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Aims and Scope

Cyprus Journal of Medical Sciences (Cyprus J Med Sci) is the scientific, peer reviewed, open access international publication organ of Cyprus Turkish Medical Association. The journal is published three times a year, in April, August, and December. As of 2020, the journal has become a quarterly publication, publishing in March, June, September, and December. The journal's publication language is English.

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 processes of the journal 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 (doaj.org/bestpractice).

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

Processing and publication are free of charge with the journal. No fees are requested from the authors at any point throughout the evaluation and publication process. All manuscripts must be submitted via the online submission system, which is available at www.cyprusjmedsci.com. The journal guidelines, technical information, and the required forms are available on the journal's web page.

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Instruction to Authors

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Originality, high scientific quality, and citation potential are the most important 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.

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

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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, www.wma.net) 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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Authors must provide the journal with the pre-print server deposition of their article accompanying its DOI during initial submission.

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

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Each person listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE - www.icmje.org). The ICMJE recommends that authorship is based on the following four criteria:

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

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

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

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

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

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

Authors are required to submit the following:
- Copyright Agreement and Acknowledgement of Authorship Form, and
- ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors) during the initial submission. These forms are available for download at www.cyprusjmedsci.com.

Preparation of the Manuscript
Title page: A separate title page should be submitted with all submissions and this page should include:
- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, highest academic degree(s), and ORCID IDs of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number), and email 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 I 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).

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" targeting the experts and specialists of the field, each item should be written as plain and straightforward as possible.

Manuscript Types
Original Articles: This is the most important type of article since it provides new information based on original research. Acceptance of original papers will be

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based upon the originality and importance of the investigation. The main text of original articles should be structured with Introduction, Material and Methods, Results, and Discussion subheadings. An original article can be signed by maximum 6 authors unless it is a multi-center study or that it required extensive labour. Please check Table I for the limitations for Original Articles.

Clinical Trials

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

Instructions for the clinical trials are listed below.

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

Data Sharing

As of I 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

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.

Clinical trial and data sharing policy of the journal will be valid for the articles submitted from I February 2020.

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.

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

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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.

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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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. 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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Acknowledgement of Reviewers

Dear readers,
Our reviewers perform very important and precious role in the evaluation of the scientific articles, make valuable contributions to the increasing quality and the rising at an international level of the Cyprus Journal of Medical Sciences.
Editorial Board would like to thank all the reviewers that are listed below for their support in Cyprus Journal of Medical Sciences in 2020.

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Serpil Ince
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Original Article

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Diagnostic Procedures for Lung Cancer According to Histological Types and Their Complications

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BACKGROUND/AIMS
This study aimed to investigate if there are any differences between the diagnostic methods used in biopsy for lung cancer on the basis of the histological cell types. In addition, the contribution of bronchoscopic washing in the diagnosis of lung cancer and complications of flexible bronchoscopy and computed tomography (CT)-guided transthoracic needle biopsy (TNB) were also investigated.

MATERIAL and METHODS
The patients who were diagnosed with lung cancer pathologically were divided into two groups—bronchoscopic biopsy and CT-guided TNB. A comparison was made between the two groups according to the lung cancer cell type. Complication rates for both procedures were calculated. In addition, the contribution of bronchoscopic washing in the diagnosis of lung cancer was also investigated in patients who underwent bronchoscopy.

RESULTS
The study included 182 lung cancer patients, out of whom 106 patients were diagnosed by bronchoscopy and 76 patients were diagnosed by CT-guided TNB. There was no significant difference between the diagnostic approaches for adenocarcinoma (ADC) (p=.22). Small cell lung cancer (SCLC) and squamous cell carcinoma (SCC) were diagnosed more accurately by bronchoscopy than TNB (p=.01, p=.01, respectively). Bronchoscopic washing was found to be positive in 3 of the patients who had negative results with bronchoscopic biopsy. There were no major complications related to bronchoscopy. The total minor complication rate of bronchoscopy was found to be 11.3%. Pneumothorax was detected in 17% of patients undergoing TNB and the total complication rate of TNB was 19.7%.

CONCLUSION
SCLC and SCC were more accurately diagnosed by flexible bronchoscopy than TNB. Bronchoscopic washing contributed in the diagnosis of lung cancers. Flexible bronchoscopy was found to be much safer and associated with lower complication rates than CT-guided TNB.

Keywords: Bronchoscopy, transthoracic needle biopsy, bronchial washing, lung cancer.

INTRODUCTION

Lung cancer is the leading cause of cancer deaths among both men and women (1). Fast and accurate detection and staging are important in order to decide most appropriate treatment for patients with lung cancer. Flexible bronchoscopy (FB) and computed tomography (CT)-guided transthoracic needle biopsy (TNB) are used for the diagnosis of lung cancer on the basis of the localization of the lesion in the lungs. TNB is used especially for peripheral pulmonary nodules, and approximately 90% of patients with pulmonary nodules can be diagnosed with TNB (2). However, pneumothorax is detected in approximately 25% of the patients who underwent TNB (3). Chest tube is required for the treatment of 15% of the patients with pneumothorax (3). Conventional FB has a diagnostic accuracy of 64% in malignant lesions and 35% in benign lesions (4). The diagnostic accuracy of FB in central, middle, and peripherally located lesions is 82%, 61%, and 53%, respectively, when lesions are classified on the basis of localization (4). Diagnostic value of FB decreases when localization of the lesion changes from central to peripheral. Bronchoscopic biopsy can be used with bronchial washing, brushing, and transbronchial needle biopsy to achieve a diagnostic yield between 65% and 88% (5). FB has been shown to be a safer procedure and associated with lesser complications such as mortality, bleeding,

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and pneumothoraxes that necessitate intervention (6). FB is an ideal technique for large, central lesions and diagnostic yields decrease between 30% and 40% without an endobronchial lesion. Bronchial washing contributes to bronchoscopy in the diagnosis of lung cancer, and it was found positive in 40% of the patients with pulmonary nodules (4). Lung cancers are detected in different locations within the lung and are classified on the basis of the histological cell types. Small cell lung cancer (SCLC) is usually centrally located (7); adenocarcinoma (ADC) is a histologically heterogeneous peripheral tumor; squamous cell carcinoma (SCC) is typically detected as a central endobronchial mass; and large cell carcinoma (LCC) is seen as poorly differentiated large peripheral masses.

This study aimed to investigate whether there is a difference between the diagnostic methods used in biopsy for lung cancer according to cell type. In addition, the contribution of bronchoscopic washing in the diagnosis of lung cancer and biopsy complications of FB and TNB were studied.

MATERIAL and METHODS

Patients who were diagnosed with lung cancer pathologically by biopsy between January I, 2018 and October I, 2019 were included in the study. The study was conducted retrospectively, and an approval was obtained from the local ethics committee.

FB was performed in conscious patients. Routine vital signs such as arterial blood pressure, heart rate and rhythm, and oxygen saturation (SpO_2) were recorded during FB. All patients were monitored for symptoms including dyspnea, chest pain, and hemoptysis after completion of FB. Oxygen was administered through a nasal cannula to ensure that SpO_2 was between 9I% and 93%. For oropharyngeal topical anesthesia, I0% lidocaine spray was used. Midazolam (I–5 mg) was used as a sedative for FB. For topical anesthesia, 2% lidocaine solution via the bronchoscope working channel was used. Complications associated with bronchoscopy were reported as procedure-related complications (hypoxemia, hemorrhage, fever, pneumothorax, bronchospasm, laryngospasm, pneumonia, and death) and sedation- and anesthesia-related complications (hypoxemia, respiratory depression, hypotension, hypertension, syncope, arrhythmias, seizures, methemoglobinemia, and death). If hemorrhage was >200 mL/d, it was recorded as a major hemorrhage, otherwise, it was recorded as a minor hemorrhage. Death or complications requiring hospitalization or admission to the intensive care unit were recorded as major complications. Complications that did not comply with this definition were accepted as minor complications. Patients were kept under observation until they achieved preprocedural level of consciousness and acceptable vital parameters. Bronchial washing was performed for all patients. In patients with endobronchial lesions during bronchoscopy, biopsy was performed first, and then bronchial washing samples were taken. I0 mL isotonic NaCl liquid was administered to the bronchial orifice where the lesion was located, and then aspirated for bronchial washing or applied to the endobronchial lesion before and after the biopsy.

Main Points:

- Small cell lung carcinoma and squamous cell carcinoma was diagnosed more accurately with flexible bronchoscopy. There was no difference between the two diagnostic methods for adenocarcinoma.
- There were no major complications associated with flexible bronchoscopy; however, minor complications developed in II.3% of the patients. Pneumothorax was detected in I7% of the patients who underwent computed tomography (CT)-guided transthoracic needle biopsy (TNB), and the total complication rate was found to be I9.73% for CT-guided TNB.
- Flexible bronchoscopy was found to be a relatively safe diagnostic method with a lower complication rate compared to CT-guided TNB in the diagnosis of lung cancer.

TNBs were performed by the interventional radiology department. Helical CT was used to guide biopsy needle placement. Patients received conscious sedation on request. Subcutaneous injection of I% lidocaine was used for local anesthesia. All patients were kept under observation for 2 hours and underwent posteroanterior chest radiography after the biopsy procedures. Complications of TNB included pneumothorax, hemorrhage, tumor seeding along the needle biopsy tract, and air embolism. The patients who were hospitalized for pneumothorax and who had a chest tube were also examined.

The patients were divided into FB and TNB groups. A comparison was made between the two groups on the basis of lung cancer cell type. In addition, the role of bronchoscopic washing was investigated in patients who underwent FB with undiagnostic results. Complication rates of FB and TNB were evaluated.

Ethics Committee Approval

This study was approved by the Ethics Committee of the Umraniye Training and Research Hospital (Approval date: I8.I2.2019, No: 239)**.** Informed consent was waived because of the retrospective nature of the study.

Statistical Analysis

Descriptive analyses (frequency distributions, percentages) were used for statistical analysis of data analysis. Chi-squared analysis was used to analyze the frequency distribution of the data and the results were evaluated at a 95% confidence interval and $p<.05$ significance level. PSPP and Microsoft Excel programs were used for data analysis (PSPP is a free software; it can be redistributed and/or modified under the terms of the GNU General Public License as published by the Free Software Foundation; either version 3 of the License, or [at your option] any later version.).

RESULTS

The study included I82 lung cancer patients, out of whom I06 patients were diagnosed by FB and 76 patients were diagnosed by CT-guided TNB (Table I). No significant difference was observed between the diagnostic approaches for ADC ($p=.22$). The diagnosis of SCLC and SCC was made more accurately by flexible bronchoscopy than by TNB and the differences were statistically significant ($p=.0I$, $p=.0I$, respectively). Patients with LCC were diagnosed with only FB, whereas patients with undifferentiated carcinoma were diagnosed with only TNB. Broncho-

TABLE I. The comparison of diagnostic methods used for biopsy for lung cancer according to cell type

	Biopsy		
	FB (N=106)	**CT-guided TNB (N=76)**	**p**
Adenocarcinoma	34 (32%)	45 (59.2%)	0.22
Large cell carcinoma	2 (1.8%)	0 (0%)	-
Small cell carcinoma	22 (20.7%)	6 (7.8%)	0.01*
Squamous cell carcinoma	48 (45.2%)	21 (27.6%)	0.01*
Undifferentiated carcinoma	0 (0%)	4 (5.2%)	-

FB, flexible Bronchoscopy; CT, computed tomography; TNB, transthoracic needle biopsy. * p <0.05

TABLE 2. The contribution of bronchoscopic washing to the diagnosis of patients (N: 106) (%) who underwent bronchoscopic biopsy

Bronchoscopic biopsy (N: 106)	Malignity negative (N: 3)	Bronchoscopic washing	Negative	0 (0%)
			Positive	3 (2.8%)
	Malignity positive (N: 103)	Bronchoscopic washing	Negative	51 (48.1%)
			Positive	52 (49%)

TABLE 3. Complications of flexible bronchoscopy (N: 106)

		N (patient) (%)
Procedure-related complications	Hypoxemia	4 (3.7%)
	Minor hemorrhage	3 (2.8%)
Anesthesia-related complications	Respiratory depression	1 (0.9%)
	Hypertension	4 (3.7%)
Total complication rate		12/106 (11.3%)

TABLE 4. Transthoracic needle biopsy-related complications

		N (patient) (%)
Complications	Parenchymal Hemorrhage	2 (2.6%)
	Pneumothorax	11 (14.4%)
	Parenchymal hemorrhage and pneumothorax	2 (2.6%)
	Total complication rate	15/76 (19.7%)

scopic washing was found to be positive in 3 of the patients who could not be diagnosed with bronchoscopic biopsy (Table 2). Bronchoscopic washing was positive for malignancy in 49% of the patients who underwent bronchoscopic biopsy and had positive results. No major complications were detected after bronchoscopy (Table 3). Hypoxemia was detected in 4 patients who underwent bronchoscopy. Minor hemorrhage was observed in 3 patients. One patient had sedative drug-induced respiratory depression. Four patients had transient elevation of arterial blood pressure. No patients died after or during FB. All of the complications were treated medically. After FB, no patients required inpatient treatment or intensive care follow-up due to complications. The total minor complication rate of FB was found to be 11.3% when procedure- and anesthesia-related complications were evaluated together.

Pneumothorax was detected in 17% (N=13) of patients undergoing TNB (Table 4). When parenchymal hemorrhage and pneumothorax were evaluated together, the complication rate was 19.7%. 8 out of 13 patients who developed pneumothorax required a chest tube. Patients who had pneumothorax and parenchymal hemorrhage and chest tube implantation were treated in hospital.

DISCUSSION

In this study, it was observed that SCLC and SCC were mostly diagnosed with FB. There was no significant difference between diagnostic methods for ADC. It was found that bronchial washings were positive in 51.8% of patients who underwent bronchoscopic biopsy and additionally diagnosed 3 patients with negative bronchoscopic biopsy. It has been observed that the complications of FB were less than TNB.

Lung cancer is a common cancer associated with high mortality rates. More than 2 million new lung cancer diagnoses were made, and 1.7 million people died due to lung cancer in 2018 (8). Lung cancer has been reported to be the cause in 14% of the newly diagnosed cancer patients and 20% of the deaths caused by cancer (8). Therefore, it is crucial to diagnose the disease without any delay and identify the stage to start an appropriate treatment immediately. There are different diagnostic tools for the diagnosis of lung cancer. FB and TNB are the most commonly used methods for the diagnosis of lung cancer. The size, localization of the lesion, relationship with patent airway, risk of complications in the patient, and current experience are important in the selection of biopsy method for the diagnosis of pulmonary nodules (9). Bronchoscopic techniques are preferred in central nodules located proximal to a patent bronchus, especially in patients at high risk of pneumothorax with TNB.

Lung tumors, depending on their location in the tracheobronchial tree, are categorized as central or peripheral. SCLC and SCC are usually centrally located and ADC and LCC are peripherally located tumors (7). As a general rule, FB is preferred for central lesions and TNB is preferred for peripheral lesions. The sensitivity of FB to detect malignancy in solitary pulmonary nodules depends on the size of the nodule, the proximity of the lesion to the bronchial tree, the presence of bronchus sign on CT, and the prevalence of cancer in the community (10). Malignancy detection rate of FB was found to be 75–94.5% in bronchoscopically visible lesions and 41.7%–81.2% in non-bronchoscopically visible lesions (11). Bronchoscopy can be used to perform bronchial washing, bronchial brushing, transbronchial needle aspiration biopsy (TBNA), and transbronchial biopsy (TBB) in addition to biopsy from endobronchial lesions (12). In the presence of an endobronchial lesion, the sensitivity of biopsy, bronchial brushing, and bronchial washing was reported to be 74%, 59%, and 48%, respectively (13). The diagnostic value of FB in bronchoscopically visible intramural tumors was reported to be about 55% and decreased further in cases where the tumor cannot be seen bronchoscopically (12). The diagnostic value of FB is approximately 88% with the combined use of bronchoscopic biopsy, bronchial washing, and brushing (10).

This study reported that FB provided a more accurate diagnosis of SCC and SCLC than that observed with TNB. It was an expected outcome because both SCC and SCLC are centrally located tumors. There was no significant difference between bronchoscopy and TNB in the diagnosis of ADC. ADCs are known to be located peripherally and therefore, although it is expected to be diagnosed with a better accuracy by TNB, there was no difference between the two diagnostic procedures. Bronchial washing was positive in approximately half of the patients who underwent FB for lung cancer in this study. The

diagnosis was made by bronchial washing in 3 patients who could not be diagnosed by bronchoscopic biopsy. These results showed the diagnostic contribution of bronchial washing in patients undergoing FB.

Complications related to FB have been reported to be between 0.1% and 11% and the procedure-related mortality rate to be between 0% and 0.1% (14). The main reason for the differences in complication rates is related to the definition of complications in the studies. A systematic analysis of the complications of FB was performed (6). Severe complications were rare and the rate of pneumothorax requiring intervention was 0%–2.1% after transbronchial biopsies (6). Oxygen desaturation was found in 0.7%–76.3% of the patients undergoing FB and bleeding was found in 2.5%–89.9% of the patients undergoing FB. In general, FB was concluded to be a safer procedure, but a consensus on the identification of complications is required. Approach to patients with comorbidity in patient selection prior to FB is very important. Particular attention is required in patients with concomitant airway obstructive pulmonary diseases such as chronic obstructive lung disease and bronchial asthma (15). In a prospective study, actual blood loss and factors that may cause bleeding were investigated in 234 patients undergoing FB (16). The results reported mild bleeding (5–20 mL) in 19 patients, moderate bleeding (20–100 mL) in 5 patients, and no severe bleeding (>100 mL) in any patient (16). In another study where FB was performed in 400 patients without comorbid diseases, complications (bleeding, pneumothorax, collapse, and infection) were detected in 3.25% of the patients (17). The low complication rates may be due to the exclusion of patients with comorbidity. In this study, no serious major complications because of FB were detected. Minor complications occurred in 11.3% of the patients, but none of them required hospitalization and were easily treatable. Differences reported in studies examining bronchoscopic complications may be due to the definition of complications. In this study, FB was found to be a safer diagnostic procedure.

TNB is preferred primarily in patients with peripheral pulmonary nodules, and approximately 90% of patients can be diagnosed with TNB. Although the diagnostic value of TNB is high, its complications are not uncommon, and they increase the risk of morbidity and mortality. Pneumothorax was detected in 25% of the patients who underwent TNB and 15% of them required chest tube treatment (3). The complication rate of TNB in this study was similar to that reported by other studies. When hemorrhage was included, the overall complication rate was 19.73%. The patients who developed pneumothorax required hospitalization and approximately half of these patients underwent tube thoracostomy. TNB is not a suitable choice in patients with previous pneumothorax and emphysema in the lung parenchyma (18). The positive predictive factors of TNB in the diagnosis of pulmonary nodules are related to nodule size (larger diameter, better accuracy), noncalcified density (better accuracy as density increases), and the distance between nodule and pleura (19). In a meta-analysis, TNB results were not diagnostic in 6.8% of patients who underwent TNB biopsy (20). 59.3% of the patients with non-diagnostic TNB were diagnosed with malignancy (20). These results suggest that further diagnostic procedures are required or TNB may be repeated in patients with negative TNB biopsy.

In this study, it was observed that bronchoscopic complications were less than those reported with TNB and did not require additional therapeutic treatment or hospitalization. In contrast, TNB complications were relatively more severe, requiring tube thoracostomy and hospitalization.

This study had some limitations. First, this study was conducted retrospectively. The presence or absence of endobronchial lesions in patients diagnosed with bronchoscopy has not been recorded separately. Furthermore, the localization of the lesions in the lungs has not been studied.

The study concluded that SCLC and SCC were more accurately diagnosed with FB than with TNB. Bronchoscopic washing helped in complementing the diagnosis of the types of cancers studied. FB was found to be much safer and associated with lower complication rates as compared with CT-guided TNB.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Umraniye Training and Research Hospital (Approval date: 18. 12. 2019, No: 239).

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Original Article

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Protective Effect of Nigella Sativa Oil Against Indomethacin-Related Small Intestine and Gastric Mucosal Damage in Rats

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BACKGROUND/AIMS
The aim of this study was to investigate the effects of Nigella sativa (NS) oil form on reducing the damage caused by indomethacin in the stomach and duodenum of rats owing to their antioxidant and anti-inflammatory properties.

MATERIAL and METHODS
The rats were divided into 4 groups: group I, saline-treated control group; group 2, NS-treated control group; group 3, saline-treated ulcer group and ulcers caused by indomethacin (30 mg/kg) and administration of physiological serum; group 4, NS-treated ulcer group, which is the group receiving NS oil after administration of indomethacin. At the end of the study, blood samples collected from animals were examined for tumor necrosis factor alpha (TNF-α), interleukin-I beta (IL-Iβ), and glutathione (GSH), malondialdehyde (MDA) levels and myeloperoxidase (MPO),and Na+/K+-ATPase activities in gastric and intestinal tissue samples.

RESULTS
Levels of TNF-α and IL-Iβ in serum and MDA and MPO values in tissue were found to be higher in the saline-treated ulcer group than in the saline-treated control group. In addition, tissue GSH and Na+/K+-ATPase levels were found to be lower. These values were found to be reversed when comparing NS-treated ulcer group to saline-treated ulcer group. Histopathological findings showed epithelial regeneration and improvement instead of dense tissue damage.

CONCLUSION
The strong antioxidant and anti-inflammatory effects of NS against potential small intestine and gastric damage were shown using an experimental indomethacin-induced ulcer model in rats. Hence, our study suggests that NS used together with indomethacin can prevent gastrointestinal damage; thus, this agent can create a new clinical therapeutic principle.

Keywords: Indomethacin, Nigella sativa oil, ulcer, glutathione

INTRODUCTION

For the treatment of fever, pain, and inflammation, non-steroidal anti-inflammatory drugs (NSAIDs) are broadly used; however, these drugs lead to severe damage of the gastrointestinal tract. In particular, indomethacin causes an increase in free oxygen radicals and inflammatory cytokine levels through neutrophil infiltration. There are many studies that show that antioxidant parameters decrease and oxidant parameters increase in damaged gastric tissue when treated by indomethacin. In the gastrointestinal tissue of indomethacin-treated animals, myeloperoxidase (MPO) and malondialdehyde (MDA) levels were increased, and antioxidant parameters such as glutathione (GSH) were decreased. Therefore, it is argued that indomethacin ulcers can be treated by increasing the antioxidant effect (I–3) Nigella sativa (NS), also known as black cumin seed, has been used for a long time as a traditional treatment method in India and in the Middle and Far

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East subcontinent parts. This ancient spice has been used for centuries by Ayurvedic (i.e., traditional Hindu medicine), Greeks, and herbal medicine practitioners to treat many diseases such as bronchial asthma, infection, gastrointestinal problems, and hypertension (4, 5). The studies have demonstrated that NS extracts show a plurality of therapeutic effects, including antioxidant, hepatoprotective, immunomodulatory, anti-inflammatory, and antitumor effects (6-8).

In our study, the anti-inflammatory and antioxidant properties of the 100% pure oil form of NS and its effect of decreasing the damage caused by indomethacin in the stomach and duodenum are investigated. In particular, gastrointestinal system damage induced by indomethacin restricts its therapeutic property, making it useful for certain symptoms. A similar study using NS has never been carried out previously, and this study could shed light on future experimental and clinical studies.

MATERIAL and METHODS

Animals and Experimental Conditions

Approval from the Ethical Committee (Marmara University Animal Care and Use Committee) was obtained before the current experimental period (Approval number: 26.2011.Mar; Approval date: 26/04/2011). The number of male and female rats that were used in this study was equal. The rats were kept at 12-hour light/dark cycles and at a constant temperature (21 ± 3°C) with 50 ± 5% humidity. The rats were fed ad libitum with standardized rat chow and water.

Animal Groups and Treatment

Each group consisted of 8 rats, randomly divided into 4 groups:

- Saline-treated control group: 0.1 mg/kg physiological saline solution was administered perorally.
- NS-treated control group: 10 ml/kg NS oil was given through gavage to rats.
- Saline-treated ulcer group: to induce ulcer, 30 mg/kg indomethacin and physiological saline solution were administered by gavage to rats.
- NS-treated ulcer group: after administering 30 mg/kg indomethacin, 10 ml/kg NS was given by gavage.

All treatments were given daily, at the same time of the day. After 6 hours of administration of indomethacin, all rats were killed. Two cc blood samples were collected from the vena cava.

Main Points:

- Indomethacin has a broad range of uses in rheumatic disorders such as rheumatoid arthritis, ankylosing spondylitis and osteoarthritis, as well as tendonitis and traumatic synovitis, but its gastropathic side effects.
- Indomethacin causes an increase in free oxygen radicals and inflammatory cytokine levels through neutrophil infiltration.
- Nigella sativa oil exerted potent anti-inflammatory and anti-oxidative actions in the serum, tissue, and histological sections of rats with indomethacin-induced gastric and intestinal mucosal damage.

The stomach and duodenum tissue samples were removed and stored at -80°C until starting the current experimental procedure.

Biochemical Analysis

Cytokine assay. To determine tumor necrosis factor alpha (TNF-α) (catalog number: KRC 3014, Biosource Europe SA, Nivelles, Belgium) and interleukin-1 beta (IL-1β) (catalog number: KRC0011, Biosource Europe SA, Nivelles, Belgium) levels from serum, they were measured by rat specific enzyme-linked immunosorbent assay (ELISA) kits according to manufacturer's protocol. Intra-assay and inter-assay precision for TNF-α were 4.1% and 8.9%, respectively. Intra-assay and inter-assay precision for IL-1β were 7.5% and 9.3%, respectively.

The Assay of Glutathione (GSH) and Malondialdehyde (MDA) levels and Myeloperoxidase (MPO) and Na^+/K^+-ATPase activities. In total, 20 mg of the duodenum and stomach tissues was obtained from each rat and then washed in cold phosphate-buffered saline for MDA, MPO, and GSH assay. To determine MDA and GSH levels and MPO and Na^+/K^+-ATPase activities, commercially available assay kits were used (catalog number: ab11897, ab105136, ab138881, Abcam, Cambridge, UK; catalog number: MBS824 3226,MyBioSource, San Diego, USA, respectively).

Histopathological Analysis

Tissue sections with ulceration were evaluated under a light microscope (Olympus BX 51; Olympus, Shibuya, Tokyo). First, specimens were fixed in 10% formalin and then embedded in paraffin wax. Second, a 5-μm thick section was taken from the specimens. This was followed by hematoxylin and eosin staining.

Statistical Analysis

GraphPad software (Prism 3.0; GraphPad Software, San Diego, CA, USA) was used for statistical evaluation. All data were expressed as means ± standard error of the mean. GSH and MDA levels, MPO and Na^+/K^+-ATPase activities in both the stomach and duodenum tissues, and TNF-α and IL-1β levels in serum between the groups of data were compared pairwise using one-way analysis of variance and Tukey's test.

RESULTS

Biochemical Findings

TNF-α and IL-1β serum levels were significantly higher in the ulcer group than those in the saline-treated control group (p<.001), whereas in the NS-treated ulcer group, those levels were found to be decreased in the ulcer group compared with the levels in the saline-treated control group (p<.001) (Table 1).

MDA levels in the stomach and duodenum tissues were found to be significantly increased in the saline-treated ulcer group compared with the levels in the saline-treated control group (p<.01 and p<.001, respectively). Administering NS significantly reduced the increase in MDA levels in both tissues (p<.01 and p<.001, respectively) (Figures 1a and b).

In the saline-treated ulcer group, GSH levels of the stomach and duodenum tissues were found to be significantly lower than those in the saline-treated control group (p<.001 and p<.01, re-

TABLE I. Indomethacin-Induced Ulcer Model in Rats with Serum Levels of TNF-a and IL-Iβ in All Groups

	Control		Ulcer	
	Saline-treated	NS-treated	Saline-treated	NS-treated
TNF-α (pg/ml)	7.93 ± 2.06	9.13 ± 1.66	38.83 ± 7.94 ***	13.57 ± 3.49 +++
IL-Iβ (pg/ml)	11.07 ± 1.70	12.89 ± 1.87	39.52 ± 3.15 ***	16.22 ± 2.78 +++

***, *P* <.001 comparisons of ulcer group to saline group and +++, *P* <.001 comparisons of NS-treated ulcer group to ulcer group.
NS: Nigella sativa; TNF-a: tumor necrosis factor alpha; IL-Iβ: Interleukin-I beta

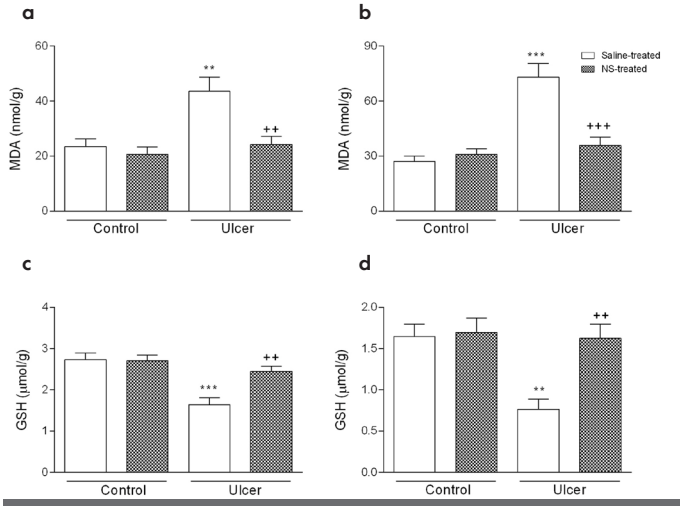

Figure I. a-d. The representative graph showing indomethacin-induced ulcer model in rats in all groups: (a) MDA levels in the stomach, (b) MDA levels in the duodenum, (c) GSH levels in the stomach, and (d) GSH levels in the duodenum.
, *P* <.01 and *, *P* <.001 comparisons of saline-treated control group; ++, *P* <.01 and +++, *P* <.001 comparisons of saline-treated ulcer group.
NS: Nigella Sativa; MDA: Malondialdehyde; GSH: Glutathione

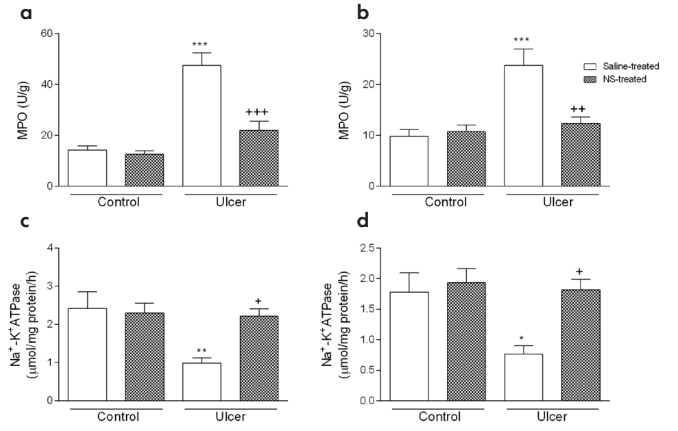

Figure 2. a-d. The representative graph showing indomethacin-induced ulcer model in rats in all groups: (a) MPO activity in the stomach, (b) MPO activity in the duodenum, (c) Na+/K+-ATPase activity in the stomach, and (d) Na+/K+-ATPase activity in the duodenum.
*, *P* <.05; **, *P* <.01 and ***, *P* <.001 comparisons of saline-treated control group; +, *P* <.05; ++, *P* <.01 and +++, *P* <.001 comparisons of saline-treated ulcer group.
NS: Nigella sativa; MPO: Myeloperoxidase

spectively). The decrease has been significantly prevented in the NS-treated ulcer group (*p*<.01) (Figure Ic and d).

The development of ulcers resulted in neutrophil infiltration, leading to a significant increase in the MPO activity in the

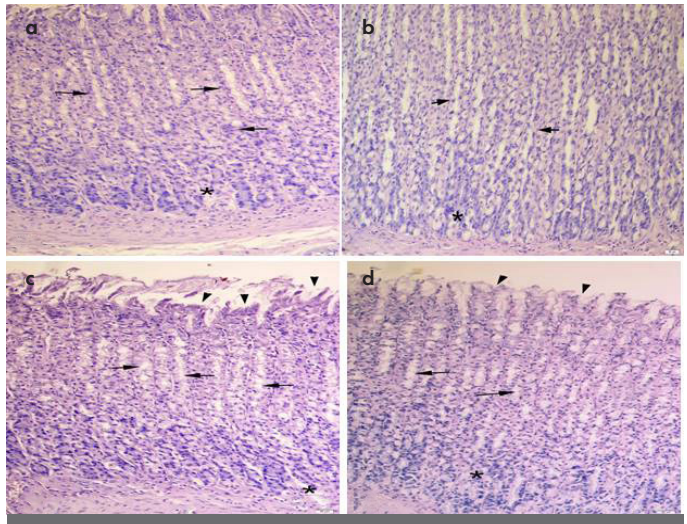

Figure 3. a-d. (a) Saline-treated control group: regular layout of the epithelial and neck cells (arrows) and the glandular portion (*), (b) NS-treated control group: similar to the saline-treated group in having regular neck cells (arrows) and a glandular portion (*), (c) Saline-treated ulcer group: severe desquamation of epithelial (arrowheads) cells and dilation of the neck (arrows) and the glandular (*) region, (d) NS-treated ulcer group: reduced desquamation of epithelial cells (arrowheads) and dilation of the neck (arrows) and the glandular region (*)
Magnification of all pictures are × 200
NS, Nigella sativa

gastric and duodenal tissues compared with the activity in saline-treated control group (*p*<.001). In addition, MPO activity was significantly reduced in the NS-treated ulcer group, which recovered the values close to those of the saline-treated control group (*p*<.001 and *p*<.01, respectively) (Figures 2a and b).

Na^+/K^+-ATPase activity in the stomach and duodenal tissues was found to be significantly lower in the saline-treated ulcer group than that in the saline-treated control group (*p*<.01 and *p*<.05, respectively). It was noticed that NS has a significant protective effect in the ulcer group (*p*<.05) (Figure 2c and d).

Histopathological Findings

Stomach. In the stomach, the morphology of neck cells and glandular cells seems to be regular in the saline-treated control group (Figure 3a), and cells in the NS-treated control group have similar morphology (Figure 3b). The saline-treated ulcer group showed severe epithelial desquamation and dilation of the neck region in cells (Figure 3c), whereas in the NS-treated ulcer group, these properties of cells had reduced (Figure 3d).

Duodenum. In the saline-treated control group, the duodenum showed a regular morphology in both epithelium and glands

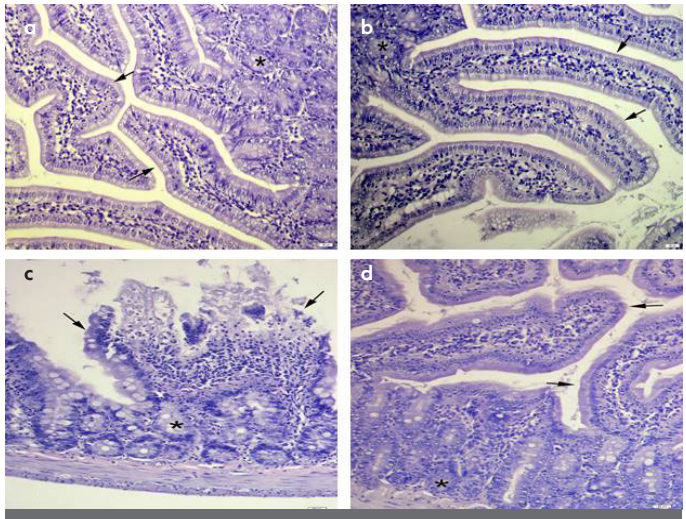

Figure 4. a-d. (a) Saline-treated control group: regular morphology with epithelium (arrows) and glands (*), (b) NS-treated control group: the epithelium (arrows) and the gland (*), (c) Saline-treated ulcer group: severe villar degeneration (arrows) and the gland (*), (d) NS-treated ulcer group: re-epithelization of the villi structure (arrows) and the gland (*).
Magnification of all pictures are × 200
NS, Nigella sativa

(Figure 4a). In addition, a similar morphology was seen in the NS-treated control group (Figure 4b). The saline-treated ulcer group revealed severe desquamation of villar epithelial and glandular degeneration (Figure 4c), whereas regeneration was prominent in both villar and glandular morphologies in the NS-treated ulcer group (Figure 4d).

