of Staining Beverages and Office Bleaching Agents on the Optical Characteristics and Surface Topography of Maxillary Incisor Teeth

İzgen Karakaya[1], Esra Cengiz-Yanardag[2]

[1]Department of Restorative Dentistry, European University of Lefke, Faculty of Dentistry, Lefke, North Cyprus
[2]Department of Restorative Dentistry, Mersin University, Faculty of Dentistry, Mersin, Turkey

Abstract

BACKGROUND/AIMS: The aim of this study was to evaluate the staining abilities of different beverages, the efficacy of two office bleaching agents and the effect of bleaching on the surface topography of maxillary incisors.

MATERIALS AND METHODS: Sixty crowns of maxillary incisors were obtained and immersed in distilled water for 24 hours. After baseline color measurements were made, the specimens were divided into three groups according to three immersion solutions [Turkish coffee (TC), red wine (RW), and distilled water (DW)]. At the end of the staining period, color measurements were repeated and then the specimens of each group were divided into two subgroups and Perfect Bleach Office+ (PBO+) or Opalescence Boost (OB) were applied. After bleaching, the color measurements were recorded again and the optical parameters of color difference (ΔE00), changes in the translucency parameter (ΔTP00) and whiteness difference (ΔWID) were calculated. For the surface analysis, atomic force microscopy was performed for one specimen from each group.

RESULTS: The highest color changes were observed with RW ($p<0.05$). Although TC showed high color changes, no significant difference was observed with the control group ($p=0.208$). The observed color and whiteness differences were higher than the acceptability thresholds ($\Delta E00>1.8$ and $\Delta WID>2.60$) and the ΔTP00 values were lower than the acceptability thresholds ($0.62<\Delta TP00<2.62$). Regardless of the type of staining solution, OB showed higher ΔE00 values ($p=0.000$). Surface roughness observed after bleaching was not higher than the critical surface roughness (0.2 µm). Differences in the surface topography of the specimens relating to the solution type were observed.

CONCLUSION: The frequent consumption of Turkish coffee and red wine can cause discolorations. Surface analysis showed that office bleaching agents can be a safe method for the treatment of discolorations with a high efficiency in color and whiteness reversal.

Keywords: Atomic force microscopy, bleaching, color, surface roughness, whiteness

INTRODUCTION

Dental discoloration has become one of the most important concerns of dentistry due to current changes in esthetical perceptions with regards to healthy, confident and whiter smiles.[1] The habits of patients, such as smoking, their medical history, their frequent use of mouth rinses, the accumulation of biofilm, their use of medications, and their diets, such as drinking colored beverages, are examples of the intrinsic and extrinsic factors which may cause dental discoloration.[2,3] The type, exposure times and concentrations of staining agents are the most important components determining the severity of any discoloration.[4-6]

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ORCID IDs of the authors: İ.K. 0000-0002-4448-556X; E.C.Y. 0000-0002-2651-2755.

Address for Correspondence: İzgen Karakaya
E-mail: izgen96h@gmail.com; ikarakaya@eul.edu.tr
ORCID ID: orcid.org/0000-0002-4448-556X

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Currently, bleaching procedures have become more popular as a result of this major concern. Mainly, there are two types of bleaching methods, namely, home bleaching and office bleaching. Office bleaching, applied by dental clinicians, generally uses higher concentrations of hydrogen peroxide (H_2O_2).[2] Due to its low molecular weight, H_2O_2 can freely penetrate into the interprismatic spaces of enamel and dentin tubules and oxidize coloring pigments.[2,7]

For the judgement of color changes during office bleaching, dental clinicians generally prefer to use shade guides and digital photography. For a more objective evaluation, the most preferred method to determine any color changes in dental practices are spectrophotometers.[8,9] Spectrophotometers measure the transmittance or spectral reflectance properties of a material at 1–25 nm intervals along the visible spectrum by using a standard illuminant, observer and recommended geometry and then express these via a three-coordinate system (L*a*b), which was introduced by Commission Internationale de l'Eclairage (CIE).[10,11]

The oxidation reaction occurring during bleaching applications can cause some chemical changes in dental surfaces which can change the surface topography.[12,13] Surface roughness is an important factor which affects biofilm accumulation, which can cause the recurrence of discoloration. Atomic force microscopy (AFM) is one of the methods used for surface analysis.[14] In addition to needing minimal sample preparation and without changing the natural conditions of specimen structure, it is capable of revealing the surface along the X, Y and Z axes.[14,15] As a result, both two- and three-dimensional images of the surfaces can be obtained at the same time.

There have been studies[14,16-20] which have investigated the effects of bleaching agents on color changes or on the surface characteristics of permanent teeth by different methods. However, to the best of our knowledge, with regards to *in vitro* studies, samples were generally the intersections of enamel or dentine, with the exception of a recent study in which the color susceptibility of premolars and the efficacy of whitening toothpaste was investigated.[3] Data regarding AFM images obtained from bleached permanent teeth is limited. Thus, the purpose of this *in vitro* study was to evaluate the color stability of maxillary incisors, the staining ability of different beverages, the efficacy of two office bleaching agents and the effects on the surface characteristics of stained maxillary incisors. The determined null hypotheses were;

1- There will be no changes in the color, whiteness and translucency of permanent teeth after staining and bleaching,

2- There will be no statistically significant difference in the staining abilities of the different beverages,

3- There will be no statistically significant difference in the efficacy of the bleaching agents,

4- There will be no differences in the surface topography and roughness of the enamel surfaces relating to the bleaching agents and/or the staining beverages.

MATERIALS AND METHODS

Specimen Preparation

A statistical power analysis using the G*Power 3.1 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) software was performed with a statistical power of 80% and significance level of 0.05 (α) to determine the number of the specimens required for the present study. Sixty maxillary incisor teeth were obtained according to a protocol (YDU2016/37-287) which was approved by the Committee for Ethics of Research of Near East University. Each tooth was examined carefully and those with no caries, fractures or any other defects were included in this study. After soft and hard deposits on the teeth were cleaned, the crowns were polished using fine (particle size: 24 µm) and superfine (particle size: 8 µm) Sof-Lex™ Discs (3M ESPE, St. Paul, MN, USA) respectively. Following this, the roots were separated from the cemento-enamel junction using a water-cooled, high speed diamond bur. Before baseline color measurements were made, the crowns were washed and placed in distilled water for 24 hours.

Color Measurements

A calibrated spectrophotometer (VITA Easyshade Compact, VITA Zahnfabrik, Bad Säckingen, Germany) was used for the color measurements, which were performed at baseline, on the 14th day of staining and after bleaching. The probe of the spectrophotometer was settled flush to the middle third area of labial surfaces and the L* (lightness), a* and b* (chromatic components) parameters were recorded according to the CIE L*a*b* color space. These parameters were recorded three times for each specimen on non-reflective backgrounds (white; L=96.3, a=0.1, b=1.9 and black; L=8.9, a=-0.7, b=1.2) and the mean values were calculated. The CM-3600a spectrophotometer (Konica Minolta, New Jersey, USA) was used to obtain the L, a and b coordinates for both white and black. In accordance with the manufacturer's instructions, calibration was repeated after each nine measurements.

Immersion in Staining Solutions

After the completion of baseline color measurements, three staining subgroups of the specimens with a sample size of 20 per subgroup were formed in terms of the type of staining beverages. The specimens were immersed either in distilled water (DW) as a control, Turkish coffee (Kurukahveci Mehmet Efendi, İstanbul, Turkey) for which 30 grams were boiled with 600 mL water and then filtered or red wine (RW, 2014 Angora, Kavaklıdere Şarapları A.Ş., Ankara, Turkey) with a volume of 20 mL for 30 minutes per day. At the end of 30 minutes of staining, the specimens were rinsed thoroughly with distilled water. The specimens were immersed in 20 mL distilled water for the remaining time of 24 hours. In a pilot study,[21] the optimal contact time of a hot beverage in the mouth was reported to be 60 seconds for each cup. Thus, to simulate a total of 12 months, with an average of 420 cups/glasses of beverage consumption, staining was applied for 14 days.

Bleaching Procedure

In the present study, Perfect Bleach Office+ (VOCO GmbH, Cuxhaven, Germany) with a concentration of 35% hydrogen peroxide; and Opalescence Boost (Ultradent Products Inc., South Jordan, UT, USA) with a concentration of 40% hydrogen peroxide were used as the bleaching agents. Specimens for each staining solution were divided into two groups with a sample size of 10 for each bleaching agent. At the end of the staining period, all of the specimens were dried well using blotting paper and air flow. After the color measurements were completed, to simulate the clinical procedures, first the lingual surfaces of the specimens were polished using prophy cups. Then, the bleaching agents were applied to the labial surfaces with an approximate thickness of 1 mm. According to the manufacturers' instructions, the applications of Perfect Bleach Office+ (PBO+) and

Opalescence Boost (OB) were 15 min and 20 min respectively. During the application, the agents were activated every 5 minutes by a micro-brush. At the end of the bleaching procedure, the specimens were washed with distilled water and dried well via air flow and blotting paper.

Optical Analysis

Optical analysis were performed using the calculated mean values of L_w*, a_w*, b_w* and L_B*, a_B*, b_B* where 'W' and 'B' refer to the background colors, namely white and black, respectively.

The following equation was used for the calculations of ΔE_{00} (color difference) values to evaluate color change between the two different measurements.[22]

$$\Delta E_{00}=\left[\left(\frac{\Delta L}{k_L S_L}\right)^2 + \left(\frac{\Delta C}{k_C S_C}\right)^2 + \left(\frac{\Delta H}{k_H S_H}\right)^2 + R_T\left(\frac{\Delta C}{k_C S_C}\right)\left(\frac{\Delta H}{k_H S_H}\right)\right]^{1/2}$$

ΔL, ΔC and ΔH are the changes in lightness, chroma and hue between the baseline and subsequent color measurements. The total color difference for the variation in perceived magnitude with the variation in the location of the color coordinate difference between 2 color measurements are adjusted by weighting functions (S_L, S_C and S_H). R_T (rotation function) is a function accounting the interaction between hue and chroma differences in the blue region. The correction terms for the experimental conditions are defined by parametric factors of K_L, K_C and K_H. The computation used for the ΔE_{00} calculations of the present study was carried out with regards to CIEDE2000 (1:1:1) where the parametric factors were defined as 1.[22,23] The perceptibility threshold (PT) for ΔE_{00} values was taken to be 0.8 and the 50%:50% acceptability threshold (AT) was taken to be 1.8 for the present study.[22]

The CIEDE2000 (1:1:1) formula was also used to calculate the translucency parameter (TP_{00}) where the color coordinates of the specimen were recorded at the same period of time but on different backgrounds, namely black or white.[24]

$$TP_{00} = \left[\left(\frac{L'_B - L'_W}{K_L S_L}\right)^2 + \left(\frac{C'_B - C'_W}{K_C S_C}\right)^2 + \left(\frac{H'_B - H'_W}{K_H S_H}\right)^2 + R_T\left(\frac{C'_B - C'_W}{K_C S_C}\right)\left(\frac{H'_B - H'_W}{K_H S_H}\right)\right]^{1/2}$$

The changes in the translucency parameter were calculated by $\Delta TP_{00}=|TP_{00}1 - TP_{00}2|$. The PT for ΔTP_{00} value was 0.62 units and the 50%:50% AT for the ΔTP_{00} value was 2.62 units for the present study.[24]

For the examination of the whiteness during this study; a new CIELAB space based whitening index (WI_D) was used:[25]

$WI_D = 0.511L^* - 2.324a^* - 1.100b^*$

Low (even negative) values of the WI_D index show lower values of whiteness while high positive values indicate higher whiteness.[25] The PT for the ΔWI_D value was 0.72 units and the 50%:50% AT for the ΔWI_D value was 2.60 units for the present study.[26]

Atomic Force Microscopy Analysis

One specimen from each group was embedded into composite blocks forming a stable and straight surface for atomic force microscopy (XE-100E, Park Systems, Induspia 5F, SangDaewon-Dong 517-13 Sungnam, Korea) analysis. The topography of the specimens was examined with a tip working in contact mode with an average rate less than 0.7 Hz within an area of 30x30 μm^2. XEI software (Park Systems, Induspia 5F, SangDaewon-Dong 517-13 Sungnam, Korea) was used to transform the data into 2D and 3D images for topography analysis. For surface analysis, the average R_a (surface roughness), R_{sk} (skewness), and R_{ku} (kurtosis) values were measured from six different lines obtained from the 2D images for each specimen.

Statistical Analysis

Descriptive statistics were performed for all groups and the distribution of ΔE_{00}, ΔTP_{00} and ΔWI_D values were checked by a normality test (Shapiro–Wilk test). The SPSS Version 18 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses and $p<0.05$ was accepted as statistically significant. For the optical parameters obtained for the differences between baseline and staining, One-Way ANOVA (Tukey for pairwise comparison) was performed for ΔE_{00}, while the Kruskal–Wallis test (Mann–Whitney U test for pairwise comparison) was performed for ΔTP_{00} and ΔWI_D. Two-Way ANOVA (Bonferroni adjusted alpha=0.05) was performed for the ΔE_{00}, ΔTP_{00} and ΔWI_D parameters obtained for the differences between staining and bleaching and also baseline and bleaching. For pairwise comparisons, the Tukey's range test was applied with 95% confidence intervals.

RESULTS

The detected mean values and standard deviations for each optical parameter are shown in Tables 1–3. While the translucency differences observed in the present study were lower than acceptability threshold ($0.62<\Delta TP_{00}<2.62$), all of the observed color and whiteness differences were higher than the acceptability thresholds ($\Delta E_{00}>1.8$ and $\Delta WI_D>2.6$).

None of the ΔTP_{00} values showed statistically significant differences during the study duration ($p>0.05$). Additionally, none of the parameters calculated for the differences between the baseline and after bleaching measurements showed statistically significant differences ($p>0.05$).

At the end of the staining period, the highest color change was observed in the RW group, which was significantly different from the control group ($p=0.001$). On the other hand, TC did not show any significant color difference with either the control ($p=0.275$) or the RW group ($p=0.108$).

When the efficacy of OB and PBO+ were compared, regardless of the type of staining solution, no significant differences were observed for

Table 1. Mean values and standard deviations of color, translucency and whiteness differences between baseline and staining

	ΔE_{00}	ΔTP_{00}	ΔWI_D
DW	4.76±3.29*	0.94±0.72	13.43±12.20
TC	7.73±3.49*,‡	0.87±0.62	17.08±13.23
RW	11.44±8.18‡	1.51±1.46	20.71±16.14

Different superscript symbols show statistically significant difference ($p<0.05$).
DW: distilled water, TC: Turkish coffee, RW: red wine, ΔE_{00}: color difference, ΔTP_{00}: translucency parameter difference, ΔWI_D: whiteness difference.

Table 2. Mean values and standard deviations of color, translucency and whiteness differences between staining and bleaching

	ΔE_{00}		ΔTP_{00}		ΔWI_D	
	OB	**PBO+**	**OB**	**PBO+**	**OB**	**PBO+**
DW	$2.88\pm0.95^{A,a}$	$4.04\pm1.86^{C,a}$	0.82 ± 0.99	0.88 ± 0.54	$5.81\pm4.15^{D,e}$	$9.67\pm3.96^{F,e}$
TC	$6.74\pm4.63^{A,b}$	$4.29\pm1.92^{C,b}$	1.23 ± 1.33	2.09 ± 2.26	$10.91\pm9.00^{D,E,f}$	$8.41\pm4.35^{F,f}$
RW	$14.45\pm6.47^{B,c}$	$4.21\pm1.76^{C,d}$	2.45 ± 1.79	0.96 ± 0.59	$16.57\pm13.48^{E,g}$	$9.84\pm4.50^{F,g}$

Different superscript lower case letters in columns and capital letters in rows indicate statistically significant differences ($p<0.05$).
DW: distilled water, TC: Turkish coffee, RW: red wine, OB: Opalessence Boost, PBO+: Perfect Bleach Office+, ΔE_{00}: color difference, ΔTP_{00}: translucency parameter difference, ΔWI_D: whiteness difference.

Table 3. Mean values and standard deviations of color, translucency and whiteness differences between baseline and bleaching

	ΔE_{00}		ΔTP_{00}		ΔWI_D	
	OB	**PBO+**	**OB**	**PBO+**	**OB**	**PBO+**
DW	3.52±2.98	5.60±1.61	0.94±0.71	1.13±1.57	8.10±8.07	12.41±10.85
TC	4.32±1.36	5.43±3.92	1.14±1.39	2.01±1.94	8.55±6.77	14.92±14.52
RW	6.24±2.06	5.18±1.80	1.02±0.68	0.76±0.47	14.07±8.92	11.22±10.83

DW: distilled water, TC: Turkish coffee, RW: red wine, OB: Opalessence Boost, PBO+: Perfect Bleach Office+, ΔE_{00}: color difference, ΔTP_{00}: translucency parameter difference, ΔWI_D: whiteness difference.

Table 4. R_a, R_{sk} and R_{ku} values obtained by AFM analysis

	R_a			R_{sk}			R_{ku}		
	Min	**Max**	**Median**	**Min**	**Max**	**Median**	**Min**	**Max**	**Median**
DW, OB	0.028	0.050	0.035	-0.487	0.444	0.014	2.329	4.480	2.863
DW, PBO+	0.110	0.219	0.154	-0.687	0.357	0.179	2.084	2.991	2.692
TC, OB	0.056	0.151	0.099	-1.977	0.052	-1.002	3.006	7.369	4.587
TC, PBO+	0.028	0.103	0.064	-1.856	-0.937	-1.281	3.735	6.548	4.201
RW, OB	0.066	0.146	0.082	-1.950	0.107	-0.382	2.708	7.523	3.158
RW, PBO+	0.079	0.268	0.156	-2.762	0.470	-1.169	1.799	11.006	4.722

DW: distilled water, TC: Turkish coffee, RW: red wine, OB: Opalessence Boost, PBO+: Perfect Bleach Office+, R_a: surface roughness, R_{sk}: skewness, R_{ku}: Kurtosis, Min: minimum, Max: maximum.

