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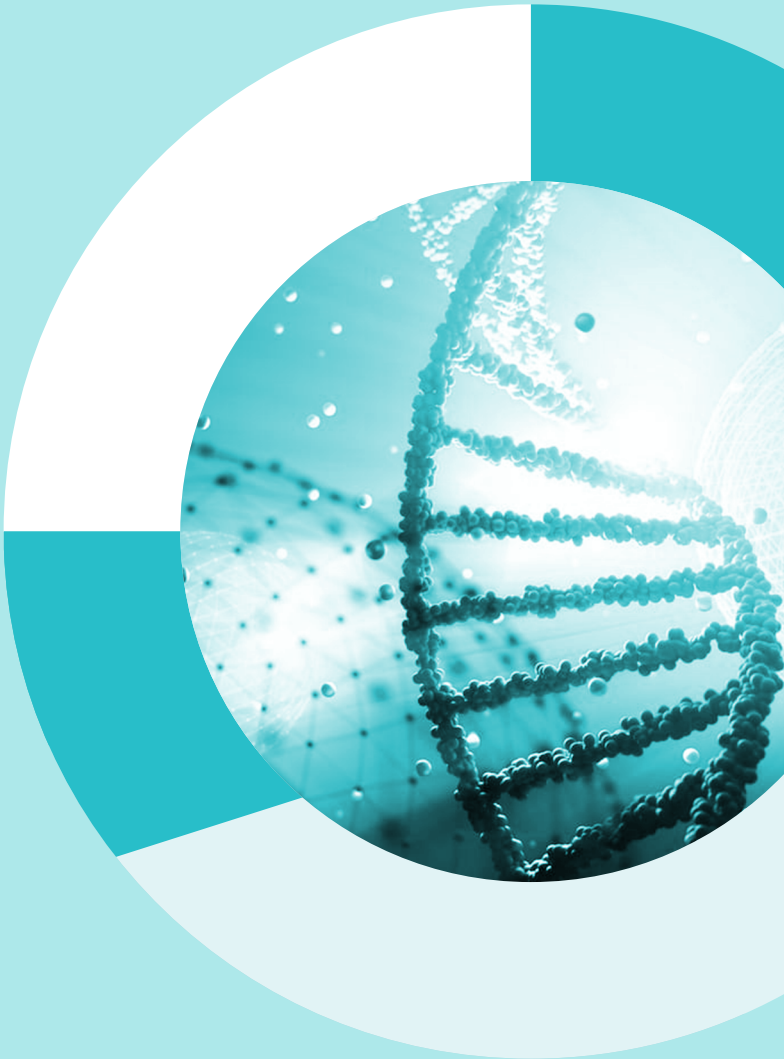
ORIGINAL ARTICLES



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.

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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.

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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.

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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.

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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:

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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.

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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:

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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.

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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.

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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.

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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.

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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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Immunoglobin G4-Related Diseases

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ABSTRACT

IgG4-related disease (IgG4-RD) is characterised by its pathological, serological, and clinical features, and its recognition is gradually increasing in the literature. This disease is generally observed in middle-aged males and older groups. IgG4 positive plasma cells and T lymphocytes infiltrate various organs, characterised by the etiology of an unknown disease. Almost all organs of the body are affected, but those most frequently affected are the pancreas, bile duct, gallbladder, salivary glands, retroperitoneal region, kidneys, lungs, and the prostate. The histopathological features of this disease are storiform fibrosis and obliterative phlebitis. Corticosteroids are useful in the treatment of this disease.

This study aims to increase the awareness of IgG4-related disease through a review of the recent literature.

Keywords: IgG4-related disease, clinical manifestations, diagnosis, treatment, recent literature

INTRODUCTION

IgG4-related disease (IgG4-RD) is an immune-mediated, systemic, fibroinflammatory disease.[1,2] However, it is not a new disease: "Mikulicz disease", "Ormond disease", "Riedel thyroiditis", "Küttner tumour" and a variety of other diseases are seen in the IgG4-RD spectrum.[3] Its most important features include tumour-like masses, IgG4-positive plasma cells, lymphoplasmacytic deposits, and typical storiform fibrosis. Serum IgG4 levels are increased in 60 to 70 percent of IgG4-RD patients.

Most patients with early-stage disease respond to glucocorticoids, but exacerbation of the disease may occur in patients after the steroids are reduced or discontinued.

Different names are used for IgG4-related diseases.[4,5] These include:

- IgG4-related disease,
- IgG4-related systemic disease,
- IgG4-syndrome,
- IgG4-associated disease,
- IgG4-related sclerosing disease,
- IgG4-related systemic sclerosing disease,
- IgG4-related autoimmune disease,
- IgG4-positive multi-organ lymphoproliferative syndrome,
- Hyper-IgG4 disease,
- Systemic IgG4-related plasmacytic syndrome,
- Systemic IgG4-related sclerosing syndrome,
- Multifocal fibrosclerosis,
- Multifocal idiopathic fibrosclerosis.

In 2001, serum IgG4 levels were detected to be high in patients with sclerosing pancreatitis (Autoimmune pancreatitis-Type 1). In 2003, these autoimmune cases were shown to be due to the involvement of other organs and blood, and autoimmune pancreatitis was considered a systemic disease. In 2012, an international study group suggested the concept of IgG4-RD.[6] IgG4-RD can affect all of the organs in the body.

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IgG4 related disease, its diagnosis, prognosis, treatment approaches, and current discussions are examined in this review.

Epidemiology

IgG4-related disease (IgG4-RD) is mostly seen in middle-aged males and older groups. However, IgG4-related sialadenitis and dacryoadenitis are slightly more predominant in women.[7] Retroperitoneal fibrosis, IgG4-related tubule interstitial nephritis (TIN), autoimmune pancreatitis (AIP), and other organ manifestations are slightly more predominant in elderly males. The gender distribution varies, according to patients with head and neck involvement.[8] In men, the disease is more common but the degree and severity of the disease in both women and men seem to be similar.[9]

Pathogenesis

The pathogenesis of IgG4-RD remains unknown.[10] Genetic predisposition, abnormal immune response (an autoimmune disorder), and allergic disorder are thought to be the underlying factors in the development of this disease.[6,11-13] No autoantigenic gene specific for this disease has been detected, and the pathogenicity of IgG4 antibodies is not fully known.[14] It was shown that the HLA-DRB1*0405 and HLA DQB1*0401 haplotypes in the Japanese population, and the HLA-DRB1*0701, and DQB1*0202 haplotypes in Koreans were related to a predisposition to type 1 AIP.[15] It was thought that the factor triggering the abnormal immune response might be microorganisms, and *Helicobacter pylori* were particularly emphasized.[16] However, later studies have shown that antibodies against PBP are associated with type 2 AIP rather than type 1 AIP. Also, it is thought that natural immunity is effective in disease development. It is mainly thought that foreign pathogen-associated with molecular patterns (PAMPs), potential self-factors, and damage-related molecular patterns (DAMPs) could be the possible triggering factors.[17]

It is still not fully understood whether IgG4-RD is an autoimmune disorder or an allergic disorder. IgG4 allergens have also been suggested to be involved in tolerance and response to specific infectious agents. Nevertheless, its physiological role is unknown.[17] High serum and tissue IgG4 levels are not specific in IgG4-related diseases. These may increase in many other diseases such as allergic disorders, Churg-Strauss syndrome, Castleman's disease, and sarcoidosis.[18] Evidence relating to allergic response includes eosinophilia seen in 40% of patients, high Th2 cytokine levels and serum IgE in the tissues affected by the disease, and a raised association with allergic rhinitis and bronchial asthma.[17] Antinuclear antibodies and rheumatoid factors may also be detected in some of those patients mentioned above.[19] There are a large number of T regulatory cells (Tregs) in peripheral circulation and the levels of interleukin (IL)-10 and transforming growth factor (TGF) produced by Tregs in the affected tissues are increased.[20,21] These cytokines help the output of IgG4.[22]

Previously, the IgG4 molecule was thought to be a direct cause of tissue injury. However, it is now known that IgG4 is not a primary element in this pathophysiology. It seems that T follicular helper cells drive the passage of the class into IgG, perhaps through the secretion of IL-4.[23]

B cells, plasmablasts in particular, play an essential role in IgG4-RD. IGG4$^+$ plasmablast may present the antigen to T cells.[24]

According to recent evidence, T-cells play a primary role in IgG4-RD pathogenesis. In IgG4-RD-affected tissues, CD4$^+$ T-cells accumulate throughout the lesions.[25]

Clinical Manifestations

One or more organs may be affected in IgG4-RD. Patients usually show the development of a mass in the affected organ (e.g., an orbital pseudotumor, nodular lesions in the lung, a renal mass resembling renal cell carcinoma) or diffuse enlargement of an organ (e.g., the pancreas).[1,8,26]

Painless swelling is observed in the organs. There may be multiple organ involvement in more than 60 percent of IgG4-RD cases.[27,28] Standard features in the affected tissues are histopathological, storiform fibrosis, obliterative phlebitis, and high serum IgG4 concentrations. Lymphadenopathy is quite common, and allergy and asthma symptoms occur in about 40% of patients.[17,29] Symptoms of systemic disease such as fever and weakness are usually not seen. IgG4-RD is often incidentally diagnosed during radiological imaging or histopathology.[17]

The most common clinical manifestations are as follows:

Type 1 (IgG4-related) autoimmune pancreatitis (AIP)

IgG4-related sclerosing cholangitis

IgG4-related dacryoadenitis and sialadenitis (Mikulicz disease)

Sclerosing sialadenitis (Küttner's tumour, IgG4-related submandibular gland disease)

IgG4-related orbital inflammation or orbital inflammatory pseudotumor

IgG4-related thyroid disease

IgG4-related respiratory disease

IgG4-related aortitis or periaortitis (chronic sclerosing aortitis and periaortitis)

Ormond's disease (IgG4-related retroperitoneal fibrosis),

IgG4-related kidney disease

Hypophysitis

Pachymeningitis

IgG4-RD is relatively rare, but recently, the awareness of this disease has increased, rheumatologists consult it more frequently, and earlier diagnosis is made.[1,2,11,17,30] Nevertheless, IgG4-RD it is usually detected incidentally by a radiologist or pathologist. Sometimes IgG4-RD remains localized to a single organ for months or even years, e.g., the salivary or lacrimal glands. It may also sometimes show signs of multiple organ involvement at the time of diagnosis.[31] According to different studies, the organ frequencies of the disease are different.[32]

Lymphadenopathy: In IgG4-related diseases, asymptomatic lymph node enlargement is the most common finding in 80 percent of patients with AIP.[32] The diagnosis of IgG4-RD by lymph node biopsy alone is quite difficult because lymph node biopsy rarely shows the degree of storiform fibrosis observed in other organs.[31]

Salivary and lacrimal gland involvement: Painless swelling in the upper eyelid, changes in facial appearance, and swelling of the submandibular gland, and parotid gland areas provide clues to the diagnosis.[17]

For example; Mikulicz disease is lacrimal, parotid and submandibular gland enlargement, and was previously called sclerosing sialadenitis (Küttner tumour).[33] Sikka symptoms are so mild that differential diagnosis with Sjögren syndrome is required. Dry mouth, dry eyes, and arthralgia are less common findings, compared to those patients with Sjögren syndrome. Allergic rhinitis, asthma, AIP, and interstitial nephritis are common. RF, ANA, Anti-SSA, and anti-SSB positivity is lower.[17,34]

Orbital disease: 25%–50% of orbital pseudotumors appear to be caused by IgG4-RD which was previously known as benign lymphoid hyperplasia. With the use of IgG4-RD diagnostic criteria, it was found that 5%–25% of cases called non-granulomatous idiopathic orbital inflammation are IgG4-RD.[35]

Autoimmune pancreatitis (AIP): AIP constitutes 2% of chronic pancreatitis cases. Its main clinical features are upper abdominal disturbance and jaundice. Due to endocrine and exocrine dysfunction of the pancreas, patients may sometimes complain of impaired glucose tolerance and also develop diarrhoea. Type 1 (IgG4-related) AIP should be differentiated from pancreatic cancer. Radiological methods such as ultrasonography (USG), computed tomography (CT), and endoscopic retrograde cholangiopancreatography (ERCP) can be used for differential diagnosis.[17]

Thyroid gland (Riedel thyroiditis): The two forms of involvement of IgG4-RD in the thyroid gland are IgG4-related thyroid disease and Hashimoto's disease.[36,37] There is usually massive growth in the thyroid gland due to lymphocytic infiltration; therefore, surgery is often required for treatment.[17]

IgG4-related sclerosing cholangitis: For a long time, such patients were defined as having "primary sclerosing cholangitis", which was responsive to glucocorticoids. Nowadays, according to histopathological findings obtained from biopsies of such patients (for example renal biopsies), they are considered to have IgG4-RD.[31]

Lungs (IgG4-related interstitial pneumonitis, IgG4-related lung disease): Many respiratory diseases have been reported that include bronchial and alveolar conditions. Most patients are asymptomatic but some patients can have cough, dyspnoea, chest pain haemoptysis and pleurisy. Furthermore, interstitial pneumonia and pseudotumor can be seen.[38,39]

Bronchi and bronchial wall thickening may also be detected via a CT scan. The affected tissues demonstrate characteristic lymphoplasmacytic infiltrates enriched in IgG4-positive plasma cells; some patients show abundant storiform fibrosis. Patients with bronchial lesions have asthma-like symptoms. Sometimes, interstitial and organized pneumonia is detected on CT.[17] Pulmonary involvement of IgG4-RD may be confused with sarcoidosis.[40] The use of the specific criteria for IgG4-RD is recommended for differential diagnosis.[17]

Retroperitoneal fibrosis and related disorders: Retroperitoneal fibrosis is a rare disorder characterized by the presence of inflammatory and fibrous retroperitoneal tissue, often involving the ureter or abdominal organs.[41] This condition is prevalent in IgG4-RD. Most of the cases with retroperitoneal fibrosis were considered "idiopathic" in the past.[42] Some drugs and malignancies are involved in the etiology of retroperitoneal fibrosis. However, an etiologic factor cannot be detected in most patients. Generally, the affected areas are around the thoracic and lumbar vertebrae, abdominal aorta, major branches of the aorta, and the ureter. CRP levels are usually found to be elevated.[17]

The association of retroperitoneal fibrosis and chronic periaortitis was previously known as Ormond's disease, which is currently classed as an IgG4-related disease.[43] Other IgG4-related diseases include sclerosing mesenteritis, sclerosing mediastinitis, and multifocal fibrosclerosis.[44-46]

Renal disease: Renal involvement in IgG4-RD is mainly seen in two significant presentations: One is a mass lesion similar to renal cell carcinoma, and the other is tubulointerstitial nephritis. The mass lesions may be bilateral and multiple, and tubulointerstitial nephritis characteristic features are observed in biopsy in IgG4-related kidney disease. Laboratory findings are subnephrotic proteinuria and moderate hypocomplementemia with levels of serum C3 and C4 components in this situation. In some patients, azotemia may occur later, and end-stage renal failure has also been observed and reported on.[31]

Other system involvements:

CNS involvement, IgG4-related hypophysitis, and pachymeningitis

Skin disease

Prostate gland

Pericardium (constrictive pericarditis)

Bone-destructive lesions in the middle ear[31]

The IgG4-related disease of the ovary[46]

Sclerosing mastitis and inflammatory pseudotumor of the breast[47,48]

Hepatic inflammatory pseudotumor, and similar to autoimmune hepatitis

Diagnosis

In Japan, diagnostic criteria have been used routinely since 2011. These criteria include:

Diffuse/focal swelling or mass in a single or multiple organs (clinic, physical examination, imaging)

IgG4 levels (≥135 mg/dL)

In histopathological examination; Lymphocyte and plasmocyte infiltration and fibrosis, Ig-G4 (+) plasma cell infiltration (IgG4 (+) / IgG (+) plasma cell ratio> 40% and> 10 IgG4 (+) plasma cells at each high magnification field)

Definitive Diagnosis: 1+2+3

Probable Diagnosis: 1+3

Possible Diagnosis: 1+2

(Other diseases should be excluded, criteria for specific diseases should be used) (Figure 1).

All criteria must be met for a definitive diagnosis. The 'Probable IgG4-RD' diagnosis is made when the physical and histopathological

criteria are met but the serological criteria are not met. In cases where serological and physical criteria are met but histopathological criteria are not met, a "possible IgG4-RD" diagnosis is made. Moreover, another important consideration is the exclusion of malignancy in the diagnosis of IgG4-RD.[17]

Diagnostic Studies

Serum IgG4 concentration: Serum IgG4 levels of most IgG4-RD diagnosed patients are high. However, serum IgG4 concentration is found to be normal in approximately 30% of patients despite the classic pathological findings of IgG4-RD. Monitoring IgG4 concentrations during treatment is not appropriate for the disease activity. As IgG4 concentrations are high at the baseline, in most patients, corticosteroid may decrease IgG4 concentration during treatment and it may even reach normal levels. Each patient should be evaluated individually for their follow-up and treatment.[31]

Other laboratory findings: Only a small number of patients may show mild high C-reactive protein (CRP) and erythrocyte sedimentation rates (ESR). In most cases, acute phase reactants are normal. Mild to moderate peripheral eosinophilia is frequent in IgG4-RD patients, being at a rate of approximately 20%. Also, mild hypocomplementemia can be detected in IgG4-RD, which is mainly the third and fourth components of the complement. IgG4-RD with tubulointerstitial nephritis may also have subnephrotic proteinuria.[31]

Imaging studies: A computed tomography (CT) scan of the chest, abdomen, and pelvis is generally preferred for the diagnosis of IgG4-RD, due to the numerous subclinical diseases and the lack of specific laboratory findings. CT scans are useful in the major conditions of pulmonary, pancreatic, and renal disease of IgG4-RD.[31]

Additional imaging studies may be required in some patients, particularly if orbital involvement is suspected. Typical imaging features on magnetic resonance imaging (MRI), CT or PET scans involve organs wrapped by inflammatory and fibrous tissue, and diffuse or focal organ infiltration.[46]

The algorithm for IgG4-RD diagnosis is shown in Figure 1.

Differential Diagnosis

Many diseases are included in the differential diagnosis of IgG4-RD. The diagnosis depends on the patient's clinic and the place of the affected organ or tissue. Firstly, it should be distinguished from other rheumatologic, oncologic, or infectious diseases.[17,30] In Table 1, the differential diagnosis of IgG4-RD is shown (Table 1).[30]

Treatment

The optimal treatment for IgG4-RD is unknown. The general approach is to manage the follow-up and treatment of the disease based on the

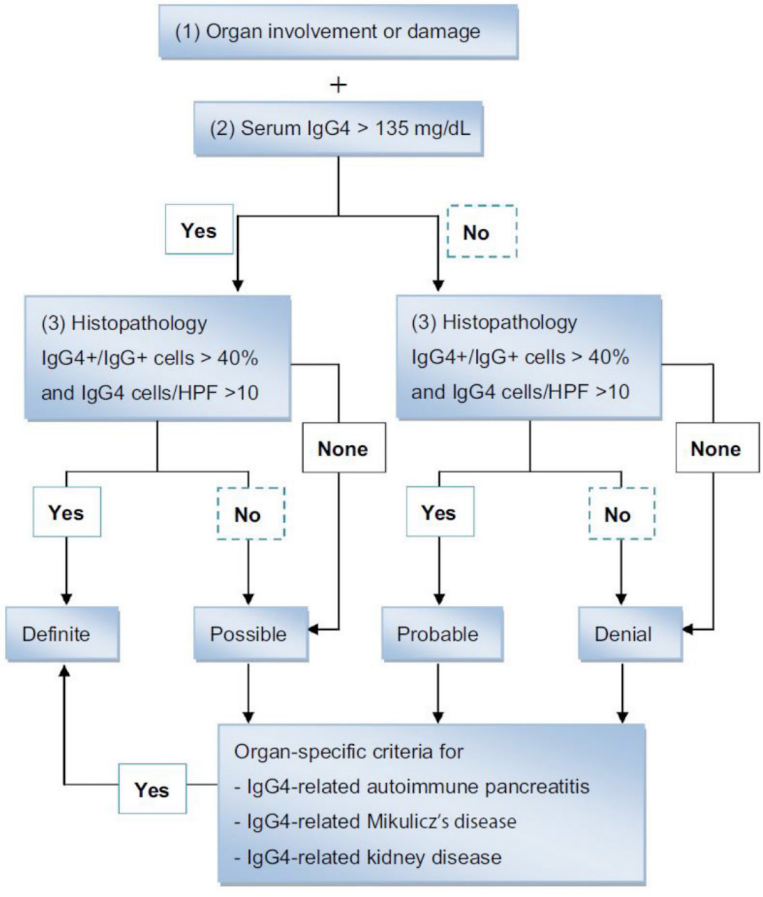

Figure 1. Diagnostic approach algorithm.
HPF: high-power field

dysfunction status of the involved organ and the case studies in the literature.

Treatment is usually started with 0.6 mg/kg/day prednisolone. This dose is continued for 2–4 weeks, followed by a 10% reduction in the dose every two weeks.[17,29] While it is not known whether maintenance therapy is required after remission, it is recommended to continue the prednisolone treatment at a dose of 5–10 mg/day due to high recurrence rates.[17] Some patient with IgG4-RD, whose disease cannot be controlled with steroid monotherapy, require glucocorticoids and other immunosuppressive agents (e.g. methotrexate, azathioprine, mycophenolate mofetil). B cell depletion with rituximab appears to be successful due to the long-term toxic effects of steroid therapy or in cases of resistance to conventional therapies or in patients with relapse. There are no randomized studies regarding the effects of rituximab. However, since rituximab provides a rapid decrease in blood plasmablast concentrations, it appears to be a useful approach for those patients with recurrent or refractory disease.[24,29]

Prognosis

Until recently, the natural course of IgG4-RD was not precisely defined. Organ dysfunction often improves with treatment. Primary unresponsiveness to glucocorticoid therapy is extremely rare in IgG4-RD patients. Therefore, the prognosis is particularly good with treatment, but relapse rates are quite high.[13,17] Problems causing morbidity and even mortality can be observed in many untreated patients that have retroperitoneal fibrosis, aortic aneurysms, portal hypertension and cirrhosis, diabetes mellitus, and kidney diseases.[46] For this reason, systemic and long-term follow-up is particularly needed in patients with IgG4-RD.

Complications: IgG4-RD can cause severe organ failure and tissue damage if early diagnosis and appropriate evaluation are not performed. However, most patients show a subacute course. Some patients may become fulminant from the onset of the disease for several weeks. Destructive bone lesions similar to Wegener's granulomatosis may occur in the sinuses, middle ear spaces, and head in some patients with IgG4-RD. Untreated cholangitis may progress to fulminant hepatic failure within months. Aortitis and periaortitis due to IgG4-RD can cause aorta aneurysms and dissections. When IgG4-RD tubulointerstitial nephritis occurs, renal functions are impaired, and even end-stage renal failure may develop.[29,30] Consequently, early diagnosis, appropriate evaluation, and optimal treatment modalities should be implemented. Patients should be monitored closely, and awareness about their relapse management should be kept in mind.

Table 1. The differential diagnosis of IgG4-related disease

Systemic autoimmune conditions and vasculitis
Sjögren syndrome
Granulomatosis with polyangiitis (Wegener granulomatosis)
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)
Giant cell arteritis
Takayasu arteritis
Granulomatous disorders
Sarcoidosis
Fungal infections (histoplasmosis, blastomycosis, coccidioidomycosis)
Malignancies
Lymphoma, particularly MALT lymphoma
Multicentric Castleman disease
Adenocarcinoma of the pancreas
Renal cell carcinoma
Bronchoalveolar carcinoma of the lung

MALT: mucosa associated lymphoid tissue.

Risk of malignancy: There are some studies showing that the risk of malignancy increases within a few years after patients are diagnosed with IgG4-RD, but other studies have found it to be unrelated.[47] In a study conducted on 158 patients in Japan between 1992 and 2012, it was found that the risk of malignancy was slightly increased in 109 patients with type 1 autoimmune pancreatitis. The most common malignancies were as follows: the lung, colon, prostate, stomach, and pancreas (the total number of malignancies was 34).[48]

Several cancer cases have also been reported in case reports including salivary duct carcinoma, pancreatic cancer, small cell and adenocarcinoma of the lung and gastrointestinal clear cell sarcoma.[11]

CONCLUSION

In the future, studies are needed to better explain the risk of malignancy in patients with IgG4-RD.

MAIN POINTS

- IgG4-RD is a chronic inflammatory disorder that shows various organ involvement.
- Serum IgG4 levels may be high in the disease and show specific histopathological features.
- There is an increase in T helper-2 and Treg-associated cytokines in IgG4-RD.
- It is essential to assess systemic organ deficiencies at diagnosis and during the follow-up of the disease and to screen for underlying malignant diseases.
- Glucocorticoids are highly effective in treatment; nevertheless, it is quite common to discontinue treatment due to relapses after reduction or side effects.[17]

ETHICS

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Concept: M.T., R.T., Design: M.T., R.T., Data Collection and/or Processing: M.T., R.T., Literature Search: M.T., R.T., Writing: M.T., R.T.

DISCLOSURES

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REVIEW

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Adult Basic Life Support Practices During the COVID-19 Pandemic Period

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ABSTRACT

Coronavirus disease 2019 (COVID-19), a global epidemic, has been spreading rapidly all over the world since December 2019. Contamination can be caused by the penetration of respiratory droplets into the mouth, nose or eyes of people or by contact of the hands with the mouth, nose or eyes after touching surfaces where respiratory droplets adhere. Shortness of breath, high fever, dry cough, and loss of the sense of taste and smell are common symptoms in patients. Basic life support applied in cardiac arrest increases the survival chance of these patient. However, during the COVID-19 pandemic period, it is known that patients, rescuers and healthcare workers are at risk during basic life support applications due to the contagiousness of the virus. Due to all of these, basic life support guidelines have been updated and some applications that emphasize the safety of rescuers have been made. In this study, changes for basic life support to be applied in patients with a diagnosis of COVID-19 or with high suspicion of COVID-19 who developed cardiac arrest were discussed.

Keywords: COVID-19, cardiac arrest, basic life support

INTRODUCTION

In December 2019, an increase in pneumonia cases of unknown cause began to be seen in Wuhan, in China's Hubei Province. On January 7, 2020, it was revealed that this situation was a new type of coronavirus and it developed as a result of human-to-human transmission.[1] The new virus was named Severe Acute Respiratory Syndrome (SARS) Coronavirus 2 (SARS-CoV-2) due to its similarity to SARS Coronavirus (SARS-CoV), which is the agent of Acute Respiratory Syndrome (The Severe Acute Respiratory Syndrome, SARS). This newly formed disease, where the virus is the causative pathogen, was declared a global pandemic by the World Health Organization (WHO) on March 11, 2020.[2,3] Coronavirus disease 2019 (COVID-19), which spread rapidly around the world, infected more than 44.5 million people in total and caused more than 1.1 million deaths, according to the data as of October 30, 2020. These numbers still continue to increase.[4]

The virus can be transmitted when respiratory droplets emitted from sick people enter the mouth, nose or eyes of others or after touching surfaces where respiratory droplets are present and subsequently touching the mouth, nose or eyes. Contact with secretions that can pass from the sick person has an important place in the contamination of the virus.[5,6] Since viruses can be detected in the respiratory secretions of asymptomatic patients, these people can also be contagious. Although the duration of contagion is not known, it is thought that it starts 1–2 days before the symptomatic period and ends with the disappearance of symptoms. In general, the incubation period varies between 2–14 days, while the median incubation period is 4.8 days.[5,7]

The COVID-19 infection is seen with many different symptoms. The most common symptoms are; shortness of breath, fever and dry cough. Apart from this, headache and sore throat, extreme weakness, loss of appetite, loss of taste and smell and diarrhea are seen. In severe cases, pneumonia, severe acute respiratory infection, kidney failure, and even death may occur.[5] Hypoxemic respiratory failure due to acute respiratory infection, ventricular arrhythmias, myocardial damage and shock are common in critically ill COVID-19 patients, making these

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patients susceptible to developing cardiac arrest.[8] During the COVID-19 pandemic, it was determined that cardiac arrest cases increased 58% in the Lombardy region of Italy, and 77% of these cardiac arrest cases were confirmed or suspected of being positive COVID-19 cases.[9] In Paris and the surrounding suburbs, it was stated that the incidence of cardiac arrest increased by two times in parallel with the increase in the number of admissions to hospitals due to COVID-19.[10]

Cardiac arrest is the cessation of cardiac functions, or the inability to take a pulse from the arteries. It is a clinical picture that progresses suddenly and unexpectedly with loss of respiration and consciousness. In cardiac arrest situations, basic life support (BLS) applications should be started quickly and effectively. Knowing the appropriate BLS steps and applying them increases the survival chance of the patient in cardiac arrest situations. Success of the BLS implementations require having sufficient knowledge.[11-13] BLS; This is a life-saving application consisting of the quick identification of unresponsive, non-breathing people outside the hospital, activation of the emergency system, chest compressions and artificial respiration cycles, and automatic external defibrillator application, which is included in basic first aid issues. BLS guidelines applied in order to bring the patient back to life in cases of cardiac arrest are updated every five years.[11,12,14] However, during the COVID-19 pandemic period, due to the contagiousness of the virus, the BLS guidelines were updated and some applications were made that emphasized the safety of rescuers/first aiders. In addition to saving the life of the person who had a cardiac arrest, the updates considered the health and safety of the rescuer. Every cardiac arrest case should be considered as a suspected COVID-19 case and the patient should be approached accordingly. Otherwise, infection rates will inevitably increase.[3,15,16]

Basic Life Support Practices in Suspected or Verified COVID-19 Adult Patients

Basic Life Support Practices by Non-Specialist People (First Aiders) (Figure 1)

- If the patient is unresponsive and does not breathe normally, a diagnosis of cardiac arrest should be carried out.
- Consciousness should be assessed by loud shouting to the patient and shaking the patient. During the respiratory assessment, it should be checked whether the patient is breathing normally. At this stage, the airway should not be opened and the rescuer should not bring his/her face close to the patient's mouth or nose to avoid a risk of infection.
- If the patient is unresponsive and breathing abnormally, the emergency health system should be activated.
- During the single-rescuer application, if possible, a phone call with emergency health professionals should be made without using the hands by means of a speakerphone.
- Rescuers should begin BLS practices after activating the emergency health system. While applying cardiac massage/chest compression to the patient, the patient's mouth and nose should be covered with a face mask, cloth or towel-like material. In this way, it is possible to prevent the spread of the virus through the respiratory tract during cardiac massage.
- Non-specialist rescuers should follow all directions from healthcare professionals until they arrive at the scene.
- After BLS applications, the rescuer should wash their hands with soap and water as soon as possible or disinfect their hands with an alcohol-based gel or solution.
- Rescuers should contact a healthcare provider because of suspected or confirmed cases of COVID-19 following BLS applications.[3,8,15,17]

Adult Basic Life Support Practices Performed by Pre-Hospital Health Professionals (Emergency Medical Staff/Emergency Call Center Personnel)

- Pre-hospital health professionals should give instructions to uneducated rescuers about chest compressions.
- If possible, the person(s) in the vicinity should be directed to bring the automatic external defibrillator (AED) to the scene.
- Due to a risk of infection, healthcare professionals are required to wear personal protective equipment. If there is an indication, only defibrillation should be applied to the patient (if the patient is suspected of being COVID-19 positive).

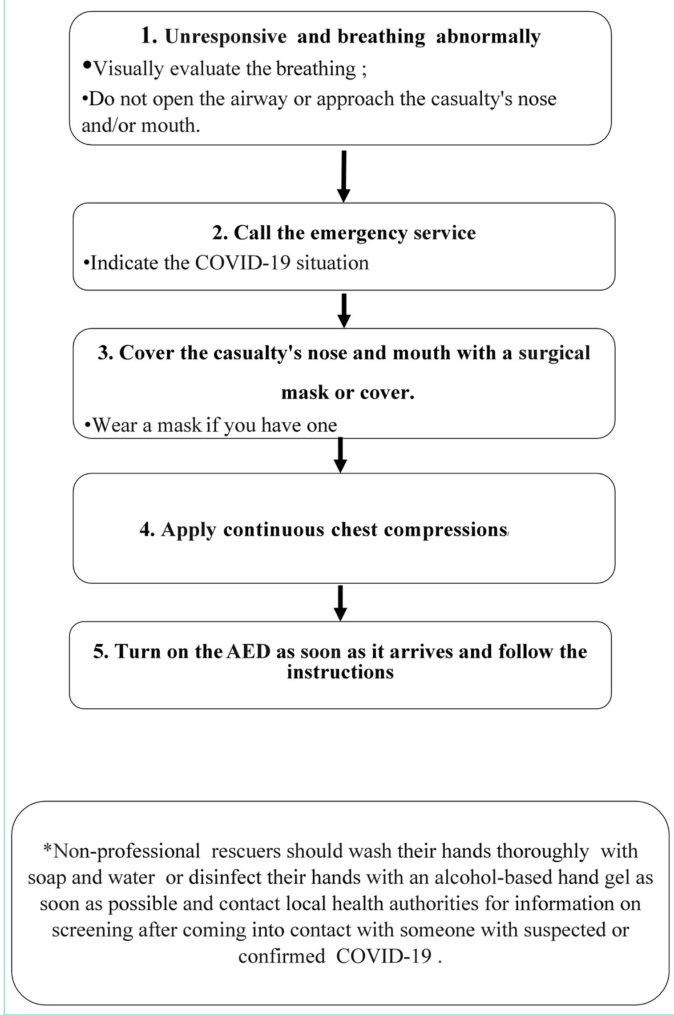

Figure 1. Basic life support practices by non-specialist people (first aiders).

AED: automatic external defibrillator, COVID-19: coronavirus disease 2019

- During the response to diagnosed or suspected COVID-19 cases, rescuers should be guided about access to personal protective equipment and training as healthcare providers, as well as healthcare professionals working in the pre-hospital area and referral units, are entitled to be protected against the risk of COVID-19 transmission.[3,8,15,17]

Adult Basic Life Support Practices Made by Health Care Professionals (Figure 2)

- Health professionals who will provide care in this regard; These should consist of health professionals who have easy access to personal protective equipment suitable for respiratory tract contamination measures and have been trained in this regard.
- Vital signs should be checked and the diagnosis of cardiac arrest should be made.
- The pads of AED and defibrillator devices that will be applied to give electroshock to patients can be used easily. However, with the help of personal protective equipment (liquid-resistant surgical mask, eye protection, gowns and gloves), precautions should be taken against contamination by droplets.
- Healthcare professionals should wear personal protective equipment during basic life support practices (cardiopulmonary resuscitation, maintaining airway clearance and breathing).
- In order to prevent aerosol risk, cardiac massage should be interrupted during ventilation and only heart massage should be applied with 30:2 balloon-valve-mask (BVM) and oxygen. However, if the rescuer team is inexperienced in this regard and is not comfortable with BVM ventilation, the use of BVM is not recommended. They should give oxygen to the patient with an oxygen mask and only perform a heart massage.
- Healthcare professionals should use a bag-mask due to the risk of aerosol formation.
- An oxygen mask should be placed on the patient's face and oxygen should be given like this.
- The mask should be held with both hands to prevent air leakage. However, in cases where there is only one rescuer, after 30 heart massage strokes, air should be provided with a bag.
- In order to minimize the risk of the virus spreading, a high efficiency particulate air filter or heat and moisture exchanger filter should be used between the self-inflating bag and mask.
- A defibrillator or automatic external defibrillator should be applied to the patient in accordance with the instructions.[3,8,15,17]

CONCLUSION

Basic preventive measures against COVID-19, for which there is no specific treatment, are life-saving.

The risk of contamination makes it difficult to perform many routine applications used during clinical practice.

Given COVID-19's prevalence, all cardiac arrest individuals should be treated as possible COVID-19 cases.

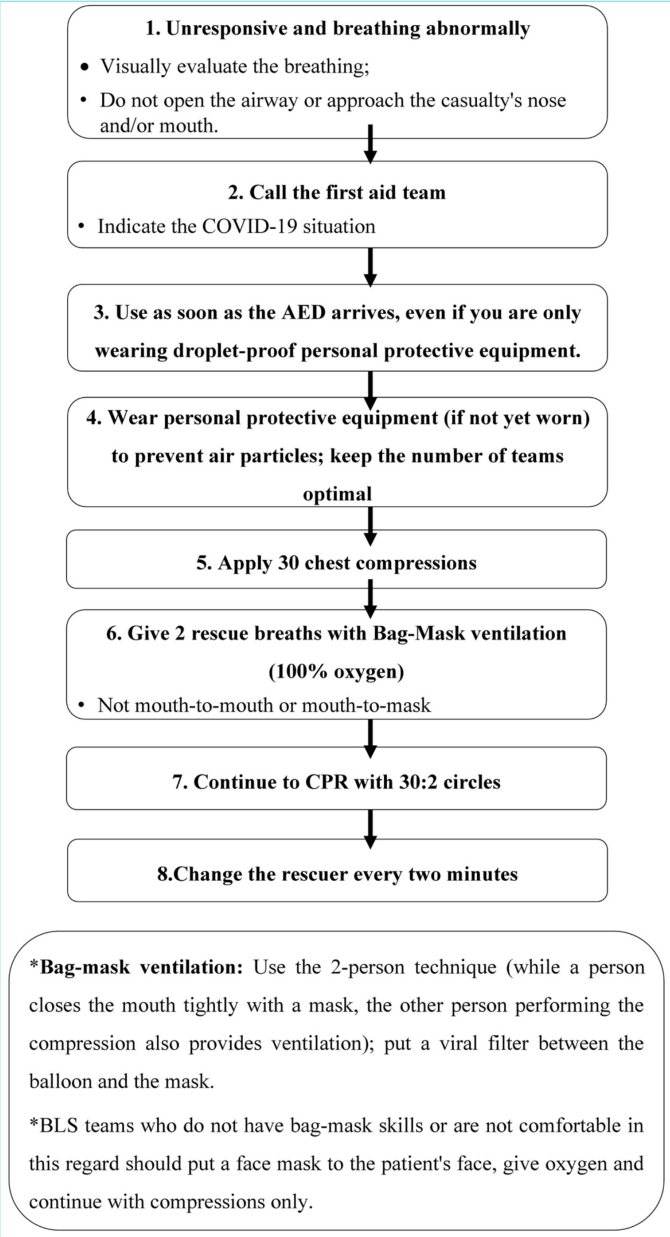

Figure 2. Adult basic life support practices made by health care professionals.

AED: automatic external defibrillator, CPR: cardiopulmonary resuscitation, BLS: basic life support

MAIN POINTS

- While the COVID-19 pandemic is still ongoing, the most at-risk groups affected by the virus are first aiders and healthcare professionals.
- The new directives and guidelines published in order to prevent the transmission of the virus should be followed and implemented.
- Each patient may be a virus carrier or an asymptomatic case. This detail should not be forgotten and the patient should be approached in this way during first aid intervention.

The importance of personal protective equipment has increased even more in this period. It is very important to wear the correct equipment

(gloves, masks, eye protectors, etc.) in cases where mandatory intervention is required.

ETHICS

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Authorship Contributions

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DISCLOSURES

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ORIGINAL ARTICLE

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Evaluation of Drug-Drug Interactions and Side Effects in COVID-19 Patients in an Intensive Care Unit

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ABSTRACT

BACKGROUND/AIM: Considering comorbidity rates in patients diagnosed with coronavirus disease 2019 (COVID-19), polypharmacy will be inevitable when the treatment for COVID-19 is added to the treatment of existing chronic disease conditions. In our study, we evaluated the effects of comorbidities, drug-drug interactions and complications on the clinical course of the disease in COVID-19 patients.

MATERIALS AND METHODS: This study was conducted retrospectively with thirty five COVID-19 patients of various age and gender groups who had been admitted to the intensive care unit in a university hospital in March and April, 2020. The demographic, laboratory and clinical data were collected.

RESULTS: In our study, the average number of days intubated in patients with acute respiratory distress syndrome and sepsis was found to be statistically significantly higher than those without complications. serious-use alternative interaction was detected in 85.7% of the patients, monitor closely interaction in 60%, and minor interaction in 34.3%. In 88.6% of the patients, at least one of these interactions was observed, while all three interactions occurred at the same time in 20% of them.

CONCLUSION: According to the results of this study, managing the risks, interventions such as drug dosage adjustment, and drug changes and monitoring of any parameters that may indicate drug side effects for the patient may be necessary.

Keywords: COVID-19, intensive care unit, drug-drug interactions, comorbidities, complications

INTRODUCTION

On April 10, 2020, the World Health Organization (WHO) identified the coronavirus disease 2019 (COVID-19) disease as a pandemic, and an estimated 2.3% of patients needed tracheal intubation. Death rates of up to 60% have been reported in critically intubated patients. According to the results of large studies conducted in the United States, 12 to 24 percent of hospitalized patients required mechanical ventilation due to respiratory-related complications.[1]

There is no accepted standard treatment to be applied for the pharmacological treatment of patients with COVID-19 to date. The fact that the treatment strategies are not clearly defined causes confusion about the management of this disease in intensive care units, and when the presence of comorbidities and polypharmacy in patients are added, the situation becomes more complex.[2]

Acute respiratory distress syndrome (ARDS), sepsis, septic shock, arrhythmia, myocarditis, cardiogenic shock and acute kidney injury are conditions that requires patients to be taken into intensive care, and all of them are among the complications of COVID-19.[3]

It is important to pay attention to the pharmacological effects and number of drugs administered to manage a patient's condition. Although those who work in intensive care units are specialist healthcare professionals, some errors may still occur in some cases. Some of the

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main reasons underlying these errors are polypharmacy, inadequate compliance with the principles of rational drug use and drug-drug interactions. Furthermore, the most important factor causing drug-drug interactions is polypharmacy. When the literature is reviewed, it is observed that as the number of drugs used by the patient increases, the rate of drug-drug interaction increases. When the number of drugs used by the patient is more than 5, the drug interaction rate increases by 21%, when this number increases to 10 or above, the interaction rate reaches 100%.[4]

It is a common fact that the use of hydroxychloroquine concomitantly with other drugs that prolong the QT period should be avoided. However, our knowledge about the potential drug-drug interactions that can be caused by drugs used in the treatment of COVID-19, especially antiviral drugs, is limited.[5]

Our study was conducted retrospectively with COVID-19 patients who were admitted to the intensive care unit of a university hospital in March and April, 2020. In our study, we evaluated the effects of comorbidities, drug-drug interactions and complications on the clinical course of the disease in COVID-19 patients.

MATERIALS AND METHODS

The study was approved by the research Ethics Committee of the İstanbul Medipol University (10840098-604.01.01-E.17838). Our study was conducted retrospectively with 35 COVID-19 patients of various age and gender groups who were admitted to an intensive care unit in a university hospital in March and April, 2020. Patients with stage 4 and 5 renal failure or liver failure were not included in this study. The laboratory results of the patients and the drug lists (orders) used in the hospital were collected in order to evaluate the interactions of favipiravir, hydroxychloroquine, azithromycin and tocilizumab used for the treatment of COVID-19 with those drugs used routinely in the intensive care unit as well as any side effects arising from their use. While evaluating interactions and examining side effects, Medscape, Liverpool COVID-19 Interactions, drugs.com, and up-to-date applications were used. The severity of drug interactions was evaluated in three separate categories, namely; serious-use alternative interaction, monitor closely interaction and minor interaction; and the rate at which each type of interaction occurred in patients was also calculated. As a result of these evaluations, the parameters that should be monitored to avoid interactions were determined. Among the variables which were found in all patients, electrocardiograms (ECGs) and laboratory values were examined respectively to check for QT prolongation and to monitor electrolyte levels. The relationship of drug-drug interactions and complications occurring in those patients with existing comorbidities were examined. The effect of complications on the number of days that patients were intubated was evaluated.

Statistical Analysis

SPSS statistics for Windows version 15 (SPSS Inc. Chicago, IL, USA) was used for the statistical analysis. Descriptive statistics are given as number and percentage for categorical variables; mean, standard deviation, minimum, maximum, median, interquartile range are given for numerical variables. The proportions were compared with the chi-square test in independent groups. Independent group comparisons of numerical variables were made using the Mann–Whitney U test for the normal distribution condition. A statistical significance level of alpha was accepted as $p<0.05$.

RESULTS

A total of 35 patients with a mean age of 63.7±13.7 years, a minimum of 30, a maximum of 94 years of age, 23 males (65.7%) 12 females (34.3%) were included in this study. The mean body mass index of the patients was 31.1±4.8 kg/m^2. 91.4% of the patients had additional comorbid diseases. The most common comorbidities were determined to be hypertension (HT) at a rate of 57.1%, Diabetes mellitus (DM) at a rate of 34.3%, Asthma at a rate of 20%, Congestive heart failure (CHF) at a rate of 17.1%, and Coronary artery disease (CAD) at a rate of 14.3%. One patient had cardiac arrest and one patient had hepatotoxicity. Complications developing in patients and their rates were found to be 85.7% ARDS, 22.9% sepsis and 8.6% septic shock. 68.6% of the patients were intubated. The mean time that the patients were intubated was 7.1±5.6 days, and the median was 5 days (Table 1).

The average number of days intubated in patients with ARDS and sepsis was found to be statistically significantly higher than those without complications ($p=0.004$, $p=0.039$) (Table 2).

Serious-use alternative interaction was detected in 85.7% of the patients, monitor closely interaction in 60%, and minor interaction in 34.3%. In 88.6% of the patients, at least one of the interactions was observed, while all three interactions occurred at the same time in 20% of them. The number of serious-use alternatives observed in the patients was found to be a maximum of 9 and a median of 3 [interquartile range (IQR): 1–4], the number of monitor closely Interactions was a maximum of 8 and a median of 1 (IQR: 0–2), and minor interaction was a maximum of 3 and a median of 0 (IQR: 0–1) (Figure 1).

The serious-use alternative interaction rates in patients are summarized in Table 3 in order of frequency. The first column represents the drug combination showing interactions, the second column represents the percentage ratio of the number of patients administered, and the last column indicates the interaction type and parameters to be monitored. Accordingly, the most common parameter to be monitored in the patients is QT prolongation with a rate of 57.14%, which can occur with the simultaneous use of hydroxychloroquine and azithromycin. The combination of drugs that should be avoided and alternative drugs that can be preferred are azithromycin and enoxaparin (37.14%).

The monitor closely interaction rates detected in patients are summarized in Table 4. The most frequent three monitor closely interactions in patients were detected between propofol and midazolam with 11.43%, azithromycin and piperacillin with 8.57%, pantoprazole and clopidogrel with 8.57%.

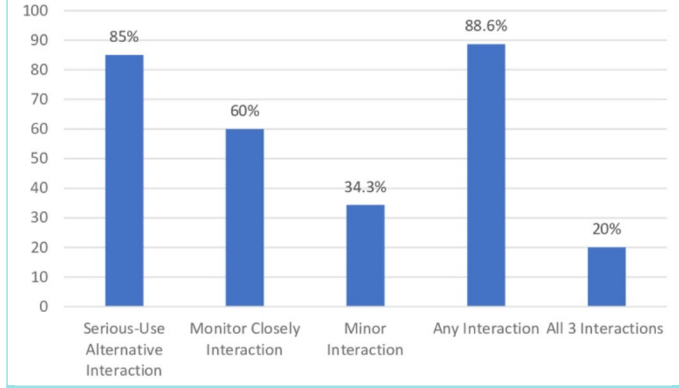

Figure 1. Rates of interaction types observed in patients.

The minor interaction rates determined in patients are summarized in Table 5 in order of frequency. The most frequent minor interaction rate was found between paracetamol and enoxaparin with a rate of 4.76%.

There was no statistically significant change in glomerular filtration rate (EGFR), aspartate aminotransferase (AST)-alanine transaminase (ALT), and SPO_2 values depending on the treatment applied (Table 6).

No statistically significant difference was found in the rates of serious-use alternative Interaction occurrence in patients with comorbidity (Table 7).

Table 1. Categorical variables reflecting the clinical characteristics of the patients

		n
Age, mean ± SD (min-max)		63.7±13.7 (30–94)
Gender, n (%)	Male	23 (65.7%)
	Female	12 (34.3%)
BMI, mean ± SD (min-max)		31.1±4.8 (21.2–43)
Comorbidity, n (%)		32 (91.4%)
Hypertension		20 (57.1%)
Diabetes		12 (34.3%)
Asthma		7 (20.0%)
CHF		6 (17.1%)
CAD		5 (14.3%)
HL		3 (8.6%)
Kidney failure		3 (8.6%)
Ca		3 (8.6%)
Hypothyroidism		2 (5.7%)
BPH		2 (5.7%)
Hypothyroidism		1 (2.9%)
AF		1 (2.9%)
Parkinson/Alzheimer		1 (2.9%)
Meningitis/Encephalitis		1 (2.9%)
Arrhythmia		1 (2.9%)
Panic attack		1 (2.9%)
Neurogenic bladder		1 (2.9%)
Goiter		1 (2.9%)
Cardiac arrest, n (%)		1 (2.9%)
Hepatotoxicity, n (%)		1 (2.9%)
Severe hypoxia, n (%)		0 (0.0%)
Complication, n (%)	ARDS	30 (85.7%)
	Sepsis	8 (22.9%)
	Septic shock	3 (8.6%)
Intubation, n (%)		24 (68.6%)
Number of days intubated, mean ± SD (min–max)		7.1±5.6 (1–26)

BMI: body mass index, CHF: chronic heart failure, CAD: chronic artery disease, HL: hyperlipidemia, Ca: cancer, BPH: benign prostate hyperplasia, AF: atrial fibrillation, ARDS: acute respiratory distress syndrome, SD: standard deviation, min: minimum, max: maximum, n: number.

No statistically significant difference was found between the rates of complications in those patients with or without serious-use alternative, monitor closely and minor interactions (Table 8).

DISCUSSION

In a retrospective study conducted by Mitra et al.[6], on 117 intensive care patients diagnosed with COVID-19, 73.5% of the patients had comorbidity. In our study, it was observed that 91.4% of the patients had additional comorbid diseases.

In our study, similar to the results of Nandy et al.[7] and Rodriguez-Morales et al.[8], the most common comorbidity was determined to be hypertension, but its incidence rate was found to be relatively much higher (57.1%). In our results, hypertension is followed by type II DM (34.3%), asthma (20%), congestive heart failure (17%) and coronary artery disease (14.3%).

Similar to the results of some other studies, the data obtained from our study show that the most common complication seen in our patients is ARDS with a rate of 85.7%. The complications following ARDS were found to be sepsis (22.9%) and septic shock (8.6%).[2,9,10]

Unlike the retrospective cohort study by Manolis et al.[11], cardiac arrest occurred in only 1 patient and no other cardiac damage was detected.

Unlike some studies, there was no significant increase in AST and ALT levels in the patients who were included in our study, and hepatotoxicity developed in only one patient.[12-14]

According to a study by Leung et al.[12], kidney involvement is also common in patients with COVID-19. The incidence of acute kidney injury was found to be around 0.5% to 29%. Acute kidney injury was found in 20% to 40% of COVID-19 patients in need of intensive care in Europe and the USA. In the study of Chen et al.[14], five out of 51 patients had acute kidney injury. Unlike these results, none of our patients developed acute kidney injury.

Compared with the results of the case series examined by Grasselli et al.[10] and the study conducted by Bhatraju et al.[15], the number of patients who needed intubation in our study was low (68.6%).

In the study of Petrilli et al.[1], 23.6% of 5,279 COVID-19 patients needed mechanical ventilation and 60.4% of these patients died.

The results we obtained seem to be consistent with the results of that study (58.3%), but they were significantly higher than the results of

Table 2. The number of days intubated in patients with or without complications

Median (IQR)		Number of days intubated	p-value*
ARDS	None	0 (0–0)	0.004
	Present	5 (1.75–8)	
Sepsis	None	2 (0–6)	0.039
	Present	6.5 (4.25–8.75)	
Septic shock	None	3.5 (0–6.75)	0.112
	Present	8 (5–9)	

*Mann–Whitney U test, ARDS: acute respiratory distress syndrome, IQR: interquartile range.

Mitra et al.[6] (15.4%) and Hur et al.[16] (15.2%).

In the study by Petrilli et al.[1], the most common comorbidities associated with decreased oxygen saturation were determined to be heart failure and chronic kidney disease. Consistent with that study, the fact that at least one comorbidity was seen in 87% of the patients who needed intubation in our study shows that oxygenation is affected by comorbidities in patients with COVID-19.

The fact that the average number of days intubated in patients with ARDS and sepsis in our study was statistically higher than those without complications confirms the results of the study by Lakoh et al.[17].

In our study, the mean duration of intubation of the patients was found to be 7.1±5.6 days, and this result seems similar to the results of the study by Hur et al.[16].