DISCUSSION

Indomethacin, a widely used NSAID, exerts adverse effects on the mucosal lining of the gastric and small intestinal wall. Gastrointestinal side effects of indomethacin have been linked to increased production of inflammatory cytokines and neutrophil infiltration, which leads to mucosal injury (9, 10).

Black cumin/seed, also known as NS, has traditionally been used as a remedy by various Middle and Far East folks (11, 13). Studies in rats have demonstrated that NS possesses some potent pulmonary protective, anti-inflammatory, antinephropathic, and anticarcinogenic effects (14-16).

The aim of this study was to investigate the efficacy of the oil form of NS in the prevention of indomethacin-induced gastric mucosal injury in a rat model. This study will provide valuable insight into the antioxidant and anti-inflammatory effects of the oil form of NS in small intestinal and gastric indomethacin-induced mucosal damage. A gastrointestinal inflammatory response caused by NSAIDs may use TNF-α and IL-Iβ as the principal signal molecules. Recent studies show that indomethacin-induced ulcer injury in rats is characterized by neutrophil accumulation and increased gastrointestinal circulatory levels of IL-Iβ and TNF-α (17-19). We have determined that the levels of TNF-α and IL-Iβ in the serum were higher in the ulcer group than those in the saline group. However, administering NS to the ulcer group significantly reduced the levels of TNF-α and IL-Iβ, and the levels became similar to those of the saline group values.

The detrimental effects of free oxygen radicals are eliminated by some natural defense mechanisms, including GSH. Previous studies have shown that indomethacin decreases GSH levels in gastrointestinal tissues (20, 21). According to Ersahin et al. (22), NS oil potent free radical scavenging properties acted against reactive hydroxyl, peroxyl, and superoxide radicals to counteract lipid peroxidation of the brain tissue caused by a subarachnoid hemorrhage in rats. This effect was carried out by the preservation of the level of the antioxidant GSH (22). We revealed a significant reduction in GSH levels in the stomach and duodenal tissues in the ulcer group compared with those in the saline group. In addition, it has been found that NS could avert this reduction to a significant degree. These compounds lead to the denaturation of intracellular enzymes and proteins, worsening tissue injury. Thus, it has been proposed that lipid peroxidation can be accurately reflected by MDA levels (23). In this study, significantly higher MDA levels in the stomach and duodenal tissues were found in the indomethacin-induced ulcer group than those in the saline group. On the other hand, NS treatment reduced MDA levels significantly. Normal neutrophil functions depend on MPO, which is produced by hydrochloric acid as a product of neutrophil oxidation. MPO levels are increased by neutrophils stimulation caused by various stimuli such as indomethacin (23). Yıldız et al. (24) showed that ischemia-reperfusion injury induced in rat liver created enhanced lipid peroxidation and inflammatory response. As a result, this leads to increased MPO levels, which were then reduced by the administration of NS (24). We found out that the indomethacin-induced ulcer group had significantly higher MPO levels in gastric and duodenal tissues than the control group, and this effect was significantly reversed by NS.

Na^+/K^+-ATPase is a vital enzyme for cellular functions that acts by maintaining membrane potential and cellular osmotic balance. Its function is sensitive and profoundly impaired by free radicals and reactive oxygen species for the transport of proteins. The red blood cell membrane is exposed to lipid peroxidation by the action of oxidative stress, culminating in alterations in membrane lipid content. This gives rise to reduced membrane fluidity and Na^+/K^+-ATPase activity in the red blood cell membrane (25, 26). According to our results, the ulcer group had a significantly lower Na^+/K^+-ATPase activity in the gastric and duodenal tissues than in the control group, and this effect was largely eliminated by NS. It has been shown that the inflammatory and histopathological analyses revealed a wide-scale indomethacin-induced gastric tissue injury involving gastric epithelial cells and glandular cells, which included mainly vacuolization and was relieved in the form of epithelial regeneration and improvement after NS administration.

Our results suggest that NS oil exerted potent anti-inflammatory and antioxidative actions in the serum, tissue, and histological sections of rats with indomethacin-induced gastric and intestinal mucosal damage.

Indomethacin has a broad range of uses in rheumatic disorders such as rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis, as well as tendonitis and traumatic synovitis. Unfortunately, its gastropathy side effects may preclude its use in these disorders. NS offers hope in this regard and may be used in con-

junction with indomethacin to overcome its detrimental gastric side effects. Our study is the first to explore this possibility, and further studies are needed to clarify this issue.

Ethics Committee Approval: Ethics committee approval was received for this study from Marmara University Experimental Animal Research Centre (The approval code (registration number) is 26.2011.Mar and the approval date is 14/04/2011.).

Informed Consent: N/A

Peer-review: Externally peer-reviewed.

Author contributions: Concept - E.G., E.Ö., H.H.A, A.Ö.Ş.; Design - E.G., A.Ö.Ş.; Supervision - E.G., A.Ö.Ş.; Resource - E.G., E.Ö., H.H.A., A.Ö.Ş.; Materials - E.G., E.Ö., H.H.A., A.Ö.Ş.; Data Collection and/or Processing - A.Ö.Ş., A.V.Ö., A.A., Ş.Ç.; Analysis and/or Interpretation - A.V.Ö., A.Ö.Ş., Ş.Ç.; Literature Search - A.A., B.K.; Writing - E.G., A.A., B.K., A.Ö.Ş.; Critical Reviews - E.G., A.Ö.Ş.

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

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Original Article

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Effect of Dual Mesh Wrap on The Stability of Colonic Anastomosis

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BACKGROUND/AIMS
Colon anastomotic leakage is the cause of significant morbidity and mortality in surgery. Therefore, we aimed to demonstrate experimentally the effect of the conventional method of wrapping them through colo-colonic anastomosis performed by dual patch on anastomotic healing and security.

MATERIAL and METHODS
The study was conducted at the Experimental Animal Research Unit of the Medical Faculty of Trakya University, Edirne, Turkey. A total of 20 Wistar Albino adult rats were used. The rats were divided into 2 groups: 10 rats in the control group and 10 rats in the dual patch group. All rats underwent partial segmental colon resection, and colo-colonic anastomosis was performed in a single layer with 5/0 polypropylene. For rats in the dual patch group, the anastomosis was wrapped up with a 1-cm-wide dual patch. In the control group, there was no operation on the anastomosis. At 7 days after the procedure, the degree of peritoneal adhesion model previously prepared according to Evans devices laparotomy was used to observe all the rats and colon burst pressure. Both histopathological examination and the examination of the perianastomotic area were performed.

RESULTS
In the rats that were treated with dual mesh, there was a statistically significant increase in anastomotic line burst pressure (P<.05), a statistically significant increase in collagen amount (P<.05), and a statistically significant decrease in abdominal adhesions (P<.05).

CONCLUSION
As a result, the colo-colonic anastomosis of winding dual patch, without causing intra-abdominal adhesions, improves security by increasing the anastomosis bursting pressure.

Keywords: Colorectal surgery, mesh, anastomotic leakage

INTRODUCTION

One of the most serious complications after colorectal surgery is anastomotic leakage, which is associated with high morbidity and mortality. In 1826, Denans (1) designed a device that performed colonic anastomosis without suture. In 1892, Murphy developed another device composed of 2 metallic rings that could connect the ends of the intestine with a button. Since then, many techniques for colonic anastomoses have been developed that aim to prevent or reduce the complications associated with anastomoses. More than half of postoperative deaths are caused by sepsis associated with anastomotic leakage (2). The frequency of anastomotic leakage after colonic resection was reported to be between 0.5% and 30% (1, 2).

Various techniques have been proposed for anastomosis, and treatment modalities have been suggested to prevent anastomotic leakage. One treatment modality is wrapping the intestinal anastomosis with various prosthetic materials, such as polypropylene mesh (2). However, polypropylene mesh can cause intra-abdominal adhesions (3).

In this study, we evaluated the effect of wrapping colonic anastomosis in a dual mesh on anastomotic stability. The dual mesh was not expected to cause intra-abdominal adhesions.

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MATERIAL and METHODS

This study was performed at the Experimental Animals Research Unit, School of Medicine, University of Trakya Ethical approval was obtained from the local ethics committee of the University of Trakya Faculty of Medicine. A total of 20 adult Wistar Albino rats aged 6 to 8 months were used. The mean weight of the rats was 210 g (180–230 g).

Anesthesia and Surgical Procedures

Rats were maintained in 12-hour dark and light conditions, with a room temperature of 22°C±1°C and humidity of 50% to 60%. Rats were fed with standard pellet feed and had access to city potable water until the day of the experiment. Rats were fasted for 12 hours before the experiment but were allowed to drink water until 30 minutes before the experiment. No colon cleansing was performed. Preprocedure anesthesia was provided using 5 to 10 mg/kg xylazine hydrochloride (Rompun, Bayer, Istanbul, Turkey) administered intramuscularly and ketamine hydrochloride (Ketalar, Pfizer, Istanbul, Turkey). Rats lying in the supine position were fixed to operating beds with adhesive bands, the abdominal hair was clipped, and the skin was cleansed using povidone-iodine (Figure 1). A midline incision was made in the lower abdominal region using a number 15 blade. A colon segment with a length of 1 or 2 cm distal to the cecum was resected. Then, a single-layer colonic anastomosis was performed using a 5/0 polypropylene suture. Rats in group I (n=10) underwent no other procedure, and the abdominal layers and skin were closed separately using 3/0 polypropylene sutures. In group II rats, the colonic anastomosis was wrapped with a dual mesh (Polymesh, Betatech Medical, Istanbul, Turkey) that was 1 cm in width and had a length equal to the circumference of the anastomosis. The mesh was wrapped so that the polypropylene layer was in contact with the colonic serosa (Figure 2). The abdominal layers and skin were then closed separately using a 3/0 polypropylene suture.

FIGURE 1. Removing of the fur and cleansing of the skin (rat model)

FIGURE 2. Attaching the dual mesh to the anastomotic suture line

Main Points:

- Winding a dual mesh around colocolic anosthomoses in rats provides better burst pressures.
- Winding a dual mesh around colocolic anosthomoses in rats provides increased collagen amount in healing anosthomosis
- Winding a dual mesh around colocolic anosthomoses in rats significantly decreases the amount of abdominal adhesions.

Evaluation

Rats were allowed to feed normally 12 hours after the surgery, and water intake was not limited. At 7 days after the surgery, all rats were anesthetized with ketamine and xylazine and killed by exsanguination. After death was confirmed, a large incision was applied to the anterior abdominal wall to expose all peritoneal cavities. The intra-abdominal adhesion was graded according to the Evans model (Table 1).

The anastomotic line was resected 2 cm from the proximal and distal parts to measure the bursting pressure of the anastomosis. The distal end of the intestinal segment was tied with a 2/0 silk suture. An 18F catheter was introduced into the proximal end, and the other end of the catheter was connected to a transducer and air pump. This system allowed us to measure the intraluminal pressure of the resected intestinal segment (mm Hg) (Figure 3). The intestinal segment was soaked in a water-filled container, and air was pumped into the lumen in a controlled manner. The point of the first air leak from the colon wall was recorded as the anastomotic bursting pressure.

FIGURE 3. Macroscopic view of the anastomosis at the end of the experiment

TABLE 1. Evans Model (intra-abdominal adhesions)

Adhesion Stage	Definition
0	No adhesion
1	Spontaneously separating adhesions
2	Adhesions separated by traction
3	Adhesions separated by dissection

Histopathological Examination

Histopathological evaluation was performed by a single pathologist at the Department of Medical Pathology, University of Trakya. The anastomotic line was cut together with 1 cm of surrounding tissue from each side and fixed in 10% formaldehyde. Fixed tissues were embedded in paraffin blocks and sectioned. Thin sections were stained with hematoxylin and eosin dye and examined using light microscopy. Images were captured by a computer. Histopathological staging of the anastomotic line was performed according to the Ehrlich-Hunt model. The following parameters were evaluated: inflammatory cell infiltration, neovascularization, fibroblast activity, and the amount of collagen (Table 2).

Statistical Analysis

Statistical evaluation was performed using the STATISTICA AXA 7.1 statistical program. Normal distribution of measurable variables was tested using the Kolmogorov-Smirnov test. Between-groups analysis was performed using variance analysis and post hoc Tamhane and Bonferroni tests (for variables with normal distribution) and with Kruskal-Wallis variance analysis and Mann-Whitney *U* tests (for variables without normal distribution). Median (minimum-maximum) values and mean ± standard deviation values were used for descriptive statistics. A *P* value <.05 was considered statistically significant.

TABLE 2. Ehrlich-Hunt model

Grade	Inflammatory cell/fibroblastic activity/neovascularization/ amount of collagen
1	Low density and separated
2	Low density and in all places
3	High density but separated
4	High density and in all places

TABLE 3. Distribution of adhesion grades according to Evans model

Adhesion scores according to Evans model	Control group (n = 10)	Dual mesh group (n = 10)
Grade 0	0	10%
No adhesion		(n = 1)
Grade 1	0	40%
Spontaneously separating adhesions		(n = 4)
Grade 2	20%	50%
Adhesions separated by traction	(n = 2)	(n = 5)
Grade 3	80%	
Adhesions separated by dissection	(n = 8)	0

TABLE 4. Adhesion score average according to Evans model

Adhesion scores according to Evans Model	Control group (n = 10)	Dual mesh group (n = 10)	p*
Mean ± SD	2.8 ± 0.42	1.4 ± 0.69	
Median (Min-Max)	3 (2–3)	1.5 (0–2)	p < 0.001

Mann–Whitney U test; * p < 0.05 statistically significant; SD: Standard deviation; Min: Minimum; Max: Maximum

TABLE 5. Bursting pressures

Bursting pressure (mmHg)	Control group (n = 10)	Dual mesh group (n = 10)	p*
Mean ± Standard deviation	140 ± 13.3	205 ± 22.7	
Median (Min-Max)	140 (120–160)	200 (180–250)	p < 0.001

Mann–Whitney U test; * p < 0.05 statistically significant

RESULTS

No mortality occurred because of anesthesia or the surgical procedure. No macroscopic anastomotic leakage was detected in the killed rats.

Evaluation of Intra-Abdominal Adhesions

Adhesions were staged as follows: stage 0, no adhesions; stage I, adhesions released without intervention; stage 2, adhesions released by pulling; and stage 3, adhesions released by dissection. Stage 3 adhesions were observed in 8 rats in group I, and stage 2 adhesions were observed in 2 rats in group I. Five rats that received the dual mesh (group II) had stage 2 adhesions, and 4 rats had stage I adhesions. One rat had no adhesions (stage 0) (Table 3).

The distribution of adhesion scores was evaluated using the Evans model. The mean adhesion scores were as follows: 2.8±0.42 for the control group (group I) and 1.4±0.69 for the dual mesh group (group II). The mean adhesion score in the dual mesh group (group II) was significantly lower than that in the control group (group I) (*P*<.001) (Table 4).

Measurement of Bursting Pressure

The mean bursting pressure was 140±13.3 mm Hg in the control group and 205±22.7 mm Hg in the dual mesh group. No bursting occurred in rats fitted with the dual mesh in the anastomotic line. However, bursting did occur in other colonic tissues. The mean bursting strength in the dual mesh group was significantly higher than that in the control group (*P*<.001) (Table 5).

Histopathological Evaluation

The anastomotic lines were histopathologically staged according to the Ehrlich-Hunt model. The scores for inflammatory cell infiltration, fibroblast activity, neovascularization, and collagen are shown in Table 6.

The mean inflammatory cell score was 3.9±0.31 in the control (group I) and 2.7±0.82 in the dual mesh group (group II). The mean inflammatory cell score was significantly lower in the dual mesh group (group II) than in the control group (*P*=.002).

The mean fibroblast activity score was 3.9±0.31 in the control group (group I) and 2.7±0.94 in the dual mesh group (group II). The mean fibroblast activity score was significantly lower in the dual mesh group (group II) than in the control group (*P*=.004).

The mean neovascularization score was 3.9±0.31 in the control group (group I) and 2.7±0.82 in the dual mesh group (group II). The mean neovascularization score was significantly lower in the dual mesh group (group II) than in the control group (*P*=.002).

The mean amount of collagen was 2.3±0.48 in the control group (group I) and 3.2±0.63 in the dual mesh group (group II). The mean fibroblast activity score was significantly higher in the dual mesh group (group II) than in the control group (*P*=.005).

TABLE 6. Histopathological staging of the anastomotic line according to the Ehrlich–Hunt model

Histopathologic staging	Control group Mean ± SD Median (Min-Max)	Dual mesh group Mean ± SD Median (Min-Max)	p*
İnflammatory cell	3.9 ± 0.31 4 (3–4)	2.7 ± 0.82 2.5 (2–4)	p = 0.002
Fibroblast activity	3.9 ± 0.31 4 (3–4)	2.7 ± 0.94 2 (2–4)	p = 0.004
Neovascularization	3.9 ± 0.31 4 (3–4)	2.7 ± 0.82 2.5 (2–4)	p = 0.002
Amount of collagen	2.3 ± 0.48 2 (2–3)	3.2 ± 0.63 3 (2–4)	p = 0.005
Total	14 ± 0.66 14 (13–15)	11.3 ± 2.05 10(9–15)	p = 0.006

Mann–Whitney U test; * p < 0.05 statistically significant; SD: Standard deviation; Min: Minimum; Max: Maximum

The total mean histological scores were significantly lower in the dual mesh group than in the control group (*P*=.006).

DISCUSSION

Colonic anastomoses are frequently used during abdominal surgery (1). Manual single-layered colonic anastomoses are performed to prevent anastomotic stenosis (1, 3, 4). An increasing number of anastomoses have been performed after surgeries to remove colorectal tumors, which is proportional to the increasing age of the population (5). The most appropriate technique for reducing the mortality and morbidity rates associated with anastomosis has still not been defined. Many experimental studies have been performed to investigate ways to support the anastomosis with prosthetic materials (6). In this study, we examined whether a dual mesh could support the colonic anastomosis. We assumed that this would cause no intra-abdominal adhesions. Dual mesh as a means of supporting anastomosis has not been investigated previously.

Any intra-abdominal intervention will inevitably result in adhesions (7), including the intraperitoneal use of a prosthetic material (such as polypropylene mesh) (8). Adhesions are the principal reason for postoperative mechanical obstruction of the intestine; therefore, they must be avoided if possible. We hypothesized that a dual mesh would provide mechanical support to the anastomosis without increasing the formation of adhesions. We found that adhesion formation was significantly lower in rats fitted with dual mesh than in control rats. This indicates that a dual mesh prevents perianastomotic and intra-abdominal adhesions, which will decrease long-term intestinal obstruction.

Wound healing can be monitored by tissue inflammation, neovascularization, fibroblast activity, and collagen levels (3). We evaluated these parameters in the anastomotic line to measure wound healing (2, 3). Healing after colonic anastomosis is directly proportional to the amount of collagen in the anastomotic line (9). Prosthetic material such as polypropylene is known to stimulate collagen production in the tissues they come into contact with (10). Therefore, a dual mesh with propylene in contact with the intestinal wall (as used in this study) should promote collagen synthesis and hence, the healing and stability of the colonic anastomosis. In agreement with previous findings, the collagen levels were higher in the anastomotic line of rats fitted with the dual mesh. However, other parameters of wound healing, such as inflammatory cell infiltration, neovascularization, and fibroblast activity, were lower in rats fitted with the dual mesh. When all parameters were analyzed together, tissue healing was found to be significantly better in rats without the dual mesh. We believe that this can be attributed to the early termination of the experiment on the seventh postoperative day. If the dual mesh were in contact with the anastomotic line for a longer time, then the other wound healing parameters would likely change in favor of the dual mesh group, as was the case for the collagen levels.

An anastomosis wrapped with a material that is relatively less elastic, such as dual mesh, is less likely to shrink and result in stenosis. No mechanical intestinal obstructions were observed in this study. However, the 7-day study period was too short to draw firm conclusions. In addition, we used rats in our study; therefore, care should be taken when extrapolating these findings to humans. Further investigations are required to determine the effectiveness of this method in humans.

We did not observe any bursting of the anastomotic line in rats fitted with the dual mesh. This shows that the dual mesh provided important mechanical support to the anastomosis. The anastomotic bursting pressure is a marker of the anastomotic line resistance to intraluminal pressure and is a reliable method for evaluating anastomotic healing. Anastomotic bursting pressure is directly proportional to the mass of collagen in the tissue, which forms cross links to stabilize the tissue (9, 10). The dual mesh used in this study provided a barrier in regions that induce anastomotic leakage (particularly in the suture holes), thereby increasing anastomotic safety.

We have shown that the use of a dual mesh reduces anastomotic bursting and intra-abdominal adhesions during the early postoperative period. Long-term follow-up of rats fitted with the dual mesh is required. In conclusion, wrapping the colonic anastomotic line with a dual mesh increases anastomotic stability by increasing collagen levels and anastomotic bursting pressure without causing intra-abdominal adhesions.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Trakya University (Approval date: 29.09.2014, No: 2014.09.02).

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Kawasaki Disease: A 10-Year Experience

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BACKGROUND/AIMS
Kawasaki disease (KD) is an acute multisystemic vasculitis that manifests with prolonged fever commonly in children and involves medium-sized vessels. Coronary artery aneurysm occurs in 15%-25% of untreated patients. This study aims to evaluate the demographic, clinical, and laboratory characteristics as well as the treatment of patients with KD who were followed up in our clinic for 10 years.

MATERIAL and METHODS
Patients who were hospitalized with the diagnosis of KD between January 2009 and January 2019 in our hospital were evaluated on the basis of the patient records. Patients meeting at least four of the principal KD criteria were categorized as complete KD (cKD), and patients meeting fewer criteria were categorized as incomplete KD. Demographic characteristics and clinical, laboratory, and echocardiography (ECHO) findings were evaluated.

RESULTS
Of the 36 patients (aged 4-62 months) involved in this study, 23 (63.9%) were male, and 30 (83.3%) were diagnosed within the first 10 days of their sickness. KD mostly occurred in children aged 12-60 months (66.7%). cKD was observed in 19 patients, and 84.2% of them were aged between 12 and 60 months. ECHO showed coronary artery involvement in nine patients—eight of whom were male—and mitral insufficiency in three patients. Intravenous immunoglobulin treatment was administered twice in seven patients, one of them developed macrophage activation syndrome.

CONCLUSION
KD should be considered in cases of prolonged fever in children, and the diagnostic criteria should be examined carefully, and if diagnosed, patients should be given the correct treatment without any delay.

Keywords: Children, Kawasaki disease, macrophage activation syndrome

INTRODUCTION

Kawasaki disease (KD) is an acute febrile multisystemic vasculitis generally seen in children aged <5 years. The etiology of the disease is still unknown. It involves medium-sized vessels and manifests itself with prolonged fever and mucocutaneous symptoms (1, 2). In untreated cases, coronary artery aneurysm (CAA) develops with a frequency of 15%-25%. The incidence of KD varies widely, depending on the geographical region and ethnicity; for example, in Japan, the annual incidence has been reported to be 309 in 100,000 children aged 0-4 years, whereas in the United States, the annual incidence is 25 in 100,000, and in England, it is 4 or 5 in 100,000 children (3-5).

The acute period in KD is usually defined as the first 10 days, and during this period, high fever is accompanied with certain symptoms that comprise the current diagnostic criteria, including bilateral nonpurulent conjunctivitis; cherry-red, cracked lips or strawberry tongue; cervical lymphadenomegaly >1.5 cm; nonvesiculobullous maculopapular or erythematous rash; as well as induration and erythema of the hands and feet (1, 2, 6). However, not all of the findings appear at the same time in KD; the symptoms are observed for a short time, and some findings regress or disappear

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by the time of diagnosis. According to the American Heart Association (AHA), complete KD (cKD) is diagnosed when four of these criteria are evident with fever lasting ≥4 days. The usual diagnostic criteria for KD are not sufficient for incomplete KD (iKD) cases with fever meeting only two or three diagnostic criteria. In such cases, the diagnosis of KD is supported by echocardiography (ECHO) in the presence of pathological appearance in the coronary arteries, pericardial effusion, or valve involvement. For such cases, supportive laboratory criteria were recommended by AHA for early diagnosis and initiation of treatment in patients meeting two or three principal criteria and having normal ECHO findings in the acute phase. In the presence of C-reactive protein (CRP) >3 mg/dl and/or erythrocyte sedimentation rate (ESR) >40 mm/h in these patients, these supporting laboratory criteria (white blood count [WBC] >15.000 per mm^3, anemia by age, platelet >450,000 per mm^3 after the seventh day, serum albumin <3.0 g/dl, alanine aminotransferase [ALT] >40 U/L, and urine WBC >10 per high power field) should be checked, and if the patients meet three or more of such criteria, they should be diagnosed with incomplete KD, treated accordingly, and monitored with ECHO (1, 6).

Therefore, this study aimed to evaluate the demographic, clinical, and laboratory characteristics of patients with KD who had been followed up at our clinic for 10 years and to evaluate the treatment and follow-up results of these patients.

MATERIAL and METHODS

For the study, the files of the patients who were hospitalized with the diagnosis of KD at the Pediatric Clinic of hospital between January 2009 and January 2019 were retrieved from the hospital records, and those who did not meet the diagnostic criteria were excluded from the study. Age, gender, admission, duration of fever, physical examination, and laboratory findings of the patients as well as the treatments provided were evaluated retrospectively. Patients meeting at least four diagnostic criteria for KD were categorized as cKD cases, whereas those meeting two or three principal criteria for KD and who were positive for KD in ECHO or those with ESR >40 mm/h and CRP positivity who met three or more supporting laboratory criteria (anemia by age, leukocytosis, thrombocytosis after the seventh day, sterile pyuria, hypoalbuminemia, and ALT elevation) were considered to have iKD (1, 6). The first day of the onset of fever was accepted as the onset of the disease, and the time to diagnosis was accepted as the period from the onset of fever to the time diagnosis was made. The patients who were diagnosed within the first 10 days were considered to have acute KD, and those diagnosed after 10 days were considered to have subacute KD.

Main Points:

- Kawasaki disease is a multisystemic disease associated with fever.
- Finding on Echocardiography is valuable for the diagnosis of Kawasaki disease, but it does not always accompany. The risk of coronary pathology is higher at younger ages.
- Early diagnosis and treatment positively affects the prognosis of the disease.

In ECHO according to the Boston formula, z score >2.5 or coronary artery internal lumen diameter (ILD) >3 mm in children aged <5 years and an ILD >4 mm in those aged >5 were accepted as dilatation or small aneurysm. Enlargement of the coronary artery segment by <1.5-fold was considered dilatation, and its enlargement by ≥1.5-fold was accepted as an aneurysm (1, 7). Patients with coronary artery dilatation greater than normal and those with no segmental aneurysm were considered to have coronary artery ectasia. Brightness in coronary arteries and mitral and aortic valve regurgitation were evaluated as findings to support the KD diagnosis (7). ECHO was repeated within 2 weeks after the onset of the disease and at the fourth week. All patients diagnosed with KD received a single dose of intravenous immunoglobulin (IVIG) 2 g/kg, continuous infusion for 12 hours, and acetylsalicylic acid (ASA) at the dose of 80-100 mg/kg/day for a few days and then 5 mg/kg/day for 4-6 weeks. Prolonged high fever lasting for 36 hours after IVIG and ASA administration was considered a nonresponse to treatment. Comparisons were made between ECHO findings, age, gender, leukocyte count, hemoglobin (Hb) levels, platelet count, ESR, CRP, albumin, and aspartate aminotransferase (AST) and ALT levels. Ethics committee approval was received for this retrospective study from the Ethics Committee of our hospital (approval date: 08/01/2019, approval number: 48670771-514.10).

Data Analysis

The research data and variables were analyzed with the Statistical Package for the Social Sciences 22.0 software package (IBM Corporation, Armonk, NY, USA) and MedCalc 14 (MedCalc Software, Ostend, Belgium). Shapiro-Wilk test and variance homogeneity were evaluated by Levene's test. Independent samples *t*-test was used with bootstrap results, and Mann-Whitney U test was used with Monte Carlo results for the comparison of two independent groups according to quantitative data. For the comparison of categorical variables, Pearson chi-square and Fisher exact tests were used. The receiver operating characteristic curve was used to reveal the true positive rate (sensitivity) against the false positive rate (specificity) for all possible cutoff values calculated for group variables as well as the positive and negative predictive values. The quantitative variables are presented in tables as mean ± standard deviation and median range (maximum-minimum), and categorical variables are shown as n (%). The variables were examined at a 95% confidence level, and a p-value <.05 was accepted as significant.

RESULTS

Medical records of 51 patients hospitalized with the diagnosis of KD were examined; 15 patients were excluded from the study because they did not meet the AHA diagnostic criteria, and the remaining 36 patients were included in the analysis. A total of 23 of the patients (63.9%) were male; the male-to-female ratio was 1:77. The ages of the patients ranged from 4 months to 62 months, with a mean age of 29.5 ± 19.129 months (Table 1).

The distribution of patients by the date of diagnosis showed that five patients (13.8%) were diagnosed with KD in 2009 and five were diagnosed in 2010, two (5.5%) in 2011, two in 2012, one (2.7%) in 2013, six (16.6%) in 2014, three (8.3%) in 2015, four (11.1%)

in 2016, five (13.8%) in 2017, and three (8.3%) in 2018. The distribution of the patients by the months in which they presented to the hospital revealed that they most frequently presented to the hospital in July (19.4%, n=7) (Figure 1).

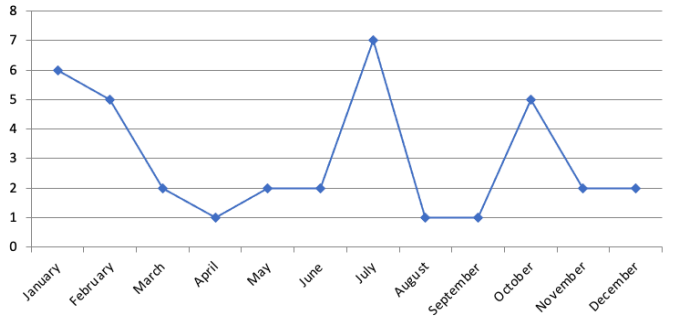

FIGURE 1. Seasonal distribution of patients

TABLE 1. Age and gender distribution of patients

			Age (months)			
			0-11 months	12–60 months	60+ months	Total
Gender	Male	N	4	15	4	23
		%	17.4%	65.2%	17.4%	100.0%
	Female	N	3	9	1	13
		%	23.1%	69.2%	7.7%	100.0%
Total		N	7	24	5	36
		%	19.4%	66.7%	13.9%	100.0%

TABLE 2. Clinical characteristics and other findings of Kawasaki patients

Principal criteria	n=36	%
Changes in oral mucosa	34	94.4
Changes in extremities	29	80.6
Polymorphous rash	28	77.8
Bilateral non-purulent conjunctivitis	26	72.2
Cervical lymphadenopathy	23	63.9
Other		
Perineal Desquamation	11	30.6
Aseptic Meningitis	4	11.1
Arthritis	3	8.3
Respiratory infections	2	5.5
Febrile convulsion	2	5.5
Gallbladder Hydrops	1	2.8
Redness at the site of the BCG scar	1	2.8
Macrophage activation syndrome	1	2.8
Anemia for age	23	63.9
WBC count >15.000/mm 3	20	55.5
Platelet count >450.000/mm 3	26	72.2
Hypoalbuminemia	4	11.1
Sterile Pyuria	11	30.6
ALT >40U/L	20	55.5

The mean time to diagnosis according to the duration of fever ranged from 4 to 20 days, with a mean of 7.69 ± 3.79 days. A total of 30 patients (83.3%) were diagnosed within the first 10 days, and of the remaining 6 patients (aged 22-62 months), 3 were diagnosed with arthritis, 1 with gallbladder hydrops, and 2 with aseptic meningitis. Their condition improved after they received IVIG treatment, and none had coronary findings.

All patients had a high fever. The most common symptom was changes in oropharyngeal mucosa, occurring in 94.4% of the cases (n=34), followed by changes in extremities in 29 patients (80.6%), polymorphous rash in 27 patients (77.8%), conjunctivitis in 26 patients (72.2%), and lymphadenomegaly in 23 patients (63.9%) (Table 2). In 1 patient, lymphadenopathy was in the submandibular region, and it was treated as infectious lymphadenitis.

Among the other findings, the most common was perineal desquamation, occurring in 30.6% of the patients, followed by aseptic meningitis (11.1%), arthritis (8.3%), gallbladder hydrops, macrophage activation syndrome (MAS), and redness in Bacillus Calmette–Guérin (BCG) vaccine scar (2.8%) (Table 2). A male patient aged 9 months with hereditary spherocytosis was

TABLE 3. Distribution of complete and incomplete Kawasaki cases by age groups

		0-11 months	12- 60 months	60 + months	
Incomplete	n	5	8	4	17
	%	29.4%	47.1%	23.5%	100.0%
Complete	n	2	16	1	19
	%	10.5%	84.2%	5.3%	100.0%
Total	n	7	24	5	36
	%	19.4%	66.7%	13.9%	100.0%

TABLE 4. Comparison of echocardiography findings and laboratory values

	Positive Echo Finding (N = 12) (Mean ± SD)	Negative Echo Finding (N = 24) (Mean ± SD)	p
WBC (×1000/mm^3)	17904.16±6057.29	14070.00±5736.00	.07
Hb (g/dL)	10.2417±1.60593	10.5000±0.81347	.97
Platelet count (×1000/mm^3)	99500.08±240258.35	268816.37±316800.79	.17
CRP (mg/dL)	151.8517±107.56330	109.3079±68.57964	.47
ALT (IU/L)	56.6667±32.49429	50.0000±27.58071	.73
AST (IU/L)	54.6667±69.90166	51.1250±37.57116	.78
Albumin (g/dL)	3.5525±0.31066	3.6454±0.28261	.38
ESR (mm/h)	80.0833±28.93396	83.7917±31.06792	.73

TABLE 5. Comparison of Echo findings by age and fever duration

	Positive Echo Finding (N = 12) (Mean ± SD)	Negative Echo Finding (N = 24) (Mean ± SD)	Test	P
Age (months)	18.00±12.358	35.25±19.501	Mann-Whitney U	.008*
Fever Duration (days)	6.25±2.340	8.42±4.201	Mann-Whitney U	.11

initially diagnosed with urinary infection, but left coronary dilatation was seen in his ECHO. Eight patients with iKD at the time of diagnosis and had no ECHO findings were treated with IVIG therapy on the basis of laboratory findings consistent with AHA criteria, and the remaining patients developed desquamation in the extremities during follow-up.

Based on AHA diagnostic criteria, 19 patients were diagnosed with cKD, and 17 patients were diagnosed with iKD. cKD and iKD cases according to age groups are presented in Table 4.

ECHO findings were normal in 24 patients, whereas 12 patients showed pathological findings, 9 of whom were male. Five of the patients with iKD had ECHO findings. Mitral insufficiency was observed in three patients, but it disappeared in all the patients except in one during the follow-up. Nine patients (25%) had pathology in the coronary arteries, and 8 of them were male. Four patients had dilatation in the left coronary artery, 1 had dilatation in the right coronary artery, 1 had an aneurysm in the bilateral coronary arteries (4.6–4.5 mm), 1 had bilateral coronary artery dilatation, and 2 patients had increased echogenicity in the coronary arteries. There was no statistically significant relationship between ECHO findings and fever duration, WBC and platelet counts, and Hb, CRP, ESR, ALT, AST, and albumin levels. However, age distribution revealed that there was a significant positivity in ECHO findings (p=.008) (Tables 4 and 5).

All patients were given IVIG at a dose of 2 g/kg over 12 hours and ASA at 80-100 mg/kg/day at an anticoagulant dose after the fever subsided. Seven patients received a second dose of IVIG because their fever did not subside, and 2 of them received pulse methylprednisolone because of persistent fever. One of them developed bilateral coronary dilatation, and the other (a male aged 5 years who was unresponsive to methylprednisolone therapy) showed no cardiac pathology; he was treated with additional cyclosporine A because he developed MAS. A total of 7 patients (19.4%) were unresponsive to IVIG therapy.