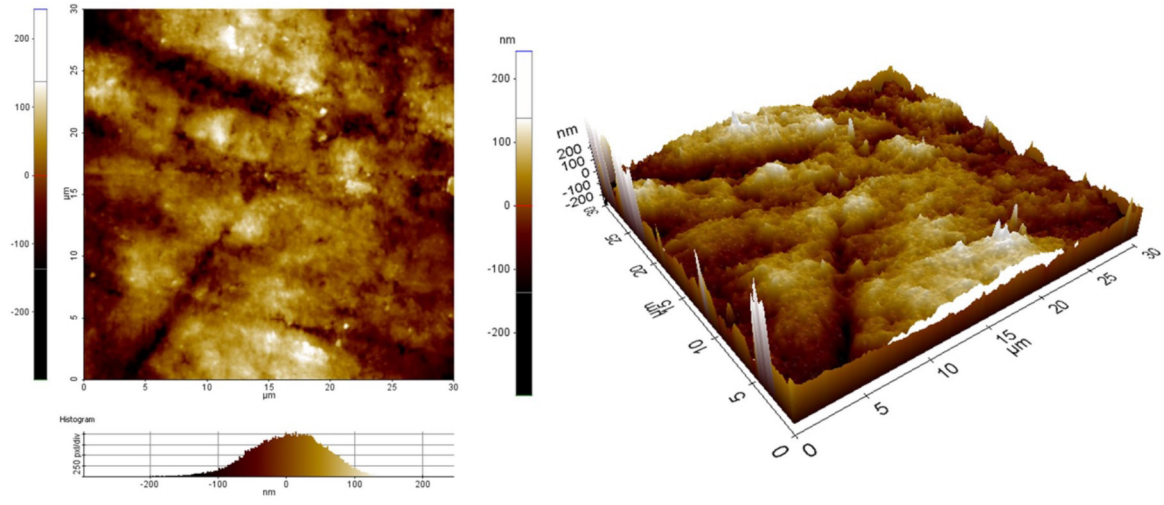

Figure 1. 2D and 3D images of OB applied DW group.
2D: two-dimensional, 3D: three-dimensional, OB: Opalescence Boost, DW: distilled water

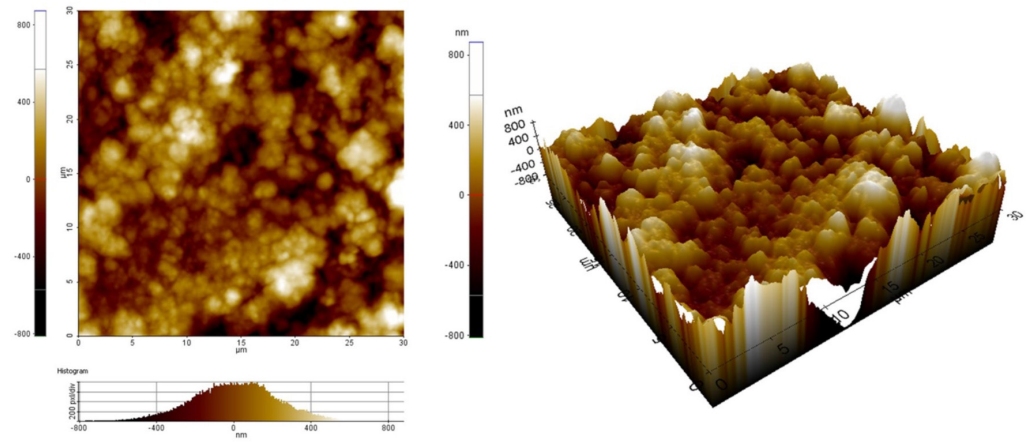

Figure 2. 2D and 3D images of PBO+ applied DW group.
2D: two-dimensional, 3D: three-dimensional, PBO+: Perfect Bleach Office+, DW: distilled water

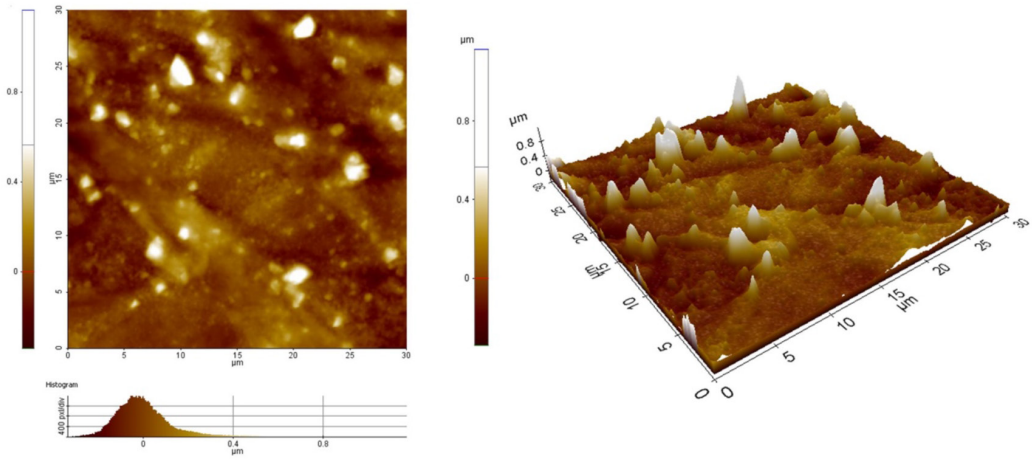

Figure 3. 2D and 3D images of OB applied TC group.
2D: two-dimensional, 3D: three-dimensional, OB: Opalescence Boost, TC: Turkish coffee

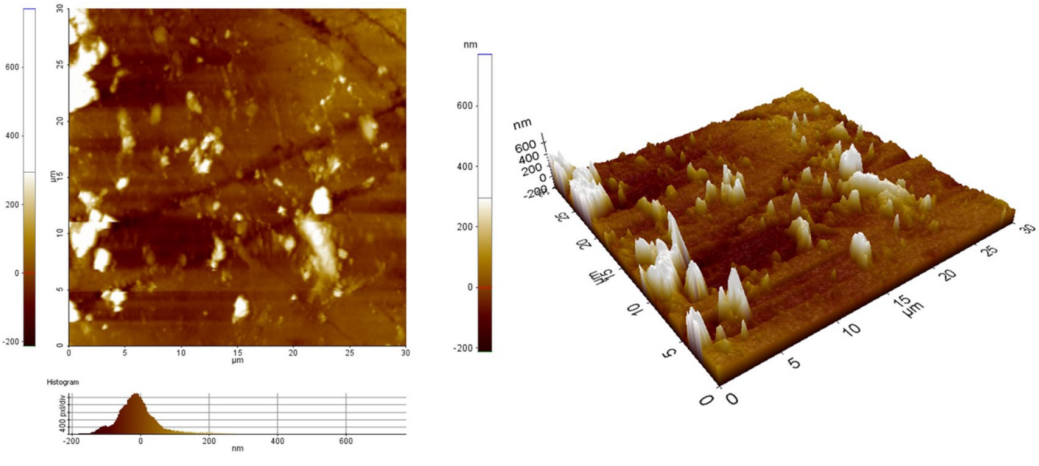

Figure 4. 2D and 3D images of PBO+ applied TC group.
2D: two-dimensional, 3D: three-dimensional, PBO+: Perfect Bleach Office+, TC: Turkish coffee

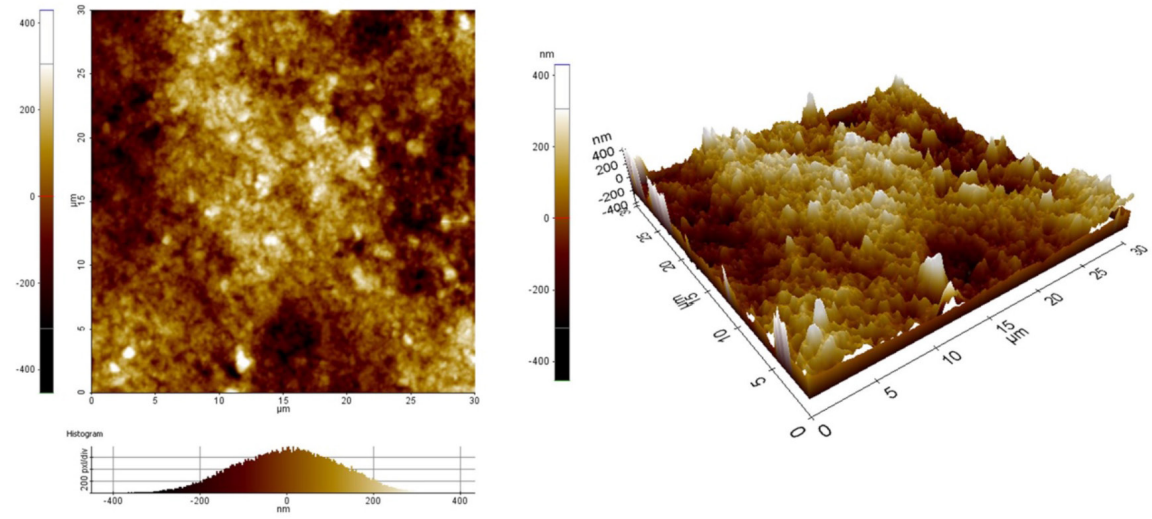

Figure 5. 2D and 3D images of OB applied RW group.
2D: two-dimensional, 3D: three-dimensional, OB: Opalescence Boost, RW: red wine

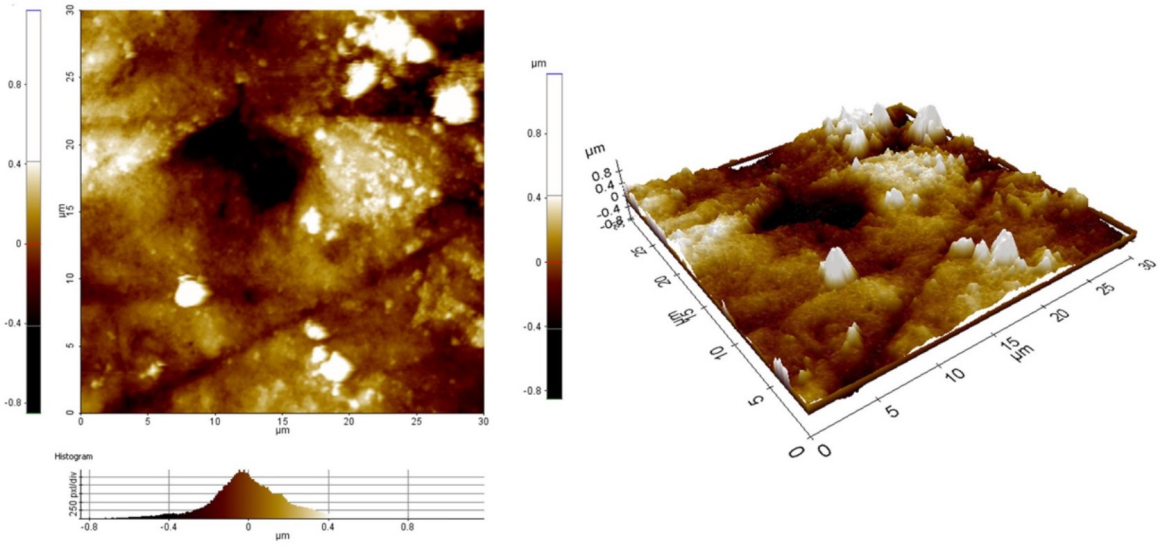

Figure 6. 2D and 3D images of PBO+ applied RW group.
2D: two-dimensional, 3D: three-dimensional, PBO+: Perfect Bleach Office+, RW: red wine

any of the optical parameters ($p>0.05$). The only statistically significant difference for OB and PBO+, was observed for the calculated ΔE_{00} values of the RW groups for the changes between bleaching and staining ($p=0.000$). For intragroup comparisons of OB, the RW group showed significantly higher ΔE_{00} values than both the control and the TC groups ($p=0.000$). For ΔWI_D values, a significant difference was only observed between the control and the RW groups for OB ($p=0.032$). For intragroup comparisons of PBO+, there was no statistically significant difference between the specimens stained with different beverages ($p>0.05$).

The 2D and 3D images obtained by AFM are shown in Figures 1–6. The results of surface analysis are shown in Table 4. All of the medians calculated for the R_a values of each specimen were lower than 0.2 µm, which is the critical R_a value needed for biofilm adhesion. Positive R_{sk} values were observed only for those specimens immersed in DW. While the distribution curve of R_{ku} was platykurtoic ($R_{ku}<3$) for both of the DW specimens, it was leptokurtoic ($R_{ku}>3$) for the other four specimens.

DISCUSSION

New trends in the present decade relating to perceptions of beauty and esthetics have resulted in an increasing demand for dental bleaching applications. One of the main causes of dental discoloration is the frequent consumption of staining beverages.

In the present study, we aimed to compare the effects of two of the most common staining beverages on the full crown of the maxillary incisor and the efficacy of two different office bleaching agents. Additionally, we aimed to analyze the surface topography of the teeth

after bleaching applications to determine the possible formation of irregularities which can make the dental structures more prone to be stained after bleaching, and if the interactions with the dental hard tissues differs due to differences in the chromogenic molecules.

As light reaches dental tissues, a sequence of interactions, such as scattering, reflection and absorption, occur between the enamel and dentin which results in color perception.[17] By separating the enamel and the dentin, these interactions are eliminated which can cause differences in color perception. According to this, for a more realistic color analysis, we opted to prepare full crown samples of the maxillary incisors. As two local and most commonly consumed staining beverages are Turkish coffee and red wine in our country, we decided to study these with a distilled water control group.

The first and the second null hypotheses of this study were partially rejected according to the results of the color and whiteness difference measurements. At the end of the staining period, all the study groups showed color changes higher than the acceptability threshold (ΔE_{00}>1.8). The changes with respect to the control group may be defined by the increase in rehydration of the dental tissues. The highest changes were observed in the RW group where there was a significant difference only with the controls (p=0.001). Although the TC group showed higher changes than the DW group, there was no statistically significant difference between either the DW or the RW groups (p>0.05). There are studies[3,27,28] supporting these results. The staining mechanism of RW can be ascribed to the lower pH caused by its acidic content (maleic acid, tartaric acid, lactic acid, succinic acid, citric acid, acetic acid) which can cause erosion which may increase the penetration of the staining pigments.[3,29] Similar to RW, TC also has a lower pH than DW. In addition to having a lower pH, the staining mechanisms of TC and RW can be ascribed to the tannin molecule found in their structure. Tannin is a staining pigment that can chemically bond to the hydroxyapatite of enamel and dentin.[29,30]

The observed color and whiteness changes after bleaching were higher than the acceptability thresholds for all groups. This shows the efficacy of both of the bleaching agents. The third null hypothesis was partially rejected because there was only a significant difference observed for the RW groups with OB and PBO+ between the staining and bleaching measurements (p=0.000).

Lower ΔE_{00} values observed in the control groups of both bleaching agents were inconsistent with the results of another study.[31] Although there was no significant difference in the control groups (p=1.000), PBO+ showed higher color differences than OB. On the other hand, lower color changes were observed in the TC and RW groups after the application of PBO+. The whiteness difference values supported these results. It may be concluded that the higher concentration of hydrogen peroxide in OB and the erosion caused by the lower pH values of TC and RW increased the diffusion of hydrogen peroxide and so increased the effect of OB more than PBO+. For intragroup comparisons, no statistically significant difference was observed in the PBO+ groups, while higher changes were observed in the RW group of OB.

The light transmission ability of a material is described as translucency. A lot of factors such as the color, mineralization level, chemical structure, thickness, hydration level etc. of enamel and dentin can affect their translucency parameter. The first null hypothesis of the present study was partially accepted according to the results of the translucency difference measurements. All of the measured changes in the translucency parameters were higher than the perceptibility threshold but lower than the acceptability threshold. Additionally, no statistically significant difference was observed between the ΔTP_{00} values of the study groups for all of the measurement periods (p>0.05). These low translucency changes are consistent with the results of some other studies.[32,33] Ma et al.[16] showed more changes in the TP of enamel in their bleaching group. These results show that neither staining nor bleaching caused critical changes in the chemical structure of enamel or dentin. However, not knowing the exact reactions at the molecular level is a limitation for the present study.

The low pH of the staining solutions and the chemical reactions occurring due to the bleaching process can cause changes in the surface characteristics of dental tissues, which may also change the color perception. Additionally, a surface roughness of more than 0.2 µm can increase biofilm accumulation, which can cause a recurrence of discoloration in a short period of time. To observe surface topography, an atomic force microscope was used in the present study.

According to the AFM analysis, the fourth null hypothesis was rejected. Differences were observed in the surface topography and roughness of each specimen. For the TC groups, the PBO+ applied specimens showed higher surface roughness values. None of the median R_a values were higher than 0.2 µm, which can be interpreted as meaning that the use of office bleaching agents is safe and the risk of recurrence related with these agents is low. The low R_a values observed in the present study were consistent with the results of other studies.[31,34] These findings are also supported by the low ΔTP_{00} values, which are affected by the surface roughness.

R_{sk} is the examination of the profile symmetry regarding the mean line.[35] When R_{sk} was analyzed, only the DW groups showed positive skewness, which is a sign of high peaks or valleys filled in. R_{ku} describes the sharpness of the probability density of the profile.[35] While the distribution curve of R_{ku} was platykurtoic (R_{ku}<3) for both of the DW groups, it was leptokurtoic (R_{ku}>3) for the other four groups. A platykurtoic distribution shows relatively fewer high peaks and low valleys, while a leptokurtoic distribution shows relatively more high peaks and low valleys in the same surface area.

The results of surface analysis may be interpreted as meaning that staining solutions with lower pH cause more demineralization and destruction at the surface but the porosities formed will not be critical for plaque adhesion or the recurrence of discoloration. With regards to this, it should be kept in mind that according to the etiological factors of discoloration, there will be differences in surface topography after the reactions by the bleaching applications have occurred. It may be better to induce re-mineralization after bleaching, especially discoloration relating to beverages with lower pH such as RW and TC, to decrease the risk of the recurrence. On the other hand, as mentioned before, not knowing the chemical reactions at the molecular level is a limitation for the present study. There is also a need for the repetition of staining after bleaching to clarify such a conclusion.

CONCLUSION

The frequent consumption of Turkish coffee and red wine can cause discolorations due to changes in the dental structures owing to their low pH and the staining pigments such as tannin, which can easily

react with the hydroxyapatite found in dentin and enamel. Oxidation reactions by hydrogen peroxide found in bleaching agents can react with these pigments and result in a perception of a whiter color of the dental tissues. Changes in the superficial structure caused by acidic beverages may increase the penetration of hydrogen peroxide and so the efficiency of the bleaching. The surface topography analysis showed that there will be differences in the surface structure after bleaching related to the type of staining molecule. Surface roughness values showed that office bleaching can be a safe method for the treatment of discolorations with a high efficiency in color and whiteness reversal but that topographic changes should be kept in mind and it may be better to induce re-mineralization especially after exposure to solutions with lower pH to minimize the risk of the recurrence.

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MAIN POINTS

- Both Turkish coffee and red wine stained the dental tissues.
- The bleaching agent with a higher concentration of hydrogen peroxide showed more efficiency in color reversal.
- Staining or bleaching did not significantly affect the translucency and surface roughness of the dental tissues.
- The low pH of the staining solutions may have affected changes in the surface topography of the enamel after bleaching.

ETHICS

Ethics Committee Approval: This study was approved by the Committee for Ethics of Research of Near East University (decision number: YDU/2016/37-287, date: 05.05.2016).

Informed Consent: Obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: İ.K., E.C.Y., Design: İ.K., E.C.Y., Data Collection and/or Processing: İ.K., E.C.Y., Analysis and/or Interpretation: İ.K., E.C.Y., Literature Search: İ.K., E.C.Y., Writing: İ.K., E.C.Y., Critical Reviews: İ.K., E.C.Y.