The meta-analysis conducted by Awortwe and Cascorbi[5] advocated that attention should be paid to symptoms that may indicate drug side effects, particularly cardiac arrhythmias, through drug-drug interactions

Table 3. Serious-use alternative interaction rates in patients and the variables to be followed

Serious-use alternative interaction	Number	%	To be followed
Hydroxychloroquine + azithromycin	20	57.14	Qt prolongation
Azithromycin + enoxaparin	13	37.14	Avoid or use alternate drug
Favipiravir + paracetamol	9	25.71	Paracetamol doses should be monitoring
Hydroxychloroquine + metoprolol	6	17.14	Qt prolongation
Hydroxychloroquine + insulin	5	14.29	Decrease doses insulin maybe required
Hydroxychloroquine + rocuronium	5	14.29	Monitor and adjust rocuronium as needed
Azithromycin + amlodipine	4	11.43	Qt prolongation
Hydroxychloroquine + amlodipine	4	11.43	Qt prolongation
Hydroxychloroquine + furosemide	4	11.43	Qt prolongation/electrolyte monitoring
Azithromycin + metoprolol	3	8.57	Qt prolongation
Hydroxychloroquine + propofol	3	8.57	Qt prolongation
Hydroxychloroquine + tocilizumab	3	8.57	Avoid or use alternate drug
Azithromycin + furosemide	2	5.71	Qt prolongation/electrolyte monitoring
Azithromycin + hydrochlorothiazide	2	5.71	Qt prolongation/electrolyte monitoring
Azithromycin + propofol	2	5.71	Qt prolongation
Hydroxychloroquine + hydrochlorothiazide	2	5.71	Qt prolongation/electrolyte monitoring
Hydroxychloroquine + clopidogrel	2	5.71	Use cautiously
Hydroxychloroquine + metoclopramide	2	5.71	Qt prolongation
Piperacillin + enoxaparin	2	5.71	Avoid or use alternate drug
Propofol + norepinephrine	2	5.71	Avoid or use alternate drug
Azithromycin + amiodarone	1	2.86	Qt prolongation
Azithromycin + dexmedetomidine	1	2.86	Qt prolongation
Azithromycin + digoxin	1	2.86	Qt prolongation
Azithromycin + heparin	1	2.86	Avoid or use alternate drug
Azithromycin + ondansetron	1	2.86	Qt prolongation
Digoxin + metoprolol	1	2.86	Avoid or use alternate drug
Heparin + cilostazol	1	2.86	Avoid or use alternate drug
Hydroxychloroquine + amiodarone	1	2.86	Qt prolongation
Hydroxychloroquine + dexamethasone	1	2.86	Use with caution
Hydroxychloroquine + dexmedetomidine	1	2.86	Qt prolongation
Hydroxychloroquine + digoxin	1	2.86	Qt prolongation
Hydroxychloroquine + ondansetron	1	2.86	Qt prolongation
Ketamine + norepinephrine	1	2.86	Use cautiously
Metoprolol + furosemide	1	2.86	Use cautiously
Ceftriaxone + enoxaparin	1	2.86	Avoid or use alternate drug
No interaction	5	14.29	-

Table 4. Monitor closely interaction rates detected in patients

	Monitor closely interaction	
	n	%
Propofol + midazolam	4	11.43
Azithromycin + piperacillin	3	8.57
Pantoprazole + clopidogrel	3	8.57
Enoxaparin + aspirin	2	5.71
Metoprolol + furosemide	2	5.71
Metoprolol + potassium citrate	2	5.71
Midazolam + norepinephrine	2	5.71
Norepinephrine + midazolam	2	5.71
Amiodarone + metoprolol	1	2.86
Aspirin + potassium citrate	1	2.86
Azithromycin + rocuronium	1	2.86
Azithromycin + tolvaptan	1	2.86
Dexamethasone + enoxaparin	1	2.86
Dexamethasone + finasteride	1	2.86
Dexmedetomidine + morphine	1	2.86
Doxazosin + metoprolol	1	2.86
Enocaparin + clopidogrel	1	2.86
Enoxaparin + ibuprofen	1	2.86
Enoxaparin + clopidogrel	1	2.86
Enoxaparin + ramipril	1	2.86
Enoxaparin + ketoprofen	1	2.86
Epinephrine + azithromycin	1	2.86
Epinephrine + furosemide	1	2.86
Furosemide + aspirin	1	2.86
Ketamine + midazolam	1	2.86
Clopidogrel + aspirin	1	2.86
Meropenem + digoxin	1	2.86
Methylprednisolone + enoxaparin	1	2.86
Methylprednisolone + midazolam	1	2.86
Methylprednisolone + rocuronium	1	2.86
Metoprolol + aspirin	1	2.86
Metoprolol + digoxin	1	2.86
Metoprolol + norepinephrine	1	2.86
Metoprolol + propofol	1	2.86
Metoprolol + tolvaptan	1	2.86
Midazolam + epinephrine	1	2.86
Midazolam + norepinephrine	1	2.86
Midazolam + tramadol	1	2.86
Norepinephrine + furosemide	1	2.86
Pentobarbital + midazolam	1	2.86
Pentobarbital + propofol	1	2.86
Pentobarbital + tramadol	1	2.86
Potassium citrate + epinephrine	1	2.86
Potassium citrate + furosemide	1	2.86
Potassium citrate + insulin	1	2.86
Propofol + tramadol	1	2.86
Ramipril + doxazosin	1	2.86
Ramipril + potassium citrate	1	2.86
Telmisartan + insulin	1	2.86
Tolvaptan + digoxin	1	2.86

n: number.

Table 5. Minor interaction rates detected in patients

	Minor interaction	
	n	%
Paracetamol + enoxaparin	5	4.76
Amlodipine + rocuronium	1	0.95
Amlodipine + rocuronium	1	0.95
Ascorbic acid + aspirin	1	0.95
Ascorbic acid + aspirin	1	0.95
Dextroz + magnesium sulphate	1	0.95
Enoxaparin + paracetamol	1	0.95
Ibuprofen + acyclovir	1	0.95
Levetiracetam + paracetamol	1	0.95
Norepinephrine + furosemide	1	0.95
Pentobarbital + pantoprazole	1	0.95
Ceftazidime + aspirin	1	0.95

n: number.

Table 6. Change in EGFR, AST-ALT-SPO_2 values depending on the treatment applied

		Mean ± SD (min-max)	Median (IQR)
EGFR	First day	78.2±34.2 (30–160)	84 (48–107)
	Median day	80.7±45.8 (21–201)	82 (44–109)
	The last day	77.1±38.3 (12–136)	79 (42–108)
	p-value*	0.774	-
AST	First day	50.5±34.0 (10.9–193)	40.7 (28.9–63.3)
	Median day	97.9±172.8 (11.2–900.7)	46.4 (27.6–76.4)
	The last day	63.5±49.4 (11.4–204.3)	48.3 (25.8–85.3)
	p-value#	0.074	-
ALT	First day	35.1±23.8 (4.2–112.7)	32 (17.3–42)
	Median day	86.1±190.0 (3.7–1041)	34.1 (21.3–52.1)
	The last day	64.8±81.4 (3.4–337)	38.1 (22.2–69)
	p-value#	0.165	-
SPO_2	First day	87.8±6.1 (73–100)	88 (84–92)
	Median day. lowest	88.1±12.5 (19–96)	90 (87–93)
	Last day. lowest	87.3±13.6 (20–99)	91 (85–94)
	p-value#	0.592	-
SPO_2	First day	95.8±3.6 (85–100)	96 (93–99)
	Median day. highest	95.3±12.4 (25–100)	98 (96–99)
	Last day. highest	94.7±12.2 (27–100)	98 (95–99)
	p-value#	0.091	-

*Repeated measures ANOVA, #Friedman test.

EGFR: glomerular filtration rate, AST: aspartate aminotransferase, ALT: alanine aminotransferase, SPO_2: oxygen saturation, min: minimum, max: maximum, SD: standard deviation, IQR: interquartile range.

Table 7. Serious-use alternative drug interactions in comorbidities

		Serious-use alternative interaction		p-value
		n	%	
Comorbidity	None	3	100.0%	1.000
	Present	27	84.4%	
Asthma	None	24	85.7%	1.000
	Present	6	85.7%	
Hypertension	None	13	86.7%	1.000
	Present	17	85.0%	
Type I DM	None	29	85.3%	1.000
	Present	1	100.0%	
Type II DM	None	20	83.3%	1.000
	Present	10	90.9%	
Ca	None	27	84.4%	1.000
	Present	3	100.0%	
Neurogenic bladder	None	29	85.3%	1.000
	Present	1	100.0%	
Goiter	None	29	85.3%	1.000
	Present	1	100.0%	
Hypothyroidism	None	29	87.9%	0.269
	Present	1	50.0%	
CAD	None	26	86.7%	0.561
	Present	4	80.0%	
CHF	None	24	82.8%	0.561
	Present	6	100.0%	
Parkinson/ Alzheimer	None	29	85.3%	1.000
	Present	1	100.0%	
BPH	None	28	84.8%	1.000
	Present	2	100.0%	
HL	None	27	84.4%	1.000
	Present	3	100.0%	
Hypothyroidism	None	30	88.2%	0.143
	Present	0	0.0%	
AF	None	29	85.3%	1.000
	Present	1	100.0%	
Meningitis/ Encephalitis	None	29	85.3%	1.000
	Present	1	100.0%	
Kidney failure	None	27	84.4%	1.000
	Present	3	100.0%	
Arrhythmia	None	30	88.2%	0.143
	Present	0	0.0%	
Panic attack	None	30	88.2%	0.143
	Present	0	0.0%	

DM: diabetes mellitus, Ca: cancer, CAD: chronic artery disease, CHF: chronic heart failure, BPH: benign prostate hyperplasia, HL: hyperlipidemia, AF: atrial fibrillation.

in this population. In our study, no statistically significant difference was found in the drug interaction rates resulting from the patients having comorbidity. No statistically significant change was found in the parameters reflecting organ functions (EGFR, AST-ALT, SPO_2, ECG) from the first day to the last day of hospitalization, depending on the treatment we applied in the intensive care unit of our hospital.[5]

In New York city, arrhythmia was reported in 18.5% of 130 patients who needed invasive mechanical ventilation, and 95.8% of these patients developed atrial arrhythmia. In an Italian cohort of 99 patients hospitalized with COVID-19, atrial fibrillation occurred in 19% of all cases and 36% of those patients with underlying cardiovascular disease. The most common cause of drug-related life-threatening ventricular arrhythmias was reported to be antiarrhythmic drug-drug interactions, and 74% of these cases were associated with QT prolongation.[18] In our study, no statistically significant difference was found between drug interaction rates and the occurrence of complications in those patients with complications.

In the study of Hosseinpoor et al.[19], which included 200 COVID-19 patients hospitalized in an intensive care unit, QT prolongation and related drug-drug interactions were evaluated. QT prolongation

Table 8. Complication occurrence rates in patients with and without serious-use alternative interaction

	Serious-use alternative interaction				p-value
	None		Present		
	n	%	n	%	
ARDS	5	100.0	25	83.3	1.000
Sepsis	3	60.0	5	16.7	0.067
Septic shock	1	20.0	2	6.7	0.380
Cardiac arrest	0	0.0	1	4.8	1.000
Hepatotoxicity	0	0.0	1	4.8	1.000
Intubation	4	80.0	20	66.7	1.000
	Monitor closely interaction				**p-value**
	None		**Present**		
	n	**%**	**n**	**%**	
ARDS	13	92.9	17	81.0	0.627
Sepsis	3	21.4	5	23.8	1.000
Septic shock	2	14.3	1	4.8	0.551
Cardiac arrest	1	4.3	0	0.0	1.000
Hepatotoxicity	16	69.6	8	66.7	1.000
Intubation	8	57.1	16	76.2	0.283
	Minor interaction				**p-value**
	None		**Present**		
	n	**%**	**n**	**%**	
ARDS	19	82.6	11	91.7	0.640
Sepsis	4	17.4	4	33.3	0.402
Septic shock	1	4.3	2	16.7	0.266
Cardiac arrest	0	0.0	1	3.3	1.000
Hepatotoxicity	0	0.0	1	3.3	1.000
Intubation	16	69.6	8	66.7	1.000

ARDS: acute respiratory distress syndrome, n: number.

occurred in 10.7% of patients. In a cohort of 138 COVID-19 patients in Wuhan, China, 44% of patients in the intensive care unit and 17% of all patients developed cardiac arrhythmias. Sudden cardiac arrests both in and out of the hospital have also been reported in patients with COVID-19. In a cohort study of 90 patients with COVID-19, those who received a combination of hydroxychloroquine and azithromycin had more QT interval prolongation than those who received hydroxychloroquine alone. Frequent electrocardiographic evaluation should be strongly considered in those patients with COVID-19 treated with hydroxychloroquine and/or azithromycin.[20] In our study, as a result of the simultaneous use of hydroxychloroquine and azithromycin, QT Prolongation was found to be the most common (32.7%) intervention to be followed. ECGs of all our patients were monitored and it was observed that QT prolongation did not occur in any of them.

In the study conducted by Surmelioglu and Demirkan[21] making suggestions about the drugs used on COVID-19 patients in intensive care units in Turkey, it was argued that polypharmacy and comorbidities increase the risk of occurrence of drug interactions. Additionally, organ dysfunctions associated with COVID-19 may affect the severity of drug interactions. Some of their suggestions include: dose adjustment, alternative drug use or drug monitoring in cases where lopinavir and ritonavir are used together; follow-up of the patient by electrocardiography and discontinuation when the clinical situation requires in cases when lopinavir, ritonavir, hydroxychloroquine and azithromycin are used in combination or with other drugs that prolong the QT interval; and dose adjustment due to the risk of increased concentrations of these drugs in the simultaneous use of hydroxychloroquine and amiodarone, dabigatran, edoxaban and immunosuppressants. Therapeutic level follow-up of drugs is among the fundamental suggestions based on the concerns that azithromycin may increase the concentrations of some drugs when used with certain narrow therapeutic index drugs such as digoxin, theophylline and warfarin despite its low drug interaction potential. The drug interaction potential of favipiravir has been found, albeit low, with the simultaneous use of theophylline and paracetamol.[21]

In the study by Brandariz-Nuñez et al.[22], which included 361 COVID-19 patients, a total of 369 potential interactions were recorded with 52 different drugs. 20.92% of these interactions are drug combinations that should be avoided. Among the results found were that 20.92% of interactions are combinations of drugs that should be avoided, 63.32% should consider treatment changes, and the remaining 15.76% require follow-up. In our study, the combination of drugs that should be avoided and alternative drugs that can be preferred was determined to be the most common for the combination of azithromycin and enoxaparin (37.14%).

Similarly to the study of Jyotsna and Hemalatha[23], in our study, serious-use alternative interaction was found in 85.7% of our patients, monitor closely interaction in 60% and minor interaction in 34.3%. Serious-use alternative interactions which recorded the highest rates of occurrence were hydroxychloroquine and azithromycin with 48.57%; enoxaparin and azithromycin with 37.14%; Paracetamol and favipiravir with 25.71%; metoprolol and hydroxychloroquine with 17.14%; Insulin and hydroxychloroquine with 14.29%; Rocuronium and hydroxychloroquine with 14.29%; Amlodipine and azithromycin with 11.43%, amlodipine and hydroxychloroquine with 11.43%; and furosemide and hydroxychloroquine with 11.43%.[23]

Limitations of the Study

Our study has several limitations. It is a single-center study with a relatively low number of patients. The patients were not randomized for treatment but were categorized according to severity when allocated to different therapeutic regimens.

CONCLUSION

Polypharmacy, which is inevitable when the treatment for COVID-19 is added to the treatment of chronic disease conditions in patients diagnosed with COVID-19, is the most important factor that causes drug-drug interactions. Our knowledge on potential drug-drug interactions that may be caused by other drugs used in the management of COVID-19, especially antiviral drugs, is limited. It is assumed that drug-drug interactions and the problems they cause are associated with poor clinical outcomes. In order to manage these risks, interventions such as drug dosage adjustment, drug change and the monitoring of parameters that may indicate drug side effects in the patient may be necessary. Therefore, awareness of drug-drug interactions is vital.

MAIN POINTS

- ARDS and sepsis, which are the most common complications in COVID-19 patients, are associated with longer intubation times.
- Serious-use alternative interaction was detected in the majority of COVID-19 patients in their treatment applied in the ICU.
- Drug-drug interactions caused by polypharmacy and complications in patients are associated with poor clinical response.
- Awareness of drug-drug interactions is vital in COVID-19 patients.

ETHICS

Ethics Committee Approval: The study was approved by the research Ethics Committee of the İstanbul Medipol University (10840098-604.01.01-E.17838).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

DISCLOSURES

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

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ORIGINAL ARTICLE

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Correlation of Rapid Antibody and RT-PCR Tests With Clinical and Radiological Findings in COVID-19 Patients Admitted to an Employee Health Outpatient Clinic

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ABSTRACT

BACKGROUND/AIM: To evaluate the results of simultaneous rapid antibody tests and Real-time polymerase chain reaction (RT-PCR) tests in patients diagnosed with coronavirus disease-2019 (COVID-19) retrospectively, and to evaluate the compatibility rates of these results with clinical and radiological findings.

MATERIALS AND METHODS: Between March 31, 2020 and July 31, 2020, simultaneous COVID-19 RT-PCR and COVID-19 rapid antibody assay were applied to the health care personnel who were admitted to a healthcare personnel COVID-19 outpatient clinic with COVID-19 complaints.

RESULTS: A total of 1010 healthcare personnel who were admitted to the healthcare personnel COVID-19 outpatient clinic were included in this study. One hundred and sixty-seven of them (16.54%) were doctors, and 363 (35.94%) were nurses or midwives. The most common symptoms were sore throat (27.92%), cough (25.94%) and weakness (14.75%). Throat nasal swab RT-PCR revealed that a total of 989 (98%) personnel had PCR negative, and 21 (2%) had PCR positive results. Sixteen (1.58%) personnel did not have a registered assay result. Rapid antibody test revealed that 1006 (99.6%) personnel had negative, and 4 (0.4%) personnel had positive results. When the assay results were evaluated with simultaneous computed tomography findings, 990 (98%) did not have any signs suggesting COVID-19.

CONCLUSION: In serological rapid assays used to diagnose COVID-19, specific antibodies in the "window period" are at undetectable levels in the patient's blood. Therefore, false negative results may be obtained. For this reason, serological tests cannot be used as the basic diagnostic tool for COVID-19 infections.

Keywords: Coronavirus, pandemic, antibody tests, RT-PCR

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INTRODUCTION

In December 2019 in Wuhan, China, a new coronavirus (2019-nCoV) was detected in individuals with acute respiratory disease.[1] Coronavirus disease-2019 (COVID-19), (Sars-CoV-2) was declared to be a pandemic by the World Health Organization (WHO) on March 11, 2020.[2] Several studies showed that COVID-19 exhibited tropism against extra pulmonary tissue cells as well as respiratory system epithelial cells in humans and it had the ability to grow on these areas.[3] The symptoms of the infection include pulmonary and extrapulmonary signs such as fever, cough, dyspnea, diarrhea, headache, and conjunctivitis.[4] Real-time-polymerase chain reaction (RT-PCR) has become the standard method for nucleic acid identification to diagnose COVID-19. However, RT-PCR tests also have several limitations. These limitations include; the need for trained personnel and certified laboratories with special, expensive equipment for the assays. However, several studies showed that false negative results may be obtained by these assays. Therefore, simple, highly sensitive assays are required for rapid response, and immediate, accurate diagnosis. immunoglobulin M (IgM) is the defense response of the body during the first virus challenge, and IgG is the memory response associated with prolonged immunity. It is suggested that rapid antibody assays detecting IgM and IgG will be important for the diagnosis and treatment of COVID-19. Rapid antibody assays have been developed to detect the presence of IgM and immunoglobulin G (IgG) within 15 minutes from serum or whole blood taken from finger capillaries.[5]

The aim of this study is to evaluate the results of simultaneous rapid antibody tests and RT-PCR tests in patients diagnosed with COVID-19 retrospectively, and to evaluate the compatibility rates of these results with clinical and radiological findings.

MATERIALS AND METHODS

The Healthcare personnel COVID-19 Outpatient Clinic of University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital, Department of Infectious Diseases opened for COVID-19 complaints of the hospital personnel in order to facilitate convenient testing for them. Between the dates of March 31, 2020 and July 31, 2020, simultaneous COVID-19 R- PCR and COVID-19 rapid antibody assay for COVID-19 were applied to the health care personnel who were admitted to the healthcare personnel COVID-19 outpatient clinic with COVID-19 complaints.

This study was approved by Ethics Committee of University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital with 2020/10-28 approval number.

RT-PCR

From the oro-nasopharyngeal swab samples of the patients, viral nucleic acid isolation kit (Bio-Speedy, Turkey) was applied for viral nucleic acid extraction. Swab samples were obtained in Viral Transport Medium (VTM), and put into a 100 µL R1 tamponade clean micro-centrifuge tube. A 100 µL respiratory sample was added to this tube. The tube was vortexed at 15 sec high speed, then incubated at room temperature for 5 minutes. The tube was centrifuged at maximum speed for 3 minutes (above 10,000 g) and 25 µL supernatant was put into a clean micro-centrifuge tube. Then, 25 µL'R2 tamponade was added and mixed. This 50 µL mixture was used for PCR immediately.

Covidien RT-q-19 PCR Detection Kit (Biospeedy, Turkey) was used.

According to the manufacturers specifications:

1) 10 µL 2X Prime Script Mix

2) 5 µL oligomix

3) 5 µL of Nucleic acid were added.

A total volume of 20 µL was obtained.

For RT-PCR, Rotor gene device (Qiagen, Germany) was programmed according to the company's recommendations.

Rapid antibody test: COVID-19 IgM/IgG rapid antibody diagnosis assay (Hotgen, China) was used in accordance with the manufacturer's recommendations.

The test tape, diluent and sample to be tested were brought to room temperature, after (15–30 min) aluminum foil was opened, and the sample number was written on the plastic face of the tape. 10 µL serum was dropped in the sample section of the tape. Three drops of sample diluent were dropped above it. It was incubated at room temperature for 15 minutes.

If a red or magenta colored line was visible in both parts (T and C line), the test was considered to be positive. If a red or magenta line was visible only in the C line, and there was no color change in the T line, the test was considered to be negative. If there was no color change in the C line, the test was considered invalid and the test was repeated.

Statistical Analysis

All statistical analyses were performed through The Statistical Package for Social Sciences 23.0 (SPSS, Chicago, IL, USA) software. The data collected within the scope of the study were summarized as mean ± standard deviation. Pearson chi-square test was used in the analysis of categorical data. A value of $p<0.05$ was considered statistically significant.

RESULTS

A total of 1010 healthcare personnel who were admitted to the healthcare personnel COVID-19 outpatient clinic of University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital Infectious Diseases were included in this study. Their mean age was 42, the gender distribution was male, 167 of them (16.54%) were doctors, 363 (35.94%) were nurses or midwives. The distribution of the healthcare personnel is shown in Table 1.

When the healthcare staff were questioned about whether they wore masks; it was found that 550 (54.45%) used masks during patient visits, and 460 (45.55%) did not. The analysis of the clinical signs of the patients included in the study showed that the most common symptoms were sore throat (27.92%), cough (25.94%) and weakness (14.75%). The clinical findings of the healthcare personnel are shown in Table 2.

Throat nasal swab RT-PCR revealed that total of 989 (98%) personnel had PCR negative, and 21 (2%) had PCR positive results. Sixteen (1.58%) personnel did not have a registered assay result.

Rapid antibody test revealed that 1006 (99.6%) personnel had negative, and 4 (0.4%) personnel had positive results.

When the assay results were evaluated with simultaneous computed tomography (CT) findings, 990 (98%) did not have any signs suggesting COVID-19. Fourteen (1.4%) had COVID-19 compatible CT findings. One (0.09%) staff member had ground glass opacity findings suggesting a different viral infection. CT findings of 36 (3.56%) people were not compatible with COVID-19. CT findings could not be obtained in six personnel (Table 3).

A total of 21 (2%) personnel had PCR positive tests. Nine hundred and ninety of 1010 personnel had CT incompatible with COVID-19 findings. Among those patients without CT findings, 859 (87%) had PCR negative, 20 had (2%) PCR positive, three had (0.3%) rapid test positive, and one patient (0.1%) had both PCR and rapid test positive results.

Among the patients with CT findings, none of the health personnel had positive PCR results. One person with CT positive and PCR negative had a positive rapid test. Table 4 presents the correlation between the clinical symptoms and assay results.

Table 1. Distribution of healthcare personnel

Position	Number	%
Doctor	167	16.53
Nurse/midwife	363	35.94
Cleaning staff	204	20.20
Computing/data entry	30	2.97
Other	246	24.36

Table 2. Clinical signs of the healthcare personnel

Symptom type	Present (%)	Absent (%)
Weakness	**14.75**	**85.24**
Lack of appetite	1.48	98.52
Fever	7.22	92.73
Muscle and joint pain	12.97	87.03
Sore throat	**27.92**	**72.08**
Nasal congestion	8.42	91.58
Cough	**25.94**	**74.06**
Dry cough	7.82	92.18
Productive cough	2.18	97.82
Headache	11.88	88.12
Changes in consciousness	0.20	99.80
Nausea	1.78	98.22
Vomiting	0.60	99.40
Diarrhea	3.56	95.84
Loss of taste	1.48	92.92
Loss of smell	0.69	98.71
Dyspnea	9.21	90.19

Significant values are shown in bold.

DISCUSSION

Since the beginning of the pandemic, medical companies and research institutes have been trying to develop assays to detect this viral infection and immunity against COVID-19. RT-PCR is considered as the gold standard for the diagnosis of the COVID-19 infection. However, this assay requires certified laboratories, expensive equipment, materials and trained personnel. Rapid tests detecting specific antibodies in blood samples may be used 3–6 days after the onset of symptoms to detect increased IgM antibodies and 8–10 days after to detect increased IgG antibodies.[6] These assays are cheap, easy to use and rapid, do not require equipment, and the results may be obtained in 15 minutes. They are easily used for screening health workers, allowing them to return to their work quickly. A disadvantage of quick tests is the probability of cross reactions with other coronaviruses (SARS-CoV, MERS-CoV).[7]

In PCR positive but rapid test negative sample results, the first thing to remember is that the absence of antibodies or their levels may be so low in the beginning of the infection. Secondly, the antibody response level of individuals' immunities may be different. Antibody response may not be observed if the immune system is suppressed. Thirdly, IgM response decreases during the second week, and may be negative when the test is applied.[5]

In Italy, 525 health care personnel were screened with rapid antibody assay, and six of them (1.1%) had positive IgM bands. Three of these cases had COVID-19 contact history. None of them had COVID-19 symptoms in these six cases, and their COVID-19 RT-PCR results were negative.[8] In a different study on 3300 patients, rapid assay was positive in six cases (0.2%).[9] In our study, 1006 (99.6%) health care personnel had negative rapid antibody assay, and four had positive results (0.4%). One of four (0.1%) had both positive PCR and rapid assay.

The results of molecular assays detecting viral RNA may be affected by accurate sampling, sample quality, transfer and storing conditions, and these may cause false negative results. If PCR does not detect the virus, we should keep in mind that the infection may be in very early or late period, and the viral load may be very low.[10-12]

Since SARS-CoV-2 is transmitted through airborne droplets, direct contact with COVID-19 patients put health care personnel at high infection risk especially if protective equipment is missing. In Italy, infection rates reported in health care workers were around 25%.[13-15]

The infection incidence of health care workers at a medical faculty was very high, 63% at the end of the first week and 22% at the end of the second week of the pandemic, among all COVID-19 cases diagnosed in the hospital. The first cases of this hospital were detected at those clinics where COVID-19 case were not expected, and one of these cases was a health care staff member. Therefore, it was suggested that health care personnel were not protected. With the precautions taken in the following weeks, this ratio decreased to 8.7% by the end of the 11th week.[16]

Table 3. Comparison of CT findings with RT-PCR results

CT findings not compatible with COVID-19	CT negative-RT-PCR negative	CT negative-RT-PCR positive	CT negative- RT-PCR positive-rapid test positive	CT positive-RT-PCR positive rapid test positive
990 (98%)	859 (87%)	20 (2%)	1 (0.01%)	1 (0.01%)

CT: computed tomography, COVID-19: coronavirus disease 2019, RT-PCR: real-time polymerase chain reaction.

Table 4. The correlation between clinical symptoms and assay results

	CT positive	RT-PCR positive	Rapid test positive	CT & rapid test & RT-PCR positive
Sore throat (280)	2 (0.7%)	16 (5.7%)	-	-
Cough (260)	4 (1.5%)	21 (8%)	1 (0.4%)	-
Weakness (146)	5 (3.4%)	15 (10.3%)	-	-

CT: computed tomography, RT-PCR: real-time polymerase chain reaction.

Since February 24, 2020, it was reported that 3387 (4.4%) of 77,262 cases in China were health care personnel, and this was considered to be a high rate, and its causes were investigated.[17,18] In our study, PCR positivity was 2% in health care personnel, which was very low compared to other studies. We suggest that the importance given to the use of personal protective equipment and the hygiene measures had been effective.

COVID-19 infection primarily involves the respiratory tract, so imaging methods such as direct radiography and CT may give supportive information for diagnosis. The value of direct radiograph is low as a diagnostic tool and is insufficient to detect pulmonary signs. However, CT may detect parenchyma findings even in asymptomatic subjects.[19]

In the early periods of COVID-19, CT may not detect any findings. A negative result in the thorax CT may indicate the condition without any parenchymal findings associated with the infection.[20]

Thorax CT is more sensitive in the diagnosis of COVID-19 pneumonia in comparison to RT-PCR assay, however, CT findings such as ground glass densities in parenchyma, and consolidation areas are not specific to COVID-19. Therefore, the diagnosis should be supported by clinical signs and laboratory results, and it is important to be confirmed by RT-PCR assay.[21]

In serological rapid assays used to diagnose COVID-19, specific antibodies in the "window period" are at undetectable levels in the patient's blood. Therefore, false negative results may be obtained. Therefore, serological tests cannot be used as the basic diagnostic tool for COVID-19 infections.

It is suggested that COVID-19, which may cause severe acute respiratory infection, infects people via droplets. If the infected person coughs, sneezes or talks, the virus is transmitted by respiratory fluids directly to the mucosa, and it may infect the other person. Additionally, if a person touches his eyes, nose or mouth after touching an infected surface, infection may occur. Hand-washing is a basic of viral infection control. Protective clothing such as masks, aprons and gloves should be worn to prevent infection.

Limitations of the Study

We had some limitations for our study. Firstly, the required training was given to the personnel who would take the samples during the sampling phase for the COVID-19 RT-PCR test. However, the same person did not perform all PCR and rapid antibody tests. This situation may have affected the quality of testing. Secondly, a limited number of antibody tests were sent to our hospital. Therefore, antibody tests could not be performed on every patient who underwent PCR test. We think that if the number of antibody tests were higher, it would be more suitable in defining large populations. These are considered as the limitations of our study.

CONCLUSION

The most important points in the fight against COVID-19 are the early detection of infected people, follow-up of contacts and isolation of diagnosed patients. Although rt pcr is the most used method for early diagnosis, new methods have been tried to be developed because it requires a well-equipped molecular microbiology laboratory and equipment. Simultaneous rapid antibody tests, which are among these other methods, are thought to replace rt pcr tests for early diagnosis. However, in the light of the results we obtained from our study; It has been observed that in the "window period", specific antibodies may be at undetectable levels in the patient's blood, which may cause false negative results. Therefore, it has been concluded that serological tests cannot be used as a basic diagnostic tool for COVID-19 infections.

MAIN POINTS

- The most important points in the fight against COVID-19 are the early detection of infected people, follow-up of contacts and isolation of diagnosed patients.
- When simultaneous rapid antibody tests and Real-time polymerase chain reaction (RT-PCR) tests are compared; rapid antibody test appears to be superior in terms of ease of use and accessibility.
- However, rapid antibody tests may cause false negative results in patients who fall within the window period.
- RT-PCR tests are still the gold standard in the diagnosis of COVID-19 infections.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital with 2020/10-28 approval number.

Retrospective Study: Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ş.K., G.D.H., Design: Ş.K., G.D.H., Data Collection and/or Processing: M.Y., M.B. Analysis and/or Interpretation: M.Y., M.B., Literature Review: Ş.K., P.Ş., G.D.H., M.Y., R.S., B.T., M.B., Writing: P.Ş., G.D.H.

DISCLOSURES

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

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ORIGINAL ARTICLE

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Investigation of 2019-2020 Seasonal Influenza Activity at a University Hospital in Northern Cyprus

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ABSTRACT

BACKGROUND/AIM: Influenza (flu) is a contagious respiratory disease caused by influenza viruses, which is more common in the late autumn, winter and early spring of the year. We aimed to estimate the rate of seasonal influenza A and B at Near East University Hospital in Northern Cyprus and to correlate the rate of the infection with the gender and age of the patients, and by month in which the infection occurred.

MATERIALS AND METHODS: Nasopharyngeal swabs collected from 844 individuals with flu like symptoms who were admitted to our hospital between December 2019 and March 2020 were involved. ABON™ Influenza A&B chromatographic immunoassay was used for the qualitative detection of Influenza A and B antigens. The rate of the infections was assessed among different ages, gender and by month.

RESULTS: Among 844 individuals, 234 (27.7%) were positive for either Influenza A virus or Influenza B virus. Among these infected cases, 97 (11.5%) and 137 (16.2%) were positive for influenza A and B, respectively. Influenza B was more dominant especially in children between 5–14 years of age. The major group of cases infected with Influenza A were aged 0–4 years. The difference between either Influenza A (p=0.679) or B (p=0.255) positivity and gender was not statistically significant. However, the rate of Influenza B differed by the month in which it occurred (p=0.034), peaking in February.

CONCLUSION: Our findings show that the rate of Influenza B was more dominant compared to the rate of Influenza A and age is an important factor in the rate of seasonal influenza. Therefore, early identification and investigation of influenza cases is critical to control human-human transmission.

Keywords: Influenza virus, immunochromotographic test, prevalence, Northern Cyprus

INTRODUCTION

Influenza (commonly referred as flu) is a contagious respiratory disease which is caused by Influenza viruses.[1] Influenza viruses, as members of the family *Orthomyxoviridae,* are enveloped, negative sense-single stranded segmented RNA viruses approximately 100 nm in diameter.[2] According to the antigenic differences in nucleoprotein (NP) and matrix (M) proteins present on the surface, which are associated with infecting a host cell, three different types (A, B and C) of Influenza viruses have been defined.[3] Influenza A [commonly

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referred as avian influenza (AI)] viruses can be further divided into subtypes based on the glycoproteins present on the surface of the viral envelope; hemagglutinin (HA) glycoproteins which allow the virus to bind to sialic acid receptors on a surface of epithelial cells in the upper respiratory tract and neuraminidase (NA) glycoproteins which let the new viruses leave the cell by simply budding out from it by cleaving sialic acid in the membrane.[4] To date, 18 distinct HA and 11 NA varying from H1 to H18 and N1 to N11 subtypes respectively, have been identified.[5,6] Influenza A and B viruses have a similar structure with eight gene segments that encode 17 proteins, however, Influenza B viruses do not have subtypes and are not associated with pandemics.[5,6] Influenza C viruses cause mild infections whereas, the Influenza D virus, which affects only cattle, does not cause infections in human. Thus, these two viruses do not pose a risk for public health.[7-9]

Influenza viruses can progress from mild to severe illnesses. Their transmission occurs from person to person with direct contact of respiratory droplets produced during coughing and/or sneezing at distances of less than 1 meter.[10] A total of 3 to 5 million cases and approximately 290,000 to 650,000 deaths associated with influenza are reported annually.[11] While the flu is generally common at the highest rates among young people, high mortality rates have been reported among the elderly, pregnant women, children below 59 months and individuals with severe and chronic illness such as chronic cardiac, pneumonia, sepsis and immunosuppressive conditions including acquired immunodeficiency syndrome (AIDS), those receiving chemotherapy, or with malignancy.[12-14] Laboratory diagnosis of Influenza by swabs or samples of secretions taken from the patient's nose or throat involve rapid antigen testing, immunofluorescence assays, rapid molecular assays such as reverse transcription polymerase chain reaction (RT-PCR) and virus culture.[15] Most of these assays provide an excellent analytical performance with high sensitivity and specificity. However, they require a longer time, and equipment and reagents which can only be used by experienced laboratory staff. As early identification and investigation of Influenza cases is critical to control human-human transmission, rapid antigen testing assays are commonly used for screening.

According to a modeling analysis of population-based surveillance data for the 2010–2013 Influenza seasons, approximately 114,018–633,001 hospitalizations, 18,476–96,667 intensive care unit (ICU) admissions, and 4,866–27,810 deaths per year were reported.[16] Moreover, it is estimated that 9.2–35.6 million illnesses, 4.3–16.7 million outpatient medical visits, and 139,000–708,000 hospitalizations can be attributed to all-season Influenza during the 2010–2016 seasons.[16] Therefore, the early identification and investigation of Influenza cases is critical to control human-human transmission and manage influenza outbreaks.

Due to the lack of scientific data on the rate of seasonal Influenza infections in Northern Cyprus, this study aimed to investigate the annual seasonal Influenza A and B virus activities in circulation during the 2019 winter and 2020 spring seasons at a university hospital in Northern Cyprus. Furthermore, the Influenza infections were evaluated with respect to multiple factors including gender, age, and the month in which they occurred to correlate these factors with the rate of the infection.

MATERIALS AND METHODS

Ethical Approval

The study was approved by Near East University Institutional Review Board (decision no: NEU/2020/79-1069, date: 28.05.2020). Since our study was retrospective, an informed consent form was not used.

Study Group and Analysis

Nasopharyngeal/oropharyngeal swab specimens collected from a total of 844 individuals with flu-like symptoms who were admitted to the Near East University Hospital clinics including the pediatric, cardiology, chest disease, emergency service, intensive care, and infectious disease clinics between December 2019 and March 2020 were investigated in the current study. Different parameters including age, gender, clinics and laboratory findings were documented and assessed all together for each case. The rate of Influenza activity was assessed among different age groups in the ranges of 0–4, 5–14, 15–44 and over 45 years. The ABON™ Influenza A&B Rapid Test Strip (Swab) chromatographic immunoassay (ABON Biopharm Co., Ltd, Hangzhou, China) was used for the qualitative detection of Influenza A and B antigens according to manufacturer's recommendations. Each chromatographic immunoassay is intended to aid in the diagnosis of Influenza A and B viruses. The manufacturer claims both the analytical sensitivity and specificity for Influenza A to be >99%. The analytical sensitivity and specificity for Influenza B is given as >99% and 98.6%, respectively.

Statistical Analysis

Categorical variables were summarized as frequencies and percentages, and continuous variables were described using their mean. The frequencies of categorical variables were compared using the Pearson chi-square and Fisher's exact tests. Tests with a $p<0.05$ were considered statistically significant.

RESULTS

A total of 844 swab samples collected from individuals who were admitted to the clinics of Near East University Hospital including the pediatric (356, 42.2%), emergency service (344, 40.8%), infectious disease (104, 12.3%), internal disease (19, 2.3%), chest disease and allergy (8, 0.9%), ear-nose-throat (8, 0.9%), cardiology (3, 0.4%) and dialysis (2, 0.2%) clinics were screened for Influenza A and B viruses in this study. The demographic characteristics of the study patients are shown in Table 1. A total of 1,688 analyses involving either Influenza A or B infection were obtained from the 844 patients. Among these individuals, 443 (52.5%) were females and 401 (47.5%) were male. Overall, from the individuals screened for Influenza viruses, 234 (27.7%) were determined as positive either for the influenza A or B virus. With regards to the overall Influenza positivity, the highest rate was obtained from those individuals coming from Nicosia (28.9%). Among the cases who tested positive for Influenza A and B, the highest rate was obtained from Nicosia and Morphou with 12% and 17.3%, respectively. No significant correlation was obtained between Influenza A and B positivity and the cities with $p=0.763$ and $p=0.838$, respectively. The seasonal pattern of Influenza activity in the cities of Northern Cyprus is given in Table 2.

Of the infected cases, 97 (11.5%) were positive for Influenza A virus and 137 (16.2%) were positive for Influenza B virus. Among the Influenza A positive cases, 48 (49.5%) were male and 49 (50.5%) were female. Moreover, 59 (43.1%) males and 78 (56.9%) females were reported as

Table 1. Clinical characteristics of the study patients

Characteristics	Patient group
Patient, n	844
Gender, M/F, n (%)	401(47.5)/443 (52.5)
Age, years (mean)	0–92 (15.74)
Clinics, n (%)	
Pediatrics	356 (42.2)
Emergency service	344 (40.8)
Infectious disease	104 (12.3)
Internal diseases	19 (2.3)
Chest disease and allergy	8 (0.9)
Ear nose and throat	8 (0.9)
Cardiology	3 (0.4)
Dialysis	2 (0.2)

M: male; F: female, n: number.

being Influenza B virus positive (Table 1). The difference between either Influenza A or Influenza B positivity and gender was not statistically significant (p=0.679, p=0.255 respectively) (Table 3).

During December 2019, a total of 70 Influenza A and B tests were performed of which 6 (17.1%) and 3 (8.6%) tested positive for Influenza A and B viruses, respectively. The number of performed Influenza tests peaked in January with a total of 980 tests, of which, 65 (13.3%) were positive for Influenza A virus and 83 (16.9%) were positive for Influenza B virus. In February 2020, a total of 490 tests were carried out in which 9% and 19.2% were positive for Influenza A and B viruses, respectively. In March 2020, 148 tests were performed, of which, 5.4% were positive for both the Influenza A and the Influenza B viruses. After February 2020, the number of tests carried out decreased by 70% in March. There was no statistically significant relationship between the rate of Influenza A virus and the month (p=0.088). However, the relationship between the rate of Influenza B virus and the month was statistically significant (p=0.034) and Influenza B was found to be the most common in February, 2020. The distribution rate of Influenza A and B virus positivity versus the month is given in Figure 1.

In this study, it was shown that age is an important factor in being infected with different types of seasonal Influenza viruses. During the Influenza season in Northern Cyprus (December 2019–March 2020), the major group of cases infected with Influenza A virus were aged 0-4 years. In addition, a steady decrease in Influenza A virus positivity (p=0.047) with increasing age in the same period showed a statistically significant relationship between the Influenza A infection rate and age. Moreover, the rate of Influenza B infection was the highest in the ages 5–14 years (p=0.000), which also confirms a statistically significant relationship between Influenza B infection and age. In Table 4, the rate of Influenza A and Influenza B virus positivity among different age groups in the ranges of 0–4, 5–14, 15–44 and over 45 years is given.

DISCUSSION

The rate of Influenza virus infection varies by 5%–20% each year.[17] This current study presents the estimation rate of seasonal influenza type A and/or B of a population who were admitted to a university hospital in Northern Cyprus in the 2019–2020 Influenza seasons. During this period, overall, for individuals screened for Influenza viruses, approximately 28% were determined to be positive for either Influenza A or B viruses. The positivity rate for Influenza B infections was higher (16.2%) compared to Influenza A infections (11.5%). Similar to a study in France, the number of Influenza B cases (29.7%) was higher than the number of Influenza A cases and the Influenza B outbreak peaked after the Influenza A outbreak.[18] In contrast, another study by Tamerius et al.[19] from the United States of America showed that the number of Influenza A infections (136,793 cases) was higher than that of Influenza B infections (86,498 cases).

Risk factors including the month of the year, age and gender play significant roles in the distribution of the Influenza illness and its treatment, which may have important public health implications.[20-22] We correlated the rate of Influenza-positivity by month between December 2019 and March 2020. Our findings show that Influenza A or B infection positivity was detected at the highest rate in December 2019. However, the highest number of tests was performed in January with a total of 980. Unusually, most of the positive cases were infected with Influenza B virus in our study. Influenza type A viruses are generally more common than Influenza type B virus due to the antigenic shift of proteins present on the virus surface or a combination with those viruses circulating in animals.[23] In similar studies, Influenza type A was reported at higher rates. Yang et al.[24] reported the positivity rate for Influenza type A (77.1%) to be higher than that of type B (22.9%) in China and other neighboring Asian countries such as Korea and Japan. Moreover, the incidence rate of Influenza type A and B were reported as 16.7 and 4.7 per 100,000 people-years, respectively in Iraq by Aufi et al.[25] After the 2009 pandemic in the World Health Organization European Region, Mook et al.[26], focused on alternating patterns of seasonal Influenza activity from 2010 to 2018 and their team showed that Influenza virus type A was the predominant circulating Influenza during five seasons (2010–2011, 2011–2012, 2013–2014, 2014–2015, and 2016–2017). Similarly, Panayiotou et al.[27] reported only Influenza A virus circulating in Cyprus in four consecutive seasons (2009–2013).

Furthermore, in February 2020, only half of the tests compared to January were performed due to a decrease in the number of patients and the positivity rate was determined to be higher for Influenza B (19.2%). During March 2020, 148 test kits were used, of which, 5.4% were positive for both Influenza A and Influenza B. After February 2020, the number of tests started to drop, reaching a 70% decrease in March, but there was no statistically significant relationship between Influenza A prevalence and the month (p=0.088). In contrast, the relationship

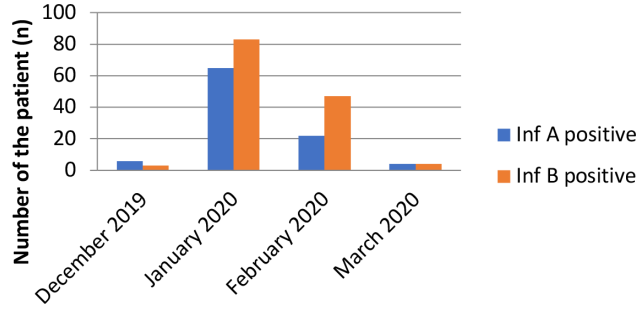

Figure 1. The distribution rate of Influenza A and B positivity by month.

*p<0.05 significant, Inf: influenza, n: number

Table 2. Seasonal pattern of Influenza activity in cities of Northern Cyprus

	Kyrenia (n, %)	Nicosia (n, %)	Morphou (n, %)	Famagusta (n, %)	p-value
Influenza A positive	17, 11.8%	69, 12%	4, 7.7%	7, 9.6%	0.763
Influenza B positive	21, 14.6%	97, 16.9%	9, 17.3%	10, 13.7%	0.838
Total positive	38, 26.4%	166, 28.9%	13, 25.0%	17, 23.3%	0.702

*p<0.05 significant, n: number.

Table 3. Influenza A and Influenza B positivity among genders

	Influenza A			Influenza B		
	Negative n (%)	Positive n (%)	p-value	Negative n (%)	Positive n (%)	p-value
Male	353 (88%)	48 (12%)	0.679	342 (85.3%)	59 (14.7%)	0.255
Female	394 (88.9%)	49 (11.1%)		365 (82.4%)	78 (17.6%)	
Total	747 (88.5%)	97 (11.5%)		707 (83.8%)	137 (16.2%)	

n: number.

Table 4. The rate of Influenza A and Influenza B positivity among different age groups

Influenza types	0–4 years, n (%)	5–14 years, n (%)	15–44 years, n (%)	>45 years, n (%)	p-value
Influenza A					
Negative	307 (86%)	187 (87.4%)	172 (91.5%)	81 (95.3%)	0.047*
Positive	50 (14%)	27 (12.6%)	16 (8.5%)	4 (4.7%)	
Influenza B					
Negative	313 (87.7%)	162 (75.7%)	153 (81.4%)	79 (92.9%)	0.000*
Positive	44 (12.3%)	52 (24.3%)	35 (18.6%)	6 (7.1%)	

*p<0.05 significant, n: number.

between the prevalence of Influenza B and the month was statistically significant (p=0.034). During the period between December 2019 to March 2020, the Influenza B positivity was more common (59%) than Influenza A (41%). In a study conducted by Basile et al.[28] in 2017–2018, it was shown that Influenza type B positivity was higher (63%) in comparison to that of Influenza type A (32.3%). In addition, according to the results of another study conducted by Karolyi et al.[29], 75.8% of Influenza positive cases were reported as Influenza type B positive in hospitalized patients via routine polymerase chain reaction (PCR). A study conducted by Yang et al.[24] showed that Influenza type B was predominant in Mongolia and Russia during the 2019 and 2020 seasons (80.7% and 77.2%, respectively).

The distribution of Influenza virus types also varies by age and by sex and this has important public health implications.[30] Children especially under the age of two years are at higher risk of serious illness compared to older children.[31] Therefore, we investigated the rate of the infections among different ages and genders in the current study. Our findings suggest that gender was not associated with the rate of Influenza infections for our study period. However, seasonal Influenza positivity was associated with age and this may be an important factor in becoming infected with the virus. The overall age distribution of Influenza type A cases was the highest among young children aged 0–4 (14.0%, p=0.047) and the lowest was detected among the elderly (4.7%). Koliou et al.[31] reported the first cases of Influenza in children aged 15 years and under in Cyprus in 2009. According to our findings, Influenza type B was most frequently determined in the 5–14 years age group (p=0.000). In a similar study by Mosnier et al.[18], Influenza type B was very common, especially in school-age children. For the Influenza species, it showed that the number of cases decreases with age and indicates a statistically significant inverse relationship.

Limitations of the Study

Our study has some limitations. The sample size and the technique we used lead to the limitations of our study. We could only test samples of individuals who attended Near East University Hospital and were tested using rapid antigen detection test kits. Although these tests provide rapid test results, they have limited analytical sensitivity to detect Influenza viruses in respiratory specimens and they do not provide information on the subtypes of specific virus strains. Therefore, a larger sample set is needed to estimate the accurate rate of seasonal Influenza viruses of the whole population in Northern Cyprus by means of molecular tests.

CONCLUSION

This study presents data on the rate of seasonal Influenza type A and B infections during the winter months between January and February and the beginning of spring. Despite the presence of Influenza, A cases, Influenza B cases remained predominant, especially in children between 0–14 years of age throughout the years 2019 and 2020. Our study shows

that the distribution of seasonal Influenza types was not associated with gender, however, age and the month of the year may have a significant role in infection rates and types. Therefore, people at risk age groups are recommended to have seasonal Influenza vaccinations as protection against pandemic Influenza strains.

MAIN POINTS

- In Northern Cyprus, there is not much data available on the prevalence of Influenza infections and this study presents scientific data on the rate of seasonal Influenza type A and B infections during the winter season.
- According to our results, the rate of Influenza B was more dominant compared to the rate of Influenza A in the period 2019-2020.
- Our findings also suggest that the seasonal Influenza positivity was associated with age, which is an important factor in becoming infected with the virus. Influenza A and Influenza B were found to be more dominant in individuals aged 0-4 years and in those between 5-14 years of age, respectively.
- Our results show that gender was not a significant factor in the rate and type of the infections. However, the rate of Influenza B infection differed by the month in which it occurred and the Influenza B activity was shown to peak in February, 2020.

ETHICS

Ethics Committee Approval: The study was approved by Near East University Institutional Review Board (decision no: NEU/2020/79-1069, date: 28.05.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

DISCLOSURES

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

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ORIGINAL ARTICLE

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A New Insight Into the Treatment-Naive HIV Infected Patients: Whole Blood Viscosity

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Abstract

BACKGROUND/AIMS: The thickness and stickiness of an individual's blood are measured by blood viscosity depending on frictional interactions between all major blood constituents such as red blood cells and plasma proteins. Blood viscosity, when it is elevated, is essential in the pathophysiology of vascular diseases. The present study employed an approach to determine if there is a correlation between blood viscosity and vascular comorbidities in human immunodeficiency virus (HIV)-positive subjects.

MATERIALS AND METHODS: Two hundred and seventeen people were selected to participate in this study. The HIV group included 110 treatment naïve patients, and the control group had 107 people of similar age and sex. Whole blood viscosity (WBV) was measured by a formula from the protein concentration of plasma and haematocrit at a high shear rate (208 s^{-1}) and a low shear rate (0.5 s^{-1}).

RESULTS: In contrast to the control group, WBV for LSR (53.5 25 vs. 39.1 25; p=0.001) and high shear rate (HSR) (16.8 1.2 vs. 15.9 1.4; p=0.001) was substantially higher in HIV infected patients. There was a substantial inverse correlation between the CD4 count and WBV in correlation analysis for LSR (r=-0.467; p<0.001) and HSR (r=-0.461; p<0.001) in patients with HIV. A significant correlation was detected for the WBV and high-sensitivity C-reactive protein (hsCRP) for LSR (r=0.506; p<0.001) and HSR (r=0.488; p<0.001) in the HIV group.

CONCLUSION: Our result shows a remarkable correlation between WBV and inflammation in treatment-naive HIV-positive individuals. The higher blood viscosity levels observed in those subjects with lower CD4 counts may also point to a link between viscosity and the severity of the immune deficiency.

Keywords: HIV, C-reactive protein, blood viscosity, CD4 cell count

Introduction

Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) poses a significant public health challenge, with a currently estimated 40 million individuals living with the virus globally.[1] HIV-infected patients' lifespans have dramatically increased since antiretroviral therapy, and as a result, HIV treatment has evolved to include long-term comorbidities.[2] Patients with HIV infection have been shown to have a variety of cardiovascular, renal, metabolic, and endocrine disorders.[3]

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The viscosity of blood is its intrinsic resistance to flow, depending on frictional interactions between all major blood constituents such as red blood cells and plasma proteins.[4]

Under normal physiological conditions, regulatory mechanisms keep the blood viscosity at a relatively stable level. However, inflammation-related disorders in these regulatory mechanisms increase blood viscosity, usually correlated with endothelial cell dysfunction. As a factor affecting tissue perfusion, blood viscosity has a potential role in cardiac disease, cerebral ischemia, renal disease, and metabolic disorders.[4-6] Understanding this hemorheological change may provide insight into the pathogenesis of HIV-related vascular diseases and their clinical sequela. The current research aims to understand the correlation between the severity of the infection and blood viscosity in newly identified, treatment-naive HIV-positive individuals.

MATERIALS AND METHODS

In this multicenter study, we retrospectively reviewed HIV-infected subjects between January 1, 2013 and December 31, 2019. Age, sex, clinical findings, laboratory, electrocardiographic, and echocardiographic imaging were studied from the patients' medical records.

The study's power analyses and sample size were computed using G*Power Version 3.1.9.2. (Aichach, Germany) The sample size was calculated using a 1:1 allocation ratio to estimate the number of people that could be enrolled in a reasonable period. According to the calculations, the minimal sample size for all groups was 210 subjects to detect differences in results with a statistical power (1-value) of 95% and a type 1 (α) error of 0.05. The HIV-infected group needed to be 105 people, and the control group needed to be 105. In the current study, a total of 217 participants were recruited. The HIV group included 110 newly diagnosed individuals (68 males, 41.3±9.1 years), while the control group consisted of 107 people (71 males, 40.8±12.0 years).

This study did not include patients with documented cardiac and cerebrovascular disease, renal failure, chronic lung disease, pregnancy, or metabolic disorders. Those patients taking antiretroviral drugs that potentially impact the blood's basic viscosity measures were also excluded from this trial. The CD4 cell counts were obtained from the patients' medical records. The participants in the control group gave their informed consent. The Ethics Committee of the University of Kyrenia approved the report (reference no: 2019/01-2015, date: 07.05.2019).

Blood samples were taken via antecubital veins and collected in serum separation gel tubes (yellow) for biochemical tests and Becton Dickinson Vacutainer for haematological tests. Glucose, hsCRP, creatinine, and lipids were delivered by conventional methods.[7] A blood counter (Cell-Dyn Ruby; Abbott Laboratories™ 08H6701) was used for whole blood counts.

Htc (%) and plasma protein concentration (TP; g/L) at a high shear rate (HSR; 208 s^{-1}) and a low shear rate (LSR; 0.5 s^{-1})[8] were used for WBV calculation using a validated method of de Simone et al.[8] and Nwose and Richards'[9] recommendations:

$$\text{HSR: WBV } (208\ s^{-1}) = (0.12 \times \text{HCT}) + 0.17 \times (\text{TP} - 2.07) \quad (1)$$

$$\text{LSR: WBV } (0.5\ s^{-1}) = (1.89 \times \text{HCT}) + 3.76 \times (\text{TP} - 78.42) \quad (2)$$

Statistical Analysis

For statistical analysis (SPSS Inc. Chicago, IL, USA), SPSS version 22 was employed. Visuals (histograms, probability plots) were used to examine all numerical variables. Analytic techniques (Kolmogorov–Smirnov/Shapiro–Wilk's test) were used to verify if they were normally distributed. Continuous variables were described as the mean ± standard deviation, or medians (with interquartile ranges). Categorical variables were defined as the number of patients and percentages. The participants in the trial were divided into two groups: control and HIV. Statistical comparisons of categorical data were made using the Pearson's χ^2 test and Fisher's exact test. The student's t-test was used for normally distributed parameters, and the Mann–Whitney U test was used for non-normally distributed values. The correlation coefficients and significance of the correlations between non-normally distributed hsCRP, CD4 counts, and WBV scores were determined using the Spearman correlation test. ROC curve analysis was used to examine the potential of WBV and its ability to predict WBV for both LSR and HSR in the context of HIV. When a significant cut-off value was found, the specificity, sensitivity, and positive and negative predictive values were presented. A p-value below 0.05 was considered to indicate a statistically significant difference.

RESULTS

The participants in this study were divided into groups based on age, gender, smoking status, and body mass index (BMI). The baseline clinical and laboratory values of the research groups are given in Table 1. The HIV group consisted of 110 individuals (68 males, 41.3±9.1 years), and the control group consisted of 107 subjects (71 males, 40.8±12.0 years).

Hematological parameters including hemoglobin, red blood cell distribution (RDW), mean platelet volume (MPV), and biochemical tests such as urea, serum creatinine, glucose, serum albumin, globulin, lipid profile, potassium, and sodium levels were not statistically significant among the groups. However, hsCRP, hematocrit, and total protein levels in the HIV group were considerably higher than those in the control group (p=0.00). White blood cell and platelet counts were considerably lower in the HIV group than in the control group (all p=0.02) (Table 1).