DISCUSSION

KD ranks first among the acquired heart diseases during childhood in developed countries (8). Missed KD cases are thought to be responsible for 5% of fatal or nonfatal myocardial ischemia seen in angiography studies on individuals aged <40 years (9, 10). KD most commonly occurs in children aged <5 years, with 76%-90% of all KD cases occurring at age <5 years (1, 3-5, 11-17). It is reported to be 1.5 times more common in males (1, 3-6). Similarly, 86.1% of our patients were aged <5 years, and the male-to-female ratio was 1:77.

The etiology of the disease is still unknown; different infectious agents have been implicated, but no definite factor has been found. The incidence of KD tends to be 10 times higher in the siblings of children with KD than in the normal population, whereas this rate is 13.8% in identical twins (18). The *SMAD5* gene, which may cause KD, has been reported to increase the risk of KD (19). The incidence of disease peaking during the winter and spring seasons, when bacterial and viral infections are common, appears to support this view (20, 21). Therefore, exposure to agents when there is genetic predisposition is thought to trigger vasculitis. In studies from different regions, seasonal distribution is variable, and it is reported to be more common in winter and spring (12-16, 20, 21). Thirteen of our cases (36.11%) occurred during winter.

KD is a complex vasculitis manifesting itself with different signs and symptoms, where clinical findings change over time. The conventional diagnostic criteria may not be seen in all cases at the same time. In various studies, conjunctival hyperemia was observed in 61.4%-97.1% of KD cases, oral cavity lesions in 59.1%-97.1% of cases, cervical lymphadenopathy in 48.6%-70.8% cases, polymorphous rash in 66.7%-85.7% cases, and changes in the extremities in 50%-78.8% of cases (11-16). In our study, oral mucosal changes were observed in 34 cases (94.4%), polymorphous rash in 27 (77.8%), conjunctivitis in 26 (72.2%), lymphadenomegaly in 23 (63.9%), and changes in the extremities in 29 cases (80.6%).

iKD cases have been reported to comprise 16.4%-56.6% of all patients with KD (17, 22-26). In their study, Tulloh et al. (5) reported that coronary artery involvement occurred in 19% of all patients with KD, total cardiac complications occurred in 28% of them, and the risk of CAA was 39% higher in patients aged <1 year. In our study, 19 of our patients (52.8%) were diagnosed with cKD, and 17 (47.2%) were diagnosed with iKD. There were only 7 patients aged <12 months, 2 of whom had cKD. Coronary involvement occurred in 5 patients among a total of 19 patients with iKD, and 2 of them were aged <12 months. In our study, 1 male patient aged <12 months with hereditary spherocytosis had coronary dilatation. The association of KD with hereditary spherocytosis has not been previously reported; therefore, we can consider this case just a coincidence. In our previous study conducted at the same center, 80.9% of the cases were diagnosed with cKD (21). The increase in the incidence of iKD cases can be attributed to the raised awareness about this disease and early diagnosis.

CAA is the most feared cardiac finding in KD. Although coronary artery involvement is a specific symptom in KD, myocarditis, pericardial effusion, and mitral and aortic valve regurgitation are also seen in acute and subacute phases during the clinical course of KD (1, 3, 6). AHA recommends that the coronary arteries be evaluated with a coronary artery z score according to body surface area. In addition, there is a different concept: if ECHO of the coronary arteries shows an internal lumen diameter ≤4 mm in patients aged <5 years, it is considered a localized dilatation or small aneurysm, whereas an internal lumen diameter between 4 and 8 mm is considered medium-sized aneurysm, and a diameter ≥8 mm is considered giant aneurysm. However, in patients aged >5 years, a diameter <1.5 times larger than that of the adjacent segment is defined as a small aneurysm, a diameter that is 1.5-4 times larger is considered a medium-sized aneurysm, and a diameter that is >4 times is considered a giant aneurysm (8). Apart from the appearance of CAA, brightness in the coronary lumen is also a characteristic finding of KD (7). AHA recommends that the first baseline ECHO be performed at the time of diagnosis in KD and then repeat ECHOs be performed between 1 and 2 weeks and a follow-up ECHO be performed between 4 and 6 weeks in uncomplicated patients (1, 6). All of our patients underwent ECHO at the time of diagnosis. In the first week, 5 patients had coronary involvement, 2 of whom had a medium-sized aneurysm and bilateral small aneurysm, 1 had left coronary artery dilatation, 2 had increased echogenicity (brightness), and 3 patients had mitral valve regurgitation.

ECHO in the second week also revealed findings in 4 patients: 3 had dilatation of the left coronary artery and 1 had dilatation of the right coronary artery. Nine patients with coronary findings recovered during follow-up between 1 and 12 months.

Because KD is a type of vasculitis affecting all medium-sized arteries in the acute phase, the symptoms tend to vary widely, which include hepatitis, interstitial pneumonia due to affected bronchial arteries, abdominal pain with gastrointestinal tract involvement, vomiting, diarrhea, gall bladder hydrops, meningeal irritability, aseptic meningitis, myocarditis, pericarditis, valvulitis in the heart, pyuria in the urinary tract, pancreatitis, lymphadenopathy, and arthritis (1, 3, 4, 8, 12-17). Perianal desquamation and BCG scar enduration are also found in patients with KD (1, 6, 15, 27). Among them, the most common finding in our patients was perianal desquamation, which occurred in 11 patients. A total of 10 patients had hepatitis, 7 had pyuria, 4 had aseptic meningitis, 3 had respiratory tract infection and arthritis, and 1 had gallbladder hydrops, MAS, and BCG scar induration.

The prevalent view is that IVIG infusion therapy reduces coronary artery involvement by up to 5% and that IVIG therapy given within the first 7 days is more effective in reducing the risk of CAA. After IVIG therapy, the fever usually decreases, and the symptoms regress. If fever persists after 36 hours after IVIG therapy, the second dose of IVIG or pulse prednisolone treatment is recommended. About 10%-20% of patients with KD did not respond to IVIG treatment (1, 6, 8, 17, 28). Of this number, 19.4% were unresponsive to IVIG therapy. One of our patients who did not respond to IVIG therapy had bilateral aneurysms, and the other had dilatation of the left coronary artery. In addition, another of our patients who did not respond to IVIG therapy had MAS.

MAS is a rare but fatal complication of KD. It has been reported that MAS is seen in 0.1%-1.9% of patients with KD, and elevated ALT, AST, triglycerides, ferritin, and decreased fibrinogen are important in the diagnosis of MAS (29, 30). The recommended drugs in the treatment of MAS include pulse methylprednisolone, infliximab, anakinra, and cyclosporin A. Our patient also recovered after treatment with cyclosporine A.

KD should always be kept in mind while evaluating the symptoms in children presenting with prolonged high fever, ECHO should be performed when necessary, and the disease should be treated promptly before patients develop any possible complications.

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The Relationship Between Depression and Sexual Function in Individuals with Chronic Obstructive Pulmonary Disease

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BACKGROUND/AIMS
It is important to determine the relationship between depression and the sexual functions of individuals with chronic obstructive pulmonary disease (COPD).

MATERIAL and METHODS
This research is a descriptive, cross-sectional, correlational study that consisted of 104 patients with COPD who were referred to the Chest Diseases Polyclinic of the Medical Faculty Hospital of one university between October 2016 and April 2017. The data of the study were collected using 3 data collection tools: the Personal Information Form, the Beck Depression Inventory (BDI), and the Arizona Sexual Experiences Scale (ASEX).

RESULTS
The results show that 20.2% of patients with COPD had severe depression. Furthermore, women with chronic obstructive lung disease were found to have more sexual problems than men, and men were found to have higher depressive symptoms than women. There was a positive, lower rate (r=0.388), significant relationship (p<.001) between the ASEX total score and the BDI total score. According to this result, as depression levels of individuals with COPD increase, their sexual problems also increase.

CONCLUSION
It is suggested that training programs for the prevention and treatment of depression and sexual dysfunction in individuals with COPD should be implemented and that psychiatric nurses and consultation-liaison psychiatric nurses should take an active role in these trainings.

Keywords: Chronic obstructive pulmonary disease, depression, sexuality

INTRODUCTION

Respiratory system diseases are among the diseases that cause serious health problems worldwide (1). Chronic obstructive pulmonary disease (COPD) is a progressive, life-threatening disease with no curative treatment resulting in airflow restriction, which can lead to complete loss of irreversible lung function (2).

The Global Burden of Disease study reported a prevalence of 251 million cases of COPD globally in 2016 (3). In a study conducted in our country, the prevalence of COPD based on clinical diagnosis and spirometry is 4% (4). In a pilot study, COPD prevalence in individuals aged >40 years was reported to be around 20% (5). There are many factors that cause COPD (6). These factors are divided into 2 groups: environmental factors and genetic factors. Chemical substances, household dust, smoking, infection, and negative socioeconomic conditions are among the causes of COPD. The most important risk factor for COPD is smoking (5, 7, 8). Lifelong smokers have a 40-50% of developing COPD, and nonsmokers have a 10% probability of developing COPD during their lifetime. In addition, exposure to dust chemical fumes, vapors, or other harmful gases in the atmosphere can also cause COPD (9).

COPD is most common in people aged at least 35 or ≥40 years, and the disease can develop at these ages (10). The Turkish Thoracic Society reports that COPD occurs at the age of ≥40 years (11). However, individuals usually present to the health institution at around age 50 years (12).

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In our country, treatment and care programs for the development of lung function are also identified while planning the care and treatment of individuals with COPD, but depression and sexual functioning that reduce the quality of life are ignored (13). In one study, 51.5% of the individuals with COPD who were assessed with the Beck Depression Scale received a score that was consistent with moderate or severe depression (14).

The prevalence of depression was 27.1% in patients with COPD and 10% in the control group (15). Studies have shown that about 40% of individuals with COPD are affected by severe depressive symptoms or clinical depression (16), that the rate of depression accompanying COPD is 44% (17), that the prevalence of depression is 72% (18), and that the rate of depression seen in those with chronic respiratory disease is 70% (19).

Symptoms of COPD, such as breathlessness, coughing, and sputum, have a negative effect on sexuality in both sex and may lead to loss of self-confidence and lack of attractiveness in the sexuality process. Fear and anxiety of dyspnea decrease sexual interest and pleasure. Morale disorders, such as depression, which is an important problem for patients with COPD, also have effects on sexual interest and function (20). In addition, some drugs used in the treatment of respiratory system diseases (bronchodilator) cause mental problems, such as depression, in individuals (21). In a study, 67.7% of erectile dysfunction was found in patients with COPD (22).

Ibanez et al. (23) reported that there was a relationship between lung function and sexual problems in a study that stated that spouses of those patients were less satisfied with sexual intercourse caused by noncommunication. In their study with women diagnosed with COPD in the age range of 30-40 years, Abd-Elsalam et al. (24). reported that the cases affecting sexual intercourse were caused by 91.9% difficulty in breathing, 62% breathlessness, 54% fatigue, 97.6% specific sex positions, 96.9% decreased sexual performance.

Whereas patients experience many problems related to depression and sexual life owing to the disease, they often cannot find an environment where they can express their problems. Patients should learn to live with COPD, a chronic disease. In this learning process, nurses have important responsibilities. The nurses who work with the patient 24 hours should provide nursing care to the patient with a holistic perspective in terms of biopsychosocial perspective in the process of patient's acceptance of the disease, learning to live with the disease, and adaptation and rehabilitation process. In addition, this paper is crucial because it is aimed to determine the relationship between depression and sexual functions in patients. Identifying and revealing this relationship will contribute to the field of nursing science.

Main Points:

- Individuals with COPD in Turkey had severe depression.
- Women with chronic obstructive lung disease had more sexual problems than men.
- Men with chronic obstructive lung disease had higher depressive symptoms than women.
- As depression levels of individuals with COPD increase, their sexual problems also increase.

There is a scarcity of studies that investigates the relationship between depression and sexual function of patients diagnosed with COPD in the world and in our country. This study is aimed to determine the relationship between the sexual life and depression symptom levels of individuals with COPD.

In this study, the following questions were asked:

1. What is the depression level of individuals with chronic obstructive pulmonary disease?
2. Is there any sexual dysfunction in individuals with chronic obstructive pulmonary diseases?
3. Is there a relationship between depression and the sexual functions of individuals with chronic obstructive pulmonary disease?

MATERIAL and METHODS

This study is a descriptive, cross-sectional, correlational study. A total of 208 patients diagnosed with COPD at a university hospital in Mersin, Turkey between October 1, 2016 and April 20, 2017 were included in the study. Of the 208 patients in Mersin, 104 patients met the inclusion criteria. So, the response rate was 50%. The inclusion criteria were individuals aged ≥40 years who had been diagnosed with COPD for at least 6 months, individuals who had active sexual life, and individuals who volunteered to participate in the study. The study was conducted with 104 patients diagnosed with COPD.

Data Collection

Data were collected using 3 data collection tools: Personal Information Form, the Beck Depression Inventory (BDI), and the Arizona Sexual Experiences Scale (ASEX). Data were collected in an empty room on the polyclinic floor and for approximately 20 minutes for each patient.

Data Collection Tools

Personal Information Form. The personal information form consists of 15 questions based on the literature (7, 8, 25-27) and includes information, such as the patient's age, sex, occupation, marital status, educational status, income status, health insurance, and sociodemographic characteristics.

BDI. BDI was developed by Beck. The BDI includes 21 items for qualifying the levels of depression. The Turkish validity and reliability of the BDI were studied by Nesrin Hisli (28). The BDI is scored from 0 to 3 for each question. Low scores indicate minimal depression, and higher scores indicate severe depression. The lowest score is 0, the highest possible total score for the whole test is 63. According to the BDI table, the scores of 1-10 indicate no depression, scores of 11-16 indicate mild mood disturbance, scores of 17-20 indicate borderline clinical depression, scores of 21-30 indicate moderate depression, scores of 31-40 indicate severe depression, and scores of 41-63 indicate extreme depression. The Cronbach alpha coefficient of reliability is 0.86.[28] In this study, the alpha coefficient of reliability was found to be 0.88.

ASEX. ASEX is used to evaluate the 5 main components of sexual function. These are arousal, desire, penile erection or vaginal lubrication, orgasm, and satisfaction. The question about penile erection and vaginal lubrication can be different in the male and female versions of ASEX. This Likert-type scale consists of

5 questions. Because there are 5 questions and each is scored from 1 to 6, the total score is from 5 to 30. Turkish validity and reliability of the scale were assessed by Atilla Soykan (29) in 2002. This scale cut-off point is ≥11 scale score point.

The Cronbach alpha value of the scale was found to be 0.89 and 0.90. A total score of ≥11, ≥5 on any item, ≥4 on 3 items indicate sexual dysfunction and is highly correlated with clinician-defined sexual dysfunctions (29). The Cronbach alpha coefficient of reliability for the sample in this study was found to be 0.90.

Statistical Analysis

The normal distribution of the data was tested with the Kolmogorov-Smirnov test, and the data were found to have a normal distribution. Frequencies and percentages were calculated for categorical variables, whereas descriptive statistics (minimum and maximum values and mean and standard deviation) were calculated for continuous variables. Independent *t*-test and 1-way analysis of variance were used to analyze the data. Tukey post-hoc test was applied to determine which variables were significant for the significant values in groups of more than 2. A chi-square test was used to calculate the relationship between the categorical variables. Pearson correlation test was used to test the relationship between the total scores of the scale. Cronbach's alpha coefficient was calculated to test the reliability of the questionnaire. The results were evaluated with a 95% confidence level at $P \leq .05$ significant level.

Ethical Approval

Ethics committee permission was received from the Clinical Research Ethics Committee of one university (06/10/2016, number: 228266), and institution permission was also obtained from the medical faculty and application center of one university. Written and oral informed consent was obtained from all patients included in the study. Data collection was completed by having patients in Chest Diseases Clinic fill the forms mentioned earlier, paying attention to the patients' privacy. The patients were informed that their information would be kept confidential and that they were free to stop participating in the research at any time.

RESULTS

A total of 57.7% of the participants were male, the age range was 40-88 years, and the mean age was 58.2±11.2 years. A total of 84.6% of the individuals with COPD were married, 57.7% were primary school graduates, 26.9% were housewives, 25.0% were retired, 88.5% had social security, 42% had a balanced income status, and 43.3% were living together with their spouse and children. The disease duration of individuals with COPD was between 6.5 and 360 months, and the mean duration was 81.4±72.5. A total of 57.7% of the individuals with COPD stopped smoking, and 23.1% continued to smoke. When COPD stages were examined, it was found that 50.0% of the individuals were in the first or mild stage, 96.2% had shortness of breath, and 82.7% had a cough and wheezing.

As presented in Table 1, 21.2% of individuals with COPD had ups and downs in their mental status, and they also had normal and moderate mood disorders. In addition, it was determined that 20.2% of individuals with COPD had severe depression. A total of 57.6% of individuals with COPD had a score of ≥17, and clinical treatment was determined to be necessary (Table 1).

When the ASEX average scores of the individuals with COPD were examined, ASEX total scores of women (19.1±7.8) were found to be higher than those of men (15.9±4.7). The average ASEX score was 17.3±6.4 (Table 2).

Table 3 shows the BDI total scale scores of individuals with COPD and the relationship between age and disease duration. There was a positive mild relationship between the total scores of the ASEX and the BDI total score (r=0.388), and this relationship was significant (p<.001). According to this result, it can be inferred that as the depression levels of individuals with COPD increase, their sexual dysfunction also increases. There was a positive, moderate, and statistically significant relationship between age and the total score of the ASEX (r=0.415; p<.001). Ac-

TABLE 1. Distribution of Beck Depression Inventory Scores of Individuals with Chronic Obstructive Pulmonary Disease (*n*=104)

BDI	n	%
1-10: The ups and downs in mental status are normal	22	21,2
11-16: Moderate mood disorders	22	21,2
17-20: Borderline clinical depression	12	11,5
21-30: Moderate depression	20	19,2
31-40: Severe depression	21	20,2
41-63: Severe depression	7	6,7

BDI: Beck Depression Inventory

TABLE 2. ASEX Average Scores of Individuals with COPD (*n*=104)

ASEX	n	Mean±SD	Lower and upper values
Sexual desire	104	3.5±1.6	1-6
Sexual arousal	104	3.3±1.5	1-6
Penile erection/vaginal lubrication	104	3.6±1.4	1-6
Sexual orgasm	104	3.4±1.5	1-6
Sexual satisfaction	104	3.5±1.4	1-6
ASEX (female)	44	19.1±7.8	6-30
ASEX (male)	60	15.9±4.7	7-30
Total scale score of the ASEX	104	17.3±6.4	6-30

ASEX: Arizona Sexual Experiences Scale, COPD: chronic obstructive pulmonary disease.

TABLE 3. The Relationship BDI and ASEX With Age and Disease Duration of the Individuals with Chronic Obstructive Pulmonary Disease

Correlation Between BDI, ASEX, Age and Disease Duration		ASEX	BDI
BDI	r	0.388	
	P	0.001**	
Age	r	0.415	0.287
	P	<.001**	0.003*
Disease Duration	r	0.133	0.168
	P	0.177	0.089

*p<.01, *p<.001. ASEX: Arizona Sexual Experiences Scale, BDI: Beck Depression on

cording to this result, it can be said that individuals with COPD have increased sexual dysfunction as their ages increase. There was a statistically significant positive and mild relationship between age and BDI total score (r=0.287; p=.003). According to this result, it can be inferred that as the ages of individuals with COPD increase, their depression levels also increase. The relationship between COPD duration and the total score of ASEX was positive, mild, and not statistically significant (r=0.133; p=.17). The relationship between COPD duration and BDI total score was not positive, was weak, and was statistically significant (r=0.167; p=.089) (Table 3).

DISCUSSION

This study was conducted to determine the relationship between depression and the sexual functions of individuals with COPD. It was found that 70.2% of the individuals diagnosed with COPD were in the age range of 40-64 years, and the average age was 52.8±8.0 years. More than half of the individuals were primary school graduates. Although COPD varies from country to country, it is a serious public health problem that threatens 10-15% of the population aged >40 years (2). In a pilot study, the prevalence of COPD in individuals aged >40 years was found to be around 20% (5). It is stated in the literature that the age of diagnosis of COPD is ≥40 years (10,11). In this study, the average age of individuals with COPD is 52.8 years, similar to that reported in the literature. In a study by Castelino et al. (30), it was found that 13.6% of individuals with COPD were not literate and that 43.6% were primary school graduates.

In this study, we found that more than half of the individuals with COPD experienced depression and that depression treatment was clinically required. Studies have shown that about 40% of individuals with COPD are affected by severe depressive symptoms or clinical depression (16), that the rate of depression accompanying COPD is 44% (17), that the prevalence of depression is 72% (18), and that the rate of depression seen in those with chronic respiratory disease is 70% (19). Our study is in parallel with the literature. For depression

levels, it is thought that COPD is a chronic disease that negatively affects the quality of life and that the prevalence of depression is high in the patients owing to their reactions to the disease and owing to the limitations and barriers caused by the disease. In this study, it was found that women experienced more sexual problems than men and that nearly all individuals with COPD (96.2%) experienced shortness of breath. A study by Ayoade et al. (31) reported that age and gender affected sexual performance, and Kaptein et al. (32) also reported that women had more difficulty in breathing during sexual intercourse than men. Ibanez et al. (23) reported a relationship between lung function and sexual problems in a study conducted on only male patients, and they also stated that spouses of those patients were less satisfied with sexual intercourse caused by noncommunication. In their study with women diagnosed with COPD in the age range of 30-40 years, Abd-Elsalam et al. reported that the cases affecting sexual intercourse were 91.9% caused by difficulty in breathing, 62% caused by breathlessness, 54% caused by fatigue, 97.6% caused by specific sex positions, and 96.9% caused by decreased sexual performance (24). The findings of this study are in parallel with the literature. Many beliefs about sexuality are exaggerated. These beliefs are often nonobjective and false. Individuals often show these beliefs in the daily press and pornographic publications by telling jokes about sexuality. These beliefs mostly depreciate and devalue women. There is a wrong belief in society that sexuality is only for men and that women should not have sex (33). It is thought that women avoid expressing their sexual problems and accepting consultations with physicians.

In this study, it was determined that the most common sexual problem was in vaginal lubrication/penile erection, followed by sexual desire, satisfaction, orgasm, and sexual arousal problems. Kahraman et al. (13) reported that the rate of erectile dysfunction was 78.6% in patients with COPD, and the severity and frequency of erectile dysfunction were higher in patients with COPD than in the control group. In their study of individuals with COPD, they stated that 78.9% of the patients had decreased sexual desire, and 76.3% had decreased the sexual intercourse (34). Yacan and Erol reported that there were fewer orgasms in cases of chronic complications (35).

In this study, we found that women with COPD had higher scores on COPD total scale scores than men in terms of sexual desire, sexual arousal, and orgasm. Levack stated that COPD predisposes women to fewer sexual problems than it does to men. He stated that men's sexual activity is more dependent on health than women's sexual activity, that having a sexually satisfying husband and a pleasurable sexual experience is more important for women, and that men are more vulnerable to lose their self-confidence and have difficulty in breathing owing to reduced sexual performance (36). This finding differs from our study. In our country, girls are taught not to be interested in sexuality while they are raised. The traditional female role is associated with a number of beliefs, such as women should control their emotions about sexuality (33). It is thought that women adopt this social role, have low education levels, and do not know how to cope with these social judgments, and because of these reasons, women develop sexual, sexual arousal, orgasm problems.

In this study, there was a positive, low, and significant relationship between the total scores of ASEX and BDI total score. According to this result, it can be inferred that as the depression levels of individuals with COPD increase, their sexual dysfunction also increases. In a randomized controlled study, the prevalence of sexual dysfunction in patients with depression was twice as high as that in the control group (50% vs 24%) (37). Reynaert et al. (38) reported that there was a strong association between depression and sexual dysfunctions and also that certain antidepressants had adverse effects on sexual function. Akyol et al. (39) have reported that sexual dysfunctions are more common in patients with high anxiety and depression scores. There is a widespread consensus that patients with depression have a higher rate of sexual dysfunction than the general population (7, 10). Karson et al. stated that lack of penile erection, the reason for sexual reluctance, and vaginismus were largely due to depression, and the pre-ejaculation was definitely due to depression. They also reported that sexual reluctance is mostly attributed to hormonal causes, but almost all of the causes are depression (40). In a study by Alacacıoğlu et al. (41), the scores of communication, satisfaction, avoidance, pre-ejaculation, and erectile dysfunction were higher in individuals with high depression scores than in individuals with low depression scores.

In this study, it was determined that patients with COPD had sexual problems and that there was a relationship between their sexual problems and their depression levels. Patients with COPD who have sexual problems (women, those with inadequate income, those with low levels of education, housewives) should be regularly followed up by nurses, evaluating their mental status and organizing regular training programs about the management of the disease and mental and sexual problems; training conducted through press and media programs is also recommended. It can be argued that nurses should be aware of the patient's sexual lifestyle and functioning. These patients should be referred to comprehensive sexual health programs for treatment, if available.

This study was conducted on patients in a single university hospital, and this was accepted as a limitation. The limitations of this study include a small sample size and recruitment from a single center. During the period in which the study was conducted, only 104 of 208 patients undergoing peritoneal dialysis treatment elected to participate in the study.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Mersin University (Approval Date: 06/10/2016, Approval Number: 228266).

Informed Consent: Written and oral informed consent was obtained from all patients included in the study.

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Original Article

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Role of the Tympanometric Gradient and Acoustic Reflex on Prognosis of Otitis Media With Effusion

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BACKGROUND/AIMS
Otitis media with effusion (OME) is a major health issue worldwide. Although it is difficult to consider any quantitative measurement in particular to be a herald of clinical recovery in OME, this study aimed to determine the role of tympanometric quantitative values, especially gradient (GR) and acoustic reflex (AR), in patients with OME who are approaching the full healing stage.

MATERIAL and METHODS
Based on the tympanic membrane findings, participants were divided into 2 groups: (A) minimal retraction group and (B) normal group. For each group, the tympanometric quantitative measurements (static compliance [SC], tympanometric peak pressure [TPP], GR, and AR) were obtained and compared statistically. In addition, the relationship of AR with tympanometric quantitative measurements was compared statistically.

RESULTS
The mean GR values in group A (n=66) and group B (n=73) were 157.06±92.85 daPa and 103.60±28.51 daPa, respectively (P=.001). Although no significant difference was found with respect to AR, statistically significant differences were observed with respect to TPP between the 2 groups.

CONCLUSION
In contrast to AR, GR and TPP values were consistent with the examination findings of the tympanic membrane observed in patients with resolved OME progressing to the full healing stage. Thus, these 2 tympanometric quantitative measurements are beneficial for the diagnosis and follow-up of patients with OME.

Keywords: Tympanometry, otitis media, acoustic reflex

INTRODUCTION

Otitis media with effusion (OME) is defined as the presence of fluid in the middle ear without signs or symptoms of an acute ear infection. The tympanic membrane is often cloudy with distinctly impaired mobility, and an air-fluid level or bubble may be visible in the middle ear (1). OME may occur during an upper respiratory infection, spontaneously because of poor Eustachian tube function, or as an inflammatory response following acute otitis media (2). Pneumatic otoscopy has been recommended as the primary method for diagnosing OME because reduced tympanic membrane mobility correlates most closely with the presence of fluid in the middle ear (3). When the diagnosis of OME is uncertain, tympanometry or acoustic reflectometry should be considered as an adjunct to pneumatic otoscopy. Tympanometry with a standard 226-Hz probe tone is reliable for infants 4 months or older and has a good interobserver agreement of curve patterns in routine clinical practice (4). The acoustic reflex (AR) is an involuntary muscle contraction that occurs in the middle ear in response to high-intensity sound stimuli or when the person starts to vocalize. If there is hearing loss, either conductive or sensorineural, of 65 dB hearing level (HL) or greater in the stimulated ear, the reflex will likely be absent (5). The quantification of tympanometric measurements facilitates the development of appropriate standards for comparing tympanometric data among clinics. These measurements include static compliance (SC), volume of external ear canal, tympanometric gradient (GR), and tympanometric peak pressure (TPP) (6).

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This study aimed to evaluate whether the otoscopic examination findings are consistent with quantitative tympanometric parameters (especially GR) and AR in patients who had a tympanogram peak in the negative range after a recent history of OME. The study also discusses the role of the quantitative tympanometric parameters (especially GR) and AR as heralds of the healing process in patients with OME.

MATERIALS and METHODS

Enrollment and Study Design

This study enrolled patients who met the study criteria, from January 2017 to March 2019, after approval of the institutional review board. In this retrospective case-control study, patient consent form was not required. Patients aged between 4 and 14 years and with a recent history of OME with a negative peak at tympanogram were included in the study. Patients who had a pure-tone average (500 Hz, 1000 Hz, 2000 Hz, and 3000 Hz) worse than 25 dB of HL, difficulty in obtaining the hearing thresholds, advanced tympanic membrane retraction, middle ear effusion, or neurological and craniofacial anomalies were excluded from the study. Pneumatic otoscopy was performed to exclude fluid in the middle ear and to determine if there was a tympanic membrane retraction.

After the inclusion of patients into the study, 2 groups were created according to tympanic membrane findings. The examination of the tympanic membrane was carried out using Barr's classifications (7), in which the tympanic membrane was divided into areas including anterior to the manubrium malleus (I), posterior superior to the manubrium malleus (II upper), and posterior inferior to the manubrium malleus (II lower) and attic (III). The touching of the eardrum with incus and head of malleus was graded as a first degree (slight) retraction in all areas except in II lower in which first degree (slight) retraction was described as an eardrum dislocated inward without connection of promontory. Patients with normal eardrums were included in group B, whereas patients who had the first-degree retraction either throughout the eardrum or in any subregion were included in group A. The quantitative tympanometric parameters were noticed in addition to AR through an impedance audiometer with a 226-Hz probe tone (AT235, Interacoustics, Denmark). GR may be calculated in 2 measurement units, milliliter and daPa. GR described as the tympanogram width at half the height of the peak of the SC was shown with pressure in this study. At any frequency, obtaining an ipsilateral AR was accepted as AR positivity. Tympanometric values (TPP, SC, and GR) and AR of patients in each group were compared statistically.

Main Points:

- This study was designed to investigate the importance of quantitative tympanometric findings in estimating the prognosis of OME. Particularly, the study of AR in the selected patients was a new entity.
- Although it is well known that tympanometric quantitative values (eg, GR, TPP) are the most discussed topics of OME, in this study, we tried to ascertain whether GR and AR have a prognostic value.
- Patients with OME who progressed to either full or near-recovery stage were divided into 2 groups, and the tympanometric values were evaluated, especially the GR and AR between these groups.
- On the basis of the results, it can be concluded that obtaining AR is mostly related to a good GR value and that GR is a valuable parameter in predicting the prognosis of OME.

Statistical Analysis

The values obtained were entered into a computer-based spreadsheet and the data analyses were carried out using the SPSS software for Windows version 9.0; a *P* value of ≤.05 was considered significant. The quantitative tympanometric data in both the groups were compared with the independent *t* test, whereas the AR differences were compared with the chi-square test.

RESULTS

The mean age of the 89 patients who enrolled in the study was 9.17±2.26 years; 45 were girls (mean age, 8.38±1.65 years) and 44 were boys (mean age, 10.00±2.55 years). In 50 of the 89 patients, both ears were included in the study. A total of 139 tympanometric measurements were obtained from 89 patients, of which 66 were in group A (abnormal tympanic membrane) and 73 were in group B (normal tympanic membrane).

The mean SC was 0.54±0.33 mL in group A and 0.55±0.32 mL in group B (*p*=.45). The mean values of TPP were -129.33±77.48 daPa and -38.64±57.98 daPa (*p*=.001) in group A and group B, respectively, and the mean values of GR were 157.06±92.85 daPa and 103.60±28.51 daPa (*p*=.001) in group A and group B, respectively.

Within the 139 measurements, AR was obtained in 65 measurements (46.8%); however, it was not detected in the remaining 74 measurements (53.2%). The mean GR of the measurements in cases with AR positivity was 114.20±59.99 daPa, whereas the mean GR of the measurements in cases with AR negativity was 141.97±79.46 daPa (*p*=.001). In group A, 32 out of 66 measurements (48.5%) of AR were positive, and in group B, 33 out of 73 measurements (45.2%) of AR were positive (*p*=.44). The relationship between AR and tympanometric quantitative parameters is shown in Table 1 for both groups individually and combined.

DISCUSSION

Tympanometry provides an objective assessment of tympanic membrane mobility, Eustachian tube function, and middle ear function by measuring the amount of sound energy reflected back when a small probe is placed in the ear canal (8,9). Tympanometric curves, or tracings, are classified into 3 main types—type A (low probability of effusion) with a sharp peak and normal middle ear pressure, type B (high probability of effusion) with no discernible peak and a flat tracing, and type C (Eustachian tube dysfunction/middle ear pathology) with a discernible peak and negative middle ear pressure (10). In addition to these tympanometric curves, quantitative parameters of tympanometry give valuable information about the condition of the middle ear and eardrum. TPP is the ear canal pressure at which the peak of the tympanogram occurs. The peak

TABLE I. Relationship between AR and tympanometric quantitative parameters in group A and group B, both individually and combined

	SC	TPP	GR
AR-positive measurements (n=65)	0.56±0.28	-77.43±92.96	114.20±59.99
AR-negative measurements (n=74)	0.53±0.36	-85.45±70.42	141.97±79.46
P value	.25	.15	.001
AR-positive measurements in group A (n=32)	0.64±0.36	-112.87±91.21	127.25±78.12
AR-negative measurements in group A (n=34)	0.45±0.27	-144.82±59.15	185.11±97.85
P value	.012	.025	.001
AR-positive measurements in group B (n=33)	0.48±0.13	-43.06±82.14	101.54±30.82
AR-negative measurements in group B (n=40)	0.61±0.41	-35.00±25.29	105.30±26.74
P value	.025	.15	.39

AR: acoustic reflex; GR: gradient; SC: static compliance; TPP: tympanometric peak pressure.

at or less from -100 daPa indicates a type C curve. The SC is the length of the vertical peak of the tympanic tracing that can be obtained by extraction of the external ear volume from the total volume. The height decreases when the SC is abnormally low, which occurs when there is stiffness in the middle ear, and it is associated with disorders such as ossicular chain fixation, cholesteatoma, otosclerosis, and fluid in the middle ear, the latter being the most common cause in children (11). In this study, the TPP values of the 2 groups were in accordance with the examination findings of the eardrums. As expected, there was no difference in SC between the groups, and this result was associated with the minimal retraction of the eardrum without a decrease in middle ear volume. Therefore, it could be concluded that TPP is more descriptive than SC during the recovery stage of OME.

GR describes the sharpness of the tympanogram peak. This calculation was popularized when it was observed that tympanograms frequently were broadly rounded in ears with OME. Duzer et al. (12) described that GR value, which was measured as a unit of milliliter, was an accessory diagnostic parameter in addition to the TPP and SC values in patients with OME. Nozza et al. (13, 14) conducted studies in participants who were between the ages of 3 and 16 years and presented with the mean value of GR of 104 daPa (ranging between 60 and 168 daPa). Unlike the study conducted by Duzer et al, GR was calculated as a unit of daPa in this study; the difference of GR between the 2 groups was so significant that the mean GR value was 157.06±92.85 daPa and 103.60±28.51 daPa in groups A and B, respectively. Both GR and TPP were revealed hitherto the 2 most important measurements to determine if an OME was in the recovery period.

AR measurement requires relatively healthy tympanic membrane, middle ear ossicles, and HL. In addition, the healthy neural way of reflex arc is important in obtaining AR, which extends from the cochlear nerve to the stapedial branch of the facial nerve (5). A positive AR is quite common in individuals with normal HL (15). When all cases were separated into 2 subgroups on the basis of AR positivity, no statistically significant differences were observed in the values of SC and TPP; however, significant differences were observed in the 2 groups in GR. As depicted in Table I, there was a statistically significant difference between the cases with positive AR and negative AR when a comparison was performed on the basis of the 3 parameters (SC, TPP, and GR) in group A. In group B, the statistical difference of SC between the cases described as positive AR and negative AR was significant, whereas the other 2 parameters were not; however, SC was unreasonably higher in patients without reflexes. In group B, the pattern of TPP values between the cases with positive AR and negative AR was similar to the pattern of SC values, but gradient was higher in AR-negative patients as expected. According to those beforementioned results, which are also briefed in Table I, it may be logical to think that GR is more effective in creating AR than other parameters.