DISCLOSURES

Conflict of Interest: The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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REFERENCES

1. Lajnert V, Kovacevic Pavicic D, Pavlic A, Pokrajac-Bulian A, Spalj S. Smile aesthetics satisfaction scale: development and validation of a new brief five-item measure of satisfaction with smile aesthetics in adults and the elderly. Inter Dent J. 2018; 68(3): 162-70.
2. Alqahtani MQ. Tooth-bleaching procedures and their controversial effects: A literature review. Saudi Dent J. 2014; 26(2): 33-46.
3. Zhao X, Zanetti F, Wang L, Pan J, Majeed S, Malmstrom H, et al. Effects of different discoloration challenges and whitening treatments on dental hard tissues and composite resin restorations. J Dent. 2019; 89: 103182.
4. Kang A, Son SA, Hur B, Kwon YH, Ro JH, Park JK. The color stability of silorane- and methacrylate-based resin composites. Dent Mater J. 2012; 31(5): 879-84.
5. Alharbi A, Ardu S, Bortolotto T, Krejci I. Stain susceptibility of composite and ceramic CAD/CAM blocks versus direct resin composites with different resinous matrices. Odontology. 2017; 105(2): 162-9.
6. Pirolo R, Mondelli RF, Correr GM, Gonzaga CC, Furuse AY. Effect of coffe and a cola-based soft drink on the color stability of bleached bovine incisors considering the time elapsed after bleaching. J Appl Oral Sci. 2014; 22(6): 534-40.
7. Kwon SR, Wertz PW. Review of the mechanism of tooth whitening. J Esthet Restor Dent. 2015; 27(5): 240-57.
8. Chen H, Huang J, Dong X, Qian J, He J, Qu X, et al. A systematic review of visual and instrumental measurements for tooth shade matching. Quintessence Int. 2012; 43(8): 649-59.
9. Gómez-Polo C, Gómez-Polo M, Celemin-Viñuela A, Martínez Vázquez De Parga JA. Differences between the human eye and the spectrophotometer in the shade matching of tooth colour. J Dent. 2014; 42(6): 742-5.
10. Chu SJ, Trushkowsky RD, Paravina RD. Dental color matching instruments and systems. Review of clinical and research aspects. J Dent. 2010; 38 Suppl 2: e2-16.
11. Kurt M, Bal BT, Bal C. Güncel renk ölçüm yöntemleri: sistematik derleme. Turkiye Klinikleri J Dental Sci. 2016; 22(2): 130-46.
12. Grazioli G, Valente LL, Isolan CP, Pinheiro HA, Duarte CG, Münchow EA. Bleaching and enamel surface interactions resulting from the use of highly-concentrated bleaching gels. Arch Oral Biol. 2018; 87: 157-62.
13. Polydorou O, Scheitza S, Spraul M, Vach K, Hellwig E. The effect of long-term use of tooth bleaching products on the human enamel surface. Odontology. 2018; 106(1): 64-72.
14. Hegedüs C, Bistey T, Flóra-Nagy E, Keszthelyi G, Jenei A. An atomic force microscopy study on the effect of bleaching agents on enamel surface. J Dent. 1999; 27(7): 509-15.
15. Omar F, Ab-Ghani Z, Rahman NA, Halim MS. Nonprescription bleaching versus home bleaching with professional prescriptions: Which one is safer? A comprehensive review of color changes and their side effects on human enamel. Eur J Dent. 2019; 13(4): 589-98.
16. Ma X, Jiang T, Sun L, Wang Z, Zhou Y, Wang Y. Effects of tooth bleaching on the color and translucency properties of enamel. Am J Dent. 2009; 22(6): 324-8.
17. Ma X, Li R, Sa Y, Liang S, Sun L, Jiang T, et al. Separate contribution of enamel and dentine to overall tooth colour change in tooth bleaching. J Dent. 2011; 39(11): 739-45.
18. Pimentel de Oliveira R, Baia JCP, Ribeiro MES, Junior MHDSES, Loretto SC. Influence of time intervals between bleaching procedures on enamel microhardness and surface roughness. Open Dent J. 2018; 12: 555-9.
19. Sa Y, Wang Z, Ma X, Lei C, Liang S, Sun L, et al. Investigation of three home-applied bleaching agents on enamel structure and mechanical properties: an in situ study. J Biomed Opt. 2012; 17(3): 035002.
20. Vieira I, Vieira-Junior WF, Pauli MC, Theobaldo JD, Aguiar FHB, Lima DA, et al. Effect of in-office bleaching gels with calcium or fluoride on color, roughness, and enamel microhardness. J Clin Exp Dent. 2020; 12(2): e116-22.

21. Celik C, Yüzügüllü B, Erkut S, Yazici AR. Effect of bleaching on staining susceptibility of resin composite restorative materials. J Esthet Restor Dent. 2009; 21(6): 407-14.

22. Paravina RD, Ghinea R, Herrera LJ, Bona AD, Igiel C, Linninger M, et al. Color difference thresholds in dentistry. J Esthet Restor Dent. 2015; 27 Suppl 1: S1-9.

23. Pecho OE, Ghinea R, Alessandretti R, Pérez MM, Della Bona A. Visual and instrumental shade matching using CIELAB and CIEDE2000 color difference formulas. Dent Mater. 2016; 32(1): 82-92.

24. Salas M, Lucena C, Herrera LJ, Yebra A, Della Bona A, Pérez MM. Translucency thresholds for dental materials. Dent Mater. 2018; 34(8): 1168-74.

25. Pérez Mdel M, Ghinea R, Rivas MJ, Yebra A, Ionescu AM, Paravina RD, et al. Development of a customized whiteness index for dentistry based on CIELAB color space. Dent Mater. 2016; 32(3): 461-7.

26. Pérez MM, Herrera LJ, Carrillo F, Pecho OE, Dudea D, Gasparik C, et al. Whiteness difference thresholds in dentistry. Dent Mater. 2019; 35(2): 292-7.

27. Bazzi JZ, Bindo MJF, Rached RN, Mazur RF, Vieira S, de Souza EM. The effect of at-home bleaching and toothbrushing on removal of coffee and cigarette smoke stains and color stability of enamel. J Am Dent Assoc. 2012; 143(5): e1-7.

28. Côrtes G, Pini NP, Lima DA, Liporoni PC, Munin E, Ambrosano GM, et al. Influence of coffee and red wine on tooth color during and after bleaching. Acta Odontol Scand. 2013; 71(6): 1475-80.

29. Nathoo SA. The chemistry and mechanisms of extrinsic and intrinsic discoloration. J Am Dent Assoc. 1997; 128 Suppl: 6S-10S.

30. Lee RJ, Bayne A, Tiangco M, Garen G, Chow AK. Prevention of tea-induced extrinsic tooth stain. Int J Dent Hyg. 2014; 12(4): 267-72.

31. Carlos NR, Pinto A, do Amaral F, França F, Turssi CP, Basting RT. Influence of staining solutions on color change and enamel surface properties during at-home and in-office dental bleaching: an *in situ* study. Oper Dent. 2019; 44(6): 595-608.

32. Caneppele TM, Borges AB, Torres CR. Effects of dental bleaching on the color, translucency and fluorescence properties of enamel and dentin. Eur J Esthet Dent. 2013; 8(2): 200-12.

33. Menezes RP, Silva PD, Leal PC, Faria-e-Silva AL. Impact of 35% hydrogen peroxide on color and translucency changes in enamel and dentin. Braz Dent J. 2018; 29(1): 88-92.

34. Kwon SR, Kurti SR, Oyoyo U, Li Y. Effect of various tooth whitening modalities on microhardness, surface roughness and surface morphology of the enamel. Odontology. 2015; 103(3): 274-9.

35. Gadelmawla ES, Koura MM, Maksoud TMA, Elewa IM, Soliman HH. Roughness parameters. J Mater Process Tech. 2002; 123(1): 133-45.

ORIGINAL ARTICLE

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Walking Speed Gender Differences in Prepubertal Children: An Observational Study

Shahin Ahmedov[1], Figen Yaman Lesinger[1], Musa Oytun[2], Barış Filiz[3], Fatih Kerem Özkan[4]

[1]School of Physical Education and Sports, Cyprus Health and Social Sciences University, Morphou, North Cyprus
[2]Faculty of Sports Sciences, Near East University, Nicosia, North Cyprus
[3]Sports Sciences, Gedik University, İstanbul, Turkey
[4]Fitness Soul Entertainment Spors Complex, İstanbul, Turkey

Abstract

BACKGROUND/AIMS: Walking speed associates with a person's functional status and balance confidence, both of which diminish with age. The difference in children's body composition and prepubertal metabolic rate suggested gender variability in their walking parameters.

MATERIALS AND METHODS: The preferred step length, cadence, and overall walking speed of 457 school children (256 boys) aged 12.65±2.16 years old were assessed during a 20 meter walk. The participants' height, weight, and heart rate values were also collected.

RESULTS: The preferred walking speed analysis demonstrated that the girls, despite their shorter height and age, moved faster than the boys (1.35±0.22 m/sec in boys. 1.43±0.22 m/sec in girls, $p<0.01$). The girls' baseline heart rate correlated with their final walking speed ($n=177$, $r=0.202$, $p<0.05$). Although, as expected, the children's step length positively correlated with their height ($n=457$, $r=0.42$; $p<0.05$), with an increase in the child's height, the step-to-height ratio decreased significantly ($n=457$, $r= -0.40$; $p<0.05$). The average walking speed in prepubertal children (1.39±0.22 m/sec) was the highest among all population groups.

CONCLUSION: Girls demonstrated better walking performance compared to boys. The preferred walking speed allows for a quick assessment of the child's physical development necessary for effective exercise programs.

Keywords: Child, gender, health, walking speed, cadence

INTRODUCTION

The step is the primary assessment unit for walking, i.e., the most common body movement form.[1] Intuitively, the step is highly distinguished and deeply embedded in the automated movement pattern of the central nervous system (CNS). As one of the essential characteristics of locomotion, step analysis is used today in health assessment and rehabilitation programs.[2,3] With the introduction of pedometers into the monitoring of physical activity, it has become possible to determine the number of steps taken per day, the total distance covered throughout the day, and other related ambulatory parameters.[4,5] Unlike self-reported information on physical activity, pedometers allow for an objective assessment of a person's level of daily activity. The total distance traveled per day depends on step length, cadence, and step velocity.[6] These variables result from the work of the CNS to control the maintenance of body balance during walking. The cadence, also called the step frequency, is determined relatively accurately by the electric circuit of the pedometer, which periodically

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ORCID IDs of the authors: S.A. 0000-0002-2492-5900; F.Y.L. 0000-0002-9556-4305; M.O. 0000-0002-0048-0281; B.F. 0000-0003-4372-7659; F.K.Ö. 0000-0002-5046-9961.

Address for Correspondence: Shahin Ahmedov
E-mail: sahin.ahmedov@kstu.edu.tr
ORCID ID: orcid.org/0000-0002-2492-5900

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opens and closes due to the movement of the foot extended for a step. Since step length is a determining factor in measuring total distance, its appropriate assessment contributes to determining the distance measured by a pedometer during the day.

It is assumed that the walking step length at the chosen pace is precise[7] and comprises 42% of a person's height.[8] Most body mass is located high enough above the ground[9] that human height acts as an essential independent variable for the preferred step length; however, the gender difference in leg length[10] entails a different center of gravity from the ground, leading to possible gender differences in step length. A previous meta-analysis demonstrated that height-matched women have slightly faster preferred walking speeds than men.[11]

Recent studies have revealed an association between walking velocity and general health and decreased walking velocity with increasing age.[12] Since the metabolic rate ultimately determines the energy expenditure during walking,[13] walking speed, as a complex functional activity, might be another vital sign of personal health status.[14-16]

This study aimed to analyze the walking steps taken by children to define possible gender differences in step length and other mentioned walking parameters. We also planned to identify the walking speed norms for children, that is, the population still unaffected by personal habits, fitness level, and age.

MATERIALS AND METHODS

A total of 457 school children (256 boys) aged 12.65±2.16 years old from three high schools in Northern Cyprus participated in this study. High schools in North Cyprus are divided into state, advanced state, and private high schools. Considering that the difference in the curriculum might affect the children's activity levels, each selected school represented one of the three categories. The total number of students in the selected schools ensured for obtaining a statistically reliable result. After receiving permission from the corresponding educational authorities and the parents' informed consent, an analysis of walking was conducted in the school gyms. Participants had to walk 20 meters twice at their preferred speed, during which the test instructor recorded the number of steps taken and the time spent walking the distance. The step length, cadence, and walking speed were calculated from the average of the recorded data. Step length was defined as the total distance (20 meters) divided by the number of counted steps, cadence (step frequency) represented the number of steps taken divided by the time spent to cover the distance, and walking speed was the distance in meters covered per second.

Additionally, we determined each participant's height and weight using a stadiometer and a weighing scale. At the start and end of the walking test, the participants had their heart rate (HR) measured in beats per minute. The independent t-test for gender differences between values and Pearson's correlation coefficient for the association between HR and the walking parameters were utilized, and the statistical significance threshold was established at $p<0.05$. The Ethics Committee of the Near East University approved this study under the reference number YDU/2021/90-1323 and date 29.04.20.2021.

RESULTS

A summary of the anthropometric and walking parameters of the boys and girls is shown in Table 1. Our observations did not confirm to the accepted assumption that step length directly correlates with an individual's height. Despite the boys' height advantage (160.93±13.51 cm in boys versus 154.66±10.89 cm in girls, $p<0.01$), there was no gender difference in step length (69.64±7.38 cm in boys versus 70.22±6.67 cm in girls, $p>0.1$). Moreover, the girls' step length-to-height ratios were significantly higher (43.4%±4.5% in boys versus 45.5%±4.3% in girls, $p<0.01$).

The girls also outperformed the boys in cadence (1.87±0.18 step/sec in boys versus 1.95±0.18 step/sec in girls, $p<0.01$) and spent less time covering the walking distance (14.31±2.41 sec for girls versus 15.23±2.63 sec for boys, $p<0.01$). These two facts ultimately contributed to their advantage in walking speed (1.35±0.22 m/sec in boys versus 1.43±0.22 m/sec in girls, $p<0.01$).

Although the children's step length positively correlated with their heights as expected ($n=457$, $r=0.42$; $p<0.05$), the step-to-height ratio decreased significantly with an increase in the child's height ($n=457$, $r=-0.40$; $p<0.05$, Figure 1).

The participants' HR evaluations also demonstrated gender differences. The girls had higher HRs compared to the boys both before and after the walking step test (Table 2). At the end of the test, the heart rates in both groups correlated with walking speed, while only the girls' baseline HR correlated with their walking speed ($n=177$, $r=0.202$, $p<0.05$).

DISCUSSION

The human body is a complex biological system where all the closely interconnected organs are in constant interaction with each other, the surrounding environment, and the social environment. The human body is a single self-regulating and self-developing system that ensures human psychological, structural, and biochemical functions' interaction with various environmental conditions.

Without knowledge of the human body's structure and the characteristics of the vital processes of its organs and organ systems, it is impossible to ensure its health, to properly organize the processes of physical education, physical development, and improvement, and to determine the volume and intensity of the loads during physical exercises. With a low level of physical performance, walking is an effective tool to increase aerobic performance.

Walking is a natural type of movement in the open air in which many muscles, ligaments, and joints are involved. It improves metabolism in the body and facilitates cardiovascular, respiratory, and other body systems. Walking intensity is easily affected by the current health condition and physical fitness level. The walking impact on the human body depends on the stride length, walking speed, and duration.

Walking speed is associated with a person's functional status[12] and balance confidence,[17] both of which diminish with age. Walking speed values gradually decrease from 1.31 m/sec in a 20-year-old to 1.06 m/sec in the elderly.[18] Our study has shown that the walking speed in the earlier, namely, prepubertal period, exceeds those of other age groups with an average of 1.39 m/s.

Despite the advantage of boys in age and height, they yielded to girls in almost all walking parameters, including speed, where girls' HRs were higher than boys' HRs. A previous study conducted with 2241 children demonstrated higher HRs for girls than for boys, starting from the age

Table 1. Anthropometric and 20-meter ambulatory parameters obtained from 457 children

Variables	Boys (n=256)	Girls (n=201)	Total (n=457)
Age (years)*	12.90±2.10	12.32±2.18	12.65±2.16
Height, (cm)*	160.93±13.51	154.66±10.89	158.17±12.80
Weight (kg)*	57.95±16.98	49.52±11.87	54.25±15.52
Step number	28.17±3.23	27.62± 3.06	27.93±3.17
Step length (cm)	69.64±7.38	70.22±6.67	69.89±7.07
Step length/height ratio (%)*	43.40±4.50	45.50± 4.30	44.33±4.50
Time (sec)*	15.23±2.63	14.31±2.41	14.82±2.57
Cadence (step/sec)*	1.87±0.18	1.95±0.18	1.91±0.18
Speed (m/sec)*	1.35±0.22	1.43±0.22	1.39±0.22

*Statistically significant gender differences ($p<0.05$), n: number.

of three years up to adolescence.[19] Scientists attribute this difference to several reasons. While both genders have the same cardiac myocyte number, male cells undergoing a more significant hypertrophy form larger hearts than those in females.[20] Due to this smaller heart size, a girl's heart must contract faster than a boy's. Another reason is the difference in the pacemaker rhythmicity.[21]

The cardiovascular system contributes to the regulation of homeostasis during physical activity. The researchers, however, identified gender differences in the heart's response to stress. While the main contributor to cardiac output in males is stroke volume, the determining factor in increasing cardiac output in females is HR.[22,23] The latter may explain the girls' baseline HR correlating with their walking speed in our study.

As one of the primary reasons for their faster walking speeds, the higher cadence in girls might be ascribed to findings demonstrated in earlier research. The cardiovascular system's response to submaximal exercise revealed a higher mechanical efficiency in females for the same load compared to males. This was reported to be due to an increase in peripheral oxygen extraction and could be a blunted response of the sympathetic nervous system in pronounced compensatory vasodilation on the restricted stroke volume in females.[24] Additionally, the difference in walking speed could also reflect the possible increase in metabolic rate in girls due to the earlier onset of puberty.[25,26]

An additional explanation for girls' superior walking performance may be their skeletal characteristics, which favor balance confidence during ambulation. Girls' lower position of the gravity center from the base of support, defined by the higher sitting height-to-leg length ratio[27] and their wider pelvic size[28] compared to boys could serve as an explanation for girls' being more confident in their walking balance. Observations have demonstrated differences in the male versus female biomechanics of the lower extremities during walking and running. These differences were associated with the ratio of pelvic width to leg length.[29]

Height, as expected, was the decisive factor in stride length; however, the child's step-to-height ratio decreased as height increased, apparently caused by the distance of the center of gravity from the base of support in tall children (Figure 1).

Table 2. Heart rate gender differences during walking step test

Walking step test	Boys (b/min)	Girls (b/min)	Significance
Heart rate before	92.97±17.98	102.13±16.76	$p<0.01$
Heart rate after	101.79±21.20	106.37±18.65	$p<0.05$

As this work has shown, universal formulas should be treated cautiously due to differences in biomechanics, physical form, and other variables. This analysis of children's preferred walking speeds showed that height and age do not give the expected advantages in step length and movement speed in the prepubertal age. Although the girls were inferior to the boys in terms of height and age and had equal step lengths, they walked faster. The latter in children results from values dependent on metabolism and body morphology; height and shape impact balance confidence.

Another important implication to consider is that the step length and cadence are essential determinants of running speed. Studies that have analyzed the effect of stride length and frequency on lower limb injuries in runners have shown that increased stride frequency reduces the risk of sports injury during running.[30] Perhaps this is one reason for the more frequent trauma of the lower limb in all of its joints in men than in women.[31]

An essential part of the general population's physical fitness assessment is accomplishing various dynamic tests requiring certain conditions and equipment for their implementation. Measurement of the preferred walking speed, the steadiness and individuality of which have been confirmed by several scientific studies, makes it possible to quickly and easily determine the physical development in various groups of the population, including children. While poor posture, orthopedic conditions, obesity, mental issues, and overall development might contribute to a child's preferred walking speed, the walking speed of both sexes directly depends on the calf muscle strength.[32] Since an increase in muscle mass is an essential indicator of healthy age-related

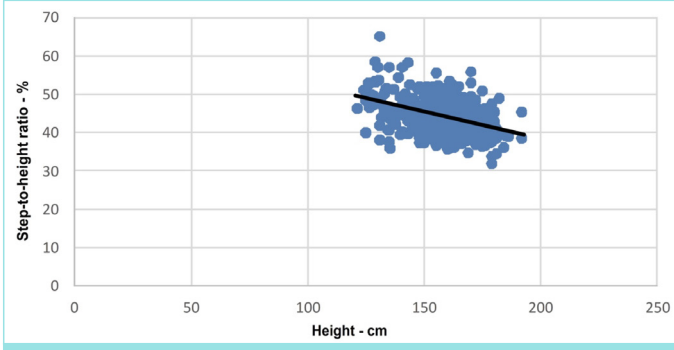

Figure 1. Association between children's height and step-to-height ratio (n=457, r= -0.40, $p<0.05$).

dynamics of the musculoskeletal systems of children, the preferred walking speed test might be used to assess the general development of a child.