When compared to the control group, HIV patients had significantly higher WBV for LSR (53.5±25 vs. 39.1±25; p<0.001) and HSR (16.8±1.2 vs. 15.9±1.4; p<0.001) (Table 2). There was a significantly inverse correlation between CD4 count and WBV for LSR (r=-0.467; p<0.001) and HSR (r=-0.461; p<0.001) in the HIV group (Figures 1 and 2) in correlation analysis. Additionally, there was significant correlation between the hsCRP and WBV for LSR (r=0.506; p<0.001) and HSR (r=0.488; p<0.001) in the HIV group (Figures 3 and 4).

A WBV for LSR cut-off value of ≥44 with a sensitivity of 74% and specificity of 72% [area under the curve (AUC)=0.809, p<0.001] and a HSR cut-off value of ≥16 with a sensitivity of 80% and specificity of 74% (AUC=0.837, π<0.001) for the prediction of HIV (Figure 5) were determined in the receiver operating characteristic curve analysis.

DISCUSSION

There is no direct study investigating the effect of WBV for both LSR and HSR in the treatment of naïve HIV-positive patients. Our research showed that HIV-infected participants have considerably higher blood viscosity levels than their age, and sex-matched controls. WBV is

responsible for the blood's intrinsic resistance to flow in vessels and it has a remarkable association with vascular diseases.[10-12] Our findings confirm that HIV-infected subjects have increased blood viscosity. A few case reports about hyper-viscosity in HIV-infected patients leading to severe vascular diseases have been described recently. Additionally, these reports claim that the risk of vascular diseases is mostly linked to the use of antiretroviral agents.[13-15]

The current consensus is that WBV is directly proportional to endothelial shear stress.[16] Due to frictional shear force, the blood flowing through the artery wall unit creates endothelial shear stress. In normal conditions, the shear stress is substantially higher than the yield stress, allowing for optimal microvascular circulation perfusion. In particular, pathophysiologic low shear stresses were found to relate to increased inflammatory parameters.[17,18] This study suggests that hyper-viscosity may be a sign of inflammation, which is linked to the pathophysiology of HIV-related vascular diseases.

It is known that blood properties are altered in situations such as inflammation, and this variance prevents adequate blood flow leading to the occurrence of cardiovascular diseases, cerebral ischemia, renal failure, and other diseases.[19,20] This alteration may be associated with relatively higher C-reactive protein (CRP) and immunoglobulins in HIV-infected patients who have been exposed to viral antigens regularly.[13,15] Several studies have shown that inflammatory parameters such as CRP increases in HIV patients.[21-23] Our research is also in accordance with previous studies. Given the significance of inflammation, it is reasonable to conclude that WBV and hs-CRP have strong positive associations for HSR and LSR in our research.

Table 1. The baseline characteristics and laboratory findings of the study groups (n=217)

Variables	Control group (n=107)	HIV (n=110)	p-value
Clinical parameters			
Age, years	41.3±9.1	40.8±12.0	0.73
Male, n (%)	68 (63%)	71 (65%)	0.87
Current smoker, n (%)	62 (58%)	74 (67%)	0.15
BMI, (kg/m²), n (%)	24.8±3.3	25.2±2.5	0.31
Laboratory parameters			
Hemoglobin, g/dL	13.6±2.1	13.9±1.9	0.27
Haematocrit, %	40.1±0.4	41.7±0.6	<0.001
WBC, $\times10^3$/µL	8.5± 2.1	7.6±3.5	0.02
MPV, $\times10^3$/µL	9.1±1.1	8.9±0.6	0.09
RDW, $\times10^3$/µL	14.5±3.1	14.2±2.8	0.45
Platelets, $\times10^3$/µL	245±76	223±69	0.02
Glucose, mg/dL	93±15	92±21	0.68
Urea, mg/dL	19 (13–25)	13 (10–16)	0.33
Serum creatinine, mg/dL	0.8 (0.7–1)	0.9 (0.8–1)	0.69
Total protein, g/L	67.2±8.1	73±6.2	<0.001
Total cholesterol, mg/dL	179±41	183±49	0.51
LDL cholesterol, mg/dL	110±35	114±38	0.42
HDL cholesterol, mg/dL	45±16	42±13	0.13
Triglycerides, mg/dL	148±75	148±101	0.92
Sodium, mEq/L	140±2.8	141±3.6	0.41
Potassium, mEq/L	4.4±0.4	4.3±0.5	0.16
hsCRP, mg/dL	0.2 (0.1–0.2)	4 (1–6)	<0.001
CD4 count	-	360 (233–647)	-

HIV: human immunodeficiency virus, BMI: Body Mass Index, hsCRP: high-sensitivity C-reactive protein, HDL: high-density lipoprotein, LDL: low-density lipoprotein, RDW: red cell distribution width, WBC: white blood cell count, MPV: mean platelet volume, n: number.

Table 2. Comparison of the study groups' WBV parameters

Variables	Control group	HIV group	p-value
WBV at HSR, 208 s^{-1}	15.9±1.4	16.8±1.2	<0.001
WBV at LSR, 0.5 s^{-1}	39.1±25	53.5±25	<0.001

HIV: human immunodeficiency virus, WBV: whole blood viscosity, HSR: high shear rate, LSR: low shear rate.

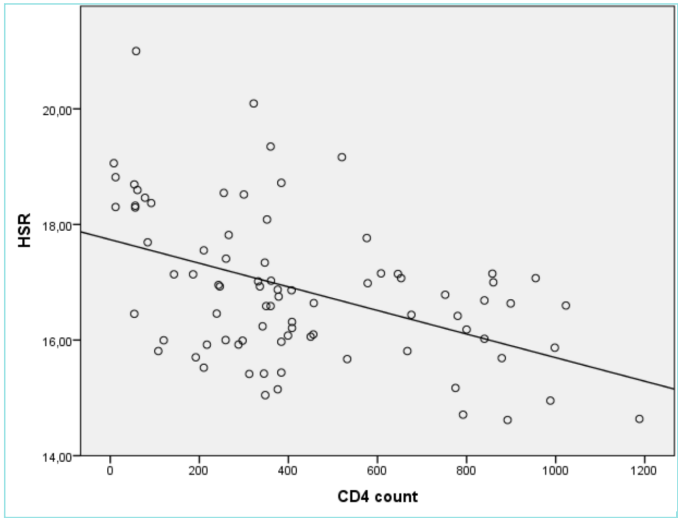

Figure 1. CD4 count and HSR correlation in the HIV group.
HSR: high shear rate, HIV: human immunodeficiency virus

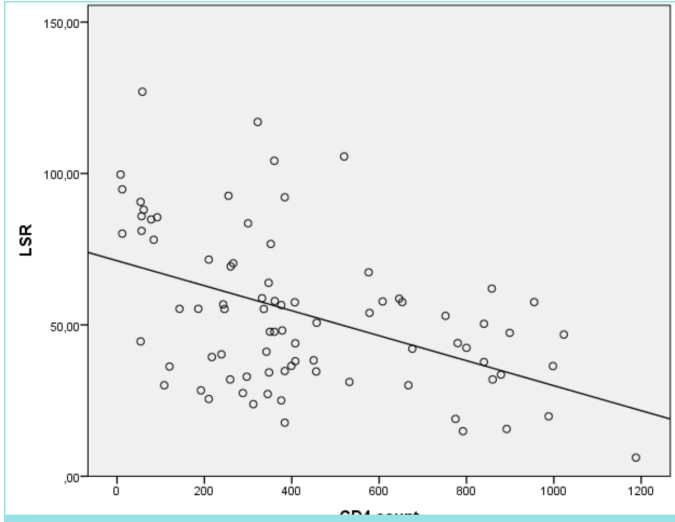

Figure 2. CD4 count and LSR correlation in the HIV group.
LSR: low shear rate, HIV: human immunodeficiency virus

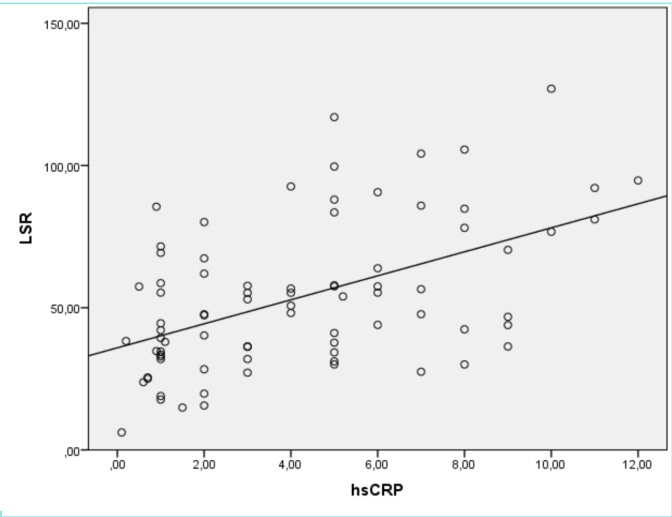

Figure 3. Hs-CRP and LSR correlation in the HIV group.
LSR: low shear rate, HIV: human immunodeficiency virus

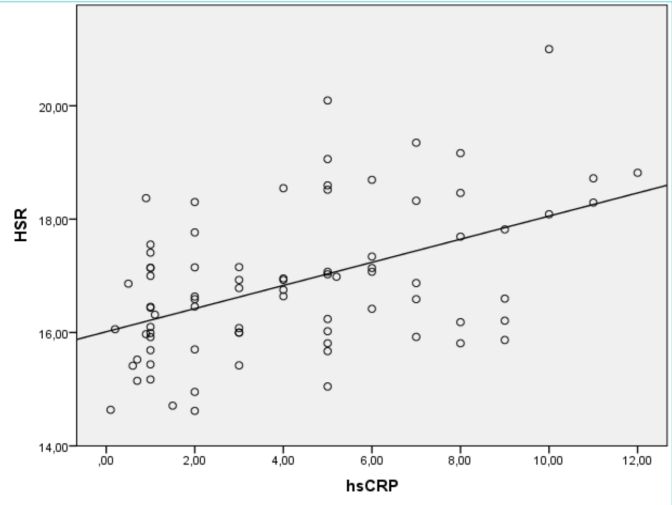

Figure 4. Hs-CRP and HSR correlation in the HIV group.
HSR: high shear rate, HIV: human immunodeficiency virus

CD4 cell count as a significant predictor of the disease severity has a vital role in the decision making and comprehension of the progression in HIV-infected patients.[24] In our study, a significant negative association was observed between CD4 and WBV.

As blood viscosity is linked to microvascular diseases, more studies are needed to determine this situation more accurately.

Limitations of the Study

Our study must be interpreted in light of certain limitations. The low sample size of our study is suboptimal for further statistical analysis. Furthermore, WBV was not validated using a viscometer to calculate viscosity reliably.

CONCLUSION

The cause of increased blood viscosity in HIV-infected individuals is probably multifactorial. Our result indicates the endothelium's

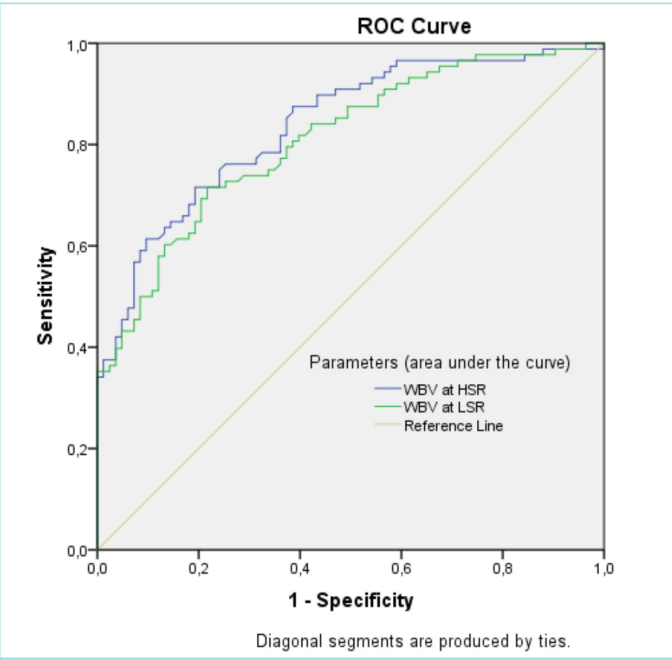

Figure 5. Receiver operating characteristic curve (ROC) analysis of WBV at the HSR and LSR for HIV prediction and 95% confidence intervals curve.
HSR: high shear rate, LSR: low shear rate, WBV: whole blood viscosity, HIV: human immunodeficiency virus

inflammatory injury, pointing to endothelial dysfunction of treatment-naive HIV-positive participants. The higher blood viscosity levels observed in those patients with lower CD4 counts may also point to a link between viscosity and the severity of the immune deficiency. Despite convincing evidence that blood viscosity regulation is beneficial for disease control, we believe that the bio-effectiveness of this feature is neglected in clinics. We recommend future studies to investigate all determinants of hemorheological alterations in HIV-infected subjects, which may provide insight into the pathogenesis of HIV-related comorbidities.

MAIN POINTS

- Treatment naïve HIV-positive individuals had elevated blood viscosity levels when compared to the control group.
- The higher levels of blood viscosity observed in those patients with lower CD4 counts may also point to a link between viscosity and the severity of immune deficiency.
- In HIV-positive individuals, increased blood viscosity can lead to vascular comorbidities.
- Blood viscosity regulation is helpful in disease control, and future studies may focus on all determinants of hemorheological alterations in HIV-infected patients.

ETHICS

Ethics Committee Approval: The Ethics Committee of the University of Kyrenia approved the study (reference no: 2019/01-015, date: 07.05.2019).

Informed Consent: The participants in the control group gave their informed consents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.E., B.B., Design: E.Ü.E., K.S., B.B., Supervision: E.Ç., K.S., Data Collection and/or Processing: F.S.Y., A.A., Analysis and/or Interpretation: E.Ç., Literature Search: H.E., E.Ç., F.S.Y., A.A., Writing: H.E., E.Ü.E., F.S.Y., A.A., Critical Review: K.S., B.B.

DISCLOSURES

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

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ORIGINAL ARTICLE

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Colour Perception Studies on Students of Nnamdi Azikiwe University Nnewi Campus, Nigeria

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ABSTRACT

BACKGROUND/AIMS: Colour blindness can be frustrating and may limit participation in some occupations. The career choices of colour blind people may be limited for safety reasons. In medical education, colour perception is important in histology, histochemistry, biochemical tests and other colour based assessments. The aim of this study was to evaluate the status of visual colour perception among medical students in Nnamdi Azikiwe University, Nnewi Campus, Nnewi, Nigeria.

MATERIALS AND METHODS: A descriptive cross-sectional study design was carried out between September and October 2019. It was approved by the Faculty of Basic Medical Sciences Ethical Board. Ocular examination including visual acuity assessment using Snellen's chart and a colour vision test with Ishihara 24 plate album was performed on 291 medical students randomly selected for the study. The data collected was analysed.

RESULTS: From the study, it was discovered that the overall prevalence of congenital colour vision deficiency was 1.7% with a male to female ratio of approximately 2:1 respectively.

CONCLUSION: This signifies that early diagnosis is valuable in career and vocational planning in order to reduce any difficulties in living and learning situations associated with colour blindness.

Keywords: Colour blindness, medical, students, vision, Ishihara, Snellen's chart

INTRODUCTION

Visual problems are an important factor that can pose a serious challenge to educational activities in the school, hence good vision is required to achieve optimum results in the learning process. Colour is a visual enhancement element that is important in enriching the learning process.[1]

Colour perception is the ability to distinguish between various wavelengths of light waves and to perceive these differences as differences in hue. The normal human eye can discriminate among hundreds of such bands of wavelengths as they are received by the colour-sensing cells (cones) of the retina. These cones have light sensitive pigments that enable humans to recognize colour. Three types of cones occur in the macula and each contains a distinctive type of pigment which is sensitive to either red, green or blue light (long, medium or short wavelengths) based on their respective wavelengths. A given colour stimulates all three types of receptors with varying effectiveness, and the pattern of these responses determines the colour perceived. Genes contain the coding instructions for the cone pigments, and when the coding instructions are wrong, the wrong pigments will be produced, and the cones will be sensitive to different wavelengths of light resulting in a colour perception deficiency. The colours that we see are completely dependent on the sensitivity ranges of these pigments.

Colour vision deficiency (colour blindness) is the inability to see differences between certain colours that can be generally

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distinguished by normal people.[2] These individuals still recognize colour though it is imperfect.[2] Colour blindness is a sex-linked genetic characteristics affecting more males than females. It occurs due to varied forms of mutation. The gene for colour blindness is recessive and carried on the X-chromosome. Red-green colour vision defects are the most common form of colour vision deficiency, where either the photo-pigment of the red or green cone is absent (Deutranopia or Protanaopia) or where the photo-pigment response of the green cone is shifted towards the red cones (Deuteranomaly) or vice versa (Protanomaly) and it is genetically determined by the X-linked recessive gene.[3] Affected individuals have trouble distinguishing between some shades of red, yellow, and green.

Blue-yellow colour vision defects (also called tritan defects), which are rarer, cause problems with differentiating between shades of blue and green and lead to difficulties in distinguishing dark blue from black. The genes responsible for the red-green colour vision defects are localized on the long arm of the X chromosome at Xq28,[4] whereas the blue pigment gene is located on chromosome 7, an autosome, at 7q32.[5] Green pigment genes vary in number among colour-normal individuals and, together with a single red pigment gene, are thought to reside in a head-to-tail tandem array within the X chromosome.[3] Although colour blindness is a hereditary trait, it has also been reported that some acquired characteristics such as metabolic disorders such as diabetes, sickle cell anaemia, damage to the eyes, nerve and brain; drugs (e.g., digoxin, ethambutols, plaquenil, chloroquine etc); and other chemicals could also predispose one to colour blindness.[6] These two forms of colour vision deficiency disrupt colour perception but do not affect the sharpness of vision (visual acuity).[7] Also, a complete absence of colour vision (total colour blindness), which is rare, may be present.

Colour blindness can be frustrating and may limit participation in some occupations. It can affect access to education, exam grades and career choices.[8] The career choices of colour blind people may be limited in a few areas of industry, transport services and the armed forces. It is accepted that colour blindness could potentially cause problems and it is recognized that there are certain job types in which the colour blind people are not suited to, mostly for safety reasons.[8] Also, colour blindness may pose occupational handicaps in certain areas of medical practice and the health sciences as colour perception is important in histology, histochemistry, biochemical tests and other colour based assessments.

According to Colour Blind Awareness,[9] there is general agreement that, worldwide, 8% (1 in 12) of men and 0.5% (1 in 200) of women have colour blindness. These figures rise in areas such as Scandinavia where there is a greater number of Caucasians per head of population. Countries such as India and Brazil have a relatively high incidence of colour blindness because of the large numbers of people with mixed race genes in their genetic history. By contrast, in sub-Saharan Africa, there are few colour blind people. Studies among some African populations have reported frequencies of 2.2% and 0.0% in males and females respectively in Libya, and 3.3% and 0.2% in males and females of Zulus descent.[10,11] Also, previous studies conducted among school children in the Southern and Northern parts of our country have reported a general prevalence of 2.6% and 1.5%, respectively.[12,13] This study, however, aims to determine the prevalence of congenital colour blindness among Nnamdi Azikiwe University Medical School students.

MATERIALS AND METHODS

Research Design

A descriptive cross-sectional survey was carried out to determine the prevalence of congenital colour blindness among medical students of Nnamdi Azikiwe University, Nnewi Campus between September and October, 2019.

Study Area

Nnamdi Azikiwe University, Nnewi Campus is situated in Okofia; one of the villages that make up Nnewi North Local Government Area, with an estimated population of about 15,000. Its latitude is 5^0 58' 26" North and its longitude 6^0 53' 32" East.

Sample

Two hundred and ninety-one students were randomly selected from the population of the study area.

Inclusion Criteria

Students' willingness to take part in the research, and being a medical student of the Faculty of Basic Medical Sciences were the inclusion criteria.

Exclusion Criteria

Students with previous ocular surgery, and the presence of a colour defect in one eye only were excluded from the study because this defect was acquired.

Instrument for Data Collection

Standard Snellen's chart, Ishihara 24 plates (Dr Shinobu Ishihara - 2017 Edition by Kanehara & Co., LTD), Eye Occluder and Test Form were used.

Ethical Consideration

Ethical approval to carry out this study was obtained from the Ethics Board of the Faculty. Only minimal identifying data was taken in order to preserve the anonymity of the students' responses and results. Prior to the investigation, a written informed consent form was obtained from the students after the procedure was explained to them. Only those who met the inclusion criteria participated in this study.

Procedure

A self-developed test form was used as part of the instrument for the collection of the students' their data on their ocular history, visual acuity and colour perception.

The procedures (for visual acuity and colour vision testing) were explained to the students prior to the examination. An eye occluder was used to occlude the eye not being tested while the other eye was being assessed.

Assessment of visual acuity was performed at a place with good daylight illumination using the standard Snellen's chart at a distance of 6 m. This was done monocularly for both eyes. All students who used spectacles had their visual acuity assessed while wearing their own spectacles. Thereafter, a colour vision test with 20 Ishihara plates was done uni-ocularly in natural daylight with the plates held at a distance of 45 cm. In the 24-plate 2017 edition, plate 1 is a demonstration plate; plates 2 to 17 and 22 to 24 are for screening, while plates 18 to 21 are for illiterates.

The students were asked to read the numerals seen on each plate within 3 secs before moving on to the next plate. Failure of the Ishihara in only one eye is suggestive of an acquired cause of colour vision deficiency, and such students were excluded from this study. Students who failed eight or more plates were considered to be colour blind.

Statistical Analysis

The collected data was entered into Microsoft Excel 2007 (One Microsoft Way Redmond, Washington, USA) and analysed with SPSS version 20 (Chicago, Illinois, USA). A descriptive analysis was performed to calculate the prevalence and percentage of occurrence. The analysed data are presented in Tables 1-4 and Figures 1 and 2.

RESULTS

A total of 291 students participated in the study consisting of 128 males and 163 females.

Table 1. Prevalence of known vision defect

Vision defect	Gender		Total
	Male, n (%)	Female, n (%)	n (%)
Yes	19 (14.7)	39 (23.9)	58 (19.9)
No	109 (85.2)	124 (76.1)	233 (80.1)
Total	128 (100)	163 (100)	291 (100)

n: number of the students.

14.7% of the males (n=19) and 23.9% of the females (n=39) have a known vision defect. The total number of students that have a known vision defect being 58 (19.9%), while 233 (80.1%) of students do not have any known vision defect.

The majority of the students (male: n=123, female: n=152) are aware of the term 'colour blindness'.

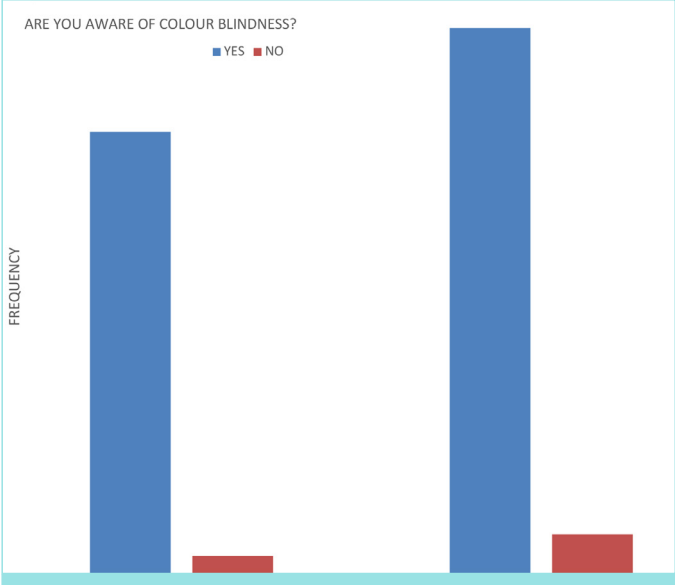

Figure 1. Distribution of students that are aware of the term 'colour blindness'.

Table 2. Distribution of students aware and those not sure of having colour blindness

	Gender		Total
	Male, n (%)	Female, n (%)	n (%)
Yes	2 (1.6)	0 (0)	2 (0.7)
No	101 (78.9)	123 (75.5)	224 (77)
Do not know	25 (19.5)	40 (24.5)	65 (22.3)
Total	128 (100)	163 (100)	291 (100)

n: number of the students.

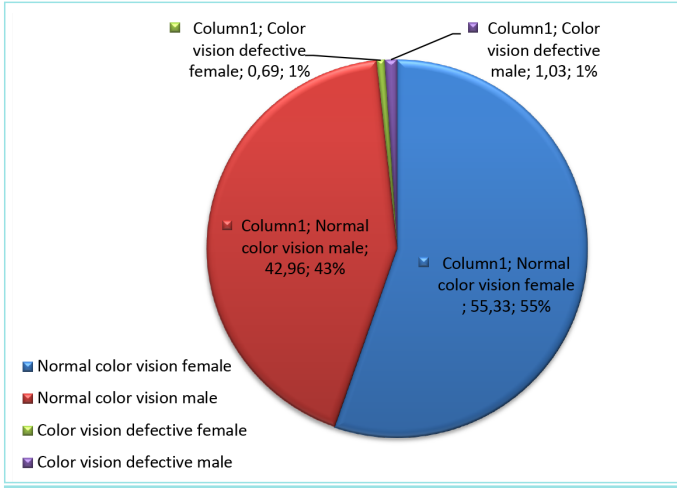

Figure 2. Prevalence of normal/defective colour vision in the population.

Majority of the students (n=224, 77%) indicated that they do not have colour blindness. Whereas 65 (22.3%) do not know if they are colour blind or not, none of the female respondents accepted being colour blind. However, two of the males knew that they have colour blindness.

One hundred and forty-four (49.5%) of the students have a normal visual acuity of 6/6 in the right eye, 137 (47.1%) in the left eye, while 121 (41.6%) have visual acuity of 6/6 when using both eyes. No male/female had visual acuity of 6/36 when both eyes were examined together. Therefore, the majority of the students including the colour blind ones have normal visual acuity.

Two hundred and eighty-six students representing 98.3% were found to have normal colour vision while only five students (1.7%) were found to have colour vision deficiency. As indicated in Table 3, colour blindness in our subjects occurs independently of visual acuity and other vision defects (myopia, hypermetropia and so on).

From the population, 2.34% and 1.23% of the male study population and female study population respectively have colour blindness, while 97.66% and 98.77% of male population and female study population respectively do not have colour blindness.

DISCUSSION

Colour blindness is a naturally challenging vision defect which can significantly affect quality of life and career choices of individuals. This study provides a description of colour vision deficiency in the study area for the first time among medical students of Nnamdi Azikiwe

Table 3. Result of visual acuity

Visual acuity	Right eye		Left eye		Both eyes	
	Male, female n (%)	Total	Male, female n (%)	Total	Male, female n (%)	Total
6/36	1 (0.8), 0 (0)	1 (0.3)	1 (0.8), 0 (0)	1 (0.3)	0	0
6/24	1 (0.8), 5 (3.1)	6 (2.1)	0 (0), 3 (1.8)	3 (1)	1 (0.8), 1 (0.6)	2 (0.7)
6/18	3 (2.3), 2 (1.2)	5 (1.7)	3 (2.3), 2 (1.2)	5 (1.7)	0 (0), 1 (0.6)	1 (0.3)
6/12	4 (3.1), 7 (4.3)	11 (3.8)	1 (0.8), 4 (2.5)	5 (1.7)	3 (2.3), 2 (1.2)	5 (1.7)
6/9	1 (0.8), 6 (3.7)	7 (2.4)	2 (1.6), 5 (3.1)	7 (2.4)	3 (2.3), 1 (0.6)	4 (1.4)
6/7.5	9 (7.0), 20 (12.3)	29 (10)	18 (14.1), 20 (12.3)	38 (13.1)	1 (0.8), 13 (8.0)	14 (4.8)
6/6	66 (51.6), 78 (47.9)	144 (49.5)	60 (46.9), 77 (47.2)	137 (47.1)	51 (39.8), 70 (42.9)	121 (41.6)
6/4	43 (33.6), 45 (27.6)	88 (30.2)	43 (33.6), 52 (31.9)	95 (32.6)	69 (53.9),75 (46.0)	144 (49.5)
Total	128 (100), 163 (100)	291(100)	128 (100), 163 (100)	291 (100)	128 (100), 163 (100)	291 (100)

n: number of the students.

University, which provides basic information on the prevalence of congenital colour blindness in the Faculty of Basic Medical Sciences of this institution. During the course of the research, both inherited and acquired colour blindness was discovered; though the number of students with normal colour vision predominates. However, this study is centred on congenital colour blindness which is caused by mutations in the gene responsible for colour vision on the X chromosome. As a result, inherited colour blindness is more prevalent in males compared to females. However, a female with two X chromosomes bearing the mutated genes will also be colour blind.

The prevalence of congenital colour vision defects as detected in this study is 1.7% (5 of 291 students) which was lower compared to figures in previous studies such as Ativie et al.[14] with 1.87% in Ugep, Cross River State and Oduntan et al.[15] with 2.5% in Lagos, Nigeria. Additionally, prevalences of 2.6% and 1.5% were reported in Southern and Northern parts of Nigeria respectively by Tabansi et al.[12] and Abah et al.[13] A comparison of the prevalences of colour blindness in other studies to the rate of 1.7% as seen in the present study showed that there is no significant difference among the Nigerian populace despite differences in habitats. Furthermore, referring to similar studies conducted in other African countries, Woldeamanuel and Geta[16] reported a congenital colour blindness prevalence of 4.2% in Southern Ethiopia. Also, Rahman et al.[10] and Pickford and Pickford[11] reported a prevalence of 2.2% and 3.57% in Libya and Zulu descent people respectively. This indicates that the prevalence of congenital colour blindness among African countries is comparative.

The prevalence of colour blindness in European Caucasians is about 8.4% in both men and women and between 4% and 6.5% in men of Chinese and Japanese ethnicity.[17] Furthermore, in Australia, there is a prevalence of 8% and 0.4% in males and females respectively.[18] Scandinavia also has a high prevalence of approximately 10%–11% in men. On the other hand, in sub-Saharan African nations, the prevalence of colour blindness is significantly lower compared to European Caucasians. Therefore, there is ample indication that the prevalence of colour blindness among black Africans is low compared to that of Caucasians (especially Scandinavians). The higher rate of colour blindness in Europeans and Asians is attributed to a large number of people with mixed race genes in their genetic history unlike that of Africans.

Table 4. Result of colour vision assessment

Colour Chart Score (numbers failed)	Colour blindness status	Male, n (%)	Female, n (%)	Total, n (%)
<8	Not colour blind	125 (97.7)	161 (98.8)	286 (98.3)
8 and above	Colour blind	3 (2.3)	2 (1.2)	5 (1.7)
Total		128 (100)	163 (100)	291 (100)

n: number of the students.

From our results, it is seen that only five students (1.7%) out of a population of 291 are colour blind. This verifies the general claim that colour blindness is a rare defect in Africa. The male respondents had a prevalence of 2.34% while females had a prevalence of 1.23%. This showed that the difference in occurrence of colour blindness between males and females is insignificant, which is in contrast to other studies conducted by Woldeamanuel and Geta[16], Ugalahi et al.[19] and Rahman et al.[10], where the prevalence of colour blindness is more in males than in females.

It was also discovered that of the five colour blind students, only two males were aware of having colour blindness. The third male who claimed not to have the defect actually had it. Likewise, the two females who were found to have colour blindness were not aware of their condition. This is in agreement to studies done by Mulusew and Yilikal[20] and Woldeamanuel and Geta[16], which reported that almost all of the study subjects were not aware of their colour vision status. Moreover, all of these five students who had colour blindness knew about this condition. Fifty-eight of the respondents, consisting of 19 males and 39 females, indicated that they have known vision defects such as myopia and hypermetropia, while the rest claim to have normal visual acuity.

Visual deficits among the medical students have been reported to be high and this negatively impacts students' learning and performance.[21] However, visual acuity assessment revealed that the majority of the respondents had normal or better than normal visual acuity. The visual acuity of the colour blind individuals was normal at a distance of 6 m except for one female colour blind individual who had myopia.

CONCLUSION

In some professions, proper colour recognition is essential and early detection of colour blindness is useful to avoid occupational hazards. This study shows that the prevalence of congenital colour blindness is 1.7% among medical students and it also raises awareness in those affected to enable them make any necessary adjustments. The prevalence of congenital colour blindness among medical school students can be said to be similar to other studies in our country. Colour blindness therefore can be considered a rare defect.

MAIN POINTS

Good vision is required to achieve optimum results in medical education and colour blindness could affect the learning process of a medical student when undertaking some tasks.

The prevalence of congenial colour blindness among medical students is 1.7% with a male to female ratio of approximately 2:1 respectively.

An early diagnosis of vision problems is valuable in career and vocational planning in order to help reduce the difficulties faced by people with vision defects.

ETHICS

Ethics Committee Approval: Nnamdi Azikiwe University Faculty of Basic Medical Science Ethics Committee (approval no: NAU/CHS/NC/FBMS/271, date: 15.10.2019).

Informed Consent: Prior to the investigation, a written informed consent form was obtained from the students after the procedure was explained to them.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: N.D., E.N., Design: N.D., E.N., D.C.I., Supervision: N.D., D.C.I., Data Collection and/or Processing: N.D., D.C.I., Analysis and/or Interpretation: N.D., D.C.I., Literature Search: N.D., D.C.I., Writing: N.D., E.N., D.C.I., Critical Review: E.N., D.C.I.

DISCLOSURES

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ORIGINAL ARTICLE

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The Association of ERG and c-erbB2 Expressions With Gleason Scoring in Adenocarcinomas of the Prostate

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ABSTRACT

BACKGROUND/AIM: We aimed to determine erythroblast transformation-specific-related gene (ERG) and c-erbB2 expression in patients with adenocarcinoma of the prostate and to investigate the association of these proteins with tumor growth and/or Gleason score, which is the main prognostic marker in these patients.

MATERIALS AND METHODS: Radical prostatectomy materials of 59 patients with acinar adenocarcinoma were included in this study. Immunohistochemical analysis for ERG and c-erbB2 was performed. The association of ERG and c-erbB2 expressions with International Society of Urologic Pathologists (ISUP) grade, tumor volume and patient age was investigated.

RESULTS: ISUP grade was 1 (equivalent to a Gleason score of 6) in 23 tumors while the rest of the cases were Gleason score >6 tumors. ERG expression was detected in 37.5% of the cases. None of the cases had c-erbB2 expression. There was no significant difference in ERG staining between the low-risk (ISUP 1) and high-risk (ISUP >1) groups (p=0.602). Evaluation of all ISUP groups with the Kruskal–Wallis test showed no significant difference across the groups in terms of ERG expression (p=0.374).

CONCLUSION: The present study reflects the ERG expression rate (37.5%) in patients with carcinoma of the prostate in Turkey. Our findings support that ERG overexpression is involved in the pathogenesis but has no association with histological grade in prostate carcinoma.

Keywords: Prostate carcinoma, Gleason score, ERG, c-erbB2

INTRODUCTION

Prostate carcinoma (PCa) is a common malignant tumor of the male genital system and the second most lethal cancer in men.[1] In cancer research, one of the main goals is to identify the mutations responsible for the transformation of a tumor into an aggressive cancer, which may advance locally and lead to distant metastasis. Identifying the mutations is of particular importance in PCa due to the relatively slow course and low mortality of this malignancy.[2]

Studies have shown the fusion of the androgen-induced *TMPRSS2* gene, also located on chromosome 21, to the proto-oncogene, erythroblast transformation-specific (ETS)-related gene (ERG) in 50% of patients with PCa.[3] This fusion results in an increased expression of the ERG protein. Increased ERG expression is thought to be important in tumor proliferation and invasion, acting as a transcription factor for the downregulation of a number of genes, and therefore, thought to be oncogenic. ERG overexpression arising from the *TMPRSS2-ERG* fusion in tissue samples can be reliably detected using immunohistochemistry (IHC).[4,5] Whether ERG overexpression in PCa is a marker of aggressive tumors and, therefore, of poor prognosis remains a matter of debate.[4,6,7] Furthermore, there are studies reporting that ERG expression is more common in western countries compared to Asia, where this rate may be as low as 30%.[3,4]

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C-erbB2 expression has been widely studied in breast, ovarian, and gastric cancers, and improved prognosis has been documented with the use of trastuzumab [the humanized monoclonal anti-human epidermal growth factor receptor 2 (HER2) antibody] in the treatment of breast carcinoma.[8,9] Different rates of c-erbB2 expression have been reported in studies investigating PCa in patients with clinically localized PCa,[10] following neoadjuvant androgen ablation,[11,12] and in high-risk carcinoma of the prostate.[9,12]

The Gleason score is an important classification developed to determine the prognosis of prostate adenocarcinoma; however, the International Society of Urological Pathology (ISUP) recommended stratification of Gleason scores into prognostic groups in 2005. In this regard, tumors with a Gleason score of 6 are considered as low-risk tumors with prognostic grade 1, and those tumors with a Gleason Score >6 as high-risk tumors.[13]

In the present study, we aimed to determine ERG and c-erbB2 expression rates in patients with prostate adenocarcinoma, to investigate the correlation between these proteins and tumor development, and to evaluate the relationship between ERG and c-erbB2 expression in ISUP low- and high-risk groups defined according to the main prognostic marker, i.e. their Gleason score.

MATERIALS AND METHODS

A total of 59 patients who underwent radical prostatectomy with a diagnosis of acinar adenocarcinoma of the prostate were included in this study. Patients' age, Gleason score (ISUP grade), tumor volume, histopathological results and information on lymph node metastasis were recorded. After retrieving 59 radical prostatectomy materials from the archive, suitable tumor tissues were selected, and IHC analysis for ERG and c-erbB2 was performed with these paraffin blocks. Sections of 4-micron thickness were obtained from 59 formalin-fixed, paraffin-embedded tissues for the IHC assay and positive-charged microscope slides were used to avoid tissue shedding. The sections were placed in an incubator at 60 °C for an hour and deparaffinized with xylene for 15 minutes. The samples were hydrated through a descending-grade series of alcohol and washed in distilled water. The samples were then placed into a BenchMark XT device. ERG (cell marque, RTU, clone EP111, USA) and c-erbB2 (cell marque, RTU, clone EP3, USA) antibodies were applied, and staining was subsequently performed. The preparations stained in the automated staining device were covered using fluid-based covering material. The results were evaluated with an Olympus Bx46 light microscope. Breast carcinoma samples were used as an internal control for c-erbB2 in this study. C-erbB2 was evaluated in line with the scaling method used for c-erbB2 synthesis in breast cancer as per the American Society of Clinical Oncology and College of American Pathologists (ASCO/CAP) 2013 HER2 testing guidelines. According to the scoring criteria we employed in our study, 3+ referred to complete, strong membranous staining in more than 10% of tumor cells; 2+ referred to incomplete, moderate membranous staining in more than 10% of tumor cells; 1+ referred to incomplete, weak membranous staining in more than 10% of tumor cells; and 0 referred to no staining or incomplete, weak membranous staining in less than 10% of the tumor cells.[14,15] The nuclear reactivity of the ERG antibody in endothelial cells was used as an internal control. A 4-step system was utilized to evaluate staining results, where 0 referred to negative, with 1+, 2++ and 3+++ considered as weak, moderate and strong staining, respectively. Staining evaluated as 2++ or 3+++ (moderate and strong) were considered ERG positive. Negative (0) and weak (1+) staining results were considered negative.[16]

An informed consent form was not required for this study as this study is made from archive materials. The study was approved by Tekirdag Namık Kemal University the Non-Interventional Clinical Trials Ethics Committee (protocol no: 2019.222.11.19, date: 19.01.2019).

Statistical Analysis

The patient demographics and data were analyzed using the SPSS 24 (IBM Corp., Armonk, NY, USA) software. The chi-square test was used to compare variables between the patients in groups, and the Kruskal–Wallis test was used for comparisons across the 4 groups. $P<0.05$ was considered statistically significant.

RESULTS

The mean age of the 59 patients who had undergone radical prostatectomy was 68.6 years [minimum (min): 54 – maximum (max): 80]. Twenty-three of these cases had tumors with Gleason score 6 (3+3) and prognostic (ISUP) grade 1 (low-risk), while the others had tumors with Gleason score >6 (high-risk). Of the 59 patients, 41 had undergone lymph node dissection and lymph node resection had not been performed in the remaining cases as no metastasis was detected in prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET−CT). Lymph node metastasis was detected in five of these patients.

ERG expression was observed in 22 (37.5%) of the cases, with three evaluated as 2++ and 19 as 3+++. The distribution of the patients according to the ISUP grading system based on the Gleason score was as follows: 25 patients were ISUP grade 1, 14 patients were ISUP grade 2, 15 patients were ISUP grade 3, and five patients were ISUP grade 4–5. Since the number of patients with ISUP grade 4 and 5 disease was small, these two groups were pooled into a single group for evaluation purposes. ERG expression of the cases by ISUP grades is presented in Table 1.

Based on ISUP grading, tumors with ISUP grade 1 (25 patients) were classified as low-grade and those with ISUP grade 2, 3, 4, or 5 (34 patients) as high-grade. Comparison of ERG staining between the patients in the low- and high-risk groups revealed no statistically significant difference ($p=0.602$). Evaluation of all ISUP groups with the Kruskal–Wallis test showed no significant difference across the groups in terms of ERG expression ($p=0.374$).

While IHC c-erbB2 staining was positive in the control tissues, no staining was detected in the tumor cells in any of the cases. Figure 1 shows one of the PCa cases and samples of ERG and c-erbB2 staining.

The patients stratified according to their age by decade and their corresponding ERG expressions are shown in Table 2. There was no statistically significant difference between the patients' age and their ERG expression ($p=0.165$).

The mean tumor volume of the cases was 22.25±19% (min: 1–max: 80). The mean tumor volume was 18.6±2.4% in the 37 ERG negative patients, and 28.3±5% in the 22 ERG positive patients. We found no significant difference in tumor volume between ERG positive and negative patients ($p=0.06$). Mean tumor volume according to the age distribution of the patients is presented in Table 3. No statistically

significant difference was noted between the patients' age and their tumor volume (p=0.1).

While three of the five patients with lymph node metastasis had ERG expression, there was no ERG expression in the other two patients.

DISCUSSION

In the present study, we detected ERG positivity in 37.5% of those patients diagnosed with PCa. This ratio is consistent with the average PCa rates reported in the USA and Asian countries. Furthermore, to the best of our knowledge, this is the first published study to investigate ERG expression in patients with PCa in Turkey. However, we found no statistically significant difference in ERG staining between low- and high-grade PCa cases. Our findings support the notion that ERG overexpression is involved in the pathogenesis, although ERG expression has no correlation with the histological grade in PCa. None of the cases included in the present study had c-erbB2 expression.

ERG, the ETS-related gene, is a transcription factor from the erythroblastosis virus E26 oncogene family located on chromosome 21.[17] Members of the ETS family are known to play key roles in embryonic development, cell proliferation, differentiation, angiogenesis, inflammation, and apoptosis. ERG is expressed in endothelial tissues, hematopoietic cells, renal cells and cells of the urogenital system. The protein encoded by this gene is required for

Table 1. ERG expression of the cases by ISUP grades

	ERG		Total
	Negative	Positive	
ISUP 1	14	11	25
ISUP 2	10	4	14
ISUP 3	7	8	15
ISUP 4–5	2	3	5
Total	33	26	59

ERG: erythroblast transformation-specific (ETS)-related gene, ISUP: International Society of Urological Pathology.

Table 2. Age distribution of patients and ERG staining by age

	Negative	Positive	Total	Rate of positivity, %
50–59	4	0	4	0
60–69	16	14	30	48
70–79	15	8	23	35
80–89	2	0	2	0
Total	37	22	59	37.5

ERG: erythroblast transformation-specific (ETS)-related gene.

Table 3. Mean tumor volume according to the age distribution of patients

	Tumor volume
50–59	20.7
60–69	28.1
70–79	15.9
80–89	10
Mean	22.25

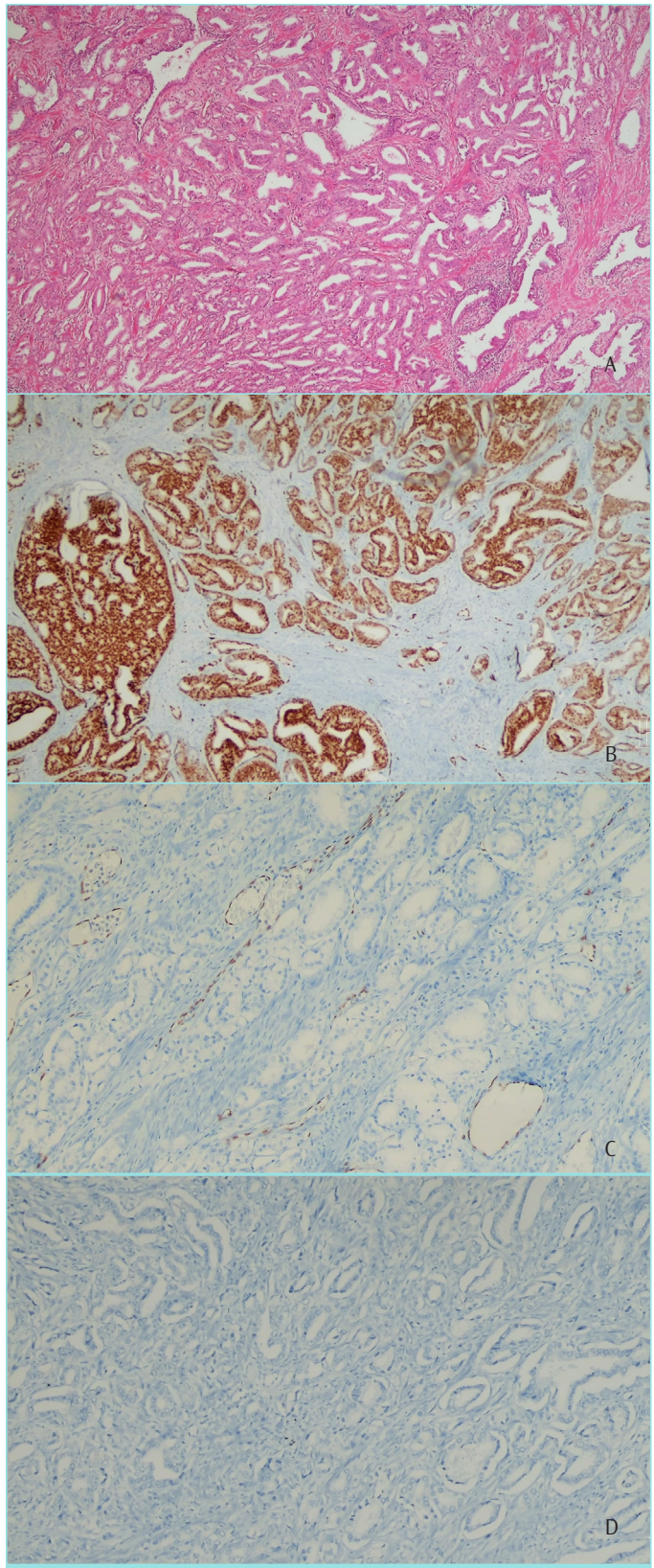

Figure 1. A) Prostate carcinoma Gleason score 6(3+3), H&E, B) ERG staining C) ERG no staining D) c-erbB2 no staining.

H&E: Hematoxylin and eosin stain, ERG: erythroblast transformation-specific (ETS)-related gene.

the induction of hematopoiesis, maturation of megakaryocytic cells, vascular cell remodeling, and subendothelial adhesion of platelets.[18] We aimed to determine the ERG expression rate in PCa patients in Turkey and to determine the role of ERG in the pathogenesis and the difference between histological grades.

After Tomlins et al.[3] described the TMPRSS2-ERG fusion in PCa in 2005, several studies investigated the frequency of ERG expression and its effect on prognosis across different populations and ethnic groups. The prevalence of ERG expression varies between 50%–70% in the Western PCa population[19,20] while this rate has been reported to be about 30% in Asian populations.[16] Tan et al.[2] investigated ERG expression by means of IHC in 80 PCa cases in Malaysia and detected ERG expression in 46% of their cohort. They found no correlation between ERG expression and tumor grade or stage. However, they reported higher rates of ERG expression in younger patients (<60 years) (p=0.01). With an expression rate of 69%, they also found significantly higher ERG expression in Indian patients compared to those from Malaysia. Aldaoud et al.[16] reported an ERG expression rate of 33.2% in patients with PCa in the Arab population, adding that ERG expression was associated with PSA level. However, it had no correlation with histological grade or patient age. In our study, we did not find a statistically significant difference between age and ERG expression (p=0.165). In the largest PCa series investigated to date, with 633 cases from a single center in China, Nie et al.[21] reported an ERG expression rate of 16.3%, demonstrating high levels of ERG expression in cases with ISUP grade 1 disease but found no significant relationship with patient age. Chaux et al.[22] compared ERG expression with IHC and ERG fusion in their study in the USA, showing TMPRSS2-ERG fusion with fluorescent *in situ* hybridization (FISH) in 45.7% of the PCa cases and ERG expression with IHC in 45.0%. Similar to other reports in the literature, their study showed that IHC analysis of ERG may be a good surrogate marker for TMPRSS2-ERG rearrangement.

The data published in the literature reflect varying rates of ERG expression across different populations. Our study was conducted in the Turkish population and our positivity rate is comparable to that reported in Malaysia, Arab countries and the USA. Higher rates have been reported in European and Indian populations. Consistent with the other findings in the literature, we did not find a significant relationship between ERG expression and Gleason score or age.

The c-erbB2 (HER2/neu) oncogene is a transmembrane tyrosine kinase receptor gene localized on chromosome 17. Using the mitogen-activated protein kinase and phosphatidylinositol 3' kinase (MAPK and PI3K) molecular signaling pathways, which are known to be involved in PCa, c-erbB2 plays an important role in the growth, differentiation and motility of cancer cells.[23] We applied c-erbB2 to PCa cases with the hypothesis that c-erbB2, which is involved in tumor differentiation and motility, would be expressed differently in different ISUP grades. Thus, we aimed to establish therapeutic targets as in breast cancer.

Bansal et al.[9] investigated c-erbB2 expression by means of IHC in 41 patients with PCa of different types and histological grades, reporting a c-erbB2 expression score of 3 in 14.6% of their cases and 2 in 4.9% (requiring confirmation with FISH), with negative results (i.e. no c-erbB2 expression) reported in 80.5% of their cohort. Other studies in the literature have reported varying rates of c-erbB2 expression with IHC in PCa, such as 62%,[24] 29%,[25] 10%[26] and 37%[27]. Mutlu et al.[15] investigated c-erbB2, AR and CD117 expression in 80 cases with prostate adenocarcinoma and 20 cases with benign prostate tissue in Turkey, reporting c-erbB2 expression in 15 cases (18.75%) with PCa. This rate was found to be 35% in the metastatic group.

In our study, we did not detect c-erbB2 expression in any of 59 cases with prostate carcinoma. All cases were analyzed with an internal control and no c-erbB2 expression was found in the normal prostate tissues and tumor cells included in our sample. We believe this may be related to the clone we used in our study. Similar to cases with breast carcinoma, therapeutic targeted treatments may be developed for PCa patients with c-erbB2 expression.

Limitations of the Study

A limitation of our study is the small number of cases and the data of only one center. More meaningful results that will reflect Turkey's average can be obtained with multicenter studies. Another limitation is that c-erbB2 expression should be confirmed by more ideal methods such as ISH.

CONCLUSION

The present study reflects the ERG expression rate (37.5%) in patients with carcinoma of the prostate in Turkey. This ratio is consistent with the average PCa rates reported in the USA and Asian countries. However, we found no statistically significant difference in ERG staining between low- and high-grade PCa cases. Although our study included only a limited number of cases, which may be a sample that is too small to reflect the average situation in Turkey, our findings on ERG expression in PCa appear comparable to the data reported in Asian and European populations. Our findings support the notion that ERG overexpression is involved in the pathogenesis, although ERG expression has no correlation with the histological grade in PCa.

MAIN POINTS

- ERG expression was detected in 37.5% of the prostate carcinoma cases.
- None of the cases had c-erbB2 expression.
- There was no significant difference in ERG staining between the low-risk (ISUP 1) and high-risk (ISUP >1) groups (p=0.602).

ETHICS

Ethics Committee Approval: The study was approved by Tekirdag Namık Kemal University the Non-Interventional Clinical Trials Ethics Committee (protocol no: 2019.222.11.19, date: 19.01.2019).

Informed Consent: An informed consent form was not required for this study as this study is made from archive materials.

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Authorship Contributions

Concept: K.D., S.K., Design: K.D., S.K., Materials: K.D., S.K., Literature Search: K.D., S.K., Writing: K.D., S.K., Critical Review: K.D., S.K.

DISCLOSURES

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ORIGINAL ARTICLE

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Evaluation of Cytotoxic, Membrane Damaging and Apoptotic Effects of *Origanum majorana* Essential Oil on Lung Cancer and Epidermoid Carcinoma Cells

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ABSTRACT

BACKGROUND/AIMS: In this study, the potential of an essential oil to cause membrane damaging and induce apoptosis was investigated in order to determine the cytotoxic effect of the essential oil obtained from *Origanum majorana* (*O. majorana*), popularly known as "sweet marjoram", on lung cancer (A-549) and epidermoid carcinoma (A-431) cells.

MATERIALS AND METHODS: In order to determine the cytotoxic dose and IC_{50} value of an essential oil, the essential oil was applied to cells in the concentration range of 5-500 µg/mL for 24, 48 and 72 hours. After those applications, CellTiter-Blue® Cell Viability Assay and 3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazoliumbromide (MTT) assay were performed on the cell lines. The lactate dehydrogenase (LDH) Activity test was used to determine the membrane damaging effect of the essential oil on A-549 and A-431 cells. Cytotoxicity experiments were followed up by caspase-3/7 activity assays to get a mechanistic insight into the associated molecular pathways.

RESULTS: It was observed that treatments of essential oil from *O. majorana* on A-549 and A-431 cells inhibited cell proliferation, that is, it had a cytotoxic effect and caused an increase in LDH activity, which is one of the membranes damaging markers, and caspase-3/7 activity, which is one of the enzymes involved in the apoptotic pathway, in both cells in comparison to controls at the end of the 24-hour incubation.

CONCLUSION: The results of this study indicate that the increase in LDH activity and caspase-3/7 activity caused by *O. majorana* essential oil treatment reveal the membrane damaging and apoptotic effects, respectively. *O. majorana* essential oil can be evaluated as a potential therapeutic agent for lung cancer and epidermoid carcinoma due to these effects. However, more research is needed to confirm this.

Keywords: *Origanum majorana*, essential oil, apoptotic effect, membrane damage

INTRODUCTION

Currently, chemotherapy treatment with existing drugs is insufficient and treatment cannot be provided in many types of cancer. Therefore, studies to develop new anti-cancer drugs appear as a promising field. Cancer researchers, who aim to enable treatment in cancer, focus on developing new agents/drugs with strong anti-cancer effects. In recent years, the use of plants as drugs in cancer treatment has become widespread due to their promising effects against a wide variety of tumor cell lines.