Marchant et al. (16) conducted a prospective study in which AR thresholds were high in patients with OME. In another study, AR was observed to be less sensitive to acute otitis media than OME and using AR in the diagnosis of OME was valuable in addition to pneumatic otoscopy (17). When the 2 groups (A and B) were compared for the presence and absence of AR, there was no difference between the groups, and sufficiently positive AR could not be obtained in group B as expected. This could be explained by the presence of subclinical middle ear inflammation in group B even with normal tympanic membrane. In addition, not only a healthy ear but also the whole pathways of reflex arc have to be intact to obtain an AR. Even if the reflex did not show a prognostic value, further studies with broad participation are required to determine its role in OME given that in this study, the cases with positive AR of group B had better GR value than those who had no reflex.

In conclusion, GR and TPP, together, are reliable tympanometric quantitative parameters in the diagnosis and follow-up of patients with OME who are progressing to the full recovery stage. There is no prognostic value of AR for patients with type C tympanograms with minimal tympanic membrane retraction during the healing stage of OME. However, to fully demonstrate the role of AR during the healing stage of OME, prospective studies with a control group are needed. AR positivity depends on many factors; as discussed in this study, the value of GR is the most prominent determinant in obtaining AR. Using GR is important for patients with OME who progress to complete healing.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Original Article

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Surgical Treatment Results of Fibrous Dysplasia and Effects of Using Grafts

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BACKGROUND/AIMS
Fibrous dysplasia (FD) is a skeletal system disorder characterized by replacement of normal bone and bone marrow with fibro-osseous tissue and proliferation of immature osteogenic cells. There is no consensus regarding the timing of orthopedic surgery, the choice of implants, and use of grafts owing to its variable clinical appearance and wider age range. This study aimed to contribute to the literature by performing a retrospective study involving patients with FD.

MATERIAL and METHODS
This retrospective study included 41 patients with FD. Patients were evaluated for the first-visit and follow-up graphs. Patients were examined for the effects of intramedullary nailing and plate fixation. The use of grafts during surgery was noted and examined in terms of increase in deformity during the operation time and follow-up.

RESULTS
Surgical intervention was performed on 45 bone lesions in 41 patients. Plate was used in 7 patients with pathological fracture, and intramedullary nail was used in 19 patients. There was a significant difference between the groups (P=.011). No deformity was detected in 16 of the 26 patients with pathological fractures. In 20 patients in whom grafts were used, cortical thickening was observed on the basis of the preoperative graphs. Graft survival rate was reported to be 83.3%.

CONCLUSION
The presence of pathological fractures affects the choice of implants by surgeons. Cortical thinning is the most important parameter than deformity in terms of the risk assessment of pathological fractures for surgical planning. Allograft survival rate is high for 4 years, on average.

Keywords: Fibrous Dysplasia of Bone , pathological fracture, allograft, monostotic fibrous dysplasia, polyostotic fibrous dysplasia

INTRODUCTION

Fibrous dysplasia (FD) is a skeletal disorder characterized by replacement of normal bone and bone marrow with fibro-osseous tissue and proliferation of immature osteogenic cells, leading to significant pain in patients (1). FD can clinically affect one or multiple bones. Attention should be given to pain, deformity development, and pathological fracture formation in the patients followed. Surgical procedures can be used for biopsy, correction of deformity, prevention of pathological fractures, or elimination of symptomatic lesions (2, 3). Cases detected because of pain or coincidentally should be followed in terms of both pathological fracture and deformity. Surgical procedures in patients without deformity are more successful.

FD is most often located in the proximal femur. Diseased bones have low resistance; therefore, long bones can easily develop bending and pathological fractures (4). Varus deformity, also called Shepherd's crook deformity, develops owing to localization of the lesion in the proximal femur and the bone structure deterioration. It is important to detect the varus deformity of the proximal femur early and correct it with valgus osteotomy. In polyostotic form, it can cause scoliosis in the spine. There is no consensus on surgical interventions in FD. Factors such as patient's age, presence of deformity, and localization and size of the lesions affect the choice of treatment of surgeons. Plates and intramedullary

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fixation implants can be used in the surgery for FD. In the literature, it is argued that intramedullary implants are superior to plates in terms of implant selection (5-7). There is no consensus on the use of grafts in the surgical treatment of FD. A good graft must have osteoinductive and osteoconductive properties and have mechanical support when the bone cortex becomes thinner, such as in FD. Long-term graft resorption rates are high, especially in young patients for treatment using grafts alone. Mechanical implant support and stable fixation should be the priority of surgical treatment (8). If a bone graft usingis planned, cortical grafts should be preferred instead of spongious bone because of their physical superiority (3). The use of bone grafts alone, including both allograft and autograft, has limited value in the treatment of FD lesions**.** This study aimed to investigate the effectiveness of surgical treatment strategy and graft use in FD.

MATERIALS and METHODS

This study included 41 patients with a pathological diagnosis of FD. Ethical approval was obtained from the hospital ethics committee (approval number and date: 237/16/07/2020) for this study. Surgical consent was obtained from patients before any surgical procedure. All the procedures were in accordance with the ethical principles of Helsinki Declaration.

Patient data included age, sex, type of FD, surgical techniques, bone graft use, cortical thickening, and time to union. Incomplete patient data, patients who were not operated on, and patients who were operated for any reason in an external center were excluded from the study. The inclusion criteria included patients diagnosed with FD and those who were operated on. A total of 63 patients were operated in our hospital, and 41 patients who met the inclusion criteria were included in the study.

Patient's first-visit graphs and follow-up graphs were examined. They were grouped according to the number of bone lesions; monostotic FD (with a single bone lesion) and polyostotic FD (with more than one bone lesions). Follow-up patients admitted with pain and diagnosed with FD and patients with a pathological fracture without an initial diagnosis of FD were identified. Angulations that impair joint movements in any plane were accepted as deformities. Surgical indication in patients included pathological fractures, severe pain, and deformities that disrupt the movements. Patients were compared for the effects of using intramedullary nailing and plates, regardless of the use of grafts. During the surgery, radiography and surgery notes were checked for the use of grafts. The properties of the graft used were recorded, and in these cases, graft survival, cortical thickening, surgery timing, and recovery times were compared between patients in whom a graft was not used. Patients who had union in the pathological fracture area and who did not increase deformity during follow-up were considered as healed.

Main Points:

- Cortical thinning was found to be a more valuable follow-up parameter in terms of pathological fracture risk.
- Intramedullary fixation was found to give more successful results.
- It was found that the use of grafts led to cortical thickening in the lesion area.
- The patients with allografts had a mean follow-up time of 46.7 (±19.7) months, and the graft survival rate was 83.3%.

All patients were operated under general or regional anesthesia, in supine position, accompanied by scopy, according to the anatomical region and general medical condition. The patients were operated by 3 surgical teams. Curettage was applied by opening a window in the bone area held in all patients. Patients for whom grafts usage was planned, curettage was performed through the opened bone window, fibular strut allografts were placed, and then plate or intramedullary nailing was applied. Only surgical curettage and grafting were performed in patients in whom location and size of the lesion did not cause mechanical instability. Patients with mechanical instability were treated with plate or intramedullary nailing, depending on the location of the lesion and the preference of the surgical team. On the basis of the bone area involvement, some patients were treated with only curettage and grafts. Patients who had first-visit graphs, follow-up graphs, postoperative early graphs, and Ist, 3rd, 6th months; Ist and 2nd years control graphs were included in the study. Patients with incomplete files and follow-up graphs were excluded from the study.

Statistical Analysis

The effectiveness of monostotic and polyostotic FD were analyzed and compared statistically using Student's *t*-test and Mann–Whitney U test. Patients were divided into 2 groups on the basis of the first-arrival complaints–complaints such as chronic pain or pathological fracture. Patients were also divided into groups on the basis of whether grafts were used and whether the implants used were plates or intramedullary nailing. Chi-square test and Fischer's exact test were used to find if the groups had any significant differences with respect to bone union and deformity increases in the patients' final control graphs. All data analyses were carried out using IBM SPSS software version 23 (IBM SPSS Corp.; Armonk, NY, USA).

RESULTS

Of the 41 patients, 21 were women and 20 were men, with an average age of 17.4 years (5–38 years). The average follow-up period was 51.3 months (24–86 months). In total, 30 (73.6%) patients had monostotic FD and 11 (26.4%) had polyostotic FD. It was determined that 23 patients with monostotic FD had only femur involvement, 4 had only humerus involvement, and 3 had only tibia involvement. The localization of the lesions was examined in patients with polyostotic FD. Lesions in femur and tibia in 6 patients; both femur and tibia in 3 patients; and humerus, femur, and tibia in 2 patients were detected. When all the patients were examined, 57 bone areas were involved in 41 patients in total, including humerus, femur, and tibia. Surgical intervention was performed in 45 bone areas of these patients. Curettage and grafting were used in 3 surgeries, plate-screw system in 18 surgeries, and intramedullary fixation in 24 surgeries. Allograft was used in 23 patients (56.1%) (Table 1).

Surgical intervention was performed in 26 (57.8%) of the patients after pathological fracture. In total, 20 patients presented with primary pathological fracture. Six patients with pathological fractures were followed up with conservative treatment. Plate was used in 7 patients with pathological fracture, and intramedullary nail implants were used in 19 patients. There was a significant difference between the groups (p=.011). Grafts were used in only 14 patients with pathological fractures. There was no significant difference between the groups (p=.522). Although deformity was detected in 10 patients with pathological fractures, 16 patients had pathological fractures without any deformity. There was no significant difference between the groups (p=.179). The mean union time was 4 months (3–6 months) in patients operated for pathological fractures.

TABLE I. Demographic Data

Demographics	Data
Gender	21 F/20 M
Type of FD	Monostotic FD 30/41
	Polyostotic FD 11/41
Lesion localization	Isolated femur 23/41
	Isolated humerus 4/41
	Isolated tibia 3/41
	Femur and tibia 9/41
	Femur, tibia, and humerus 2/41
Number of surgeries	45
Type of surgery	Curettage and grafting: 3/45
	Plate-screw fixation: 18/45
	İntramedullary nailing: 24/45
Pathologic fracture	26/45 (first clinical diagnosis in 20 patients)
Use of allograft	24/45
Deformity	14/45

FD: fibrous dysplasia.

Deformity was found in 14 patients (31.1%); plate fixation was used in 6 patients, and intramedullary fixation was applied in 8 patients. There was no significant difference in the choice of fixation in these patients (p=.627). Allograft was used in 8 patients with deformity. There was no significant difference between the groups in terms of graft use (p=.298). Two of the patients were found to have Shepherd's crook deformity. The patients were treated with valgus osteotomy.

In 20 of the 24 surgical procedures using allografts, cortical thickening was detected according to the preoperative graphs (Figure 1). There was a significant difference in cortical thickening between the group with allograft and the group without allograft (p=.000). The mean follow-up period of patients using allograft was 46.7 (±19.7) months. Allograft survival rate was found to be 83.3%. It was found that there was cortical thickening in patients using allograft, regardless of patient age and remodelization capacity (Figure 2).

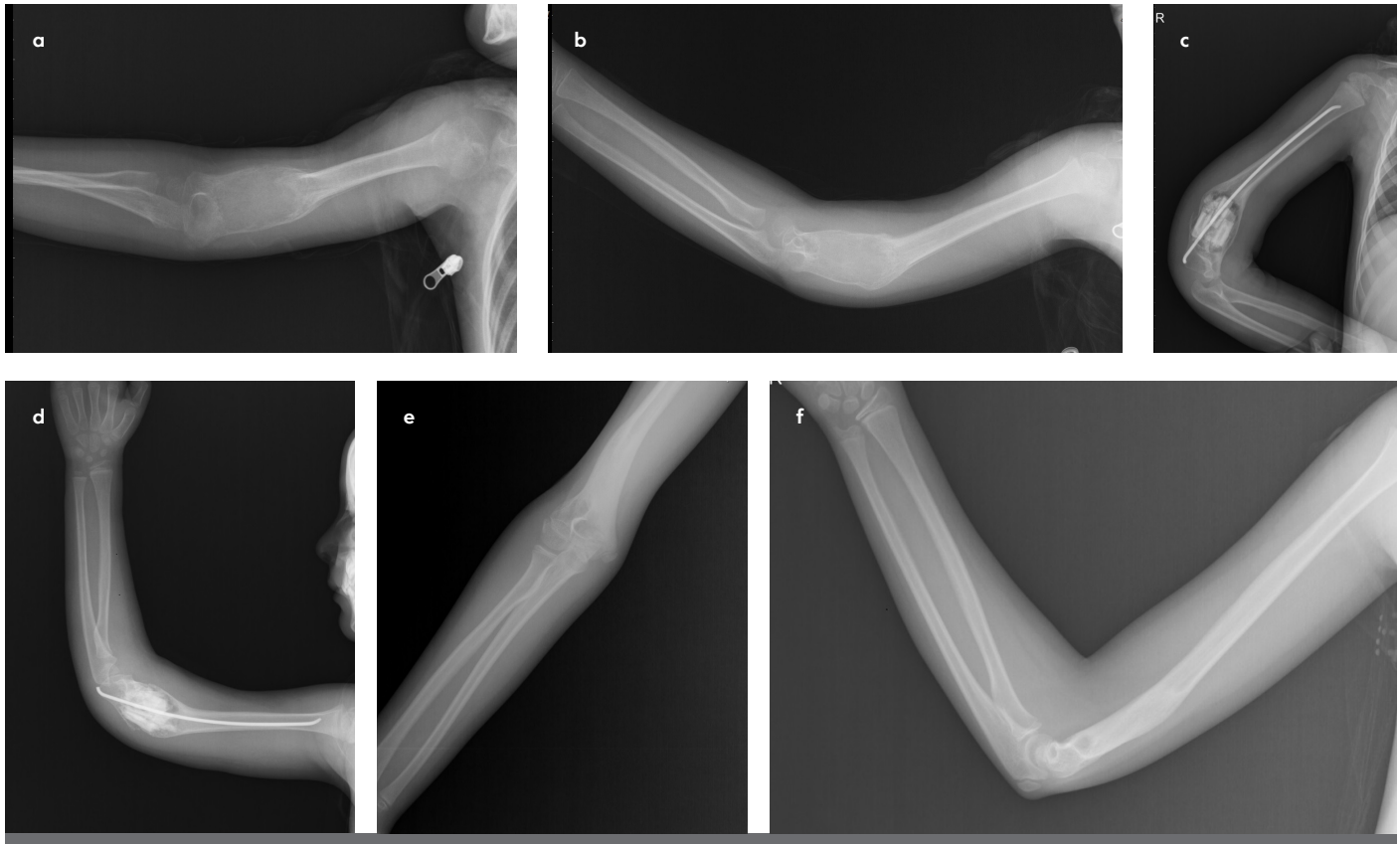

Figure 1. a-f. A 9-year-old girl with a right distal humeral fracture resulting from a simple fall. (a, b) Preoperative X-rays; (c, d) Postoperative X-rays; (e, f) X-rays 56 months after surgery

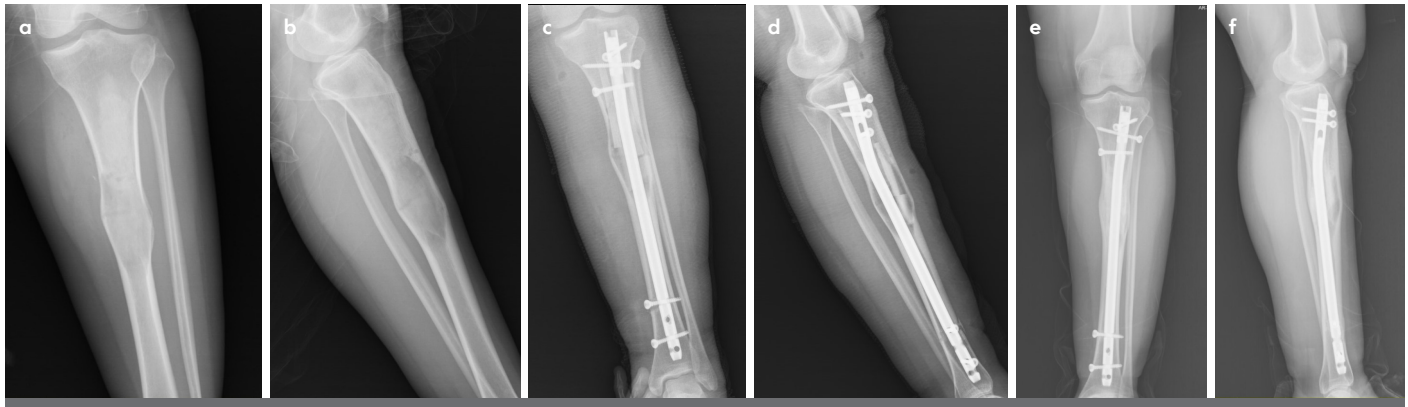

Figure 2. a-f. A 20-year-old girl with severe pain; left tibial lesion. (a, b) Preoperative X-rays; (c, d) Postoperative X-rays; (e, f) X-rays 60 months after surgery

DISCUSSION

FD is a tumor-like lesion of bone and constitutes 5% of the benign bone lesions. FD has been associated with an activating mutation in the gene that encodes the alpha subunit of the stimulating G protein on the 20th chromosome. FD is able to hold all bones in the body. Its involvement in a single region is called monostotic FD, and its involvement in more than one region is called polyostotic FD. The polyostotic type is less common and can occur as part of McCune–Albright syndrome. FD, café-au-lait spots, and endocrine anomalies, such as puberty precox, may accompany McCune–Albright syndrome. Polyostotic FD tends to occur mostly on one side of the body (2). Most lesions are monostotic, asymptomatic, detected coincidentally, and can be followed up by clinical observation.

It shows similar distribution among genders. There is no consensus on surgical procedures owing to a wide age range and variable clinical presentation. Patients can appear with severe pain or pathological fracture. In some patients, it can be detected coincidentally on radiographs taken for another reason. In the patients included in this study, the monostotic FD rate was 73.6%. Femur involvement was detected in 34 of the 41 patients (82.9%). Although the long bones of the lower extremity are typically involved with FD lesions, other bones may also be involved. FD lesions are most commonly observed in the femur and tibia. It can also be observed in the skull, ribs, and more rarely, in the pelvis (3, 5). In a study in which 173 patients were examined for the extracranial located skull and scalp pathologies, only 1 patient was found to have FD located in the skull bones (9).

Surgical intervention is performed in case of deformity increase or pathological fracture on the follow-up of patients. In surgical intervention, it should be aimed to obtain a painless and sufficiently stable bone. Surgical interventions include curettage, curettage and grafting, and implant fixation of bone with or without allografts. If more than two-thirds of the bone is involved with the lesion, curettage alone may not be sufficient because the bone is likely to be unstable (10). One of the most important points that we should emphasize in our study is that it was observed that only 10 of the 26 patients with pathological fractures developed deformity and subsequently pathological fractures occurred. In other words, pathological fracture may occur before deformity develops. Most patients with pathological fractures developed a fracture without deformity. The authors would like to emphasize that cortical thinning may be a more important sign in terms of pathological fracture. In this study, intramedullary fixation was selected in 19 of the 26 patients who developed pathological fractures by 3 different surgical teams. There was a significant difference compared with the use of plates (p=.011). There are supporting studies in the literature that report that intramedullary fixation gives more successful results than plate-screw systems. In a study performed by Demiralp et al. (11), prophylactic intramedullary nails were applied to patients with monostotic FD without the use of allografts, and successful results were obtained.

No significant difference was found between both the implant selection and the use of allografts among 14 patients with deformity. Shepherd's crook deformity, which is a progressive varus deformity especially in the proximal femur, is the most common deformity. Patients with FD with involvement of the proximal femur develop post-stress recurrent occult fractures in the proximal femur. Over time, varus, anteversion, and anterior bowing occur, resulting in Shepherd's crook deformity. Patients come with antalgic walking and limb length discrepancy. Supporting evidence in the literature state that early treatment is more successful in patients with progressive deformity. In its treatment, it can be corrected by valgus osteotomy (3, 12, 13). Shepherd's crook deformity was detected in 2 of our patients. The patients were treated with valgus osteotomy.

The use of allografts is one of the controversial issues regarding surgical treatment of FD. In the study by Lindner et al. (14), high recurrence rates were observed in patients using iliac crest autograft, and it was emphasized that better results were obtained from fibrous cortical allografts. There are publications defending that a high rate of resorption develops in long-term follow-ups, especially when used at a young age. In this study, the mean follow-up time of 24 patients where allografts were used was 46.7 (±19.7) months, and graft survival rate was 83.3%. Fibular strut allograft was used in 22 patients and chips allograft in 2 patients. Despite the disadvantages of allograft, such as risk of immune rejection, disease transmission potential, and development of infection, it has osteoconductive properties but has limited osteoinductive potential (15). Leet et al. (8) found that graft survival rate was less in young patients with FD who were followed for an average of 19.6 years. In the average half of the patients, grafts were observed to be completely resorbed. In this study, the high graft survival may be due to the short follow-up period. In this study, 51.3 months (24–86 months) of follow-up was a limitation in terms of graft survival.

Another point that should be emphasized in patients with graft is the cortical thickening detected around the lesion. Although no cortical thickening was detected in any of the patients without graft in this study, significant cortical thickening was observed in the group using the graft (p<.001). Kuznetsov et al. (16) observed that stem cells carrying mutant genes in the skeletal system decreased in time with apoptosis in young patients. This explains the progress in lesions with age and the inverse correlation with graft resorption. In polyostotic and young patients, the use of grafts is more unsuccessful than older patients with monostotic FD, and therefore, it will be more appropriate to decide for graft use on the basis of the age of the patient and the characteristics of the lesions. The limitations of the study are the wide age range of the patients, the presence of involvement in different bones, and the examination of different FD types. Long-term follow-up is required for allograft survival in larger patient series.

In conclusion, the presence of pathological fractures affects the choice of implants by surgeons. Cortical thinning is most important than deformity in terms of the risk assessment of pathological fracture for surgical planning. Intramedullary fixation in patients with FD gives more successful results. The use of grafts should be decided based on the age of the patient and localization of the lesions. Although the average survival of fibular cortical strut allografts has decreased over the years, cortical thickening in the lesion area is one of its important advantages.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dicle University Medical Faculty (approval number and date: 237/16/07/2020).

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

Peer-review: Externally peer-reviewed.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Original Article

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Immunohistochemical Expression of Cyclooxygenase-2 and Its Relationship With Prognostic Parameters in Breast Cancer

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BACKGROUND/AIMS
Cyclooxygenase-2 (COX2) plays an important role in the development of some human cancers, especially in the development of pulmonary, colon, and breast carcinomas. Overexpression of COX2 has been involved in the pathogenesis of a wide range of malignancies, such as colon, breast, and lung cancer, and has been associated with carcinogenesis and tumor progression. The COX2 pathway has been involved in several processes associated with tumor progressions, such as angiogenesis, proliferation, and invasion. This study aimed to determine whether COX2 can be used as a prognostic marker in breast cancer.

MATERIAL and METHODS
We evaluated immunohistochemical expressions of COX2 in 100 patients with invasive ductal breast carcinoma and compared its utility as a prognostic parameter. In the evaluation of the data, chi-square test was used to assess the relationship between mean, standard deviation, and COX2 and the relationship between other independent variables in the Statistical Package for the Social Sciences version 24 software package.

RESULTS
A positive correlation was found between COX2 expression and estrogen receptor positivity, tumor grade, Ki67 proliferation index, tumor size, advanced age, and triple-negative subtypes (P<.005). However, there was no association with HER2 positivity, progesterone receptor positivity, and nonluminal type.

CONCLUSION
In breast cancer, COX2 expression has a positive correlation with some prognostic parameters; however, it has an inverse correlation with some others.

Keywords: Breast cancer, COX2, immunohistochemistry

INTRODUCTION

Breast cancer is the most common malignancy in women, and its malignancy is one of the most common causes of death (1). Molecular characterization of this malignancy is an indicator for tumor prognosis and aggression. The classical molecular parameters of breast cancer are estrogen receptor (ER), progesterone receptor (PR), and cerbB2 expressions, and Ki67 proliferation index (2, 3).

Previous studies have shown that cyclooxygenase (COX)-2 plays an important role in the development of some human cancers, especially pulmonary, colon, and breast carcinomas, as well as preinvasive lesions. COX catalyzes the synthesis of prostaglandin endoperoxidase from arachidonic acid, which means that it is the first step in the biosynthesis of prostaglandins and thromboxane and is also known as prostaglandin endoperoxide synthase.

Of note, 2 prostaglandin synthase isoforms have been identified, which are often referred to as COX1 and COX2 (4). Although COX1 is structurally produced by most body tissues, COX2 is an inducible enzyme and is produced under certain conditions, such as inflammation and tumor microenvironment. COX2 plays a role in estrogen regulation by producing prostaglandin E2 that increases the expression of cytochrome P450 enzyme complex (also known as aromatase) that

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catalyzes estrogen production, which is mediated through androgen (5).

COX2 is the enzyme that regulates the inflammatory process and the first step of prostaglandin synthesis. Tissue expression of COX2 is regulated by cytokines, endotoxins, and growth factors (6). Overexpression of COX2 has been defined in the pathogenesis of a wide range of malignancies, such as colon, breast, and lung cancer, and has been associated with carcinogenesis and tumor progression, such as angiogenesis, proliferation, and invasion (7-9). COX2 plays a role in the induction of apoptosis (10). High COX2 expression is more common in poorly differentiated tumors than in well- and moderately differentiated tumors. It has been shown that COX2 expression also correlates with poor prognostic factors, such as high Ki-67 proliferative rate and low differentiation (1).

We aimed to evaluate COX2 expressions in invasive ductal breast cancer and adjacent benign breast tissue and to correlate them with clinical and histological prognostic parameters, including hormone receptor status.

MATERIAL and METHODS

This study was based on the retrospective analysis of tumors diagnosed as invasive breast carcinoma (without special type) from patients who underwent mastectomy between 2014 and 2019. A total of 100 patients were included in the study. A total of 4-µm-thick sections were prepared from the paraffin block of tumors, and ER (clone: 6F11, 1:50, Leica Biosystems, Thermo Fisher Scientific, IBM SPSS Corp, Germany), PR (clone: Pgr16, 1:100, Leica Biosystems), Ki67 (clone: MM1 optimized for use, Leica Biosystems), cerbB2 (clone: 10A7, 1:40, Leica Biosystems), and COX2 (clone: SP21, 1:50, Thermo Fisher Scientific, Waltham, MA, USA) antibodies were applied by Leica Bond-Max brand fully automatic immunohistochemistry device. For each slide, hematoxylin was used as the counterstain. Immunohistochemical staining was evaluated with a light microscope (BX46 Clinical Microscope, Olympus, Tokyo, Japan). A minimum of 500 tumor cells was counted for the immunohistochemical evaluations per antibody.

Immunohistochemical staining percentages for ER and PR were made according to Allred's criteria, and the staining intensity of positive tumor cells was also categorized into 4 groups (0, no staining; 1, weak staining; 2, medium staining; and 3, strong staining). CerbB2 receptor status was considered negative for 0 and 1+ test results and positive for 3+ test results; however, tumors with the 2+ test results were retested by FISH.

Main Points:

- It is important to monitor the progression of breast cancer, which is the most common type of cancer in women, and to direct the treatment. Therefore, the searches for various prognostic markers of this cancer continue.
- It is still early for COX2 to be an immunohistochemical prognostic marker for breast cancer because different results have been found in different studies.
- Further standardized studies may be needed before it can be considered a prognostic marker.

Medium to strong nuclear staining of >1% of tumor cells for ER and >20% of tumor cells for PR was considered positive. For Ki67, cases showing >14% medium/strong nuclear tumor staining were considered positive. Cytoplasmic immunoreactivity of COX2 was graded according to the German Immuno Reactive Score (12). The staining intensity was graded from 0 to 3 (0=no staining, 1=weak staining, 2=moderate staining, 3=strong staining). For statistical calculations, the COX2 status was evaluated by establishing 2 thresholds: positive and negative (negative and weak staining were grouped as negative, whereas medium and strong staining were grouped as positive [Figure 1]).

Breast Cancer Classification

Breast cancer was classified as follows:

1. Luminal A: when estrogen/progesterone are positive, cerbB2 is negative, and Ki67 is low (<14%).
2. Luminal B negative, cerbB2 negative: when estrogen is positive, cerbB2 is negative, and ki67 is high (≥14%) and/or progesterone is positive (<20%).
3. Luminal B negative, cerbB2 positive: when estrogen is positive, cerbB2 is positive, there is any ki67 and any PR.
4. CerbB2 positive (nonluminal): when cerbB2 is positive, and estrogen/progesterone is negative.
5. Triple negative: estrogen/progesterone and cerbB2 are negative.

Statistical Analysis

In the evaluation of the data in this study, chi-square test was used for the assessment of the relationships between the mean, standard deviation, and COX2 and other independent variables by the Statistical Package for the Social Sciences 24 package program (IBM SPSS Corp.; Armonk, NY, USA). The relationships between COX2 and triple negative and those between COX2 and ER-positive, PR-positive, and cerbB2-positive cases were assessed. In the analyses, $P<.05$ values were accepted as statistically significant.

RESULTS

The distribution of the surrogate subtypes of breast cancer in 100 samples was 56 (56%) luminal A; 9 (9%) luminal B, cerbB2

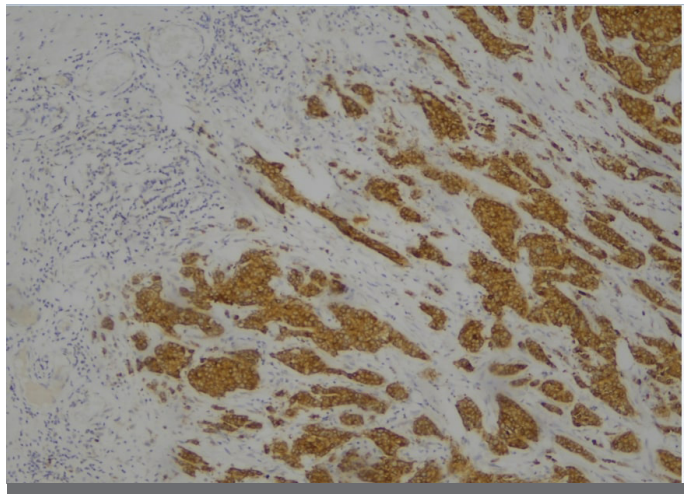

FIGURE 1. Cytoplasmic staining of the tumor cells with COX2 antibody (×100 magnification)

TABLE I. The demographic characteristics of the cases

Demographic Parameters		n (100)	%
Tumor grade	Grade I	20	20
	Grade 2	62	62
	Grade 3	18	18
Tumor size	2cm<	27	27
	2cm≥	73	73
Age	30-48	40	40
	49≥	60	60
Lymph node metastasis	(+)	34	34
	(-)	66	66

TABLE 2. COX2 and Independent Variables

Prognostic parameters	COX2 X±SD	Level of significance
Grade	.66±.76	
Low (GI)	.40±.50	
Medium (G2)	.66±.47	X2=0.01
High (G3)	.94±.23	p<0.05
ER+	.77±42	X2=0.04
		p<0.05
PR+	.58±.50	X2=0.094
		p>0.05
cerbB2+	.67±.49	X2=0.095
		p>0.05
Ki67(above 14%)	.82±.38	X2=0.09
		p<0.05
Tumor size >2cm	.80±.40	X2=0.00
		p<0.05
Age 49≥	.81±.39	X2=0.00
		p<0.05
Lymph node metastasis (+)	.85±.34	X2=0.01
		p<0.05
Triple negativity	.94±.25	X2=0.011
		p<0.05

negative; 12 (12%) luminal B, cerbB2 positive; 7 (7%) cerbB2 positive (nonluminal); and 16 (16%) triple negatives. The demographic characteristics of the cases are shown in Table 1. For threshold definition, negative and poor staining results were grouped as negative, whereas medium and strong staining results were grouped as positive. When the statistical results were examined, the correlations between advanced/intermediate grades and COX2 expression (χ^2=0.01, P<.05) and that between ER positivity and COX2 expression (χ^2=0.004, P<.05) were statistically significant. It was determined that there was no statistical relationship between CerbB2 positivity and COX2 expression (χ^2=0.095, P>.05) and between PR positivity and COX2 expression (χ^2=0.094, P>.05). In addition, the relationships between Ki67 and COX2 expression (χ^2=0.09, P<.05), between tumor size >2 cm and COX2 expression (χ^2=0.00, P>.05), between age >49 years and COX2 expression (χ^2=0.00, P>.05), and between lymph node metastasis and COX2 expression (χ^2=0.01, P>.05) were found statistically significant. The relationship between COX2 expression and triple-negative subtype was found to be statistically significant (χ^2=0.00, P<.05) (Table 2).

Pathological parameters, such as peritumoral angiolymphatic invasion, perineural invasion, dermal invasion, in situ carcinoma component, luminal A, luminal B, and nonluminal subtypes were not associated with COX2 expression.

DISCUSSION

COX2 expression has been widely described in breast cancers. It shows high expression in tumor breast tissue compared with that in benign breast tissue and seems to have a clinical potential use in predicting the prognosis (13). In an analysis of 12 studies, COX2 positivity was found in 42% of the tumors (14). In our study, 67% of tumors showed positivity for COX2. COX2 was found to be associated with increased tumor grade and poor prognosis among patients with estrogen-independent breast cancer because it is a main agent in the inflammation-cancer signal axis (15). Although COX2 expression was presented as a prognostic parameter in basal carcinomas, it showed no prognostic significance in luminal A cancers (16). However, Serra et al. (17) declared that COX2 expression was not related to clinical and pathological subtypes, tumor characteristics, and prognosis. COX2 positivity was found in the invasive and in situ carcinomas and also around the tumor (14, 17, 18).

In a retrospective study of 303 high-grade breast cancers, COX2 was evaluated immunohistochemically, and a positive correlation was observed between COX2 overexpression and high tumor grade; however, no correlation was found with ER positivity (15).

There are some other studies that found a reverse correlation between ER and COX2 expressions (19), and some others showed a positive correlation (20) such as in our study. Ristimaki et al. (20) suggested that elevated COX2 expression in ER-positive cancers could be because of the enhancement of the microenvironment for cancer cells to grow by inducing estrogen production. In addition, some studies have found a strong association of COX2 overexpression with ER negativity and the worse prognosis (21).

Triple-negative breast cancers do not have ER, PR, and HER2 expressions, and they constitute 15% of all breast cancers and are associated with aggressive progress, high metastasis, and poor prognosis (22). It has been reported that COX2 expression is increased in triple-negative and HER2+ (nonluminal) tumors (23, 24). In our study, COX2 expression seemed to be increased in triple-negative tumors, but no statistically significant relationship was observed with the HER2+ group. There are variations in the literature regarding COX2 positivity and negativity; therefore, it is difficult to compare between studies. Different results may occur in different immunohistochemical analyses owing to different antibodies, nonstandardized staining methods and differentiation differences of the tumors, and the differences in COX2 expression analysis.

A recent meta-analysis of 21 studies and 6739 patients with breast cancer showed that the presence of high COX2 levels predicted a larger tumor size and lymph node metastasis, similar to our finding (25). When Ki67 is highly expressed as a nuclear cell proliferation marker in breast cancer, it is associated with a poor prognosis (26). There are studies emphasizing that there is a correct relationship between the number of cells expressing Ki67 and proliferation (27) or that there are no significant statistical results with Ki67 expression (28). In this study, a positive correlation was found between the high value of Ki67 (>14%) and COX2 expression.