The walking speed issue has become especially relevant today as the problem of coronavirus disease-2019 (COVID-19) has acquired the character of a pandemic. This year's research has confirmed the importance of walking speed as an independent risk factor for coronavirus. Even for those of average body weight, individuals with slow walking speeds had a greater risk of contracting COVID-19.[33]

Step length is a determining parameter of walking speed. In this regard, the relative dependence of the step length on body height and the decreased former-to-latter ratio with increased height observed in our study deserves special attention. The distance of the gravity center from the base of support, rather than the individual's height, determines walking step length. Studies indicate that short stature is a positive factor in reducing disease incidence and increasing life longevity in the population.[34,35] Given the advantage in the high speed of ambulation of people of short stature, it seems reasonable to define the relationship between body proportions (e.g., the ratio of leg length to body height) and stride rates in a healthy population and people with pathology. Further studies are necessary to clarify this suggestion.

CONCLUSION

In summary, the age and gender-specific walking differences may serve as a valuable reference for the early detection of various health problems and appropriate decision-making in favor of suitable corrective exercise programs.

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MAIN POINTS

- Prepubertal girls outperformed boys in terms of preferred walking speed and cadence, despite having younger age and lower stature.
- Both at the beginning and at the end of the test, the girls' heart rate was higher and the girls' pretest heart rate correlated with their preferred walking speed
- Although the step length is proportional to height, the step length-to-height ratio decreases as height increases.
- The walking speed test might be used to assess the general development of a child.

ETHICS

Ethics Committee Approval: The Ethics Committee of the Near East University approved this study under the reference number YDU/2021/90-1323 and date 29.04.20.2021.

Informed Consent: After receiving permission from the corresponding educational authorities and the parents' informed consent, an analysis of walking was conducted in the school gyms.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.A., F.Y.L., Design: S.A., F.Y.L., M.O., Supervision: S.A., Data Collection and/or Processing: F.Y.L., M.O., B.F., F.K.Ö., Analysis and/or Interpretation: S.A., M.O., Literature Search: S.A., F.Y.L., Writing: S.A., Critical Review: F.Y.L.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Bassett Jr DR, Toth LP, LaMunion SR, Crouter SE. Step counting: a review of measurement considerations and health-related applications. Sports Med. 2017; 47(7): 1303-15.
2. Shin SH, Chan GP. Adaptive step length estimation algorithm using optimal parameters and movement status awareness. Med Eng Phys. 2011; 33(9): 1064-71.
3. Sayeed T, Samã A, Catalã A, Rodríguez-Molinero A, Cabestany J. Adapted step length estimators for patients with Parkinson's disease using a lateral belt worn accelerometer. Technol Health Care. 2015; 23(2): 179-94.
4. Pillay JD, van der Ploeg HP, Kolbe-Alexander TL, Proper KI, van Stralen M, Tomaz SA, et al. The association between daily steps and health, and the mediating role of body composition: a pedometer-based, cross-sectional study in an employed South African population. BMC Public Health. 2015; 15: 174.
5. Inoue S, Takamiya T, Yoshiike N, Shimomitsu T. Physical activity among the Japanese: results of the National Health and Nutrition Survey. Proceedings of the Proceedings of the International Congress on Physical Activity and Public Health; 2006 April 17–20; Atlanta, GA: U.S. Department of Health and Human Services; 2006. p. 79.
6. Hunter JP, Marshall RN, McNair PJ. Interaction of step length and step rate during sprint running. Med Sci Sports Exerc. 2004; 36(2): 261-71.
7. Collins SH, Kuo AD. Two independent contributions to step variability during over-ground human walking. PLoS One. 2013; 8(8): e73597.
8. Hatano Y. Use of the pedometer for promoting daily walking exercise. Int Counc Health Phys Educ Recreat J. 1993; 29(4): 4-8.
9. Winter DA. Human balance and posture control during standing and walking. Cait Posture. 1995; 3(4): 193-214.
10. Seeman E. Clinical review 137: Sexual dimorphism in skeletal size, density, and strength. J Clin Endocrinol Metab. 2001; 86(10): 4576-84.
11. Frimenko R, Whitehead C. Do men and women walk differently? A review and meta-analysis of sex difference in non-pathological gait kinematics. United States Air Force Research Laboratory. 711th Human Performance Wing Interim research: 2014. p.11.
12. Perry J, Garrett M, Gronley JK, Mulroy SJ. Classification of walking handicap in the stroke population. Stroke 1995; 26(6): 982-89.
13. Weyand PG, Smith BR, Schultz NS, Ludlow LW, Puyau MR, Nancy F Butte NF. Predicting metabolic rate across walking speed: one fit for all body sizes? J Appl Physiol. 2013; 115(9): 1332-42.

14. Studenski S, Perera S, Wallace D, Chandler JM, Duncan PW, Rooney E, et al. Physical performance measures in the clinical setting. J Am Geriatr Soc. 2003; 51(3): 314-22.

15. Montero-Odasso M, Schapira M, Soriano ER, Varela M, Kaplan R, Camera LA, et al. Gait velocity as a single predictor of adverse events in healthy seniors aged 75 years and older. J Gerontol A Biol Sci Med Sci. 2005; 60(10): 1304-9.

16. Lord SE, Rochester L. Measurement of community ambulation after stroke: current status and future developments. Stroke. 2005; 36(7): 1457-61.

17. Mangione KK, Craik RL, Lopopolo R, James D. Tomlinson JD, Brenneman SK. Predictors of gait speed in patients after hip fracture. Physiother Can. 2008; 60(1): 10-8.

18. Ble A, Volpato S, Zuliana G, Zuliani G, Guralnik J, Bandinelli S, et al. Executive function correlates with walking speed in older persons: the InCHIANTI study. J Am Geriatr Soc. 2005; 53(3): 410-5.

19. Semizel E, Öztürk B, Bostan OM, Cil E, Ediz B, The effect of age and gender on the electrocardiogram in children. Cardiol Young. 2008; 18(1): 26-40.

20. De Simone G, Devereux RB, Daniels SR, Meyer RA. Gender differences in left ventricular growth. Hypertension. 1995; 26(6 Pt 1): 979-83.

21. Ramaekers D, Ector H, Aubert AE, Rubens A, Van de Werf F. Heart rate variability and heart rate in healthy volunteers. Is the female autonomic nervous system cardioprotective? Eur Heart J. 1998; 19(9): 1334-41.

22. Spina RJ, Ogawa T, Miller TR, Kohrt WM, Ehsani AA. Effect of exercise training on left ventricular performance in older women free of cardiopulmonary disease. Am J Cardiol. 1993; 71(1): 99-104.

23. Fleg JL, O'Connor F, Gerstenblith G, Becker L C, Clulow J, Schulman S P, et al. Impact of age on the cardiovascular response to dynamic upright exercise in healthy men and women. J Appl Physiol. 1995; 78(3): 890-900.

24. Wheatley CM, Snyder EM, Johnson BD, Olson TP. Sex differences in cardiovascular function during submaximal exercise in humans. SpringerPlus. 2014; 3: 445. DOI: 10.1186/2193-1801-3-445

25. Jasik CB, Lustig RH. Adolescent obesity and puberty: The "perfect storm". Ann N Y Acad Sci. 2008; 1135: 265-79.

26. Green JL. The heart rate method for estimating metabolic rate: review and recommendations. Comp Biochem Physiol A Mol Integr Physiol. 2011; 158(3): 287-304.

27. Ya-qin Z, Li H. Reference charts of sitting height, leg length and body proportions for Chinese children aged 0-18 years. Ann Hum Biol. 2015; 42(3): 223-30.

28. Fredriks AM, Buuren VS, Fekkes M, Verloove-Vanhorick SP. Are age references for waist circumference, hip circumference and waist-hip ratio in Dutch children useful in clinical practice? Eur J Pediatr. 2005; 164: 216-22.

29. Chumanov ES, Wall-Scheffler C, Heiderscheit BC. Gender differences in walking and running on level and inclined surfaces. Clin Biomech. 2008; 23(10): 1260-8.

30. Schubert AG, Kempf J, Heiderscheit BC. Influence of stride frequency and length on running mechanics: A Systematic Review. Sports Health. 2014; 6(3): 210-17.

31. Francis P, Whatman C, Sheerin K, Hume P, Johnson MI. The Proportion of Lower Limb Running Injuries by Gender, Anatomical Location and Specific Pathology: A Systematic Review. J Sports Sci Med. 2018; 18(1): 21-31.

32. Bendall MJ, Bassey EJ, Pearson MB. Factors affecting walking speed of elderly people. Age Ageing. 1989; 18(5): 327-32.

33. Yates T, Rezieh C, Zaccardi F, Rowlansds AV, Seidu S, Davies MJ, et al. Obesity, walking pace and risk of severe COVID-19 and mortality: analysis of UK Biobank. Int J Obesity. 2021; 45(5): 1155-9.

34. Samaras TT, Elrick H. Height, body size and longevity. Acta Med Okayama. 1999; 53(4):149-69.

35. Samaras T, Elrick H. Height, body size, and longevity: Is smaller better for the human body? West J Med. 2002; 176(3): 206-8.

ORIGINAL ARTICLE

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A Comparative Study on Cultural Competence of Healthcare Professionals in Primary and Secondary Healthcare Institutions: A Cross Sectional Study

Mümin Savaş[1], Ayla Tuzcu[2]

[1]Department of Public Health Nursing, Faculty of Health Sciences, Adıyaman University, Adıyaman, Turkey
[2]Department of Public Health Nursing, Faculty of Nursing, Akdeniz University, Antalya, Turkey

Abstract

BACKGROUND/AIMS: It is noteworthy that there are limited studies examining the cultural competence levels of the multidisciplinary team in primary and secondary care. The aim of the study was to compare the level of cultural competence in healthcare professionals working in primary and secondary healthcare institutions and to determine factors related to the level of cultural competence.

MATERIALS And METHODS: A cross-sectional survey design was used to collect data. Totally, 87 healthcare professionals working in primary healthcare services and 348 nurses working in secondary healthcare services between March-May 2018 participated in this cross-sectional study. Data were collected using descriptive information form, the Nurse Cultural Competence Scale form in Turkish, and the Primary Health Care Professionals' Cultural Competency Scale.

RESULTS: Mean score of primary healthcare professionals in terms of cultural competence was found to be 66.58±13.47 while mean score of Secondary Health Care Nurses was 67.44±13.27. No difference was found between two groups. The level of cultural competence in primary healthcare professionals was increased by factors such as the fact that working time was short in primary healthcare services (odds ratio: 0.81), going abroad for business or touristic purposes (odds ratio: 0.14), meeting individuals/families from different cultures in healthcare services (odds ratio: 0.14), and the satisfaction of providing health service to migrants/asylum seekers (odds ratio: 0.15). The level of cultural competence in secondary care nurses was increased by the satisfaction of working with migrants and asylum seekers.

CONCLUSION: It was found that cultural competence of healthcare professionals in primary and secondary care was at medium level. It might be beneficial to brief healthcare workers during undergraduate study and in-service training on different cultures and to encourage them to meet people from different cultures in order to increase their cultural competence.

Keywords: Cultural competency, culturally competent care, primary healthcare, nurse

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ORCID IDs of the authors: M.S. 0000-0001-9240-7833; A.T. 0000-0002-1291-7970.

Address for Correspondence: Ayla Tuzcu
E-mail: aylatuzcu@hotmail.com
ORCID ID: orcid.org/0000-0002-1291-7970

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INTRODUCTION

Due to factors such as direct or indirect impact of globalization, poverty, regional conflicts, the concept of migration is rapidly increasing in the world.[1] Nearly 272 million people in the world are international migrants in 2019, and this figure constitutes 3.5% of the global population. The direction of migration is mostly from Asian and African countries where socio-economic conditions are low to European and North American countries where standards of living are much higher.[2]

Due to its position in the junction between Asia and Europe, Turkey has always been a country of origin, of transit, and of destination. Today, Turkey hosts one of the major migrant populations in the world. In recent years, there has been an increase in migrant population due to the crisis in Syria. Migrants and refugees, nearly 90% of whom are from Syria, come to Turkey from different countries.[3] This has become an obligation for healthcare institutions to face different languages, communication styles, attitude, expectations, and perspectives of individuals receiving the services.[4] Therefore, it is of the utmost importance for healthcare professionals to become sensitive and to improve their cultural competence in order to meet health requirements of individuals from different cultures.[5]

Culturally competent care is defined as a multi-dimensional learning process combining intercultural skills (cognitive, practical, and emotional), including intercultural self-efficacy as an important factor, and aiming to provide culturally suitable healthcare. Moreover, cultural competence is a process requiring constant effort in order to create a working environment suitable for cultural history of individuals, families, and communities receiving professional healthcare.[6] The acquisition of culturally competent and culturally suitable care depends on improving the cultural competence.[7,8]

Misunderstandings between people from different cultures and healthcare providers are caused by lack of cultural awareness, cultural knowledge, and flexibility in healthcare providers. Hence, it is rather important for these professionals to be sensitive and to improve their cultural competence in order to meet health requirements of individuals coming from different cultures. Moreover, improvement of cultural competence is a process requiring more than just cultural awareness.[9] In the qualitative study conducted by Hart and Mareno[10], causes of difficulties in terms of providing culturally efficient care for nurses were defined as the variety of patient population, lack of sources to provide culturally efficient care, and prejudice. Felemban et al.[11] stated that nurses without cultural knowledge would cause misunderstandings while providing care; thereby increasing the risk of error and the possibility of causing fatal consequences. In the study conducted by Hendson et al.[12], it was found that providing culturally efficient care became an obligation for nurses due to the reasons such as migrant families having different beliefs and norms and communication obstacles.

Providing culturally competent care requires having and using necessary cognitive, affective, and psychomotor skills in order to fill the gaps often occurred while interacting with culturally different individuals.[13] Culturally competent care requires having and using necessary cognitive, affective, and psychomotor skills in order to fill the gaps often occurred while interacting with culturally different individuals. There are different scales used for determining cultural competence of healthcare professionals.[14] These tools that can be applied to individuals from different cultures and healthcare professionals have been used in order to evaluate the cultural competence of healthcare professionals and nurses in primary and secondary healthcare services.[15-18]

The frequency of encountering individuals from different cultures for healthcare professional has increased due to intense migration in Turkey in recent years.[3] The number of refugees is remarkably high in Adıyaman province, bordering Syria in the southeastern part of Turkey. It is required to understand and explain factors affecting cultural competence of healthcare professionals encountering these disadvantaged individuals from a different cultural history. This study aimed to evaluate and compare level of cultural competence in healthcare professionals in primary and secondary healthcare services in Adıyaman city center.

In this study, the following questions were asked:

1. What are the cultural competence levels of primary health care professionals (PHCP) and secondary health care nurses (SHCN)?

   Is there a difference between the cultural competence levels of primary health care professionals (PHCP) and secondary health care nurses (SHCN)?

2. Which demographic factors and cultural experiences are associated to the level of cultural competence of PHCP and SHCN?

MATERIALS AND METHODS

Study Design

This cross-sectional study was conducted in Adıyaman province, bordering Syria in the southeastern region of Turkey, between March–May 2018.

Setting and Sample

The universe for primary healthcare was composed of healthcare professionals working as nurse, midwife, and health officer in all primary healthcare institutions in the city center affiliated with Adıyaman Provincial Health Directorate (Public Health Services Presidency, Family Health Centers, Healthy Life Centers, and Homebased Healthcare Services) (n=90). The sample size for this group was calculated using G*Power 3.1.10 program (Aichach, Germany). The sample size was found to be 62 at 0.95 power, 0.5 effect size (d), and with a confidence interval (CI) of 95%. Totally 87 healthcare professional working in primary healthcare services and having volunteered to take part in the study constituted the sample (Figure 1).

Data Collection

The universe for secondary healthcare was composed of 500 nurses working in Adıyaman University, Adıyaman Training and Research Hospital between March–May 2018. The healthcare institution classified as secondary healthcare center at the time of research ethics committee approval of the study was transformed into tertiary healthcare institution after data collection process. Therefore, the secondary healthcare term was used throughout the study. The sample size for secondary healthcare was found to be 342 at 0.95 power, 0.5 effect size (d), and with a CI of 95%. 348 nurses working in secondary healthcare institutions were included in the study. Of the participants, 46 of them were not included due to their working in operation room, 83 due to having official leave or medical reports, and 23 due to not willing to

fill the questionnaires (Figure 1). The fact that the study sample was composed of 87 healthcare professionals for primary healthcare and 348 healthcare professionals for secondary healthcare provided a higher strength level for the study.

Measurements

For collecting the research data, a "Descriptive Information Form", "Nurse Cultural Competence Scale (NCCS)", and the "Primary Health Care Professionals' Cultural Competency Scale (PHCP-CCS)" were used.

Descriptive Information Form

Form based on the literature and prepared by researchers[15-18] questions evaluating demographic characteristics and cultural history of participants were included. In the demographic features section, age, gender, working year, current institution and for how long they have been working in that institution were questioned. In the cultural history section, whether they knew any languages other than Turkish, whether they had living-working-studying experience abroad, whether they had been to abroad for business or touristic purposes for a short period of time, whether they had a training on providing care for different cultures in vocational or in-service training, the frequency of interacting with foreign friends or neighbors from different cultures, the frequency of encountering individuals/families from different cultures in healthcare services, and the level of satisfaction while providing service for migrants/asylum seekers were questioned.

Nurse Cultural Competence Scale (NCCS)

The scale was developed by Perng and Watson[18] in 2012. The Turkish version of the scale was published by Gözüm et al.[15] There are three dimensions and 20 items evaluating cultural competence (12 items), cultural knowledge (6 items), and cultural sensitivity (2 items) in the scale. The scale is evaluated using answers such as "strongly agree", "agree", "indecisive", "disagree", and "strongly disagree". Scores in the scale vary between 20–100, and the level of cultural competence increases as the total score increases.[18] The reliability coefficient of Turkish version of NCCS was 0.96,[15] whereas the reliability coefficient of NCCS used in this study was 0.94.

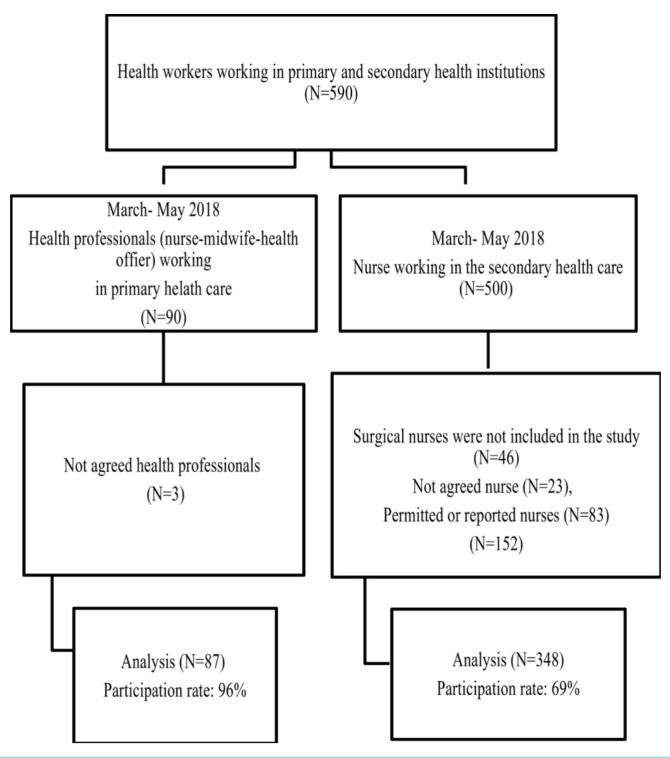

Figure 1. It shows the sample of the study and explains the reasons for those who did not participate in the study.