As a result of the great variety in Turkey's ecology, it has many medicinal and aromatic plants and, in parallel, approximately 30% of the species in its flora are aromatic plants. Aromatic plants are the main source of essential oils.[1] Approximately three thousand essential oils are known and three hundred of them are commercially important today.

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These are also widely used in the fields of food, cosmetics, health and perfumery.[2]

Many drugs with known antineoplastic properties are originated from plants. For example, many anticancer drugs used today such as vinblastine, irinotecan, topotecan, and vincristine are obtained from plants. In this context, it is important both scientifically and economically to obtain and evaluate medicinal plants and their essential oils in their pure form.

Researching new treatment strategies that use natural components obtained from plants against cancer, which is one of the most important diseases of our age, has become one of the most important issues today. Due to their structure, essential oils can easily interact with the cell walls and membranes and thus they damage the cell membrane. Additionally, essential oils can cause ionic mitochondrial membrane depolarization in eukaryotic cells. They decrease the membrane potential by affecting the Ca^{2+} cycle and other ionic channels.[2,3]

The most scientifically researched aromatic plant is thyme. The genera, including the thyme species that are traded and widely used in Turkey, are *Origanum*, *Thymbra*, *Coridothymus*, *Satureja* and *Thymus*.

Studies have shown that the *Origanum* species have antibacterial, antifungal, antiviral, antioxidant, anti-inflammatory, antiplatelet, anticarcinogenic, cytotoxic, antidiabetic, acetylcholinesterase and butyrylcholinesterase inhibitor, and insecticidal effects. In addition, it has traditionally been used for gastrointestinal disorders. This genus is also known to be rich in essential oils.[4]

Origanum majorana L. (Lamiaceae) (*O. majorana*), also known as "sweet marjoram", has been used effectively as a spice since ancient times.[5] It is in the "generally recognized as safe (GRAS)" category due to its use in the treatment of different diseases.[6] In another study, the instrumental analysis of *O. majorana* L. essential oil was performed using the GC-MS method, and thus the components and ratios of the essential oil were determined. Carvacrol (52.50%) and linalool (45.4%) were determined to be the two compounds with the highest ratio.[7]

Apoptosis is one of the most frequently used mechanisms in the development of anticancer drugs. The mechanisms regulating apoptosis in the cell are highly complex.[8] One of the most important events linked to the apoptosis mechanism is caspase activation.[9]

The cytotoxic and apoptotic effects of *O. majorana* essential oil, which we think may be a new agent candidate that can be used in cancer treatment, in A-549 (wild-type p53) and A-431 (mutant p53) cells were investigated. Thus, we aimed to investigate whether or not this essential oil has any effect on p53 status according to the response of the cells.

MATERIALS AND METHODS

Plant Material Used

The essential oil to be used in the studies was obtained from *O. majorana* collected from Turkey (Alanya-730 m). The collected plant samples were dried under suitable conditions. The classification of the collected plant samples was made by experts working in this field.

Obtaining the Essential Oil

The essential oil was obtained after the dried *O. majorana* to be used in the study was kept under suitable conditions. The root parts of the plant were separated and the essential oil was obtained from the remaining stem parts (aerial parts) (100 g). 100 g of the plant was weighed and placed in flask for 3 hours and pure water was added to the plant. The essential oil was obtained by a steam distillation method in Clevenger apparatus. The essential oils obtained were kept at +4 °C until they were to be used in the study.

Cell Culture

The cells used in this study (A-549-wild-type p53, A-431-mutant p53) were obtained from the American Type Culture Collection (ATCC). The content of the cell culture medium we used in our experiments was 10% fetal bovine serum constituted RPMI supplemented with 1% penicillin-streptomycin.

Cell Viability Assays

After the essential oil was dissolved with dimethylsulfoxide (DMSO), it was diluted with the medium and added to the wells containing the cells in the concentration range of 5–500 µg/mL and incubated for 24, 48 and 72 hours. After incubation, the viability of the cells was measured with Cell Titer-Blue® cell viability assay and 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.

Resazurin, the active ingredient of Cell Titer-Blue® cell viability assay, is a non-toxic, blue-colored, non-fluorescent compound that can pass through the cell membrane. Once inside the cell, it is reduced to resofurin, which fluoresces strongly red. It has an important sensitivity due to its fluorescent feature.[10]

MTT assay is a method in which the amount of cell proliferation is determined based on the colorimetric measurement of formazan dyes or enzymatic activity due to MTT reduction. The method is based on the principle of colorimetric determination of color change in cells incubated with the MTT agent. The MTT method was applied after the cells were treated with the essential oil for 24, 48 and 72 hours. After incubation, absorbance values were measured at 490 nm.[11] The 50% inhibitory concentration (IC_{50}) value was calculated by determining the % cell viability curve with the help of the Microsoft Excel program. The tests were repeated three times.

Measurement of Lactate Dehydrogenase (LDH) Release

With the LDH activity assay, one of the methods used in the evaluation of cell death, the activity of the cytoplasmic enzyme released from dead or damaged cells is measured when the integrity of the cell membrane is disrupted. LDH, a stable cytoplasmic enzyme found in all cells, can easily be released into the cell culture supernatant when the cell plasma membrane is damaged.

Changes in LDH enzyme activity were determined by applying the essential oil (IC_{50}) to the cells for 24 hours. LDH enzyme activity was determined by the method specified in the "Lactate Dehydrogenase Activity Assay Kit" (MAK066) produced by Sigma-Aldrich. Measurements were made in triplicate.

Caspase-3/7 Activity

One of the caspases that plays a key role in apoptotic signaling is caspase 3/7. Caspase 3/7 is the main caspase that gains activity in the early stages of apoptotic cell death and causes death to occur. Caspase 3/7 enzyme activity was determined by the method specified in the "ApoTox-Glo™ Triplex Assay" kit produced by Promega after the

treatment of *O. majorana* essential oil (IC_{50}) for 24 hours. Cell lysis occurs with the addition of the reagent, which is one of the kit components, to the medium. Cleavage of the substrate by caspase is followed by the generation of a "sparkling" luminescence signal produced by luciferase. The luminescence that occurs is proportional to the amount of caspase activity present. The experiments were performed in triplicate.

Statistical Analysis

The values of the control and test samples were given with mean and standard error (SE). Statistical analysis of the obtained data was made with Minitab 18 program (State College, PE, USA) (DC Montgomery, 2001). Analysis of variance (ANOVA) was used for comparison between the means of three or more independent (unrelated) groups according to some variable. Tukey's multiple comparison test was applied to indicate the significance level of the differences. Statistical differences were considered significant at $p<0.05$.[12]

RESULTS

Determination of the Cytotoxic Effect of *O. Majorana* Essential Oil on A-549 and A-431 Cells

The cytotoxic effects of essential oils obtained from *O. majorana* on the A-549 and A-431 cell lines were measured using the MTT and Cell Titer-Blue® cell viability assays. After the cells were incubated with the essential oil, the IC_{50} (the concentration that kills 50% of the cells) and IC_{70} (the concentration that kills 70% of the cells) values of the essential oil were calculated for each cell (Table 1). According to the cytotoxicity results we obtained, we determined that the Cell Titer-Blue® cell viability assay was more sensitive than the MTT assay. For this reason, we made evaluations according to the concentrations we calculated using the data obtained from the CellTiter-Blue cell viability assay in the other parameters we studied. According to both assays, it was observed that the cytotoxic effect increased in parallel with increasing concentrations and incubation times in both A-431 cells and A549 cells (Figures 1 and 2). According to the MTT assay, after 24, 48 and 72 hours essential oil incubations, IC_{50} values were calculated to be 266, 222 and 182 µg/mL in A-549 cells, and 218, 187 and 140 µg/mL in A-431 cells, respectively (Table 1). In addition, according to the CellTiter-Blue® Cell Viability assay, after 24, 48 and 72 hours of essential oil incubation, the IC_{50} values of cells were calculated to be 243, 203 and 167 µg/mL in A-549 cells and 182, 145 and 111 µg/mL in A-431 cells, respectively (Table 1). These results showed that the incubation time affected the essential oil's cytotoxic effects on both A-549 and A-431 cells. The essential oil was found to be more effective on A-431 cells (mutant p53) than A-549 cells (wild-type p53). It was found that DMSO (0.5%, v/v), which we used to dissolve the essential oil, did not affect the cell viability in either A-431 or A-549 cells when treated for the same time periods.

Lactate Dehydrogenase (LDH) Activity Measurement

Lactate dehydrogenase (LDH) is the enzyme that converts lactic acid to pyruvic acid in the presence of NAD^+. Lactic acid occurs with the disruption of cell integrity. That is, with the death of cultured cells, the integrity of the cell membrane is disrupted and the contents of the cytoplasm come out. Since the lactate dehydrogenase enzyme is usually found in every cell, it helps in determining membrane damage depending on the enzyme activity.[13] To evaluate the effect of *O. majorana* essential oil on the cell membrane, LDH activity, which is also a marker of early apoptosis and released from cells into the medium, was measured.[14]

After the application of the essential oil at IC_{50} concentration to A-549 and A-431 cells for 24 hours, LDH activities in the cells were determined

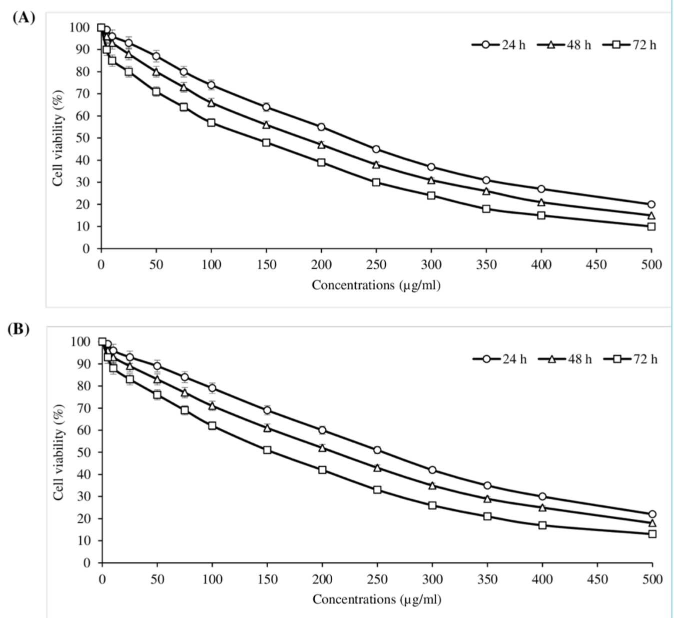

Figure 1. The cytotoxic effects of *O. majorana* essential oil on A-549 cells after 24, 48 and 72 hours measured by **(A)** The CellTiter-Blue-Cell Viability Assay; **(B)** MTT Assay. Results are presented as viability ratio compared with the control group (treated with only the medium-untreated cells). Values are expressed as the mean of three separate experiments ± SE. Error bars represent standard error of the mean from three replications.

SE: standard error

Table 1. Summary of the cytotoxic effects of *O. majorana* Essential oils on A-549 and A-431 cells

Cells treatments	Es. oil (µg/mL) (CellTiter.) X ± SE	Es. oil (µg/mL) (MTT) X ± SE
A-549, 24 h, IC_{50}	243±2.99''''	266±2.32⋔
A-549, 24 h, IC_{70}	348±3.66*	377±2.13ε
A-549, 48 h, IC_{50}	203±4.00£	222±3.45£
A-549, 48 h, IC_{70}	298±3.71≠	322±2.88⁑
A-549, 72 h, IC_{50}	167±2.21§	182±2.34€
A-549, 72 h, IC_{70}	259±2.34⋔	274±2.66⋔
A-431, 24 h, IC_{50}	182±3.03€	218±2.78£
A-431, 24 h, IC_{70}	300±2.88≠	317±2.31⁑
A-431, 48 h, IC_{50}	145±2.66$	187±3.03€
A-431, 48 h, IC_{70}	253±3.72⋔	283±2.99≠
A-431, 72 h, IC_{50}	111±2.41*	140±2.88$
A-431, 72 h, IC_{70}	212±3.05£	223±2.76£

Values followed by different asterisks within a column are significantly different ($p \leq 0.05$).
SE: standard error, Es. oil: essential oil, CellTiter: CellTiter-Blue cell viability assay. X is an average of five repetitions.

(Figure 3). It was observed that LDH enzyme activity increased 4.8 times in A-549 cells and 5.4 times in A-431 cells to which IC_{50} essential oil concentrations were applied, compared to the control group cells (only treated in the medium).

LDH activity in A-431 cells increased to a greater extent in comparison to LDH activity in A-549 cells, and LHD activity in both A-431 and A-549 cells was higher compared to the control group. LDH enzyme activity in A-431 cells was statistically different when compared to the LDH enzyme activity in A-549 cells ($p<0.05$).

Measuring the Effects of Essential Oil on Caspase-3/7 Enzyme Activity in A-549 and A-431 Cells

The apoptosis inducing potential of the essential oil was observed after 24 hours of *O. majorana* essential oil treatment on A-549 cells and A-431 cells. Caspase-3/7 activity in A-431 cells increased 2-fold at the end of 24 hours incubation, while caspase-3/7 activity in A-549 cells increased 4-fold (Figure 4). It was observed that the apoptotic effect of the essential oil, in terms of increasing the caspase-3/7 activity, in A-549 cells was two times higher than the apoptotic effect of the essential oil in A-431 cells. After the essential oil treatment, the highest increase in caspase-3/7 activity was observed in A-549 cells compared to the control.

The LDH and caspase 3/7 activity observed after the essential oil treatments was statistically different from the control groups (treated with only the medium-untreated cells) in all cell lines ($p<0.05$). The LDH and caspase 3/7 activity of essential oil treatments in A-549 was statistically different from the LDH and caspase 3/7 activity of essential oil treatments in A-431 ($p<0.05$).

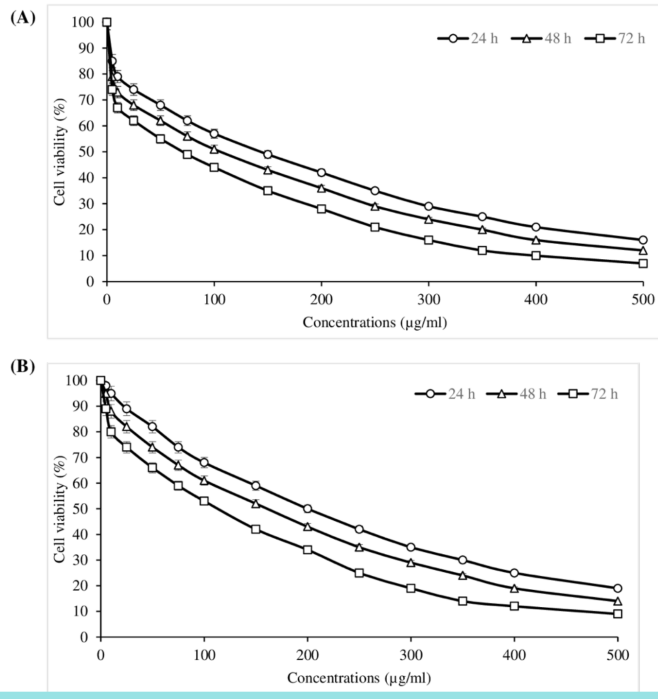

Figure 2. The cytotoxic effects of *O. majorana* essential oil on A-431 cells after 24, 48 and 72 hours measured by **(A)** The CellTiter-Blue-Cell Viability Assay; **(B)** MTT Assay. Results are presented as viability ratio compared with the control group (treated with only the medium-untreated cells). Values are expressed as the mean of three separate experiments ± SE. Error bars represent standard error of the mean from three replications.

SE: standard error

DISCUSSION

Lung and epidermoid cancers are among the most common types of cancer seen all over the world. Chemotherapy is an important strategy used in the treatment of lung and epidermoid cancers. However, the

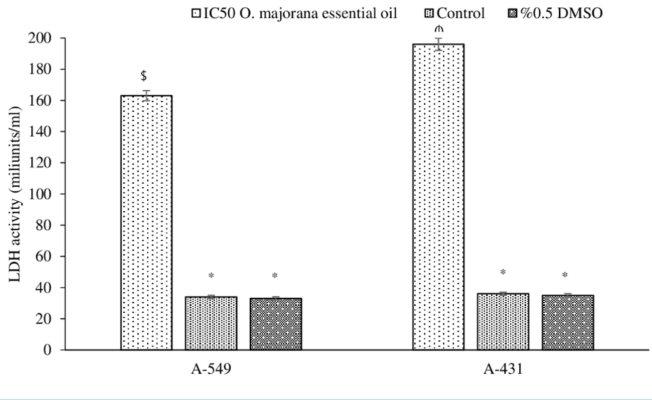

Figure 3. Lactate dehydrogenase activities in A-549 and A-431 cells after being treated with *O. majorana* essential oil. Values are expressed as the mean of three separate experiments ± SE. Error bars represent standard error of the mean from three replications, and bars with the same asterisks indicate no significant difference (ANOVA with Tukey's test, $p\leq0.05$). Different asterisks represent significant differences among treatments (ANOVA, $p\leq0.05$) in A-549 and A-431 cells. One unit of LDH activity is defined as the amount of enzyme that catalyzes the conversion of lactate into pyruvate to generate 1.0 µmole of NADH per minute at 37 °C.

SE: standard error, LDH: lactate dehydrogenase

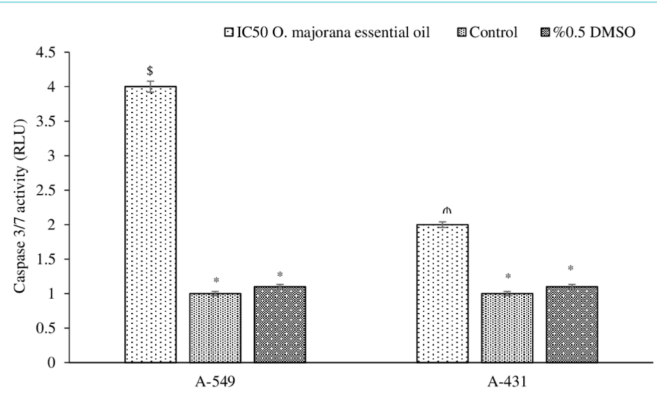

Figure 4. Effect of *O. majorana* essential oil on caspase-3/7 activity in A-549 and A-431 cells. Values are expressed as the mean of three separate experiments ± SE. Error bars represent standard error of the mean from three replications, and bars with the same asterisks indicate no significant difference (ANOVA with Tukey's test, $p\leq0.05$). Different asterisks represent significant differences among treatments (ANOVA, $p\leq0.05$) in A-549 and A-431 cells.

SE: standard error, RLU: relative light unit

desired success has not been obtained from chemotherapy to date. Therefore, it is desired today to use therapeutically effective compounds that can be obtained from natural sources with little or no adverse effects on healthy cells in the treatment of cancer. In this respect, it is very important to evaluate the therapeutic effects of natural resources in cancer research.

O. majorana, which belongs to the Lamiacea family, has attracted the attention of many scientists due to its high essential oil potential. *O. majorana* is one of the most important aromatic plants that contain major antioxidants such as flavonoids and triterpenoids.[15] Phenolic acids and flavonoids have been reported to play a role in the prevention of human pathologies.[16] The Food and Drug Administration regard *O. majorana* to be generally safe.

Dose and time dependent inhibition by *O. majorana* essential oil and linalool were observed with IC_{50} values of 100, 80 and 63 µg/mL for essential oil and 81.5, 72.7 and 64.7 µg/mL at 24, 48 and 72 hours, respectively on Hep G2 cells as assessed by CellTiterBlue® Cell Viability Assay.[7] In that study, the results showed that incubation time affected the cytotoxic effects of the essential oil and linalool on Hep G2 cells. In another study, *O. majorana* essential oil and linalool were found cytotoxic in terms of concentration and time-dependence in both parental and epirubicin-resistant (drug resistant) H1299 cells. The cytotoxic effects of *O. majorana* essential oil for 24, 48 and 72 hours were found to be higher than linalool in both parental and drug-resistant cells. Also, it was observed that *O. majorana* essential oil and linalool were less cytotoxic on drug resistant cells than parental cells. In other studies, eugenol, eucalyptol, terpinen-4-ol camphor, carvacrol and thymol, which are found as components in many essential oils, showed more cytotoxicity in parental H1299 cells than epirubicin-HCl resistant H1299 cells.[17,18] The essential oils from wild and cultivated forms of *Salvia pisidica* showed cytotoxicity on H1299 cells.[19]

LDH, one of the important enzymes of the glycolytic pathway, is found in the cytoplasm of all cells. LDH is rapidly released into the cell culture medium when the plasma membrane is damaged. An increase in the number of dead or plasma membrane-damaged cells results in increased LDH activity in the culture supernatant.[13] In our study, we tried to reveal the membrane damaging effects of *O. majorana* essential oil by determining the changes in LDH activity after treatment of IC_{50} *O. majorana* essential oil on cells for 24 hours. It was found that the LDH enzyme activity increased with respect to control cells in cells subjected to *O. majorana* essential oil treatment. Our LDH activity result supports cell viability results. In our previous study, *O. majorana* essential oil and its oxygenated monoterpene component linalool resulted in increased malondialdehyde levels on both parental and drug resistant H1299 cells.[20] Also, eugenol, eucalyptol, terpinen-4-ol, camphor, carvacrol and thymol, which are found as components in many essential oils, showed membrane damaging effects in parental and epirubicin-HCl resistant H1299 cells.[17,18] The essential oil of *Origanum onites* (Lamiaceae) and its two phenolic components, thymol and carvacrol increased MDA levels with respect to controls on Hep G2 cells.[21] Some plant essential oils showed membrane damaging effects in a dose dependent manner on cancer cells.[22]

In our study, caspase-3/7 activity, one of the apoptotic death markers, was measured in A-431 cells and A-549 cells after essential oil treatment. Our results suggest that *O. majorana* essential oil induced apoptosis in all cells. It has been reported that a water extract of *O. acutidens* caused cytotoxic and apoptotic effects in breast cancer cells such as MCF-7, MDA-MB-468 and MDA-MB-231. This apoptotic effect was demonstrated by showing that caspase-7 protein expression and the number of TUNEL-positive cells increased at the end of the application.[23] In our study, it was demonstrated that *O. majorana* essential oil caused higher caspase-3 activity in both cells compared to the control cells, and it was revealed that the essential oil induced intense apoptotic effect in the cells. As a result, *O. majorana* essential oil treatment induced apoptosis in both cells.

When the cytotoxic effects of *O. majorana* essential oil in A-549 and A-431 cells were compared in our study, it was observed that this essential oil was more effective in A-431 cells. The reason why the essential oil has different cytotoxic effects on these cells may be due to the different properties of the cells. A-549 has functional p53 and EGFR copy number of 3.4, and A-431 cell line has mutant p53 and expresses EGFR in high amounts. The results obtained from our LDH activity experiment support our cytotoxicity results. In addition, it has been demonstrated that this essential oil exerts its cytotoxic effect by stimulating the apoptotic mechanisms in both cells. The new experiences/gains we have obtained as a result of our study may lead to the evaluation of plant-derived compounds in epidermoid and lung cancer studies.

Limitations of the Study

There are some limitations to our study. Firstly, despite essential oils very important natural bioactive properties, they have certain disadvantages such as hydrophobic behavior in aqueous environments, losses due to their volatile properties, and rapid consumption of their bioactive properties due to uncontrolled activity. In addition, undesirable changes may occur in their chemical compositions over time, due to the fact that they are quickly affected by factors, depending on their storage conditions, such as oxygen, humidity, temperature, and light. For all these reasons, we should have used different methods to ensure the stability of essential oils and to protect and/or increase their bioactive properties. Secondly, we could not ascertain the mechanism of action which the essential oil stimulated in the cells. We only showed that *O. majorana* essential oil has a cytotoxic effect by causing membrane damaging and apoptotic effects; however, with further studies, this may be discovered. Thirdly, the effects of the main components of the essential oil on the cytotoxic effects of the essential oil were not ascertained within the scope of our study. The main components may be determining the cytotoxic effect of the essential oil. Building on the promising results we obtained from our study, further steps can be taken to investigate the effects and mechanisms of action of this essential oil *in vivo*. Thus, results that can lead to clinical studies can be obtained.

CONCLUSION

The results of our study show that *O. majorana* essential oil can be suggested as a natural herbal source in the production of new anticancer drugs, with the findings that it causes cytotoxic effects, membrane damage and apoptotic effects in A-549 and A-431 cells. Thus, new strategies that can be used in the treatment of lung and epidermoid carcinoma will be determined. The use of essential oils for the development of drugs for cancer treatment will also contribute to

the protection of human health. We believe that a better understanding of the intracellular mechanisms of essential oils obtained from other plants, similar to the essential oil obtained from *O. majorana*, will bring new strategies for the production of drugs used in cancer treatments.

MAIN POINTS

- *O. majorana* essential oil showed cytotoxic activity depending on concentrations and time on A-549 and A-431 cells according to both CellTiter-Blue® Cell Viability and MTT tests.
- *O. majorana* induces cytotoxicity on A-549 and A-431 cells in a membrane-damaging and apoptotic effects mediated manner.
- *O. majorana*'s anti-tumoral property suggests that it could be a potential source of lung and epidermoid carcinoma treatments.

ETHICS

Ethics Committee Approval: The study does not require ethics committee approval since it does not involve any human or animal subject.

Informed Consent: The study does not require informed since it does not involve any human or animal subject.

Peer-review: Externally peer-reviewed.

DISCLOSURES

Financial Disclosure: The author declared that this study had received no financial support.

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The Relationship of Food Addiction With Emotional Control and Socio-Cultural Factors in University Employees

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ABSTRACT

BACKGROUND/AIMS: The aim of this study was to examine the relationship between food addiction in university employees with emotion control, sociodemographic and sociocultural factors and social media use.

MATERIALS AND METHODS: The study was conducted on 213 administrative and academic staff working at a foundation university. The data was collected by a demographic fact sheet, the Social Media Addiction Scale-Adult Form (SMAS-AF), the Courtauld Emotion Control Scale (CECS) and the Yale Food Addiction Scale (YFAS).

RESULTS: The average age of the participants was 36±10 years and 65.7% of them were women. Of all the participants, 4.7% (n=10) were found to be addicted to food and 80% (n=8) of these were women. A significant inverse relationship was found between SMAS-AF and CECS total scores. As social media addiction increases, emotion control decreases. Among those with food addiction, the proportion of those with a low-income levels was greater compared to any other income group. There was no significant relationship between food addiction and gender, age, social media addiction, or emotion control. A significant negative correlation was found between age and the total score of social media addiction.

CONCLUSION: In our study, the prevalence of food addicts among university employees was low. The fact that the rate of the food addicts was higher in women and those who were single and those who had low-income levels reveals that gender, marital status and income levels are important socio-cultural factors. While no relationship was found between food addiction and emotion control or social media addiction, higher scores of SMAS-AF were noted in single and low-income users.

Keywords: Food addiction, emotion control, socio-cultural factors, social media addiction

INTRODUCTION

Food addiction is described as an increased risk of encountering obesity and associated health problems as a result of excessive consumption of certain foods. Although it is not quite right to describe food as an addictive object in the same way as abused substances, consuming processed foods and foods containing high fat and carbohydrates in order to meet reward needs rather than physiological needs make the expression "food addiction" meaningful.[1] In recent years, with the increasing obesity epidemic around the world, there is an opinion that the binge eating disorder and overeating behaviors seen in obese individuals can be recognized as "food addiction".[2]

It is clear that an individual's emotional condition, which is a major determinant in addictive actions, also has an impact on uptake behavior and disorders. Studies have revealed that a person's emotional state affects their nutrient uptake, leading to less nutrient uptake in normal-weight people, and more nutrient uptake in overweight

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people.[3,4] Fluctuations in mood and negative behaviors affect the tendency towards delicious foods.[5] Furthermore, it has been observed that distortions in the hedonic system are counterproductive to the suppression of hunger and that in situations, such as stress or regret, the body is triggered to turn to food even if it does not need it.[6,7] Many sociologists think that sociocultural factors influence body perception and eating behaviors, and especially the family, environment and social media play a very important role in the formation of binge uptake and food addiction.[8-10] Sociocultural factors that concern the individual and society are mainly race, gender, education, material status, technological ability and the environment. A study on the population in Arab countries found that belief, gender, education, income level, mass media usage and food preferences, which are the main sociocultural factors, play an important role in the amount of food consumed in that region.[11,12]

Although there are studies in the literature on the relationship of food addiction between obesity and mood, research on emotion control and socio-cultural factors are insufficient. Therefore, this study aimed to analyze the effects of social media use, socio-cultural factors and emotion control on food addiction in university employees.

MATERIALS AND METHODS

The universe of this study included 879 executives and academic staff from a foundation university in İstanbul, Turkey. The study was approved by the Ethics Committee of Üsküdar University (no: 6135134/2019-619, date: 27.12.2019) and conducted according to the principles of the Helsinki Declaration. The sample size was calculated to be 98 participants with 0.05 error and 95% confidence interval. A total of 213 volunteers participated in this study. Individuals aged 18 years and below, employees with any disability or substance abuse history were excluded. The questionnaires to be applied within the scope of the research were handed out to the volunteers. They were given a week to fill in the questionnaires and they were collected 1 week later. The demographic information form, the Yale Food Addiction Scale (YFAS), the Social Media Addiction Scale-Adult Form (SMAS-AF), and the Courtauld Emotion Control Scale (CECS) were used to collect the data.

Demographic Information Form

Age, gender, education level, profession, income level, marital status, and smoking/alcohol use were asked in the demographic information form. In addition, accommodation, drug use, disease status, social media use, its frequency and its duration were investigated.

Yale Food Addiction Scale

This scale was developed in 2009 by Gearhardt et al.[13] according to DSMIV-TR drug addiction diagnosis criteria. It was designed to diagnose behavioral food addiction. This scale includes seven diagnostic criteria. At least one of the diagnostic criteria ranging from 0 to 7 must be met to say that the food addiction criteria was observed, and at least three of seven diagnostic criteria must be met for a diagnosis of food addiction. The validity and reliability of this scale in Turkey was proven in 2012 by Bayraktar et al.[14] in a study using 300 university students.

Social Media Addiction Scale-Adult Form

This form has a five-point Likert type structure. The scale has two sub-dimensions which are virtual tolerance and virtual communication. One hundred is the highest score that can be obtained from the scale, and the lowest score is 20. A higher score indicates a "social media addict". The validity and reliability of this scale in Turkey was carried out in 2017 by Şahin and Yağcı.[15]

Courtauld Emotion Control Scale

This scale was developed by Watson and Greer in 1983.[16] This scale was prepared to determine to what extent an individual control his/her reactions. It has not been prepared to determine to what extent an individual reflects or suppresses his/her feelings, such as anger, anxiety and unhappiness. It has three subscales. All subscale scores range from 7 to 28, and the total score ranges from 21 to 84. Emotion control increases as the score increases. The validity and reliability of this scale for the Turkish population was proven in a study of university students by Okyayuz.[17]

Statistical Analysis

The SPSS 24 (Chicago, IL, USA) statistical program was used to calculate the data. The Independent Sample t-test, the ANOVA test, and the chi-square test were used to analyze the relationship between scale scores and sociocultural variables. Correlation analysis was used to investigate the relationship between food addiction, emotion control, and social media addiction scores.

RESULTS

In this study, there were 213 participants and 140 (65.7%) of them were women and 71 (33.3%) were men. The average age of the participants was 36±10 years. There were two volunteers who did not want to report their gender. The findings were calculated in accordance with this situation. 120 (56%) of the participants did not smoke; 106 (50%) did not use alcohol; 179 (84%) did not have any chronic disease; 131 (62%) did not use Facebook, while 119 (56%) used Google+ and 119 (56%) used Twitter, 154 (72%) used Instagram, 158 (74%) used Youtube; 152 (71%) followed social media from desktop and mobile devices (laptop, tablet, smartphone); and 137 (64%) had been using social media for over 7 years and 113 (53%) spent 1–3 hours per day on social media.

In this study, the frequency of food addiction was found to be 4.7% (n=10). Of those with a food addiction, 80% (n=8) were female, 50% smoked, 80% had low-income levels, 70% (n=7) were single, and 60% (n=6) had been educated to primary school level or less. 108 (98.2%) of those without food addiction had a middle-income level (p=0.03) and 103 (99%) were married (p=0.02). There were no statistically significant differences between food addiction and gender (p=0.50), smoking (p=0.79), alcohol use (p=0.59), housing (p=0.07), social media usage time (p=0.17) and social usage media frequency (p=0.07) (Table 1). There was no statistically significant difference between the YFAS subscale scores and the gender variable.

SMAS-YF had a virtual tolerance sub-dimension average of 22.37±6.71; a virtual communication sub-dimension average of 18.15±5.84; and a total score average of 40.32±11.33. When the demographic data and SMAS-AF were compared, there was no significant difference between the total score obtained from the scale and smoking (p=0.48), housing (p=0.214) and social media usage time (p=0.061). The mean total score of the scale was significantly higher in those who used alcohol (p=0.045), those with low incomes (p=0.003), those who were single (p=0.001) and those who used social media for more than 7 hours a day (p=0.000). There was no statistically significant difference between the average SMAS-AF score and sub-scale score averages and YFAS results (Table 2). A negative correlation was found between the SMAS-AF total

Table 1. Comparison of sociodemographic and sociocultural data and YFAS scores

		Food addiction				p-value
		No		Yes		
		n	%	n	%	
Gender	Male	69	97.2	2	2.8	0.50
	Female	132	94.3	8	5.7	
Smoking	Yes	40	93	3	7	0.79
	Sometimes	39	95.1	2	4.9	
	Quit	9	100	0	0	
	No	115	95.8	5	4.2	
Alcohol use	Yes	21	93.4	5	6.6	0.59
	Sometimes	73	93.6	3	6.4	
	Quit	8	100	0	0	
	No	101	97.3	2	2.7	
Income	Low (2000–4999)	80	90.9	8	9.1	0.03
	Middle (5000–9999)	108	98.2	2	1.8	
	High (10,000+)	14	100	0	0	
Marital status	Married	103	99	1	1	0.02
	Single	87	92.6	7	7.4	
	Divorced	13	86.7	2	13.3	
Housing	Alone	35	94.6	2	5.4	0.07
	With Family	161	96.4	6	3.6	
	With close relative	3	75	1	25	
	With friends	4	80	1	20	
Social media usage time	1–3 years	19	100	0	0	0.17
	4–6 years	51	91.1	5	8.9	
	More than 7 years	132	96.4	5	3.6	
Social media daily usage frequency	Less than 1 hour	62	95.4	3	4.6	0.07
	1–3 hour	110	97.3	3	2.7	
	4–6 hour	24	85.7	4	14.3	
	More than 7 hour	6	100	0	0	

YFAS: Yale Food Addiction Scale, n: number.

score (p=0.000), Virtual Tolerance (p=0.000) and Virtual Communication (p=0.001) subscale mean scores in relation to age.

According to CECS, the mean of "anger" was 15.17±3.81, the mean of "anxiety" was 15.16±2.75, the mean of "unhappiness" was 14.98±3.52 and the mean of the total points was 45.33±8.95. There was no statistically significant difference between the average CECS score and the sub-scale score averages and the YFAS results (Table 3). There was no statistically significant difference between gender and the subtypes of CECS "anger" (p=0.129), "anxiety" (p=0.598) and "unhappiness" (p=0.727) in this study. The CECS total scores (p=0.766), 'Anger' (p=0.889), "anxiety" (p=0.844) and "unhappiness" (p=0.356) scores were found to have no statistically significant association between the sub-scale score averages and age. A statistically inverse relationship (r=-0.195; p<0.004) was found between the average SMAS-AF total score and the average CECS total score.

DISCUSSION

The frequency of food addiction was found to be 4.7% in our study. According to the CECS, the average total score of the participants was determined to be 45.33±8.95. This shows that the participants had moderate emotion control. The average total score of SMAS-AF was found to be 40.32±11.33. This shows that the participants were not inclined to social media addiction. In various studies to date on food addiction in adults, it has been reported that sociodemographic and sociocultural factors, gender, smoking, alcohol use, income level, marital status, accommodation, social media usage time of the mother, and education status of the mother and father are relevant.[18-21] One study found that women who have low income had a poor relationship with food addiction.[20] In another study, it was determined that low-income women saw eating desire and food addiction as similar and common behaviors, and for them, food addiction was out of control. Women who had low income described food addiction as less common and more serious.[22] In a study by Ramachandran et al.[19], it was reported that there is a relationship between obesity and upper economic levels. In that study, it was found that the group with food addiction had a moderate economic status. A study of 1,048 randomly selected Chinese university students (540 men and 508 women) found that anxiety caused by high-intensity living conditions predicted overeating.[23] In a study aimed to identify the prevalence of internet addiction and related

Table 2. Comparison of SMAS-AF scores in the presence of food addiction

	Food addiction	n	Avg ± SD	p-value
SMAS total	Yes	10	40.73±12.54	0.908
	No	203	40.30±11.30	
SMAS virtual tolerance	Yes	10	22.33±6.41	0.985
	No	203	22.38±6.74	
SMAS virtual communication	Yes	10	19.80±8.21	0.527
	No	203	18.07±5.72	

Avg: average, SMAS-AF: Social Media Addiction Scale-Adult Form, SD: standard deviation, n: number.

factors among young adults (19–35 years old) in Bangladesh, internet addiction was found to be significantly related to lifestyle, time spent on the internet per day, family life, physical activity and smoking habits.[24] In our study, it was seen that, in general, people with food addiction had low income and were single.

Even though food addiction is thought to be more related to food, sudden emotional changes are known to cause excessive eating behaviors and addiction. In the research conducted by Innamorati et al.[25], it was stated that food addiction occurs when strong emotions arise and there is a problem in understanding these emotions. It was determined in a study conducted in 2017 that negative mood affects eating behavior and may be related to food addiction.[26] In another study, it was found that loneliness and emotional dysregulation were significantly positively related to food addiction.[27] In one study on emotion regulation strategies and food addiction, it was observed that the condition such as emotional openness, negative emotion, impulsivity, and self-distrust were more common in those volunteers with food addiction than in the volunteers who did not have any addiction.[28] In our study, no significant correlation was found between the total dependency of the Courtauld Emotion Control Scale and the anger-happiness-anxiety sub-dimension total scores. However, in the presence of food addiction, the CECS total score was found to be slightly lower.

When the literature was examined, it was seen that food addiction is interrelated with emotional eating.[29-31] Irregular feeding attitudes are rapidly increasing, especially among adolescents and young women in their twenties. Social media can lead to irregular eating behaviors that are affected by diverse factors such as popularizing unrealistic beauty ideals. In one study, the results suggested that food addiction was connected with a higher body mass index in women and older and white people and/or people with lower incomes.[21] In another study, Duran et al.[32] investigated the effect of stress and social media use on eating behaviors in university students. A statistically significant difference was identified between the degree of stress and eating behavior disorders, and it was found that the increase in stress severity caused abnormal eating behavior. It has been determined that increasing the duration of social media use causes eating behavior disorders.[32] In another study in which video-based effects were examined, it was indicated that the "*mukbang*" style of video on social media affects emotional control and may cause food addiction.[33] In a study investigating the effect of social media attention on eating attitudes and body dissatisfaction in Filipino adolescents, the results confirm the effects of social media on adolescents' eating attitudes and body dissatisfaction.[34] A study of eleven adolescents found that phone addiction was associated with greater emotional regulation difficulties, irregular nutrition, restricted eating, food addiction, and higher body fat.[35] On the other hand, in our study, no statistically significant difference was found between the average SMAS-AF score and the mean subscale scores and the results of the YFAS.

Table 3. Comparison of CECS scores in the presence of food addiction

	Food addiction	n	Average	p-value
CECS total	No	203	129	0.23
	Yes	10	105	
CECS - anger	No	203	135	0.13
	Yes	10	105	
CECS – anxiety	No	203	129	0.23
	Yes	10	105	
CECS - unhappiness	No	203	113	0.73
	Yes	10	106	

CECS: Courtauld Emotional Control Scale, n: number.

Limitations of the Study

In our study, individuals aged 18 years and below, employees with any disability, disease or substance abuse history were excluded. Only adults working in one university were examined. One of the important limitations is that the height and body weight of the participants were not investigated in our study. Therefore, the relationship between BMI and the scales used in the study could not be examined. As the relationship between obesity and food addiction is well-known, if such a study is conducted in obese patients, the frequency of food addiction will be found to be relatively higher. Thus, the effect of emotion control in food addiction can be better determined. In addition, it is recommended to conduct multi-center studies on people who have different professions and live in different cities.

CONCLUSION

In our study, the prevalence of those with food addiction among university employees was found to be low. The fact that the majority of those with food addiction were mostly single women with a low income levels reveals that gender, marital status and income level are important sociocultural factors. While food addiction was not associated with emotion control and social media addiction, higher total scores of SMAS-AF among single and low-income users, those who use alcohol and those who use social media for more than 7 hours a day point to the contribution of sociocultural factors in social media addiction. Eating behavior and nutritional preferences are not only physiological needs, but also emotional and social needs.

It is recommended to carry out similar studies in different populations in the future as it is thought that the low rate of food addiction in the sample examined within the scope of our study may be a factor in the lack of a relationship between emotion control and social media addiction. Specifically, it is thought that the effect of emotion control can be better evaluated in a sample of overweight individuals who have more common emotional eating behaviors.

MAIN POINTS

- In our study in which the effect of various factors on food addiction among university employees was investigated, it was found that especially having a low-income level, being single and being female were important factors.

- There were significant negative correlations between a person's age and their social media addiction and emotion control.
- It can be concluded that social media addiction, as with other addictions, may negatively affect emotional control, mental health and quality of life over time.

ETHICS

Ethics Committee Approval: Ethics committee approval was received for this study from the Non-Interventional Research Ethics Board (date: 27/12/2019, approval number: 6135134/2019-619) of Üsküdar University.

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.Ö., Design: E.R., A.Ö., Supervision: A.Ö., Data Collection and/or Processing: E.R., G.Ç., H.D., N.K., T.A., A.Ö., Analysis and/or Interpretation: E.R., G.Ç., H.D., N.K., T.A., Literature Search: E.R., G.Ç., H.D., N.K., T.A., Writing: E.R., G.Ç., H.D., N.K., T.A., A.Ö., Critical Reviews: E.R., G.Ç., H.D., N.K., T.A., AÖ.

DISCLOSURES

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ORIGINAL ARTICLE

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The Effects of Achievement-Focused Motivation on Lifelong Learning Tendencies of Nursing Students

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ABSTRACT

BACKGROUND/AIMS: Nurses need to have lifelong learning to be able to follow up the most current information and practices in the area of healthcare, acquire the information, skills and qualifications required for the safe conduct of nursing practices, to continue to offer good-quality healthcare services and to improve health services. The aim of this study was to determine the effects of achievement-focused motivation on the lifelong learning tendencies of nursing students.

MATERIALS AND METHODS: This descriptive and cross-sectional study was performed with the participation of 264 nursing students. The data were collected using a Personal Information Form, the Achievement-Focused Motivation Scale and the Lifelong Learning Tendency Scale. Descriptive statistics, Independent-Samples t-test, One-Way ANOVA and Pearson's Correlation Analysis were utilized for the evaluation of the data collected.

RESULTS: The mean of scores obtained by the participants from the Achievement-Focused Motivation Scale and the Lifelong Learning Tendency Scale were respectively 143.24±24.99 and 70.28±11.94. Upon assessment of the correlation between the means of the scores obtained by the participants from the Achievement-Focused Motivation Scale and the Lifelong Learning Tendency Scale, it was found that there was a statistically significant relationship between the participants' scores in the Achievement-Focused Motivation Scale and its sub-scales and their scores in the Lifelong Learning Tendency Scale ($p<0.01$).

CONCLUSION: It was ascertained that the nursing students' lifelong learning tendencies developed as their achievement-focused motivation levels went up.

Keywords: Achievement-focused motivation, lifelong learning tendency, nursing student, education

INTRODUCTION

Motivation is defined as "the motive which urges individuals to take action for showing decisiveness in their behaviors and for fulfilling a goal", and it is a force which ensures the continuity of actions. One of the domains in which the concept of motivation is most commonly used is an educational institution. It is asserted that having high levels of motivation in the learning process starting in childhood at educational institutions and continuing throughout life affect individuals' learning efforts positively.[1,2] In the education and instruction process, motivation is a phenomenon which stimulates and mobilizes students and enables them to gain benefits from their activities by transforming their knowledge base, technical skills and conceptual skills.[3] Individuals who are able to have immediate access to information, add new information to their knowledge base and share information with other people are characterized as powerful, highly

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motivated and academically successful.[2,3] It is asserted that raising the level of education is also effective in boosting motivation. This is why individuals need to renew, develop, constantly upgrade and transform themselves. Fast developments in the domain of science and technology also accelerate this renewal process of information, and developments in the knowledge base and the renewal of existing information results in information obtained through educational institutions becoming obsolete.[4,5] In this sense, the need for those individuals who are capable of following up developments in the field of science and technology, who have access to rapidly changing information, who restructure information and who promote their self-development has increased.[5,6] The need for individuals to develop and renew themselves has brought the concept of lifelong learning to the forefront.[1]

The concept of lifelong learning is used as synonymously for adult education and constant learning and it covers all formal or informal education activities which increase personal, social or professional knowledge, skills and values likely to be gained in any phase of life.[7] It is discerned that the importance of lifelong learning progressively increases in professions where the human being is the essential component. Lifelong learning is also of importance to nursing professionals who are rapidly affected by scientific and technological developments and spend a long time with patients as part of the delivery of healthcare services.[1,8] Nurses need to have lifelong learning to be able to keep up to date with the most current information and practices in the field of healthcare in order to acquire the information, skills and qualifications required for the safe conduct of nursing practices, to continue to offer high-quality healthcare services and to improve health services.

The American Association of Colleges of Nursing, and also, the American Nurses Association and several accredited institutions refer to the lifelong learning responsibilities of nurses.[7] The profession of nursing should strengthen its professional infrastructure and produce and share knowledge with regards to its area of service. It is necessary to focus on this concept so that it will be internalized, especially during the university years and also to support motivational parameters which are likely to encourage student nurses to internalize this concept. Students of nursing colleges are prospective nurses who will play protective and constructive roles in the healthcare of individuals and/or society. In order to contribute to the development of the profession of nursing, institutions offering nursing education are expected to raise the quality of education, and nursing students are supposed to acquire lifelong learning attributes during their college education.[9]

Radi found a statistically significant relationship between Saudi nursing students' academic achievements and their levels of motivation to attend university.[1] Those nursing students with high motivation levels also had higher academic achievement levels. It was particularly emphasized that those individuals who had outstanding academic achievements and focused on having accomplishments had more effective learning activities and processes and continued in this manner throughout their lives.[1] Moreover, in the study by Osma et al.[10], it was asserted that the most significant factor affecting students' academic achievements during their university years was their level of motivation during their higher education, and ensuring pedagogical reinforcement was essential for the maintenance and enhancement of motivation in order to attain perfection. Furthermore, in the study performed by Odanga[11] in Kenya with the participation of 224 students, it was stated that those students who had self-discipline, had forward-looking future goals, were skilled in time-management and had instruction and learning settings which supported autonomy had higher self-motivation levels, as well as higher academic achievement levels. In addition, in their study, it was highlighted that, for students to be able to have high academic achievement levels, to have access to lifelong learning and to motivate themselves, they should be instructed and educated by means of strategies which would raise their motivation levels.[11] After a review of the relevant literature, it was observed that studies on nursing students were intended to identify only the lifelong learning qualities or motivation, but there were only a limited number of studies analyzing the correlations between motivation and lifelong learning tendencies.[1,2,8,12,13] It is clear that promoting the achievement-focused motivation of nursing students together with their lifelong learning qualities will likely assure the protection and development of the healthcare of both individuals and the society. Starting from this point, the aim of this study is to identify the effects of achievement-focused motivation on the lifelong learning tendencies of nursing students.

Research Questions:

In this study, answers are sought to the following fundamental questions:

1. What are the achievement-focused motivation and lifelong learning tendency levels of nursing students?

2. Which factors influence the level of achievement-focused motivation and lifelong learning trends in nursing students?

3. Does the achievement-focused motivation of nursing students have an impact on their lifelong learning trends?

MATERIALS AND METHODS

Study Design

A descriptive and cross-sectional design was used in this study.

Setting and Sample

The population of this study consisted of all nursing students who were first, second, third and fourth-year students at the Nursing Department of the School of Health Sciences, İstanbul Gelişim University in the spring semester of the academic year of 2018–2019 (n=300). Sample selection was not performed, and it was aimed to include the whole population in the study. The voluntary participation rate in this study was 88% (n=264). The inclusion criteria of the study comprised the following:

Being a nursing student in the spring semester of the academic year of 2018–2019,

Having no visual or auditory impairments,

Being open to communication and collaboration,

Having no history of psychiatric illness

Agreeing to participate in this study.

Data Collection Instruments

The data were collected by a Personal Information Form, the Achievement-Focused Motivation Scale and the Lifelong Learning Trends Scale for Turkish students.

Personal Information Form

The Personal Information Form was prepared by the researchers based on the literature.[1,4,8,12-14] The form consists of 14 close-ended questions about the students' socio-demographic characteristics such as age, gender, the last school of graduation, mother's education level, mother's profession, father's education level, father's profession, family type, family income status, where they live, whether they chose nursing voluntarily, any membership of student associations and their grade point average (GPA).

Achievement-Focused Motivation Scale (AFMS)

The Achievement-Focused Motivation Scale which was developed by Semerci [15] to identify the achievement-focused motivation of students was utilized in this study. The Achievement-Focused Motivation Scale, which is scored on the basis of a 5-point Likert scale, comprises 35 items and has four sub-scales. These sub-scales are (a) external effects (12 items), (b) internal effects (9 items), (c) growth of aim (6 items) and (d) self-consciousness (7 items) (minimum score: 35, maximum score: 175). High scores obtained from the overall scale and its sub-scales indicate high levels of motivation. The Cronbach's Alpha Coefficient calculated for the overall scale was 0.89.[15] In this study, the Cronbach's Alpha Coefficient was found to be 0.91.

Lifelong Learning Tendency Scale (LLTS)

This scale, which was developed by Erdoğan and Arsal[16], has two sub-scales, namely, "willingness to learn" and "openness to development", and it comprises 17 items. It is a 5-point Likert-type scale (minimum score: 17, maximum score: 85). High scores obtained from this scale demonstrate that lifelong learning tendencies are high. The Cronbach's Alpha Coefficient calculated for the overall scale was 0.86.[16] In this study, the Cronbach's Alpha Coefficient was found to be 0.95.

Data Collection

The data were collected by the second author between April 15 and May 10, 2019. The Personal Information Form, AFMS and LLTS were applied to all students on different days. The researcher went to each classroom and informed the instructors of the classes about the study before the data collection process. In order to avoid any interruption in the classes where the questionnaire was applied, permission was obtained from the responsible instructor of the class. A questionnaire was applied at the end of a class. Before collecting the data, the purpose of the study was explained to the students, and the voluntary and confidential nature of the study was emphasized. After reading the contents of the consent form, the questionnaire forms were distributed to those who agreed to participate in the study. The participants voluntarily consented and were told they could withdraw from the study at any time without consequences. After the forms were completed, they were collected by the second author. Data collection lasted approximately 20–25 min.

Statistical Analysis

Data analysis was performed using SPSS 21.0 (Statistical Package for the Social Sciences, Chicago, IL, USA). Categorical variables are presented as frequencies and percentages. Continuous variables are expressed as mean and standard deviation (SD). To evaluate the normality of the data distribution, Shapiro–Wilk or Kolmogorov–Smirnov tests were used. Independent-samples t-tests were used for two groups which had continuous variables, and one-way analysis of variance (ANOVA) was used for more than two groups. The relationship between the scales was tested using Pearson's correlation analysis. A two-tailed p-value <0.05 was considered significant for all analyses.

Ethics Committee Approval

Before data collection, ethics committee approval was obtained from the Ethics Committee of Non-Interventional Clinical Studies of Burdur Mehmet Akif Ersoy University (decision number: GO 2019/36, date: 06.02.2019). Written permission was obtained from the Director's Office of the School of Health Sciences (decision number: 2019-13-2, meeting date: 08.04.2019). The written consents of the students who participated in the study were obtained after reading an informed consent text. This study was conducted in accordance with the Good Clinical Practices of the World Medical Association (WMA) and the Declaration of Helsinki (and/or the World Psychiatric Association HAWAII Declaration).

RESULTS

Upon the review of descriptive characteristics in association with the scores obtained by the nursing students from AFMS and LLTS, it was found that the mean score obtained from the "external effects" sub-scale of AFMS was 52.34±7.84, the mean score obtained from the "internal effects" sub-scale of AFMS was 27.95±6.02, the mean score obtained from the "growth of aim" sub-scale of AFMS was 27.95±6.02, and the mean score obtained from the "self-consciousness" sub-scale of AFMS was 27.76±6.07. It was ascertained that the mean score obtained from the overall AFMS was 143.24±24.99, and the mean score in the overall LLTS was 70.28±11.94 (Table 1).

The descriptive characteristics of the nursing students are presented in Table 2. Upon the comparison of the descriptive characteristics with their scores from AFMS and LLTS, it was found that the class year of the nursing students had statistically significant relationships with the "internal effects" and "growth of aim" sub-scales of AFMS (p=0.024, p=0.035). It was discerned that the mean score of the first-year nursing students from the "internal effects" sub-scale (29.32±7.08) was higher than those obtained by the second-, third- and fourth-year nursing students. It was identified that the "external effects" sub-scale of AFMS had statistically significant relationships with the education level and profession of the participants' mothers (p=0.005). It was ascertained that those participants with mothers who were primary school graduates or had lower education levels had higher mean scores in the "external effects" sub-scale (53.02±8.23) than those whose mothers had higher levels of education, and those students whose mothers were housewives had higher mean scores in the "external effects" sub-scale (52.85±7.94) than those with mothers

Table 1. AFMS and sub-scales with LLTS scores

AFMS and sub-scales	Min-max/n	Mean ± SD	Cronbach Alpha
External effects	25–60/264	52.34±7.84	0.92
Internal effects	7–35/264	27.95±6.02	0.91
Growth of aim	7–35/264	27.95±6.02	0.88
Self-consciousness	11–35/264	27.76±6.07	0.90
AFMS total	67–175/264	143.24±24.99	0.91
LLTS total	29–85/264	70.28±11.94	0.95

AFMS: Achievement-Focused Motivation Scale; LLTS: Lifelong Learning Tendency Scale, min: minimum, max: maximum, SD: standard deviation, n: number.