In carcinogenesis, inflammatory cytokines, growth factors, endotoxins, and oncogenes trigger the induction of COX2 and cause tumor progression by participating in COX2 tumor proliferation, invasion, angiogenesis, apoptosis resistance, and metastasis (29, 30). Therefore, it is associated with poor prognosis in patients with cancer (20).

We have found a correlation of COX2 expression with some of the prognostic parameters in breast cancer. However, it appears to be early for COX2 immunoexpression to be used daily as a prognostic marker in breast cancer. It may be a good prognostic marker if it gains support from further studies with large series.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Muğla Sıtkı Koçman University (Approval date:180170/No:149).

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Original Article

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Incidence and Risk Factors of Sports Injuries Among National Competitive Deadlifters

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BACKGROUND/AIMS
The purpose of this study is to evaluate the injury incidence and potential injury risk factors related to deadlifting exercises.

MATERIAL and METHODS
A total of 50 national deadlift contestants participated in this study. All 50 participants were enquired about demographics, training routines and injury characteristics before the competition via face-to-face interviews. The potential risk factors for common sports injury and deadlift-related injury were evaluated.

RESULTS
Twenty-one participants (42%) sustained any kind of sports injury in the preceding year. Ten participants had injuries related to deadlifting exercises. The most injured body parts during training were the lumbopelvic area (n=15), shoulder (n=12), and knee (n=4). All 10 athletes who had deadlift-related injuries described complaints over the lumbopelvic area. While all predictors were statistically insignificant in univariate analysis, stretching time was significantly different in multivariate analysis between the injured and non-injured groups of competitors (p=.039). As the stretching time increased, the probability of injury risk also increased.

CONCLUSIONS
All deadlift-related injuries were on the lumbopelvic area. The stretching time was significantly different between the injured and non-injured groups. Every athlete who performed stretches for more than 15 min had deadlift-related lumbopelvic injuries. These results provide useful information for physicians, therapists, and trainers in planning warm-up routines for exercise programs.

Keywords: Deadlift, strength training, weightlifting, injuries, stretching

INTRODUCTION

Deadlift exercise is a multi-joint resistant exercise that consists of lifting the barbell from the ground to thigh level and slowly lowering the weight to the starting position. Together with squat and bench press exercises, deadlifting is also a part of powerlifting competitions. Deadlifting is gaining popularity as one of the most compound exercises that involves the thigh, hip, back, and core muscles (1). Recent studies have shown the beneficial effects of deadlifting for back pain (2). In addition, deadlifting may help develop muscular power (3) and improve lower body strength (4). However, deadlifting is frequently associated with an increased risk for injury. Most athletes tend to refrain from deadlifting because of their fear of injury. Nonetheless, the injury rates of deadlifting remain unclear. Few researchers have addressed the injury incidence and risk factors, mostly using data obtained from online forms (5). Prior studies were online questionnaires, which are known to have limitations compared with face-to-face surveys (6). In this study, we collected data directly from competing athletes via face-to-face interviews before a national deadlifting contest. The purpose of this study is to evaluate the injury incidence and potential injury risk factors related to deadlifting exercises.

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MATERIAL and METHODS

Data used in this cross-sectional study were obtained through face-to-face interviews with the contenders before a national deadlifting contest. All athletes performed conventional deadlift exercise during the competition. Conventional deadlift exercise was performed by bending forward at the knees and grabbing the loaded barbell from the ground, followed by lifting the barbell from the ground to thigh level. When the back and torso of the athletes were straight and in erected position, the barbell was slowly lowered to the starting position.

All athletes competing in the contest were enquired before the competition at the registry desk. As the official competition committee agreed and gave permission to our study, Ethical Committee report was not taken additionally. The authors directly explained and provided detailed information to participants regarding the questionnaire. All 50 participants of the contest filled in the survey. The potential risk factors for common sports injury and deadlift-related injury were evaluated.

An injury was defined as a condition of pain or physical impairment that affected the training of athletes in terms of total withdrawal from routine training more than 1 week, modification of training intensity or duration for 2 weeks, or referral to health care for any musculoskeletal problem as described previously (3).

Demographic data of athletes, including education levels and occupational environment, were assessed. The athletes were also enquired about the use of any kind of dietary supplement and any special equipment during deadlift trainings (i.e., weight belt). The participants were enquired about their weight training experience, training frequency in a week, regular guidance by a personal trainer, total training duration, deadlift experience, deadlift frequency in a week, deadlift training duration, and the mean and maximum deadlift training weights. In addition, each athlete was enquired about the warm-up, stretching, and cool-down exercise characteristics.

Regarding injury evaluation, the participants were asked to report whether they had experienced any injuries during trainings and particularly, any injuries related to deadlift trainings in the preceding year. Location of the injury, referral to any kind of health care professional, and treatment modality were assessed. The athletes were also asked whether they felt any discomfort in that body area before the injury, and their opinion on the probable cause of their injury (excessive weight/posture or technique error/fatigue/recurrence of old disability/insufficient rest/poor nutrition). The complete questionnaire form is shown in Appendix.

Main Points:

- Our study showed that the injuries in our competitive deadlifter athletes are similar to that of other weight training sports.
- Injuries occurred most commonly in the lumbopelvic area, shoulder, and knee.
- Athletes reported "poor technique/posture," followed by "excessive weight" as the most common causes of injuries.
- We found that stretching time was significantly different between the injured and non-injured groups of competitors (p=.039).
- As the stretching time increased, the probability of injury risk also increased. These results suggest that the type and duration of stretching prior to exercise should be considered cautiously by trainers and athletes if they wish to minimize the rate of sports injuries and deadlift-related injuries.

Statistical Analysis

The study was completed by 50 people who provided oral consent to participate in the study. The representative power of the sample was calculated using post-hoc power analysis. In this analysis, the injury rate of our study was calculated as p=.20, and according to the studies in the deadlift population, the rate of injury was calculated as p=.40 (95% CI, 0.30–0.50) and post-hoc power 87.2% when α =.05. Predictors that may affect deadlift injury were first analyzed using univariate tests. Student's t-test and Mann–Whitney U tests were used for analyzing arithmetic means. Fisher's exact test and Kolmogorov–Smirnov Z tests were used for analyzing frequency. Injury status while performing deadlift movement in the two groups defined as non-injured and injured was analyzed using binary logistic regression (BLR). For performing BLR analysis, the model was first examined using Hosmer and Lemeshow test and if appropriate, the analysis was performed.

RESULTS

Fifty participants (6 women/44 men) above the age of 18 years were included in this study. More than half of our participants were university students, and only 5 athletes had a physically demanding job. Assessment of 33 athletes who received nutritional support revealed that the most preferred support types were whey protein and creatine pills. Demographic characteristics of the athletes included in our study are presented in Table 1.

Table 2 summarizes the data about training characteristics of the participants. Only 10 athletes routinely trained with a personal trainer, whereas 40 athletes did not have regular training guidance. Most of the athletes (62%) performed deadlifting exercises 2 days a week. Nearly one-third of all participants preferred using a weight belt during deadlift exercises. Athletes mostly preferred full body exercises (36%) and dynamic stretching (36%) as warm-up procedures. None of the athletes preferred static stretching as a warm-up procedure.

No injury occurred during the competition. According to our questionnaire results, 21 participants sustained any kind of sports injury in the preceding year. Ten injuries were related to deadlifting exercises. The most injured body parts during training were the lumbopelvic area (n=15), shoulder (n=12), and knee (n=4). Regarding deadlift-related injuries, 10 athletes described complaints over the lumbopelvic area. Referral to a health care professional was necessary for 14 athletes, and the most common diagnosis was "paravertebral muscle sprain" (n=8), followed by "rotator cuff injury" (n=5). One athlete was operated for meniscus tear. Fourteen athletes stated that they felt discomfort in that body area before the injury. When the participants were assessed for their opinion on the probable cause of their injury, 11 athletes stated "poor technique/posture" as the most proba-

ble cause, while 5 athletes reported "excessive weight" as the probable cause. All predictors were statistically insignificant in univariate analysis (Table 3). However, in multivariate analysis, stretching time was significantly different between the injured and non-injured groups of competitors. Statistical analysis revealed that as the stretching time increased, the probability of injury risk also increased (Table 4).

DISCUSSION

This study aimed to investigate the training characteristics of competitive deadlifters and define the internal or external risk factors predisposed to sports injuries. Our findings showed that the most commonly injured body parts were the back (n=14) and shoulder (n=11). Previous studies on injury rates of weight training athletes also showed that the back and shoulder area are the most common injury sites.(5, 7–12) Although we performed this study in athletes who participated in the national deadlifting contest, only 47% (10/21) of the injuries were related to deadlifting. All deadlifting-related injuries (n=10/10) occurred in the lumbopelvic area. During the execution of conventional deadlift movement, high axial compression forces apply on the lumbar spine and increases progressively from LI to L5. The high compressive force could be the main reason for the high rates of lumbopelvic area injuries (13). Deadlifters not only train in deadlift movement, but also perform other compound movements such as powerlifting, Olympic weightlifting, and CrossFit as part of their strength training routine. Their routine mostly includes bench press, overhead press, clean, and different types of squats, which are similar to that in other weightlifting sports. In particular, clean, bench press, and overhead press exercises apply a high rate of stress to the shoulder joint (11, 12, 14). Anatomically, the shoulder joint is not a weight-bearing joint in hu-

TABLE I. Demographic profile of participants

Sex, n (%)	
Male	44 (88.0)
Female	6 (12.0)
Age (mean ±SD, y)	24.1±6.2
Height (mean ±SD, cm)	175.8±7.6
Weight (mean ±SD, kg)	82.2±15.7
Body mass index (mean ±SD, kg/m^2)	26.5±4.2
Level of education, n (%)	
High school	7 (14.0)
University student	33 (66.0)
Higher education or college	10 (20.0)
Working style, n (%)	
Office work	45 (90.0)
Other physical occupation	5 (10.0)
Getting nutritional support	
Yes	33 (66.0)
No	17 (34.0)
Getting nutrient type, n (%)	
BCAA	18 (36.0)
Whey	12 (24.0)
Creatine	18 (36.0)
Vitamin	2 (4.0)

BCAA, branched-chain amino acids

TABLE 2. Athlete characteristics

Duration of participation in deadlifting, n (%)	
<6 months	19 (38.0)
6–<12 months	7 (14.0)
1–<2 years	9 (18.0)
≥2 years	15 (30.0)
Deadlifting frequency, n (%)	
1 day/week	14 (28.0)
2 days/week	31 (62.0)
≥3 days/week	5 (10.0)
Deadlifting duration, n (%)	
<10 min	7 (14.0)
10–20 min	13 (26.0)
20–30 min	18 (36.0)
≥30 minutes	12 (24.0)
Deadlift weight (mean±SD, kg)	141.0±42.4
Deadlift weight maximum (mean±SD, kg)	182.3±50.9
Warm-up duration, n (%)	
<5 min	5 (10.0)
5–10 min	12 (24.0)
10–15 min	13 (26.0)
≥15 min	20 (40.0)
Stretching duration, n (%)	
<5 min	24 (48.0)
5–<10 min	12 (24.0)
10–<15 min	10 (20.0)
≥15 min	4 (8.0)
Cooling duration, n (%)	
<5 min	24 (48.0)
5–10 min	16 (32.0)
10–15 min	6 (12.0)
≥15 min	4 (8.0)
Weight belt use, n (%)	
No/rare	18 (36.0)
Always/often	32 (64.0)
Participation in another sport, n (%)	
No	19 (38.0)
Yes	31 (62.0)
Sports injury, n (%)	
No	29 (58.0)
Yes	21 (42.0)
Deadlifting injury, n (%)	
No	40 (80.0)
Yes	10 (20.0)

TABLE 3. Case of injury in deadlift sport by various characteristics

	Injured, n		
	No	Yes	P value
Age, y, mean ±SD [a]	24.1±5.7	24.1±8.2	t=.023, P=.982
Sex, n			X2 FET, P=.656
Male	35	9	
Female	5	1	
Body mass index (mean ±SD, kg/m^2 [a])	26.1±3.7	27.9±5.7	t=1.256, P=.215
Working style, n			X2 FET, P=.258
Office work	37	8	
Other work	3	2	
Duration of participation, n			KSZ=0.78, P=.581
<6 months	13	6	
6–<12 months	7	0	
1–<2 years	8	1	
≥2 years	12	3	
Deadlifting frequency, n			KSZ=0.071, P=1.00
1 day/week	11	3	
2 days/week	25	6	
≥3 days/week b	4	1	
Deadlifting duration, n			KSZ=0.354, P=1.00
<10 min	6	1	
10–<20 min	9	4	
20–<30 min	16	2	
≥30 min	9	3	
Deadlift weight (mean±SD, kg)	141.5± 36.1	139.0± 64.2	MWU= 0.329, P=.747
Weight belt use, n			X2 FET, P=.722
No/rare	16	3	
Always/often	24	7	
Warm-up duration, n			KSZ=0.707, P=.699
<5 min	3	2	
5–<10 min	11	1	
10–<15 min	12	1	
≥15 min	14	6	
Stretching duration, n			KSZ=1.131, P=.155
<5 min	20	4	
5–<10 min	11	1	
10–<15 min	9	1	
≥15 min	0	4	
Cooling duration, n			KSZ=0.778, P=.581
<5 min	17	7	
5–<10 min	16	0	
10–<15 min	5	1	
≥15 min	2	2	

[a]t-test, [b]1 person 7 days/week, all others 3 days/week, FET: Fisher's exact test, KSZ: Kolmogorov–Smirnov Z,
MWU: Mann–Whitney U

TABLE 4. Case of injury in deadlift sport by various characteristics were analyzed using binary logistic regression

				95% C.I. for EXP(B)	
	B	P	Odds Ratio	Lower	Upper
Age, years	-0.035	.663	0.965	0.823	1.132
BMI, kg/m^2	0.130	.343	1.139	0.871	1.489
Sex (Ref. Female)	-0.902	.668	0.406	0.007	25.094
Occupation (Ref. Other works)	-2.198	.161	0.111	0.005	2.405
Weight belt (Ref. uses)	-1.125	.342	0.325	0.032	3.308
Nutritional support (Ref. taking)	-0.157	.874	0.854	0.122	5.973
Other sports (Ref. participating)	-0.037	.971	0.964	0.130	7.146
Duration of deadlifting participation	-0.278	.567	0.757	0.292	1.964
Deadlifting times/week	-0.184	.545	0.832	0.459	1.509
Deadlift weight mean, kg	-0.006	.680	0.994	0.966	1.023
Warm-up duration	-0.426	.445	0.653	0.219	1.947
Stretching duration	1.405	.039	4.077	1.073	15.487
Cooling duration	-0.230	.714	0.794	0.231	2.727
Constant	0.199	.965	1.220		

Hosmer and Lemeshow test: X2=7.64, P=.470
[a]. Variable(s) entered in step 1—Continues variables: age, BMI, deadlift mean weight; ordinal variables: deadlift participation, deadlift duration/ week, warm-up, stretching, cooling duration; categorical variables: participation in other sports, use of weight belt, sex, occupation, and nutritional support.

mans; Kolber et al. (14) suggested that the high load caused by exercises makes shoulder joint susceptible to injury. Bench press and overhead press movements also place the shoulder in inappropriate positions, such as abduction and end range external rotation; these positions put additional risk on the shoulder joint. These conditions could be the reason behind the high rate of shoulder injuries in our group.

During the pressing phase of compound lift movements, especially during overhead movements, athletes may lose the correct form of exercise, and this could place the lumbar spine in an extreme lordotic position. Extreme lordotic position could lead to training-related back injuries even if athletes do not execute isolated back exercises (8).

According to our questionnaire results, stretching time was the only significantly different variable between the injured and non-injured competitors (p=.039). Inconsistent results have been reported on the preventive effects of stretching on sports injuries. Several authors have suggested that stretching has a beneficial effect on sports injury prevention, and a proper warm-up should be performed prior to athletic performance to decrease sports injury rates.(15–20) Conversely, numerous reviews conclude that there is no sufficient evidence on the preventive effects of stretching.(21–23) It increases range of motion (ROM), tendon compliance, and blood flow and decreases muscle stiffness. Although stretching is an important part of warm-up procedure, the type and duration of stretching should be considered cautiously. We offer two possible mechanisms on the predisposing effects of stretching in strength training athletes.

First, weightlifting requires maximal performance and pushes athletes to their limits. However, impaired maximal muscular performance due to stretching has been reported in previous studies (16, 19, 24–26). Stretching-induced force decrease is duration dependent. It has been shown that the longer the stretch duration, the greater the force reduction (18, 20, 26). Longer duration of stretching exercises (above 45–90 seconds) (26) and static stretching seem to cause performance impairments more often than dynamic stretching (24). According to our findings, as the stretching time increased, the probability of injury risk also increased. Maximal force and performance reduction could impair protective core muscle contraction that provides lumbar stabilization, thus leading to lumbar region injuries (27, 28). Our study focused on competitive deadlifters who attempt to lift the maximal load for one repetition by producing maximal strength. During deadlifting, the L4/L5 mean compression value was 17 192 N, and L4/L5 mean moments value was 988.3 N.m. (29). Although different lifting techniques such as sumo style deadlift seem to reduce these forces by 10% (29), these forces still apply a very high load on the lumbar region. Thus, core and lumbar stability are essential for proper load balance within the spine and to provide appropriate kinetic chain. The absence of core and lumbar stability could lead to tendon, ligament, and endplate injuries (28–30).

Secondly, reduced spinal excitation due to stretching exercises is proposed to be the reason for increased ROM and decreased muscle stiffness. Increased ROM and decreased stiffness may be important for preventing muscle and tendon injuries, as it provides resistance to stretch. However, longer muscles and reduced excitability can impair protective reflexes. Muscle spindle sensitivity reduces because of the reduced activity of large diameter afferents caused by repeated stretching (31–33). Any reduction in muscle spindle reflex can be dangerous and predispose injuries in athletes when having such high loads on the spine while lifting.

We collected data directly from each competing athlete via face-to-face interviews before a national deadlifting contest. The data of previous studies on injury rates of strength training athletes were collected via online questionnaires (5, 10), which are known to have limitations compared with face-to-face surveys. Online or telephone interviews might not reach every athlete. For instance, e-mail invitations might be deleted before they are read, athletes' telephone numbers might be wrong, or their e-mail addresses might be inactive (34, 35). Importantly, online or telephone interviews might have a selection bias compared with face-to-face interviews, as certain athletes may answer more questions than the others. As our face-to-face interview allowed us to collect data from each participant, we have not missed any data.

There are some limitations to our study. First, as the study included only athletes who participated in the national deadlifting contest, the number of participants was low. This might have affected the results to a certain extent. Second, injuries were not categorized by their severity. Therefore, we were unable to analyze the relationship between risk factors and severity of injuries. Third, as the participants were not enquired about their leisure time activity and risk factors related to their work, the effects of these factors could not be investigated.

The injury incidence among athletes participating in national deadlifting contest was 42%. The most commonly injured body parts were the shoulder, lumbopelvic area, and knee. All deadlift-related injuries were on the lumbopelvic area. The stretching time was significantly different between the injured and non-injured groups of competitors (p=.039). Every athlete who performed stretches for more than 15 min had deadlift-related lumbopelvic injuries. These results provide useful information in defining the predisposing factors of sports injuries in deadlifters.

Ethics Committee Approval: N/A

Informed Consent: The participants were informed about the study and their consent was obtained.

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APPENDIX

QUESTIONNAIRE FORM ON THE INCIDENCE AND RISK FACTORS OF SPORTS INJURIES AMONG NATIONAL COMPETITIVE DEADLIFTERS

Age:..... Gender:..... Weight:..... Height:.....

Telephone:.....

E-mail address:.....

Education :.....

Occupation:.....

Alcohol:..... Smoking:.....

Nutritional support:.....

I. Sports discipline:

- o Powerlifter
- o Bodybuilder
- o CrossFit
- o Fitness
- o Other:.....

2. How long have you been doing weight training?

- o 0–6 months
- o 6–12 months
- o 1–2 year(s)
- o More than 2 years

3. How many days do you train in a week?

4. Does a personal trainer supervise your workouts?

- o Yes
- o No

5. Average training duration:

- o 0–30 min
- o 30–60 min
- o 60–90 min
- o 90–120 min
- o Above 120 min

6. How long have you been deadlifting?

- o 0–6 months
- o 6–12 months
- o 1–2 year(s)
- o More than 2 years

7. How many days do you perform deadlifts in a week?

8. Do you use a weight belt?

- o Always
- o Often
- o Rarely
- o Never

9. Average time you spend on deadlifts per day:

- o 0–10 min
- o 10–20 min
- o 20–30 min
- o Above 30 min

10. Your deadlift weights:

Average:.....
Max:.....

11. Average warm-up time before training:

- o 0–5 min
- o 5–10 min
- o 10–15 min
- o Above 15 min

12. Warm-up type:

- o Full body exercises (running, rowing, jumping rope, etc.)
- o Dynamic stretch
- o Static stretch
- o Exercise-specific warm-up (such as perform deadlift movement before deadlift exercise or perform squat movement before squat exercise)
- o Warm-up by gradually increasing the weight up to the training weight
- o Other :.....

13. Stretching time before training:

- o 0–5 min
- o 5–10 min
- o 10–15 min
- o Above 15 min

14. Cooling exercises and stretching time after training:

- o 0–5 min
- o 5–10 min
- o 10–15 min
- o 15 min

15. Do you participate in any sports other than weightlifting? (football/basketball/swimming/running/ .....)

16. How many days per week do you participate in a sport other than weight sports?

17. How many days of rest do you have in your training program?

18. Have you ever experienced injuries in the past year?

- o 0
- o 1
- o 2
- o 3 or more

19. Have you ever experienced injuries during deadlifting in the past year?

o 0
o 1
o 2
o 3 or more

20. Deadlift injury localization:

o Neck
o Back
o Waist
o Shoulder
o Elbow
o Wrist
o Hip
o Knee
o Ankle
o Other

21. Did you seek medical advice? If yes, what was your diagnosis?

22. Prior to the injury, did you feel any discomfort in the injured area?

23. In your opinion, the factor causing this injury was:

o Excessive weight
o Posture error
o Fatigue
o Recurrence of old injury
o Inadequate rest
o Diet plan problems

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Original Article

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Plateletcrit as a Determinant of Diffusion-Restricted Lesion Volume in Diffusion-Weighted Imaging

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BACKGROUND/AIMS
Platelet indices have predictive and prognostic roles in ischemic events. This study aimed to evaluate the correlation between plateletcrit (PCT), one of the platelet indices that provide more comprehensive data about total platelet mass, and diffusion-restricted lesion volume by diffusion-weighted magnetic resonance imaging (DW-MRI).

MATERIAL and METHODS
All the patients admitted to the emergency department between September 2018 and September 2019 were retrospectively analyzed. Patients who underwent both DW-MRI and complete blood count for any reason were included. All DW-MRI results were interpreted again, and restricted lesion volumes were calculated by a radiologist. Lesions >4 cm3 in volume were considered as large restrictions. Statistical analysis was performed using IBM Statistical Package for the Social Sciences Statistics for windows, version 22.0.

RESULTS
A total of 505 patients were included, of whom 285 (56.4%) had no diffusion-restricted lesions on DW-MRI. Platelet indices were compared between the patients with diffusion restriction and those without restriction on DW-MRI. In-group comparisons of these parameters between small and large restrictions were also conducted. There were no significant differences between the groups in terms of age, gender, and platelet indices. Correlations of stroke volume and platelet indices were also analyzed, and we found no correlations between these parameters (P>.05 for all).

CONCLUSION
This study showed us that neither plateletcrit nor other platelet indices were predictors of diffusion restricted lesion volume in diffusion-weighted imaging.

Keywords: Diffusion magnetic resonance imaging, blood platelets, mean platelet volume, platelet count

INTRODUCTION

Stroke, with a prevalence of 2.6% in individuals aged >20 years, is an important cause of death around the world.[1] Approximately 85% of strokes are ischemic in origin, and it is well documented that there is a direct relationship between ischemic stroke and platelet indices, stemming from the role of platelet activation in the process of atherosclerosis (1, 2).

Platelet indices such as mean platelet volume (MPV), platelet count (PC), and platelet distribution width (PDW) are part of a routine complete blood count (3). It has been shown that platelets with larger volumes are more active enzymatically and metabolically and thus have higher thrombotic ability (4, 5). Plateletcrit (PCT), another platelet index, has the great advantage of providing more comprehensive data about total platelet mass because it is equivalent to MPV and PC (PCT = PC × MPV/10) (3, 6, 7).

Diffusion-weighted magnetic resonance imaging (DW-MRI) is the hallmark imaging approach for acute cerebral infarction, especially in emergency departments, because of the restricted diffusion usually developing within 1 hour of insult (7).

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Although this imaging abnormality is less frequently seen with neoplasms, intracranial infections, and demyelinating processes, the vast majority of restricted-diffusion abnormalities on MRI result from acute stroke (7). It is also known that early ischemic lesion volume on DW-MRI is an independent predictor of stroke outcome (8).

Many existing studies have shown the predictive or prognostic roles of PCT in many different ischemic events, such as cerebrovascular accidents, coronary lesions, and even recurrent abortions (9-11). However, to the best of our knowledge, there is no study on PCT and its association with diffusion-restricted lesion volume on DW-MRI. This study aimed to evaluate the correlation between these 2 parameters to understand whether PCT might be a predictor of diffusion-restricted lesion volume on DW-MRI.

MATERIAL and METHODS

This study was conducted in a training and research hospital after obtaining the approval of the local ethics committee. All patients admitted to the emergency department between September 2018 and September 2019 were retrospectively analyzed. Patients who underwent both DW-MRI and a complete blood count for any reason were included in the study. Patients lacking either of these examinations, patients with hematological disorders affecting platelets, and patients with a history of acute trauma were excluded.

Neuroimaging Protocol and Analysis

Standard DW-MRI examinations of the subjects in the supine position were performed using a 1.5-T clinical scanner (MAGNETOM Avanto, Siemens Healthineers, Erlangen, Germany). DW-MRI was performed with the following parameters: 8 slices, 4300/102 ms (repetition time/echo time), slice thickness of 5 mm, gap of 1 mm, field of view of 22 cm, and b values of 0 and 1,000 s/mm^2. The lesion volumes were determined after the images were transferred to a workstation (syngo.via, Siemens Healthineers). An experienced reader (CÖ, a radiologist with 10 years of experience) blinded to the laboratory data reviewed all DW-MRI results to manually measure the ischemic lesion volumes by using the volume of interest (VOI). Ischemic areas observed in diffusion images were manually marked using VOI. Marking was performed on all sections where ischemic areas were observed, and then the ischemic volume was automatically calculated by the device. In cases with more than one ischemic focus, the measurement of each ischemic area was done separately, and the total volume of ischemic areas was calculated. Lesions greater than 4 cm^3 were considered as large restrictions; this threshold was determined according to a study of Mohamed et al. (2).

Main Points:

- To the best of our knowledge this is the first study investigating the relationship between platelet indices and lesion volume on diffusion-weighted magnetic resonance imaging (DW-MRI)
- Plateletcrit was not a predictor of diffusion-restricted lesion volume on DW-MRI
- There was also no correlation between the other platelet indices (platelet count, mean platelet volume, and platelet distribution width) and diffusion-restricted volumes.

Measurement of Platelet Indices

In general practice, the blood of a patient is sampled immediately after admission to the emergency department and before the administration of medications and intravenous fluids. Samples were collected in ethylenediaminetetraacetic acid tubes and were processed in the laboratory of the emergency department within 2 hours using a Mindray BC-6800 hematology analyzer (Mindray). The normal ranges of platelet indices in our laboratory are as follows: PC, 156–373 × 10^3/μL; MPV, 6.9–10.8 fL; PDW, 12-25; and PCT, 0%-10%.

Statistical Evaluation

Statistical analysis was performed using IBM Statistical Package for the Social Sciences Statistics for windows, version 22.0 (IBM SPSS Corp.; Armonk, NY, USA). Categorical variables are provided as frequency and percentage. Continuous variables are given as median and interquartile range (IQR). The Shapiro–Wilk test was used to determine normality. The Mann–Whitney U test was used for two-group comparisons of continuous variables. Pearson chi-square tests were used to compare categorical variables. The Spearman correlation test was used for correlation analyses. Values of $P<.05$ were considered statistically significant.

RESULTS

A total of 505 patients, including 291 women (57.6%) and 214 men (42.4%) with a median age of 73 (IQR: 64-81) years, were included in this study. The most common complaints during the emergency department admission were general disturbances (25.1%), motor deficiencies (17.4%), dysarthria (13.3%), and vertigo (11.3%). There were no diffusion-restricted lesions on DW-MRI for 285 patients (56.4%). In the other patients, diffusion restrictions were most commonly seen as cortical (n=66), focal (n=40), and diffuse subcortical (n=39) restrictions. The outcomes of the patients were also analyzed; 257 (50.7%) were discharged, 51 (10.1%) were transferred to a stroke center, and 94 (18.6%) were admitted to the intensive care unit (Table 1).

Platelet indices were compared between the groups of patients with and without diffusion restriction on DW-MRI. In-group comparisons of these parameters between patients with small (Group 2a; patients with restrictions <4 cm^3) and large (Group 2b; patients with restrictions ≥4 cm^3) restrictions were conducted. There were no significant differences between the groups in terms of age, sex, and platelet indices ($p>.05$ for all) (Table 2).

The correlations of diffusion-restricted lesion volume and platelet indices were also analyzed. We found no correlation between these parameters ($p>.05$ for all). There was no correlation between platelet indices and stroke volume even when the analysis was repeated while including only cortical restrictions (Table 3).

DISCUSSION

Our results showed that PCT was not a predictor of diffusion-restricted lesion volume on DW-MRI. As in PCT, there was also no correlation between the other platelet indices (PC, MPV, and PDW) and diffusion-restricted volumes.

Platelet indices, given automatically by most cell counters, have been used in clinical practice only for the differential diagnosis

TABLE 1. General characteristics of the patients

Characteristic	Number	Percent (%)
Age, years	73 (IQR: 64-81)	
Gender		
Female	291	57.6
Male	214	42.4
Complaint at admission		
General disturbance	127	25.1
Motor deficiencies	88	17.4
Dysarthria	67	13.3
Vertigo	57	11.3
Sensorial deficiencies	37	7.3
Syncope	29	5.7
Seizure	19	3.8
Others	81	16
Diffusion-restricted lesion on DW-MRI		
None	285	56.4
Cortical	66	13.1
Focal	40	7.9
Diffuse subcortical	39	7.7
Subcortical	35	6.9
Lacunar	28	5.5
Mass lesion	5	1
Lacunar + diffuse subcortical	5	1
Lacunar + Subcortical infarct	2	0.4
Outcome		
Discharged	256	50.7
Transmitted to a stroke center	51	10.1
Admitted to an intensive care unit	94	18.6
Admitted to the neurology department	69	13.7
Admitted to other departments	35	6.9

DW-MRI, diffusion-weighted magnetic resonance imaging; IQR, interquartile range.

of thrombocytopenic disorders. Recent studies did indicate that platelet indices and thrombotic events were strictly related, but the cause-and-effect relationship between them is still unclear (12). PCT, also known as platelet mass, is a platelet index calculated using PC and MPV and is accepted as an indicator of circulating platelets in a unit volume of blood (2, 3). It has been shown that high PCT values on admission are independently associated with long-term adverse outcomes in patients with acute coronary syndromes (3, 5). Akpınar et al. also showed that PCT might be a useful predictor of slow coronary flow phenomenon, a delayed opacification of distal vessels on coronary angiography in the absence of significant epicardial coronary stenosis (13).

Stroke is another clinical entity that results in changes in platelet indices whose role in the pathogenesis of atherothrombosis and inflammation has been already documented (14). Studies on the prediction value of PC and MPV for the outcome of stroke survivors have yielded inconsistent findings (15). However, Mohammed et al. showed that PCT was significantly correlated with poor functional outcomes in cases of acute stroke (2).

Lesion volume is believed to be an important parameter reflecting the primary pathological condition, and the extent of this pathological condition is related to neurological deficits and functional outcomes (16). Vincent et al. showed that the DW-MRI lesion volume measured within 48 hours of symptom onset was an independent risk factor for functional independence (8).

TABLE 3. Correlation of platelet indices with stroke volume

Platelet indices	Correlation with stroke volume for all restrictions (n=220) P-value	Correlation with stroke volume for only cortical restrictions (n=66) P-value
PC	.895	.64
MPV	.319	.87
PDW	.764	.17
PCT	.869	.76

MPV, mean platelet volume; PC, platelet count; PCT, plateletcrit; PDW, platelet distribution width.

TABLE 2. Comparison of platelet indices between the groups

		Group 1	Group 2	P1	P2
Variables		Group 2a	Group 2b	Groups 1 and 2	Groups 2a and 2b
Age	74 (63-81)	71 (64-79.25)	74.5 (63-81)	.70	.47
Gender					
Female	165 (58%)	63 (53%)	63 (62%)		
Male	120 (42%)	55 (47%)	39 (38%)	.89	.21
PC	233.000 (194,000-288,000)	236.000 (192,750-290,750)	225.000 (187,750-285,000)	.88	.51
MPV	9.60 (8.85-10.50)	9.75 (8.97-10.50)	9.75 (9.07-10.40)	.34	>.99
PDW	16.10 (15.90-16.40)	16.10 (15.90-16.40)	16.10 (15.90-16.40)	.89	.70
PCT	2.30 (1.90-2.70)	2.20 (1.90-2.82)	2.20 (1.90-2.62)	.63	.59

Data are presented as median (IQR) or number (%). Group I includes patients with no diffusion restriction on DW-MRI, Group 2a includes patients with <4 cm^3 diffusion restriction on DW-MRI, and Group 2b includes patients with ≥4 cm^3 diffusion restriction on DW-MRI.
DW-MRI, diffusion-weighted magnetic resonance imaging; MPV, mean platelet volume; PC, platelet count; PCT, plateletcrit; PDW, platelet distribution width.

Different molecules, such as free fatty acids, vitamin D, and circulating endothelial microparticles have been investigated as determinants of ischemic lesion volume (17-19). However, no previous study investigating the relationship between platelet indices and lesion volume has been found in the literature.

DW-MRI is a preferred imaging modality in emergency settings because restriction usually develops within 1 hour of insult. The majority of restricted-diffusion abnormalities result from acute stroke, and the diagnosis may be difficult when this imaging feature results from different causes because many diseases, such as seizures, neoplasms, head injury, and even cyanide poisoning, hyperglycemia, or phenylketonuria can cause diffusion restriction (7). Therefore, all diffusion-restricted lesions were included in this study. To our knowledge, this is the first study investigating the relationship between platelet indices and diffusion-restricted lesion volume on DW-MRI.

This study has some limitations. First, because this was a retrospective study, we could not follow the patients and only evaluated the data during the emergency department process; therefore, we did not know the definitive diagnosis and outcomes of the patients. Second, platelet indices are affected by many clinical situations such as inflammation and comorbid diseases, and we did not exclude these confounding factors. However, because it would not have been possible to exclude those confounding factors in clinical practice, we planned the study considering that platelet indices should predict diffusion-restricted lesion volume in the presence of those confounding factors if they had a real predictive role.

In this study on the role of platelet indices in determining diffusion-restricted lesion volume on DW-MRI, no relationship was found between restricted lesion volume and the measured variables (PCT, PC, MPV, and PDW). To accurately determine the relationship of platelet indices with diffusion-restricted lesion volume and outcome in stroke survivors, further studies need to be conducted with larger sample sizes and patients with definitive diagnoses.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Keçiören Training and Research Hospital (Approval date: 27.11.2019, No: 2012-KAEK-15/1991).

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Original Article

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An Assessment of the 100 Most Frequently Cited Articles Related to Bicuspid Aortic Valve in the Literature

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BACKGROUND/AIMS
Bicuspid aortic valve disease may cause both aortic stenosis and regurgitation; therefore, it manifests as different symptoms. Aortic stenosis in patients with bicuspid aortic valve exhibits ambiguous hemodynamic effects; moreover, it may remain asymptomatically until the effective orifice area is narrowed below 1.5–2 cm^2. In this study, we aimed to evaluate 100 articles related to bicuspid aortic valve that have been most frequently cited in the literature.