Primary Health Care Professionals' Cultural Competency Scale (PHCP-CCS)

The Turkish version of NCCS was adapted to be applied to primary healthcare professionals by Gözüm et al.[16] While adapting the scale, some terms in items were modified. There are three dimensions and 20 items evaluating cultural competence (12 items), cultural knowledge (6 items), and cultural sensitivity (2 items) in the scale. The scale is evaluated using answers such as "strongly agree", "agree", "indecisive", "disagree", and "strongly disagree". Scores in the scale vary between 20–100, and the level of cultural competence increases as the total score increases.[16] The reliability coefficient of PHCP-CCS was 0.84[16] whereas the reliability coefficient of the scale used in the study was 0.93. Data were collected using face-to-face interview method with healthcare professional in the units they were assigned to within approximately 15–20 minutes.

Data Analysis

Data were analyzed using Statistical Package fort the Social Sciences (SPSS) 23.0 package program (IBM SPSS Corp., Armonk, NY, USA). In descriptive statistics, continuous variables were defined as mean ± standard deviation (SD) whereas categorical variables were defined as frequency and percentage. The comparison of demographic features, cultural history, and cultural competence mean scores of both groups was carried out using chi-square and *T-test*.

In examining the relationship of demographic features and cultural experiences with the level of cultural competence using single variable analyses, t-test, Mann–Whitney U test, Kruskal–Wallis Analysis, One-Way ANOVA and Dunn–Bonferroni tests were used. In multivariate analysis, possible factors confirmed in previous analyses were examined using multivariate logistic regression analysis in order to determine independent predictors of cultural competence. Hosmer–Lomeshow test was used for the model fit. All independent variables were included in logistic regression model. As the dependent variable, the level of cultural competence was the continuous variable. Mean cultural competence scores of two groups were dichotomized in order to conduct multivariate logistic regression analysis. Mean cultural competence score was 66.58 in PHCP whereas it was 67.44 in SHCN. Accordingly, the level of cultural competence was categorized as "below average" in 66 or below, and "above average" in 67 or above. Due to the low number of those stating, "*I am (very) satisfied*" and "*It does not matter*" in the evaluation of factors related to PHCP-CCS and not being able to establish a proper logistic regression model, the ones giving these answers were combined. Moreover, another criterion for this decision was that those choosing both of these answers had similar cultural competence scores.

RESULTS

Mean age of those taking part in the study was 33.22 (±7.88) in primary healthcare, and 33.11 (±7.64) in secondary healthcare services. The majority of participants in both groups were women, and 59.8% of those in primary care and 64.9% of those in secondary care had undergraduate level or higher education. Of the participants, 54% of them in primary care and 63.5% of them in secondary care had a professional experience less than 10 years ($p>0.05$, Table 1).

The frequency of encountering individuals/families from different cultures was found to be higher in SHCN than in PHCP ($p<0.05$; Table 1). The rate of those who had not had any experience about the satisfaction of providing services for migrants/asylum seekers was found to be higher in PHCP than in SHCN. Moreover, the rate of those stating they were not satisfied, or it did not matter was found to be higher in secondary healthcare compared to primary healthcare ($p<0.05$, Table 1).

Mean score of PHCP-CCS was 66.58 (±13.47), and mean score of nurses in secondary healthcare was 67.44 (±13.27). There was not any difference between cultural competence scores in primary and SHCN ($p>0.05$). It was found that mean scores of PHCP-CCS were not related to age, gender, education, and duration of working in primary healthcare services ($p>0.05$). It was found that the level of cultural competence of those working for less than 10 years was higher than those working for 10 years and more ($p<0.05$). It was found that mean scores of PHCP-CCS were not associated with factors such as speaking a foreign language, having a living-working-studying experience abroad, having been abroad for business or touristic purposes for a short period of time, the presence of and close interaction with foreign friends-partners-relatives-neighbors from different cultures in their private life, and the satisfaction of providing services for migrants and asylum seekers ($p>0.05$). It was found that the mean score of PHCP-CCS in those having frequent and very frequent interactions with foreign friends or neighbors from different cultures was higher than those having no or rare interaction with individuals from different cultures ($p<0.05$). The rate of those encountering individuals/families from different cultures in healthcare services "frequently and very frequently" was found to be higher than those encountering these individuals "never and rarely" ($p<0.05$).

It was found that the mean scores of NCCS in the secondary health services were not related to age, gender, the year of work in the profession, the period of work in education and secondary health care ($p>0.05$). Moreover, it was found that the mean scores of NCSS were not associated with factors such as speaking a foreign language, having living-working-studying experience abroad, having been abroad for business or touristic purposes for a short period of time, the frequency of interaction with foreign friends or neighbors from different cultures in private life, and the frequency of encountering individuals/families from different cultures in healthcare services ($p>0.05$). However, a significant difference was found between the level of satisfaction in providing services for migrants and asylum seekers and the mean of NCCS. It has been found that the mean of NCSS of those stating, "I am satisfied/very satisfied" about providing care for migrants and asylum seekers was higher than those who were "not satisfied at all/were not satisfied" ($p<0.05$).

Factors related to the mean of PHCP-CCS were analyzed using logistic regression analysis. It was found that the mean of PHCP-CCS was increased by shorter working hours in primary care 0.81 times, by having been abroad for business or touristic purposes for a short period of time 0.14 times, and frequently and very frequently encountering individuals/families from different cultures in healthcare services 0.14 times ($p<0.05$; Table 2). It was also found that the mean of PHCP-CCS of those stating that they "were not satisfied at all/were not satisfied" on the level of satisfaction in providing care for migrants and asylum seekers was decreased 0.15 times ($p<0.05$, Table 2).

It was found in logistic regression analysis that the mean of NCCS in secondary healthcare institution was not related to demographic factors ($p>0.05$). It was also found that the cultural competence of those stating that they "were not satisfied at all/were not very satisfied" on the level of satisfaction in providing care for migrants and asylum seekers was decreased 0.53 times ($p<0.05$). In addition, it was also found that being satisfied with providing care for migrants and asylum seekers was significant with the mean of NCCS ($p<0.05$, Table 3).

DISCUSSION

Comparing the Level of Cultural Competence in PHCP and SHCN

It was concluded in this study that the level of cultural competence in PHCP and SHCN was at medium level and that there was not any difference between the level of cultural competence in PHCP and SHCN. In three similar studies, it was found that the level of cultural competence in nurses was at medium level.[18,19] In a study conducted by Gözüm et al.[15] at a hospital in Turkey, it was observed that the level of cultural competence in nurses was higher than the level found in this study. In a study conducted in primary healthcare services in Turkey, it was found that the level of healthcare professionals was at medium level and that it was in consistency with the results obtained in this study.[16] The fact that the level of cultural competence in healthcare professionals was found to be lower than the level found in the aforementioned study conducted in Turkey[15] is believed to be caused by factors such as intense migration to Adıyaman only from Syria and the fact that healthcare professionals encounter a certain migrant group in healthcare services.

Comparing the Cultural Experiences in PHCP and SHCN

The rate of those frequently encountering individuals/families from different cultures was 24.1% in primary healthcare, and 37.6% in secondary healthcare in this study. A significant difference was found between these two groups. In two different studies conducted in secondary healthcare in Korea, the frequency of encountering patients from different cultures was found to be 81.6% and 94.3%.[20,21] It was found that 73.5% of nurses in secondary healthcare provided services for patients from different cultures in Thailand[22] and that the majority of nurses (91%) provided care for patients from different cultures in Taiwan.[23] In studies conducted in primary and secondary healthcare in Turkey, it was observed that the frequency of providing services for individuals from different cultures in nurses varied between 71% and 94%.[14,24,25] The fact that PHCP in this study encountered individuals from different cultural history than SHCN may be explained by the presence of migrant health centers and refugee camps in the region where the study was conducted. Since basic healthcare services are provided in migrant health centers and camps, PHCP encounter refugees less in healthcare services.

Table 1. Comparison of demographic characteristics and cultural experiences of PHCP and SHCN

Demographic characteristics and cultural experiences	PHCP (n=87)		SHCN (n=348)		Analysis	
Age, years	**n**	**%**	**n**	**%**	**χ^2**	**p**
<35	45	51.7	213	61.2	2.593	0.107
≥35	42	48.3	135	38.8		
Age (mean ± SD)	33.22	7.881	33.11	7.643	0.994***	0.321
Gender						
Female	80	92.0	292	83.9	3.638	0.056
Male	7	8.0	56	16.1		
Total working period in professional						
<10 years	34	39.1	169	48.6	2.515	0.113
≥10 years	53	60.9	179	51.4		
Education level						
High school and associate degree	35	40.2	122	35.1	1.121	0.571
Undergraduate and graduate	52	59.8	226	64.9		
Working period in primary and secondary health care						
<10 years	47	54.0	221	63.5	2.646	0.104
≥10 years	40	46.0	127	36.5		
Speaking a foreign language						
No	54	62.1	182	52.3	2.677	0.102
Yes	33	37.9	166	47.7		
Living-working-education experience in abroad						
No	85	97.7	332	95.4	…….****	0.547
Yes	2	2.3	16	4.6		
Traveling abroad for business or touristic purposes for a short period of time						
No	66	75.9	284	81.6	1.462	0.227
Yes	21	24.1	64	18.4		
Having friends, spouses, relatives and neighbors from different cultures in private life						
No	57	65.5	233	67.0	0.065	0.799
Yes	30	34.5	115	33.0		
Frequency of interaction with friends or neighbors from different cultures in private life						
No-rarely	73	83.9	291	83.6	0.004	0.948
Often-very often	14	16.1	57	16.4		
Frequency encountering individuals/families from different cultures in healthcare services						
No-rarely	66	75.9	217	62.4	5.585	**0.018***
Often-very often	21	24.1	131	37.6		
Satisfaction of providing services for immigrants/asylum seekers						
I have no experience	45	51.7	83	23.9	27.225	**0.000****
I am not satisfied at all- I am not satisfied	26	29.9	164	47.1		
I am satisfied-I am very satisfied	6	6.9	23	6.6		
It does not matter to me	10	11.5	78	22.4		

p<0.05*, p<0 .001**, t-test***, Fisher's exact test****.
PHCP: primary health care professionals, SHCN: secondary health care nurses, SD: standard deviation, n: number.

It was found in this study that the rate of PHCP who did not have any experience in terms of providing services for migrants/asylum seekers was higher than that of the rate of SHCN. Moreover, the level of dissatisfaction in SHCN was found to be higher compared to PHCP. In a study, it was concluded that the level of satisfaction in providing care for different individuals from their own culture in healthcare professionals was higher and that having sufficient information on different cultures increased the level of satisfaction.[26] In another study, it was observed that 19.4% of nurses were satisfied with providing care for foreign patients and that 32.5% of them were willing to do

Table 2. Logistic regression analysis: factors that may be associated with PHCP-CCS score mean (n=87)

	β	SE	p	OR	95% CI	
					Lower	Upper
Age, years	0.18	0.01	0.067	1.19	0.99	1.45
Gender Male: 1 Female: 0	1.94	1.51	0.200	6.92	0.36	133.39
Working period in profession	**0.10**	**0.13**	**0.420**	**1.11**	**0.87**	**1.41**
Education level High school and associate degree: 0 Undergraduate and graduate: 1	0.57	0.60	0.340	1.77	0.55	5.71
Working time in primary health care	-0.21	0.11	0.047	0.81	0.66	0.99
Speaking a foreign language Yes: 0 No: 1	-0.17	0.64	0.787	0.84	0.24	2.93
Traveling abroad for business or touristic purposes for a short period of time Yes: 0 No: 1	-2.00	0.81	0.013*	0.14	0.03	0.65
Having friends, spouses, relatives and neighbors from different cultures in private life Yes: 0 No: 1	-0.18	0.70	0.800	0.84	0.21	3.32
Frequency of interaction with friends or neighbors from different cultures in private life Often-very often: 0 No-rarely: 1	-1.11	1.11	0.318	0.33	0.04	2.92
Frequency encountering individuals/families from different cultures in healthcare services Often-very often: 0 No-rarely: 1	-2.01	0.86	0.020*	0.14	0.03	0.73
Satisfaction of providing services for immigrants/asylum seekers I am satisfied-I am very satisfied- It does not matter to me: 0 I am not satisfied at all- I am not satisfied: 1 I have no experience: 2	-1.87 0.46	0.94 0.62	0.133 0.046* 0.459	0.15 0.63	0.02 0.19	0.97 2.13
Constant	-6.06	3.23	0.061	0.00		

p<0.05*

PHCP-CCS: Primary Health Care Professionals' Cultural Competency Scale, SE: standard error, OR: odds ratio, CI: confidence interval, n: number.

so.[27] In a study conducted in Turkey, it was found that the majority of nurses (83.6%) did not face any problems due to cultural and religious values while providing care for patients.[28] In a study, 69.4% of nurses working at a hospital in the western part of Turkey and 74.2% of nurses working at a hospital in the eastern part of Turkey stated that cultural background of patients was important in terms of providing nursing services.[29] The fact that the level of dissatisfaction in providing care for individuals from different cultures was found to be higher in secondary healthcare than in primary healthcare may have been caused by the frequent encounters of SHCN with refugees and asylum seekers from Syria.

The Relationship of Demographic Characteristics and Cultural Experiences in PHCP and SHCN with the Level of Cultural Competence

When the relationship between demographic characteristics of PHCP and their cultural competence was analyzed, it was observed that shorter working hours in primary healthcare increased cultural competence. On the contrary, in a study conducted in Taiwan,[27] it was found that working hours of nurses at hospitals was not associated with the level of cultural competence. The fact that the level of cultural competence decreased in the present study as working hours increased in primary healthcare may have been caused by longer encounters of healthcare professionals with refugees only from Syria.

It was concluded that PHCP frequently encountering individuals/families from different cultures in healthcare services increased their cultural competence, and this was found to be suitable with two studies conducted in Turkey.[15,16] Similarly, in a study conducted in Taiwan, it was concluded that the most important indicator of the level of cultural competence was the frequency of providing care for different cultures and that cultural competence of those frequently providing care for these individuals increased.[23] On the contrary, in a study conducted in primary healthcare services in

Table 3. Logistic regression analysis: factors that may be associated with NCCS score mean (n=348)

	β	SE	p	OR	95 % CI	
					Lower	Upper
Age, years	0.05	0.04	0.152	1.05	0.98	1.13
Gender Male: 1 Female: 0	-0.40	0.32	0.211	0.67	0.36	1.26
Working period in profession	-0.21	0.04	0.587	0.98	0.91	1.06
Education level High school and associate degree: 0 Undergraduate and graduate: 1	0.31	0.26	0.227	1.37	0.82	2.28
Working period in secondary health care institution	-0.05	0.03	0.132	0.95	0.90	1.01
Speaking a foreign language Yes: 0 No: 1	0.33	0.23	0.154	1.39	0.88	2.20
Traveling abroad for business or touristic purposes for a short period of time Yes: 0 No: 1	-0.01	0.62	0.984	0.99	0.29	3.34
Having living-working-studying experience abroad Yes: 0 No: 1	0.37	0.34	0.281	1.44	0.74	2.82
The presence of friends, spouses, relatives, neighbors from different cultures in your private life Yes: 0 No: 1	0.44	0.28	0.079	1.55	0.90	2.66
Frequency of interaction with friends or neighbors from different cultures Often-very often: 0 No-rarely: 1	-0.06	0.36	0.877	0.95	0.47	1.92
Frequency encountering individuals/families from different cultures in healthcare services Often-very often: 0 No-rarely: 1	0.21	0.25	0.396	1.24	0.76	2.02
Satisfaction of providing services for immigrants/asylum seekers I am satisfied-I am very satisfied-It does not matter to me: 0 I am not satisfied at all- I am not satisfied: 1 I have no experience: 2	 -0.63 -0.50	 0.28 0.29	0.046* 0.023* 0.084	 0.53 0.61	 0.31 0.35	 0.92 1.07
Constant	-1.72	1.14	.133	0.18		

p<0.05*

NCCS: Nurse Cultural Competence Scale, SE: standard error, OR: odds ratio, CI: confidence interval, n: number.

Portugal, the level of cultural competence was found to be higher in healthcare professionals with less interaction with migrants than in those with frequent interactions.[30] The fact that frequent encounters with individuals from different cultures in healthcare delivery has a positive impact on the level of cultural competence is an expected result of the present study.

It was concluded that having been abroad for business or touristic purposes for a short period of time increased cultural competence of PHCP and that this was in consistency with the results of studies conducted in Japan and South Korea.[16,31] On the contrary, in another study conducted in South Korea, the experience of having been abroad was not related to the cultural competence of nurses.[20] The fact that the level of cultural competence in this study is higher in PHCP having been abroad may be explained by the fact that interacting with individuals from different cultures has a positive impact on cultural competence.

The level of cultural competence increased in PHCP as the level of satisfaction in providing care for migrants and asylum seekers increased and this was found to be suitable with the study conducted by Gözüm et al.[16] It was found that the level of cultural competence in SHCN being satisfied or very satisfied for refugees and asylum seekers increased ($p<0.05$), and that this was suitable with two different studies conducted in Thailand and Turkey.[16,22] On the contrary, in a study with nursing students in Saudi Arabia, it was concluded that there was not any difference between choosing to provide care for patients from different cultures and the level of cultural competence.[32] The fact that

the level of competence is high in PHCP and SHCN being satisfied with providing care for individuals from different cultures is an expected result of the present study.

In this study, the level of cultural competence in PHCP and SHCN in a region of intense migration was found to be at medium level. The level of cultural competence in PHCP increased by factors such as shorter working hours in primary healthcare, having been abroad for business or touristic purposes, frequent encounters with individuals/families from different cultures in healthcare services, the level of satisfaction in terms of providing care for migrants and asylum seekers. The level of cultural competence of SHCN increased by the level of satisfaction in providing care for migrants and refugees. It might be beneficial to brief healthcare workers during undergraduate study and in-service training on different cultures and to encourage them to meet people from different cultures in order to increase their cultural competence. Moreover, conducting qualitative studies that can explain the causes of decreases in the level of cultural competence due to longer working years in the profession is of the utmost importance.

Limitations of the Study

The present study has two limitations. The first one is that healthcare professionals in Adıyaman frequently encounter refugees only from Syria. The second one is that data are collected from healthcare professionals in a city center in the southeastern part of Turkey and that results obtained in the present study could not be adapted to the entire country.

CONCLUSION

In this study, the level of cultural competence in PHCP and SHCN in a region of intense migration was found to be at medium level. The level of cultural competence in PHCP increased by factors such as shorter working hours in primary healthcare, having been abroad for business or touristic purposes, frequent encounters with individuals/families from different cultures in healthcare services, the level of satisfaction in terms of providing care for migrants and asylum seekers. The level of cultural competence of SHCN increased by the level of satisfaction in providing care for migrants and refugees. It might be beneficial to brief healthcare workers during undergraduate study and in-service training on different cultures and to encourage them to meet people from different cultures in order to increase their cultural competence. Moreover, conducting qualitative studies that can explain the causes of decreases in the level of cultural competence due to longer working years in the profession is of the utmost importance.

MAIN POINTS

- Cultural competence is an important component in providing culturally sensitive and effective care in healthcare services, reducing inequalities and improving health outcomes.
- Determining the cultural competence levels of healthcare professionals employed at health institutions is important in terms of planning interventional work.
- The findings of this study present the factors that are related to the cultural competence of healthcare professionals employed at primary and secondary health institutions.

ETHICS

Ethics Committee Approval: Official approval for the present study was obtained from the Clinical Research Ethics Committee of Akdeniz University, Faculty of Medicine (approval no: 70904504/38, date: 17.01.2018).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.T., M.S., Design: A.T. M.S., Supervision: A.T., Data Collection and/or Processing: M.S., Analysis and/or Interpretation: A.T., M.S., Literature Search: M.S., Writing: M.S., A.T., Critical Review: A.T.