Table 2. Comparison of the Achievement-Focused Motivation Scale (AFMS) and Lifelong Learning Tendency Scale (LLTS) with socio-demographic characteristics of the nursing students

Descriptive characteristics	Number	%	External effects sub-scale	Internal effects sub-scale	Growth of aim sub-scale	Self-consciousness sub-scale	AFMS Total	LLTS Total
Age*								
18–21 years	188	71.2	55.00±8.42	28.44±6.21	28.44±6.21	28.06±6.47	144.53±26.74	70.82±12.29
22–25 years	69	26.1	54.00±6.34	26.47±5.35	26.47±5.35	26.76±4.99	138.85±19.75	69.10±10.96
26 years and above	7	2.7	54.00±4.41	29.42±5.19	29.42±5.19	29.57±3.69	151.71±17.68	77.14±7.88
Test statistics			0.470	2.955	2.295	1.477	1.727	2.529
p-value			0.626	0.054	0.054	0.230	0.180	0.082
Gender**								
Female	198	75.0	52.85±7.90	28.28±6.26	28.28±6.26	28.03±6.33	144.95±26.05	70.64±12.54
Male	66	25.0	50.81±7.49	26.96±5.15	26.96±5.15	26.98±5.21	128.10±20.83	69.18±9.92
Test statistics			0.067	3.429	3.429	2.282	4.317	5.337
p-value			0.067	0.124	0.124	0.227	0.054	0.389
Class year*								
First year	85	32.2	52.91±9.94	29.32±7.08	29.32±7.08	29.70±7.42	149.32±31.93	70.22±15.32
Second year	48	18.2	52.64±6.38	27.77±4.90	27.77±4.90	26.43±5.09	141.14±19.78	71.79±9.94
Third year	107	40.5	51.78±6.60	27.45±5.38	27.45±5.38	26.99±4.91	140.00±20.23	69.63±9.96
Fourth year	24	9.1	52.25±7.42	25.70±5.93	25.70±5.93	27.04±6.01	138.33±22.74	70.33±10.35
Test statistics			1.695	1.167	2.910	2.377	4.273	1.532
p-value			0.761	**0.024**	**0.035**	0.110	0.118	0.974
				a>d; a>c	**a>d; a>c**			
Grade point average (GPA)			**2.64±0.46 (1.50-3.80)**					
Mothers' education level*								
Primary school or below	183	69.3	53.02±8.23	28.18±6.24	28.18±6.24	28.04±6.35	145.25±26.72	70.91±13.18
Secondary school	59	22.3	52.15±5.57	27.15±5.96	27.15±5.96	27.57±5.67	139.84±20.31	69.00±9.20
Tertiary education	22	8.4	42.27±8.10	28.27±4.01	28.27±4.01	26.00±4.42	135.63±19.08	68.47±5.81
Test statistics			5.481	0.681	0.681	1.149	2.174	0.852
p-value			**0.005**	0.507	0.507	0.319	0.116	0.428
			a>c; b>c					
Mothers' profession*								
Housewife	213	80.7	52.85±7.94	28.14±6.25	28.14±6.25	28.17±6.20	144.83±26.05	71.29±12.11
Worker	34	12.9	52.05±5.65	26.67±5.21	26.67±5.21	26.58±5.54	128.55±18.27	64.76±11.82
Civil servant	17	6.4	46.52±8.29	28.23±4.27	28.23±4.27	25.05±4.56	132.64±19.59	68.58±5.60
Test statistics			5.324	0.885	0.885	2.842	2.588	4.696
p-value			**0.005**	0.414	0.414	0.060	0.077	**0.010**
			a,b>c					**a,b>c**
Fathers' education level*								
Primary school or below	155	58.7	53.34±8.50	28.56±6.66	28.56±6.66	28.25±6.68	146.34±28.03	70.53±14.10
Secondary school	81	30.7	51.12±5.55	27.08±4.91	27.08±4.91	27.24±4.93	138.98±17.97	69.87±8.10
Tertiary education	28	10.6	50.39±9.00	27.14±4.85	27.14±4.85	26.60±5.45	138.35±22.58	70.03±7.67
Test statistics			3.153	1.896	1.896	1.301	2.949	0.087
p-value			**0.044**	0.152	0.152	0.274	0.054	0.917
			a>b					

Table 2. Continued

Descriptive characteristics	Number	%	External effects sub-scale	Internal effects sub-scale	Growth of aim sub-scale	Self-consciousness sub-scale	AFMS Total	LLTS Total
Fathers' profession*								
Civil servant	25	9.5	48.68±8.78	32.64±6.86	26.28±5.26	26.40±5.40	134.00±22.87	69.08±8.24
Worker	153	53.0	51.68±8.34	35.35±7.77	27.64±6.09	27.22±6.28	141.91±25.96	69.26±13.66
Retired	67	25.4	55.91±4.70	37.04±8.05	30.13±5.73	30.19±5.38	153.28±20.28	74.22±8.24
Not working	19	7.1	49.94±7.18	30.31±8.12	25.05±5.16	25.36±5.31	130.68±23.49	66.10±8.90
Test statistics			7.976	5.443	5.443	5.651	6.926	3.776
p-value			**0.000**	**0.001**	**0.001**	**0.001**	**0.000**	**0.011**
			c>a,b,d	**c>a,b,d**	**c>a,b,d**	**c>a,b,d**	**c>a,b,d**	**c>a,b,d**
Family type*								
Nuclear family	199	75.4	51.94±8.20	34.88±7.87	27.96±6.15	27.63±6.23	142.44±25.86	69.14±12.66
Expanded family	4	1.5	53.00±8.86	40.50±3.10	31.00±35.91	27.75±5.50	152.25±19.27	80.00±3.82
Broken family	61	23.1	53.60±6.42	35.72±7.55	27.73±5.70	28.19±5.64	145.26±22.36	73.36±8.63
Test statistics			1.056	0.549	0.549	0.196	0.559	4.370
p-value			0.349	0.548	0.548	0.822	0.572	**0.014**
								c>a
Family income level*								
Income below expenditure	21	8.0	54.76±4.65	37.23±7.05	29.19±4.90	29.61±5.60	150.80±19.15	73.42±8.20
Income equal to expenditure	161	61.0	52.51±6.34	34.82±7.07	27.74±5.51	27.60±5.11	142.68±21.19	71.63±9.30
Income above expenditure	82	31.0	51.40±0.60	35.30±9.13	28.06±7.15	27.62±7.71	142.39±32.15	66.81±16.03
Test statistics			1.635	0.550	0.550	1.097	1.050	5.389
p-value			0.197	0.577	0.577	0.349	0.351	**0.005**
								b>c
Place of residence*								
At home with family	105	39.8	54.06±0.13	36.40±7.08	28.77±5.60	28.74±4.90	147.98±19.12	73.28±10.23
At home with roommate	46	17.4	49.45±7.01	31.95±7.29	26.50±4.66	25.67±5.34	133.58±20.27	69.91±8.11
In apartment/dormitory	113	42.8	51.92±9.68	35.32±8.25	27.79±6.76	27.71±7.09	142.76±30.01	68.04±14.03
Test statistics			6.031	5.455	5.455	4.181	5.524	5.8133
p-value			**0.003**	**0.005**	**0.005**	**0.016**	**0.004**	**0.003**
			a>b; a>c	**a>b**	**a>b**	**a>b**	**a>b**	**a>b ; a>c**
Voluntary selection of the profession**								
Yes	217	82.2	53.24±7.34	35.89±7.46	28.31±6.03	28.27±6.09	145.73±24.45	70.91±12.36
No	47	17.8	48.19±8.75	31.80±8.33	26.31±5.76	25.42±5.48	131.74±24.45	67.34±9.31
Test statistics			2.392	0.412	0.001	1.049	0.460	1.664
p-value			**0.000**	**0.001**	**0.039**	**0.003**	**0.000**	0.063
Membership to student clubs**								
Yes	35	13.3	48.40±12.82	33.22±10.46	24.74±8.66	25.51±9.03	131.88±39.66	65.48±21.21
No	229	86.7	52.95±6.60	35.46±7.25	28.44±5.36	23.11±5.43	144.97±21.51	71.01±9.66
Test statistics			47.516	20.119	33.349	33.178	46.648	56.086
p-value			**0.001**	0.113	**0.001**	**0.018**	**0.004**	**0.010**

*Independent-Samples t-test was used in comparisons with two groups which had continuous variables, whilst **One-Way Analysis of Variance (ANOVA) was utilized in comparison of more than two groups.
Significant values are shown in bold.

employed in other professions. Furthermore, it was found that there was a statistically significant relationship between the profession of the participants' mothers and their mean scores obtained from LLTS (p=0.010). Table 2 shows that those students whose mothers were housewives had higher mean scores in LLTS than those with mothers employed in other professions. In addition, it was found that the mean scores of the participants from the "external effects" sub-scale of AFMS had statistically significant relationships with the education level and profession of the participants' fathers (p=0.044, p=0.000). It was ascertained that the mean score obtained from the "external effects" sub-scale from those students with fathers who were primary school graduates or had lower education levels (53.34±8.50) was higher than those with fathers who had higher levels of education. It was found that the mean score obtained from the "external effects" sub-scale from those participants who had retired fathers (55.91±4.70) was higher. It was identified that the residence place of the participants had statistically significant relationships with their mean scores in the "external effects", "internal effects", "growth of aim" and "self-consciousness" sub-scales of AFMS, the overall AFMS and the overall LLTS (respectively p=0.003, p=0.005, p=0.005, p=0.016, p=0.004, p=0.003), and the mean scores obtained from those participants living with their families in the "external effects", "internal effects", "growth of aim", "self-consciousness" sub-scales of AFMS, the overall AFMS and the overall LLTS (54.06±0.13) were higher than for those living in other places of residence. Likewise, it was found that the voluntary selection of the profession of nursing by the participants had statistically significant relationships with their mean scores in the "external effects", "internal effects", "growth of aim" and "self-consciousness" sub-scales of AFMS, the overall AFMS and the overall LLTS (respectively p=0.000, p=0.001, p=0.039, p=0.003, p=0.000, p=0.063). The mean scores obtained by the participants voluntarily selecting the profession of nursing in the "external effects", "internal effects", "growth of aim", "self-conscious" sub-scales of AFMS, the overall AFMS and the overall LLTS were higher than those obtained from those participants who entered the profession of nursing involuntarily. It was ascertained that student club membership had statistically significant relationships with the mean scores obtained from the participants in the "external effects", "growth of aim" and "self-consciousness" sub-scales of AFMS, the overall AFMS and the overall LLTS (p=0.001, p=0.001, p=0.018, p=0.004, p=0.010, respectively) (Table 2).

Upon evaluation of the correlation between the mean scores obtained by the participants from AFMS and LLTS, it was found that the mean score obtained by the participants in the "external effects" sub-scale of the AFMS had statistically significant positive relationships with their mean scores in the "internal effects" sub-scale (p=0.000, r=0.716), "growth of aim" sub-scale (p=0.000, r=0.721), "self-consciousness" sub-scale (p=0.000, r=0.765) of AFMS, the overall AFMS (p=0.000, r=0.899) and the overall LLTS (p=0.000, r=0.700) at a level of 1%. It was determined that the mean score obtained by the participants in the "internal effects" sub-scale of AFMS had statistically significant positive relationships with their mean scores in the "growth of aim" sub-scale (p=0.000, r=0.786) and "self-consciousness" sub-scale (p=0.000, r=0.753) of AFMS, the overall AFMS (p=0.000, r=0.911) and the overall LLTS (p=0.000, r=0.689) at a level of 1%. Moreover, it was observed that the mean score obtained by the participants in the "growth of aim" sub-scale of AFMS had statistically significant positive relationships with their mean scores obtained from the "self-consciousness" sub-scale (p=0.000, r=0.758) of AFMS, the overall AFMS (p=0.000, r=0.896) and the overall LLTS (p=0.000, r=0.682). It was seen that the mean score of the participants in the "self-consciousness" sub-scale of AFMS had statistically significant positive relationships with their mean scores in the overall AFMS (p=0.000, r=0.900) and the overall LLTS (p=0.000, r=0.721). It was found that there was a statistically significant positive relationship between the mean scores obtained by the participants from the overall AFMS and the overall LLTS (p=0.000, r=0.774). The participants' GPAs had statistically significant positive relationships with their mean scores in the "internal effects" sub-scale (p=0.005, r=0.171), "growth of aim" sub-scale (p=0.000, r=0.252) and "self-consciousness" sub-scale (p=0.007, r=0.167) of AFMS, the overall AFMS (*p*=0.001, r=0.196) and the overall LLTS (p=0.004, r=0.178) (Table 3).

DISCUSSION

Motivation for learning has become a precondition for the fulfillment and sustainability of lifelong learning in the information society of the

Table 3. Correlation between AFMS-Subscales and LLTS with GPA

		External effects	Internal effects	Growth of aim	Self-conscious	AFMS total score	LLTS total score
External effects	r	1	0.716	0.721	0.765	0.899	0.700
	p	-	0.000	0.000	0.000	0.000	0.000
Internal effects	r	0.716	1	0.786	0.753	0.911	0.689
	p	0.000	-	0.000	0.000	0.000	0.000
Growth of aim	r	0.721	0.786	1	0.758	0.896	0.682
	p	0.000	0.000	-	0.000	0.000	0.000
Self-conscious	r	0.765	0.753	0.758	1	0.900	0.721
	p	0.000	0.000	0.000	-	0.000	0.000
AFMS total score	r	0.899	0.911	0.896	0.900	1	0.774
	p	0.000	0.000	0.000	0.000	-	0.000
LLTS total score	r	0.700	0.689	0.682	0.721	0.774	1
	p	0.000	0.000	0.000	0.000	0.000	-
GPA	r	0.132	0.171	0.252	0.167	0.196	0.178
	p	0.092	0.005	0.000	0.007	0.001	0.004

p<0.01; AFMS: Achievement-Focused Motivation Scale, LLTS: Lifelong Learning Tendency Scale, GPA: grade point average

21st century. In the context of this precondition, in order to adapt to changing technology and the information age and gain the necessary knowledge, skills, attitudes and qualifications, it is important to raise individuals who are able to self-learn, research, wonder, question, look from a critical perspective, solve problems, become highly motivated and perceive learning as a process continuing throughout their lives.[4,13] For this reason, this study was conducted to determine the effects of achievement-focused motivation on the lifelong learning tendencies of nursing students in light of the relevant literature.

In this study, the mean score of the participants in LLTS was 70.28±11.94. Upon a review of the relevant literature, it was seen that there are studies arguing that participants have lifelong learning tendencies.[6,17-20] As nursing students are highly inclined toward lifelong learning, it is thought that they are interested in lifelong learning and have sufficient motivation, and even if they are faced with difficulties in organizing and performing lifelong learning activities, they can overcome these difficulties as they have positive tendencies toward lifelong learning.

In this study, the mean score of the participants in the overall AFMS and their mean sub-scale scores were seen to be at a high level. This result was in a similar vein to the findings in the relevant literature,[1-3,6,21,22] and high scores obtained from the overall AFMS and its sub-scales indicate that the college department in which students are enrolled has an effect on their achievement-focused motivation levels and lifelong learning tendencies, and students have positive feelings toward their college and instructors.

It was found that the place of residence of the participants had effects on their scores in LLTS and AFMS. It was determined that the mean scores obtained in LLTS and AFMS from those participants living with their families were significantly higher than those obtained from those participants living in a home with roommates, in dormitories or in apartments. In the light of these results, it may be argued that living together with family promotes the students' confidence which emanates from a family setting leads students to assume positive roles, enhances their knowledge, skills, attitudes, achievements, motivation and lifelong learning tendencies and has positive effects on these students.

It was found that the mean scores of the participants in LLTS were in general high on the basis of their class year. However, there was no statistically significant difference in the mean LLTS scores in this respect ($p>0.05$). It was discerned that, in the relevant literature, on the one hand, there are studies with analogous results,[19] while on the other hand, certain studies contradicted this finding of this study.[18,20,23,24] Additionally, the class year of the participants had statistically significant relationships with their mean scores in the "internal effects" sub-scale and "growth of aim" sub-scale of AFMS ($p<0.05$). The mean score obtained by the first-year nursing students in the "internal effects" sub-scale of AFMS (29.32±7.08) was found to be higher than those obtained by the second-, third- and fourth-year students. As the class years advanced, the mean scores obtained from the "internal effects" sub-scale decreased. It is thought that the differences in research findings are likely to have arisen from differences in schools, areas of practical application, the students' expectations and whether these expectations were met or not.

It was ascertained that the profession of the participants' fathers had statistically significant associations with their mean scores in LLTS and AFMS and its sub-scales, whilst the profession and education level of the participants' mothers had statistically significant associations only with their mean scores in LLTS and the "external effects" sub-scale of AFMS. The study performed in 2016 by Denat et al.[13] stated that the education level of parents had no effect on lifelong learning tendencies. The study conducted in 2017 by Karaduman and Tarhan[19] identified that, on the basis of the education level of fathers, there was a statistically significant difference in lifelong learning tendencies, whereas the education level of mothers had no statistically significant effect on lifelong learning tendencies. In light of these results, it may be inferred that gender roles have effects on the scores obtained from AFMS and LLTS. In addition, in view of the fact that the students' fathers had better professions and higher education levels than their mothers did, and most mothers were housewives (80.7%) according to an examination of the sociodemographic data of this study, it is thought that the fathers supported their children in terms of lifelong learning in addition to the patriarchal family structure of the Turkish society.

It was found that those participants who voluntarily selected nursing as a profession had significantly higher AFMS and LLTS scores. Ünal and Akay[25] identified a moderately positive relationship between students' lifelong learning tendencies and their attitudes toward the profession. Çelik and Karaca[22] suggested that nurses who willingly performed their profession had higher motivation scores. In view of these results, it is thought that the voluntary selection of the profession of nursing by the participants has positive effects on their studies, achievements and lifelong learning motivation.

In this study, those participants who were members of student clubs had significantly higher AFMS and LLTS scores. Even if there is no study performed on the effect of student club membership on motivation and lifelong learning tendencies in the relevant literature, it is considered that those participants who are involved in different extracurricular activities such as training courses, seminars, the internet and library had higher lifelong learning and motivation scores.[14,26] In light of these results, it is considered that participation of students in activities such as joining student clubs and following up club events encourages them to assume more responsibilities, raises their motivation and contributes positively to their lifelong learning processes.

In this study, according to the review of the participants' AFMS and LLTS scores on the basis of their GPAs, the participants with higher GPAs had significantly higher mean scores in AFMS and LLTS. This result of the study was in parallel with findings in the relevant literature,[1,27-30] and it is thought that students with higher GPAs have higher levels of achievement-focused motivation and lifelong learning tendencies as they manage their self-orientation better, successfully identify their learning needs, direct their own learning processes, and also the college program in which they were enrolled enabled them to develop lifelong learning tendencies.

Limitations of the Study

The results of this study do not represent all nursing students in Turkey and are limited to the students who received education at the school where the study was conducted.

CONCLUSION

Nursing is a profession which emphasizes and supposes that lifelong learning is essential. It is asserted that having high motivation levels

and obtaining lifelong learning qualities during the college years will enable nursing students to succeed in playing effective roles in healthy individual/societal transformations, obtaining different perspectives towards health problems and enhancing the quality of solutions.[4,13,14]

With this study, it was found that the nursing students had high levels of achievement-focused motivation and life-long learning tendencies. Moreover, it was identified that the nursing students' levels of achievement-focused motivation had an effect on their lifelong learning tendencies, and as the levels of achievement-focused motivation increased, lifelong learning tendencies were also enhanced. It was determined that certain variables such as the place of residence, father's profession, mother's profession, voluntary selection of the profession, membership to student clubs and GPA affected the achievement-focused motivation and lifelong learning tendency scores.

In light of these results, "orientation seminars" should be organized in order to raise the motivation levels of students, who have started and will continue to have their academic careers away from their families, and to promote their adaptation to the new educational setting. With a view to exchanging learnt knowledge and skills and raising motivation, during trainings on nursing skills, an inter-class coaching system may be implemented by prioritizing the concepts of "being a guiding light" and "helping". In order to ensure that students can internalize the profession of nursing better and enhance their lifelong learning tendencies, "professional career days" which host leading figures of the profession should be organized. Education on how students can access lifelong learning resources (internet, library, seminar, convention, conference, training course, student club membership and so on) should be provided to students in order to promote their motivation and accomplishments in university settings, and systems and settings to which they would have easy access should be created. Elective courses that will motivate and support students' lifelong learning should be added to the curriculum by instructors, and also educational methods that will enable students to take responsibility should be developed by lecturers interactively with students. In order to identify the weaknesses of students with low GPAs and raise their levels of achievement-oriented motivation, meetings should be scheduled with their advisors.

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MAIN POINTS

- Lifelong learning is important for nursing staff who spend a long time with patients, as well as providing health service delivery.
- Success in the professional life is related to academic success during the university years, lifelong learning and motivation.
- It was observed that as the success-oriented motivation of the nursing students increases, they tend towards lifelong learning.
- It is thought that strategies developed by nursing schools to promote lifelong learning and raise motivation will raise the education quality and enhance the quality of healthcare services offered to patients.

ETHICS

Ethics Committee Approval: Before data collection, Ethics committee approval was gained from the Ethics Committee of Non-Interventional Clinical Studies of Burdur Mehmet Akif Ersoy University (decision number: GO 2019/36, date: 06.02.2019).

Informed Consent: The written consents of the students who participated in the study were obtained after reading an informed consent text.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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ORIGINAL ARTICLE

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An Assessment of Restless Legs Syndrome and Sleep Quality in Pregnant Women

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ABSTRACT

BACKGROUND/AIM: This study was conducted to review Restless Legs Syndrome (RLS) and some variables believed to be associated with RLS and to assess the relationship between the RLS and sleep quality in pregnant women.

MATERIAL AND METHODS: The study group consisted of 449 pregnant women. The diagnostic criteria developed by the International RLS Study Group were used to assess the diagnosis and severity of RLS, and the Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality.

RESULT: The ages of pregnant women in the study group ranged from 18 to 45 years with a mean age of 28.78±5.31 years. RLS was diagnosed in 114 pregnant women (25.4%). The incidence of RLS was higher in those with a low to average family income, those having a nuclear family, those with a history of a gynecological surgery, those having irregular periods before pregnancy, those with a history of lower back pain during pregnancy and those with a history of macrosomia. No difference in terms of sleep quality was determined in those women with or without RLS. RLS is an important health problem in pregnant women. There is a moderate negative correlation between the severity of RLS and sleep quality.

CONCLUSION: It will be advantageous to refer pregnant women with RLS to specialists for final diagnosis and treatment. More extensive studies are required to demonstrate the relationship between RLS and quality of sleep.

Keywords: Pregnant women, Restless Legs Syndrome, sleep quality

INTRODUCTION

Restless Legs Syndrome (RLS) was first described by Thomas Willis in 1685 in patients with sleep disruption and restlessness in their legs and referred to as "anxietas tibiarum". Later in 1945, Dr. Karl-Axem Ekbom used the definitions of "irritable legs" and "restless legs" for the disorder which is also known as the Ekbom Syndrome.[1] RLS is a sensorimotor disorder characterized by an irresistible urge to move the legs and uncomfortable sensations, worsening at rest, which may be accompanied by dysesthesia that prevents falling asleep.[2]

Patients frequently express immediate relief when they move their legs in bed, get up and walk or dangle their legs off the bed. Symptoms are usually bilateral in the legs, and occasionally in the arms, starting during relaxation, prolonged inactivity and at night before sleeping. Symptoms disappear in the daytime.[3] While diagnosis of RLS is based on clinical

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history and evaluation, laboratory and imaging methods can also be used when needed. Neurological examination is usually required. Five criteria developed by the International Restless Legs Syndrome Study Group (IRLSSG) must be met for a final diagnosis of RLS.

Pregnancy is considered an important risk factor for the onset or worsening of RLS symptoms. It is believed that hormonal (prolactin, progesterone, estrogen levels), psychomotor and behavioral changes during pregnancy as well as changes in sleeping habits and in folic acid-iron levels may have an impact on RLS.[4]

Studies have shown that RLS affects sleep, cognitive functions and quality of life adversely and can be disturbing enough to require medical treatment.[5,6] There is a close relationship between RLS and sleep disorders which are known to be associated with undesirable effects in pregnancy such as intrauterine growth restriction or preeclampsia.

This study was conducted to review RLS and some variables believed to be associated with RLS and to assess the relationship between RLS and sleep quality in pregnant women.

MATERIALS AND METHODS

This was a cross-sectional study conducted on pregnant women who applied to Sakarya Training and Research Hospital from July 1, 2017 to November 1, 2017.

A questionnaire consisting of three sections was prepared based on literature in line with the aims of this study. The first section contained socio-demographic and pregnancy-related characteristics of pregnant women, the second section included questions on the presence and severity of RLS and the third section involved questions from a scale which was used to assess sleep quality.

The required approval of the Sakarya University Non-interventional Ethics Committee dated June 22, 2017 and number 71522473/050.01.04/141 and approval from Sakarya Training and Research Hospital management were obtained before collecting data in this study. The rules stated in the Helsinki Declaration were complied with during the stages of data collection.

The minimum sample size was calculated to be 449 in this study (power test = 0.847, RLS prevalence = 0.05 and margin of error = 0.07). Pregnant women presenting at the pregnancy polyclinic of Sakarya Training and Research Hospital during the study were informed about the subject and aims of this study and their verbal consent was obtained. A total of 449 pregnant women who agreed to take part in the study comprised the study group. Previously prepared questionnaires were completed by the investigators via a face-to-face interview method to collect the data.

Diagnosis criteria developed by the International RLS Study Group were used to assess diagnosis and severity of RLS.[5,6] A reliability and validity study of the scale in Turkey was conducted by Sevim et al.[7] If four of the following criteria were present, RLS was diagnosed: an urge to move the legs (a) caused by uncomfortable and unpleasant sensations in the legs; (b) worsening during periods of rest or inactivity such as lying down or sitting, (c) relieved by movement, such as walking or stretching, "at least as long as the activity continues" and (d) only occurring or worse in the evening or night rather than during the day. There were 10 items on a 5-point Likert-type scale which was used to assess RLS severity. Each item was scored from 0 to 4 in an ascending order of severity. The total score that can be obtained from the severity scale ranges from 0 to 40 where higher scores denote increasing severity of RLS.

The PSQI[8] was used to assess sleep disturbances over the past month. The PSQI is an 18-item self-reported questionnaire. These items produce seven component scores ranging from 0 (no difficulty) to 3 (severe difficulty). The components are sleep duration, sleep disturbance, sleep latency, day-time disturbance, habitual sleep efficiency, sleep quality, and taking sleep medications. The sum of the scores of the components yields a measure of global sleep quality which ranges from 0 to 21. Getting a score of 5 or more in the PSQI is defined as poor sleep quality. The index was translated into Turkish by Agargun et al.[9]

The data was evaluated in the IBM® SPSS® (version 20.0) (Chicago, IL, USA) Statistical Package Program. Chi-square test, Mann–Whitney U test and Spearman's Correlation analysis were used to analyze the data. The statistical significance value was accepted as $p<0.05$.

RESULTS

The ages of the pregnant women in the study group ranged from 18 to 45 with a mean age of 28.78±5.31 years. RLS was diagnosed in 114 pregnant women (25.4%) in this study. The distribution of women with or without RLS in the study group by some socio-demographic characteristics is given in Table 1.

In the study group, 137 women (30.5%) were having their first pregnancy and there were 152 women (33.9%) who had not given birth before. Ninety-seven women (21.6%) had irregular menstruation before pregnancy and 283 women (63.0%) had a history of lower back pain during pregnancy. The distribution of women with or without RLS in the study group by some pregnancy-related characteristics is given in Table 2.

The scores obtained from the Pittsburgh Sleep Quality Index (PSQI) by the participants in the study group ranged from 0 to 18 with a mean score of 6.86±3.50. The distribution of the scores obtained from the PSQI by the women with or without RLS is given in Table 3.

The scores obtained from the RLS Severity Scale ranged from 0 to 37 with a mean score of 15.17±7.97. A negative correlation was found between the scores obtained from the RLS Severity Scale and from the PSQI from the pregnant women (r_s=-0.444; p=0.001). The distribution of the scores obtained from the RLS Severity Scale and from the PSQI from the women in the study group is given in Figure 1.

DISCUSSION

Emerging with the urge to move the legs and causing uncomfortable sensations in the extremities, RLS may develop at any age in the general population but more frequently during pregnancy and with advancing age.[10] Pregnancy is considered among the important risk factors for the onset and worsening of RLS symptoms. RLS is believed to be associated with hormonal factors (prolactin, progesterone, estrogen) in pregnancy, psychomotor/behavioral factors, motor changes, changes in sleeping habits, anxiety and metabolic factors (low folate and iron levels).[4,10] The prevalence of RLS was reported to be about 10.0% in pregnant women. Studies conducted in several countries reported the prevalence of RLS ranged from 13.5% to

34%.[11,12] Some studies conducted in Turkey found that the prevalence of RLS ranged from 19.0% to 26.0%.[13,14] In our study, approximately one quarter of the pregnant women had RLS, which is consistent with the literature.

With advancing age, the production of endogenous dopamine reduces; therefore, the prevalence of RLS increases with age. In view of the studies on the general population, Taşdemir et al.[15] found that the prevalence of RLS is 3.5 times higher in women compared to men and it increases with advancing age. On the other hand, some studies reported no relationship between the prevalence of RLS and age.[14,16] Sahin et al.[13] found no relationship between the prevalence of RLS and age. The present study could not determine a difference regarding the prevalence of RLS between age groups.

It is possible that the prevalence of RLS is lower among those women with a high education level as they are more conscious and well-informed about the early diagnosis and treatment of RLS as with all diseases and disorders. Moreover, one study mentioned that the higher prevalence of RLS in women with a low education level may be associated with the number of child-births. In their study conducted in India, Rangarajan et al.[17] similarly reported a higher prevalence of RLS in those with a low education level. In our study, no relationship was determined between education levels and the prevalence of RLS.

It is believed that unfavorable living conditions such as unemployment, poor income perception, etc. may increase the development of RLS.[18] The epidemiological study of Cho et al.[19] reported that there was a relationship between income perception and RLS and that the prevalence of RLS decreases with higher income levels. The higher prevalence of RLS among individuals with low-income levels may be

Table 1. Distribution of women with or without Restless Legs Syndrome in the study group by sociodemographic characteristics

Socio-demographic characteristics	Restless Legs Syndrome			Statistical analysis
	No (%)[a]	Yes (%)[a]	Total (%)[b]	X^2; p-value
Age group (year)				
≤24	86 (76.8)	26 (23.2)	112 (24.9)	3.456; 0.326
25–29	131 (77.5)	38 (22.5)	169 (37.6)	
30–34	70 (68.0)	33 (32.0)	103 (22.9)	
≥35	48 (73.8)	17 (26.2)	65 (14.5)	
Education level				
Primary school or lower	73 (69.5)	32 (30.5)	105 (23.4)	5.464; 0.141
Secondary school	94 (82.5)	20 (17.5)	114 (25.4)	
High school	101 (72.7)	38 (27.3)	139 (31.0)	
University	67 (73.6)	24 (26.4)	91 (20.3)	
Employment status				
Unemployed	220 (72.8)	82 (27.2)	302 (67.3)	1.513; 0.219
Employed	115 (78.2)	32 (21.8)	147 (32.7)	
Family income status				
Low-Middle	191 (70.7)	79 (29.3)	270 (60.1)	5.353; 0.021
High	144 (80.4)	35 (19.6)	179 (39.9)	
Family type				
Nuclear	243 (71.7)	96 (28.3)	339 (75.5)	6.266; 0.012
Extended	92 (83.6)	18 (16.4)	110 (24.5)	
History of a physician-diagnosed disease requiring constant drug use				
No	291 (74.8)	98 (25.2)	389 (86.6)	0.07; 0.932
Yes	44 (73.3)	16 (26.7)	60 (13.4)	
History of a physician-diagnosed gynecological disease				
No	311 (74.9)	104 (25.1)	415 (92.4)	0.126; 0.722
Yes	24 (70.6)	10 (29.4)	34 (7.6)	
History of any gynecological surgery				
No	291 (72.9)	108 (27.1)	399 (88.9)	4.559; 0.033
Yes	44 (88.0)	6 (12.0)	50 (11.1)	
Regular physical exercise				
No	225 (81.2)	52 (18.8)	277 (61.7)	16.714; 0.001
Yes	119 (64.0)	62 (36.0)	172 (38.3)	
Total	335 (74.6)	114 (25.4)	449 (100.0)	

[a]Percentage for the row, [b]Percentage for the column.

associated with poor dietary habits, particularly iron deficiency. Eckeli et al.[20] reported no relationship between the prevalence of RLS and family income levels. Our study found that the prevalence of RLS is higher in those whose family income level is low-middle. However, there was no difference regarding the prevalence of RLS between those women with or without a revenue-generating job.

In studies conducted in Nordic countries and Germany, no relationship was established between household and RLS.[18-21] However, it was determined that the prevalence of RLS is higher in pregnant women with a nuclear family in our study. We assume that this is because pregnant women lack enough support for housework, resulting in increased work-loads and stress levels.

It has been reported that patients with RLS usually have concomitant chronic diseases such as hypertension, diabetes mellitus and depression.[18,22,23] Our study revealed no difference regarding the prevalence of RLS between those with or without a history of a physician-diagnosed diseases requiring constant drug use. A similar result was also reported in the study of Unruh et al.[24]

While it is likely that the prevalence of RLS is higher in those women with a gynecological problem or a history of any kind of surgery, the literature presented no such finding. This study revealed no difference regarding the prevalence of RLS between those women with or without a history of a physician-diagnosed gynecological disease. However, it was determined that the prevalence of RLS is higher in women with a history of gynecological surgery. It is clear that more extensive studies are required to establish such a relationship.

Ohayon et al. found that regular exercise reduces the risk of RLS;[25] however, another study reported that exercise before sleep increases the risk of RLS.[23] Another study established a gradual relationship between exercise and RLS according to the intensity of exercise.[18] Our study findings established that the prevalence of RLS is higher in those with a history of regular physical exercise. This may be related to the fact that the exercise frequencies, durations and timings of pregnant women are not known.

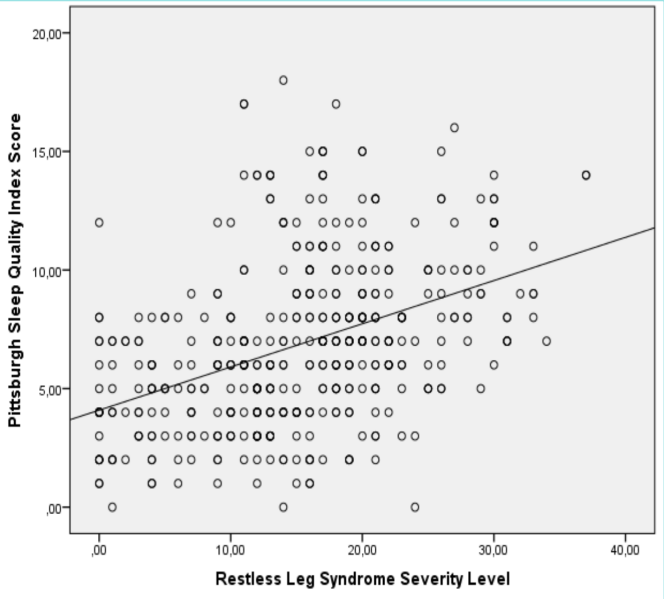

Figure 1. Distribution of scores obtained from the RLS Severity Scale and from the Pittsburgh Sleep Quality Index for the women in the study group

RLS: Restless Legs Syndrome

It is known that RLS symptoms may increase during pregnancy. Moreover, it has been reported that the number of childbirths may be a major factor for a higher prevalence of RLS in women. Berger et al.[18] reported a strong relationship between the prevalence of RLS in pregnant women and the number of childbirths. In our study, no relationship was determined between the number of childbirths and pregnancies and the prevalence of RLS. Shang et al.[26] established no difference regarding fertility in women with or without RLS.

It is known that hormone levels, primarily estradiol, increase during pregnancy. It is believed that increased prolactin levels in the third trimester may reduce dopamine levels, which may have an important role on RLS pathogenesis.[27] Several studies have reported that the prevalence of RLS is higher in the third trimester of pregnancy and that existing symptoms may be more severe.[14,17,27] Our study revealed no difference regarding the prevalence of RLS between women who had reached 28th week of gestation and those who had not.

Hormonal changes which are considered the main factor in women with irregular menstruation and a history of dysmenorrhea may be associated with RLS. In our study, there was no difference regarding the prevalence of RLS in women with or without a history of dysmenorrhea before pregnancy. However, it was determined that the prevalence of RLS is higher in those women with irregular menstruation before pregnancy. More extensive studies are required to establish such relationships.

In contrast to the findings of some epidemiological studies, there are studies which have demonstrated that body mass index is associated with a higher RLS risk. This relationship may result from a decrease in the number of dopamine receptors in the brains of obese individuals.[27] Despite these studies, the relationship between BMI in pregnancy and RLS has not been established clearly. Our study determined no difference regarding the prevalence of RLS in obese and non-obese women. There are other researchers who have reported similar results.[11,27]

Some studies concluded that there is no relationship between birth weight and RLS.[27,28] This study found a higher prevalence of RLS in women with a history of macrosomia. More extensive studies are required to establish such a relationship.

In our study, there is a moderate negative correlation between the severity of RLS and sleep quality. It was reported that 5%–10% of people with RLS had insomnia and disrupted sleep. All night long restlessness and an urge to move the legs make it difficult to fall asleep and to stay asleep, a reduced total-sleep time, impaired sleep-quality and these cause daytime drowsiness, chronic sleep deprivation, emotional disturbances and pathological fatigue in severe cases.[14,16,29] Yuksel et al.[16] found that RLS increases sleep-disorders which are associated with undesirable effects in pregnancy such as intrauterine growth restriction or preeclampsia. No difference in terms of sleep quality was determined in those women with or without RLS in the study group.

The limitations of this study include the fact that it is a cross-sectional study and it was not possible to establish a definitive diagnosis with the scales used.

Table 2. Distribution of women with or without Restless Legs Syndrome in the study group by pregnancy-related characteristics

Pregnancy-related characteristics	Restless Legs Syndrome			Statistical analysis X^2; p-value
	No (%)[a]	Yes (%)[a]	Total (%)[b]	
Number of pregnancies				
1	96 (70.1)	41 (29.9)	137 (30.5)	2.771; 0.428
2	81 (77.9)	23 (22.1)	104 (23.2)	
3	85 (78.0)	24 (22.0)	109 (24.3)	
4 and above	73 (73.7)	26 (26.3)	99 (22.0)	
Gestational week				
≤28	87 (79.1)	23 (20.9)	110 (24.5)	1.544; 0.214
≥29	248 (73.2)	91 (26.8)	339 (75.5)	
Number of childbirths				
0	106 (69.7)	46 (30.3)	152 (33.9)	5.346; 0.148
1	79 (73.8)	28 (26.2)	107 (23.8)	
2	85 (82.5)	18 (17.5)	103 (22.9)	
3 and above	65 (74.7)	22 (25.3)	87 (19.4)	
Menstrual regularity before pregnancy				
Irregular	63 (64.9)	34 (35.1)	97 (21.6)	5.464; 0.019
Regular	272 (77.3)	80 (22.7)	352 (78.4)	
History of dysmenorrhea before pregnancy				
No	215 (77.6)	62 (22.4)	277 (61.7)	3.452; 0.063
Yes	120 (69.8)	52 (30.2)	172 (38.3)	
Obesity before pregnancy				
No	275 (73.5)	99 (26.5)	374 (83.3)	1.060; 0.303
Yes	60 (80.0)	15 (20.0)	75 (16.7)	
History of lower back pain during pregnancy				
No	137 (82.5)	29 (17.5)	166 (37.0)	8.721; 0.003
Yes	198 (70.0)	85 (30.0)	283 (63.0)	
History of trauma during pregnancy				
No	310 (74.7)	105 (25.3)	415 (92.4)	0.000; 1.000
Yes	25 (73.5)	9 (26.5)	34 (7.6)	
History of macrosomia*				
No	199 (79.3)	52 (20.7)	251 (84.5)	4.357; 0.037
Yes	30 (65.2)	16 (34.8)	46 (15.5)	
Total	335 (74.6)	114 (25.4)	449 (100.0)	

[a]Percentage for the row, [b]Percentage for the column, *: Pregnant women who had given birth previously.

Table 3. Distribution of scores obtained from the Pittsburgh Sleep Quality Index for women with or without RLS in the study group

RLS	n (%)	Pittsburgh Sleep Quality Index Median (minimum-maximum)
No	335 (74.6)	6.0 (0.0-18.0)
Yes	114 (25.4)	7.0 (0.0-14.0)
Total	449 (100.0)	7.0 (0.0-18.0)

z=1.384, p=0.166, RLS: Restless Legs Syndrome, n: number.

CONCLUSION

RLS is an important health problem in pregnant women. There is a moderate negative correlation between the severity of RLS and sleep quality. It may be advantageous to refer pregnant women with RLS to specialists for a definite diagnosis and treatment. More extensive studies are required to demonstrate the relationship between RLS and quality of sleep.

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The authors would like to thank the pregnant women who participated in this study.

MAIN POINTS

- Restless Legs Syndrome is an important health problem in pregnant women.
- The Pittsburgh Sleep Quality Index was used to assess sleep quality.
- There is a moderate negative correlation between the severity of Restless Legs Syndrome and sleep quality.

ETHICS

Ethics Committee Approval: The required approval of the Sakarya University Non-interventional Ethics Committee dated June 22, 2017 and number 71522473/050.01.04/141 and approval from Sakarya Training and Research Hospital management were obtained before collecting data in this study.

Informed Consent: Pregnant women were informed about the subject and aims of this study and their consent was obtained. **Peer-review:** Externally peer-reviewed.

Authorship Contributions

Concept: S.Ş., K.Ö., A.U., Design: S.Ş., K.Ö., A.U., Data Collection and/or Processing: D.S.G., K.Ö., Analysis and/or Interpretation: A.U., S.Ş., K.Ö., Literature Search: S.Ş., K.Ö., A.U., D.S.G., Writing: S.Ş., D.S.G., K.Ö., A.U.

DISCLOSURES

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

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ORIGINAL ARTICLE

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A Comparison of Gluten-Containing and Gluten-Free Food Products in Terms of Cost and Nutrient Content in the City of Antalya, Turkey

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ABSTRACT

BACKGROUND/AIMS: Gluten is a protein that constitutes the main structure of flour, and thus, its removal from food products causes many gluten-free products in the market to be low in quality and taste while high in cost. Therefore, the purpose of this study was to compare gluten-containing and gluten-free food products.

MATERIALS AND METHODS: In this study, which is descriptive-comparative in nature, 64 gluten-free products and their 64 gluten-containing equivalent products in the same categories were randomly selected in large supermarkets in Antalya.

RESULTS: 50% of the products in this study were gluten-free, and bread and bakery products constituted the major group with 31.3%. The average price of all gluten-free products in this study was found to be significantly higher compared to gluten-containing products ($p<0.01$). The protein levels of the gluten-free products in all categories except for cereal were found to be significantly lower in comparison with the gluten-containing products ($p<0.01$). The average amount of fat in gluten-free flour ($p<0.05$), the average amount of sugar in the gluten-free pasta group ($p<0.01$) and the average energy level of the gluten-free cereals were found to be lower ($p<0.05$) in comparison to their equivalent gluten-containing food products.

CONCLUSION: In this study, it was found that gluten-free products are not only limited in availability and more costly but they also have significantly lower protein values. Therefore, it is important to monitor the development of children with celiac disease and to support their diet with alternative food sources.

Keywords: Gluten, gluten-free food, nutrient content, cost

INTRODUCTION

Although a gluten-free diet is a lifetime treatment regime in order to prevent small intestine damage as a result of gluten exposure in people with celiac disease,[1,2] the number of individuals who follow a gluten-free diet is higher than the number of individuals diagnosed with celiac disease, and the popularity of these products in recent years has increased over time and transformed into a health service.[3]

The preference for healthy gluten-free food products plays an important role, particularly in curing individuals with celiac disease, as nutrition is the only method of treatment.[4] However, it is not easy to sustain a gluten-free diet. It is not enough for patients only to avoid grain products containing gluten. They also should be on the alert constantly,[5] because excessive consumption of food products containing grain and the use of grain and its derivatives for purposes including colouring, preserving, or stabilizing products makes it difficult for celiac patients to adjust to

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a gluten-free diet.[1] Also, as a protein constituting the main structure of flour, gluten contributes to the structure and appearance of many baked products. Thus, the removal of gluten from food products causes many gluten-free products in the market to be lower in quality and taste while higher in price.[2,6] Additionally, patients following a gluten-free diet are known to be exposed to nutrition that has high levels of fat and energy but low levels of nutrients such as iron, zinc, magnesium, calcium, vitamins D and B12, and folate.[7-9]

Although a gluten-free diet is considered to be a healthy diet in general, considering the potential of this diet to cause certain nutritional deficiencies, celiac patients should be aware when selecting gluten-free products that are both nutritious and economical in order to prevent any problems. This condition imposes an increased financial and emotional burdens on patients. In spite of this, no studies have been carried out in Turkey comparing gluten-free and gluten-containing products in terms of cost, energy, and content. Therefore, this study was designed to compare gluten-free products with gluten-containing products in terms of cost, energy and content.

MATERIALS AND METHODS

Design of the Study

This study was planned as a descriptive-comparative research with the purpose of comparing packaged gluten-free products with gluten-containing products in terms of cost, energy, and nutrient content.

Categorization of Food Products

In this study, products with a label or in the statement of "gluten-free" on the packaging were categorized as gluten-free food products, while those without such a label or statement were considered as gluten-containing food products. According to the Communiqué for Food Products Suitable for Gluten Intolerance in the Turkish Food Codex,[10] a food product is labelled as "gluten-free" when the gluten level in food products produced for individuals with gluten intolerance does not surpass 20 mg/kg. According to the Turkish Food Codex Labelling and Consumer Information Communiqué,[11] it is mandatory to include the amount of energy and nutrients (fat, sugar, protein, salt) in 100 grams of food products on the packaging. In this study, the contents of energy, protein, fat, sugar and salt in 100 grams of both gluten-free and gluten-containing products sold in Antalya were compared. Also, a cost-comparison for 100 grams was completed for these products. Five food categories representing the majority of packaged food products were used in selecting and comparing gluten-free and gluten-containing products based on traditional grain formulations. These food categories were: 1) flour, 2) bread and bakery products (cake, cookies, biscuits, pizza etc.), 3) pasta (pasta, noodles, vermicelli etc.), 4) snacks (chocolate, wafers, pretzels, chips, etc.), and 5) cereals.

Sample of the Study

For the purpose of comparing the nutrient content and costs of gluten-free and gluten-containing products, all of the gluten-free products sold in the five biggest supermarkets in Antalya were included in the "gluten-free" group and the same number of their equivalent "gluten-containing" products in the same categories were included in the sample. Thus, a total of 64 gluten-free food products in 5 categories sold in supermarkets included in the study and their equivalent 64 gluten-containing food products in the same categories were randomly selected. The two sub-catorgory sample sizes (64 and 64) provide the total sample size (128) proposed by Cohen in calculating the medium effect size for the statistical methods in which the difference between the two group averages was calculated.[12] The data were collected between August 2018 and September 2018 by the researchers in the designated supermarkets. Non-packaged bakery products and food products without a food label were not included in the sample. With the consideration of potential influences on the results, food products with the labels "no added sugar" or "low sodium" were not included in the sample. In stores where the same products or different sizes of the same products (with no difference in nutrient content) were sold, the product was counted only once and the average price of these products was taken. For products of different sizes, their prices for 100 grams were calculated and included in the sample. For this, the direct package price of the products with 100 grams packs was taken, and for those products larger than 100 grams, the cost for 100 grams was calculated by proportioning. Micronutrients, vitamins, minerals, and fiber in these food products were not included in this study.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 23 (Chicago, IL, USA) software was used in analysing the data. Number and percentage for the distribution of food groups; mean, standard deviation and Mann–Whitney U tests were used to compare the prices and nutritional content of gluten-containing and gluten-free foods. $P<0.05$ was accepted as statistically significant.

RESULTS

Table 1 presents the distribution of food groups included in the sample by categories. As can be seen, 50% of the products are gluten-free and 50% are gluten-containing. The major group in these categories is bread and bakery products with 31.3%, and the smallest group is cereals with 9.4% (Table 1). A comparison of the mean prices of gluten-free and gluten-containing products in each category is presented in Table 2. The mean price of all gluten-free food groups was significantly higher than that of the gluten-containing group ($p<0.01$ for cereals, and $p<0.001$ for others) and the greatest price difference was seen in the snacks category, with a six-fold difference (Table 2).

Table 3 shows a comparison of nutrient amounts in gluten-containing and gluten-free products in each category. The protein level of gluten-free products in all categories except for cereals was found to be significantly lower compared to the gluten-containing products ($p<0.01$). Also, the amount of fat and sugar in gluten-free and gluten-

Table 1. Distribution of foods by groups (n=128)

	n	%
Gluten content		
Gluten-containing	64	50.0
Gluten-free	64	50.0
Food group		
Flour	32	25.0
Bread and bakery products	40	31.3
Pasta group	24	18.8
Snacks	20	15.6
Breakfast cereals	12	9.4

n: number.

containing flour showed a significant difference ($p<0.05$). The average fat amount in gluten-free flour was lower while the amount of sugar was 22 times higher compared to gluten-containing flour. However, the amount of sugar in the gluten-free pasta group was lower than in the gluten-containing pasta group ($p<0.01$). In the cereal group, only the energy level showed a significant difference ($p<0.05$), with the energy of gluten-free cereal being lower. The nutrient amounts in gluten-free and gluten-containing products in other food categories did not show any significant differences ($p>0.05$).

DISCUSSION

In this study comparing the content and prices of gluten-free and gluten-containing food products, only 64 gluten-free products were accessed despite the fact that the biggest stores in Antalya were included in the sample. This situation may contribute to the difficulty of obtaining gluten-free products especially for those individuals with celiac disease or gluten allergy. In addition to the limited availability of gluten-free products, the higher prices of these products may also have a negative impact. This study shows that the prices of gluten-free products in each food category are higher and that the differences can be up to 6 times higher. Other studies have also shown similar results, revealing that gluten-free products are limited in availability and more costly.[13,14] Since gluten contributes to the appearance and texture of many baked products as it is the protein that forms the main structure of flour, removing gluten from foods causes many gluten-free products on the market to be lower in content and more expensive.[2,6]

Table 2. Prices of gluten-containing and gluten-free food by groups (n=128)

Food category	Gluten-containing foods (for 100 g)*		Gluten-free foods (for 100 g)*		p-value**
	Mean	SD	Mean	SD	
Flour	1.13	0.66	2.72	1.57	0.000
Bread and bakery products	2.04	1.37	9.47	6.28	0.000
Pasta group	0.85	0.77	2.45	2.33	0.000
Snacks	2.97	1.58	17.99	9.01	0.000
Breakfast cereals	2.83	0.66	9.73	2.98	0.004

*Prices of 100 grams of food product have been compared. Prices were given in TL, **The difference between the groups was evaluated by the Mann–Whitney U test and $p<0.05$, SD: standard deviation, n: number.

Table 3. Comparison of nutrients for gluten-containing and gluten-free products by food categories (n=128)

Food category	Energy (kcal)		Protein (g)		Fat (g)		Sugar (g)		Salt (g)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Flour										
GC	349.86	18.92	11.09	4.85	6.31	7.30	0.20	0.49	0.02	0.04
GF	355.48	22.40	3.82	3.03	4.05	6.29	4.36	8.56	0.23	0.41
p-value*	0.336		**0.000**		**0.021**		**0.018**		0.056	
Bread and bakery products										
GC	435.90	91.90	7.17	2.55	18.00	9.17	20.39	12.64	0.77	0.37
GF	432.65	111.64	3.64	1.95	18.89	10.16	16.63	12.49	0.65	0.51
p-value*	0.957		**0.000**		0.685		0.273		0.228	
Pasta group										
GC	353.42	9.81	12.06	1.08	1.93	1.14	3.21	1.17	0.02	0.03
GF	354.38	8.25	9.51	2.81	1.74	0.88	2.27	1.61	0.03	0.08
p-value*	0.523		**0.000**		0.523		**0.004**		0.322	
Snacks										
GC	474.53	49.47	8.22	1.63	20.77	8.57	23.21	16.76	1.17	0.95
GF	489.00	56.33	3.97	2.23	23.57	8.69	19.80	18.93	1.29	1.04
p-value*	0.427		**0.001**		0.326		0.545		0.910	
Breakfast cereals										
GC	379.83	6.49	8.83	1.40	4.10	2.09	19.53	6.53	0.78	0.26
GF	366.82	8.50	11.02	2.68	4.22	2.58	9.43	11.08	0.55	0.71
p-value*	**0.016**		0.128		0.810		0.149		0.335	

The amounts of energy, protein, fat, sugar and salt in 100 grams of food product have been compared. *The difference between the groups was evaluated by the Mann–Whitney U-test and $p<0.05$, GC: gluten-containing, GF: gluten-free, SD: standard deviation, n: number.

This study showed that gluten-free products in each category except for cereals contain lower protein levels. Other studies conducted in different countries have shown similar results, in which gluten-free products contained low levels of protein.[13-16] As gluten constitutes a significant portion of the total protein content in grains, the finding of protein deficiency due to the removal of gluten from flour-products is an expected result.[10,17] Although the level of protein in grains is around 10%, it provides the basic needs of a continually increasing population, particularly in developing countries, as a protein source.[18] At the same time, bread and bakery products in countries such as Turkey, in which the Mediterranean diet is dominant, constitute the widest part of the food pyramid as a fundamental carbohydrate and energy source.[19] Considering that the majority (56.3%) of the gluten-free products available on the market in our study area consist of flour and bakery products, the lack of protein in these products becomes more important. Using different sources of protein is an important way to bridge this gap. With this in mind, by using gluten-free grains, legumes, grain-like products (buckwheat, amaranth, and quinoa) and animal proteins in formulations, a variety of products with improved nutrients can be produced.[6,20]

It is known that gluten-free products contain more carbohydrates compared to gluten-containing products.[21,22] In this study, the amount of sugar contained in gluten-free flour was found to be 22 times greater than gluten-containing flour. In gluten-free bakery products, to eliminate the poor appearance and taste due to gluten removal, rice flour, rice bran, and brown rice flour that do not contain gluten protein are used rather than whole wheat flour.[23] However, as the need for daily calories and carbohydrates of individuals with celiac disease or gluten allergy is similar to that of the normal population, it is important to prevent problems that may occur as a result of excessive carbohydrate consumption.[24] Therefore, using natural products such as beans, legumes and starchy vegetables as alternatives to grains and using natural carbohydrate sources such as potatoes in lieu of gluten-free flour is recommended.[25]

One of the key findings in this study is that the average amount of sugar contained in gluten-free products in the five food categories except for flour was lower. At the same time, the average fat and energy amounts in products were found to be significantly lower in only one food category of the gluten-free products. Although previous studies reported that the amount of fat, sugar, salt, and energy in gluten-free products was higher,[14,25-27] this study showed no significant difference between gluten-free and gluten-containing products in the food groups in terms of these parameters. This may be a result of positive developments in the manufacturing sector towards eliminating the disadvantages of gluten-free products in recent years. For example, to eliminate the negative effect of gluten removal on the quality of pasta, the use of formulations such as xanthan gum, guar gum, casein, egg white or fermented peas rather than flour can explain why gluten-free pasta now has low sugar levels.[28,29] However, there are also studies reporting that the levels of sugar, fat, and energy in gluten-free products do not show significant differences compared to gluten-containing products.[15,30] This is especially important for individuals who must consume gluten-free diets, such as celiac patients, to maintain a healthy weight and protect themselves from complications due to excessive consumption of these nutrients.[31]

CONCLUSION

Although not having gluten in food products is the main characteristic of a gluten-free diet, it can also lead to unintended results including nutritional deficiency and nutritional imbalance. However, having sufficient nutrient content in a gluten-free diet is important, particularly in children, because children are in constant need of maximum energy and food as they are growing, developing, and active. Thus, the nutrient quality of gluten-free products available on the market has received more attention in recent years. This study shows that the prices of gluten-free products are higher and that the number of available products on the market is limited. At the same time, the protein levels in gluten-free products are lower and the level of sugar in flour is significantly higher. That is why it is important to protect children and all individuals who follow a gluten-free diet from certain complications. Thus, it is important to raise awareness in parents, health care professionals working with children, and educators about the negative aspects of a gluten-free diet, alternative nutrition, and monitoring development.