MATERIAL and METHODS
The study was performed using advanced mode of the search engine server Institute for Scientific Information Web of Science. For this purpose, the words "TS=bicuspid or TI=bicuspid" were reviewed. The search was carried out, and the 100 most cited articles were determined. The total and annual cite count for each article and information about the authors and the journals were determined via WOS and PubMed.

RESULTS
The mean cite count of the 100 most cited articles was found to be 238.10±227.48. The annual cite counts of the studies varied from 4 to 185, and the mean value was calculated as 20.93±25.25. The first 3 subjects were clinical BAV (41%), pathology of BAV (15%), and genetics of BAV (15%). There was no statistically significant difference between the continent of the corresponding author and overall and annual cite counts. In addition, no statistically significant difference was observed between the journal's continent and overall and annual cite counts ($p>.05$).

CONCLUSION
This study is the first in the literature to identify the 100 most cited articles related to BAV. The majority of these studies were based on clinical evaluation of BAV. We found an increase in the number of studies on percutaneous transcatheter interventions over the last 5 years.

Keywords: Bicuspid aortic valve, bibliometrics, aortic aneurysm, aortic stenosis

INTRODUCTION

In the current era, several studies have been conducted by different international or national institutes and surgical disciplines to determine the most cited articles for medical sciences (1-4). When a scientific paper references another scientific paper, it is identified as "cited." The scientific articles that had been a resource of or that strengthened the findings are accepted as cited if they are referred in any part of another scientific paper. The impact factor of the article is evaluated according to the frequency of citation. The more cited articles and the journals with a higher impact factor are considered more qualified (5, 6).

The first bibliographic study on the 100 Citation Classics From the Journal of the American Medical Association published in the Journal of the American Medical Association was written by Garfield et al. (5). Since then, numerous stud-

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ies investigating the most cited articles have been presented not only in general medical journals but also in specialized journals (7). For example, Ahmad et al. (8) presented the 100 most cited articles on bariatric surgery between 1945 and 2014, and Amina et al. (9) reported the 50 most frequently cited articles on bariatric and endocrinological surgery published between 1950 and 2000.

No study has investigated the relationship between bicuspid aortic valve (BAV) and the citation number of published articles related to this issue. BAV disease may cause both aortic stenosis and regurgitation; therefore, it manifests as different symptoms. Aortic stenosis in patients with BAV exhibits ambiguous hemodynamic effects; moreover, it may remain asymptomatically until the effective orifice area is narrowed below 1.5–2 cm^2 (9-13). However, a valve replacement should be performed in high-risk patients with severe aortic stenosis because these patients rapidly become symptomatic. On the other hand, aortic regurgitation may occur primarily or as a consequence of BAV. Calcification, myxomatous degeneration, infective endocarditis, rheumatic fever, and some drugs (e.g., fenfluramine, phentermine) may also cause aortic regurgitation (13-17). This complex is identified as bicuspid aortic syndrome, and the treatment algorithms are developed according to guidelines (18-20).

In this study, we aimed to determine the 100 most cited articles on BAV and evaluate these studies according to authors' characteristics, the origin of countries, institutes, and the journals that have published these articles via the Institute for Scientific Information (ISI) Web of Science (WOS) search engine.

MATERIAL and METHODS

This study was conducted after ethical approval (number: 377-GOA 2018/03-09) was obtained and was performed using advanced mode of ISI WOS search engine. The words "TS=bicuspid or TI=bicuspid" were searched, and articles published between 1975 and 2018 were included. The search was done on June 14, 2018. Consequently, the 100 most cited articles related to BAV that have been published in international journals were identified. The list was created to evaluate the 100 most cited articles related to BAV in the literature. The first authors of each article were reviewed, and it was checked whether they were a part of another article in the same list. The overall and annual cite count and information about authors, articles, and journals were determined via WOS and PubMed. Letters to the Editor and case reports were excluded from the study.

Main Points:

- This is the first study analyzing BAV from bibliometric point of view. A majority of these studies have investigated BAV clinically.
- There was no difference observed between the continent of the first author and the annual citation number. Moreover, no difference was observed between the continent of the journal and the annual citation number.
- The articles that had been published after 2010 had remarkably higher citation number (p <.05); this was interpreted as an increase in interventional cardiology publications for BAV syndrome.
- We believe that the citation numbers of studies on innovative materials (e.g., sutureless, bioprosthesis valves, etc.) for aortic valve will constantly increase in the following years.

Statistical Analysis

Statistical analyses were performed using the SPSS (IBM SPSS Corp.; Armonk, NY, USA) version 20.0 software. Categorical data are presented in absolute (n) and relative (%) frequencies. All data are expressed as the mean value±standard deviation. For the comparison of the groups, Kruskal Wallis and Mann-Whitney U tests were performed. P <.05 was considered statistically significant in all statistical tests.

RESULTS

A total of 4,130 studies that have been published between 1975 and 2018 were found after a search using the keywords "TS=bicuspid or TI=bicuspid" in the WOS search engine. Among all the 100 most cited articles list, the most cited article had 2,001 citations and the less cited had 108 citations. We did not cite all the 100 articles because we have included them in the last citation. The information about the first authors of the 100 articles on BAV is shown in Table 1.

The analysis of institutions of the corresponding authors is presented in Table 2.

The most cited article was written by Hoffman et al. (22). The article was titled "The Incidence of Congenital Heart Disease" and was published in the Journal of the American College of Cardiology in 2002. The first 3 journals where the 100 articles had been published were found to be Circulation (18%), Journal of The American College of Cardiology (17%), and Journal of Thoracic and Cardiovascular Surgery (11%). In Table 3, citation numbers and mean values of the 100 articles are listed. When the researchers were investigated according to their nationality, the USA (56%), Canada (17%), and Germany (7%) were listed on top. Moreover, 22% of the authors were non-European citizens. All the 100 articles had been published in journals indexed in the science citation index.

However, there was a significant relation between the publishing year and the mean annual citation number; in particular, the articles that had been published after 2010 had remarkably higher citation number (p<.05). Type of the papers had a significant association with citation numbers and annual citation numbers; in particular, the Guideline-type articles had much more total citation and annual citation numbers (p<.05). Articles written by non-surgeon authors had higher annual citation numbers than the articles in which the first author was a surgeon. In addition, there was a significant difference related to annual citation numbers among journals (p<.05). For instance, USA- and UK-originated journals had remarkably higher annual citation numbers when study subjects were considered. Guideline-type articles also had significantly higher total and annual citation numbers (p<.05). The characteristics of the 100 articles related to BAV are presented in Table 4.

TABLE I. The first authors of the 100 most cited articles about BAV in the literature

	Frequency	Percent		Frequency	Percent
Nishimura, RA	3	3,0	Januzzi, JL	1	1,0
Warmes, CA	3	3,0	Keane, MG	1	1,0
David, TE	2	2,0	Lee, TC	1	1,0
Aicher, D	2	2,0	Lopez, L	1	1,0
Fedak, PWM	2	2,0	Macatee, TL	1	1,0
Hoffman, JIE	2	2,0	Mahadevia, R	1	1,0
Hope, MD	2	2,0	Markl, M	1	1,0
Hinton, RB	2	2,0	Mazzanti, L	1	1,0
Maron, BJ	2	2,0	McKellar, SH	1	1,0
Michelena, HI	2	2,0	Mohamed, SA	1	1,0
Loeys, BL	1	1,0	Mohler, ER	1	1,0
Andelfinger, G	1	1,0	Nataatmadja, M	1	1,0
Barker, AJ	1	1,0	Niessen, K	1	1,0
Basso, CB	1	1,0	Nistri, S	1	1,0
Ben S	1	1,0	Niwa, K	1	1,0
BEPPU, S	1	1,0	Nkomo, VT	1	1,0
Biben, C	1	1,0	Okamoto, RJ	1	1,0
Biner, S	1	1,0	Pachulski, RT	1	1,0
Bissell, MM	1	1,0	Pelliccia, Antonio	1	1,0
Bonderman, D	1	1,0	Pierpont, Mary Ella	1	1,0
Boodhwani, M	1	1,0	Regitz-Zagrosek, Vera	1	1,0
Boon, RA	1	1,0	Roberts, CS	1	1,0
Borger, MA	1	1,0	Roberts, WC	1	1,0
Braverman, AC	1	1,0	Robicsek, F	1	1,0
Caira, FC	1	1,0	Russo, CF	1	1,0
Casselman, FP	1	1,0	Sabet, HY	1	1,0
Combs, MD	1	1,0	Schaefer, B. M.	1	1,0
Cripe, L	1	1,0	Sedmera, D	1	1,0
David, Tirone E.	1	1,0	Sievers, HH	1	1,0
Davies, Ryan R.	1	1,0	Siu, SC	1	1,0
De Sa, M	1	1,0	Snider, P	1	1,0
Della Corte	1	1,0	Svensson, LG	1	1,0
Ergin, MA	1	1,0	Sybert, VP	1	1,0
Fahed, Akl C.	1	1,0	Tadros, TM	1	1,0
Feng, QP	1	1,0	Takach, TJ	1	1,0
Fernandes, SM	1	1,0	Tang, GHL	1	1,0
Garg, V	1	1,0	Topaz, O	1	1,0
Gotzsche, CO	1	1,0	Tzemos, N	1	1,0
Gridley, Thomas	1	1,0	Verma, S	1	1,0
Hahn, RT	1	1,0	Von Kadolitsch, Y	1	1,0
Huntington, K	1	1,0	Ward, C	1	1,0
Ikonomidis, JS	1	1,0	Wijesinghe, N	1	1,0
Immer, FF	1	1,0	Yasuda, H	1	1,0
Lung, B	1	1,0	Zegdi, R	1	1,0
			Total	100	100,0

TABLE 2. The institutes of the 100 most cited articles about BAV in the literature

	Frequency	Percent		Frequency	Percent
Mayoclinic	11	11,0	Hosp Univ Penn	1	1,0
Univ Toronto	10	10,0	Indiana Univ	1	1,0
Northwestern Univ	4	4,0	Italian Natl Olymp Comm	1	1,0
Univ Calif San Francisco	4	4,0	Jackson Lab	1	1,0
Cincinnati Childrens Hosp	3	3,0	London Hlth Sci Ctr	1	1,0
Washington Univ	3	3,0	Mt Sinai Med Ctr	1	1,0
Cleveland Clin	2	2,0	Natl Cardiovasc Ctr	1	1,0
Baylor Univ	2	2,0	NHLBI	1	1,0
Harvard Univ	2	2,0	Niguarda Hosp	1	1,0
Med Univ S Carolina	2	2,0	RES INST	1	1,0
Minneapolis Heart Inst Fdn	2	2,0	St. Luke's International Hospital	1	1,0
Univ British Columbia	2	2,0	Texas Heart Inst	1	1,0
Univ Cincinnati	2	2,0	UKSH, Klin Herzchirurg	1	1,0
Univ Ottawa	2	2,0	Univ Bologna	1	1,0
Univ Padua	2	2,0	Univ Hosp Bern	1	1,0
Univ Western Ontario	2	2,0	Univ Hosp Hamburg Eppendorf,	1	1,0
Aarhus Univ Hosp	1	1,0	Univ Hosp Homburg	1	1,0
Beth Israel Deaconess Med Ctr	1	1,0	Univ Hosp Saarland	1	1,0
Boston Univ	1	1,0	Univ Massachusetts	1	1,0
Carolinas Med Ctr	1	1,0	Univ Miami	1	1,0
Cedars Sinai Med Ctr,	1	1,0	Univ Naples	1	1,0
Charite, Inst Gender Med	1	1,0	Univ New S Wales	1	1,0
Childrens Hosp & Med Ctr, Div Dermatol, Seattle	1	1,0	Univ Oxford	1	1,0
Childrens Hosp Montefiore	1	1,0	Univ S Manchester	1	1,0
Clin Univ St Luc	1	1,0	Univ Schleswig Holstein	1	1,0
Columbia Univ	1	1,0	Univ Texas, SW Med Ctr	1	1,0
Geargetown Univ	1	1,0	Univ Utah	1	1,0
Ghent Univ Hosp	1	1,0	Univ Vienna	1	1,0
Goethe Univ Frankfurt	1	1,0	University of Melbourne	1	1,0
Hop Europeen Georges Pompidou	1	1,0	University of Minnesota	1	1,0
Hop Xavier Bichat	1	1,0	Total	100	100,0

DISCUSSION

Owing to the development in intervention methods and new-generation aortic valves, indications in the guidelines and management are being updated consistently. However, contemporary studies are needed to obtain better knowledge about bicuspid aortic syndrome. This study is the first study analyzing BAV from bibliometric point of view. A majority of these studies have investigated BAV clinically. There was no difference observed between the continent of the first author and the annual citation number. Moreover, there was no difference between the continent of the journal and the annual citation number. The articles that had been published after 2010 had remarkably higher citation numbers (p<.05); this was interpreted as an increase in interventional cardiology publications related to BAV syndrome.

Aortic stenosis is the most common valvular disease in developed countries (17-19). The underlying etiology may be a degenerative disease, BAV, or rheumatic cardiac disease. However, the etiology of BAV is still unclear (17). Early calcium deposit occurs; subsequently, genetic predisposition and BAV morphology lead to increased physical stress on the leaflets. Further studies may clarify the underlying mechanisms of this complex disease, delaying the progress at early stages. Abnormal valvular structure, turbulence, fibrosis, rigidity, and calcification lead to stenosis in valvular orifice; thus, valvular degeneration increases. BAV is the most common cause of congenital calcific aortic stenosis and is reported with a rate of 2% in the general population (1-4). Progressive calcification often develops in the fifth and sixth decades, is more common in valve structure with single commissure, and has male dominance (19-22). However, it may coexist with an aneurysm related to medial degeneration.

TABLE 3. Overall and mean annular citation numbers and the mean of the 100 most cited articles about BAV in the literature

	Article	Year	Authors	Citation number	Mean Annular citation number
1	The incidence of congenital heart disease Journal Of The American College Of Cardiology 2002; 39:1890-00 .	2002	: Hoffman, JIE; Kaplan, S	1990	117.06
2	2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary.2014;63:2438-88	2014	Nishimura, Rick A.; Otto, Catherine M.; Bonow, Robert O.; et al.	911	182.20
3	Mutations in NOTCH1 cause aortic valve disease 437:270-74.	2005	Garg, V; Muth, AN; Ransom, JF; et al.	698	49,86
4	ACC/AHA 2008 Guidelines For The Management Of Adults With Congenital Heart Disease Journal Of The American College Of Cardiology 2008;23:E1-121 .	2008	Warnes, Carole A.; Williams, Roberta G.; Bashore, Thomas M.; Et Al.	632	57,45
5	The revised Ghent nosology for the Marfan syndrome journal Of Medical Genetics 2010;47:476-85.	2010	Loeys, Bart L.; Dietz, Harry C.; Braverman, Alan C.; et al.	590	65,56
6	ESC Guidelines on the management of cardiovascular diseases during pregnancy The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC) European Heart Journal 2011:32:3147-97.	2011	Regitz-Zagrosek, Vera; Lundqvist, Carina Blomstrom; Borghi, Claudio; et al.	541	67,63
7	2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Circulation 2014;129:E121-E643 .	2014	Nishimura, Rick A.; Otto, Catherine M.; Bonow, Robert O.; et al.	540	108,00
8	ACC/AHA 2008 Guidelines for the Management of Adults With Congenital Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease): Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons Circulation. 2008;118:E714-	2004,00	Warnes, Carole A.; Williams, Roberta G.; Bashore, Thomas M.; et al.	537	48,82
9	Genetic basis for congenital heart defects: Current knowledge - A scientific statement from the American heart association congenital cardiac defects committee, council on cardiovascular disease in the young Circulation 2007;115:3015-38	2007	Pierpont, Mary Ella; Basson, Craig T.; Benson, D. Woodrow, Jr.; et al.	445	37,08
10	Recommendations for Quantification Methods During the Performance of a Pediatric Echocardiogram: A Report From the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council journal Of The American Society Of Echocardiography.2010;23:465-95.	2010	Lopez, Leo; Colan, Steven D.; Frommelt, Peter C.; et al.	411	45,67
11	Clinical and pathophysiological implications of a bicuspid aortic valve Circulation2002;106:900-4.	2002	Fedak, PWM; Verma, S; David, TE; et al.	392	23,06
12	Clinical significance of the bicuspid aortic valve Heart 2000;83:81-85	2000	Ward, C	366	19,26
13	Prevalence of congenital heart disease By: Hoffman, JIE; Kaplan, S; Liberthson, RR American Heart Journal 2004;147:425-39 .	2004	Hoffman, JIE; Kaplan, S;Liberthson, RR	365	24,33
14	Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation Circulation 2005;111:920-25	2005	Roberts, WC; Ko, JM	355	25,36
15	2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Circulation2014;129:2440-92 .	2014	Nishimura, Rick A.; Otto, Catherine M.; Bonow, Robert O.; et al	334	66,80
16	Bicuspid Aortic Valve Disease Journal Of The American College Of Cardiology2010;55:2789-2800.	2010	Siu, Samuel C.; Silversides, Candice K.	307	34,11
17	A classification system for the bicuspid aortic valve from 304 surgical specimens Journal Of Thoracic And Cardiovascular Surgery2007;133:1226-33	2007	Sievers, Hans-H.; Schmidtke, Claudia	299	24,92
18	Bicuspid aortic valve is heritable Journal Of The American College Of Cardiology 2004;44:138-143	2004	Cripe, L; Andelfinger, G; Martin, LJ; et al.	292	19,47
19	Aortic root dilatation in young men with normally functioning bicuspid aortic valves Heart1999;82:19-22.EART	1999	Nistri, S; Sorbo, MD; Marin, M; et al.	285	14,25

TABLE 3. Overall and mean annular citation numbers and the mean of the 100 most cited articles about BAV in the literature (Continued)

	Article	Year	Authors	Citation number	Mean Annular citation number
20	Prevalence of sudden cardiac death during competitive sports activities in Minnesota high school athletes Journal Of The American College Of Cardiology 1998;32:1881-84.	1998	Maron, BJ; Ohman, TE; Aeppli, D	275	13,10
21	Structural abnormalities of great arterial walls in congenital heart disease - Light and electron microscopic analyses Circulation 2001;103:393-400.	2001	Niwa, K; Perloff, JK; Bhuta, SM; et al.	271	15,05
22	Association Of Aortic Dilation With Regurgitant, Stenotic And Functionally Normal Bicuspid Aortic Valves Journal Of The American College Of Cardiology 1992;19:283-88.	1992	Hahn, Rt; Roman, Mj; Mogtader, Ah; et al.	253	9,37
23	Incidence of Aortic Complications in Patients With Bicuspid Aortic Valves Journal Of The American Medical Association 2011;306:1104-12.	2011	Michelena, Hector I.; Khanna, Amber D.; Mahoney, Douglas; et al.	244	30,50
24	Notch signaling in vascular development and physiology Development 2007;134:2709-18.	2007	Gridley, Thomas	246	20,50
25	Outcomes in adults with bicuspid aortic valves: Tzemos, Nikolaos; Therrien, Judith; Yip, James; et al. Journal Of The American Medical Association 2008;300:1317-25.	2008	Tzemos, Nikolaos; Therrien, Judith; Yip, James; et al.	238	21,64
26	Bicuspid aortic valves are associated with aortic dilatation out of proportion to coexistent valvular lesions Circulation2000;102:35-39.	2000	Keane, MG; Wiegers, SE; Plappert, T; et al.	238	12,53
27	Histologic abnormalities of the ascending aorta and pulmonary trunk in patients with bicuspid aortic valve disease: Clinical relevance to the Ross procedure Journal Of Thoracic And Cardiovascular Surgery1999;118:588-96.	1999	de Sa, M; Moshkovitz, Y; Butany, J; et al.	237	11,85
28	Vascular matrix remodeling in patients with bicuspid aortic valve malformations: Implications for aortic dilatation Journal Of Thoracic and Cardiovascular Surgery2003;126:797-806.	2003	Fedak, PWM; de Sa, MP; Verma, S; et al.	236	14,75
29	The adult with congenital heart disease - Born to be bad? Journal Of The American College Of Cardiology2005;46:1-8	2005	Warnes, CA	227	16,21
30	Dilation of the pulmonary autograft after the Ross procedure, LOUISIANA Date: APR 18-21, 1999 Sponsor(s): Amer Assoc Thorac Surg journal Of Thoracic and Cardiovascular Surgery 2000;119:210-18	2000	David, TE; Omran, O; Ivanov, J; et al	223	11,74
31	Cardiac septal and valvular dysmorphogenesis in mice heterozygous for mutations in the homeobox gene Nkx2-5 Circulation Research 2000;87:888-95	2000	Biben, C; Weber, R; Kesteven, S; et al.	217	11,42
32	A comparison of outcomes of mitral valve repair for degenerative disease with posterior, anterior, and bileaflet prolapse Journal Of Thoracic and Cardiovascular Surgery 2005;130:1242-49	2005	David, TE; Ivanov, J; Armstrong, S; et al.	213	15,21
33	Ascending Aortic Dilatation Associated With Bicuspid Aortic Valve Pathophysiology, Molecular Biology, and Clinical Implications Circulation2009;119:880-90.	2009	Tadros, Thomas M.; Klein, Michael D.; Shapira, Oz M.	210	21,00
34	Should the ascending aorta be replaced more frequently in patients with bicuspid aortic valve disease? journal Of Thoracic And Cardiovascular Surgery2004;128:677-83.	2004	Borger, MA; Preston, M; Ivanov, J; et al.	209	13,93
35	Human degenerative valve disease is associated with up-regulation of low-density lipoprotein receptor-related protein 5 receptor-mediated bone formation journal Of The American College Of Cardiology 2006;47:1707-11.	2006	Caira, FC; Stock, SR; Gleason, TG; et al.	208	16,00
36	Bicuspid Aortic Valve: Four-dimensional MR Evaluation of Ascending Aortic Systolic Flow Patterns Radiology2010;255:53-61.	2010	Hope, Michael D.; Hope, Thomas A.; Meadows, Alison K.; et al.	206	22,89
37	Natural history of asymptomatic patients with normally functioning or minimally dysfunctional bicuspid aortic valve in the community Circulation2008;117:2776-84.	2008	Michelena, Hector I.; Desjardins, Valerie A.; Avierinos, Jean-Francois; et al	205	18,64
38	Extracellular matrix remodeling and organization in developing and diseased aortic valves Circulation Research 2006;98:1431-38.	2006,00	Hinton, RB; Lincoln, J; Deutsch, GH; et al.	206	15,85
39	Characterizing the young patient with aortic dissection: Results from the international registry of aortic dissection (IRAD) journal Of The American College Of Cardiology 2004;43:665-69. Volume: 43 Issue: 4 Pages: 665-669	2004	Januzzi, JL; Isselbacher, EM; Fattori, R; et al.	200	13,33
40	Aortic dissection in pregnancy: Analysis of risk factors and outcome Annals Of Thoracic Surgery2003;76:309-14.	2003	Immer, FF; Bansi, AG; Immer-Bansi, AS; et al.	198	12,38

TABLE 3. Overall and mean annular citation numbers and the mean of the 100 most cited articles about BAV in the literature (Continued)

	Article	Year	Authors	Citation number	Mean Annular citation number
41	Congenitally bicuspid aortic valves: A surgical pathology study of 542 cases (1991 through 1996) and a literature review of 2,715 additional cases Mayo Clinic Proceedings1999;74:14-26.	1999	Sabet, HY; Edwards, WD; Tazelaar, HD; et al.	196	9,80
42	Heart Valve Development Regulatory Networks in Development and Disease Circulation Research;105:408-21.	2009	Combs, Michelle D.; Yutzey, Katherine E.	195	819,50
43	Genetics of Congenital Heart Disease The Glass Half Empty Circulation Research2013;112:707-20.	2013	Fahed, Akl C.; Gelb, Bruce D.; Seidman J. G.; et al.	192	32,00
44	Abnormal aortic valve development in mice lacking endothelial nitric oxide synthase. Circulation 2000;101:2345-48.	2000	Lee, TC; Zhao, YD; Courtman, DW; et al.	191	10,05
45	Mechanisms underlying aortic dilatation in congenital aortic valve malformation Circulation 1999;99:2138-43	1999	Bonderman, D; Gharehbaghi-Schnell, E; Wollenek, G; et al.	189	9,45
46	The bicuspid aortic valve Current Problems In Cardiology 2005;30:470-522.	2005	Braverman, AC; Guven, H; Beardslee, MA; et al	188	13,43
47	The bicuspid aortic valve: an integrated phenotypic classification of leaflet morphology and aortic root shape Heart 2008;94:1634-38.	2008	Schaefer, B. M.; Lewin, M. B.; Stout, K. K.; et al.	183	16,64
48	4D flow MRI: journal Of Magnetic Resonance Imaging 2012;36:1015-36.	2012	Markl, Michael; Frydrychowicz, Alex; Kozerke, Sebastian; et al.	183	26,14
49	A prospective study to assess the frequency of familial clustering of congenital bicuspid aortic valve Journal Of The American College Of Cardiology 1997;30:1809-12.	1997	Huntington, K; Hunter, AGW; Chan, KL	183	8,32
50	MicroRNA-29 in Aortic Dilation: Implications for Aneurysm Formation Circulation Research 2011;109:115-U66	2011	Boon, Reinier A.; Seeger, Timon; Heydt, Susanne; et al.	178	22,25
51	Abnormal extracellular matrix protein transport associated with increased apoptosis of vascular smooth muscle cells in Marfan syndrome and bicuspid aortic valve thoracic aortic aneurysm Circulation2003;108:329-33.	2003	Nataatmadja, M; West, M; West, J; et al.	174	10,88
52	Periostin is required for maturation and extracellular matrix stabilization of noncardiomyocyte lineages of the heart Circulation Research 2008;102:752-60.	2008	: Snider, Paige; Hinton, Robert B.; Moreno-Rodriguez, Ricardo A.; et al.	170	15,45
53	Dissection Of The Aorta Associated With Congenital-Malformation Of The Aortic-Valve Journal Of The American College Of Cardiology 1991;17:712-16.	1991	Roberts, Cs; Roberts, Wc	167	5,96
54	Ablation of specific expression domains reveals discrete functions of ectoderm- and endoderm-derived FGF8 during cardiovascular and pharyngeal development Development 2003;130:6361-74.	2003	Macatee, TL; Hammond, BP; Arenkiel, BR; et al.	166	10,38
55	The congenitally bicuspid aortic valve: How does it function? Why does it fail? Annals Of Thoracic Surgery 2004;77:177-84.	2004	Robicsek, F; Thubrikar, MJ; Cook, JW; et al.	162	10,80
56	Bicuspid Aortic Valve Is Associated With Altered Wall Shear Stress in the Ascending Aorta Circulation-Cardiovascular Imaging 2012;5:457-66.	2012	Barker, Alex J.; Markl, Michael; Buerk, Jonas; et al.	160	22,86
57	Epidemiology of valvular heart disease in the adult Nature Reviews Cardiology 2011;8:162-72.	2011	Iung, Bernard; Vahanian, Alec	159	19,88
58	Development And Progression Of Aortic-Valve Stenosis - Atherosclerosis Risk-Factors - A Causal Relationship - A Clinical Morphological-Study Clinical Cardiology1991;14:995-99.	1991	Mohler, Er; Sheridan, Mj; Nichols, R; et al.	160	5,71
59	Long-term results of aortic valve-sparing operations for aortic root aneurysm Journal Of Thoracic And Cardiovascular Surgery 2006;132:347-53.	2006	David, Tirone E.; Feindel, Christopher M.; Webb, Gary D.; et al	157	12,08
60	Failure to prevent progressive dilation of ascending aorta by aortic valve replacement in patients with bicuspid aortic valve: comparison with tricuspid aortic valve Circulation 2003;108:291-94.	2003	Yasuda, H; Nakatani, S; Stugaard, M; et al.	155	9,69
61	Anomalous Coronary-Arteries - Angiographic Findings In 80 Patients International Journal Of Cardiology 1992;34:129-38.	1992	Topaz, O; Demarchena, Ej; Perin, E; Et Al.	155	5,74

TABLE 3. Overall and mean annular citation numbers and the mean of the 100 most cited articles about BAV in the literature (Continued)

	Article	Year	Authors	Citation number	Mean Annular citation number
62	Is it reasonable to treat all calcified stenotic aortic valves with a valved stent? Results from a human Anatomic study in adults Journal Of The American College Of Cardiology 2008;51:579-84.	2008	Zegdi, Rachid; Ciobotaru, Vlad; Noghin, Milena; et al	150	13,64
63	Heart Valve Structure and Function in Development and Disease Annual Review Of Physiology 2011;73:29-46. VOL 73	2011	Hinton, Robert B.; Yutzey, Katherine E.	150	18,75
64	Sinus of valsalva aneurysm or fistula: Management and outcome Annals Of Thoracic Surgery 1999;68:1573-77.	1999	Takach, TJ; Reul, GJ; Duncan, JM; et al	152	7,60
65	Prevalence Of Cardiovascular Malformations And Association With Karyotypes In Turners-Syndrome Archives Of Disease In Childhood 1994;71:433-36.	1994	Gotzsche, Co; Kragolsen, B; Nielsen, J; Et Al.	152	6,08
66	Remodeling of chick embryonic ventricular myoarchitecture under experimentally changed loading conditions Anatomical Record 1999;254:238-52.	1999	Sedmera, D; Pexieder, T; Rychterova, V; et al.	151	7,55
67	Task force 4: HCM and other cardiomyopathies, mitral valve prolapse, myocarditis, and Marfan syndrome Journal Of The American College Of Cardiology 2005;45:1340-45.	2005	Maron, BJ; Ackerman, MJ; Nishimura, RA; et al.	146	10,43
68	Natural history of ascending aortic aneurysms in the setting of an unreplaced bicuspid aortic valve Annals Of Thoracic Surgery 2007;83:1338-44.	2007	Davies, Ryan R.; Kaple, Ryan K.; Mandapati, Divakar; et al.	147	12,25
69	Development of heart failure and congenital septal defects in mice lacking endothelial nitric oxide synthase Circulation 2002;106:873-79.	2002	Feng, QP; Song, W; Lu, XR; et al	142	8,35
70	Congenital heart disease in patients with Turner's syndrome Journal Of Pediatrics 1998;133:688-92.	1998	Mazzanti, L; Cacciari, E	137	6,52
71	Predictors of ascending aortic dilatation with bicuspid aortic valve: a wide spectrum of disease expression European Journal Of Cardio-Thoracic Surgery 2007;31:397-04.	2007	Della Corte, Alessandro; Bancone, Ciro; Quarto, Cesare; et al	136	11,33
72	An echocardiographic survey of primary school children for bicuspid aortic valve American Journal Of Cardiology 2004;93:661-63.	2004	Basso, C; Boschello, M; Perrone, C; et al	136	9,07
73	Congenital heart disease in patients with Turner's syndrome Journal Of Pediatrics 1998;133:688-92.	1998	Mazzanti, L; Cacciari, E	137	6,52
74	Novel NOTCH1 mutations in patients with bicuspid aortic valve disease and thoracic aortic aneurysms Journal Of Thoracic And Cardiovascular Surgery 2007;134:290-96.	2007	McKellar, Stephen H.; Tester, David J.; Yagubyan, Marineh; et al.	134	11,17
75	Cardiovascular malformations and complications in Turner syndrome Pediatrics 1998;101:e11	1998	Sybert, VP	133	6,33
76	Notch signaling in cardiac development Circulation Research 2008;102:1169-1181.	2008	Niessen, Kyle; Karsan, Aly	132	12,00
77	KCNJ2 mutation results in Andersen syndrome with sex-specific cardiac and skeletal muscle phenotypes American Journal Of Human Genetics 2002;71:663-68.	2002	Andelfinger, G; Tapper, AR; Welch, RC; et al	132	7,76
78	Aortic Dilation in Bicuspid Aortic Valve Disease Flow Pattern Is a Major Contributor and Differs With Valve Fusion Type Circulation-Cardiovascular Imaging 2013;6:499-07.	2013	Bissell, Malenka M.; Hess, Aaron T.; Biasiolli, Luca; et al.	130	21,67
79	Surgical treatment of the dilated ascending aorta: When and how? Annals Of Thoracic Surgery 1998;67:1834-39.	1999	Ergin, MA; Spielvogel, D; Apaydin, A; et al.	129	6,45
80	Aortic-Aneurysm In Patients With Functionally Normal Or Minimally Stenotic Bicuspid Aortic-Valve American Journal Of Cardiology 1991;67:781-82.	1991	Pachulski, Rt; Weinberg, Al; Chan, Kl	128	4,57
81	Aortic valve repair leads to a low incidence of valve-related complications European Journal Of Cardio-Thoracic Surgery 2010;37:127-132.	2010	Aicher, Diana; Fries, Roland; Rodionycheva, Svetlana; et al.	124	13,78
82	Repair-oriented classification of aortic insufficiency: Impact on surgical techniques and clinical outcomes journal Of Thoracic And Cardiovascular Surgery 2009;137:286-94.	2009	Boodhwani, Munir; de Kerchove, Laurent; Glineur, David; et al.	124	12,40
83	22q11.2 distal deletion: A recurrent genomic disorder distinct from DiGeorge syndrome and velocardiofacial syndrome American Journal Of Human Genetics 2008;82:214-21.	2008	Ben-Shachar, Shay; Ou, Zhishuo; Shaw, Chad A.; et al.	124	11,27
84	Evidence for efficacy of the Italian national pre-participation screening programme for identification of hypertrophic cardiomyopathy in competitive athletes European Heart Journal 2006;27:2196-200	2006	Pelliccia, Antonio; Di Paolo, Fernando M.; Corrado, Domenico; et al.	123	9,46

TABLE 3. Overall and mean annular citation numbers and the mean of the 100 most cited articles about BAV in the literature (Continued)

	Article	Year	Authors	Citation number	Mean Annular citation number
85	4D Flow CMR in Assessment of Valve-Related Ascending Aortic Disease Jacc-Cardıovascular Imagıng 2011;4:781-87	2011	Hope, Michael D.; Hope, Thomas A.; Crook, Stephen E. S.; et al.	120	15,00
86	Valve Configuration Determines Long-Term Results After Repair of the Bicuspid Aortic Valve Clrculatıon 2011;123:178-85.	2011	Aicher, Diana; Kunihara, Takashi; Abou Issa, Omar; et al.	119	14,88
87	Novel missense mutations (p.T596M and p.P1797H) in NOTCH1 in patients with bicuspid aortic valve Bıochemıcal And Bıophysıcal Research Communıcatıons 2006;345:1460-65.	2006	Mohamed, SA; Aherrahrou, Z; . Liptau, H; et al	119	9,15
88	Aortopathy Is Prevalent in Relatives of Bicuspid Aortic Valve Patients Journal Of The Amerıcan College Of Cardıology 2009;53:2288-95.	2009	Biner, Simon; Rafique, Asim M.; Ray, Indraneil; et al.	115	11,50
89	Tricuspid valve repair with an annuloplasty ring results in improved long-term outcomes Cırculatıon 2006;114:1577-81.	2005	Tang, GHL; David, TE; Singh, SK; et al.	115	8,85
90	Morphology of bicuspid aortic valve in children and adolescents Journal Of The Amerıcan College Of Cardıology 2004;44:1648-51.	2004	Fernandes, SM; Sanders, SP; Khairy, P; et al.	115	7,67
91	Bicuspid aortic valve associated with aortic dilatation - A community-based study Arterıosclerosıs Thrombosıs And Vascular Bıology 2003;23:351-66.	2003	Nkomo, VT; Enriquez-Sarano, M; Ammash, NM; et al.	114	7,13
92	Mechanical properties of dilated human ascending aorta Annals Of Bıomedıcal Engıneerıng 2002;30:624-35.	2002	Okamoto, RJ; Wagenseil, JE; DeLong, WR; et al.	113	6,65
93	Aortic Dilatation in Patients with Bicuspid Aortic Valve New England Journal Of Medıcıne 2014;370:1920-29.	2014	Verma, Subodh; Siu, Samuel C.	110	22
94	Expression of matrix metalloproteinases and endogenous inhibitors within ascending aortic aneurysms of patients with bicuspid or tricuspid aortic valves Journal Of Thoracıc And Cardıovascular Surgery 2007;133:1028-36.	2007	Ikonomidis, John S.; Jones, Jeffery A.; Barbour, John R.; et al.	111	9.25
95	Predictors of aneurysmal formation after surgical correction of aortic coarctation journal Of The Amerıcan College Of Cardıology 2002;39:617-24.	2002	von Kodolitsch, Y; Aydin, MA; Koschyk, DH; et al.	111	6,53
96	Relationship of aortic cross-sectional area to height ratio and the risk of aortic dissection in patients with bicuspid aortic valves Journal Of Thoracıc And Cardıovascular Surgery 2003;126:892-93.	2003	Svensson, LG; Kim, KH; Lytle, BW; et al.	108	6,75
97	Aortic complications after bicuspid aortic valve replacement: Long-term results Annals Of Thoracıc Surgery 2002;74:1773-76.	2002	Russo, CF; Mazzetti, S; Garatti, A; et al.	110	6,47
98	Intermediate-term durability of bicuspid aortic valve repair for prolapsing leaflet European Journal Of Cardıo-Thoracıc Surgery 1999;15:302-08.	1999	Casselman, FP; Gillinov, AM; Akhrass, R; et al	110	5,50
99	Transcatheter Aortic Valve Implantation in Patients With Bicuspid Aortic Valve Stenosis jacc-Cardıovascular Interventıons 2010;3:1122-25.	2010	Wijesinghe, Namal; Ye, Jian; Rodes-Cabau, Josep; et al	108	12,00
100	Valvuloplasty For Aortıc-Insufficıency journal Of Thoracıc And Cardıovascular Surgery 1991;102:571-77. Volume: 102 Issue: 4 Pages: 571-577	1982,00	Cosgrove, Dm; Rosenkranz, Er; Hendren, Wg; Et Al.	107	3,82

Recently, bibliometric studies have been conducted in several fields of medicine worldwide. These studies may be based on both medical and surgical fields consequently. These studies investigating citation indexes and impact factors of previously published articles may also be seen in journals. The most commonly used parameters to evaluate the impact of a study are annual citation numbers. However, more cited articles are identified to be more scientific. These parameters also have limitations. The ISI is a USA-based scientific research association. The main functions of the ISI are to determine the candidate journals for indexing and to control them regularly. Nowadays, the ISI does not index all scientific journals because the journals have to meet the specified criteria. Nonetheless, the ISI serves as a citation and index database search engine, and this service contains published scientific papers since 1945. In addition, it is possible to access some valuable information such as personal, mean, and annular citation statistics via the WOS search engine (1-10). (ISI= Instute of scientific information. WOS=web of science is an online subscription-based scientific citation indexing service orginally produced by the scientific information institude (ISI) in 1964.)