DISCLOSURES

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REFERENCES

1. International Organization for Migration [IOM]. Global Migration Trends Factsheet; 2015. Available from: URL: https://gmdac.iom.int/global-migration-trends-factsheet/ (Accessed on April 20, 2019).
2. International Organization for Migration [IOM]. Migration and Migrants: A Global Overview. In World Migration Report 2020. Available from: URL: https://publications.iom.int/system/files/pdf/wmr_2020.pdf (Accesed on April 20, 2019).
3. International Organization for Migration [IOM]. Migration in Turkey; 2020. Available from: URL: https://turkey.iom.int/migration-turkey/ (Accessed on March 20, 2019).
4. Keleşmehmet H. Immigrant health in the World and in Turkey. J Turk Fam Phys 2018; 9(4): 119-26.
5. Öztürk E, Öztaş D. Transcultural nursing. Batman Univ Journal Life Sci 2012; 1(1): 293-300.
6. Transcultural C.A.R.E Associates. The process of cultural competence ın the delivery of healthcare services. 2019. Available from: URL: http://transculturalcare.net/the-process-of-cultural-competence-in-the-delivery-of-healthcare-services (Accessed on March 10, 2019).
7. Jeffreys MR. Chapter 8: Educational issues for students, organizational staff, patients, and communities. J Transcult Nurs. 2010; 21(4_suppl): 338S-56S.
8. Shen Z. Cultural competence models and cultural competence assessment instruments in nursing: A Literature Review. J Transcult Nurs. 2015; 26(3): 308-21.
9. Giger JN. Introduction to Transcultural Nursing. J. N. Giger, (Eds.), Transcultural Nursing Assessment and Intervention (7th ed). Elsevier Health Sciences; 2016. pp. 1-12.
10. Hart PL, Mareno N. Nurses' perceptions of their cultural competence in caring for diverse patient populations. J Cult Competence Nurs Healthcare. 2016; 6(1): 121-37.
11. Felemban E, O'Connor M, McKenna L. Cultural view of nursing in Saudi Arabia. Mid East J Nurs. 2014; 8(4): 8-14.
12. Hendson L, Reis MD, Nicholas DB. Health care providers' perspectives of providing culturally competent care in the NICU. J Obstet Gynecol Neonatal Nurs. 2015; 44(1): 17-27.

13. Schim SM, Doorenbos AZ. A three-dimensional model of cultural congruence: Framework for intervention. J Soc Work End-Of-Life & Palliat Care. 2010; 6(3-4): 256-70.

14. Loftin C, Hartin V, Branson M, Reyes H. Measures of Cultural Competence in Nurses: An Integrative Review. Sci World J. 2013; 1-10. DOI: 10.1155/2013/289101

15. Gözüm S, Tuzcu A, Kirca N. Validity and reliability of the Turkish version of the nurse cultural competence scale. J Transcult Nurs. 2016; 27(5): 487-95.

16. Gözüm S, Tuzcu A, Yurt S. Developing a cultural competency scale for primary health care professionals. Psikoloji Çalışmaları 2020; 1-22. DOI: 10.26650/SP2019-0043.

17. Noji A, Mochizuki Y, Nosaki A, Glaser D, Gonzales L, Mizobe A, Kanda K. Evaluating cultural competence among Japanese clinical nurses: Analyses of a translated scale. Int J Nurs Pract. 2017; 23: e12551.

18. Perng SJ, Watson R. Construct validation of the nurse cultural competence scale: A hierarchy of abilities. J Clin Nurs. 2012; 21(11-12): 1678-84.

19. Songwathana P, Siripan S. Thai Nurses' Cultural competency in caring for clients living at a multicultural setting. Sigma Theta Tau International's 24th 2013; 19(1): 19-31.

20. Chae DH, Lee CY. Development and psychometric evaluation of the Korean version of the cultural competence scale for clinical nurses. Asian Nursing Res. 2014; 8(4): 305-12.

21. Choi SY, Kim KS. The effects of work characteristics, supervision, and cultural competence on nurses' burnout. IJBSBT. 2014; 6(4): 187-200.

22. Bunjitpimol P, Somrongthong R, Kumar R. Factors affecting nursing cultural competency in private hospitals at Bangkok, Thailand. Int J Healthcare. 2016; 2(1): 5-11.

23. Lin CN, Mastel-Smith B, Alfred D, Lin YH. Cultural Competence and Related Factors among Taiwanese Nurses. J Nurs Res. 2015; 23(4): 252-61.

24. Arli SK, Bakan AB. An investigation of the relationship between intercultural sensitivity and compassion in nurses. Int J Intercult Rel. 2018; 63: 38-42.

25. Kürtüncü M, Arslan N, Çatalçam S, Yapıcı G, Hırçın G. Association between cross-cultural sensitivities and socio-demographic characteristics and empathy levels of nurses working at inpatient treatment institutions. J Res Develop Nurs. 2018; 9557(1): 44-56.

26. Han W, Lee S. Racial/ethnic variation in health care satisfaction: The role of acculturation. Soc Work Health Care. 2016; 55(9): 694-710.

27. Bunjitpimol P, Somrongthong R, Kumar R. Factors affecting nursing cultural competency in private hospitals at Bangkok, Thailand. Int J Healthcare. 2016; 2(1): 5-11.

28. Karadag E, Kilic SP, Ugur O, Akyol MA. Attitudes of nurses in Turkey toward care of dying individual and the associated religious and cultural factors. JORH. 2018; 58(1): 1-14.

29. Kilic SP, Besen DB, Tokem Y, Fadiloglu C, Karadag G. An analysis of the cultural problems encountered during caregiving by the nurses working in two different regions of Turkey. Int J Nurs Pract. 2014; 20(3): 310-9.

30. Dias S, Gama A, Cargaleiro H, Martins MO. Health workers' attitudes toward immigrant patients: a cross-sectional survey in primary health care services. Hum Res Health. 2012; 10(1): 14.

31. Chae D, Park Y. Development and cross-validation of the short form of the cultural competence scale for nurses. Asian Nurs Res. 2018; 12(1): 69-76.

32. Halabi JO, Beer J. Exploring the cultural competence of undergraduate nursing students in Saudi Arabia. Nurse Educ Today. 2018; 6: 9-15.

CASE REPORT

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The Management of Multiple Traumatized Anterior Teeth with Four-Year Follow-Up

Mohamad Abduljalil[1], Umut Aksoy[1], Aysa Ayalı[2], Kaan Orhan[3]

[1]Department of Endodontics, Near East University Faculty of Dentistry, Nicosia, North Cyprus
[2]Department of Oral and Maxillofacial Surgery, European University of Lefke, Faculty of Dentistry, Lefke, North Cyprus
[3]Department of Dentomaxillofacial Radiology, Ankara University Faculty of Dentistry, Ankara, Turkey

Abstract

Traumatic dental injuries are recognized as a public dental health problem worldwide and they manifest with a number of different types. They may occur alone or in a variety of combinations where both a fracture and a luxation injury affect the same tooth. A thorough diagnostic procedure plays an essential role in avoiding the risks of overlooking or misinterpreting concomitant injuries and preventing any subsequent healing complications. This case report discussed the management of traumatized anterior teeth. It clearly indicates how the correct diagnosis and appropriate treatment of combined dental injuries associated with multiple teeth, guided by the current evidence-based recommendations, can be successful. The establishment of continuous updates of knowledge among dental practitioners can maximize the chances of success in the management of traumatic dental injuries. The present case report can serve this purpose.

Keywords: Trauma, intrusion, fracture, root canal, follow-up

INTRODUCTION

The tooth and its supporting structures can be affected by different types of traumatic injuries. A thorough diagnostic procedure plays an essential role in avoiding the risks of overlooking or misinterpreting concomitant injuries, and preventing any subsequent healing complications.[1,2] The management of simple dental traumas can be treated by fillings with/without root canal treatment. However, complicated dental injuries, including fractures and luxation of the tooth, may require endodontic, surgical, orthodontic, and/or prosthodontic combination treatment.[3] In addition, complicated trauma requires long-term follow-up (up to 5 years).[4] The aim of this case report is to present in detail the successful management and outcome of multiple traumatized anterior teeth with a 4-year follow-up.

CASE PRESENTATION

A 21-year-old male was admitted to our clinic 3 hours after he suffered fractures of the upper anterior teeth. The patient presented with lacerated and swollen lips. He stated that he had attended a local hospital where he had received emergency treatment. His medical history was unremarkable for metabolic or neurological disorders.

Intraoral examination revealed the presence of luxation injuries and crown fractures of the maxillary central incisors (#11, #21) and the left lateral incisor (#22) as well as gingival lacerations and bleeding (Figure 1). In addition to enamel fracture, tooth #11 was displaced in the palatal direction. Tooth #21 appeared to be intruded by about 5 mm and had an enamel-dentin fracture without exposing the pulp, while tooth #22 had a complicated crown fracture without any displacement.

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ORCID IDs of the authors: M.A. 0000-0002-2244-9285; U.A. 0000-0001-7281-508X; A.A. 0000-0002-8817-4202; K.O. 0000-0001-6768-0176.

Address for Correspondence: Mohamad Abduljalil
E-mail: mohamad_abduljalil@hotmail.com
ORCID ID: orcid.org/0000-0002-2244-9285

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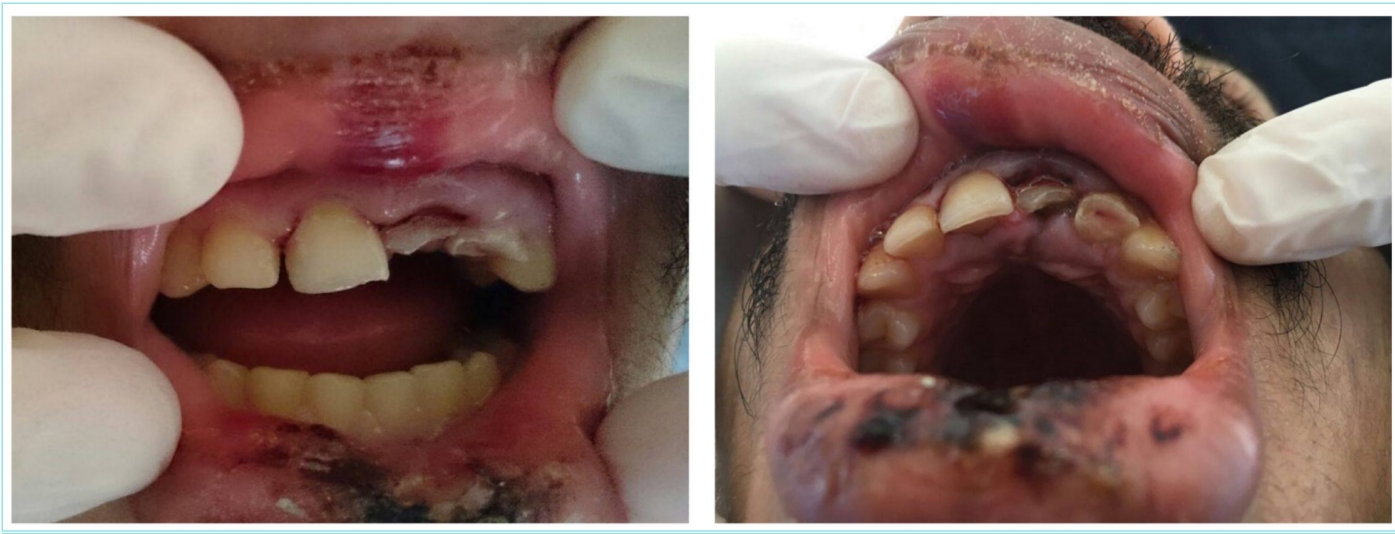

Figure 1. Clinical presentation of the injured teeth, front view and occlusal view.

Clinical examination showed no mobility in teeth #11 and #21 but slightly increased mobility in tooth #22 in response to lateral finger pressure. Teeth #11, #21 and #22 exhibited a positive response to percussion and palpation sensibility tests. Among these teeth, only #22 responded to cold tests and an electric pulp test. The diagnosis was confirmed via radiographic examination (Figure 2). No fractures were found in the jaws, alveolar bones, or teeth roots near the injured area. The periodontal ligament space was enlarged in the apical area of #11. The cement-enamel junction of #21 appeared to be located more apically than #22. A final diagnosis was made as lateral luxation with enamel fracture of tooth #11, intrusion with an uncomplicated crown fracture of tooth #21, and subluxation with a complicated crown fracture of tooth #22.

The patient's confirmation regarding the treatment procedures was obtained and the management was started by cleaning the area with a physiological saline solution in order to obtain better visualization. Local anesthesia was administered and a firm digital pressure was applied to the laterally luxated tooth #11, aiming to reposition it into its correct location. The immediate surgical repositioning of tooth #21 was performed by gently pulling it down with forceps into its original socket (Figure 3). Following this, a flexible splint was used to fix the traumatic teeth. This splint was applied from tooth #13 to tooth #23 using orthodontic wire and flowable composite resin (Figure 4). In the same session, the endodontic treatment of tooth #22 was started under rubber dam isolation. The process was carried out using the ProTaper Universal rotary system with different irrigation solutions. Then, the root canal of the tooth was dressed with calcium hydroxide. The patient was warned to only ingest soft food for 1 week and oral hygiene instructions were given. An antibiotic was prescribed for 5 days and chlorhexidine rinses for 2 weeks.

The early follow-up intervals were on the third and seventh days to check the healing of the wound surfaces and the stability of the splint. 10 days after the trauma, the root canal of tooth #22 was obturated using AH Plus sealer and gutta-percha. The endodontic treatment

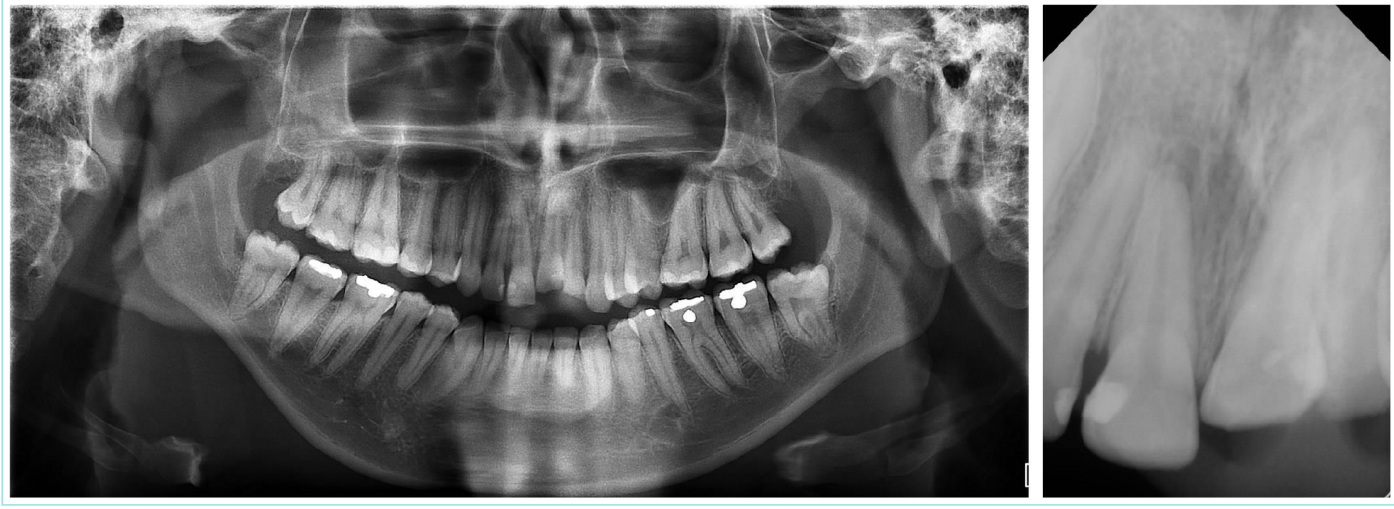

Figure 2. Radiographic images of the injured teeth. OPG X-ray and periapical radiographs.
OPG: orthopantomagram

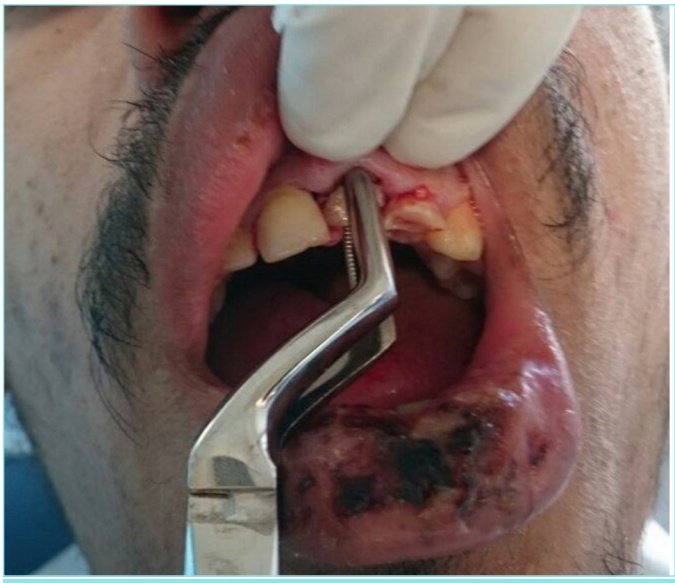

Figure 3. Clinical image of the teeth #21 during surgical pulling down with forceps.

for teeth #11 and #21 was initiated and calcium hydroxide dressing was applied for 4 weeks. The splint was removed during the following visit (4 weeks after injury) and the teeth were examined clinically and radiographically. No abnormal mobility and no pain on percussion or palpation were detected in the teeth. Thirty-three days post-injury, the endodontic treatment of teeth #11 and #21 was completed (Figure 5). Then, the fractured teeth were restored with composite resin to satisfy the esthetic and functional demands of the patient (Figure 6).

The patient was advised to attend follow-up visits at 4-, 6- and 12-month intervals. However, the patient visited another dental clinic 4 years after the trauma and a cone-beam computed tomography with periapical radiographs was taken. The clinical and radiographic examinations revealed good healing with the absence of any abnormalities (Figure 7). Informed consent was obtained from the patient who participated in this study.

DISCUSSION

The outcome of traumatic dental injuries is related to the time of treatment after trauma, the injury type, and the quality of treatment. It is important to consider that dental trauma complications such as root resorption and tooth necrosis can occur several months or even years after the injury.[5] Lacerations of the lips caused by trauma lead to an increased risk of becoming infected with microorganisms.[6] Thus, the lacerated lip was disinfected and the wound was sutured with a prophylactic broad-spectrum antibiotic treatment.

An intrusion injury, in which the periodontal ligament, root surface, and surrounding bone are severely damaged, is different compared to other luxation traumas. The survival of this type of trauma may be doubtful and there is a high probability of external root resorption.[7] In our case, tooth #21 was repositioned surgically and fixed with a flexible splint for 4 weeks.