In this study, gluten-free products in the food aisles of the largest supermarkets in Antalya were included in the sampling, and businesses such as small markets were not included. Therefore, the results of the study cannot be generalized to the whole food retail sector.

MAIN POINTS

- The number of gluten-free products on the market is limited and their prices are higher.
- The protein value in gluten-free products is very low.
- The amount of sugar (except for flour), fat, energy and salt in gluten-free products was not significantly higher than their counterparts.

ETHICS

Ethics Committee Approval: Ethics committee approval was received for this study from Akdeniz University Clinical Research Ethics Committee (decision no: 532, date: 25.07.2018).

Informed Consent: Informed consent is not necessary due to the nature of this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.M., E.K., Design: A.M., E.K., Supervision: A.M., Data Collection and/or Processing: E.K., Analysis and/or Interpretation: A.M., Literature Search: A.M., E.K., Writing: A.M., Critical Reviews: A.M., E.K.

DISCLOSURES

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ORIGINAL ARTICLE

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The Relationship of Between the COVID-19 Pandemic and Professional Belonging Levels of Student Midwives

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ABSTRACT

BACKGROUND/AIMS: The relationship between the professional belonging levels of midwifery students and the effects of coronavirus disease 2019 on the social order and health system was evaluated.

MATERIALS AND METHODS: This planned cross-sectional and descriptive work was carried out as web-based study. The study was completed with 210 senior midwifery students at the undergraduate level who had volunteered to participate in this study.

RESULTS: Age, home, and family type are significant predictors of professional sense of belonging ($p<0.05$). The fact that being called to duty in cases of shortages of healthcare staff and a punishment system for a refusal to give care in terms of health policies are significant predictors of the level of professional belonging. Not finding it appropriate to invite students for duty in cases of a shortage of healthcare workers is associated with a higher level of professional belonging ($p<0.05$). The excess of relationship factors between the factors relating to education and the sense of belonging to other groups is striking. Feelings of inadequacy of being able to graduate, adequate professionalism, concerns about starting the profession, and satisfaction with this profession are significant predictors for the sense of professional belonging.

CONCLUSION: The levels of professional belonging of the student midwives are quite high. Health care policies in the pandemic process can affect this sense of belonging. Especially the changes, setbacks and adaptation processes experienced in education are important in terms of professional belonging. More findings are needed on how we can reinforce this awareness and emotion in the digital environment.

Keywords: Professional belonging, midwife, pandemic, COVID-19, education

INTRODUCTION

The cause of the pneumonia cases, which first appeared in Wuhan, China towards the end of 2019, was identified as the new type coronavirus disease 2019 (COVID-19) on January 7, 2020. COVID-19 was declared a pandemic by the World Health Organization (WHO) on March 11, 2020, due to a dramatic increase in the rate of cross-country spread, morbidity, and mortality (3.4%) across countries. Turkey's first case was announced on the same date. As a result of restrictions at the national level, the higher education board suspended education for 3 weeks as of March 16, 2020, and education on digital platforms was resumed in all universities with distance education as of March 23, 2020.

As in many countries of the world, the pandemic in our country caused an interruption that led to rapid and dramatic changes in the nature of midwifery education. In the short term, it has led to different approaches being adopted in order to reduce the impact on theoretical and clinical training of the current midwifery students and to seek the best approaches for both midwifery students and lecturers during the COVID-19 pandemic. In Turkey,[1] vocational courses in midwifery education are carried out simultaneously with theoretical and clinical

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practice. In this process, in which patient interaction was completely stopped, training suddenly started to be given in a digital environment. The training was carried out on digital platforms, either live or recorded. Midwifery education in Turkey has various graduation criteria. For instance, 4th Grade midwifery student must have performed at least 40 normal vaginal births accompanied by a responsible instructor and a clinical midwife. Due to the closure of universities and the national restrictions imposed during the pandemic period and due to the fact that it is an "applied education", especially the development of practical skills of the midwifery students who are candidates to graduate was interrupted. These practical skills are now often being developed on digital platforms through training videos and case discussions. In this process, the basic graduation criteria are based on the requirements set by the European Union directives and the time to be completed. Midwifery students who completed these criteria have entered the workforce.

The impact of social distancing, staying at home, or working with women who are likely to be infected, with some shortcomings, on graduate students is thought-provoking. Some researchers state that one in five students felt more anxious or depressed than they were in the period before COVID-19.[2] Digitization, currently a clear necessity, can result in a loss of experience, which has the potential to significantly damage education.[3] In this context, Luyben et al.[4] points out that while policymakers grapple with decisions that will affect all of us, we have only a limited overview of what students are going through and what directions the virus is taking us in. In spite of the pandemic, there is an important issue in this context that midwifery trainees continue their efforts to obtain the required competencies and skills at the same level as before the interruption.

Medical education has a different education structure than nursing and midwifery professions which has an education system coordinated with the clinic. This pandemic process has underlined the importance of nurses and midwives, who are an indispensable part of the team. It is imperative to acknowledge that our most valuable resource in fighting this pandemic is nurses. Also, midwives, who are an important part of preventive public health services, have continued their duty to maintain maternal and child health with optimum care despite all difficulties. During this challenging process, many pregnant women (especially women with previous loss) stated that they were really afraid of becoming COVID-19 positive, with feelings of insecurity, and anxiousness. This means that women need more support and reassurance by all healthcare professionals, during pregnancy, childbirth, and puerperium.[5] For many midwives, the care given during labor and birth evokes images of a professional strengthening the first bonds of a new family, rubbing her back, dealing face to face with the woman, and holding her hand.[6] However, it was not possible to provide care with this approach during the pandemic process. In this context, determining how the process affects the prospective graduate vocational school of health service students will allow us to make various predictions about these new groups who will join the workforce. Studies have been carried out during the COVID-19 period and past pandemics with students in the field of health (studies were conducted during the periods of SARS, Influenza, H1N1, MERS).[7-15] In those studies, issues such as stress, coping strategies, educational problems, and voluntary work were often investigated. There is only a limited number of studies evaluating professional belonging in the research findings, and no specific evaluated study was found.[15] Professional belonging defines a person's professional commitment as a psychological connection based on an affective response between the person and his or her profession.[16] A midwife's ownership of her profession, her willingness to take on her responsibilities towards her profession, her willingness to develop herself in the professional field, her belief in the values of her profession and her determination to continue her profession show the midwifery affiliation. A midwife with high professional belonging feels safer and happier in her professional journey. A midwife who does not have a professional belonging can turn to jobs that are not their own duty, they can avoid the workload and act intolerantly towards the patients they serve. Considering Maslow's hierarchy of needs, it can be seen that professional belonging has a very close relationship with the concepts of job satisfaction, and organizational and institutional commitment. In cases where there is job satisfaction or organizational and institutional commitment, professional belonging can also be considered high. In this context, factors affecting professional belonging can be summarized as follows; professional status, wage, teammates working together, working conditions, job security, public perception, the personality of the employee, conflict in the role, education, economic security, career opportunities, financial and moral rewards, participation in decisions, the work itself, the attitude of managers, and powers and responsibilities.[17] Increasing workloads, and uncertainties and concerns in the field of work during the pandemic process are thought to cause a loss of motivation among our colleagues and affect professional belonging.

In this study, the relationship between the professional belonging levels of midwifery students and the effects of COVID-19 on the social order and health system was evaluated. It is important to evaluate the factors that affect the feelings of professional competence of this group who participate in the workforce in extraordinary circumstances and their ability to cope with the forces that will be encountered in the health system in order to guide their education. In this process, to which we have not yet reached a solution, it is important to develop an awareness of professional belonging while adapting to the changes in education. It is a very unfamiliar issue to create this feeling in the students without them interacting with the patient or entering the care environment in the clinic. However, with a forward-looking point of view, it is possible to say that this has become a fundamental requirement for this occupation.

MATERIALS AND METHODS

Study Design and Sampling

This planned cross-sectional, correlational and descriptive study was conducted as a web-based research between June 15–20, 2020. In line with the aim of this study, a purposive sample was selected and only 4th-grade students of the midwifery department studying at the undergraduate level were invited to take part in this study. The invitation to participate in this study was shared on the website of the student committee of the Anatolian Midwives Association, a national professional association. The target population of the study was 317 senior midwifery students who had enrolled in the student committee. It was aimed to reach the whole target population. The minimum sample size was calculated at a significance level of $p<0.05$ at a 95% confidence interval. The sample size was calculated using the sampling formula with a known population. Research data on the level of professional

belonging of midwives reported in the study conducted by Baskaya et al.[17] were used, and the sample size was identified as 151. The study was completed with 210 students who volunteered to participate.

Research Questions

What is the level of professional belonging of the student midwives?

Can health care policies in the pandemic process affect this sense professional of belonging?

Data Collection

The data collection phase was conducted in an online environment. All quantitative data were collected using a web-based online survey form within a specified time period. Individuals who headed to the link address given in the introduction of the information about the study first encountered an illuminated consent section. Individuals who approved the information participated in the study by completing the research form. The completion time of the online form was 5 minutes on average.

Data Collection Tools

The online survey form consisted of two parts. The first part includes introductory features, and the second includes the "Midwifery Belonging Scale (MBS)" developed to determine the levels of professional belonging.

Introductory Information Form

The introductory information form was originally prepared by the researchers in line with the related literature.[13,17] In the first part of the introductory information form, introductory features such as age, class, marital status, socioeconomic characteristics, and information about attitudes towards the preference of the midwifery profession were present.

In the second part, there were factors that may be related to occupational belonging, which examines the pandemic process and the effects of the pandemic on healthcare professionals and education. The questions related to education were prepared in line with the academic researchers' own observations and experiences. Questions related to healthcare services were prepared in line with studies conducted in past pandemics and the news encountered in the media during this pandemic process.[8-12] The first draft of the form consisted of 32 questions. The questions were evaluated by an expert group and evaluated in terms of their similar meaning, understandability and expressions. The expert group consists of two faculty members from the midwifery department and an academic psychologist as an external observer. In line with the expert group reviews and suggestions, the form was finalized with 25 questions.

Midwifery Belonging Scale

To determine the level of professional belonging of midwives, a scale developed by Baskaya et al.[17] was used. MBS, consisting of 22 articles with four sub-dimensions in total, namely: Emotional belonging, performance of professional roles and responsibilities, professional development and utilization of opportunities, and limits of duty and authority in the profession. The scale items consist of 22 items, all of which are positive, scaled between 1–5 (ranging from "Absolutely disagree" to "Absolutely agree"). The scores that can be obtained from this scale range between 22–110. The higher scores obtained from this scale are interpreted as meaning having high professional belonging. In the 2020 study of Baskaya et al.[17], the Cronbach alpha (α) value of this scale was stated to be 0.905. The Cronbach alpha (α) value of this study was 0.902 and the item Cronbach alpha (α) values were between 0.892–0.910. This value is required to be at least 0.70.[18] As a result of the Cronbach alpha values obtained, the scale was seen to be statistically reliable.

Statistical Analysis

The data were analyzed using descriptive and parametric statistical analysis methods via the Statistical Program for Social Science 20.0 (SPSS) (IBM, Chicago, IL, USA). The descriptive characteristics of the participants, their attitudes, beliefs, and the related factors towards sexuality during pregnancy, their comfort levels during counseling, and related factors were analyzed as frequency and percentage. In the comparison of dependent and independent variables, Student's t-test was performed to determine the difference between two sets of data, and the One-Way ANOVA test was performed for the difference between three or sets of data. Multiple Linear Regression analysis was used to determine the relationship of dependent and independent variables with each other. Regression analysis results showed with regression coefficient (β), coefficient of determination (R/R^2), and goodness of fit of the model (F and p) values. The statistical significance level was taken as $p<0.05$.

Ethical Considerations

Ethics committee permission was taken from the Near East University Hospital Scientific Research Evaluation Ethics Committee before the research started (approval number: 2020/78-1054). The voluntary nature, the option to terminate at any time and anonymous quality of the study were stated to the participants in the illuminated consent section.

RESULTS

The average age of the students was 22.48±1.76 years. The majority of the students, almost all of whom (95.2%) are single, are members of a nuclear family, and approximately two-thirds stated that their income level is moderate. The rate of those who willingly choose to receive midwifery education is 66.2%, and the rate of satisfaction with their preference over the years is 87.6% (Table 1).

The findings regarding the situations of the students encountering a COVID-19 positive case, their concerns about healthcare workers in this process, their feelings of educational competence, and their feelings and thoughts about working conditions during the pandemic period are shown in Table 2. It seems that the students tend to think positively about volunteer work or being called to duty in cases of shortages of healthcare staff. 37.6% of them stated that the COVID-19 positive patient can be denied care, while 17.1% of them think that they should be punished in cases of refusal to care for a COVID-19 patient. The vast majority of the group stated that they could quit school if they were in the first year of their education, but for now, there were only three students who stated that they could quit the profession (Table 1).

The MBS total scores of students was 98.42±10.24 (minimum–maximum: 43–110). The mean scores of the subscales were as follows; 31.83±3.76 for emotional belonging, 31.82±3.74 for performance of

professional roles and responsibilities, 16.95±2.48 for professional development and utilization of opportunities and 13.31±2.24 for limits of duty and authority in the profession (Table 2).

The factors associated with professional belonging levels and the Multiple Linear Regression Analysis Model were examined in three groups: namely, introductory features, health policy, and educational. Age, home, and family type are descriptive characteristics; they are meaningful predictors of the sense of professional belonging ($p<0.05$). The factors relating to volunteering, denial of care, and colleagues were included in the model under the heading of health policies. Of these factors, the fact that there is a system of punishment for being called to duty and refusing to work only in the event of incompetence are meaningful predictors of the level of professional belonging. Not finding it appropriate to invite students for duty in cases of shortages of healthcare workers is associated with a high level of professional belonging ($p<0.05$). Similarly, the belonging of those who find it inappropriate to be punished for rejection of care work increases. The high level of relationship factors between these factors relating to education and the sense of belonging to other groups is striking. The feeling of inadequacy to be able to graduate, adequate professionalism, concerns about starting the profession, and satisfaction with this profession are significant predictors to the sense of professional belonging (Table 3).

DISCUSSION

In this study, factors affecting students' perspectives on their profession and their level of professional belonging due to the COVID-19 pandemic were researched. It was observed that the urgent change process emerging, especially in the form of education, was a factor affecting the level of professional belonging of the students. However, it was determined that positive attitudes towards health policies were positive predictors that affected the sense of professional belonging.

The average age of the students participating in this study was found to be 22.48±1.76 years, 66.2% of the students stated that they wanted to receive a midwifery education (Table 1). In the study conducted by Görgen and Bingöl[19] on nursing and midwifery students, 61.3% of the students stated that they chose this department willingly. Again, in a similar study conducted by Söğüt et al.[13], it was stated that the average age of the students was 21 years. These studies are in line with our findings. Research has shown that diseases such as coronavirus, which cause great devastation in societies, increase the rate of anxiety in people.[20,21] According to research conducted by the Mental Health Association in our country, 50% of the population stated that they were afraid of getting coronavirus; 59% of them stated that their worries about their health increased; 61% of them stated that their worries about their future increased; and 48% of them stated that their feeling of uneasiness increased.[22] These situations such as the students' stress levels, difficulties with accessing education, and COVID-19 positive cases around them were associated with an increase in the students' anxiety and difficulty in coping mechanisms.[13,15,23] It was observed that the students participating in the study have a tendency to think positively about volunteering or being invited to work in cases of shortages of health care staff. 37.6% of them stated that they can refuse care to a COVID-19 positive patient, while 17.1% of them think that they should be punished in such cases of refusal. The majority of the group stated

Table 1. Introductory information of participants (n=210)

Variables		n (%)
Age	≥22	133 (63.3)
	23 and above	77 (36.7)
Marital status	Single	200 (95.2)
	Married	10 (4.8)
Type of family	Nuclear	187 (89.0)
	Extended	23 (11.0)
Perception of income level	Good	34 (16.2)
	Middle	161 (76.7)
	Poor	15 (7.1)
Choosing the midwifery department willingly	Yes	139 (66.2)
	No	21 (10.0)
	Partially	50 (23.8)
Satisfaction with your choice	Yes	184 (87.6)
	No	6 (2.9)
	Partially	20 (9.5)

n: number of participants.

Table 2. Distribution of participants' various situations, attitudes and feelings regarding the pandemic (n=210)

Variables		n (%)
COVID-19 positive person around him/her	Yes	53 (25.2)
	No	157 (74.8)
The person who died due to COVID-19 around him/her	Yes	23 (11.0)
	No	187 (89.0)
Thoughts on volunteer work	I will work	178 (84.8)
	I will not work	6 (2.9)
	I am undecided	26 (12.4)
Is it a professional responsibility to work voluntarily?	Yes	143 (68.1)
	No	67 (31.9)
Calling students for duty in case of shortage of staff	Available	168 (80.0)
	Unavailable	42 (20.0)
What they feel for their working colleagues?	I am worried about them	55 (26.2)
	They are heroes	155 (73.8)
Can a health worker refuse care to a COVID-19 positive patient?	Yes	79 (37.6)
	No	131 (62.4)
Should he/she be punished if he/she refuses care to a COVID-19 patient?	Yes	36 (17.1)
	No	174 (82.9)
Does he/she continue his/her training in the first year of his/her education?	Yes	20 (9.5)
	No	190 (90.5)
Feeling competent to graduate	Yes	151 (71.9)
	No	24 (11.4)
	Partially	35 (16.7)
Feeling professional	Yes	60 (28.6)
	No	86 (41.0)
	Partially	64 (30.5)
Anxiety about starting a profession	Yes	105 (50.0)
	No	79 (37.6)
	Partially	26 (12.4)
Quitting the profession due to the pandemic	Yes	3 (1.4)
	No	207 (98.6)

COVID-19: coronavirus disease 2019, n: number of participants.

that if they were in their first year of education, they could drop out of school (Table 2). Although stress levels and associated emotional changes were not examined in this study, we think that these variables may be related to professional belonging levels.

Monforte-Royo and Fuster[24] stated that in the year celebrating Florence Nightingale's 200th birthday and designated as "the International Year of Nurses and Midwives" by the WHO, all students who graduated as midwifery nurses during the COVID-19 epidemic could be called 'coronial'.[24] This coronial group was deprived of the intensive clinical experience and responsibility for further practice, especially in the final 3 months of their training. The transition from student to qualified professional life is a complex phenomenon. Various studies mention that the first year of work is difficult for new graduates. It has been stated that they experience stress as a result of their expectations and the team's expectations from them, with the struggle to make the right decisions, and to adapt to a high workload.[25,26] These students have never seen such high rates of patient death, and have never had to work in a health system and its chaotic conditions where treatment protocols are constantly updated. In addition, they have not had experiences such as a fear of being infected, feeling unprepared to work in the midst of a pandemic, pressure to provide care, and isolation from their families to avoid exposing them to the risk of infection. All these are factors that can affect the level of professional belonging and the feelings, thoughts, and attitudes associated with starting their profession. Among the students participating in this study, the fact that there is only a punishment system for recruitment and refusal of care is one of the significant predictors of the level of occupational affiliation, and in cases of a shortage of healthcare workers, it was found that this was associated with a high level of occupational belonging ($p<0.05$). Similarly, the belonging of those who find it inappropriate to be punished for refusal to care for COVID-19 patients increases. The relationship between the factors relating to education and the sense of belonging to other groups is striking. The inability to graduate, the feeling of adequate professionalism, concerns about starting the profession and satisfaction with this profession are significant predictors of the sense of professional belonging (Table 3). Dos Santos[27] stated in his qualitative study that financial factors are effective in the sense of belonging and career plans of student nurses who will graduate during the pandemic process. Contrary to this data, our study findings showed that the perception of the economic level was not a meaningful predictor of a sense of professional belonging. As noted in many studies in the literature, unwillingness to enter a profession is associated with a low sense of belonging.[28-31] Hence, the findings of this study are in line with this.

According to these findings, midwifery students were mostly willing to work voluntarily and believed that this was a professional responsibility. However, these are not significant predictors of professional belonging. On the other hand, the sense of belonging of those who stated that it would be appropriate to be invited in case of staff shortages was approximately 3 times higher. Herman et al.[7], in their study during the influenza epidemic, mentioned an increase in the risk of contracting the disease, although it was encouraging that healthcare students believed that they had an obligation to volunteer during a pandemic. In a study with midwives on Ebola, a previous regional epidemic, it stated that in addition to the fear of being infected with the virus, the public had to deal with the fear of this infectious disease. They stated

Table 3. Multiple linear regression analysis model of predictive factors of professional belonging level of participants (n=210)

Factors	B	SE B	β	t	p	95% CI for B		Model summary	
						Lower	Upper	R/R^2	Φ/p
Demographic									
Age	-3.787	1.427	-0.178	-2.653	**0.009**	-6.601	-0.973		
Family type	-6.624	2.203	-0.202	-3.007	**0.003**	-10.967	-2.281	R=0.288	F=3.690
Economic level	1.160	1.451	-0.054	-0.800	0.425	-4.022	1.701	R^2=0.083	p=0.003
Covid positive person	1.916	1.791	-0.081	-1.070	0.286	-5.447	1.614		
The person who died due to COVID-19	1.260	2.483	0.038	0.507	0.612	-3.636	6.156		
Health policy									
Voluntary work	-1.760	1.065	-0.115	-1.652	0.100	-3.860	0.340		
Volunteering responsibility	-2.141	1.752	-0.084	-1.222	0.223	-5.596	1.314		
Being called for duty in cases of staff shortages	3.836	1.596	0.165	2.404	**0.017**	0.690	6.982	R=0.312	F=3.653
Feeling of colleague	-1.984	1.509	-0.094	-1.314	0.190	-4.960	0.992	R^2=0.097	p=0.002
Positive case care denial	-3.150	1.933	-0.116	-1.630	0.105	-6.961	0.661		
Penalty for denial of care	4.915	2.372	0.141	2.072	**0.040**	0.238	9.592		
Education									
Will he/she continue his/her education in his/her first year?	-0.583	0.832	-0.043	-0.700	0.485	-2.224	1.058		
Feeling competent to graduate	-2.563	0.829	-0.193	-3.092	**0.002**	-4.198	-0.929		F=11.322
Feeling professional	3.449	0.900	0.234	3.830	**0.000**	1.673	5.224	R=0.501	p<0.001
Anxiety about starting the profession	13.049	5.345	0.151	2.441	**0.015**	2.510	23.588	R^2=0.251	
Choosing the midwifery department willingly	-1.457	0.751	-0.121	-1.940	0.054	-2.937	0.024		
Satisfaction with your choice	-4.823	1.074	-0.284	-4.489	**0.000**	-6.942	-2.705		

Significant values are shown in bold.
CI: confidence interval, SE: standard error, COVID-19: coronavirus disease 2019, n: number

that the fear of being a risk to their families, which they coped with in different ways, was another important source of stress.[32] The fact that all participants stated that they would not hesitate to provide care in the event of encountering a COVID-19 positive pregnant woman and the fact that there were few concerns about starting their profession suggests that they ignore some risks in this process, which they are still alien to. This is an extremely positive reflection of their high sense of professional belonging.

It was an interesting and impressive result of this study that those who did not feel competent to graduate had higher levels of professional belonging. In applied professions, the patient-healthcare professional relationship is an emotional one. Although the system continues theoretically, the lack of practice in the clinic reinforces a sense of inadequacy for students with a high sense of belonging. In such extraordinary times, there is little specific information about treatment and care, especially in the initial phase. Current protocols cannot provide clear guidance on many of the practical and ethical dilemmas they will face. Infection control procedures are often restrictive, strict and leave limited opportunities to improve the level of care of pregnant women during pandemic times, especially for midwives, who inherently involve cooperation and touch with pregnant woman as part of their duties. These limitations might help develop professional creative skills, as noted by Erland and Dahl.[32] This pandemic is a process in which changes and rapid adaptation to this change is occurring in many areas. We think that these difficult conditions will lead individuals with a high awareness of professional belonging to think more analytically and practically.

CONCLUSION

The level of professional belonging of student midwives is quite high.

More studies are needed on how we can consolidate this consciousness and emotion in the digital environment. In addition to this, we recommend conducting online meetings, symposiums or social activities to improve students' sense of occupational belonging, as well as conducting studies that evaluate this group, who joined the workforce under extraordinary conditions, in terms of concepts such as burnout, post-traumatic stress, professional satisfaction and professional adaptation.

MAIN POINTS

- Socio-demographic factors such as age and family type are predictors of a sense of belonging.
- Health care policies in the pandemic process can affect the sense of belonging.
- Especially the processes of change, failures and adaptation in education are important in terms of professional belonging.

The reason for having a high sense of belonging of senior students can be because we do many stages of education in a face-to-face environment.

ETHICS

Ethics Committee Approval: Ethics committee approval was obtained from the Near East University Hospital Scientific Research Evaluation Ethics Committee (approval number: 2020/78-1054).

Informed Consent: Written informed consent was obtained from the who participated in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.Y, B.A.V., Design: F.Y., B.A.V., Supervision: F.Y., B.A.V., Data Collection and/or Processing: F.Y., B.A.V., Analysis and/or Interpretation: F.Y., B.A.V., Literature Search: F.Y. B.A.V., Writing: F.Y. B.A.V., Critical Reviews: F.Y. B.A.V.

DISCLOSURES

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ORIGINAL ARTICLE

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Assessment of ELR, NLR, MPV, and CRP Levels in Patients With Acne Vulgaris

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ABSTRACT

BACKGROUND/AIMS: Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit. The relationship between some of the hematological parameters active in inflammation such as the neutrophil/lymphocyte ratio (NLR), the mean platelet volume (MPV), and C-reactive protein (CRP) has been demonstrated. In recent years, eosinophil cells have been shown to be associated with inflammation, and the eosinophil/lymphocyte ratio (ELR) has been shown to be an indicator of inflammation in some diseases. In this study, we aimed to evaluate the relationship between the ELR, NLR, MPV, and CRP levels, which are indicators of systemic inflammation, with acne severity parameters in patients with acne vulgaris.

MATERIALS AND METHODS: A prospective study was planned with patients in our clinic who were diagnosed with acne vulgaris, who required routine blood parameters, and whose global acne score was calculated. The relationship between these parameters, which are an indicator of systemic inflammation and acne severity, was investigated.

RESULTS: In our findings, MPV was found to be the strongest hematological marker for acne severity and inflammation. There was a significant difference between acne severity and ELR, and this difference was higher in the severe acne group.

CONCLUSION: As far as we are aware, there has been no study on ELR levels in acne to date; this is the first study to evaluate this rate. Based on our findings, it is thought that ELR increases with the severity of acne and can be accepted as an indicator. In this context, we believe that there is a need for controlled studies involving the role of eosinophils in blood, tissue, and inflammation in the pathogenesis of acne. It is possible that the role of eosinophils in pathogenesis will explain itch-dominated acne patients and may also lead to the development of new targets for treatment.

Keywords: Acne vulgaris, eosinophil/lymphocyte ratio, neutrophil/lymphocyte ratio

INTRODUCTION

Acne vulgaris can be seen in all age groups. It is a chronic inflammatory disease of the pilosebaceous unit that usually affects about 85% individuals during the adolescent period.[1] In the etiopathology of acne, the increase in sebum production, follicular epidermal hyperprofillation, inflammation and propionibacterium acnes are relevant.[2]

In recent years, the relationship between acne vulgaris and some hematological parameters active in inflammation such as neutrophils, lymphocytes, and platelets has been demonstrated.[3] In addition, it has been shown that parameters such as neutrophil/lymphocyte ratio (NLR), mean platelet volume (MPV), C-reactive protein and (CRP) are accepted as indicators of inflammation and acne vulgaris.[3]

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In recent years, eosinophil cells have also been associated with inflammation, and the eosinophil/lymphocyte ratio (ELR) has been shown to be an indicator of inflammation in some diseases.[4] There is no study in the literature showing the relationship between acne vulgaris and ELR. In this study, we aimed to evaluate the relationship between ELR, NLR, MPV, and CRP levels with acne severity in terms of both their role in inflammation and their role in pathogenesis in patients with acne vulgaris.

MATERIALS AND METHODS

A prospective study was planned with volunteers who were diagnosed with acne vulgaris in our clinic who required routine blood parameters and whose global acne score was calculated. In the sample size calculation made by G power analysis, we planned to include at least 76 cases with a 95% confidence interval, a 5% error margin, and an 80% power. Informed consent was obtained from the patients. Patients with hematological and systemic diseases who used medication for a chronic disease and who were smokers or used alcohol and/or illegal substances were excluded.

ELR, NLR, MPV, and CRP levels were obtained from hematological and biochemical parameters. Global acne score values, and, in accordance with this value, mild, moderate, severe, and very severe acne groups were defined. The study was approved by Local Ethics Committee of Necmettin Erbakan University (date: 2019, number: 1936).

Statistical Analysis

The IBM® SPSS® Statistics Version 16.0 (Chicago, IL, USA) statistical program was used to analyze the data. The relationships between numerical data were evaluated by an independent samples t-test, a One-Way analysis of variance, and a Pearson correlation coefficient in cases where normality assumptions were provided and nonparametric responses of the same tests in cases where normality was not achieved. The relationships between categorical variables were determined by a chi-square test. For statistical significance, cases where p-value was less than 0.05 were considered significant.

RESULTS

Of the 76 cases of individuals aged 16–35, 49 were women. The mean age of the patients was 20.78±5.62 years, and the mean global acne score was 30.54±7.89. According to the global acne score, 6 (7.9%) of the cases had mild acne, 28 (36.8%) had moderate acne, 35 (46.1%) had severe acne, and 7 (9,2%) had very severe acne.

There was no significant difference between the eosinophil/lymphocyte ratio and the CRP levels in independent groups when mild/moderate and severe/very severe acne groups were analyzed according to global acne severity ($p>0.05$); the neutrophil/lymphocyte ratio ($p=0.022$) and the MPV levels ($p=0.007$) were significantly different between the groups (Table 1).

There were no significant differences in the neutrophil/lymphocyte ratio and the CRP levels between the four groups (mild, moderate, severe, very severe) according to their global acne severity ($p>0.05$). However, eosinophil/lymphocyte ratios ($p=0.040$), and MPV levels ($p=0.014$) were significantly different between the groups (Table 2). When paired group comparisons were made, it was found that the difference between severe and very severe acne groups was caused by the eosinophil/lymphocyte ratio ($Z= -2.449$, $p=0.014$). The difference for MPV was found to be due to the MPV ratio between the mild and severe acne groups ($p=0.007$).

DISCUSSION

Systemic inflammation is responsible for comorbidities in many diseases,[5] and these comorbidities are thought to be correlated with the severity of the systemic inflammation.[6] Studies have shown that some hematological parameters active in inflammation such as neutrophil and platelet and values such as the neutrophil/lymphocyte ratio (NLR) and the mean platelet volume (MPV) are indicative of inflammation.[3,6,7] There is also inflammation in the etiopathogenesis of acne vulgaris.[1]

CRP is one of the most well-known inflammatory markers and has been studied in many inflammatory diseases.[8-10] However, in the literature, no significant difference was found between groups with acne vulgaris and control groups in terms of CRP and it could not be associated with disease severity.[8] In our study, in accordance with the literature, no significant difference was found between the severity of acne vulgaris and CRP between the groups.

Neutrophils initiate the first step of defense in systemic inflammation.[11] The NLR value is an important parameter. It is obtained by dividing the total number of neutrophils by the number of lymphocytes. It has been shown that the NLR increases in many diseases with systemic inflammation.[7,11,12] It was found that the rate of NLR in acne inversa was higher compared to the control group.[12] In the literature, changes in the NLR rates after isotretinoin have been investigated in acne vulgaris patients; while some researchers have not observed a significant difference,[13,14] in other studies, it has been shown that NLR is significantly higher in acne cases compared to control groups and that it regresses with effective treatment.[15] In our study, the severity of acne vulgaris was compared to NLR, and there was a significant difference between severe/very severe and mild/moderate acne groups, but there was no significant difference when these acne groups were compared as quads.

Platelets are small discoid cells with an average life of approximately 8–10 days.[16] The MPV value is a marker for the function and activation of platelets.[17] A high MPV value indicates increased platelet production, and a low value indicates decreased production.[18] Increased MPV has been shown in low-grade severe inflammatory conditions such as recurrent aphthous stomatitis, Behcet's disease, psoriasis, and chronic hepatitis B.[19] These measurements showed that the MPV was directly related to the inflammatory grade. It has been observed that MPV values decrease with isotretinoin treatment in patients with acne vulgaris.[20,21] However, it is unclear whether the decrease in MPV value is due to decreased inflammation or bone marrow suppression. In the literature, there is no direct study investigating the relationship between the severity of the acne vulgaris disease and MPV. In our study, a significant difference was found between the acne vulgaris severity and MPV in both pair and quadruple groups. We think that the MPV value can be monitored in acne vulgaris severity follow-up.

Eosinophils are primarily white blood cells that play a very important role in the pathogenesis of allergic reactions.[22] In recent years, the role of eosinophils and the eosinophil/lymphocyte ratio in showing systemic inflammation has been discussed in many studies.[4,22,23] It was reported to be effective in demonstrating stent restenosis.[4] It has been reported

that the ELR is higher in patients with nasal polyposis compared to a control group.[22] Increased ELR was also detected in smokers.[23] There are no studies investigating the role of eosinophils in tissue and whole blood in acne cases in the literature. The role of eosinophils in the pathogenesis of acne is not fully understood. In our study, there was no significant difference between the pairs of severe-very severe and mild-moderate severe groups classified according to global acne severity. However, when the groups of four were compared, a significant difference was found, the difference being that the ELR value in the severe acne group was high. Based on these values, it is thought that ELR increases with the severity of acne and can be accepted as an indicator. In this context, we believe that there is a need for controlled studies involving the role of eosinophils in blood, tissue, and inflammation in the pathogenesis of acne. It is possible that the role of eosinophils in the pathogenesis of acne will lead to a better understanding of itch-dominated acne patients and may also lead to the development of new targets for treatment.

CONCLUSION

According to our findings, MPV was found to be the most powerful hematologic marker for acne severity and inflammation. As far as we are aware, there has been no study of ELR levels in acne to date, and this is the first study to evaluate this rate. In conclusion, we think that the ratio of MPV and ELR may be a follow-up indicator for acne vulgaris severity.

Table 1. Analysis of mild to moderate and severe to very severe acne groups according to global acne severity

Parameters		Global Acne Score		p-value
		Mild-moderate severe	Severe-very severe	
CRP	Mean ± standard deviation	0.87±0.93	1.28±1.45	0.753
	Median (min–max)	0.69 (0.00–4.60)	0.85 (0.10–5.60)	
MPV	Mean ± standard deviation	10.07±0.67	10.49±0.69	**0.007**
	Median (min–max)	10.00 (9.00–11.90)	10.30 (9.30–12.00)	
Eosinophil/Lymphocyte ratio	Mean ± standard deviation	0.08±0.15	0.07±0.03	0.234
	Median (min–max)	0.05 (0.02–0.94)	0.06 (0.03–0.15)	
Neutrophil/Lymphocyte ratio	Mean ± standard deviation	1.59±0.62	1.98±0.70	**0.022**
	Median (min–max)	1.51 (0.14–3.13)	2.06 (0.75–3.53)	

Significant p-values are shown in bold.
CRP: C-reactive protein, MPV: mean platelet volume, min: minimum, max: maximum.

Table 2. Analysis of the groups of mild, moderate, severe, and very severe acne according to global acne severity in four groups

Parameters		Global Acne Score				p-value
		Mild	Moderate	Severe	Very severe	
CRP	Mean ± standard deviation	1.20±1.70	0.81±0.71	1.27±1.54	1.36±1.03	0.740
	Median (min–max)	0.45 (0.27–4.60)	0.80 (0.00–2.56)	0.30 (0.10–5.60)	1.10 (0.10–2.80)	
MPV	Mean ± standard deviation	9.81±0.29	10.13±0.72*	10.55±0.71*	10.17±0.53	**0.014**
	Median (min–max)	9.75 (9.50–10.30)	10.00 (9.00–11.90)*	10.40 (9.30–12.00)*	10.00 (9.70–11.00)	
Eosinophil/Lymphocyte ratio	Mean ± standard deviation	0.06±0.03	0.09±0.17	0.07±0.03**	0.04±0.02**	**0.040**
	Median (min–max)	0.05 (0.02–0.13)	0.05 (0.02–0.94)	0.07 (0.03–0.15)**	0.03 (0.03–0.11)**	
Neutrophil/Lymphocyte ratio	Mean ± standard deviation	1.15±0.62	1.69±0.58	2.03±0.72	1.74±0.61	0.054
	Median (min–max)	1.35 (0.14–1.81)	1.54 (1.05–3.13)	2.07 (0.92–3.53)	1.71 (0.75–2.69)	

The groups marked with *, **, and underscored indicate the groups from which the difference originates. Significant p-values are shown in bold.
CRP: C-reactive protein, MPV: mean platelet volume, min: minimum, max: maximum.

MAIN POINTS

- According to our findings, MPV was found to be the most powerful hematologic marker for acne severity and inflammation.
- As far as we are aware, there has been no study of ELR levels in acne to date, and this is the first study to evaluate this rate. When the groups of four were compared, a significant difference was found, the difference being that the ELO value in the severe acne group was high. Based on these values, it is thought that ELO increases with the severity of acne and can be accepted as an indicator. In this context, we believe that there is a need for controlled studies involving the role of eosinophils in blood, tissue, and inflammation in the pathogenesis of acne.
- It is possible that the role of eosinophils in the pathogenesis of acne will lead to a better understanding of itch-dominated acne patients and may also lead to the development of new targets for treatment.
- In conclusion, we think that the ratio of MPV and ELO may be a follow-up indicator for acne vulgaris severity.

ETHICS

Ethics Committee Approval: The study was approved by the Ethics Committee of Necmettin Erbakan University (date: 2019, number: 1936).

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: M.D., S.A.T., Design: M.D., S.A.T., Supervision: M.D., S.A.T., Analysis and/or Interpretation: M.D., S.A.T., E.N.Y.Ö., B.I., Literature Search: M.D., S.A.T., E.N.Y.Ö., B.I., Writing: S.A.T., E.N.Y.Ö., B.I., Critical Review: M.D., S.A.T.

DISCLOSURES

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Determining the Attitudes, Behaviours and Affecting Factors of Female Seasonal Agricultural Workers Relating to the Early Diagnosis of Cervical Cancer

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ABSTRACT

BACKGROUND/AIMS: This study was conducted for the purpose of examining the attitudes and behaviours of female seasonal agricultural workers relating to the early diagnosis of cervical cancer.

MATERIALS AND METHODS: This descriptive study was carried out between February and June, 2016. The sample of the study consisted of 210 female seasonal agricultural workers.

RESULTS: It was determined that they obtained the highest score (30.32±6.38) from the lower dimension of perceived severity and the lowest score (22.63±3.96) from the lower dimension of perceived obstacles of the Attitude toward the Early Diagnosis of Cervical Cancer Scale. It was determined that the lower dimension of perceived sensitivity of the Attitude toward the Early Diagnosis of Cervical Cancer Scale was affected by age and educational background and the lower dimension of perceived benefits by age, educational background and language spoken at home ($p<0.05$).

CONCLUSION: As a consequence, it can be recommended to conduct interventional nursing studies to increase attitudes and behaviours.

Keywords: Seasonal agricultural worker woman, cervical cancer, early diagnosis

INTRODUCTION

Gynaecological cancers are the most common type of cancer among women in the world and in our country.[1] Cervical cancer, which is one of the gynaecological cancers, is the most common important health problem in the world, after colorectal and breast cancer.[2] According to data from Globocan 2018, while the age-standardized speed rate of cervical cancer is 13.1/100,000, the mortality rate is 6.9/100,000.[3] While the age-standardized speed rate of West Asian countries, which include Turkey is 4.1/100,000, the mortality rate has been reported to be 2.5/100,000.[4] Our country is one of the West Asian countries that have the lowest incidence of cervical cancer.[5]

Thanks to successful smear test applications, morbidity and mortality rates due to cervical cancer have decreased by more than 70% in many countries.[6] While 5% of women in developing countries undergo screening tests, this rate reaches up to 90% in developed countries.[7] Studies have shown that the rate of having a pap smear test is not at the desired level.[8,9-12] In one study conducted with the participation of 966 women, in which the awareness of the pap smear test was explored in

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Turkey, this awareness level was found to be 75.7%.[13] In addition, it has been reported that false attitudes and beliefs can be as effective as the level of knowledge in the participation rates of women regarding pap smear test screening.[8]

In Turkey, seasonal agricultural workers are an important risk group in terms of their working and living conditions, poverty and access to health services. For reasons such as poverty, and the inability to access health services, providing health care to seasonal agricultural workers in the environment in which they work is very important. In this process, the nurses involved in the teams that provide this service are key people. Considering that nurses are effective in improving early diagnosis behaviours, nurses have important roles in developing early diagnosis behaviours in this risk group. This study, which was conducted on female seasonal agricultural worker, provides both the identification of attitudes and behaviours related to cervical cancer in this at-risk group and can guide the planning and implementation of future nursing studies. In addition, there are no studies in the literature regarding the attitudes and behaviours of women toward the early diagnosis of cervical cancer. Therefore, this study was conducted to determine the attitudes, behaviours and affecting factors of women relating to the early diagnosis of cervical cancer.

MATERIALS AND METHODS

Research Type: This was a descriptive research.

Time of the Research: The study was carried out between February and June, 2016.

Population and Sample of the Research: The population of this research consisted of married women over the age of 35, who work as seasonal agricultural workers and live in those neighbourhoods where agricultural workers live densely. The 30 cluster sampling technique of the World Health Organization was used in the sample selection. Seven people within each cluster were contacted (210 people in total). The starting points for the clusters were selected by a simple random method from the streets in the above-mentioned neighbourhoods.[14] The research was carried out in two neighbourhoods where seasonal agricultural workers predominately lived. The streets of the neighbourhoods were considered as clusters. Female seasonal agricultural workers who were married and aged 30–65 were included in this study. Women who were single, non-seasonal agricultural workers, under 30 or over 65 were not included in this study.

Data Collecting Tools

Data were collected using the seasonal agricultural workers information form and the attitude scale for the early diagnosis of cervical cancer.

The Seasonal Agricultural Workers Information Form consists of 23 questions including descriptive characteristics, characteristics related to cervical cancer, and characteristics related to seasonal agricultural labour. This form was created by the researcher after reviewing the literature.[15-17]

The Attitude Scale Related to the Early Diagnosis of Cervical Cancer

This scale was developed in 2009 by Özmen and Özsoy[16] to explore the attitudes of women towards the early diagnosis of cervical cancer. The scale consists of nine items for the perceived sensitivity sub-dimension, eight items for the perceived seriousness sub-dimension, seven items for the perceived obstacles sub-dimension, and six items for the perceived benefits sub-dimension. It is a Likert type scale. The scoring of the scale is ordered from "I strongly disagree" with 1 point to "I fully agree" with 5 points. Of the 30 items in the scale, 22 are positive and eight are negative. Scoring of negative expressions is done in reverse order. The highest score that can be achieved in the scale is 150 and the lowest score is 30. The Chronbach Alpha value calculated for the whole attitude scale is 0.89. The Chronbach Alpha value that was obtained through this study for the whole scale was 0.75.

Dependent and Independent Variables

The dependent variables are the early diagnosis behaviours of cervical cancer, the scale score averages and the independent variables are the descriptive characteristics, characteristics related to cervical cancer and characteristics related to seasonal agricultural labour.

Statistical Analysis

SPSS 16.0 (Chicago, IL, USA) software was used in the evaluation of the data. Descriptive statistics (number, percentage, average), significance tests of difference between the two averages (t-test in independent groups), Mann–Whitney U test, Kruskal–Wallis analysis, and Variance analysis were used in the analysis of the data.

Ethical Dimension of the Research

Written permission was received from the Ethics Committee of Harran University (decision numbered: 16/01/22 and dated: 01.25.2016). In addition, informed consent was obtained from the participants. Permission was obtained from the relevant institution.

RESULTS

38.1% of the women were in the 35–39 age range, 83.7% were illiterate, 89.0% had health insurance, 70.5% considered their income to be poor, 55.2% spoke Arabic at home, 97.1% had children (Table 1).

When the data were analysed, it was found that 86.7% had no family history of cancer. 79.5% of the women did not have regular gynaecological examinations, 42.6% did not have any symptoms of disease, 50.5% knew of cervical cancer, 48.2% had learned about it from healthcare personnel, 15.7% had routine screening, 22.4% had had pap smears, and that 82.2% of those who had not had pap smears did not have a pap smear as they did not have enough information about it (Table 2).

It was seen that, 40.5% of the women stayed in the agricultural production area for 7 months or more, 75.7% of them had been working as SAWs for 7 years or more, 85.2% stayed in tents in the agricultural production area and 60.0% did not have the chance to access health services while in the agricultural production area, 81.0% of them stated that they were not protected against the harmful effects of pesticides, and 70.0% of those protected did so by covering their mouths.

The average score of the perceived sensitivity sub-dimension of the women was 27.24±6.29, the average score of the perceived seriousness sub-dimension was 30.32±6.38, the average score of the perceived obstacles sub-dimension was 22.63±3.96, and the average score of the perceived benefits sub-dimension was 22.90±4.63.

There was found to be a statistically significant difference between the average score of the perceived sensitivity sub-dimension (K-W=19.930,

p=0.001) and the perceived benefits sub-dimension (K-W=17.312, p=0.004) of the attitude scale. There was a statistically significant difference between the average scores of the perceived sensitivity sub-dimension (KW=10.028 p=0.040) and the perceived benefits sub-dimension (KW=10.020, p=0.040) of the attitude scale (Table 3).

There was a statistically significant difference found in the average score of perceived benefits sub-dimension (t=2.654, p=0.009) of the attitude scale according to the status of women having regular gynaecological examinations. A statistically significant difference was found among the average scores of the perceived sensitivity sub-dimension (t=3.599, p=0.000), the perceived seriousness sub-dimension (t=2.678, p=0.008) and perceived benefits sub-dimension (t=2.522, p=0.021) of the attitude scale according to the status of women having knowledge about cervical cancer. Additionally, there was a statistically significant difference found between the average scores of the perceived sensitivity sub-dimension (t=2.320, p=0.021) and perceived benefits sub-dimension (t=2.957, p=0.003) according to the status of women having pap smear tests (Table 4).

DISCUSSION

In this study, it was found that 22.4% of SAW women had had a pap smear test and 82.2% of those who had not had a test did not have enough information about the test (Table 2). In a similar study conducted with women in a health centre region; it was found that most of the women who had had pap smear tests (80.8%) had not done so regularly. It was found that women did not have a pap smear tests for reasons such as not knowing that it is necessary to give a swab sample from the cervix, not

Table 1. Distribution of socio-demographic characteristics of women (n=210)

Variables	Number (n)	Percent (%)
Age		
35–39	80	38.1
40–44	43	20.4
45–49	31	14.8
50–54	32	15.2
55–59	14	6.7
60 age and above	10	4.8
Educational background		
Illiterate	176	83.7
Literate	26	12.4
Primary	8	3.8
Health insurance		
Present	187	89.0
Absent	23	11.0
Income status		
High	6	2.8
Medium	56	26.7
Low	148	70.5
The language spoken in home		
Turkish	11	5.2
Arabic	116	55.2
Kurdish	83	39.6
Having a child(ren)		
Yes	204	97.1
No	6	2.9
Total	210	100.0

n: number.

Table 2. Distribution of some characteristics of female seasonal agricultural workers (n=210)

Characteristics	Number (n)	Percent (%)
Cancer history in the family		
Yes	28	13.3
No	182	86.7
Having regular gynaecological examinations		
Yes	43	20.5
No	167	79.5
The reason for not having gynaecological examinations (n=167)		
Do not have any signs of medical problems	71	42.6
Omission	70	42.0
Being shy	13	7.8
Lack of health insurance	9	5.3
Financial difficulty	4	2.3
Awareness of the cervical cancer		
Yes	106	50.5
No	104	49.5
Where did you find out about cervical cancer? informaiton? (n=106)		
Medical personnel	51	48.2
From other women in the community	32	30.2
Media	23	21.6
Awareness of cervical cancer in relation to routine screen tests		
Yes	33	15.7
No	177	84.7
Screen test known of (n=33)		
Pap smear test	25	75.7
Biopsy	6	18.2
Blood analysis	2	6.1
Where information was learnt (n=33)		
Medical personal	29	87.8
From other women in the community	3	9.1
Media	1	3.1
Pap smear test status		
Yes	47	22.4
No	163	77.6
The reason for pap smear test status (n=47)		
Cervical problems with the decision of the doctor	32	68.1
Due to cervical cancer screening	11	23.4
Due to regular health check	4	8.5
The reason for not having pap smear test (n=163)		
Lack of knowledge	134	82.2
Inability to spare the time	11	6.7
Not having any sign of medical problems	8	4.9
Being shy	5	3.1
Thinking that it is early for testing	3	1.9
Financial difficulty	2	1.2

n: number.

Table 3. The comparison of the average scores of attitude scale relating to the early diagnosis of cervical cancer according to the socio-demographic characteristics of the female seasonal agricultural workers

The Attitude Scale related to the early diagnosis of cervical cancer sub-dimensions					
Characteristics	**n**	**Sensitivity X±SD**	**Seriousness X±SD**	**Obstacles X±SD**	**Benefits X±SD**
Age					
35–39	80	3.18±0.65	3.94±0.68	3.17±0.50	4.02±0.66
40–44	43	2.92±0.64	3.67±0.74	3.23±0.56	3.79±0.65
45–49	31	3.23±0.63	3.90±0.70	3.31±0.52	3.94±0.66
50–54	32	2.61±0.73	3.44±1.03	3.24±0.71	3.35±0.93
55–59	14	3.09±0.68	3.91±0.79	3.25±0.51	3.89±0.75
60 age and above	10	2.81±0.82	3.65±1.03	3.37±0.71	3.28±1.07
Statistical value		**K-W=19.930 p=0.001**	K-W=8.849 p=0.115	K-W=2.374 p=0.795	**K-W=17.312 p=0.004**
Educational status					
Illiterate	176	2.97±0.69	3.78±0.77	3.23±0.56	3.81±0.76
Literate	26	3.17±0.64	3.70±0.90	3.27±0.56	3.62±0.79
Primary	6	3.55±0.60	4.31±0.98	3.07±0.72	4.50±0.39
Statistical value		**K-W=10.028 p=0.040**	K-W=3.741 p=0.442	K-W=2.263 p=0.687	**K-W=10.020 p=0.040**
Health insurance					
Present	187	3.01±0.71	3.78±0.80	3.21±0.56	3.78±0.79
Absent	23	3.14±0.59	3.84±0.77	3.36±0.60	4.05±0.47
Statistical value		MU=-1.063 p=0.288	MU=-0.270 p=0.787	MU=-1.295 p=0.195	MU=-1.460 p=0.144
Income status					
High	6	3.20±0.89	3.58±0.96	3.00±0.61	3.58±1.25
Medium	56	3.09±0.67	3.68±0.81	3.18±0.57	3.69±0.79
Low	148	2.99±0.70	3.83±0.78	3.26±0.56	3.87±0.73
Statistical value		K-W=0.457 p=0.756	K-W=2.055 p=0.358	K-W=1.672 p=0.433	K-W=2.338 p=0.311

Significant values are shown in bold.
SD: standard deviation, n: number.

considering it necessary, being shy, a lack of money, or thinking that it is a painful procedure.[18] Similar to this study, in another study conducted in 2018, it was found that 28.7% of women had had at least one pap smear test and that 42.7% of those who had never had a pap smear test did not know about this test[19]. According to the study conducted by Ramathuba et al.[20] in Africa in 2016, only 3.2% of the participants had had a pap smear test and a lack of information was shown to be the reason for this rate being so low. In another study conducted on Turkish women, a lack of information was found to be one of the reasons why they had not had a pap smear test.[21] In a study conducted on Vietnamese women, about 50% of the participants believed that cervical cancer can be easily treated if diagnosed early and having a pap smear test is the most important way to prevent cervical cancer. In the same study, it was found that women with these thoughts were more likely to have pap smears than those who did not.[22] In this study, it is seen that the rate of having pap smear tests is not at the desired level, and this situation could be related to insufficient access to health services while working in agricultural production areas. At the same time, a woman's lack of family history of cancer, not knowing about screening tests for the early diagnosis of cervical cancer, and living in the field for a long time may have also negatively affected their pap smear test history.

In this study, it was observed that perceived sensitivity had the highest average score and perceived obstacles had the lowest average score. Increasing perceived sensitivity is important in terms of increasing the likelihood that individuals participate in positive health behaviours.[23] In one study conducted by Ersin et al.[24], the average sensitivity perception score was reported to be 26.88±4.56. In another study conducted in Iran, an increase in perceived sensitivity was observed in the experimental group.[25] In this study, it is considered that the sensitivity perceptions of SAW women are not at the desired level and this situation may adversely affect the likelihood of early diagnosis behaviours. Also, in this study, the average score of the perceived seriousness sub-dimension was found to be 30.32±6.38 (Table 4). In a similar study, the average score of seriousness perception was found to be 25.32±4.66.[8] In another study, the average score of perception of seriousness was found to be lower at 19.23±4.81.[24] According to the Health Belief Model, the perception of seriousness involves evaluating both the medical and clinical outcomes of an illness.[23] The results obtained from this study may be an indication that SAW women can evaluate the results of cervical cancer. In this study, the average score of the perceived obstacles sub-dimension was found to be 22.63±3.96. In another study, the perceived obstacles sub-dimension average score

Table 4. The comparison of average scores of the attitude scale relating to the early diagnosis of cervical cancer according to the cancer-related characteristics of seasonal agricultural worker women

The Attitude Scale related to the early diagnosis of cervical cancer sub-dimensions					
Characteristics	**n**	**Sensitivity X±SD**	**Seriousness X±SD**	**Obstacle X±SD**	**Benefit X±SD**
Cancer history in the family					
Yes	28	3.23±0.79	3.67±0.98	3.17±0.41	3.83±0.98
No	182	2.99±0.69	3.80±0.76	3.24±058	3.81±0.73
Statistical value		MU=-1.781 p=0.075	MU=-0.357 p=0.721	MU=-1.025 p=0.305	MU=-0.533 p=0.594
Having regular gynaecological examinations					
Yes	43	3.19±0.68	3.98±0.63	3.17±0.49	4.09±0.60
No	167	2.98±0.69	3.74±0.82	3.24±0.58	3.74±0.79
Statistical value		t=1.811 p=0.072	t=1.827 p=0.069	t= -0.752 p=0.453	**t=2.654 p=0.009**
Awareness of cervical cancer					
Yes	106	3.19±0.62	3.93±0.72	3.17±0.53	3.94±0.72
No	104	2.85±0.73	3.64±0.84	3.29±0.58	3.68±0.80
Where did you learn this information? (n=106)					
Medical personnel	51	3.28±0.63	3.99±0.71	3.10±0.53	4.13±0.69
Media	23	3.25±0.66	4.03±0.67	3.20±0.51	4.11±0.46
From women in the community	32	3.01±0.54	3.76±0.76	3.26±0.56	3.54±0.76
Statistical value		K-W=0.033 p=0.856	K-W=0.006 p=0.806	K-W=0.571 p=0.470	K-W=0.079 p=0.778
The awareness of the cervical cancer in relation to routine screening tests					
Yes	33	3.22±0.67	3.92±0.70	3.18±0.52	3.88±0.66
No	177	2.99±069	3.76±0.81	3.24±0.57	3.80±0.79
Screen tests known of (n=33)					
Pap smear tests	25	3.31±0.70	3.93±0.71	3.18±0.52	4.01±0.69
Biopsy	6	3.05±0.61	4.02±0.71	3.30±0.31	3.61±0.34
Blood analysis	2	2.66±0.31	3.43±0.61	2.78±1.11	3.08±1.11
Statistical value		K-W=2.377 p=0.305	K-W=1.302 p=0.521	K-W=0.721 p=0.697	K-W=4.859 p=0.088
Pap smear test status					
Yes	47	3.23±0.65	3.97±0.78	3.16±0.54	4.10±0.72
No	163	2.96±0.70	3.73±0.79	3.16±0.54	3.73±0.76
Statistical value		**t=2.320 p=0.021**	t=1.786 p=0.076	t=-1.003 p=0.317	**t=2.957 p=0.003**

Significant values are shown in bold.
SD: standard deviation, n: number.

was found to be low.[24] Perceived obstacles is defined as those factors that prevent or complicate protective behaviours related to health.[26] The results obtained from this study may be due to the fact that the women stay in agricultural production areas for long periods, their lack of access to health services and their low-income status. The average score of the perceived benefits sub-dimension in this study was found to be 22.90±4.63. In their study, Ersin et al.[24] found the average score of the perceived benefits sub-dimension to be 17.86±3.27. Perceived benefits are an individual's belief in preventing a disease by changing their behaviour.[23] The result obtained from this study indicates that women's belief in preventing cervical cancer is not sufficient. This suggests that their awareness levels may be low.