In a study by Ohba et al. (4), including the 100 most cited articles on optics, it was determined that these articles have mostly been published in the Archives of Ophthalmology, Ophthalmology, and American Journal of Ophthalmology. Yoon et al (11) listed the most cited articles regarding radiology between 1945 and 2012; these articles were divided into 4 groups according to neuroradiology, interventional, hepatic cancers, and breast imaging. In another study conducted in 2000, articles regarding anesthesiology have been published in the journals of Sweden, Norway, Finland, and the UK for 2 decades. In this

TABLE 4. The characteristics of the 100 most cited articles about BAV in the literature

	Subgroups	n	Overall citation number mean±SD	Annular Citation Number mean±SD	p value (Overall citation number)	p value (Annular Citation Number)
Year	1990-1994	7	162,42±43,38	6,01±1,60	0,875	<0,001
	1995-1999	12	181,83±57,66	8,91±2,84		
	2000-2004	27	265,77±356,51	16,42±21,23		
	2005-2009	32	229,00±151,22	19,71±14,39		
	>2010	22	272,13±210,99	39,55±39,88		
EU or non-EU	Europa	22	203,68±134,59	17,21±14,31	0,154	0,641
	Non-Europa	78	247,80±247,30	21,98±27,55		
Authors' Nationalities	USA	56	268,98±286,49	25,47±31,73	0,932	0,336
	Canada	17	195,70±75,95	13,91±5,91		
	Germany	7	210,85±157,18	19,94±14,29		
	Italy	6	155,50±64,46	9,58±2,98		
	Japan	3	182,66±78,47	9,82±5,20		
	Belgium	2	358,50±330,21	39,14±37,67		
	UK	2	250,50±168,99	20,65±1,66		
	Australia	2	195,5±30,40	11,15±0,38		
	France	2	157,5±4,94	17,06±4,33		
	Switzerland	1	198	12,38		
	Austria	1	189	9,45		
	Denmark	1	152	6,08±		
Type	Guideline	8	514,00±228,36	74,50±52,66	0,001	<0,001
	Review	20	319,70±414,90	24,65±25,49		
	Retrospective	43	198,48±99,49	14,95±8,64		
	Meta-analysis	3	174,00±38,15	17,07±13,53		
	Prospective	11	145,72±52,19	8,77±3,44		
	Case Report	9	177,88±91,23	16,29±7,15		
	Experimental	6	173,83±18,01	11,19±5,79		
Surgical or non-Surgical	Surgical	45	180,66±66,01	13,31±6,04	0,080	0,040
	Non-surgical	55	285,09±293,81	27,17±32,43		
Departments	Cardiovascular Surgery	45	180,66±66,01	13,31±6,04	0,201	0,081
	Cardiology	25	281,00±208,95	31,52±41,13		
	Pediatrics	13	415,84±503,78	31,25±30,05		
	Pathology	5	172,20±31,13	11,23±3,05		
	Radiology	5	158,80±38,41	22,31±4,22		
	Genetics	4	266,75±220,80	23,71±28,14		
	Biology	2	206,0000±56,56	15,44±7,15		
	Engineering	1	115	6,7		
Journals	Circulation	18	265,27±142,36	27,56±27,33	0,124	0,035
	Journal of the American College of Cardiology	17	373,11±468,95	32,60±48,16		
	Journal of Thoracic and Cardiovascular Surgery	11	185,27±59,59	12,99±4,20		
	Circulation Research	7	185,42±27,96	18,49±7,26		
	Annals of Thoracic Surgery	6	150±29,95	9,34±2,80		
	Heart	3	280,00±92,60	16,84±2,61		
	American Journal of Cardiology	3	129,00±8,54	6,14±2,65		

TABLE 4. The characteristics of the 100 most cited articles about BAV in the literature

	Subgroups	n	Overall citation number mean±SD	Annular Citation Number mean±SD	p value (Overall citation number)	p value (Annular Citation Number)
	European Journal of Cardio-Thoracic Surgery	3	124,66±14,50	10,32±4,33		
	European Heart Journal	2	331,50±294,86	29,27±28,02		
	JAMA-Journal of the American Medical Association	2	244,50±4,94	26,45±6,42		
	Development	2	206,00±56,56	15,44±7,15		
	Circulation-Cardiovascular Imaging	2	146,50±21,92	22,48±0,92		
	American Journal of Human Genetics	2	128,00±5,65	9,51±2,48		
	Nature	1	699	49,93		
	Journal of Medical Genetics	1	592	65,78		
	American Heart Journal	1	365	24,33		
	Journal of the American Society of Echocardiography	1	416	46,22		
	Radiology	1	207	23		
	Mayo Clinic Proceedings	1	198	9,90		
	Current Problems in Cardiology	1	188	13,43		
	Journal of Magnetic Resonance Imaging	1	184	26,29		
	Nature Reviews Cardiology	1	161	20,13		
	Clinical Cardiology	1	161	5,75		
	International Journal of Cardiology	1	155	5,74		
	Annual Review of Physiology	1	152	19		
	Archives of Disease in Childhood	1	152	6,08		
	Anatomical Record	1	151	7,55		
	Journal of Pediatrics	1	138	6,57		
	Pediatrics	1	134	6,38		
	Jacc-Cardiovascular Imaging	1	121	15,13		
	Biochemical and Biophysical Research Communications	1	119	9,15		
	Arteriosclerosis Thrombosis and Vascular Biology	1	115	7,19		
	Annals of Biomedical Engineering	1	115	6,76		
	New England Journal of Medicine	1	111	22,20		
	Jacc-Cardiovascular Interventions	1	108	12		
Country of the journal	USA	78	239,28±242,85	21,91±27,29	,024	,036
	UK	12	309,75±196,12	24,31±19,44		
	Netherlands	7	150,71±27,40	8,83±2,90		
	Germany	3	124,66±14,50	10,32±4,33		
Continent of the jorunal	Europa	78	239,28±242,85	21,91±27,29	0,881	0,251
	Non-Europa	22	233,90±166,37	17,48±16,15		
Study Interest	Clinical	40	171,50±59,60	12,40±6,00	0,008	<0,001
	Incidence	11	407,72±557,34	27,76±32,33		
	Genetics	15	227,00±131,89	19,97±16,47		
	Pathology	15	177,26±47,46	11,23±2,94		
	Guideline	8	514,00±228,36	74,50±52,66		
	Imaging	5	158,80±38,41	22,31±4,22		
	Classification	3	250,33±56,61	18,16±4,73		
	Pathophysiology	2	296,00±140,00	21,47±2,50		

study, journals from Finland and Norway had significantly increased citation numbers within years. Furthermore, the percentage of the citation number also increased in journals from all these countries.

Bibliographic evaluation-based studies have become widespread in the cardiovascular field. Kolkailah et al. (23) presented a bibliographic study on behalf of the 50th anniversary of heart transplantation. In this study, there was no correlation between the journal citation index and the yearly issue number. Usman et al. (24) assessed the 100 most cited articles related to valvular diseases and remarked that the number of interventional studies had increased recently. Compatible with this, we observed that studies on interventional valve placement and valve repair techniques have constantly increased in terms of number and citation. We interpreted these findings as a result of the popularity of the newly emerging interventional and valve spearing methods. On the other hand, Lai et al. (25) presented bibliographic research on aortic dissection and presented a historical development of surgical techniques. Liao et al. (26) evaluated the 100 most cited articles related to coronary artery diseases and remarked on the development in treatment options. Shuaib et al. (27) observed a decrease in the non-invasive cardiology field when compared with similar studies on cardiovascular diseases. They explained that these results were a consequence of improved bridging with revascularization methods, and the guidelines supported this. Considering our findings regarding the increased citation number of the studies about intervention methods, we concluded a similar comment, and we attributed this to a collaboration of clinicians as a heart team. Pennel et al. (28) observed an increase in citation number in the last 5 years when they evaluated the 100 most frequently cited articles related to cardiovascular magnetic resonance imaging (MRI). They attributed this finding to the increased patient population with cardiovascular diseases and the use of MRI. Oh et al. (29) conducted a bibliographical study on hypertension, and they detected an increased citation number in correlation with developing technologies and highlighted this acceleration.

Study Limitations

This study has several limitations. First, the most cited articles were determined via WOS and PubMed. Moreover, it is known that citation numbers may vary among different databases. Although these studies have evaluated overall and annular citation numbers, the list had not been formed in this manner. Second, although the overall citation number and annular citation rates have received broad acceptance in terms of evaluation of a scientific paper, a value of an article cannot be assessed only by the aforementioned parameters.

To the best of our knowledge, no study has evaluated BAV and the citation numbers of articles related to this subject in the literature. This study includes detailed information about the 100 most cited articles on BAV and presents their assessment. Consequently, we believe that the citation numbers of studies on innovative materials (e.g., sutureless, bioprosthesis valves, etc.) for aortic valve will constantly increase in the following years. Bibliographic articles using scientific search engines may contribute to determining the subjects that should be focused on in cardiovascular surgery. Furthermore, such studies should be updated regularly for reliable data analysis.

Ethics Committee Approval: Ethics committee approval was received for this study from the 9 Eylül University Faculty (number: 377-GOA 2018/03-09).

Informed Consent: N/A

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Original Article

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Does High Citrus Production Increase The Frequency of Consumption and Affect The Prevalence of Dental Erosion?

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BACKGROUND/AIMS
The authors have investigated the prevalence and reasons for erosive tooth wear, which has a complex and multifactorial etiology, in adolescents and adults in the eastern Mediterranean coastal city of Mersin, Turkey.

MATERIAL and METHODS
This cross-sectional, descriptive study was performed from June 2019 to February 2020 using a survey at the Faculty of Dentistry, Mersin University, Turkey. The questionnaire forms containing an informative section about the study were distributed to the participants. Data on general sociodemographic variables and risk factors were obtained. The survey consisted of 16 questions, including questions on demographic information, general health status, oral health status, and acidic dietary intake time; an oral examination was performed at the end of the survey. The data were statistically analyzed using the Student's t-test and one-way ANOVA.

RESULTS
There was a significant difference in the total erosion scores of the patients with respect to age (p=.000), whereas no significant differences among the total erosion scores of the patients regarding gender were observed. The presence of erosive tooth wear was significant in terms of the frequency of consuming sour snacks and fruit juice.

CONCLUSION
Dental erosion was associated with both internal and external risk factors. Maxillary and mandibular anterior teeth had more erosive wear.

Keywords: Citrus consumption, dental erosion, epidemiology, prevalence, tooth surface loss

INTRODUCTION

Dental erosion is the irreversible progressive loss of dental hard tissues as a result of chemical acid or electrochemical mechanisms from a nonbacterial source. The erosive potential of erosive agents depends on chemical factors (pH, mineral content, and calcium-chelation properties) or biological factors (tooth anatomy, the relationship between soft tissue and teeth, saliva flow rate, and buffering capacity). Furthermore, behavioral factors, including eating and drinking habits, regular exercise resulting in dehydration and a decrease in salivary flow, excessive oral hygiene, and an unhealthy lifestyle, are predisposing factors for dental erosion (1).

The presence of acid solutions in the frequent and prolonged oral environment at values below the critical pH (5.5) causes the destruction of the enamel tissue due to erosion. Acidic solutions may be of internal or external origin; nevertheless, the frequent consumption of acids is not alone responsible for dental erosion (2). There can be predisposing factors, such as acquired dental pellicle, weakened tooth structure, and reduced buffering capacity, that may influence a person's susceptibility to erosive tooth wear. In terms of long-term dental health, erosive tooth wear has been becoming progressively important according to epidemiological studies, with some evidence showing that the prevalence of dental erosion has increased (3). In the previous studies related to the prevalence of erosion, different results have been reported for deciduous and permanent dentition (4). It was stated that different erosion rates were seen in

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studies on the prevalence of erosion owing to the differences in scoring systems, sample selection, and research techniques. Therefore, it can be complicated to evaluate the results of the prevalence studies.

There is no diagnostic device that measures the amount of wear for clinical detection of dental erosion; therefore, clinical appearance is the most important symptom in the diagnosis of erosive lesions. Generally, erosion begins on the tooth surface, with a flat, bright, and shallow concave shape. Then, it displays a stepped surface appearance as long as the causative agent is not eliminated (3). Different index systems have been used by researchers from the past to the present to evaluate and score dental wear. Eccles (5) has broadly classified lesions as baseline, early, small, and severe without definite criterion definitions, thus allowing a broad interpretation. Xhonga and Valdmanis (6) measured erosion lesions with a periodontal probe and made the scoring in four levels: none, small (<2 mm), medium (up to 3 mm), and heavy (>3 mm). Tooth Wear Index is a numerical scale used to measure tooth tissue loss in millimeters and to determine the presence of secondary dentin (6). Basic Erosive Wear Examination was introduced at a conference in Basel, Switzerland in 2007, and it provides a simple scoring system that can be used with the diagnostic criteria of all available indices (7). The index designed by Lussi et al. (8) records the severity of erosion and is a more detailed modification of the index designed by Eccles and Jenkins (5).

There are many studies on the prevalence of dental erosion (9). However, the literature review revealed no data regarding the dental erosion status of individuals who lived in the eastern Mediterranean coastal city of Mersin, which is one of the most important cities in terms of citrus production in Turkey. The aim of this study was to determine the status of dental erosion in adolescent and adult individuals owing to the consumption of citrus products in Mersin. The null hypotheses were as follows:

1. There is no difference among the total erosion scores of the participants according to the age groups.
2. There is no difference in the prevalence of dental erosion between adolescents and young adults in terms of the importance of the research area with high citrus production.

MATERIAL and METHODS

This cross-sectional study was conducted from June 2019 to February 2020 using a survey. The protocol of this study was approved by the ethics committee of the Mersin University (Turkey) and was conducted in accordance with the most recent guidelines of the Declaration of Helsinki. The study was conducted following the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines (10). The sample size was calculated on the basis of the total target population for adolescents and adults (openepi.com/SampleSize) aged >16 years who were living in Mersin. The total number of adolescents and adults and a precision level of ±5% for the 80% confidence interval were used to calculate the number of participants to be included. As a result of the sampling calculation, it was determined that a minimum of 106 participants should randomly be selected.

Main Points:

- Dental erosion is an irreversible progressive loss of dental hard tissues.
- Dental erosion can be a public health concern because of its high prevalence in population research.
- The scoring methodology appears precious for assessing erosion in populations.

Ethical Approval

The study protocol was approved by the clinical research ethics committee of the Mersin University (approval number: 2019/215-22.05.2019). The study conformed with the most recent guidelines of the Declaration of Helsinki and was performed according to the guidelines of the STROBE checklist. Before participation, all patients or their parents/legal guardians received oral and written study information and signed a written consent form.

Routine intraoral and radiological examinations of the 1,957 patients were performed in the Department of Oral and Maxillofacial Radiology, Mersin University. A total of 489 of these patients were diagnosed with noncaries cervical lesions (NCCLs) and were directed to the Department of Restorative Dentistry. Intraoral and radiological examinations were repeated, and their anamnesis was detailed in this department. Subsequently, a questionnaire was applied to the participants who had dental erosion. Eligibility criteria were as follows: those with age >16 years, those who gave consent to participate in the study, those who completely answered the questionnaire (Figure 1). Exclusion criteria consisted of cases of abrasion, attrition, and abfraction (which are NCCLs but were not included) and those with age <16 years. A total of 163 patients (n=163) participated in this survey.

The research questions were modified using a survey prepared by Chu et al. (11) and Pineda et al. (12). A pilot testing on 20 patients was conducted, and no adjustments to the questionnaire were made. The questionnaire used in this study consisted of three sections and 16 questions. After a part explaining the purpose of the questionnaire, the first section was about obtaining the demographic data (sex, age, profession) of the participants. The second part of the questionnaire consisted of health problems and medications, tooth brushing habits, the use of fluoride, and dietary habits (Table 1). At the end of the questionnaire, a clinical examination was performed for the participants who

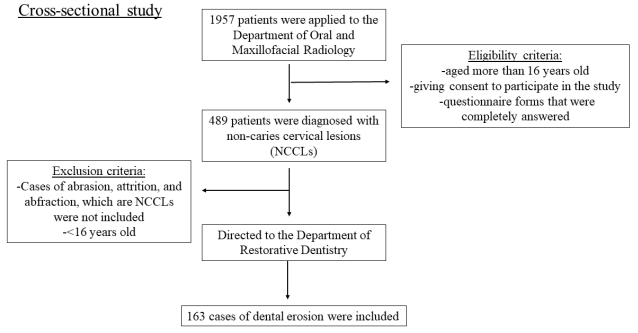

FIGURE 1. Flow chart for the study

gave permission. One standardized examiner (A.T.E.A.) who was trained to identify erosive lesions performed the clinical examinations. The participants were seated under an artificial source of light and assessed with a dental mirror. The examiner dried the teeth with gauze before the clinical examination. The surfaces (occlusal/incisal, buccal, and lingual) of the teeth except those of the third molars were evaluated for each individual in this study. The status and prevalence of tooth erosion were scored using the modified criteria of Lussi (8).

Statistical Analysis

All data were stored in specially arranged computer files. The statistical analyses were performed using the Statistical Package for the Social Sciences, version 25.0 (IBM SPSS Corp.; Armonk, NY, USA). The Student's *t*-test was used to compare the total erosion scores of the patients according to sex, systemic disease, drug usage, consumption of sports drinks, and the patients' perception of dental problems. One-way analysis of variance test was used to compare the total erosion scores of the patients according to the age, the type of systemic disease, the number of daily brushing of teeth, the usage of fluoride toothpaste and auxiliary substances while brushing the teeth, and the consumption of sour snacks, fruit juice, and acidic beverages.

RESULTS

A total of 59.5% of 163 patients were female, and 40.5% were male. It was observed that 25.2% of the participants were aged between 16-25 years, 38% were aged between 26-40 years, and 36.8% were aged >40 years. There were no differences in the total erosion scores of the patients according to sex, whereas there were significant differences according to age groups (p=.001). The participants aged >40 years had significantly higher erosion scores than those in the 16-25 and 25–40 age groups (Table 2). The comparison of the total erosion scores of the patients in terms of systemic disease and drug usage is summarized in Table 3. There was no significant difference according to the type of systemic diseases (p>.05). The scores of patients with systemic disease were significantly higher than those of patients without systemic disease. There were significant differences among the total erosion scores according to drug usage (p=.002).

Table 4 shows that the total erosion scores of the patients did not differ according to the number of daily brushing of teeth and the use of fluoride toothpaste, auxiliaries, and mouthwashes (p>.05). On the other hand, there was a significant difference in the number of patients according to the consumption of sour snacks (p=.01). The patients who responded "always" to the question about sour snacks consumption were significant-

TABLE 1. The questionnaire used in the study

Questions	Responses			
Age				
Sex	Male		Female	
Profession				
Health problems and medication	Hypertension, diabetes, heart disease, gastroesophageal reflux disease (GERD)		Chewable tablets, syrup, effervescent vitamin supplement for example vitamin C	
Daily brushing frequency	I time per day	More than two per day	Every other day	Once a week
Use fluoride tooth paste or mouth wash	No	Rarely	Sometimes	Always
Use auxiliaries (carbonate, lemon, table salt, vinegar, etc.) when brushing your teeth?	No	Rarely	Sometimes	Always
Consume sour snacks (citrus fruits like oranges, lemons etc.)	No	Rarely	Sometimes	Always
Fruit juice consumption	No	Rarely	Sometimes	Always
Acidic beverage consumption	No	Rarely	Sometimes	Always
Consumption of sports drinks (eg Powerade, Burn, Redbull)	No	Rarely	Sometimes	Always
Sports habits (swimming, etc.)	No	Rarely	Sometimes	Always
The last dental examination	Less than a year ago	Among one to three years	More than three years	
Do you think you have a dental problem?	Caries	Periodontal problem	Hypersensitive teeth	

TABLE 2. Scoring of tooth erosion[8]

Grade	Anterior Teeth	Posterior Teeth
0	No erosion	No erosion
I	Loss of surface enamel, dentine not involved	Enamel erosion on cusp tips ("cupping" with dentine not obviously involved) or erosion of fissures that cannot be attributed to attrition.
2	Erosion extending into dentine	Erosion extending into dentine that cannot be attributed to attrition
3	Severe dentine erosion (in at least 4 anterior teeth) and/or the pulp chamber visible	Erosion extending well into dentine and close to the pulp

ly higher than those who responded "sometimes." It was observed that the total erosion scores of the patients showed a significant difference in terms of fruit juice drinking (p=.03). The patients who consumed fruit juice "always" were significantly higher than those who consumed "sometimes." The consumption of carbonated and sports drinks and the habit of performing sports activities did not affect the erosion scores (p>.05).

The total erosion scores of the patients who had their last dental examination dates differed and having dental problems or tooth hypersensitivity did not show a significant difference (p>.05). It was determined that there was a significant difference in terms of the patient's periodontal problem (p=.01). Total erosion scores of patients who had periodontal problems were higher than the scores of those who did not have (Table 4).

A total of 4,564 dental examinations were performed by examining 28 different teeth of 163 patients. A total of 78.92% of the teeth (n=3,602) had no erosion score, 17.62% (n=804) had one, 3.13% (n=143) had two, and 0.33% (n=15) had three. Maxillary and mandibular anterior teeth had more erosive wear, whereas the mandibular posterior teeth were the least commonly affected (Table 5). In a large proportion of the patients, the erosion scores of the teeth in the first, third, fourth, and sixth sextants were zero. However, it was observed that the teeth in the second and fifth sextants had intense signs of erosion.

TABLE 3. Comparison of the total erosion scores of the patients by demographic information, systemic disease, and drug use

	N	Mean	Sd	p
Age				
16-25	41	5,80	4,80	p[a]=0,001*
25-40	62	5,63	3,47	
>40	60	9,13	6,24	
Sex				
Female	97	6,81	4,92	p[b]=0,66
Male	66	7,18	5,64	
Type of Systemic Disease				
No Systemic Disease	91	6,22	4,44	
Hypertension	9	11,33	9,04	
Diabetes	4	9,25	8,22	
Heart disease	8	9,00	9,74	p[a]=0,062
GERD	27	6,70	3,35	
Other	24	7,38	4,82	
Systemic Disease				
No	91	6,22	4,44	p[b]=0,040*
Yes	72	7,90	5,95	
Drug Use				
No	119	6,20	4,36	p[b]=0,002*
Yes	44	9,02	6,66	

[a]p values are based on One-way ANOVA test
[b]p values are based on The Student t-test
*p<0,05 is significant, Sd: Standard deviation

TABLE 4. The comparison of the total erosion scores according to frequency distribution for risk factors

	N	Mean	Sd	p
Number of daily brushing teeth				
One per day	73	6,96	4,89	p[a] =0,99
More than two per day	60	6,90	5,75	
Every other day	11	6,91	4,53	
Once a week	19	7,21	5,37	
Use of fluoride toothpaste				
No	3	9,33	8,08	p[a] =0,65
Rarely & Sometimes	20	6,40	3,80	
Always	140	6,99	5,35	
Use of auxiliaries when brushing teeth				
No	103	6,63	5,24	p[a] =0,72
Rarely	19	7,11	4,95	
Sometimes	35	7,69	5,08	
Always	6	8,00	6,96	
Using mouthwash				
No	95	6,56	4,82	p[a] =0,35
Rarely	35	8,29	5,76	
Sometimes	28	6,96	5,97	
Always	5	5,40	3,05	
Consuming sour snacks				
No	12	6,92	3,94	p[a] =0,003*
Rarely	23	6,5	506	
Sometimes	64	5,41	3,76	
Always	64	8,75	6,18	
Drinking fruit juice				
No	52	7,77	5,27	p[a] =0,03*
Rarely	43	6,79	4,45	
Sometimes	48	5,38	3,28	
Always	20	9,05	8,60	
Consuming carbonated drinks				
No	45	7,84	6,00	p[a] =0,60
Rarely	37	6,46	4,47	
Sometimes	49	6,57	5,58	
Always	32	6,91	4,23	
Consuming sports drinks				
No	147	7,08	5,41	p[b] =0,38
Yes	16	5,88	2,75	
Sports habit				
No	115	6,67	4,76	p[a] =0,40
Rarely	23	6,78	5,49	
Sometimes	15	9,07	7,92	
Always	10	7,60	4,62	
Last Dental Examination Dates				
More than 1 year ago	101	7,23	5,18	p[a] =0,62
Between 1-3 years	30	6,90	5,15	
More than 3 years	32	6,19	5,46	

[a]p values are based on One-way ANOVA test
[b]p values are based on The Student t-test
*p<0,05 is significant, Sd: Standard deviation

TABLE 5. Distribution of dental erosion degrees by mouth region

	Dental Erosion Degree, N (%)				
Sextant	**0**	**1**	**2**	**3**	**Total**
1 (17-14)	617 (94,6)	26 (4,0)	9 (1,4)	-	652 (100,0)
2 (13-23)	577 (59,0)	322 (32,9)	69 (7,1)	10 (1,0)	978 (100,0)
3 (24-27)	624 (95,7)	20 (3,1	6 (0,9)	2 (0,3)	652 (100,0)
4 (37-34)	564 (86,5)	70 (10,7)	18 (2,8)	-	652 (100,0)
5 (33-43)	667 (68,2)	287 (29,3)	23 (2,4)	1 (0,1)	978 (100,0)
6 (44-47)	553 (84,8)	79 (12,1)	18 (2,8)	2 (0,3)	652 (100,0)

DISCUSSION

Nowadays, with the enhancement of consumption rates of acidic beverages, the percentage of dental erosion is increasing (13). The main dietary acids for erosion are citric, phosphoric, malic, and tartaric acids. Fruits such as orange and lemon and vegetables mainly contain citric acid, which is followed by malic acid. In addition, citric acid is being added to many of the commercially produced products. Among the many agricultural products grown in Turkey, the production of citrus species is also playing an important role, and when the provinces that export most of the citrus fruits are examined, the Mersin region is in the first place. Thus, the purpose of this study was to determine the status of dental erosion in adolescent and adult individuals in Mersin.

It is recognized that epidemiological prevalence studies did not use an ideal index for clinical staging and monitoring of dental erosion and that there is no simple assessment system meeting all the needs of both clinicians and investigators (6). There are different dental index systems that vary according to the evaluation type, scoring system, and tooth selection (14). This study was aimed to determine the severity of dental erosion and to identify whether the lesion involved enamel or enamel and dentine. We considered that having this information clinically could be critical for treatment decisions and important for prevalence studies. The modified criteria of the Lussi index, which evaluates the teeth separately in the anteroposterior areas according to the wear severity of the hard tooth tissue and has been used widely by European researchers (6) to score the facial, lingual, and occlusal surfaces of all teeth except those of the third molar, was preferred in this study.

According to the findings of this study, a significant difference was observed in total erosion scores with respect to the age of the participants. Therefore, the first hypothesis of this study, which suggested, "there is no difference among the total erosion scores of the participants according to the age groups," is rejected. Similar to this study, Vered et al. (15) reported a significant difference between the mean total erosion scores of five different age groups (15-18, 25-28, 35-38, 45-48, and 55-60 years). Regarding sex, there was no significant difference between male and female participants in this study (Table 3). This finding is in accordance with the previous studies conducted by Chu et al. (11) and Luciano et al. (16) who reported that no significant differences were observed between male and female individuals about the prevalence of dental erosion.

The prevalence of erosion has been reported to be 11%-100% in adolescents and 4%-82% in adults (1). In this study, the prevalence of erosive tooth wear was 33.3% (163 participants), and the total erosion scores of the participants aged >40 years were significantly higher than the scores of those aged 16-25 and 26-40 years (Table 3). Therefore, the second hypothesis of this study, which suggested, "There is no difference in the prevalence of dental erosion between adolescents and young adults in terms of the importance of the research area with high citrus production," is rejected. Similar to the findings of this study, Pineda et al. (12) reported that the prevalence of erosive wear was 31.7% in a sample of adolescents aged 14-19 years, and Mathew et al. (17) stated that the prevalence of erosive wear was 36.5% in a population of individuals aged 18-28 years. Kitasako et al. (18) evaluated the prevalence of erosion on all tooth surfaces of adults aged 15-89 years in Tokyo, Japan, and reported that the prevalence in the group who had erosion was 26.1%. In this study, the prevalence of erosive tooth wear limited to enamel was found to be 17.6% (804 teeth) overall in 4,564 teeth, and the prevalence of erosive wear with exposed dentin was found to be 3.5% (158 teeth). Our findings are in consonance with those of the previous study conducted by McGuire et al. (19) in the United States who reported that the prevalence of erosive wear with exposed dentin was 5.5%. With the progression of age, changes in saliva structure (decreased buffering capacity, hyposalivation, and pH) owing to factors such as systemic disease and eating or drinking habits may play a role in the exacerbation of erosive lesions. Nevertheless, it is thought that physiological or pathological gingival recessions that occur depending on age also increase the predisposition to erosion.

The presence of exogenous and endogenous acids in the diet has proven to play a role in the initiation and progression of dental erosion. Erosive tooth wear occurs more common in anorexia nervosa, bulimia, nervous vomiting, alcohol usage, and pregnancy cases (20). In addition, the passage of stomach contents into the esophagus without difficulty is defined as gastroesophageal reflux disease (GERD). The relationship between erosion and GERD has been shown in many studies, and erosive wear are frequently encountered on the palatinal and lingual surfaces of the teeth (21). According to the findings of this study, the scores of the patients with systemic diseases were significantly higher than the scores of the patients without, and there were significant differences in the total erosion scores with respect to the presence of systemic diseases and drug usage. A total of 27 of the participants (19%) had GERD in this study, and this was shown as the reason for the difference (Table 2). This is in agreement with the findings reported by Picos et al. (22).

The frequency distribution for risk factors of this study is summarized in Table 4. There was a significant association between the presence of erosive tooth wear and the frequency of consuming citruses such as orange, lemon, or other and fruit juice ($p<.05$). The excessive consumption of sour snacks due to the high production in the region of the study may be the reason for this difference. On the other hand, there was no significant difference between the other risk factors and participants' erosion tooth wear. As a reason for this difference, it is thought that the consumption of such products increases in the location of this study owing to the high production. It has been reported that excessive and frequent consumption of citrus fruits due to their bioactive components, such as citric acid, ascorbic acid, and polyphenol, damages the hard tissues of the teeth (23). Jarkander et al. (24)

investigated the prevalence and risk factors of dental erosion on adolescents in Stockholm and reported that soft drink consumption and the consumption of juice or sports drinks were significantly correlated with clinically diagnosed erosive wear. However, not in accordance with the results of this study, Luciano et al. (16)] reported that no significant difference was found between the citrus fruit and juice consumption and dental erosion risk in individuals aged between 12-30 years in the Brazilian city. On the other hand, in this study, it was determined that the total erosion scores of the participants who had periodontal problems were higher than those of patients who did not have periodontal problems (Table 4). It is known that the exposure of tooth crown and root surfaces due to the periodontal problems increases the frequency of dental erosion clinically (25).

Although dental erosion-related wear occurs on all surfaces of the tooth, it is reported that it often occurs on the palatal region of the maxillary anterior teeth and the occlusal surfaces of the lower first molar (26). Consistent with the literature, the second and fifth sextants had more erosive wear, whereas the mandibular posterior teeth were the least commonly affected (Table 5). The reason why more erosive wear on the anterior teeth was seen was that some participants expressed that they especially ate the lemon by biting it. However, in this study, in a large proportion of the participants, the erosion scores of the teeth in the first, third, fourth, and sixth sextants were zero. These results are not similar to those of the previous study conducted by Pineda et al. (12) and Bardolia et al. (27) who stated that the most affected regions were the occlusal surfaces of mandibular first molars. Most of the participants stated that they usually ate lemon by biting, which may be the reason for the excessive wear of the anterior teeth (caused by erosion) found in this study. In our study, it was observed that erosive tooth wear was more common in individuals aged >40 years, as stated before. Differences between anterior and posterior teeth depending on age may be explained by variations in dental restoration situations (crowns, onlays, inlays) or intraoral location because posterior teeth are more often missing or have full-coverage restorations than anterior teeth. The number of teeth remaining in the mouth could also be responsible for erosive tooth wear. In agreement with this result, Vargas-Ferreira et al. (28) and Gurgel et al. (29) reported the buccal surface of the maxillary central incisors as the most affected erosive wear site. On the other hand, Auad et al. (30) observed that erosive wear mostly occurs on the palatal surface of anterior teeth. The discrepancy between previous findings and these results may be explained by the evaluation type, specific population properties, different scoring systems, tooth selection, or diversity of the diagnostic criteria.

Cross-sectional studies provide limited data in a short period and at a one-time point. These studies are generally used to determine the prevalence of a disease in a population, but there is no recall and control over. The first limitation of this study is that the total erosion scores of the patients were compared according to the consumption frequency of carbonated drinks, sour snacks, or fruit juice. Therefore, further clinical studies should be designed to investigate the properties of saliva, such as flow and buffering capacities. The second limitation is the determination of total erosion tooth wear using one scoring system. Using different dental indices together will contribute to the sensitivity and specificity of the studies.

To manage dental erosion, it is important to diagnose the lesions at an early stage, identify possible etiology, and have knowledge regarding the protective and risk factors and their interactions. Clinicians should make recommendations to the patients considering the etiological factors for oral care and consider the individual needs and motivation of the patients to provide their oral health.

On the basis of the findings of this study and within the limitations, it seems appropriate to conclude that individuals aged >40 years have a higher risk in terms of the total erosion scores. The prevalence of erosive tooth wear may be associated with age, systemic disease, drug use, and consumption of sour snacks and fruit juice. Erosive tooth wear was observed on mostly maxillary and mandibular anterior teeth, whereas total erosion scores were lowest in the mandibular posterior teeth.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Mersin University (approval no: 2019/215-22.05.2019).