One of the major complications after dental trauma is root resorption. Due to the slow progress of resorptions, traumatic teeth should be followed up after treatment for a long period (up to 5 years).[7] Factors such as necrosis of the pulp caused by trauma or the presence of bacteria inside the root canal may result from inflammatory resorption which can be controlled or prevented by effective root canal treatment.[8] Replacement resorption (ankylosis) occurs due to prolonged or inappropriate management of traumatic injury.[9] Previous studies have shown that the prevalence of the root resorption in avulsed or replanted teeth varied between 57% and 80% and, in intrusion trauma,

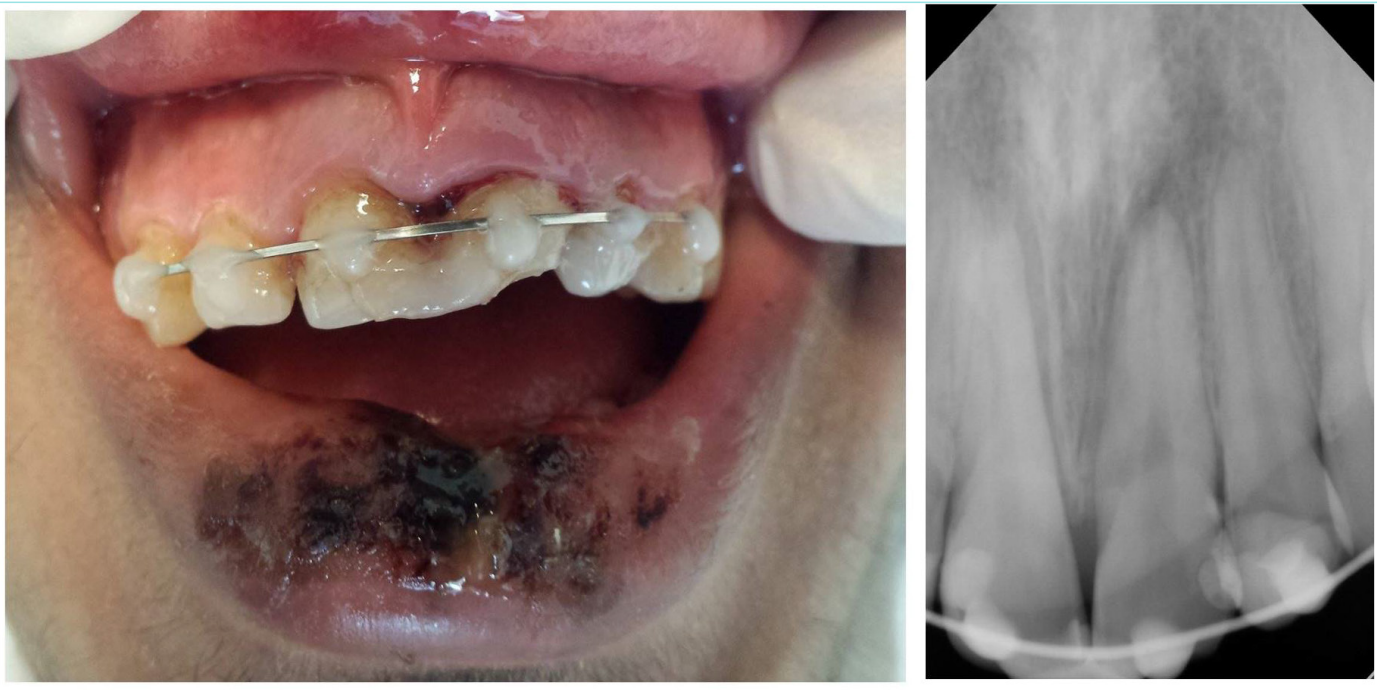

Figure 4. Flexible splint was used to fix the traumatic teeth with a control radiograph after fixing.

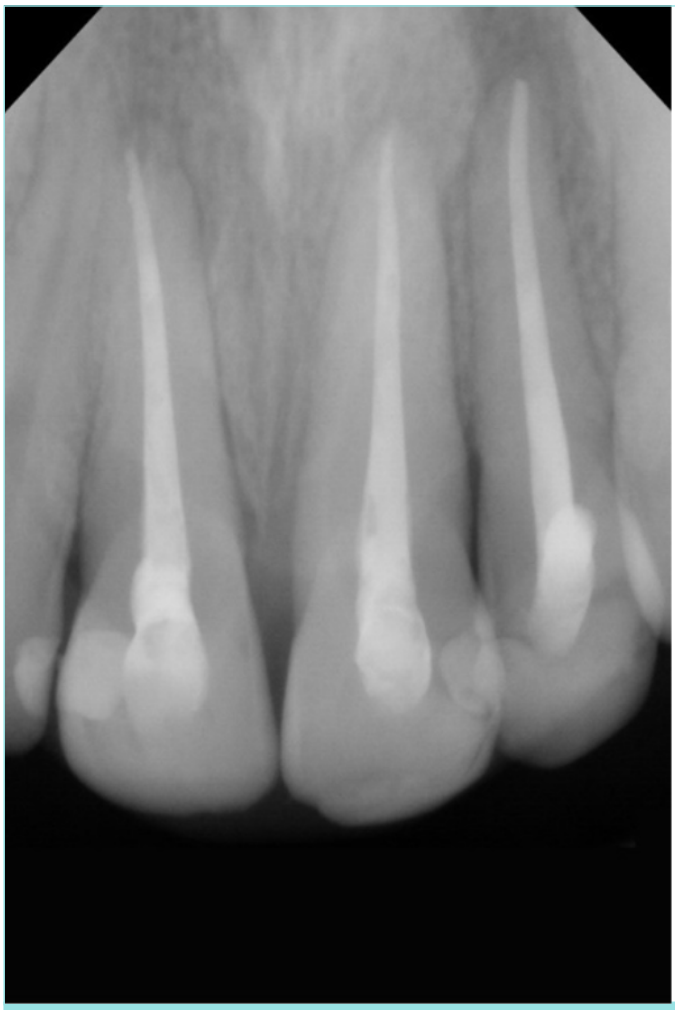

Figure 5. Post-obturation radiograph of teeth #11, #21 and #22.

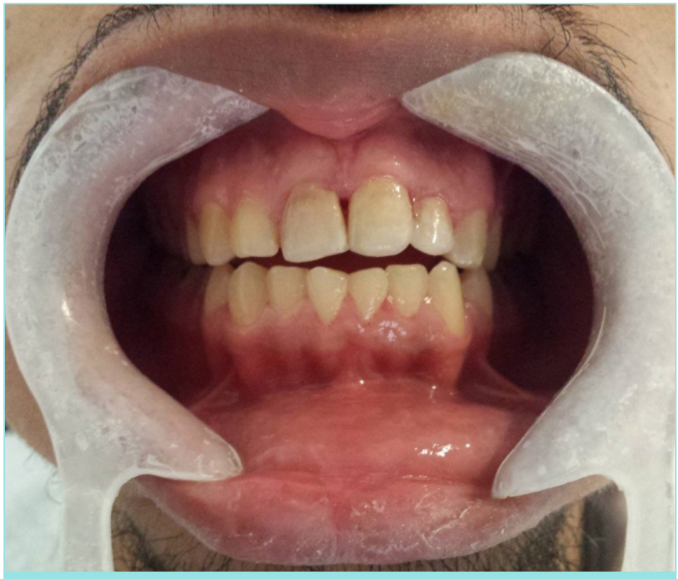

Figure 6. Clinical image immediately after endodontic treatment and restoration procedures.

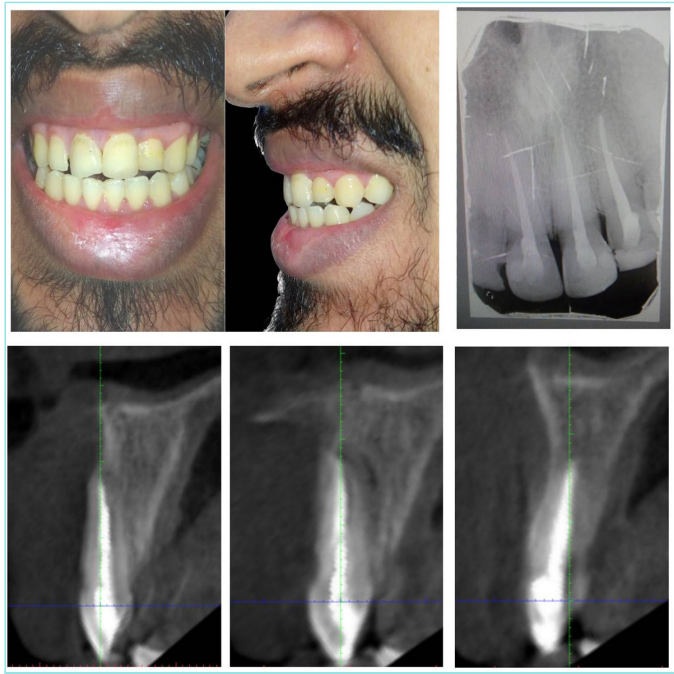

Figure 7. Four-year follow-up with clinical images, periapical radiograph, and CBCT images of teeth #11, #21, #22, respectively, showed complete healing of periapical bone without evidence of periradicular pathology or cervical resorption.

CBCT: cone-beam computed tomography

it was between 38%–66%.[10,11] External root resorption is a pathologic process which occurs due to several factors including trauma, infection, orthodontic tooth movement or pressure, and it leads to inflammatory reaction and destruction of the protective barrier on the root surface. External root resorption after dental trauma is a high-risk complication and its treatment is unpredictable and often ineffective.[12]

In addition to surgical and orthodontic treatments, endodontic treatment is highly effective in the management of traumatic dental injuries. Endodontic treatment plays no role in treating teeth where external or replacement resorptions are seen, but it is effective in preventing the inflammatory resorption and maintaining the tooth for a longer time. Calcium hydroxide is considered the treatment of choice in the prevention of inflammatory root resorption due to its antibacterial effects and alkaline pH properties.[13]

MAIN POINTS

- Traumatic dental injuries are recognized as a public dental health problem worldwide.
- An appropriate clinical and radiological diagnosis plays a significant role in the management of dental trauma.
- Regular updates regarding knowledge in dental traumatology is required.

ETHICS

Informed Consent: Informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.A., U.A., A.A., K.O., Design: M.A., U.A., A.A., K.O., Data Collection and/or Processing: M.A., U.A., A.A., K.O., Analysis and/or Interpretation: M.A., U.A., A.A., K.O., Literature Search: M.A., U.A., A.A., K.O., Writing: M.A., U.A., A.A., K.O., Critical Review: M.A., U.A., A.A., K.O.

DISCLOSURES

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REFERENCES

1. Lauridsen E, Hermann NV, Gerds TA, **Kreiborg S**, **Andreasen JO**. Pattern of traumatic dental injuries in the permanent dentition among children, adolescents, and adults. Dent Traumatol. 2012; 28(5): 358-63.
2. Lauridsen E, Hermann NV, Gerds TA, **Ahrensburg SS**, **Kreiborg S**, **Andreasen JO**. Combination injuries 2. The risk of pulp necrosis in permanent teeth with subluxation injuries and concomitant crown fractures. Dent Traumatol 2012; 28(5): 371-8.
3. Rai P, Pandey RK, Khanna R. A multidisciplinary approach to the management of traumatic intrusion in immature permanent teeth. BMJ Case Rep. 2016; 2016: bcr2014208571.
4. Orhan K, Aksoy U, Kalender A. Cone-beam computed tomographic evaluation of spontaneously healed root fracture. J Endod 2010; 36(9): 1584-7.
5. Robertson A. A retrospective evaluation of patients with uncomplicated crown fractures and luxation injuries. Endod Dent Traumatol. 1998; 14(6): 245-56.
6. Agrafioti A, Tsatsoulis IN, Papanakou-Tzanetaki SI, **Kontakiotis EG**. Primary inadequate management of dental trauma. J Clin Diagn Res. 2016; 10(7): ZD12-3.
7. Andreasen FM, Andreasen JO. Luxation injuries of permanent teeth: General findings. Andreason JO, Andreasen FM, Andreasen L, editors. Textbook and color atlas of traumatic injuries to the teeth. 4th ed. Oxford, UK: Blackwell Munksgaard; 2007. p.372-403.
8. Pohl Y, Filippi A, Kirschner H. Results after replantation of avulsed permanent teeth. I. Endodontic considerations. Dent Traumatol. 2005; 21(2): 80-92.
9. Fuss Z, Tsesis I, Lin S. Root resorption--diagnosis, classification and treatment choices based on stimulation factors. Dent Traumatol. 2003; 19(4): 175-82.
10. Majorana A, Bardellini E, Conti G, **Keller E**, **Pasini S**. Root resorption in dental trauma: 45 cases followed for 5 years. Dent Traumatol. 2003; 19(5): 262-5.
11. Chappuis V, von Arx T. Replantation of 45 avulsed permanent teeth: a 1-year follow-up study. Dent Traumatol. 2005; 21(5): 289-96.
12. Campbell KM, Casas MJ, Kenny DJ. Ankylosis of traumatized permanent incisors: pathogenesis and current approaches to diagnosis and management. J Can Dent Assoc. 2005; 71(10): 763-8.
13. Trope M, Barnett F, Sigurdsson A, Chivian N. The Role of Endodontics After Dental Traumatic Injuries. Hargreaves KM, Berman LH, editors. Cohen's Pathways of the Pulp. 11th ed. St. Louis: Elsevier; 2016.p.758-89.

CASE REPORT

CYPRUS
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Trichilemmal Horn

Siddharth P. Dubhashi[1], Riddhima S. Dubhashi[2]

[1]Department of Surgery, All India Institute of Medical Sciences (AIIMS), Nagpur, India
[2]Department of Surgery, Dr. V.M. Government Medical College, Solapur, India

Abstract

A trichilemmal horn is a rare benign follicular lesion with trichilemmal differentiation. This is a case report of a 73-year-old female who presented with a large growing cutaneous horn over her left zygoma. The histopathology of the excised lesion revealed a trichilemmal horn. Various theories have been formulated to explain this condition. A diagnosis of a trichilemmal horn should be considered when a cutaneous horn shows trichilemmal keratinisation in the absence of dermal inflammation.

Keywords: Trichilemmal horn, keratosis, keratinisation, acanthosis, follicular tumour

INTRODUCTION

Cutaneous horns are protrusions from the skin consisting of cornified material, which can be straight or curved, and lacking a bony core.[1] Trichilemmal horn is a rare benign follicular lesion with trichilemmal differentiation.[2] It is usually seen on photo-exposed areas of elderly individuals with fair skin.[3]

CASE PRESENTATION

A 73-year-old female with vitiligo presented with an asymptomatic protruding, rapidly growing lesion over the left zygoma. It had been present for 5 months. It was a cutaneous horn measuring 10x5 cm (Figure 1). There was no evidence of cervical lymphadenopathy. Dermatological examination revealed hypopigmented patches in a non-dermatomal pattern. Systemic examination was within normal limits. The lesion was excised totally. Histopathology revealed mild acanthosis and hyperkeratosis. The dermis showed a proliferation of epithelial cells having abundant eosinophilic cytoplasm and vesicular nuclei exhibiting abrupt keratinisation without a granular layer. The base of the lesion showed palisading of the basal layer and trichilemmal keratinisation (Figure 2). A diagnosis of trichilemmal horn was made.

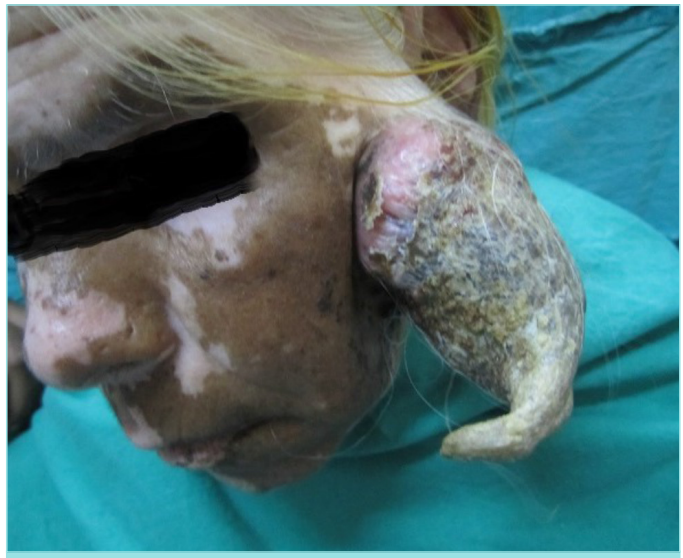

Figure 1. Trichilemmal horn over the left zygoma.

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ORCID IDs of the authors: S.P.D. 0000-0003-0442-3310; R.S.D. 0000-0003-4049-3471.

Address for Correspondence: Siddharth P. Dubhashi
E-mail: spdubhashi@gmail.com
ORCID ID: orcid.org/0000-0003-0442-3310

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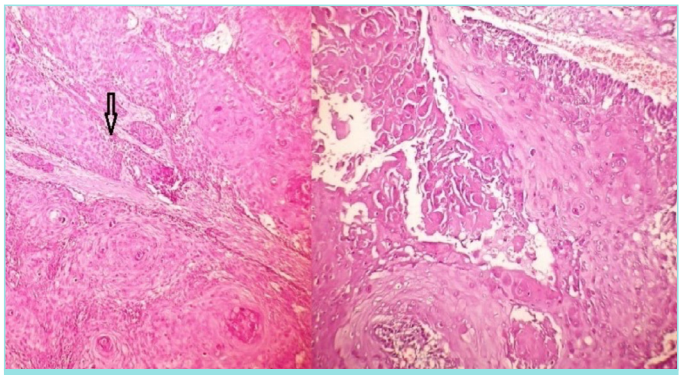

Figure 2. Photomicrograph showing, **A)** sheets of epithelial cells with palisading of basal cell layers (Arrow) (H&E, x100), **B)** Trichilemmal cells showing keratinisation without granular layer (H&E, x400).

H&E: Hematoxylin and eosin stain

DISCUSSION

The follicular tumour was first described by Headington in 1976 as trichilemmal keratosis and the term trichilemmal horn was coined by Brownstein in 1979. Trichilemmal horn presents as an exophytic keratotic lesion usually between 1 and 2 cm in diameter, mostly on the head or extremities in elderly patients. Histologically, the lesion shows a squamous cell epithelium composed of a row of palisading cuboidal cells. There is abrupt keratinisation of the epithelium without a granular cell layer forming a dense eosinophilic keratin.[2] Cutaneous horns may be associated with keratosis, verruca, trichilemma, Bowen's disease, epidermoid carcinoma, malignant melanoma or basal cell carcinoma.[4] Skin malignancies also have association with Xeroderma Pigmentosum. The reported case had no history of excessive sun exposure. There was no evidence of malignancy in the sections obtained from the base of the lesion.

Various theories have been put forth to explain the pathogenesis of trichilemmal keratosis. It is considered to originate from the outer root sheath of the hair follicles. CD 34 is a specific marker for the external root sheath epithelium of hair follicles and tumours derived from or differentiated towards this type of epithelium. Positive CD 34 immuno-staining has been seen in cases of trichilemmal keratosis.[5] It is postulated that Human Papilloma Virus (HPV) may be involved in the pathogenesis of this tumour because intra-nuclear inclusion bodies, morphologically similar to HPV, have been identified in electron microscopy studies.[6] The relationship between the development of trichilemmal keratosis and trichilemmal cyst has also been cited.[5] The lesion may also represent a phenotypic change of the epidermal keratinocytes.[7]

MAIN POINTS

- The reported case gives details regarding a rare lesion of a large trichilemmal horn.
- Complete excision of the base of the lesion is essential to establish a diagnosis.
- The diagnosis of a trichilemmal horn should be considered when a cutaneous horn shows trichilemmal keratinisation in the absence of dermal inflammation.