A statistically significant difference was found between the average sensitivity and benefits sub-dimension scores of the attitude scale relating to the early diagnosis of cervical cancer according to the age of the women ($p<0.05$) (Table 3). In another study, it was stated that perception of obstacles increases in those women between the ages of 52–63 but there was no significant difference in their perceptions of seriousness and sensitivity.[26] The result obtained from that study may be an indication that the importance given to health care decreases with age.

A significant difference was found between the sensitivity and benefits sub-dimensions in relation to the educational status of the women ($p<0.05$) (Table 3). In the study of Uluocak and Bekar[27], it was found

that the total score average of the attitude scale relating to the early diagnosis of cervical cancer was higher in those with a postgraduate education or higher. As the level of education increases, it is expected that sensitivity and benefit perception scores will increase.

The perceived sensitivity, benefits and seriousness sub-dimension scores of those women who had regular gynaecological examinations were found to be higher, and their average scores of the perceived obstacles sub-dimension was found to be lower than those who did not (Table 4). In a study conducted by Kızılırmak and Kocaöz[28], it was found that the perceived obstacles sub-dimension scores of those women who had regular genital examinations were low. In that same study, it was also found that those who had gynaecological examinations had low perceptions of pap smear test obstacles. The results of the study may be due to the belief that regular gynaecological examinations will reduce the risk of having cervical cancer.

The perceived sensitivity, seriousness and benefits sub-dimension scores of those women who knew about cervical cancer were found to be significantly higher and their average scores of the perceived obstacles sub-dimension were found to be lower (Table 4). In a study similar to our study, it was found that the pap smear perceived benefits and the health motivation of those women who received information about cervical cancer and screenings was significantly higher and their perception of obstacles was lower.[29]

In this study, the average sensitivity and perceived benefits sub-dimension scores of having a pap smear test were significantly high (Table 4). Aşılar et al.[29] reported that the benefit perceptions of those who had pap smear tests were significantly higher and their perceptions of obstacles were lower. In another study conducted by Özmen and Özsoy[16], the perceived sensitivity, seriousness and benefit scores of those women who had pap smear tests was significantly higher than for those women who did not have tests. According to a study conducted by Demirgöz Bal[8] on women working in a Public Education Centre, the average scores of seriousness and benefit perceptions of those women who had pap smear tests were found to be higher. The result obtained from our study is an expected result. On the other hand, our result may be due to the fact that SAW women believe that having a pap smear test and the support they receive from health professionals will make it easier for them to protect themselves from cervical cancer. It can also be said that awareness of pap smear tests has positive effects on women's beliefs related to health.

CONCLUSION

It was found that SAW women had the highest score from the perceived seriousness sub-dimension and the lowest score from the perceived obstacles sub-dimension of the attitude scale relating to the early diagnosis of cervical cancer. It is clear that the ratio of women who have pap smear tests and gynaecological examinations is not at the desired level. It is recommended that continuous health education should be provided by health professionals via mobile health services in those areas where SAW women work in order to increase the sensitivity, seriousness and benefit perceptions of SAW women and their rate of having pap smear tests and also to reduce their perception of obstacles.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee of Harran University (decision numbered 16/01/22 and dated 01.25.2016).

Informed Consent: Written permission was received from the women who participated in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.Y., F.E., Design: F.Y., F.E., Supervision: F.E., Data Collection and/or Processing: F.Y., Analysis and/or Interpretation: F.Y., F.E., Literature Search: F.Y., F.E., Writing: F.Y., F.E., Critical Review: F.E.

DISCLOSURES

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

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MAIN POINTS

- It was found that SAW women had the highest score from the perceived seriousness sub-dimension of the attitude scale relating to the early diagnosis of cervical cancer
- It was found that SAW women had the lowest score from the perceived obstacles sub-dimension of the attitude scale relating to the early diagnosis of cervical cancer.
- It is clear that the rate of women who have pap smear tests and gynaecological examinations is not at the desired level.

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ORIGINAL ARTICLE

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Fear of Birth: An Increasing Fear in Pregnancy During the COVID-19 Period

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ABSTRACT

BACKGROUND/AIMS: The inadequate prenatal and postnatal services due to the deployment of health services to coronavirus disease-2019 (COVID-19) related arrangements has led to an increased number of patients experiencing a fear of contracting COVID-19 in addition to their fear of childbirth. Therefore, this study aimed to examine the relationship between the fear of COVID-19 and the fear of childbirth.

MATERIALS AND METHODS: The study was designed in descriptive and correlational types. Three hundred forty-three pregnant women included in the study using descriptive and correlational methods were evaluated using the COVID-19 Fear Scale (CFS) and the Fear of Birth Scale (FOBS) for Pregnant Women.

RESULTS: The mean age of the pregnant women participating in the study was 29.07±5.90 years and the mean gestational week was 35.51±2.70 weeks. It was observed that pregnant women had more fear of COVID-19 (19.69±7.63) due to the fear of contracting the virus during the pandemic period, and as a result, the participants experienced a fear of birth (64.25±29.30). It was observed that there was a significant, positive, and moderate relationship between CFS and FOBS in the pregnant women ($p<0.001$). It was found that 15.8% of the development of fear of birth is due to a fear of COVID-19.

CONCLUSION: Healthcare professionals can use practical scales to assess pregnancy and COVID-19 fears.

Keywords: Pregnancy, fear, birth, COVID-19

INTRODUCTION

Pregnancy is a time of significant physiological change to meet the needs of the developing fetus and prepare the mother-to-be for labor and birth. These physiological changes can have psychological implications on pregnant women, inducing anxiety and depression.[1-3] Pregnant women may experience anxiety about the labor and delivery process, but if this anxiety negatively impacts their quality of life, it is termed tocophobia (fear of birth).[4] Cesarean rates have been reported as higher in nulliparous women with tokophobia.[5]

Fear of Birth (FOB) can be classified as mild, moderate, or severe.[6] There are some factors closely associated with FOB, namely low socio-economic status, lack of social support, pre-existing distrust of healthcare workers, feeling alone in an unfamiliar environment during labor, excessively worrying about the well-being of the baby, fear of pain during labor, inadequate milk supply and the possibility of cesarean section.[6-8] FOB can complicate pregnancy, labor, and the postpartum period with an increased rate of cesarean deliveries, excessive need for pain medications, postpartum depression, attachment problems between the mother and newborn and fetal asphyxia.[6-8] FOB can be seen before pregnancy due to other women's adverse birth experiences.[9]

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FOB may be intensified during pandemics. It has been shown that anxiety and excessive stress during pregnancy are accentuated by social isolation. This may be associated with adverse birth outcomes such as premature birth.[10] Coronavirus disease-2019 (COVID-19) was declared a pandemic by The World Health Organization. It has led to large-scale unprecedented negative impacts on public health, the economy, social life, and education.[11]

Pregnant women are worried about the well-being of their unborn babies, themselves, and their loved ones. As a result, many women perceive healthcare institutions as high-risk areas in terms of contracting COVID-19, and pregnancy follow-ups have been compromised due to this fear. In addition, the inadequate prenatal and postnatal services due to the deployment of health services to COVID-19 related arrangements has led to an increased number of patients experiencing childbirth with a fear of contracting COVID-19.[12]

This study aims to investigate the possible relationship between the fear of childbirth and the fear of contracting COVID-19 disease during the COVID-19 pandemic.

MATERIALS AND METHODS

Research Type

The study was designed in descriptive and correlational types.

Research Questions

1. What is the fear of birth in pregnant women in the COVID-19 period?

2. What is the fear of COVID-19 in pregnant women during the COVID-19 period?

3. Is there a relationship between the fear of birth and the fear of COVID-19 in pregnant women during the COVID-19 period?

4. Are there other factors affecting the development of the fear of birth in pregnant women during COVID-19?

Population and Sample

This study was conducted in the antenatal outpatient clinic of a tertiary pandemic hospital between December 1, 2020 and December 30, 2020. The study comprised pregnant women over 30 weeks of gestation presenting to a tertiary pandemic hospital in the Marmara region of Turkey. A total of 343 pregnant women included in the study were selected based on the criteria below:

- Pregnant women who can speak and write Turkish,
- Between 19 and 45 years old,
- Not previously diagnosed with COVID-19 disease,
- No pre-existing psychiatric illness,
- No high-risk pregnancy diagnosis,
- Women who consented to participate in this study.

Data Collection Tools

Data was collected via three different questionnaires; the first questionnaire consists of questions regarding demographic features. The second was the COVID-19 fear scale questionnaire. The third was the fear of birth scale questionnaire, which was specifically designed for pregnant women. The demographic features in the first questionnaire included age, education, employment status, and risk stratification of the ongoing pregnancy.

The Coronavirus disease-2019 (COVID-19) Fear Scale: The COVID-19 fear scale was initially developed by Ahorsu et al.13 and adapted for use in the Turkish population by Bakioğlu et al.3 and comprises seven different points. The scale is one-dimensional and consists of seven items. There are no reverse-coded items on the scale. The scale's total score reflects the perceived (or experienced) level of fear of COVID-19 by an individual. Therefore, the higher the score, the higher the level of fear of COVID-19. The Cronbach's alpha value was found to be 0.880 during the initial scale development. We found it to be 0.979 in our study, and this value falls in the reliable range.

The Fear of Birth Scale for Pregnant Women: The Fear of Birth scale was developed by Haines et al.[14] for measuring the fear of birth, and this scale was adapted to Turkish society by Serçekus et al.[15]. Pregnant women were presented with the question, "How do you feel about the approaching birth?" Two different 100 mm lines are used; (0) calm and (100) worried, and (0) no fear at all, and (100) intense fear. The cut-off value for the scale is defined as 50 after calculating the average of two lines. Fear of birth is present if the score is 50 or above. This scale can be applied to both pregnant women and their partners. The Cronbach's value of this scale was found to be 0.920, and we found the Cronbach's value to be 0.785 in our study, which is consistent with the reliable range.

Data Collection Process

The data collection process was carried out voluntarily. Pregnant women attending for pregnancy follow-up were informed about the study by the researchers. A single room was arranged for the pregnant women who agreed to participate in this study to fill in the questionnaire. The researchers ventilated the room for 30 minutes after each person completed the questionnaire. Then, the next participant was taken to the room, and a new pen was given to each participant to fill in the questionnaire. The form was completed in an average of 10–15 minutes.

Statistical Analysis

Statistical analyses were conducted using the Statistical Package for Social Sciences Version 23 (SPSS Inc., Chicago, IL, USA). Number, percentage, mean and standard deviation were used in descriptive statistics. Mann–Whitney U test was used for group comparison, while Pearson chi-square test was used for scale correlation analysis. Results were accepted at a 95% confidence interval and the statistical significance as $p<0.05$.

Before starting this study, written approval (2020-10-27T20_29_46) was obtained by registering with the Ministry of Health of the Republic of Turkey (https://bilimselarastirma.saglik.gov.tr/). In addition, institutional permission from the pandemic hospital where the study was conducted and ethics committee approval (ethics committee no: 01/12/2020-583) from the university scientific research ethics committee was obtained. Furthermore, before commencing this study, informed consent was obtained in line with the voluntary principle, informing the participants about the study and confirming that their personal information would be protected. In addition, research and publication ethics were followed in this study.

RESULTS

The mean age of the pregnant women participating in this study was 29.07±5.90 years and the gestational week was 35.51±2.70 weeks. In addition, 13.4% of the participants were smokers, and 48.1% were primary school graduates. It was observed that 27.1% of the pregnant women were having their first pregnancy, and 92.2% of those who gave birth before did not have any problems in their previous deliveries.

It was observed that 43.7% of the participants had at least one relative diagnosed with COVID-19 during their pregnancy (Table 1). When the pregnant women were asked about their behavior during the COVID-19 period, it was seen that 13.1% answered "no" and 57.1% answered "I do not know" to whether a mother diagnosed with COVID-19 can breastfeed her baby.

During this period, 94.5% of the participants were found to have increased the frequency of washing their hands, 39.4% did not go out unless it was necessary, and 99.1% gave importance to wearing a mask when they had to go out, while all participants were observed to comply with social distancing (Table 1).

According to the scores obtained from the COVID-19 Fear scale, it was found that the scale mean score of pregnant women was 19.33±7.52, while the majority of the participants scored 21 points and above (Figure 1).

The fear of birth scale mean score of the participants was 61.7±30.09, and according to the cut-off score, 25.7% (n=88) did not have a fear of birth, while 74.3% (n=255) experienced a fear of birth. Additionally, it was concluded that 81 pregnant women (23.6%) who gave ten total points on the scale experienced a severe fear of birth (Figure 2).

It was observed that pregnant women had more fear of COVID-19 (19.69±7.63) due to the fear of contracting the virus during the pandemic period, and as a result, the participants experienced a fear of birth (64.25±29.30). The researchers found that those who were worried about having COVID-19 before birth experienced an increased fear of COVID-19 (20.08±7.36) and fear of birth (63.24±30.15). Furthermore, it was found that pregnant women experienced more fear of COVID-19 (19.66±7.42) and fear of childbirth (63.22±29.65) due to the concern of having COVID-19 after birth, similar to before birth. In addition, it was observed that the participants who were worried about being separated from their babies after birth experienced more fear of COVID-19 (19.34±7.40) and fear of birth (62.68±30.29) (Table 2).

The total scores of the scales used in the study were examined with the Kolmogorov–Smirnov Normality test and found to be normally distributed ($p>0.05$). Relationships between the scales were examined with Pearson's Moments Multiplication Correlation. According to the statistical analysis results performed for this purpose, it was observed that there was a significant, positive, and moderate relationship between the COVID-19 Fear Scale and the Fear of Birth Scale of pregnant women ($p<0.001$) (Table 3).

In this study, the predictive power of COVID-19 fear on the fear of childbirth in pregnant women was examined. In order to search for an answer to this basic issue. Regression analysis of the scales to predict total means was performed. When Table 4 is examined, it is seen that the COVID-19 fear level is a significant predictor of the fear of birth [$R = 0.400$, $R^2 = 0.160$, $F(1,360) = 64.958$, $p<0.001$]. It can be said that the fear of COVID-19 can explain 15.8% of the total variance regarding the fear of birth. According to the regression analysis results, the regression equation for predicting fear of birth is given below.

Fear of Birth = (30.821) + (1.160) x COVID-19 Fear Scale

DISCUSSION

In this study examining both the Fear of Childbirth and the fear of contracting COVID-19, it was seen that the fear of COVID-19 was a predictor in the development of Fear of Childbirth. In addition, this study found that the fear of COVID-19 (mean: 19.33 points) in pregnant women was at a medium level (Figure 1).

In the study where the Turkish validity version of the scale used was made, the mean score of the scale was determined to be 19.44.[3] In a study in which the fears of female and male participants (n=649) about COVID-19 disease were examined, it was emphasized that the fear of COVID-19 was higher in women, and this was because women were more emotional.[16] Women have an emotional nature due to both their gender and the factor of pregnancy. Since most pregnant women (n=223) see healthcare workers as their source of information on COVID-19, expressing their feelings and thoughts about COVID-19 will partially reduce their fears and comfort them. It is seen that approximately one-fourth (23.6%) of the pregnant women participating in this study experienced severe fear of birth (Figure 2). In the last trimester of pregnant women in a study conducted on this issue in Turkey, there was increased concern regarding birth and baby care.[17] In a study examining the prevalence of indigenous and immigrant pregnant women (n=606) in Sweden, it was found that 22% of local pregnant women and 37% of immigrants experienced birth fear.[18] In a study conducted with a different scale in Egypt, it was seen that 55.33% of women experienced fear of birth.[19] The high rate of fear of birth in pregnant women in different countries such as Sweden and Egypt are similar to our study. The high level of fear of birth in different societies with cultural differences suggests that this fear is universal and requires the awareness of health professionals working in obstetrics. We are convinced that delivery should be evaluated with simple, understandable scales or questionnaires, if possible, before planning or during a pregnancy. When a pandemic situation such as COVID-19 is added to this process, it can be seen that this fear increases. There are not enough studies in the literature regarding the fear of childbirth during a pandemic period. Therefore, it should not be forgotten that healthcare professionals should consider this finding. There was a significant relationship between the participants' fear of contracting COVID-19 before and after birth, between the worry of separation with the baby after birth, and the fear of COVID-19 and the fear of birth (Table 2). In a study conducted in Iran, it was reported that the fear of having COVID-19 during pregnancy affects the mental health of the pregnant women. Pregnant women worry about contracting the disease and infecting their babies and loved ones.[20] In one study that stated that women with a fear of delivery during pregnancy had a high tendency to postpartum depression, it was emphasized that there was a significant relationship between smoking, low education levels, a history of psychiatric illnesses before pregnancy, depressive symptoms during pregnancy, and the fear of delivery.[21] In a case report study in which a pregnant woman gave birth at home due to an excessive fear of COVID-19, it was stated that the pregnant woman did not want to go to the hospital despite Rh incompatibility, and the postnatal period was managed at home by the midwife who had followed the pregnancy.[22]

Table 1. Descriptive data of participants			
Sociodemographic variables		**n**	**%**
Age	29.07±5.90 years (min: 19 - max: 44)		
Smoking	Yes	46	13.4%
	No	297	86.6%
Income status	Income is more than expenses	104	30.3%
	Income is less than expenses	13	3.8%
	Income is equivalent to expenses	226	65.9%
Family type	Nuclear family	279	81.3%
	Extended family	64	18.7%
Working status	Yes	63	18.4%
	No	280	81.6%
Educational status	Primary education	165	48.1%
	High school/associate degree	140	40.8%
	Undergraduate-Postgraduate	38	11.1%
Obstetric history			
Pregnancy week	35.51±2.70 weeks (min: 30 - max: 40)		
Conceiving method	Spontaneous	328	95.6%
	Assisted reproductive techniques	15	4.4%
Planned pregnancy status	Yes	254	95.6%
	No	89	4.4%
Previous delivery status	Yes	250	72.9%
	No	93	27.1%
Problems in previous birth	Yes	20	7.8%
	No	235	92.2%
Chronic disease status	Yes	32	9.3%
	No	311	90.7%
Time between pregnancies	First pregnancy	97	28.3%
	Less than 1 year	12	3.5%
	1–2 years	56	16.3%
	More than 2 years	178	51.9%
Previous delivery method	Normal vaginal delivery	119	49.0%
	Cesarean section	124	51.0%
Nearby COVID-19 infection status	Yes	150	43.7%
	No	193	56.3%
Information status about COVID-19			
COVID-19 positive mother's ability to breastfeed her baby	Yes	102	29.7%
	No	45	13.1%
	Unknown	196	57.1%
Information sources about COVID-19	Media	102	29.7%
	Internet	35	10.2%
	Health employee	223	65.0%
Hand washing frequency (according to pre-pandemic)	Yes	324	94.5%
	No	19	5.5%
Not going out unless required	Yes	135	39.4%
	No	208	60.6%
Wearing a mask when you have to go out	Yes	340	99.1%
	No	3	0.9%
Compliance with social distancing when having to go out	Yes	343	100%
	No	0	0

COVID-19: coronavirus disease 2019, n: number.

In a study conducted on social media in the United States, it was reported that pregnant women (n=592) wanted to stay at home until the birth began and planned to leave hospital as soon as possible after birth, thus thinking that they would reduce their risk of contracting COVID-19. In addition, it was found in this study that some of the pregnant women (n=81) did not intend to give birth in a hospital, and they were worried that they might become infected in the hospital and be separated from their babies.[23] Healthcare professionals may need to explain to pregnant women the demonstrated or possible effects of COVID-19 on the fetus and newborn in a language that the lay-person can understand. Good feelings such as being pregnant and knowing that you will be a mother should not be allowed to be overshadowed by such fears. In addition, investigating the social support (spouse, mother, sibling, friend, etc.) sources of pregnant women may also be effective in managing such fears.

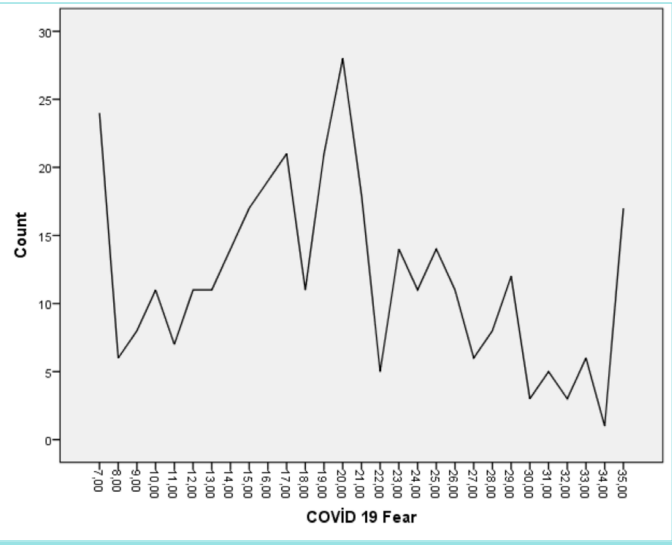

Figure 1. Distribution of COVID-19 fear responses.

According to the scores obtained from the COVID-19 Fear scale, it was found that the scale mean score of pregnant women was 19.33±7.52, while the majority of the participants scored 21 points and above.

COVID-19: coronavirus disease 2019

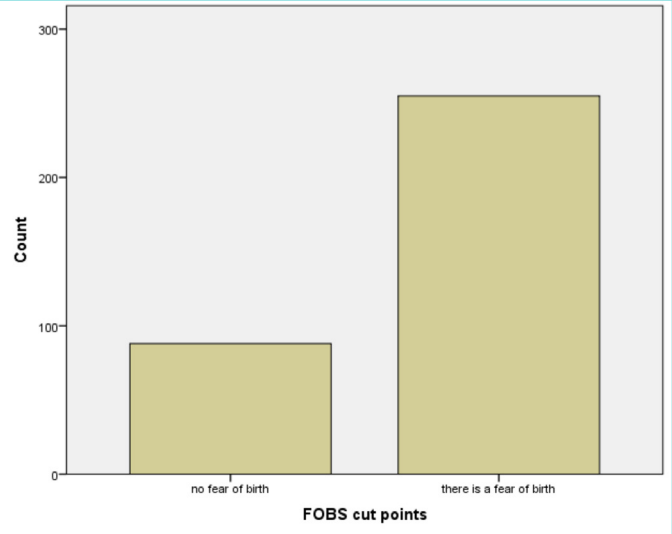

Figure 2. Distribution of FOBS responses.

The fear of birth scale mean score of the participants was 61.7±30.09 and according to the cut-off score, 25.7% (n=88) did not have a fear of birth, while 74.3% (n=255) experienced fear of birth. It was concluded that 81 pregnant women (23.6%) who gave ten full points on the scale experienced severe fear of birth.

FOBS: The fear of birth scale, n: number

One of our study findings is a significant positive correlation between the fear of childbirth and the fear of COVID-19 (Tables 3 and 4). In a qualitative study examining the adaptation of seven pregnant women to the pandemic process, researchers found three themes (pregnancy perception in a pandemic, coping with pregnancy, and supporting pregnant women).[24] In a study conducted with 190 pregnant women in Pakistan, it was reported that 74.7% of women were afraid of contracting COVID-19. It was observed that fear was higher in those who received service from a public hospital, had four or more pregnancies, and had low economic and educational levels.[25] Another study emphasized that 84.6% of pregnant women (n=242) had a high level of prenatal anxiety and fear of contracting COVID-19.[24] Some women may consider a home birth because they fear being infected with COVID-19 and the delivery room environment. However, delivery at home can adversely affect the health of the mother and baby.[25] In a study comparing counseling and art therapy under the leadership of a healthcare professional to cope with the fear of childbirth, it was found that neither method was superior to the other; they are both effective in controlling the fear of birth.[7] In order to control the fear of birth, methods such as health professional counseling, group therapy, telephone support, cognitive behavioral therapy, and obtaining birth preparation support from a health professional are recommended.[26] Our research examining the relationship between the fear of birth and the fear of COVID-19 shows similar features with other studies. We think that a pregnant woman's ability to visit the hospital and delivery room environment in which she plans to give birth, communicate with the healthcare professionals involved in the delivery, and to participate in birth preparation training will help pregnant women control their fear of birth and COVID-19.

It is not known precisely when the COVID-19 pandemic will end. In addition to the possible social and economic uncertainties in this process, being at risk of becoming sick inevitably causes people to experience intense stress and anxiety. In such a period, undergoing significant periods of a women's life such as pregnancy and childbirth, will increase the stress and anxiety experienced. Therefore, preventive health care, education, and consultancy services should be provided without delay during pregnancy follow-up during a pandemic period.

When pregnant women come to their health check-ups, in addition to routine obstetric examinations, fear of childbirth and fear of COVID-19 should be evaluated with practical scales or brief questioning by healthcare professionals. According to these evaluation results, it is recommended that at risk pregnant women be followed closely, and if necessary, they should be referred to a psychologist or psychiatrist.

Limitations and Strengths

This study has several limitations such as the fact that generalization cannot be made since this study was carried out in a single center and also that a psychological assessment tool based on individuals' reports may weaken its objectivity. However, the study's strengths are its ability

Table 2. Evaluation of the COVID-19 fear effect on the fear of birth

	COVID-19 fear value, mean (SD)	p-value; U	Fear of birth value, mean (SD)	p-value; U
The fear of contraction corona virus on arrival				
Yes (n=302, 88%) No (n=41, 12%)	19.69±7.63 16.68±6.10	0.010; 3819.000	64.25±29.30 43.29±29.76	0.000; 4657.500
Worry of contraction COVID-19 before birth				
Yes (n=296, 86.3%) No (n=47, 13.7%)	20.08±7.36 14.59±6.81	0.000; 3893.500	63.24±30.15 52.34±28.22	0.008; 5308.500
Concern of contracting COVID-19 after birth				
Yes (n=315, 91.8%) No (n=28, 8.2%)	19.66±7.42 15.53±7.76	0.003; 2928.000	63.22±29.65 45.17±30.65	0.003; 2946.500
Worry of being separated from baby after birth				
Yes (n=319, 93.0%) No (n=24, 7.0%)	19.34±7.40 19.20±9.20	0.589; 3575.500	62.68±30.29 49.37±24.59	0.027; 2804.500

Mann–Whitney U test, p<0.05.
COVID-19: coronavirus disease 2019, SD: standard deviation, n: number.

Table 3. Relationship of COVID-19 fear and fear of birth scale

		Fear of birth scale
COVID-19 fear	r	0.400
	p	**0.000**

r: Pearson's correlation coefficient. P-values of the statistically significant correlation coefficients were shown as bold p<0.001.
COVID-19: coronavirus disease-2019.

Table 4. Findings regarding the power of COVID-19 fear effect on the fear of birth

Dependent variable: fear of birth

Independent Variables	β	SE_B	Std β	T	p-value
Constant	30.821	4.117		7.486	0.000
Fear of COVID-19	1.600	0.198	0.400	8.060	0.000

$R = 0.400/R^2 = 0.160$/Adjusted $R^2 = 0.158$
$F_{(1,360)} = 64.958$, p=0.000
SE: standard error, Std: standard, COVID-19: coronavirus disease 2019.

to raise awareness of the fear that may occur during pregnancy in order to provide the necessary support.

MAIN POINTS

- When pregnant women come to their health check-ups, in addition to routine obstetric examinations, fear of childbirth and fear of COVID-19 should be evaluated with practical scales or brief questioning by healthcare professionals.
- According to the evaluation results, it is recommended that the pregnant women at risk be followed closely, and if necessary, they should be referred to a psychologist or psychiatrist.
- COVID-19 is a contributing factor in the increase of the fear of birth.

ETHICS

Ethics Committee Approval: Ethics committee approval was obtained from Sakarya University Scientific Research Ethics Committee (decision no and date: 583-01/12/2020).

Informed Consent: Informed consent was obtained in line with the voluntary principle, informing the participants about the study and confirming that their personal information would be protected.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.T., K.G., Design: Ö.T., K.G., Supervision: Ö.T., K.G., M.S.B., Data Collection and/or Processing: Ö.T., Ö.D., K.G., M.S.B., Analysis and/or Interpretation: Ö.D., Literature Search: M.S.B., Writing: Ö.T., K.G., M.S.B., Critical Review: Ö.T., M.S.B.

DISCLOSURES

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ORIGINAL ARTICLE

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Current Threat in COVID-19; Asymptomatic Carriers

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ABSTRACT

BACKGROUND/AIM: Asymptomatic infections are not low in their inability to spread the virus and have no special clinical signs. Consequently, the detection of asymptomatic infections is the central issue for early prevention and control of the coronavirus disease-2019 (COVID-19) around the world. This study aimed to assess the demographic, clinical, and laboratory findings of symptomatic and asymptomatic patients with a diagnosis of COVID-19.

MATERIALS AND METHODS: In this retrospective single-center study, 165 laboratory-confirmed COVID-19 patients who were asymptomatic or symptomatic and followed up at home or in the hospital between March 15, 2020, and May 23, 2020, were included.

RESULTS: Among all 165 patients, 21 (12.7%) were asymptomatic and 144 (87.2%) were symptomatic. The median age of the symptomatic patients was higher than the asymptomatic patients, and there were no asymptomatic patients over 65 years older. Twenty-one patients were asymptomatic at admission, but four of them (19%) developed symptoms in the follow-up. Although the white blood cell (WBC) and lymphocyte counts were within the normal range for all patients, the asymptomatic

patients had a significantly higher WBC and lymphocyte count than the symptomatic patients. The symptomatic patients had higher median C-reactive protein levels than the asymptomatic patients. For the typical CT findings for COVID-19, there were fewer in the asymptomatic infections (12 cases, 57.1%) than those in the symptomatic infections (103 cases, 71.5%). There were 17 (10%) patients in need of intensive care and the mortality rate was 6.1%.

CONCLUSION: Asymptomatic infections spread silently in COVID-19. More importance should be given to the identification and quarantine of asymptomatic patients to eliminate COVID-19 transmission and to allow for the early diagnosis of pre-symptomatic patients.

Keywords: COVID-19, SARS-CoV-2, pre-symptomatic, asymptomatic, control

INTRODUCTION

In late December 2019, a series of unexplained pneumonia cases were identified in Wuhan, China, which attracted the attention of health officials. As a result of studies, a new coronavirus (2019-nCoV) was identified by Chinese scientists on January 7, 2020. At the same time, the International Committee on Taxonomy of Viruses (ICTV) declared that the new coronavirus to be severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). The World Health Organization announced "COVID-19" as the name of this new disease on February 11, 2020.[1] Globally so far, nearly 145 million people have been infected with COVID-19, and more than 3 million people have died.[2] Drug and vaccination studies on this subject are ongoing. In the absence of effective treatment, the key points to control COVID-19 rests on the

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early recognition and containment of an infected person, and the interruption of transmission.[1]

COVID-19 is a complicated illness with a broad spectrum of clinical patterns. Although approximately 20% of patients progress with moderate or severe disease, some remain asymptomatic.[3] Asymptomatic infections have no certain incubation period owing to the absence of clinical signs.[4] Knowing the frequency of asymptomatic infections will allow for a comprehension of the epidemiological capability of COVID-19 transmission and the genuine universality of the illness.

As reported in the literature, the incidence of asymptomatic carriers ranges from 1.6% to 51.7%.[1]

Asymptomatic patients with SARS-CoV-2 infection may become symptomatic during follow-up.[5] Asymptomatic patients are not low in their capacity to spread the infection and these patients are likely to give rise to new rounds of outbreaks. Thus, the detection of asymptomatic infections is the central issue for the early prevention and control of COVID-19 around the world.[6,7]

This study aimed to assess the demographic, clinical and laboratory findings of symptomatic and asymptomatic patients admitted to our university hospital with a diagnosis of COVID-19.

MATERIALS AND METHODS

Study Design and Patients

The study was conducted retrospectively in the Faculty of Medicine of Erciyes University. Patients who were asymptomatic or symptomatic and followed up at home or in the hospital between March 15, 2020 and May 23, 2020 were included in this study. Case definitions were made according to the Republic of Turkey Ministry of Health guidelines.[8]

Data Collection

Epidemiological, demographic, clinical, laboratory, treatment, and outcome data were obtained from the hospital's electronic records. In addition, chest computed tomography (CT) findings of the patients before treatment were recorded.

Definitions

Asymptomatic infection: Patient samples were positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction test (RT-PCR), and the absence of typical clinical symptoms or signs.

People who were close contacts of those patients diagnosed with COVID-19 in our hospital were screened by performing a COVID-19 PCR test and thus, asymptomatic patients were found.

Symptomatic infection: Patient samples were positive for SARS-CoV-2 by RT-PCR in conjunction with the typical clinical symptoms and signs.

Pre-symptomatic infection: Asymptomatic infection at admission and development of typical clinical symptoms and signs during follow-up.

Typical findings in chest CT:

- Peripheral, bilateral (multilobar) ground glass areas
- Multifocal ground glass areas (consolidation, crazy paving pattern can also be seen)

Atypical findings in chest CT

- Round or non-peripheral multifocal, diffuse, perihilar or unilateral ground glass areas
- Lobar or segmental consolidation or tree in bud view without areas of ground glass
- Cavitation
- Pleural effusion with interlobular septal thickening

Normal chest CT: No finding of pneumonia.[8]

Laboratory Procedures

Laboratory data include complete blood cell count, renal and liver function, creatine kinase, lactate dehydrogenase, electrolytes, coagulation profile (prothrombin time, active thromboplastin time,

INR, D-dimer and fibrinogen), myocardial enzymes, serum ferritin, CRP, procalcitonin and these were monitored periodically. Combined throat/nasal swab samples were tested for SARS-CoV-2 RNA.

Trained personnel collected the nasopharyngeal/oropharyngeal swabs and transferred the samples onto viral transport media. The SARS-CoV-2 RNA from these samples was determined using the Biospeedy COVID-19 RT-PCR kit (Bioeksen R&D Technologies Ltd., Republic of Turkey Ministry of Health, Istanbul, Turkey) according to the manufacturer's protocols. All tests were carried out with the Roto-Gene platform (Qiagen, Hilden, Germany).

From those whom combined nose and throat swab samples were taken:

- Patients who were possible cases and were admitted to our hospital.[8]
- Patients whose first COVID-19 PCR result was negative, but clinically, laboratory or
- Radiologically were likely to be considered COVID-19 (with 24-hour intervals) and those
- Patients with positive COVID-19 PCR results included in this study.
- A control COVID-19 PCR sample was taken from patients with stable vital signs for 72 hours during treatment.
- For patients with a positive PCR results and whose treatment was completed, a PCR scan was
- Performed every 48 hours until a negative result was obtained.
- Patients whose positive PCR test turned negative were discharged.

In each case, symptoms such as fever, cough, nasal congestion, dizziness, fatigue, shortness of breath, arthralgia, etc. that occurred during their hospitalization were recorded.

Statistical Analysis

Histogram, q-q plots and Shapiro–Wilk's test were examined to assess the data normality. The Levene test was used to test variance homogeneity. To compare the differences between the symptomatic and non-symptomatic groups, either independent two samples t-test or Mann–Whitney U tests were applied for continuous

variables, Pearson chi-square analysis or Fisher's exact test were applied for categorical variables. Kaplan–Meier plots were generated to compare the survival probabilities between the patient groups. Additionally, univariate and multiple Cox proportional hazards regression analysis were conducted to identify the risk factors of survival time. Significant variables at $p<0.05$ were included into a multiple model and forward elimination was performed using Wald statistic.

The proportional hazards assumption was assessed using Schoenfeld residuals. Hazard ratios were calculated with 95% confidence intervals. The Hosmer–Lemeshow test was used to assess the goodness of fit of the built model. To check for multiple testing, all p-values were adjusted using the Benjamini–Hochberg procedure. Adjusted p-values less than 5% were considered to be statistically significant. All analyses were conducted using R 3.5.1 (www.r-project.org) and TURCOSA (Turcosa Analytics Ltd. Co., Turkey, www.turcosa.com.tr) software.

Ethical Consideration

The study was approved by the Research Ethics Commission of University of Erciyes, Turkey (2020/357-2020.07.08).

RESULTS

Demographic Characteristics

In the planned study interval, 1157 patients admitted to our hospital were possible cases and 165 of them were determined as definite cases and were incorporated into this study. The flow diagram of the patients enrolled in this study is shown in Figure 1. Of these patients, 21 (12.7%) were asymptomatic and 144 (87.2%) were symptomatic. The demographic data of these two groups are shown in Table 1. The median age of the patients was 46 years and a preponderance of them was male (53%).

Asymptomatic patients had a lower median age than symptomatic patients, and there was no asymptomatic patient over 65 years. According to age, there was no significant differences between the groups ($p=0.114$). Twenty-seven (12.7%) patients were healthcare workers [5 (23.8%) of the asymptomatic patients and 16 (11.1%) of symptomatic patients]. There were 10 (6.1%) patients with a travel history abroad in the prior 14 days and all of them were symptomatic. From all of the patients, 41.8% had a history of exposure with cases diagnosed with COVID-19 in their family or at work and this rate was significantly higher in the symptomatic patients (71.4%) ($p<0.05$). There were 52 (31.5%) patients with a minimum of one comorbidity. The most frequent comorbidities were hypertension (18.2%), diabetes mellitus (DM) (12.7%) and coronary artery disease (CAD) (9.7%).

Distribution of Symptoms in COVID-19 Patients

The symptom distribution of those patients who were symptomatic at the time of admission is shown in Figure 2. Among the 144 symptomatic patients, the most common symptom was coughing (63.2%).

Other symptoms were fever (55,6%), dyspnoea (31.3%), myalgia (30.6%), sore throat (29.9%) and headache (17.4%). Twenty-one patients were asymptomatic at admission, but four of them developed symptoms in the follow-up. The demographic, clinical and laboratory findings of pre-symptomatic patients are shown in Table 2. Among them, 75% of these patients were 50 years or older and were male. Two patients had at least one comorbidity and one patient who became symptomatic had a history of malignancy. No significant difference was found when laboratory findings (lymphocyte count, CRP, D-dimer) were observed at the time of admission. Only the patient with malignancy had a high level of CRP (70 mg/L). Three pre-symptomatic patients were found to have abnormal chest CT findings. Invasive mechanical ventilation was needed for just one patient who had malignancy but it was not fatal.

Laboratory and Radiologic findings

A comparison of first admission laboratory and radiological findings between the symptomatic and asymptomatic groups is shown in Table 3. Whereas the white blood cell (WBC) and lymphocyte counts were within the normal range for all patients, the asymptomatic patients had a significantly higher WBC and lymphocyte count than the symptomatic patients. The symptomatic patients had higher median CRP levels than the asymptomatic patients and there was statistically significant difference between the two groups ($p<0.05$). When the radiological findings of all the patients were evaluated, 115 (69.7%) were typical for COVID-19, 26 (15.8%) were normal and 18 (10.9%) were atypical. For the typical CT findings for COVID-19, there were fewer in the asymptomatic infections (12 cases, 57.1%) than those in the symptomatic infections (103 cases, 71.5%). Among the 21 asymptomatic patients, 13 (61.9%) had abnormal radiological findings and 8 (38.1%) patients had no signs of pneumonia on chest CT. There was no significant difference between the symptomatic and asymptomatic patient groups in terms of age, gender, comorbidity, laboratory findings (except CRP levels) or prognosis.

Treatment and Prognosis

A comparison of the treatment and prognosis between the symptomatic and asymptomatic groups is shown in Table 4. Almost all of the patients (98.8%) received hydroxychloroquine treatment. Favipiravir treatment rates were higher in the symptomatic patients ($p<0.05$). There was no significant difference for other antiviral or antibacterial treatment rates in these groups. The median duration of hospitalization was 7 days and it was higher in the symptomatic patients ($p<0.05$). There were 17 (10%) patients in need of intensive care and the mortality rate was 6.1%. Invasive mechanical ventilation was needed for just one asymptomatic patient, but it was not fatal. No significant difference in terms of the

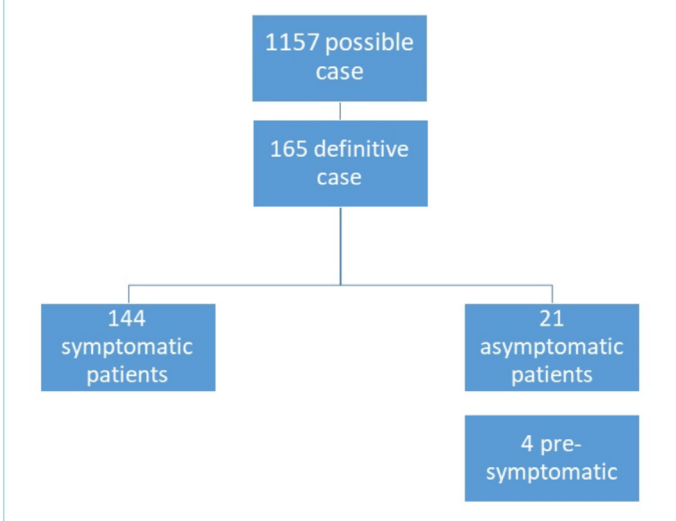

Figure 1. Flow diagram of patients enrolled in this study.

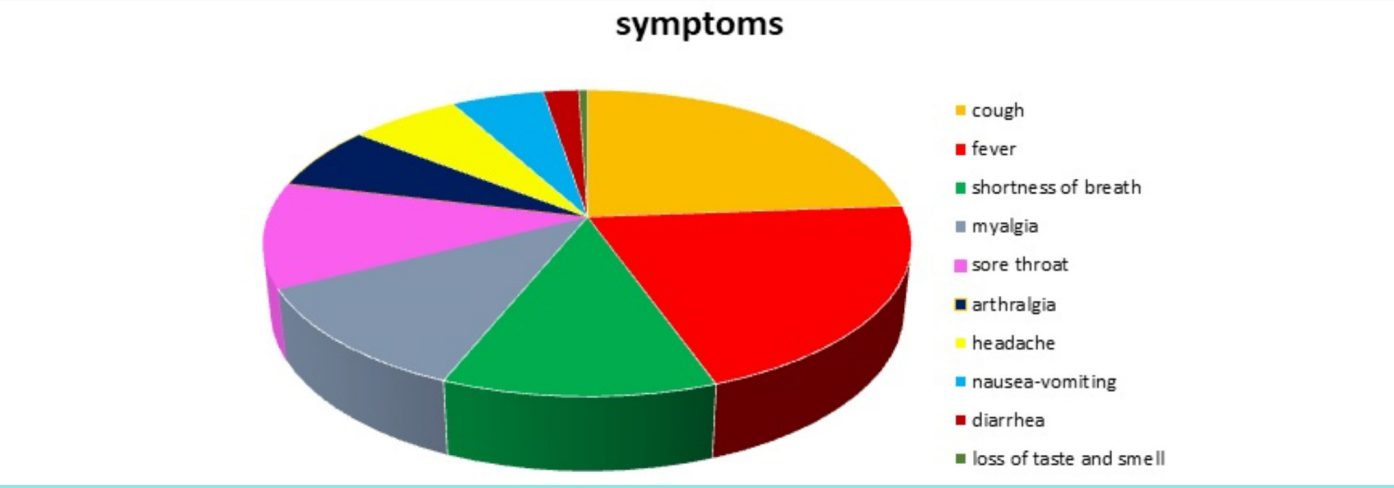

Figure 2. Symptom distribution of patients diagnosed with COVID-19.
COVID-19: coronavirus disease-2019

presence of nosocomial infection, invasive mechanical ventilation, and mortality between these two groups was found.

DISCUSSION

Asymptomatic carriers have a significant role in the spread of COVID-19 disease.[9]

Asymptomatic patients are a silent source of infection, who can unknowingly place others at risk of infection as they have fewer admissions to hospital. Therefore, they can lead to a global increase in morbidity and mortality with the expansion of the pandemic.[1,10] Identifying asymptomatic patients is one of the most important strategies in disease control. This study included 165 COVID-19 patients and 21 (12.7%) of them were asymptomatic at admission. In a study conducted in 72,314 patients in China, 1.6% were found to be asymptomatic, whereas another study found that the incidence of asymptomatic infection was 30.8% in 565 Japanese people who were evacuated from Wuhan. The incidence of asymptomatic patients on the "Diamond Princess" ship, which was quarantined in early February, 2020 due to COVID-19 disease, was found to be 51.7%. In these last two studies, it has been suggested that the reason for the higher incidence is close contact in a certain closed area.[1]

In this study, the median age of the symptomatic patients was higher than the asymptomatic patients, but there was no significant difference between these groups. Also, there were no asymptomatic patients over 65 years of age. In previous studies comparing the demographic data of asymptomatic and symptomatic patients with COVID-19, asymptomatic patients were younger than the symptomatic ones.[11,12] In the literature, people with comorbidity or the elderly are more vulnerable to serious diseases.[13,14] There were 52 (31.5%) patients with a minimum of one comorbidity in this study. The most frequent comorbidities were hypertension (18.2%), DM (12.7%) and CAD (9.7%). There was no significant difference in terms of comorbidities between our groups.

Among the 165 patients with COVID-19, cough was the most common symptom (63.2%) and the second was fever with a rate of 55.6%. More than 370,000 patients diagnosed with COVID-19 in the United States

Table 1. Comparison of patient characteristics between symptomatic and asymptomatic groups

Variables	Asymptomatic (n=21)	Symptomatic (n=144)	Total (n=165)	p-value	adj.p
Age (years)	42.38±11.33	47.01±16.99	46.42±16.42	0.114	0.277
Over 50 years old	6 (28.6)	61 (42.4)	67 (40.6)	0.229	0.360
Over 65 years old	0 (0.0)	25 (17.4)	25 (15.2)	**0.046**	0.253
Male (gender)	13 (61.9)	75 (52.1)	88 (53.3)	0.399	0.488
Healthcare worker	5 (23.8)	16 (11.1)	21 (12.7)	0.151	0.277
Imported cases	0 (0.0)	10 (6.9)	10 (6.1)	0.364	0.488
Exposure history	15 (71.4)	54 (37.5)	69 (41.8)	**0.003**	0.033
Comorbidity	3 (14.3)	49 (34.0)	52 (31.5)	0.069	0.253
Hypertension	1 (4.8)	29 (20.1)	30 (18.2)	0.128	0.277
Diabetes mellitus	1 (4.8)	20 (13.9)	21 (12.7)	0.480	0.528
Coronary heath diseases	1 (4.8)	15 (10.4)	16 (9.7)	0.696	0.696

Values are expressed as n (%) or mean ± SD, significant p-values are shown in bold.
SD: standard deviation, n: number.

Table 2. Characteristics of pre-symptomatic patients

Variables	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	50	39	56	57
Gender	Male	Male	Male	Female
Days of hospitalization	5	6	60	18
Exposure history	Yes	Yes	No	No
Any pre-existing comorbidity	Yes	No	Yes	Yes
Comorbidities	HT, CAD	No	Malignancy	DM
The median duration of PCR negativization	20	5	20	10
Symptom	Cough-weakness	Myalgia	Fever-dyspnoea	Fever
Thorax CT finding	No	Typical	Typical	Typical
WBC (x10³/µL)	3950	6450	2220	6330
Lymphocyte count (x10³/µL)	1080	1880	1580	1280
Lactate dehydrogenase (u/L)	223	190	243	150
D-dimer (µg/L)	290	420	420	250
CRP (mg/L)	2,30	5,32	70,16	24,43
Treatment	Hydroxychloroquine + Azithromycin	Hydroxychloroquine + Azithromycin +Oseltamivir	Hydroxychloroquine + Azithromycin +Favipiravir+ Oseltamivir	Hydroxychloroquine + Azithromycin +Oseltamivir
Nosocomial infection	No	No	Yes	No
Intubation	No	No	Yes	No
Intensive care unit	No	No	Yes	No
Outcome	Discharge	Discharge	Discharge	Discharge

HT: hypertension, CAD: coronary artery diseases, DM: diabetes mellitus, PCR: polymerase chain reaction,WBC: white blood cell, CT: computed tomography, CRP: C-reactive protein.

reported to the Centers for Disease Control and Prevention (CDC) and the most common symptoms were cough (50%), fever (43%), myalgia (36%), headache (34%), and dyspnea (29%).[15] Similar frequencies of clinical findings were found in other studies.[13,16] Of our patients, twenty-one were asymptomatic at admission, but four of them (19%) developed symptoms during follow-up. These symptoms were similar to those of the symptomatic patients. In a skilled nursing facility, 27 (56%) of 48 confirmed COVID-19 cases were classified as asymptomatic at the time of diagnosis. However, 24 of them developed symptoms within 7 days of their follow-up.[5]

A study conducted in a nursing home in the United States showed that 23 novel coronary pneumonia virus RT-PCR tests were positive, 10 were symptomatic and 13 were asymptomatic.

Among them, 10 patients were reported to have developed symptoms within 7 days of testing and three of them with positive test results continued to be asymptomatic, suggesting that hidden infections account for approximately 13% (3/23) of the total number of infections.[17] As a result of these studies, it can be stated that, the earlier that testing is performed, the higher the rate of detected asymptomatic infections will be. In China, a total of 81,802 COVID-19 cases were reported as of April 7, 2020 and 1,190 of them were asymptomatic and 1095 of these asymptomatic patients were under follow-up. In the light of these results, the frequency of "true" asymptomatic infection was found to be between 1.5 % and 2.8%. On the other hand, the authors emphasized that this is unlikely to show the true prevalence of asymptomatic infection. The rate of asymptomatic case detection was found to be high due to the careful follow-up of close contacts.[9] Therefore, it is essential to follow asymptomatic patients, as they may not be true asymptomatic cases.

When the laboratory findings of all the patients were compared, WBC and lymphocyte values were within the normal range and the asymptomatic patients had a significantly higher WBC and lymphocyte counts than the symptomatic patients. Similarly, another study reported that WBC and lymphocyte count levels were significantly higher in asymptomatic infections than in symptomatic patients which confirmed that the lymphocyte count was important in clearing the virus.[11,12] Previous studies showed that CRP levels may be considered as a determinant of disease severity.[7,18] Considering our data, the CRP levels were found to be significantly higher in the symptomatic patients.

In our study, approximately 70% of the patients had typical radiological findings for COVID-19.

The proportion of asymptomatic patients with typical CT findings for COVID-19 was close to

the symptomatic patients (57.1%, 71.5% respectively). As a result, there was also a significant presence of tomography findings in those patients without clinical symptoms and they should be tested for COVID-19. Recent studies support this inference. In one study that included 24 asymptomatic patients, 50% had findings of ground-glass or patchy shadows in the lungs and 20% had atypical imaging abnormalities.[6] In a similar study of 55 patients with asymptomatic infection, 67% were found to have pneumonia on admission; only two patients developed hypoxia, and all were discharged.[7] The close follow-up of asymptomatic patients with radiological findings on chest tomography at admission is recommended for progression.

Table 3. Comparison of admission laboratory and radiological findings between symptomatic and asymptomatic groups

Variables	Asymptomati (n=21)	Symptomatic (n=144)	Total (n=165)	p-value	adj.p
WBC (x10³/µL)	6130 (4690–7300)	5745 (4735-7218)	5810(4740-7215)	0.870	0.979
Lymphocyte count (x10³/µL)	1640 (1285–2425)	1490 (1100-1927.5)	1520(1105-1960)	0.145	0.447
Neutrophil count (x10³/µL)	3540 (2525–4980)	3580 (2833-4653)	3580(2710-4645)	0.694	0.807
Hemoglobin (g/L)	14.15±1.81	13.94±1.74	13.97±1.74	0.602	0.807
Platelet count	247,000 (193,000–320,000)	230,000 (187,250–296,750)	230,000 (189,000–299,500)	0.303	0.671
Aspartate aminotransferase (u/L)	22.0 (17.5-27.5)	22.0 (17.0–32.0)	22.0 (17.0–31.0)	0.736	0.807
Alanine aminotransferase (u/L)	22.0 (15.5–36.7)	21.0 (14.9–29.0)	21.0 (15.0–30.0)	0.373	0.671
Lactate dehydrogenase (u/L)	210 (167–236)	203 (174–244)	203 (172–242)	0.637	0.807
Troponin (ng/mL)	0.004 (0.003–0.006)	0.005 (0.003–0.007)	0.0045 (0.003–0.007)	0.369	0.671
Creatine kinase (U/L)	83.0 (57.8–95.8)	84.0 (52.5–111.0)	84.0 (54.0–110.0)	0.979	0.979
Fibrinogen (mg/dL)	368.0 (312.0–418.5)	347.0 (270.5–473.8)	353.0 (278.0–455.0)	0.728	0.807
D-dimer (µg/L)	370 (235–420)	410 (250–610)	385 (250–590)	0.149	0.447
Ferritin (ng/mL)	192.0 (89.0–343.5)	219.5 (130.8–457.3)	210.0 (124.5–432.5)	0.573	0.807
CRP (mg/ L)	4.25 (1.47–7.49)	10.10 (3.13–37.15)	8.82 (2.77–31.45)	**0.006**	0.108
Procalcitonin (ng/mL)	0.030 (0.020–0.045)	0.050 (0.030–0.090)	0.040 (0.030–0.083)	0.057	0.266
Blood urea nitrogen (mg/dL)	12.0 (11.0–15.5)	12.0 (9.5–16.2)	12.0 (9.7–16.0)	0.762	0.807
Creatinine (mg/dL)	0.80 (0.67–1.00)	0.84 (0.70–1.04)	0.83 (0.70–1.03)	0.333	0.671
Triglyceride (mg/dL)	173.0 (138.5–206.5)	128.5 (92.3–173.5)	136.0 (94.0–178.0)	0.059	0.266
Torax CT finding					
No CT	0 (0.0)	6 (4.2)	6 (3.6)		
Normal	8 (38.1)	18 (12.5)	26 (15.8)		
Atypical	1 (4.8)	17 (11.8)	18 (10.9)	**0.020**	0.180
Typical	12 (57.1)	103 (71.5)	115 (69.7)		
Asymptomatic patientwith typical CT finding	13 (61.9)	-	-	-	

Values are expressed as n (%), mean ± SD or median (1st–3rd quartiles), significant p-values are shown in bold.
SD: standard deviation, WBC: white blood cell, CT: computed tomography, n: number.

Table 4. Comparison of treatment and prognosis related variables between symptomatic and asymptomatic groups

Variables	Asymptomatic (n=21)	Symptomatic (n=144)	Total (n=165)	p-value	adj.p
Hydroxychloroquine	21 (100.0)	142 (98.6)	163 (98.8)	0.999	0.999
Azithromycin	11 (52.4)	91 (63.2)	102 (61.8)	0.341	0.686
Favipiravir	1 (4.8)	36 (25.0)	37 (22.4)	**0.047**	0.259
Oseltamivir	7 (33.3)	67 (46.5)	74 (44.8)	0.256	0.686
The median duration of PCR negativization	6 (5-16.5)	6 (5-8)	6 (5-8.8)	0.168	0.581
Days of hospitalization	6 (3.5-7)	8 (6-11)	7 (5-11)	**0.004**	0.044
Nosocomial infection	2 (11.1)	10 (7.5)	12 (7.9)	0.636	0.999
Prone position	1 (5.20)	20 (17.5)	21 (15.9)	0.304	0.686
Intensive care unit	1 (4.8)	16 (11.1)	17 (10.3)	0.700	0.999
Intubation	1 (4.8)	11 (7.6)	12 (7.3)	0.999	0.999
Mortality	0 (0.0)	10 (6.9)	10 (6.1)	0.364	0.686

Values are expressed as n (%) or median (1st–3rd quartiles), significant p-values are shown in bold.
PCR: polymerase chain reaction, n: number.

CONCLUSION

In summary, we compared the demographic, clinical and laboratory findings of symptomatic and asymptomatic patients confirmed with COVID-19 in our university. In the light of this information, those with an absence of lymphopenia and low CRP levels are more likely to have the disease asymptomatically. Due to the high risk of the silent spread of the disease by asymptomatic people, testing programs should include those without symptoms. More importance should be given to the identification and quarantine of asymptomatic patients in order to eliminate COVID-19 transmission and to allow for the early diagnosis of pre-symptomatic patients. Transmission can be greatly reduced if both asymptomatic and symptomatic patients can be appropriately quarantined.

MAIN POINTS

- The detection of asymptomatic infections is the central issue for the early prevention and control of COVID-19 around the world.
- Asymptomatic patients at admission may develop symptoms in follow-up. When earlier tests are performed for possible cases, the rate of asymptomatic infections will be seen to increase.
- Those of younger age, with an absence of lymphopenia, low CRP levels, and no signs of pneumonia on chest CT are more likely to have the disease asymptomatically.

ETHICS

Ethics Committee Approval: The study was approved by the Research Ethics Commission of the University of Erciyes, Turkey (2020/357-2020.07.08).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.İ., Z.T., Design: F.İ., Z.T., B.B.K., Supervision: G.Z., B.A., O.Y., Data Collection and/or Processing: F.İ., Z.T., G.K.Ü., B.B.K., Analysis and/or Interpretation: F.İ., Z.T., G.K.Ü., Literature Search: F.İ., Z.T., B.A., O.Y., Writing: F.İ., Z.T., G.Z., Critical Review: B.A., O.Y.

DISCLOSURES

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

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ORIGINAL ARTICLE

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Long-Term Results of the Arthroscopic Meniscectomy Following Non-Traumatic Tears Due to Mucoid Degeneration and Traumatic Tears

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ABSTRACT

BACKGROUND/AIM: In this study, we aimed to radiologically and clinically compare the long-term results of arthroscopic meniscectomy in patients with non-traumatic meniscal tears due to mucoid degeneration (MD) (Group A) and those with traumatic tears (Group B). MD of the meniscus may indicate degenerative osteoarthritis (OA) of the knee or it may be a manifestation of a tendency to OA. Hence, non-traumatic meniscal tears of the knees treated with arthroscopic meniscectomy are more likely to develop into degenerative OA.

MATERIALS AND METHODS: A total of 38 patients (Group A: n=20 and Group B: n=18) aged 18 to 45 years, who underwent arthroscopic meniscectomy between 1995 and 2005, with an average follow-up period of 15 years (range: 11–21 years) were retrospectively analyzed. A senior orthopedic surgeon's arthroscopic database was used. The Lysholm score was used for the clinical comparison between the study groups. Radiographic changes were graded using the Kellgren–Lawrence classification of knee OA.

RESULTS: The demographic features and treatment protocols were the same for both groups. After a mean 15-year follow-up, the Lysholm score was found to increase following arthroscopic meniscectomy. Radiographic evaluation revealed grade 1 early degenerative changes in both groups according to the Kellgren–Lawrence classification.

CONCLUSION: The clinical and radiological outcomes of both the study groups were statistically similar in terms of clinical recovery and radiographic degenerative findings.

Keywords: Meniscus mucoid degeneration, knee trauma, sports injury

INTRODUCTION

The menisci play a critical role in knee biomechanics, including in the prevention of articular degenerative changes.[1,2] Other crucial functions of these fibrocartilaginous structures include shock absorption, load distribution, enhancing articular viscosity, contributing to knee stability, and proprioception.[3-5]

Meniscal tears usually develop as a result of knee trauma in young people; tears may also develop without any significant trauma in some cases. However, non-traumatic tears have not received much attention in the literature.[6] Degenerative lesions of the meniscal tissues can be classified as dystrophic or metastatic calcifications, hyaline acellular degeneration, or mucoid degeneration (MD).[7] MD of the meniscus should therefore be suspected when the meniscus is torn in a young healthy knee without any history of significant trauma. MD is characterized by an excessive accumulation of proteoglycan fragments in the interstitial tissue of the menisci.[6,8] Despite its relatively common occurrence, it has received little attention in the literature and its etiology remains

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uncertain. Therefore, more emphasis on MD is deemed necessary owing to its tendency to cause the loss of the meniscus, depending on the type of the tear. A previous study conducted at our department revealed that advanced stages of meniscal MD are correlated with increased proteoglycan fragment concentrations in the synovial fluid. Our findings suggest that this correlation may be associated with the degenerative processes occurring in the joint.[8]

In selected cases, arthroscopic partial meniscectomy has been accepted as the standard treatment of certain choices for meniscal tears, when preservation is not possible.[9,10] However, several studies with long-term follow-ups (>10 years) have shown that arthroscopic meniscectomy increases the risk of degenerative changes in the knee joint and has adverse effects on the functional and clinical outcomes.[2,11,12] Subtotal meniscectomy has also been known to be associated with early degenerative changes in the knee joint to a lesser extent in comparison to total meniscectomy. Hede et al.[13] reported on the long-term results of partial and total meniscectomies in a randomized controlled study and revealed that the size of a resected meniscal tissue is correlated with a decrease in the functional outcomes of the knee. Another study also proved that meniscectomy causes irreversible damage to the knee joint.[4,12]

The present study aimed to compare the clinical and radiological outcomes of arthroscopic meniscectomy in patients with non-traumatic meniscal tears due to MD (Group A) and those with traumatic tears (Group B). Therefore, the hypothesis of this study is that non-traumatic meniscal tears due to MD have worse clinical and radiological outcomes than traumatic tears.

MATERIALS AND METHODS

A total of 38 patients aged 18–45 years who were treated arthroscopically by a senior orthopedic surgeon in our clinic between 1995 and 2005 and who had visited the outpatient clinic within the previous 2 years were included in our study (we requested our patients to visit for follow-up every 4 or 5 years in the period 5 years after the operation). Patients were selected for this study using the senior orthopedic surgeon's patient archive. All patients were diagnosed, treated, and followed up by a single surgeon. MD was diagnosed clinically during the operation. Those patients with a history of anterior cruciate ligament rupture and meniscal repair, those with a repeat surgery on the same knee, and those lacking preoperative and postoperative evaluation as well as non-ambulatory care were excluded from this study.

Among the patients with cartilage lesions detected during arthroscopic meniscectomy, debridement with a shaver was applied to Outherbridge grade 1 and 2 patients and microfractures were applied to grade 3 and 4 patients. Patients who had microfractures as a result of arthroscopic meniscectomy were advised to perform a range of motion exercises for 4 weeks without weight, whereas the other patients were allowed to move with full weight.

When the patients visited the outpatient clinic, their examinations and X-ray evaluations were conducted by an orthopedic surgeon and a senior orthopedic assistant. A total of 20 patients with non-traumatic meniscal tears due to MD were assigned to Group A and 18 patients with traumatic meniscal tears were assigned to Group B (Figure 1).

In this study, the patients in both groups A and B were evaluated in terms of age, sex, body mass index (BMI; kg/m^2), time to follow-up, duration of complaints, physical examination, knee-related radiological and functional scores, and their preoperative and postoperative Lysholm scores.

Approval for this study was obtained from the Non-Interventional Ethics Committee of Dokuz Eylül University decision no: 2015/27-19, date: 03.12.2015).

Statistical Analysis

Firstly, the patients in the two groups were compared in terms of their age, BMI, follow-up times, duration of complaints, and their affected knee. Parametric and nonparametric data between the two groups were compared both within and between the groups. Gender, operated side of the knee, duration of complaint, follow-up duration, preoperative cartilage lesions, postoperative physical examination findings, Kellgren–Lawrence classification, and the type of operation performed were evaluated using the Chi-Square test. Preoperative and postoperative Lysholm scores were evaluated using the Wilcoxon test. BMI was evaluated using the student's-test. A p-value of <0.05 was considered statistically significant.

SPSS 22.0 statistical analysis software (IBM, Chicago, IL, USA) was used for all analyses.

RESULTS

A total of 38 patients, including 20 patients with meniscal tears without trauma (Group A) and 18 patients with traumatic meniscal tears (Group B), were evaluated. The mean distribution of age, gender,

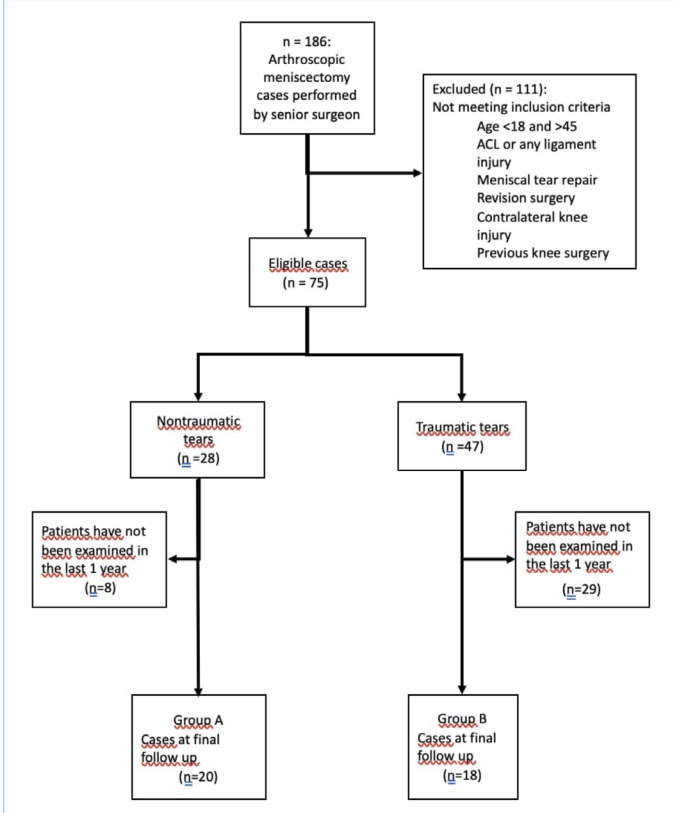

Figure 1. The patient selection scheme used in the study.
ACL: anterior cruciate ligament, n: number

BMI, and follow-up period in both the groups was similar. The average duration of complaints in Group A and Group B was 24.5 and 8.3 months, respectively (p=0.013). The involvement of menisci and tear localization was similar in both the groups (p=0.387 and p=0.127, respectively) (Table 1). The distribution of side meniscal tears and localization meniscal tears was also similar (Table 2). Regarding the type of arthroscopic meniscal resection, 16 partial and four subtotal meniscectomies were performed in Group A and 11 partial, six subtotal, and 1 total meniscectomies were performed in Group B; hence, no significant difference was noted between the groups ($p_{chi\text{-}squared}$=0.32). Chondral lesions according to the Outerbridge classification system were similar between the two groups ($p_{chi\text{-}squared}$=0.152). Groups A and B showed similar outcomes in terms of the location of the cartilage lesions (femur, tibia, and patella) ($p_{chi\text{-}squared}$=0.712; Table 3). Cartilage lesions were treated as described in the method section. Joint line tenderness was positive in eight patients in Group A and in 10 patients in Group B. However, no significant difference was noted between the two groups (p=0.338).

According to the Kellgren–Lawrence classification system, 15 patients (39.5%) were classified as grade 0, nine patients (23.7%) as grade 1, six patients (15.8%) as grade 2, three patients (7.9%) as grade 3, and one patient (2.6%) as grade 4. The Kellgren–Lawrence grade at the follow-up showed a mean value of 1±1.1 for Group A and 1±1.2 for Group B. No significant difference was noted between the two groups according to Kellgren–Lawrence (p=0.72) classification.

Lysholm scores significantly improved in both groups at follow-up. In addition, the results were found to be similar in both groups at follow-up (p=0.609) (Table 4). Evaluation of the final control Lysholm scores revealed 65% excellent and 35% good results in Group A, 72.7% excellent and 22.8% good results in Group B, and 68.4% excellent and 28.9% good results for all patients (Table 5).

DISCUSSION

In this study, improvement in the postoperative Lysholm scores was noted in both groups, but no statistical significance was detected between the groups in terms of radiological and clinical results. As a result, recovery was recorded in both groups after 15 years of follow-up. Radiologically, the Kellgren–Lawrence scores were also similar in both groups. During our research, we found no study on the comparison of the outcomes of traumatic and non-traumatic meniscus tears due to MD.

MD may lead to a loss of meniscus and result in early degenerative changes in the knee joint. Chatain et al.[14] reported that 5 years after arthroscopic meniscectomy, degenerative changes in the knee in patients aged >35 years were more common than those in younger patients. In another study by Burks et al.[15], 146 patients with a 15-year follow-up period were evaluated and it was concluded that age does that affect degenerative changes in the knee joint. The findings of the present study were similar to those reported by Chatain et al.[14] In the present study, the average age of the patients in Groups A and B was 35 years. Considering our follow-up period of 15 years, detection of early degenerative findings seems likely. When preoperative and follow-up ages were considered, radiographic changes seemed suggestive of early osteoarthritis (OA). Our study results are similar to those of Chatain et al.[14] Although they did not divide the patients into those with traumatic and those with non-traumatic meniscal tears, the lesion mechanism in the patients without a history of trauma could be traced to MD, as in our study.

In a prospective cohort study by Lizaur-Utrilla et al.[16], 258 patients underwent arthroscopic partial meniscectomy, including 115 patients with degenerative meniscal tears and 143 with traumatic tears. The patients belonged to the middle

Table 1. Demographic information of the patients

Demographic information	Group A (n=20)	Group B (n=18)	p-value
Age (year, median, min–max)	37.5 (18–42)	38.5 (19–44)	0.986*
BMI (kg/m², mean, SD)	28.5 (3.9)	28.2 (4.34)	0.813**
Follow-up (year, median, min–max)	15 (11–18)	14 (11–21)	0.929*
Gender			
Male	13(65%)	9(50%)	0.363
Female	7(35%)	9(50%)	
Average duration of complaints (months, mean)	24.5	8.3	**0.013**

*Mann–Whitney U test for comparison of non-parametric values, **t-test for comparison of parametric values.
Significant values are shown in bold.
min: minimum, max: maximum, SD: standard deviation.

Table 2. Distribution of meniscaltears of side and meniscaltears of localization

	Medial	Lateral	Medial-Lateral	
Group A	11	7	2	p=0.387
Group B	11	7	0	
	Anterior	**Middle**	**Middle-Posterior**	**Posterior**	
Group A	0	4	8	8	p=0.127
Group B	0	0	8	10	

Table 3. Cartilage lesions noted according to Outerbridge Classification and localization

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	
Group A	11	6	1	2	0	p=0.152
Group B	8	3	6	1	0	
	Normal	**Femur**	**Tibia**	**Patella**		
Group A	11	4	7	1		p=0.71
Group B	9	6	5	2		

Table 4. Lysholm Scores changes

Lysholm Score	Pre-operative	Post-operative	p-value
Group A (mean, SD)	74.7±9.7	87.1±11.2	p<0.001*
Group B (mean, SD)	67.8±18.4	85.1±13.3	p<0.001*

*paired t-test, SD: standard deviation.

age group (45–60 years) and had no or only mild signs of OA. In Lizaur-Utrilla et al.'s[16] study, parallel to our study, no radiological difference was found between the two groups. However, in their study, the mean age of the patients was higher, the follow-up periods were shorter, and whether or not the degenerative tears were based on MD was not specified. On the other hand, in a multicenter comparative prospective cohort study conducted by Thorlund et al.[17], 115 traumatic patients and 227 patients with degenerative meniscal tears aged 18–55 years who were treated with arthroscopic partial meniscectomy were followed up for approximately 1 year. After the 1-year follow-up, the functional recovery of the traumatic tears was found to be better than that of the degenerative tears.[17] Based on these previous studies, we can state that although the results of traumatic and degenerative meniscal tears treated with arthroscopic partial meniscectomy were more favorable for traumatic tears in the short term, no functional difference was noted in the long term.

Ferrer-Roca and Vilalta[7] stated that meniscal tears due to mucoid MD are usually horizontal, whereas Smillie[18] stated that MD usually leads to radial tears in the medial meniscus and horizontal tears in the lateral meniscus. In the present study, although statistically not significant, most of the tears in the MD group were found to be either horizontal or complex and slightly more common in the medial meniscus rather than in the lateral meniscus. In contrast to those in the MD group, traumatic meniscal lesions showed a tendency to be longitudinal and complex rather than horizontal.[19] Arthroscopically repaired menisci were excluded from the study.

Some long-term studies (>10 years)[2,11] on arthroscopic meniscectomy have reported that degenerative changes have negative effects on functional and clinical results. However, in short-term follow-up studies, arthroscopic meniscectomy reportedly relieved meniscal symptoms.[20,21] Rockborn and Gillquist[22], in their long-term study (a follow-up period of 12–15 years) of 60 meniscectomy patients aged 20–40 years, revealed significant degeneration radiologically, good functional scores, and an increased interest in active sports in comparison to the preoperative period. A detailed review of the findings of Rockborn and Gillquist[22] indicated similar results to those of the present study. In addition to the other studies mentioned earlier, this study was also a long-term study and early degenerative changes were detected in the knee joint; however, the functional and clinical outcomes of our study were satisfactory.

In a study by Hoser et al.[23], 29 patients with a history of arthroscopic meniscectomy and an average age of 43.8 years were followed up for approximately 10.3 years and their average Lysholm score was found to be 80.5±16.7. The authors grouped patients according to their Lysholm scores and reported 45.2% as excellent, 12.9% as good, 16.1% as fair, and 25.8% as poor outcomes. In the present study, the average postoperative Lysholm scores of groups A and B were 87.1 and 85.1, respectively. There was an increase in the scores when compared with the preoperative values indicating clinical recovery. When the Lysholm scores at follow-up were analyzed separately for the groups, the results were 65% as excellent and 35% as good in Group A and 72.7% as excellent, 22.8% as good, and 5.5% as poor in Group B. Overall, the results were 68.4% as excellent, 28.9% as good, and 2.6% as poor. Higher Lysholm scores in the present study than those in the study by Hoser et al.[23] may be attributed to a lower average age and the higher activity levels of our patients.

Limitations of the Study

To date, no study in the literature has compared degenerative meniscal tears due to MD with traumatic meniscus tears, which makes the long-term follow-up period in the present study the strength of this study. However, the retrospective nature of the study and small sample size are the weak points of this study.

CONCLUSION

We observed that 97% of the patients who had undergone arthroscopic meniscectomy with a mean follow-up of 15 years in this study had good or excellent outcomes and their long-term radiographical and clinical outcomes after arthroscopic meniscectomy were similar for those patients who had either traumatic or non-traumatic meniscal tears due to MD.

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Table 5. Lysholm Scores changes

Pre-op and post-op Lysholm Scores		Poor 0–20	Moderate 21–40	Moderate-Good 41–60	Good 61–80	Excellent 81–100
Group A	Pre-op	-	-	2 (10%)	12 (60%)	6 (30%)
	Post-op	-	-	-	7 (35%)	13 (65%)
Group B	Pre-op	1 (5.5%)	1 (5.5%)	3 (16.6%)	7 (38.8%)	6 (33.3%)
	Post-op	-	-	1 (5.5%)	4 (22.8%)	13 (77.7%)

Pre-op: pre-operative, Post-op: post-operative.

MAIN POINTS

- Meniscus MD, which causes meniscus tears in young patients with minor traumas, has been rarely studied.
- The long-term results of those patients who had undergone meniscectomy with the correct indication are good.
- When traumatic tears and tears due to MD were compared clinically and radiologically, no difference was found.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee of the Dokuz Eylül University Medical School (decision no: 2015/27-19, date: 03.12.2015).

Informed Consent: This study was designed and implemented resrospectively, no consent to participate.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Y.E.B., Design: Y.E.B., Supervision: H.P., Data Collection and/or Processing: Y.E.B., O.N.E., Analysis and/or Interpretation: Y.E.B., O.N.E., H.P., Literature Search: Y.E.B., O.N.E., H.P., Writing: Y.E.B., O.N.E., Editing: H.P.

DISCLOSURES

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

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CASE REPORT

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Pancreatic Ewing's Sarcoma Synchronously Diagnosed in a Patient of Carcinoma Cervix: A Case Report and Literature Review

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ABSTRACT

Extraosseous Ewing's sarcoma is a rare neoplasm. It has been reported in several sites such as the prostate, lungs, kidney, biliary tract, oral cavity, uterus, gonads, stomach, cervix, urinary bladder, vagina, and salivary glands. However, Ewing's sarcoma/primitive neuroectodermal tumors (ES/PNET) of the pancreas is an extremely unusual finding. Although there are a handful of pancreatic ES/PNET cases in the literature, our case intensifies the importance as it was diagnosed in a patient with carcinoma of the cervix. Our case aims to add value to the body of literature considering a second primary neoplasm of a rare entity at an unusual site.

Keywords: Pancreas, Ewing's sarcoma, synchronously, carcinoma, cervix

INTRODUCTION

Ewing's sarcoma/primitive neuroectodermal tumour (ES/PNET) is an unusual malignant neoplasm. In rare cases, PNETs may arise in solid organs that contain neuroendocrine cells. James Ewing first described Ewing's sarcoma (ES) in 1921, while the extra osseous Ewing's sarcoma or PNET was first described by Tefft in 1969.[1,2] ES/PNET comprises four subtypes: peripheral primitive neuroectodermal tumour (pPNET), Ewing's sarcoma of bone (ESB), Askin's tumour, and extraosseous Ewing's sarcoma (EES). ES/PNET has been reported in several case reports and series with unusual sites such as the salivary glands, oral cavity, adrenal gland, jejunum, pericardium, lung, stomach biliary tract, kidney, heart, prostate, cervix, vagina, gonads, uterine corpus, and pancreas.[3] Here, we report a rare case of ES/PNET in the pancreas of a 51-year old woman with synchronous carcinoma cervix. Reporting on such a rare form will help us in improving the characterization of the pathology, while contributing to cancer treatment advancement. In the future, it will also serve as guidance in the treatment of such rare cases.

CASE PRESENTATION

A 51-year-old female presented to our hospital in July 2018 with a history of vaginal bleeding accompanied with leukorrhea. She also complained of lower back pain.

Her speculum examination showed an ulceroproliferative growth over the cervix which bled on touch. Computed tomography (CT) revealed a large 7x6.8x6.6 cm mass lesion involving lower uterine segment and upper vagina with multiple iliac nodes. A biopsy was carried out. The patient was diagnosed with squamous cell carcinoma of the cervix (Figure 1A). On immunohistochemistry, tumour cells showed strong nuclear positivity for P40 (Figure 1B).

The patient completed concurrent radiotherapy (50 Gray in 25 fractions) along with five cycles of cisplatin. The patient also received three fractions of intracavitary brachytherapy.

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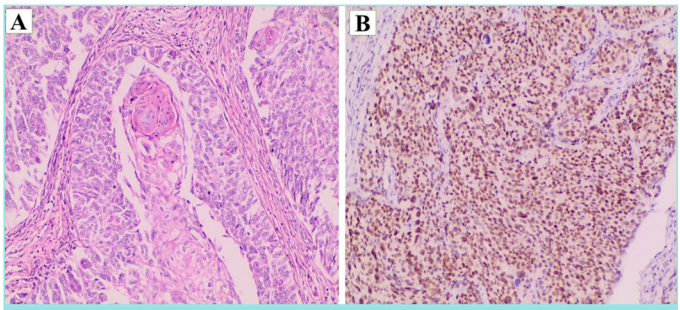

Figure 1. (A) H and E (20x) image from cervix showing diffuse sheets of cells having squamous differentiation infiltrating into surrounding connective tissue. **(B)** p40 IHC on cervix lesion showing nuclear positivity in the tumor cells.

Magnetic resonance imaging (MRI) was performed on routine follow-up after two months. A regression in the previously visualized cervical lesion was noted. There was a resolution of the previously mentioned pelvic nodes. A well-defined altered signal intensity heterogeneously enhancing tissue lesion measuring 58x44x50mm in size arising from the tail of the pancreas was noted. The possibility of a second primary of neoplastic origin rather than a metastatic one was suspected.

A whole body PET-CT scan showed a large FDG avid mass involving the tail of pancreas with metabolically active left para-aortic nodes just below the level of left renal hilum [maximum standardized uptake value (SUV_{max}): 12.7].

Tumour markers, CA-19.9 and carcinoembryonic antigen (CEA test) were tested to rule out pancreatic adenocarcinoma and were found to be within normal limits. Fine needle aspiration cytology (FNAC) was positive for malignant cells.

The patient underwent laparoscopic distal pancreatic splenectomy. Gross analysis of the specimen showed a pancreatic segment of 13x12x7.5 cm infiltrated by a vague nodular grey mass measuring 6.2x5.5x4 cm at the tail end.

On histology, the tumour showed diffuse sheets of round cells (Figure 2A). The tumour cells exhibited small round cells with a large central nucleus and scanty cytoplasm. (Figure 2B). The tumour cells showed minimal nuclear pleomorphism. Brisk mitosis was noted.

On immunohistochemistry, these tumour cells showed perinuclear dot-like positivity for Pan-CK (Figure 2C); CD99 (Mic-2) showed cytoplasmic membranous positivity (Figure 2D), and Fli-1 showed strong nuclear staining (Figure 2E). Immunohistochemically, the cells were negative for CD-56, Desmin, LCA, AR, ER, Cyclin D1. Hence the diagnosis of Ewing/PNET was made.

The patient had received one cycle of vincristine, doxorubicin (Adriamycin), and cyclophosphamide (VAC) and one cycle of ifosfamide and etoposide (IE). The patient is scheduled for three cycles of VAC and three cycles of IE followed by radiation therapy with vincristine. The patient is currently doing well.

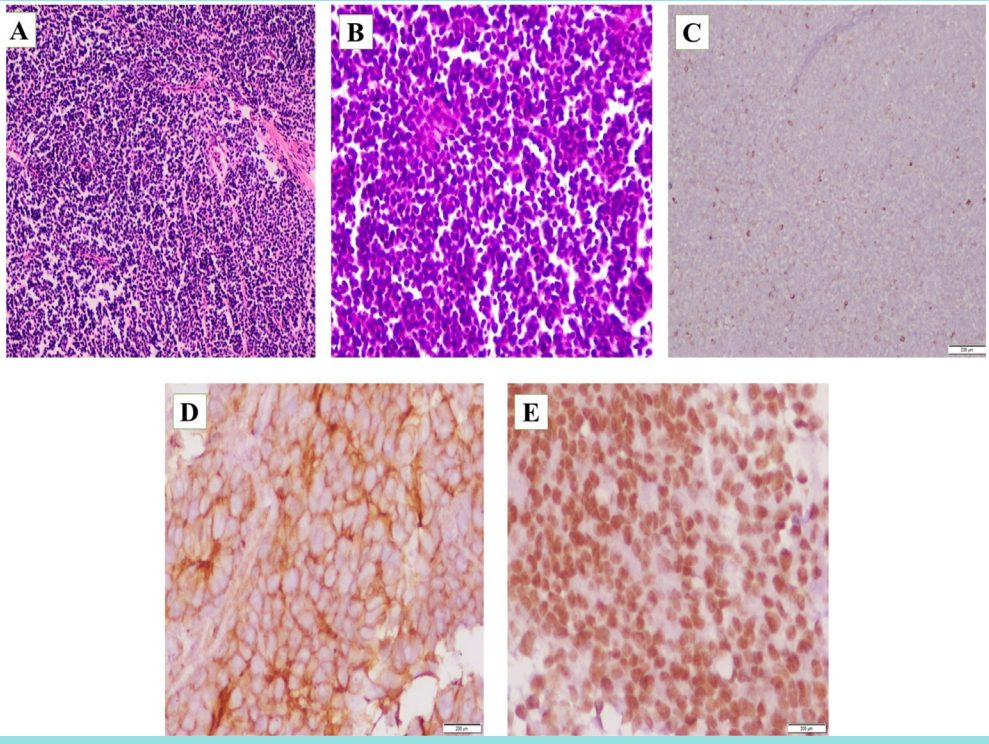

Figure 2. (A) H and E (10x) of pancreatic tumor showing diffuse sheets of round cells. **(B)** H and E (40x) of pancreatic tumor showing small round cells with large central nucleus and scanty cytoplasm. **(C)** PAN-CK: Tumor showing perinuclear dot like positivity. **(D)** CD99 showing cytoplasmic membranous positivity. **(E)** Fli-1 showing nuclear positivity.

p40 IHC: p40 Immunohistochemistry, PAN-CK: pan-CK, pan-cytokeratin

Table 1. Present and previous reported reports of Ewing sarcoma/peripheral primitive neuroectodermal tumours

No	Reported by (study type)	Site and nature	Clinical presentation	Radiologic diagnosis	Pathological	Immunohistochemistry	Diagnostic procedure	Cytogenetics
1.	Schutte and Knight[4] (case report)	Upper abdominal mass	Pubic hair, breast bud development, and vaginal bleeding	Enhancing mass lesion in the body of the pancreas	Venous and lymphatic vessel invasion	Negative - AEI/AE3. Moderate – EMA. Strong - Strong - SOM, Chromogranin A, S-100, VIM, CD99, ER, PR, and INB	Distal pancreatectomy	NR
2.	Movahedi-Lankarani et al.[6] (case series)	Head of the pancreas	Jaundice and/or abdominal pain	NR	Typical morphologic features of PNETs	Expressed O13 (CD99, p30/32MIC2)	Whipple resection, biopsy	Evidence of t(11;22)(q24;q12) chromosomal translocation
3.	Mao et al.[8], (case report)	Tumor grown superiorly to the infrahepatic space, postero-lateral aspect of the duodenum, and inferiorly to the hepatic flexure of colon	Mild abdominal pain, anorexia, polyuria, polydipsia, weight loss, and immobile firm mass that was tender to deep palpation	A large mass was seen between the liver, the pancreas and the right kidney with focal irregular intensification in the arterial period	a thin and flat neoplasm which was seen in the uncinate process of pancreas	Negative – SOM, ^{131}I-MIBI	Surgical resection	NR
4.	Kim et al.[9] (case series)	Body of the pancreas	Incidentally detected	Pancreatic cancer/ metastatic tumour/ neuroendocrine tumour	INR	INR	Biopsy/chemotherapy	INR
5.	Rao et al.[14]	Body and tail of the pancreas	Abdominal pain	Exophytic pancreatic mass or exophytic gastrointestinal stromal tumour (GIST) from the posterolateral wall of the stomach was proposed	Peripherally compressed pancreatic tissue was seen and no tumour infiltration was discerned	Positive - CD99, Negative - AE1/AE3, DES, SYP, and CHR	Distal pancreatectomy	NR
6.	Teixeira et al.[17] (case report)	Pancreatic head and body	Epigastric pain, cutaneous pruritus, jaundice, choluria, and acholia	A voluminous expansive lesion in pancreatic head and body, with well delimited borders was observed	Neoplasm of small round blue cells with scant cytoplasm arranged in nests with fibrovascular stroma was seen	Positive - CD99, VIM, automated CKM, and CD56. Negative - CHR, SYN, NBL, MYG, automated CD10, β-catenin, automated RP (ribosomal protein), and LCA	GDPSx	NR
7.	Welsch et al.[12] (case report)	Pancreatic tail	Acute abdominal pain	A mass arising from the pancreatic tail compressing the stomach and spleen	Nests of medium-sized round or oval tumour cells with enlarged round or oval nuclei and scant cytoplasm surrounded by fibrovascular septae and focally, Homer-Wright rosettes were observed	Positive – CD99, VIM, cytokeratin (KL-1,18), cytokeratin 18, EMA, SYN, CD56, and CD117. Negative - Cytokeratins (7, 8 and 19), CEA, AFP, ⊠1ACT, protein S100, melan A, and HMB-45.	Left pancreatic resection	Tumour cell nuclei showed one fused signal and one dislocated hybridization signal on on chromosome 22q12, indicative of a chromosomal translocation involving the EWS gene

Table 1. Present and previous reported reports of Ewing sarcoma/peripheral primitive neuroectodermal tumours

No	Reported by (study type)	Site and nature	Clinical presentation	Radiologic diagnosis	Pathological	Immunohistochemistry	Diagnostic procedure	Cytogenetics
8.	Khuri et al.[18] (case report)	Pancreatic tail	Upper abdominal pain and coffee ground vomiting	Mass at lesser curvature of the stomach, with compression on the splenic vein was observed	Mass invading the gastric wall, pancreas, and splenic hilum was observed	Positive – CD99, FLI1, VIM, and Ki67. Negative - Cytokeratin, S100, CD20, CD3, CD79A, PAX5, CD30, CD43, DOG-1, CD68, CD163, CD33, MPOX, and DES	Distal pancreatectomy	Positive for EWSR1 gene rearrangement (11:22 translocation)
9.	Nishizawa et al.[19] (case report)	Pancreatic head	Upper abdominal discomfort and nausea	Giant tumour with mild enhancement occupied the pancreatic head	Atypical small round cells with scant cytoplasm, and each had a round nucleus with a distinct nuclear membrane	Positive - CD99, NSE, NEAM, VIM, SYN, and CAM5.2. Negative - CHR A, AE1/AE3, cytokeratin (7 and 20), carbohydrate antigen 19-9, and CD10	PD	Breakpoint region 1 gene, 22q12 rearrangement was proven
10.	Perek et al.[20] (case report)	Head and the body of the pancreas	Malaise and fever	Subhepatic, hypodense, solid mass with hyperdense borders and focal necrotic areas	Irregular nuclear membranes with occasional cleaving, round or oval nuclei without any distinctive cytoplasm; coarser chromatin pattern and more prominent nucleoli	Positive – CD99, and ß2-microglobulin	Surgical resection	Inconclusive

AE1/AE3: cytokeratin AE1/AE3, NSE: neuron-specific enolase, CHR: chromogranin, SYN: synaptophysin, EMA: epithelial membrane antigen, CKM: creatine kinase muscle, VIM: vimentin, DES: desmin, MYG: myogenin, LCA: leucocyte common antigen, AFP: α1-fetoprotein, α1ACT: α1-antichymotrypsin, NBL: neuroblastoma, ACT: actin, INS: insulin, GLU: glucagon, MPOX: myeloperoxidase, FLI1: friend leukemia integration 1, SOM: somatostatin, NSE: neuron-specific enolase, NEAM: neural cell adhesion molecule, ER: estrogen receptors, PR: progesterone receptors, INB: inhibin, ^{131}I-MIBI: Methoxyisobutyl isonitrile, GDPSx: gastroduodenopancreatectomy, PD: pancreaticoduodenectomy, CT: computed tomography, USG: ultrasonography, NR: nor reported, INR: individually not reported.

DISCUSSION

PNETs comprise nearly 1% of all sarcomas with an estimated five-year survival rate of 50%.[4-7] PNETs have been reported to develop in solid organs, although this is rare. In some cases, PNETs have been found arising from the pelvis, thoracopulmonary region, and the lower limbs of children and young adults.[6] In organs that contain neuroendocrine cells such as the pancreas, PNETs are extremely rare and account for only 0.3% of all primary tumours.[8,9] To the best of our knowledge, there are only a few pancreatic ES/PNET cases seen with synchronous tumours reported in the literature.[1-20] Herein, we present the first synchronous case of PNET with a squamous cell carcinoma of the cervix.

Patients with such neoplasms are often asymptomatic or have a poorly symptomatic course even in advanced stages, as observed in our case.[8,9]

ES/PNET is comprised of small round cell tumours, morphologically. They are poorly differentiated tumours. There are several entities that have small round cell morphology such as desmoplastic small round cell tumour (DSRCT), lymphoma, extra-adrenal neuroblastoma, pancreatic endocrine tumour (PET), visceral small cell neuroendocrine carcinoma (SCNC), extra-renal Wilm's tumour, and pancreatoblastoma.[14-17]

In terms of imaging tests, abdominal MRI and CT are the most useful in the detection of such tumours. However, their diagnosis is not easy as there are no specific patterns in the radiological findings as shown in Table 1.[13] A histopathological test with immunohisotchemistry is required to confirm the diagnosis of ES/PNET as in our case, but it varies from case to case (Table 1).[13]

Although pancreatic ES/PNETs are an extremely rare disease, they should be considered in the differential diagnosis of the pancreatic mass panel. We also suggest that cases with pancreatoblastoma, undifferentiated small cell carcinoma, and neuroendocrine carcinomas should be investigated for ES/PNET.[17] The clinical presentation of the tumour is diffuse while its histological findings are not exclusive.

In our case, the pathologic diagnosis was based on the positive immunoreactivity for CD99, Fli-1, and PAN-CK in many of the tumour cells. The diagnosis of pancreatic ES/PNET is made by a combination of clinical, pathological, immunohistochemical, and cytogenetic features. However, in our case, cytogenetic features were not taken into account due to limited resources.

Molecular analysis of translocation and cytogenetic evaluation have been a recognized and dominant adjunct for sarcoma diagnosis and classification. As per the evidence, ES/PNET demonstrate chromosomal translocations including the EWS gene on chromosome 22 and a member of the ETS family of genes. The most common translocation include t (11; 22) (q24; q12) that results in the fusion product EWS-FLI1 which is observed in 85%–95% of cases.[7] The second most common translocation is t (21; 22) (q22; q12) which is observed in nearly 5%–10% of cases.[7]

The standard treatment of PNET involves the use of systemic multi-agent chemotherapy along with surgery and/or radiotherapy.[12] Poor outcomes are associated with tumour dissemination in comparison to a localized disease at the time of diagnosis.[12]

In conclusion, Ewing's sarcoma/PNET of the pancreas is a rare pancreatic malignancy. To the best of our knowledge, this is the first case of Ewing's sarcoma synchronously diagnosed in a patient with carcinoma cervix.

Round cell tumours of the pancreas can be diagnosed as lymphomas, neuroendocrine carcinomas or PNET. Thus, a combination of histology and immunohistochemistry is required to differentiate PNET from other round cell tumours of the pancreas. We think that our case may contribute to the literature for this rare and unusual entity.

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MAIN POINTS

- Ewing's sarcoma/primitive neuroectodermal tumor (ES/PNET) is an unusual malignant neoplasm.
- ES/PNET synchronous with carcinoma cervix is extremely rare and reporting it can help in improving the characterization of the pathology, while contributing to the cancer treatment advancement.

ETHICS

Informed Consent: There is informed consent of patient for this case report.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: R.P., S.G., R.N., Design: R.P., S.G., Y.V.R., R.N., Supervision: S.G., R.N., Data Collection and/or Processing: R.P., S.G., Y.V.R., R.N., Analysis and/or Interpretation: R.P., S.G., Y.V.R., R.N., Literature Search: Y.V.R., Writing: Y.V.R., Critical Review: R.P., S.G., R.N.

DISCLOSURES

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CASE REPORT

CYPRUS
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Ascending Aorta and Aortic Root Replacement With the Bentall Procedure in a Patient With Dextrocardia and Situs Inversus Totalis

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ABSTRACT

We report a case of situs inversus totalis with severe aortic regurgitation, ascending aorta aneurysm and aortic root dilatation in an adult patient. This is the first report in the literature concerning a Bentall operation which was performed successfully in situs inversus totalis patient. The post-operative period of our patient was uneventful and he was discharged from the hospital after 10 days.

Keywords: Situs inversus totalis, dextrocardia, Bentall procedure, ascending aort aneurysm

INTRODUCTION

Situs inversus totalis is an autosomal recessive congenital anomaly characterized by the opposite positioning of the thoracic and abdominal organs in a reverse mirror image. Dextrocardia is a component of situs inversus totalis. In this particular case, aortic valve insufficiency, aortic root and ascending aorta dilatation were also co-existent. We report a successful Bentall operation that can be a reference for the treatment plans of similar cases in the future

CASE PRESENTATION

A 57-year-old male patient with known dextrocardia was admitted to the cardiology department with shortness of breath and chest pain complaints. In spite of his suspicious symptoms such as chronic sinusitis, chronic rhinitis and red eye that were consistent with primary ciliary dyskinesia syndrome; he was fertile and did not suffer from any lower respiratory tract diseases. Physical examination revealed the presence of a sinus rhythm and a diastolic murmur becoming more prominent at the left parasternal border.

Echocardiography showed dextrocardia with left ventricular (LV) dilatation, a slightly depressed LV ejection fraction (45%–50%) and severe aortic regurgitation. Sinus valsalva, sinotubular junction and ascending aorta measurements were recorded as 52 mm, 49 mm and 47 mm, respectively (Figure 1). After, contrast enhanced computerized tomography (CT), the patient was diagnosed with "Situs Inversus Totalis" (SIT) which is the presence of reversed mirror images of all thoracoabdominal organs (Figures 2 and 3).

Surgery was performed under general anesthesia using standard median sternotomy. After the pericardiectomy, dextrocardia and right-sided aortic arch were observed. The brachiocephalic trunk and both vena cava were located on the left side of the patient (Figure 4). No venous return abnormalities were detected. Despite the dilatation of the proximal ascending aorta, there was a safety cross clamping area just below the brachiocephalic trunk. Cardiopulmonary bypass was established by the chief surgeon standing on the right side of the patient by using the left sided right atrial appendage and the distal ascending aorta for cannulation. After the aortic cross clamp, both anterograde and retrograde cardioplegia were given and subsequently, aortotomy was performed. The aortic wall was extremely thinned, the valve ring

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was dilated and the cusps were highly degenerated. For complete myocardial protection, selective cardioplegia was also applied.

Severe aortic regurgitation, ascending aorta aneurysm and dilatation of the aortic anulus led us to consider that valve sparing surgery would not be beneficial; therefore, the team decided to replace the root and the ascending aorta completely by performing the Bentall procedure. Both coronary buttons were prepared as usual and the aortic valve was excised. A 25 mm mechanical aortic valve (SJM™ Masters Series Mechanical Heart Valve SJM) was sutured to the 30 mm dacron graft and this was implanted with a continuous suturing technique, by using a 4/0 propylene suture. After the re-connection of the coronary buttons, the tubular graft length was trimmed and distal anastomosis was completed. The patient was weaned from the cardiopulmonary bypass with normal sinus rhythm. No complications were observed in the early postoperative period and no inotropic support was required. The patient was extubated at the 6th hour of the post-operative period and was discharged from the hospital after 10 days.

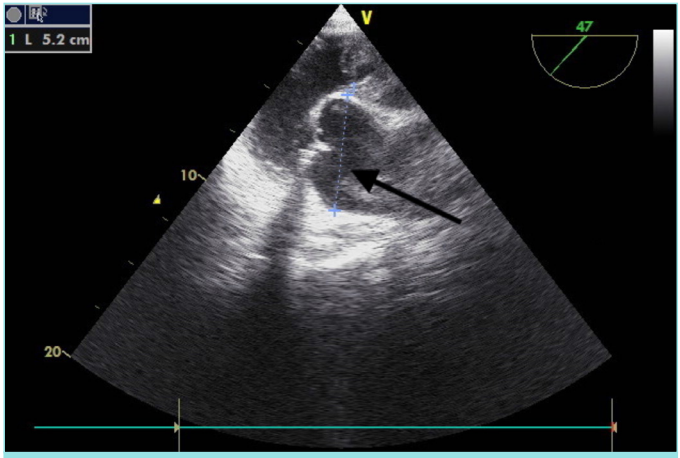

Figure 1. Preoperative aortic root measurements by transthoracic echocardiography and sinus valsalva was measured at 5.2 cm and is shown with an arrow.

Figure 2. Preoperative CT scans showed reverse mirror images of all thoracoabdominal organs.

CT: Computed tomography

DISCUSSION

SIT is an autosomal recessive congenital anomaly characterized by opposite positioning of the thoracic and abdominal organs as mirror images. Dextrocardia with SIT is a very rare condition occurring in approximately 1–2 per 10,000 in the general population.[1] Apart from the small percentage of SIT patients that have other congenital heart anomalies, such as transposition of the great vessels or heart defects, most affected adult patients live a normal lifespan and diagnosis takes place by chance when an X-ray or CT scan is performed for another reason.[2]

Figure 3. Preoperative CT scans showed reverse mirror images of all thoracoabdominal organs.

CT: Computed tomography

Reverse positioning of the internal organs takes place during embryological development. Although the genes that regulate the anatomical positioning of the organs are known, the specific genetic cause of dextrocardia with SIT is still unidentified. Some patients have association with primary ciliary dyskinesia called Kartagener syndrome and are diagnosed in the early childhood period. For the genetic research of this case, blood samples of the patient and family were collected and further investigations were performed.

In our opinion, the pre-operative evaluation, the imaging techniques that were used and the surgical plan were the key points in the success of this case. CT imaging presented the anatomical abnormalities sufficiently and it was extremely helpful for planning the cannulation strategy, setting-up the operative tools and positioning the team during the surgery. However, conventional angiography was also applied in order to eliminate the presence of concurrent coronary artery disease and venous perfusion defects. No coronary artery lesions or venous perfusion defects were found. As neither a left atrial approach nor coronary bypass surgery were required, in contrast with some articles in the literature, the surgical team decided to implement the conventional positioning where the chief surgeon stands on the right side of the patient.[3] The surgery was successfully completed with no difficulties or complications encountered.

Ascending aortic aneurysm is a life-threatening disease related with rupture and aortic dissection risk. As is well-known, a well-planned elective surgery, applied by experienced centers, is the curative treatment. The Bentall procedure is still the most helpful technique, especially for ascending aortic aneurysms that include aortic root dilation and aortic valve regurgitation and are inappropriate for valve sparing surgery.[4]

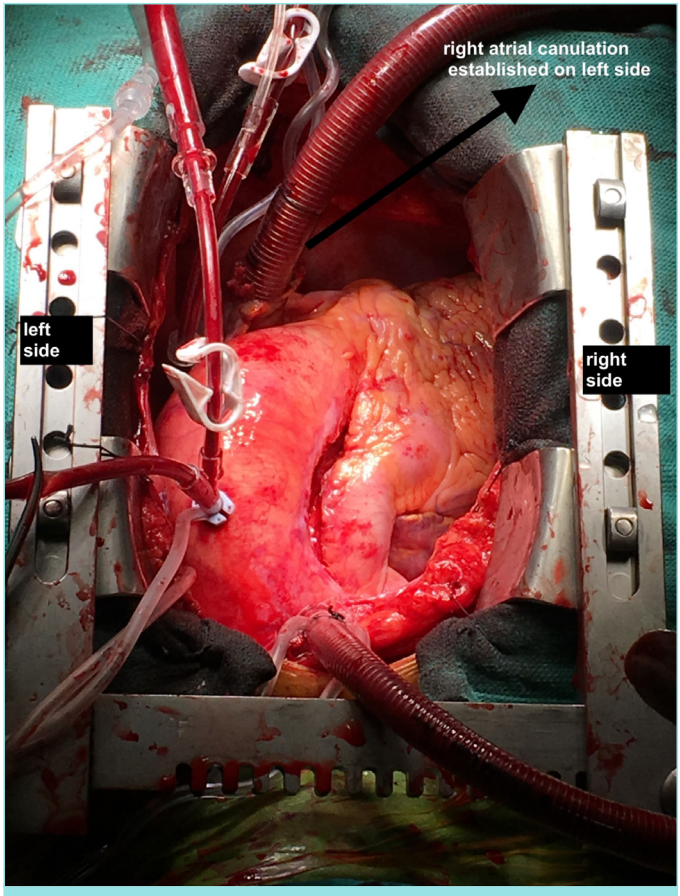

Figure 4. Preoperative view.

In conclusion, the presence of SIT with dextrocardia is an extremely rare condition. In this particular case, aortic valve insufficiency, aortic root and ascending aorta dilatation were also co-existent with SIT with dextrocardia. In the literature, no cases which involved the use of the Bentall procedure were reported. In our opinion, the Bentall procedure can be safely applied to such cases without any requirement to change the positions of the surgical team in the surgery. This particular case can be a reference for the treatment plans of similar cases which may be encountered in the future.

MAIN POINTS

- The Bentall Operation is still a life-saving procedure in aortic root dilatation and severe aortic regurgitation if aortic valve sparing techniques are not suitable.
- Complete diagnosis and well-planned operation techniques carried out by experienced centers is the key point of success in such cases.
- A small percentage of SIT patients have additionally heart defects which may lead to diagnosis in early childhood.
- Chronic sinusitis, chronic rhinitis, red eyes and infertility may be associated with primary ciliary dyskinesia in SIT patients and these patients should undergo genetic investigation for Kartagener syndrome.

ETHICS

Informed Consent: Informed consent was obtained from the patient before the surgery.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

DISCLOSURES

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CASE REPORT

CYPRUS
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Transparent Foreign Body Randomly Found in the Nasopharynx During Adenotonsillectomy

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ABSTRACT

During a preoperative examination, foreign objects may be missed due to their transparency and, as a result, these objects may obstruct the tracheal airways. This article was written to show the risk of foreign bodies escaping within the airway. As in this experience, each surgery shows that the risks involved and, in some cases, the results are unexpected.

Tonsillectomy and adenotonsillectomy operations are performed all over the world. All operations have peri-operative and post-operative complications. During an adenotonsillectomy operation I had undertaken, I came across an unexpected situation that I had not previously encountered, either through experience or in the medical literature.

Keywords: Adenotonsillectomy, foreign body nasopharynx

INTRODUCTION

Tonsillectomy and adenotonsilectomy operations are performed all over the world. All operations have perioperative and postoperative complications. During an adenotonsilectomy operation I had undertaken, I came across an unexpected situation that I had not previously encountered, either through experience or in the medical literature.

CASE PRESENTATION

A 13-year-old patient was admitted to our outpatient clinic suffering from breathing difficulties and uncomfortable nightly breathing patterns. Endoscopic examination of the patient revealed adenoid tissue sufficient to fill the choana patency and grade IV tonsil tissue according to Friedman Scala. No foreign body was seen.

An adenotonsillectomy operation was recommended to the patient's family and they accepted. Pre-operative blood tests were normal. Under general anesthesia, adenotonsillectomy was carried out in the operating room according to the procedure.

After the necessary bleeding control, saline was poured into the surgical site and the washing phase was completed. The oropharynx was aspirated first.

Afterwards, a nelaton catheter was used for nasal and nasopharynx aspiration. A drain was encountered in the transition from the right nasal cavity to the nasopharynx. Some resistance was encountered in the passage of the nasopharynx from the right nasal cavity. While the catheter was being pushed forward with a little force, a transparent leaf-shaped foreign body came into the oropharynx area (Figure 1).

This material was taken out and the required washing was completed and the operation was terminated. Post-operative follow-up was not different from other operations.

DISCUSSION

Nasopharynx is a place where the foreign bodies inserted into the nose and mouth of children can be located.[1]

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Foreign bodies placed or inhaled into the nose can pass through the nasopharynx and settle there. These foreign bodies may mimic upper airway infections or may manifest as a mild swelling of the soft palate.[1]

If an X-ray is taken, radiographs may be seen on the lateral radiographs, and foreign material that is opaque can be seen by the X-ray.

In children, foreign bodies such as buttons, beads, pea-type foods, and toy pieces, as well as rings, teeth, leeches, and fish are found.[2] Iatrogenic gauze forgotten in the nasopharynx has also been found.[3] In addition, vomiting and coughing may also be the cause of foreign bodies being deposited in the nasopharynx.[2]

The standard approach in suspicious foreign body aspiration is physical examination, bronchoscopy, esophagoscopy and radiographic examination (chest radiography at inspiration and expiration and lateral neck radiography). Even if the foreign substance is removed, we should consider that a second foreign body may be present. As explained in one article, even in cases suggesting an acute aerodigestive foreign substance, a foreign substance can also be found in the nasopharynx.[4] Nasopharynx foreign bodies can lay dormant for years without symptoms.[5,6] The presence of foreign bodies in the nasopharynx can be determined, either as a result of the observation of nasopharyngeal obstructions following coughing attacks or by random detection.[7-9] As foreign bodies travel to the stomach, they orient superiorly after a gag reflex thus settling in the nasopharynx.[7] Aspiration performed without providing the necessary airway safety may result in death.[10] A nasopharynx foreign body can also result in adenoid hypertrophy and obstructive sleep apnea.[11]

In conclusion, the nasopharynx is a potential void where foreign bodies can be deposited. Even though nasopharynx examination is performed in the pre-operative evaluation, the foreign body may be overlooked as in this case. The foreign body of the nasopharynx can be determined after the examination. Therefore, the examination of the nasopharynx from both sides is important in pre-operative evaluation.

As in my case, we should keep in mind that unexpected situations may occur in every operation.

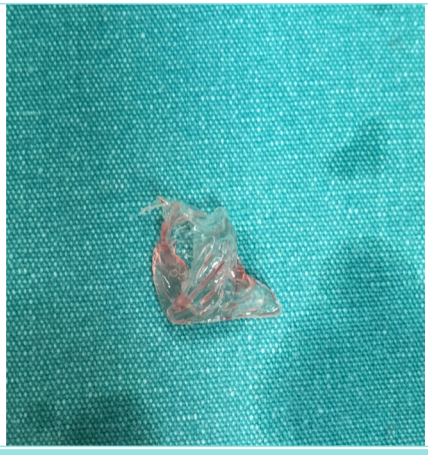

Figure 1. Foreign body identified during operation

MAIN POINTS

- This case emphasizes the importance of careful physical examination before an operation.
- In every operation, the surgeon can come across unexpected situations and complications.
- Nasopharyngeal foreign bodies can result in life-threatening conditions.

ETHICS

Informed Consent: Informed consent was taken.

Peer-review: Externally peer-reviewed.

DISCLOSURES

Financial Disclosure: The author declared that this study had received no financial support.

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