ETHICS

Informed Consent: Written informed consent was obtained from the patient for the publication of this case report.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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DISCLOSURES

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REFERENCES

1. Souza LN, Martins CR, de Paula AM. Cutaneous horn occurring on the lip of a child. Int J Paediatr Dent. 2003; 13(5): 365-7.
2. Haro R, González-Guerra E, Fariña MC, Martín-Moreno L, Requena L. Cuerno tricolémico: presentación de un nuevo caso y revisión de la literatura. [Trichilemmal horn: a new case and review of literature]. Actas Dermosifiliogr. 2009; 100(1): 65-8.
3. Rais JP, Tellechea O, Cunha MF, Baptista AP. Trichilemmal carcinoma: review of 8 cases. J Cutan Pathol. 1993; 20(1): 44-9.
4. Bondeson J. Everard Home, John Hunter, and cutaneous horns: a historical review. Am J Dermatopathol. 2001; 23(4): 362-9.
5. Poblet E, Jimenez-Reyes J, Gonzalez- Herrada C, Granados R. Trichilemmal keratosis: A clinicopathological and immunohistochemical study of two cases. Am J Dermatopathol. 1996; 18(5): 543-7.
6. Kimura S. Trichilemmal keratosis (horn): a light and electron microscopic study. J Cutan Pathol. 1983; 10(1): 59-67.
7. Nakamura K.Two cases of trichilemmal-like horn. Arch Dermatol. 1984; 120(3): 386-7.

CASE REPORT

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Management of an Infected Giant Dentigerous Cyst Associated with Maxillary Third Molar

Aysa Ayalı[1], Gökçe Savtekin[2]

[1]Department of Oral and Maxillofacial Surgery, Near East University, Nicosia, North Cyprus
[2]Clinic of Oral and Maxillofacial Surgery, Government Hospital, Famagusta, North Cyprus

Abstract

Dentigerous cysts are the most frequent type of developmental cysts of the jaw and the second most frequent type of odontogenic cysts after radicular cysts. Dentigerous cysts are usually asymptomatic and discovered incidentally during routine radiographic examination. Therefore, they can grow to a massive size before they are diagnosed. In some cases, cysts can become infected and patients refer with pain or swelling like symptoms. The considered definitive treatment for dentigerous cysts is the enucleation of the cyst and the extraction of the associated tooth. The purpose of the current report is to present the treatment of a large infected dentigerous cyst associated with the maxillary third molar. A 71-year-old man referred to our oral and maxillofacial surgery department with a painful swelling in the left maxillary posterior site. Intraoral examination revealed a soft, diffused, cyst like swelling in the gingivobuccal sulcus. Panoramic radiography showed a relatively large, unilateral radiolucency extending from the left canine tooth to the left tuberosity area enveloping the impacted third molar. Cone beam computerized tomography showed a cystic lesion measuring 35 mm horizontally, 27 mm vertically and 30 mm sagittally with the palatal and buccal cortical bone expanded and destructed. The cyst was totally enucleated together with the impacted third molar and the patient recovered without complication.

Keywords: Dentigerous cyst, enucleation, infection, treatment

INTRODUCTION

Dentigerous cysts (DCs) are the most frequent type of developmental jaw cysts and the second most frequent type of odontogenic cysts after radicular cysts.[1] They occur due to fluid accumulation among the reduced enamel epithelium and enamel surface of an impacted tooth,[1,2] and are form as a result of the follicle separation from around the crown of the impacted tooth.[1,3] They can occur in a wide range of age groups, mostly in men,[1,4] and most frequently involve the mandibular third molars, maxillary canine and the maxillary third molars, respectively.[5,6] DCs are usually asymptomatic and are discovered incidentally during routine radiographic examination. Therefore, they can reach a massive size before they are diagnosed. In some cases, cysts can become infected and patients refer with pain or swelling like symptoms. The considered definitive treatment of the DCs is the enucleation of the lesion and the extraction of the accompanying tooth.[7] In some cases, decompression or marsupialization may be required depending on the location and the size of the cyst, the age of the patient, the dentition and the involvement of vital structures.[7,8] The purpose of the current report is to present the case of the treatment of a giant infected dentigerous cyst associated with the maxillary third molar.

CASE PRESENTATION

A 71-year-old man referred to our oral and maxillofacial surgery department with a painful swelling in the left maxillary posterior site. Intraoral examination revealed a soft, diffused, cyst like swelling in the gingivobuccal sulcus. A panoramic radiography showed a

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ORCID IDs of the authors: A.A. 0000-0002-8817-4202; G.S. 0000-0001-8870-6603.

Address for Correspondence: Ayşa Ayalı
E-mail: aysaayali@hotmail.com
ORCID ID: orcid.org/0000-0002-8817-4202

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relatively large, unilateral radiolucency extending from the left canine tooth to the left tuberosity area enveloping the impacted third molar (Figure 1). The roots of the first premolar and second molar teeth were also involved. A fine needle aspiration was performed and yellow pus fluid was obtained. Cone beam computerized tomography (CBCT) showed a cystic lesion measuring 35 mm horizontally, 27 mm vertically and 30 mm sagittally with the palatal and buccal cortical bone expanded and destructed (Figure 2). The inferior wall of the maxillary sinus was not invaded but displaced superiorly. The patient gave informed consent for surgery and photographs. The full thickness mucoperiosteal flap was raised under general anesthesia. Since the buccal bone was totally perforated, the cyst was easily detected (Figure 3), and totally enucleated together with the impacted third molar (Figure 4). The left maxillary first premolar and second molar teeth were also extracted as they were devital and had no bony support. Microscopic evaluation revealed hyperplastic non-keratinized, stratified squamous epithelium. According to radiographic, clinical and histopathological findings, the lesion was diagnosed as an infected dentigerous cyst related with the impacted maxillary third molar tooth. The patient recovered without complication and remained under follow-up for 12 months. No complaints or complications were observed.

DISCUSSION

Dentigerous cysts account for approximately 14%–20% of all epithelium-lined cysts of the jaws.[1,9] Although dentigerous cysts can be observed in patients across a wide range of ages, they are detected most commonly in patients between 10 and 30 years of age with a slight male majority.[10] In the present case, the patient was a 71-year- old white man. A dentigerous cyst encircled the crown of an unerupted/impacted tooth by its follicle expansion, and was attached to its neck. It is important that this description be applied with certainty and that the diagnosis of dentigerous cyst is not made uncritically on radiologic findings alone, otherwise other odontogenic cyst and tumors, such as odontogenic keratocyst (OKC) or unilocular ameloblastoma involving neighboring impacted teeth, can be misdiagnosed as dentigerous cysts.[2,11] In a previous study,[12] the authors reported on 2646 pericoronal lesions which were mostly follicular tissue (67%) with no evidence of pathology. Of the remaining cases, many were dentigerous cysts (752), and 79 of these showed mucous metaplasia in the epithelial linings. Among the other pathological lesions in this sample were Odontogenic keratocysts (71), odontomas (19), ameloblastomas (13), calcifying odontogenic cysts (6), carcinomas (6), calcifying epithelial odontogenic tumors (4) and odontogenic myxoma (1).

Generally, DCs are detected during routine radiologic examination. However, in some cases, they may be found because of secondary infections.[5] Such infections may occur in a dentigerous cyst which is associated with a partially impacted tooth or by spreading from a periodontal or periapical lesion that effects the neighboring tooth as reported in the current case. Although the patient presented in this report had symptoms of infection, discovery of the cyst was late in the course of the development of the lesion as it grew to a large size, causing expansion and erosion on the buccal and palatal bone. The lesion could be clearly detected on panoramic radiograph. However, CBCT is more valuable in cases of large cystic lesions which damage the adjacent bony structures as observed in our patient. Furthermore, CBCT was useful for surgical planning.

The DC may be seen unilocular or multilocular, with well-defined radiolucency, enveloping the crown of the unerupted tooth on the radiograph.[13] The radiolucency appears in the cervix of the associated tooth. DCs seem to have more effect than other jaw cysts in causing root resorption of the adjacent teeth as presented in our case. In a previous study,[14] the authors reported that the dentigerous cyst's ability to cause root resorption may be due to its origin from the dental follicle and the potency of the latter to resorb the deciduous predecessor roots of the teeth whose crowns they surround.

The treatment approaches for dentigerous cysts are based on the age of the patient, the cyst size and site, the relationship of the anatomical structures with the cyst, and the potency for eruption into the occlusion of the unerupted tooth involved.[5,15] Usually, if the lesion is small,

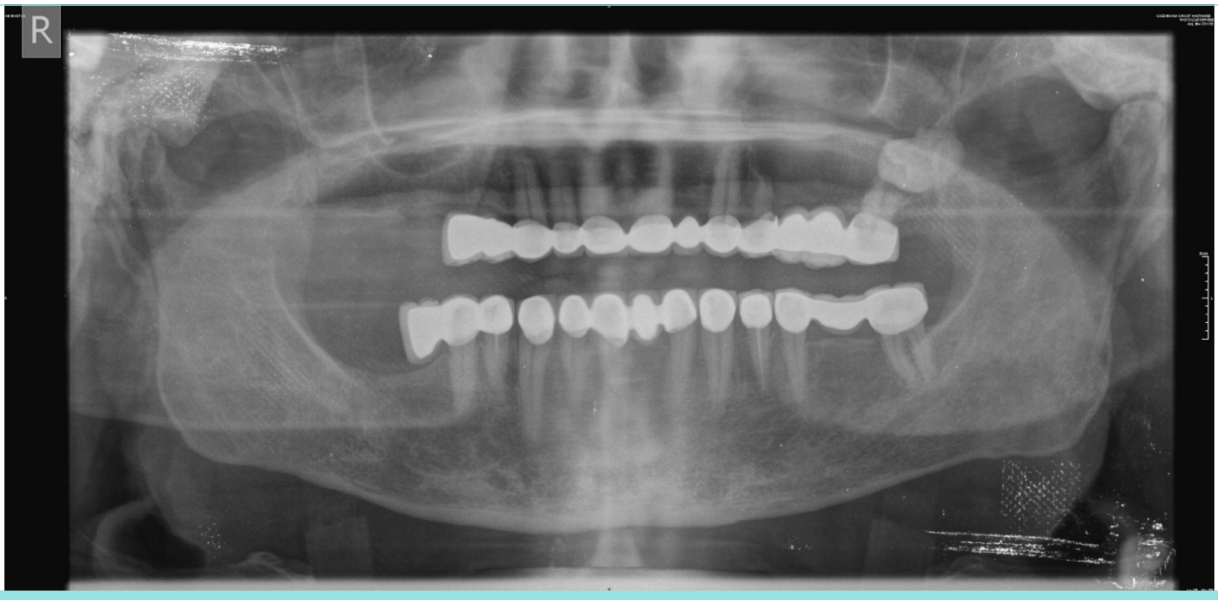

Figure 1. Panoramic radiograph of the lesion.

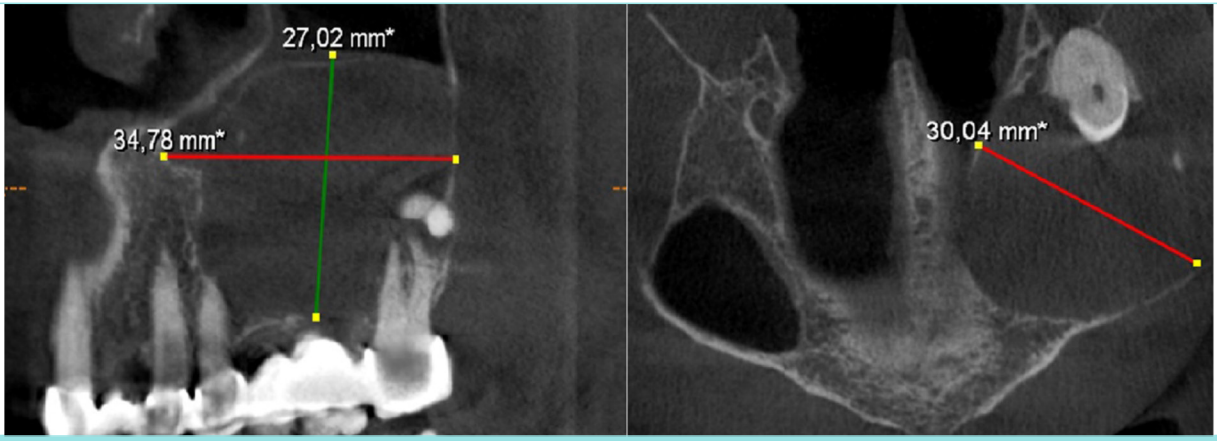

Figure 2. CBCT images of the lesion.
CBCT: Cone beam computed tomography

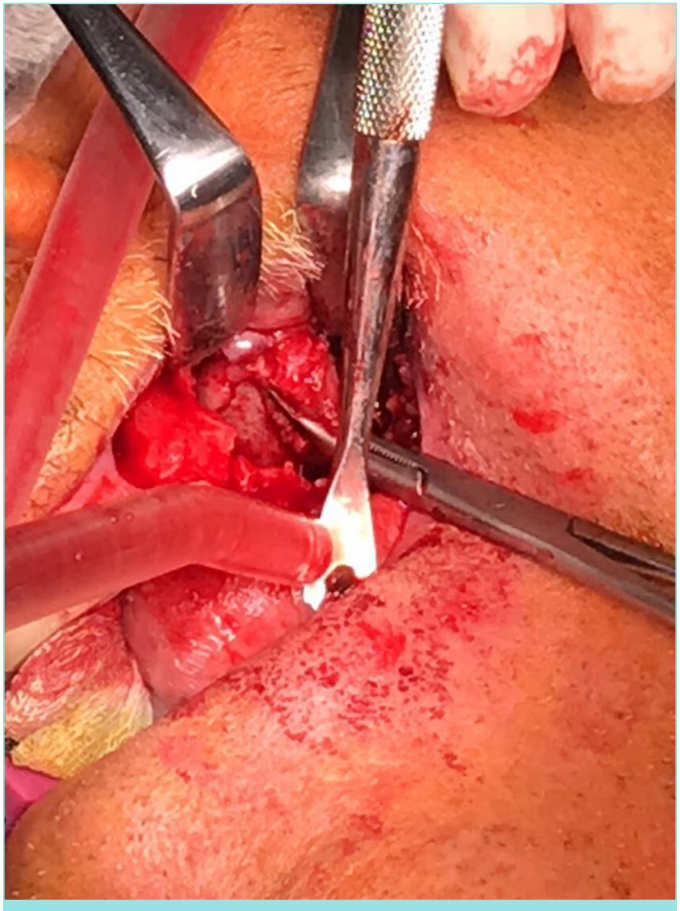

Figure 3. Intraoperative view of the cystic lesion.

enucleation together with the extraction of the associated tooth is the standard treatment for dentigerous cysts to prevent recurrence.[1,11] However, extensive cysts require marsupialization or decompression to decrease the size of the lesion before enucleation.[7] Although the lesion in the present case was relatively large, it was not involved with vital structures. Moreover, considering the disadvantages of decompression, such as discomfort for the patient due to the decompression stent, difficult oral hygiene care in the decompression or marsupialization area,

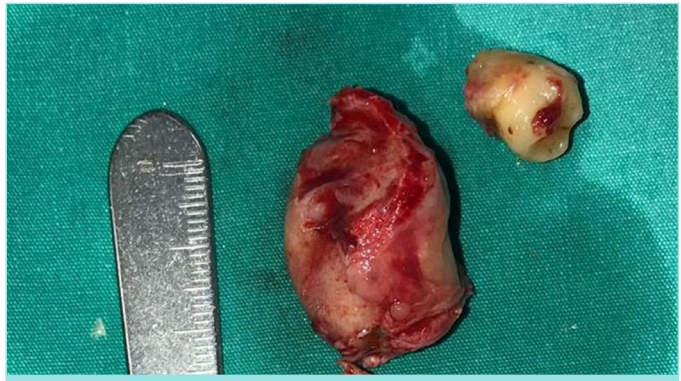

Figure 4. Enucleated cystic lesion.

especially when the dentigerous cyst is in the posterior area, and poor patient cooperation during a prolonged healing time, the immediate enucleation procedure was preferred. Some authors recommend immediate bone grafting following the enucleation procedure to fill the residual cavity.[16] However, in the present case, a grafting procedure was not preferred since the cyst was infected and there was no residual cavity left due to buccal and palatal bone destruction.

In conclusion, an early diagnosis and proper treatment planning for such cases is important to avoid further complications.

MAIN POINTS

- Dentigerous cysts can grow to a massive size before they are diagnosed.
- Dentigerous cysts can become infected and may cause pain or swelling like symptoms.
- The considered definitive treatment of dentigerous cysts is the enucleation of the cyst and the extraction of the associated tooth.

ETHICS

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.A., G.S., Design: A.A., G.S., Data Collection and/or Processing: A.A., G.S., Analysis and/or Interpretation: A.A., Literature Serach: A.A., Writing: A.A., Critical Review: A.A.

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REFERENCES

1. Shah KM, Karagir A, Adaki S, Pattanshetti C. Dentigerous cyst associated with an impacted anterior maxillary supernumerary tooth. BMJ Case Rep. 2013; 2013: bcr2012008329.
2. Anthonappa RP, Ekambaram M, Neboda CNG, King NM, Rabie AM. Genetic basis of dentigerous cysts associated with supernumerary teeth: A narrative review. J Investig Clin Dent. 2018; 9(1).
3. Dinkar AD, Dawasaz AA, Shenoy S. Dentigerous cyst associated with multiple mesiodens: a case report. J Indian Soc Pedod Prev Dent. 2007; 25(1): 56-9.
4. Neville BW, Damm DD, Allen CM, Bouquot JE. Oral and Maxillofacial Pathology, In: Oral Maxillofac. Pathol. 3rd Ed. St. Louis Saunders, 2008: pp.679-81.
5. Gendviliene I, Legrand P, Nicolielo LFP, Sinha D, Spaey Y, Politis C, et al. Conservative management of large mandibular dentigerous cysts with a novel approach for follow up: Two case reports. Stomatologija. 2017; 19(1): 24-32.
6. Scariot R, da Costa DJ, Rebellato NL, Müller PR, Gugisch RC. Treatment of a large dentigerous cyst in a child. J Dent Child (Chic). 2011; 78(2): 111-4.
7. Cakarer S, Selvi F, Isler SC, Keskin C. Decompression, enucleation, and implant placement in the management of a large dentigerous cyst. J Craniofac Surg. 2011; 22(3): 922-4.
8. Jones TA, Perry RJ, Wake MJ. Marsupialization of a large unilateral mandibular dentigerous cyst in a 6-year-old boy--a case report. Dent Update. 2003; 30(10): 557-61.
9. Xu GZ, Yang C, Fan XD, Hu YK, Yu CQ. Functional surgery for the treatment of dentigerous cyst in the maxillary sinus. J Craniofac Surg. 2015; 26(2): e84-6.
10. Bonardi JP, Gomes-Ferreira PH, de Freitas Silva L, Momesso GA, de Oliveira D, Ferreira S, et al. Large Dentigerous Cyst Associated to Maxillary Canine. J Craniofac Surg. 2017; 28(1): e96-7.
11. Kim KS, Mun SK. Extensive dentigerous cyst associated with a mesiodens: CT findings. Ear Nose Throat J. 2013; 92(8): E6-8.
12. Curran AE, Damm DD, Drummond JF. Pathologically significant pericoronal lesions in adults: Histopathologic evaluation. J Oral Maxillofac Surg. 2002; 60(6): 613-7; discussion 618.
13. Zhang LL, Yang R, Zhang L, Li W, MacDonald-Jankowski D, Poh CF. Dentigerous cyst: a retrospective clinicopathological analysis of 2082 dentigerous cysts in British Columbia, Canada. Int J Oral Maxillofac Surg. 2010; 39(9): 878-82.
14. Struthers P, Shear M. Root resorption by ameloblastomas and cysts of the jaws. Int J Oral Surg. 1976; 5(3): 128-32.
15. Henien M, Sproat C, Kwok J, Beneng K, Patel V. Coronectomy and dentigerous cysts: a review of 68 patients. Oral Surg Oral Med Oral Pathol Oral Radiol. 2017; 123(6): 670-4.
16. Scolozzi P, Lombardi T, Richter M. Upper lip swelling caused by a large dentigerous cyst. Eur Arch Otorhinolaryngol. 2005; 262(3): 246-9.