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

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Challenges Experienced of Nurses Caring for Syrian Refugee Children

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BACKGROUND/AIMS
This study was carried out to determine the challenges experienced by the nurses providing care to Syrian pediatric patients.

MATERIAL and METHODS
This study was conducted on 13 nurses working in newborn service, preschooler and school-age children service, pediatric service, and newborn intensive care service of a hospital that provides care for Syrian pediatric patients in a city on the Syrian border of Turkey. Data were collected using a semi structured interview form and a focus group method. Themes were determined by content analysis.

RESULTS
Themes that were determined in the study included the challenges arising from communication, life circumstances, cultural differences, and compassion fatigue, and recommendations for overcoming these challenges were made.

CONCLUSION
The results of this study can be a guide for making the necessary arrangements so that nurses can provide more effective care while working with patients who have similar characteristics, and these results can be a guide for similar problems that may be experienced in different countries.

Keywords: Child, nurses, refugees, focus groups, interview

INTRODUCTION

The internal conflict in the Syrian Arab Republic began in the early spring of 2011 and has forced millions of people to seek asylum in countries in the region. As of September 2018, over 5.6 million people have fled the country since the beginning of the internal conflict, seeking safety in Jordan, Lebanon, Turkey, and beyond (1). Turkey, the country that hosts more Syrians than any other country, shelters 3.5 million Syrian refugees, of whom, 1.5 million are children (2). The issue of meeting the healthcare needs of children and families is rapidly becoming more significant (3). The highest number of applications made for receiving healthcare services was for the children of Syrian refugees (4). Studies suggest that refugees experience mental problems along with physical ones resulting from their displacement (3, 5, 6). Therefore, it is necessary to provide comprehensive healthcare services to this group. There are studies conducted to determine the problems regarding Syrian patients' needs and difficulties, but the number of studies specifying the difficulties that nurses face while providing care to this group is still limited (7-10). Whereas Syrian patients experienced difficulties in communicating, in meeting their personal needs, and in correctly following treatment instructions, nurses experienced difficulty in communicating with Syrian refugees and their families in the clinic. The studies in this field suggest that describing the patients' opinions can act as a guide for planning nursing care; however, these studies also imply that description of nursing care should be considered for patients' medical results. This study aims to determine the challenges nurses face while providing care to Syrian pediatric patients and their families. The results of this study are thought to have positive effects on healthcare services provided for children who are refugees and their families.

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MATERIALS and METHODS

This study was conducted with 13 nurses working in a children's hospital that provides care for Syrian children and their parents in Şanlıurfa province, the province with the second largest population of Syrian refugees in Turkey (11). The inclusion criterion was working with Syrian pediatric patients for at least 6 months.

The data were collected using a semistructured interview form and a focus group method. Information about nurses' demographical characteristics was obtained through a sociodemographic form. There were a total of 6 open-ended questions focused on the challenges the nurses experienced when providing care to Syrian pediatric patients. Before initiating the study, a pilot study was conducted with 5 nurses to determine whether or not the questions were suitable. The interview was conducted 1 time by 2 researchers. One researcher conducted the interview, whereas the other observed. The interview was conducted in a hospital seminar room for 1 h, 18 min, and 33 s. The interview was conducted until thematic saturation was reached. The interview was recorded using an audio system.

The following questions were asked:

1. How did you feel when you first provided care to a Syrian pediatric patient? Can you share your feelings and experiences with us?
2. How was the experience of providing care service to pediatric patients and their parents who migrated from Syria? What are your personal feelings toward this experience?
3. What sort of challenges do the nurses experience when they provide care to pediatric patients who migrated from Syria?
4. In your opinion, how should nurses providing care to Syrian children be supported?
5. What should be done to improve the nursing care for Syrian children?
6. Is there anything you want to add?

Nurses' sociodemographic characteristics were analyzed using descriptive statistics. In this study, a total of 13 nurses were interviewed using the focus group method. A total of 13 pages of documentation were obtained after completing the interviews. The data were assessed using content analysis, and the main themes and subthemes were determined after the researchers independently compared the coding processes (12, 13).

Main Points:

- The experienced by nurses' difficulties were identified as communication, cultural difference, living conditions and compassion fatigue.
- Suggestions for reducing these challenges included improving the number and quality of interpreters; enhancing cultural competence through initiatives, such as planning trainings to cope with cultural differences; and providing support for dealing with compassion fatigue.
- This is the first study with nurses working with children, the group most affected by the war. The results of this study can be used as a guide for similar problems that may occur in different countries.

Written approval for the study was obtained from the institutions (14.01.2015). The participants signed an informed approval form.

RESULTS

Demographic characteristics and unit and duration of working with Syrian pediatric patients are presented in Table 1. The mean age of nurses was 31.4±6.80 (24–46) years; 92.3% of the nurses were female. Although the average work duration of the nurses was 8.30±5.31 (1–17) years, they have been working in the pediatric unit for an average of 3.69±2.05 (1–9) years. The main theme and subthemes were set in the study (Table 2). The five main themes and subthemes are described in the following sections:

Theme I: Challenges Related to Communication

The language barriers and interpreters' qualitative and quantitative insufficiencies are included in the subthemes of this theme.

Subtheme I: Language Barrier. A nurse aged 30 years who has 6 years of experience stated the challenges about language as follows: "We have problems in communicating with the children. We usually play games, talk and use words on their level to communicate so that we can prepare them for the process, but we cannot use these techniques with Syrian children so we cannot prepare them for the process."

Subtheme II: Interpreters' Qualitative Insufficiency. One of the subthemes of communication challenges is interpreters' qualitative insufficiency. Nurses stated that they were unsure whether the things they said were communicated correctly because the interpreters' qualitative skills were insufficient. A nurse aged 46 years stated the following:

We said something negative about a child's condition but mother's facial expression was happy. .... we asked the interpreter to tell the mother that the child's condition was serious and an operation was necessary, but the mother's facial expression did not indicate any concerns—so we understood that our statement was misinterpreted.

Subtheme III: Interpreters' Quantitative Insufficiency. In addition to qualitative insufficiencies in communication, the insufficient number of interpreters in the hospital was another subtheme. A nurse working with Syrian patients for 4 years stated as follows: "We cannot always find an interpreter: there is only one interpreter in the hospital who cannot keep up with the demands."

Theme II: Challenges Related to Living Conditions

Nurses stated the challenges arising from living conditions. Along with patients' financial problems, the bureaucratic process negatively affected the treatment and care.

Subtheme I: Financial. The nurse working in the intensive care unit described the effect of financial problems on treatment as follows: "You need diapers or creams for baby care which are something health care personnel occasionally buy with her/his own money. Although the government provides diapers and other needs, it is not enough. You tell the mother to buy these things but she cannot afford."

TABLE 1. Demographic characteristics of the nurses

Code	Age	Gender	Graduation	Work year	Clinic	Caregiving years
1	46	Female	Undergraduate	17	Newborn	4
2	30	Female	Undergraduate	6	5.breastfed	4
3	38	Female	Undergraduate	15.5	4.breastfed	4
4	25	Female	Undergraduate	3.5	Newborn	3.5
5	24	Female	Undergraduate	9	3.breastfed	9
6	32	Female	Undergraduate	8	NICU	1
7	25	Female	Undergraduate	1	1.breastfed	1
8	28	Male	Undergraduate	5	6.breastfed	1
9	28	Female	Undergraduate	5	5.breastfed	4
10	28	Female	Undergraduate	5	2.child	4
11	36	Female	Undergraduate	12	Newborn	4
12	41	Female	Undergraduate	17	Infection	4
13	28	Female	Undergraduate	4	3. child	4

TABLE 2. Themes for the nurse's challenges

Themes	
Theme I. Communication	Language Barrier
	Qualitative insufficiency of interpreter
	Quantitative insufficiency of interpreter
Theme II. Migrants' living conditions	Financial
	Bureaucratic
Theme III. Cultural differences	Nutrition
	Hygiene
Theme IV. Sense of providing effective care	Sadness
	Empathy
	Feeling of insufficient
Theme V. Recommendations	Communication
	Cultural differences
	Living conditions
	Workload

Subtheme II: Bureaucracy. Failure to reach the family because of bureaucratic procedures can delay the treatment. A nurse working for 3.5 years in a newborn clinic stated, "Arrival and departure times to camps are big problem. We cannot reach the family while the baby sleeps. They cannot get information about the baby because they cannot go back and forth."

Theme III: Challenges Related to Cultural Differences

The themes regarding the challenges due to cultural differences are related to nutrition and hygiene.

Subtheme I: Nutrition. Nurses stated that Syrian mothers especially have different nutrition habits and that their perceptions toward breastfeeding are dramatically different. Nurse 9 stated, ".....: Syrian mothers think that feeding babies with baby formula is a symbol of wealth. Therefore, they do not want to breastfeed their baby."

Subtheme II: Hygiene. Nurses stated that mothers' hygiene habits and conditions negatively affected the care services. The statement of nurse 11, who was aged 36 years and had worked in the newborn unit for 12 years, about cultural differences is, "Their cleaning habits are quite different. The mothers go to toilet on bare feet and try to breastfeed their babies when they return..." Nurse 13 states that "The mother sits down in a filthy environment, she puts her plate on the floor and eats from it. She says this is clean for her." Stating the effect of hygiene on care, nurse 12 stated, "They come here infested with lice. Nurses wash them with a special shampoo. Giving care to those people is a difficult process for them and for health care personnel."

Theme IV: Effects of Compassion Fatigue on Care

Subtheme I: Sadness. Nurses stated that their feelings reflect on their emotions when they provide care. Nurses stated that when providing care to the children, they know that these children do not deserve the situation in which they were, which makes them sad.

With a sad facial expression, nurse 12 working in the pediatric infection unit for 17 years made the following statement when she provided care to a Syrian pediatric patient:

The reasons for psychological problems of Syrian children are very different and sad. A mother said that a bomb was dropped on the house of my daughter's uncle when she was there. Since that incident, she has been crying all the time and she does not want doors to be closed. These are the children we care for.

Subtheme II: Empathy. On how they empathize with mothers, nurse 10 stated, "The people we provide care lost their country, do not have home or family, and they have no peaceful place to stay. There are mothers whose relatives were killed in front of their eyes and left them their children;" nurse 3 stated, "These families have changed countries and entrust their children to the person speaking in a different language. From this perspective, it is also a very difficult situation for families. I can understand them, but it hurts me sometimes I feel tired;" and nurse 1 stated, In my childhood, there was always gunfire. So I can understand

what they feel. I feel their fears, the happiness of survival. Even the words of love with Syrian mothers are different, when I love her child, firstly she tries to understand what I did and then she smiles. As her we are different in them."

Subtheme III: Feeling of Being Insufficient. The nurses also stated that an increase in the number of general patients and intensive care patients led to an increase in the workload, which in turn made them feel dissatisfied. They stated that infectious diseases negatively affected the maintenance process. A total of 6 nurses working in the newborn intensive care unit expressed their feelings: "...We focus on getting the job done when our workload is too much .... the number of patients we care for everyday is growing incredibly; it is getting harder to provide care; I feel like I cannot provide sufficient care."

Theme V: Recommendations for Decreasing the Challenges

Subtheme I: Communication. Several solutions could reduce the factors responsible for the difficulties nurses encounter while providing care. These solutions include increasing the number of qualified interpreters in health care, employing Syrian healthcare personnel in the hospital to salvage communication challenges, establishing counseling units, and planning training activities (about the common Arabic words and sentences) for nurses.

Comments from nurse 5 working in the pediatric unit are as follows:

The personnel in counselling unit should have a healthcare background: we are having difficulty in communicating because many interpreters do not have a healthcare background. When we tell the interpreters that the patient's condition is bad, interpreters cannot express the health condition correctly. A mother needed to have MRI scan, but she was told she had to have an operation, thus she started crying. We handled the situation, but what she experienced because of a misunderstanding was unpleasant. For that reason, I think communication should be prioritized.

Subtheme II: Cultural Differences. Nurse 3, who has been working in the pediatric unit for 16 years, expressed her suggestions to overcome the challenges caused by cultural differences:

Information could be provided about how we could approach them .... If we had knowledge of their cultural expectations, our treatment and care could be better. They were strangers to us as much as we were strangers to them. We live in the same way. Information on the characteristics of these patients could be provided within the scope of longer in-service trainings. Employment could be offered to those who could help us.

Subtheme III: Living Conditions. Nurses also made suggestions on how to improve living conditions, increase financial support, and support the use of primary healthcare services.

A nurse working in newborn intensive care unit for 8 years stated the following:

Even though we think that sufficient amount of support is provided, families still suffer. We had to use other families' diapers while waiting for other materials to arrive. The families should be supported financially. Infant diapers for all patients should be available at the hospital without a charge. If patients' problems are eliminated, we could feel comfortable.

Subtheme IV: Workload. Although the nurses stated that providing care to Syrian patients increased their workload in many dimensions, the expectation and recommendations for this problem were much more limited than the suggestions on how to improve patient conditions.

Nurse 4 stated in one sentence that the number of staff could be increased, whereas a pediatric unit nurse 7 made the following recommendation: "The healthcare personnel and the patients need to be systematically and psychologically supported."

DISCUSSION

This study examined the challenges experienced by the nurses providing care to Syrian pediatric patients and the nurses' recommendations on how to eliminate the challenges. The results of this study are similar to the literature on refugee patients (10-14), but these results are not comparable because our study was the first to be conducted with nurses working with children who are affected the most by war. The challenges specified by Glenn's study (14) were related to cultural, professional, and individual differences, whereas the subthemes of communication, hygiene, and empathy in the study by Sevinç (10) showed similarity to the subthemes of this study.

Language barrier was one of the factors causing communication challenges. Interpreting assistance to remove this language barrier was not a solution. The use of a common language is the main facilitator of effective communication for the nurses who provide care to traumatic children and parents to learn the patients' history, plan and implement care, and monitor and obtain results. Although the results suggest that the communication challenges can still emerge despite the use of a common language, this study identified the use of different languages along with the fact that the patients were pediatric patients as the major factors causing the difficulty in care. The studies examining the challenges experienced by the patients defined the failure to use a common language as a communication barrier (15-18). This language barrier in effective care can be overcome by employing bilingual health professionals (19). Therefore, this study highlights interpreters' qualitative insufficiencies in healthcare service as well as quantitative insufficiencies reflecting the limited number of interpreters, and it suggests that a sufficient number of interpreters who are experienced in health care should be employed.

Although Syrians' needs for food, shelter, and health care are provided free of charge by the Disaster and Emergency Management Presidency with the cooperation of the Ministry of Health (20, 21), nurses stated that poor living conditions due to economic insufficiency affected the care for the patients. The Syrians living outside the sheltering centers meet their needs in accordance with their economic statutes because the aids for them are more limited than the aids for those living in the centers, which negatively affects the care. Our results are in line with the literature emphasizing that healthcare providers' awareness of the patient's living conditions and requirements in

this field is significant for the optimization of patient outcomes (22, 23).

Cultural diversity is one of the factors that cause difficulty in the implementation of health care. Unlike the literature on nutrition, the biggest difference between Syrian patients and nurses was related to breastfeeding (24, 25). Breastfeeding is largely supported in Turkey, whereas Syrian mothers do not like breastfeeding their babies, which causes difficulty for the nurses. Nurses need to be aware of cultural, social, economic, and lifestyle differences that directly affect the health of refugees.

One of the cultural differences is hygiene. Nurses have mentioned the cultural differences in the hygiene practices of Syrian mothers. Nurses said that if the hospital management provided nurses with information about the cultures of Syrian patients, care would be better. They also stated if their living conditions are improved and training in hygiene is planned, their hygiene may be more positively affected. In this way, cultural harmony can be achieved. Thus, the hygiene of Syrian patients is supported. Nurses are waiting for initiatives from the authorities to help them understand Syrian patients' cultural characteristics to overcome these challenges. A study by Almontaser and Bauman (25), who made recommendations for nurses working with Syrian refugees, suggests that hospital management should support nurses in developing cultural sensitiveness and competencies. Although the studies conducted with refugee patients suggested the necessity for nurses' cultural competency, for respect for Syrian patients, and for adopting a nonaccusative attitude toward them, the study by Sagar (15) and Sevinç et al. (10) stated that nurses empathized with mothers and patients despite all challenges (a large number of patients, the increase in the number of patients who need care, and the language barrier and the insufficient number of interpreters).

The empathy and sadness nurses experienced while providing care to the patients were stated. In addition, one of the difficulties experienced by nurses is increased workload because both the burden of care and the number of Syrian patients are very high. The increased workload arising from Syrian patients' practices made nurses feel work centered and dissatisfied. As a result, nurses stated that they felt insufficient. In their study conducted on nurses in the pediatric clinic, Meyer and his colleagues (26) found that compassion fatigue affected job satisfaction. Working with a work-centered mentality and the feeling of insufficiency, sadness, and empathy are among the determinants of compassion fatigue. Although nurses continue to work with empathy and compassion today, empathy and devotion increase the risk of compassion fatigue. It is known that nurses who provide nursing care, constantly observe patients' experience of suffering and fear, and try to understand those experiences are at a greater risk of compassion fatigue. The sample in this study consisted of intensive care nurses and nurses working in pediatric patient care with patients who are exposed to very severe trauma, such as war, which increased the likelihood for those nurses to experience compassion fatigue. Although individual efforts are significant for coping with compassion fatigue, the power of corporate support is indisputable. Nurses in this study stated that they need support. Such managerial initiatives can support nurses working with Syrian patients in dealing with compassion fatigue.

The generalizability of the results is limited because this study was carried out with nurses working in the same institution and with limited numbers. The research results can be generalized to nurses included in the sampling.

Nurses providing care to the children of Syrian refugees suffer from challenges owing to living conditions, cultural differences, compassion fatigue, and particularly, communication-based language barriers. Suggestions for reducing these challenges included improving the number and quality of interpreters; enhancing cultural competence through initiatives, such as planning trainings to cope with cultural differences; and providing support for dealing with compassion fatigue.

Qualitative and quantitative studies with larger sampling to identify the challenges experienced by nurses working with Syrian patients with traumatic patient profiles will increase the comparability of our results. This study is a guide because it is one of the first studies to determine the challenges experienced by nurses providing care to children who constitute the group that is most affected by war. The results of this study can be a guide for making the necessary arrangements such that nurses can provide more effective care while working with patients who have similar characteristics, and these results can aid similar problems that may be experienced in different countries.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Harran University Hospital (Approval date: 14.01.2015, No: 2015/4-24).

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

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Perception of Aging Among Nursing Students

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BACKGROUND/AIMS
The perception of aging by health professionals who serve the older people affects the quality of care; hence, this study aimed to identify nursing students' perception of aging.

MATERIAL and METHODS
This descriptive study by the nursing faculty of two different state universities included 543 nursing students who showed willingness to participate. For data acquisition, a questionnaire was provided to the study participants; the questionnaire included the students' socio-demographic features and their perception of aging. The data were assessed using numbers, percentages, mean±standard deviation values, and the chi-square statistical test.

RESULTS
The mean age of the students was 22.00±1.20 years, and 88.8% were female. Most of the students agreed with the concept that in older individuals, "cognitive skills take a turn for the worse and learning ability is lost" (79.4%). Assessments of the students showing care for older individuals indicated that the students tended to be more patient with older individuals (94.5%). Gender and the students' academic level affected their perception of aging.

CONCLUSION
The study results found that nursing students' perceptions of older individuals were positive; however, certain perspectives and behaviors toward provision of care to older people were negative.

Keywords: Aging, nursing, students, perception

INTRODUCTION

The aging of the world population is one of the most important challenges of the 21st century. In several countries, the number of older individuals and the rate of increase in the aging proportion have reportedly surged (1). Turkey is one of the countries experiencing this demographic transformation, with a rapidly aging population. The older individual population presently constitutes 8.5% of the total population in Turkey. The life expectancy is 75.3 years for men and 80.7 years for women (2). A striking phenomenon related to the increasing older population in Turkey is that the specific population of people aged 75-80 years continues to increase. The increase in the aging population impacts all aspects of the society, ranging from social safety, education, and job opportunities to family life, along with the burden placed on the health system. Aging is an area of special importance, and it is necessary for health professionals to provide solutions to the specific health care needs of the older population. Nursing is a crucial profession in which health care is provided to the aging population. Geriatric nursing is rapidly developing as an area of expertise; however, special knowledge, ability, and talent are prerequisites for nurses to provide efficient geriatric nursing services (3, 4). The current demographic changes, together with the increased need for high-quality health care services, pose challenges for nurses in the provision of care to aging individuals (5).

Attitudes about old age and older individuals, prejudices, and beliefs impact decision-making and behaviors toward older individuals. Attitudes toward the older individual shape and influence the behavior of health professionals and the quality of the care provided to the older individual (6, 7). Studies have shown that the nursing students identified as members of the young group act in a prejudiced manner toward older individuals because of a lack of general in-

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formation, negative myths, and stereotyped attitudes (8-10). Negative myths and attitudes may negatively affect the care provided to older individuals (10). Certain studies have shown that nursing students believe that health professionals demonstrate negative attitudes toward aging individuals (11, 12). These attitudes affect the quality of nursing care provided to the older individual and may ultimately dissuade caregivers from obtaining sufficient information concerning older individuals, thus neglecting their autonomy or integrity, and jeopardizing their dignity (13-15). Eltantawy (16) has reported that nursing students harbor prejudice regarding the care of older individuals for the past 30 years. Nurses have demonstrated less desire to work in geriatric clinics and nursing homes, and show inclination to work with pediatric or adult patients (16). The quality of nursing care provided to older individuals depends on how education is imparted to nursing students and how nursing students are prepared for providing nursing service. Adebusoye et al. (12), Eltantawy (16), and Oyetunde et al. (17) have reported that nurses' attitudes and behaviors toward the aging population affect their expectations regarding working life and their approach toward their patients (12, 16, 17). The increase in the proportion of the older population and the concomitant chronic illnesses associated with aging cause decreased physical functionality and increased dependency; hence, correct attitudes of nurses, sufficient working knowledge, and skills for providing geriatric care should be emphasized. Owing to the above-mentioned issues, the perceptions of nurses (who provide care to older individuals) on aging and older individuals must be identified.

MATERIALS and METHODS

Study Sample

This study comprised 570 students who were second-, third-, and fourth-year students tutored by the nursing faculty of two state universities in Ankara, Turkey. As first-year students possess less knowledge and expertise, they were not included. In this study, sample selection was not conducted, and the study was targeted to reach all students who received instructions during April-May 2017. The final sample comprised 543 students who agreed to participate (95.0%).

Data Collection Tools

Information on the sociodemographic status of the students and their views and perceptions on aging was assessed using a questionnaire (8, 10, 13, 15, 18). The questionnaire was also used to gather information regarding the students' behaviors while providing nursing care services to older individuals. The questions were developed by researchers after conducting a literature review aimed at determining the perception of nursing students on aging. These questions were not an inventory; hence, total score was not calculated.

Main Points:

- Negative myths and attitudes may negatively impact the care provided to older individuals.
- The manner in which education is imparted to nursing students to prepare them for providing nursing services may influence their perceptions of aging and the aging population.
- Educational activities must be planned to change the negative perceptions and attitudes and to create awareness among nursing students about the aging process.

Ethical Considerations

Ethics committee approval was obtained from Ankara Yıldırım Beyazıt University Ethics Committee (31.03.2017/06). Participants were provided with verbal and written information about the purpose of the study and were provided with the opportunity to raise queries.

Data Collection

After obtaining ethical approval and official permission for the conduction of the study, the investigators informed the students about the study aspects in a classroom and invited interested students for participation. Questionnaires were provided to the students 15 minutes before the commencement of lectures and were collected after complete responses were received.

Statistical Analysis

Data were assessed using the Statistical Package for the Social Sciences 16 program (IBM SPSS Corp.; Armonk, NY, USA) using numbers, percentages, mean±standard deviation values, and the chi-square statistical test. For the present study, $p<0.05$ was considered statistically significant.

RESULTS

The mean age of the students was 22.00±1.20 years, and 88.8% students were female. Among the study participants, 23.9% were second-year students, 33% were third-year students, and 42% were fourth-year students. Regarding questions on living conditions, 51% of all the participants indicated that they were living with their grandmother or grandfather. Responses indicated that the majority of the students (83.1%) gained experience in providing care to older individuals during their clinical practices (Table 1).

TABLE 1. Students' demographic features

Demographics	Number (n)	Percentage (%)
Nursing school level		
Second year	130	23.9
Third year	179	33.0
Fourth year	228	42.0
Sex		
Female	482	88.8
Male	61	11.2
Age (mean: 22.00±1.20 years)		
20-25 years	538	98.4
>25 years	3	0.6
Living with people aged ≥65 years		
Yes	277	51.1
No	265	48.9
Provision of care to older individuals in clinical settings		
Yes	451	83.1
No	91	16.8

The study results showed that the students associated the word aging with terms like illness (59.5%), compassion (56.7%), and weakness (47.5%) (Table 2) upon hearing the word aging. Among the participants, 35.4% declared that they preferred to spend time with young patients rather than with older patients; additionally, 21.2% of the participants declared that they preferred to explore solutions for issues in young patients rather than for those in older patients. Regarding responses for communication with older patients, 35.4% of the students expressed that they provided simplified information and mimicked baby talk when providing information to older patients; furthermore, 88.8% of the students were more respectful to the older patients, 88.4% of students were more respectful because of older patients' cultural characteristics, 17.5% of the students were wary of older patients, 54.7% of the students preferred to share information about the older patient's relatives, and almost all students were more patient (tolerant) with older patients (Table 3).

TABLE 2. Concepts/terms associated with aging based on the students' responses*

Concepts/terms	Number (n)	Percentage(%)**
Illness	323	59.5
Compassion	305	56.7
Weakness	258	47.5
Dependence	189	34.8
Wisdom	175	32.2
Loneliness	174	32.0
Dependency	162	29.8
Mental decline	62	11.4
Happiness	31	5.7
Depression	21	3.9
Poverty	19	3.5
Sloppiness	19	3.5
İsolation	15	2.8
Independence	13	2.4
Ugliness	11	2.0
Political power	9	1.7
Abundance	7	1.3

*There may be more than one answer. **Percentages were calculated from answers.

Regarding the nurses' perceptions of older persons, we observed that 63.2% agreed with the statement "60-65 years of age means senility," 54.5% agreed with the statement "the aging period refers to inability and a period of illness," and 79.4% agreed with the idea that "cognitive skills take a turn for the worse and learning ability is lost." As shown in Table 4, most of the students did not agree with certain ideas, such as, "Old people demonstrate self-pity, and are unfeeling, bad-tempered, grumpy, and constantly complaining" (86.7%), "All old people are alike" (84.0%), "The memory of older people is weak, and almost all of them are dotards" (79.7%), "Older individuals are less active" (79.2%), and "Old people are abandoned and alone, and they cannot pursue activities" (70.9%). Other statements that most of the students did not agree with included "Older people are not interested in sexuality, and interest in sexuality is inconvenient" (82.5%), "Most older people are unhappy and do not get pleasure from life" (75.7%), "Sexuality is not important during the senility period" (74.4%), and "As the individuals are approaching the end of life, provision of special health care is not necessary; moreover, these services are not helpful" (91.0%).

The students' sex and graduation year ($p<0.05$) affected their perception of old age. Female students' perception was more favorable (positive) than that of male students. The higher the curriculum level, the more positive the perception of old age; for

TABLE 3. Students' perspectives on the provision of care to older individuals

Perspectives	Yes		No	
	Number (n)	Percentage (%)	Number (n)	Percentage (%)
I like to spend time with young patients more than with older patients	192	35.4	350	64.6
I tend to give more attention to young patients' problems than older patients' problems	115	21.2	427	78.8
I mimic baby talk while explaining information to older individuals	192	35.4	350	64.5
I pay more respect to older individuals because of their age	482	88.8	57	10.6
I maintain distance from older individuals	95	17.5	444	81.8
I prefer to spend less time with older patients	43	7.9	496	91.3
I prefer to explain information about older patients to their relatives	297	54.7	240	44.2
I tend to have more patience with older patients	513	94.5	26	4.8
I am more respectful of older patients' social characteristics	480	88.4	61	11.2
I tend to prioritize to older patients for routine procedures	360	66.3	181	33.3
I give more respect to older patients' choices and decisions	375	69.1	163	30.0
I prefer to meet the informational demands of young patients rather than older patients	82	15.1	459	84.8
I feel more comfortable with myself with older patients	304	56.0	233	42.9
I prefer to take responsibility for older patients' total care and treatment because of their age	248	45.7	295	54.3
I prefer to obtain information on older patients from their relatives	263	48.4	280	51.6

TABLE 4. Students' perspectives about aging and older individuals

Perspectives (opinion)	Yes		No	
	Number (n)	Percentage (%)	Number (n)	Percentage (%)
60-65 years of age defines the aging period	343	63.2	199	36.6
Aging is a period of disability and illness	296	54.5	244	44.9
Old people are abandoned and alone; they cannot pursue in activities	157	28.9	385	70.9
All old people are alike	85	15.7	456	84.0
Old people engage in self-pity, and are unfeeling, bad-tempered, grumpy, and always complaining	70	12.9	471	86.7
Old people are difficult to live with	222	40.9	318	58.6
Old people are always in the dark; they cannot accommodate to new ideas	203	37.4	337	62.1
Old people in the future will exhibit similar features as the current group of old individuals.	62	11.4	480	88.4
Cognitive skills undergo impairment. with aging, and older people have loss of learning ability	431	79.4	109	20.1
Old people are less active	107	19.7	430	79.2
The memory of old people is weak, and almost all old people are dotards	109	20.1	433	79.7
Most old people function inadequately in the work environment	329	60.6	212	39.0
Most old people are unhappy; they don't derive pleasure from life	128	23.6	411	75.7
Depression is normal for old patients because there are many losses during the aging period	415	76.4	125	23.0
Urination/defecation control is lost during aging	207	38.1	335	61.7
Sexuality is not important during aging	132	24.3	404	74.4
Old people do not desire sex and do not have sexuality	105	19.3	432	79.6
Old people are not interested in sexuality; interest in sexuality is inconvenient	92	16.9	448	82.5
Interest in the sexuality of old people is inconvenient	83	15.3	456	84.0
As the individuals are approaching the end of life, provision of special health care is not necessary; moreover, this care is not helpful	44	8.1	496	91

example, fourth-year students' perception was more positive (favorable) than that of second-year students.

DISCUSSION

As the population of older people continues to increase, nurses play an important role in the health care system and are expected to play a more vital role in providing health care for older people. Therefore, the assessment of nurses' perceptions and perspectives on aging and on the provision of care to older individuals is important for the expanding geriatric population in terms of healthy aging.

Based on the recent advancements in the knowledge of the aging process with respect to physical and social changes, old age has been evaluated in two ways, namely positive and negative. An example of the positive evaluation is that older people are wise, are experienced, have high social status, are worthy of utmost respect, and exert an influence on others. An example of the negative evaluation is that aging is a weakness (deficiency) and that it results in irreversible losses (19). Certain myths or stereotyped phrases are described as features shared by the members of certain social groups, and the myths or stereotypes have shaped beliefs about typical behaviors or attitudes (19). When associated with positive or negative connotations and thoughts or beliefs about aging and old age, attitudes that lead to discriminatory behavior or prejudice toward members of a particular group can potentially emerge. The negative myths surrounding the stereotypes of old age-myths of physical and mental disability-are based on the belief that old age is synonymous with disease. This belief and the resulting myths are maintained by negative stereotypes in society at large and in various age groups (20).

In this study, the assessment of students' views on older people mostly focused on the physiologic and cognitive changes associated with aging. The most common perceptions include the following: aging is synonymous with illness, older people are weak, mental abilities decline with aging and learning ability is lost, depression is normal in older people because there are losses in the aging period, older individuals are alone and it is impossible for them to pursue activities, and most older people function inadequately in the working environment. These results showed that the study participants had certain stereotypical thoughts and myths and that there are a few topics about the aging process on which awareness should be generated among nursing students. The students' perceptions and perspectives may have been influenced by general misinformation in the society, and this misinformation can pose risks for older people.

Studies have shown that the provision of health care to older people is not a common practice among nursing students (21, 22). This practice is associated with factors of the perception of old age, attitudes, work experience, and trouble in the work environment (23, 24). Attitudes toward older individuals shape the healthcare delivery behavior of healthcare professionals and exert a direct impact on the quality of care provided to older

people (6, 7). In studies that involved nursing students, two types of attitudes-appreciation of older people and prejudice against them-have been reported (8, 24, 25). An appreciative attitude is related to the understanding of older individuals, and prejudice is associated with discriminatory thoughts on the rights of the aging individuals or an inability to realize the needs of the aging individuals (8, 24).

This study found that the majority of participants believed that older people are sensitive and require special attention and that older people deserve respect and appreciation. The students did not support prejudice toward the older people.

Ünsar et al. (26) have reported that students have positive faith and perception. Özdemir and Bilgili (18) have declared that nursing students have a positive attitude toward the older individuals (18). However, Frost et al. (27) and Van Leeuwen et al. (28) have claimed that students have a negative attitude to the aging population.

Studies that have evaluated nursing students' attitudes, perspectives, and perceptions of the older individuals have indicated that gender is an important factor; female students have a more positive attitude toward the older individuals than male students (25, 29, 30). The probable reason is that women consider their cultural care role seriously. Our study results are similar to those reported in literature and show that male students are more unfriendly toward older patients than female students and that they do not develop a close relationship with older patients. Male students tend to believe that older people are less active and that special health services are not necessary for them.

Education is the most important factor in changing the professional attitude of nursing students toward the aging individuals (24). Upper-class level (third-year or fourth-year) nursing students are expected to exhibit a more positive attitude for gaining understanding and knowledge of the needs of the aging population because these students have received more information about geriatrics and gerontology (31). Strugala et al. (31) have suggested that there exists a relationship between the educational level and the attitudes of nursing students. Additional factors that may negatively influence a nurse's behavior toward older patients are those not directly related to old age, for example, attending evening school while working to obtain additional education; difficult working conditions of nurses in some countries, such as those in Poland; heavy workloads; or experiencing burnout. Hanson (32) has reported that both nursing students and professional nurses exhibit negative attitudes toward the aging individuals at certain instances, the most important cause being the lack of information about the aging process. Studies by Hweidi and Al-Obeisat (9) also support a relationship between education and attitudes. Ünsar et al. (18) and Özdemir and Bilgili (26) found that fourth-year students' behavior toward old people was more positive. Similar studies produced similar results and showed that upper-class students' attitudes toward the aging population were more positive (21, 33). Our study results supported similar results because the students of the highest level of medical school curriculum (fourth-year students) were observed to exhibit negative attitudes toward aging and the aging process in some cases; however, they generally exhibited a positive attitude.

If students live with an older individual at home, the students may establish a good emotional connection with the older individuals and may prefer to spend more time with them. It is thought that through this daily interaction, these students begin to holistically understand the aging process and develop positive perspectives toward aging and the aging process. Several authors have stated that living with older people in the same home and establishing a close emotional connection at home affects attitudes and feelings toward the aging population (34, 35). Bulut et al. (18) and Özdemir and Bilgili (36) showed that students who share good relationships with their grandmother and grandfather have a more positive attitude toward the aging population.

In clinical settings, students who provide health care to older individuals share increased emotional connections with the older individuals and gain positive perceptions of aging. Studies similar to ours have reported that students who have gained clinical experience with older individuals harbor more positive thoughts toward them (9, 37).

The increasing population of older individuals poses challenges for the healthcare system and for the nurses who have been entrusted with duties of providing first-line care for the aging population. Nurses' attitudes and perceptions on aging affect the quality of care. Therefore, awareness of nurses' and nursing students' attitudes and perceptions of older people and of the aging process is important. An investigation into the myths and stereotypes that influence these attitudes is also crucial. Avoidance of prejudice and stereotypes and the development of positive perceptions by nurses and nursing students are important for increasing the quality of care and increasing older individuals' satisfaction with the care provided. Our study results show that nursing students generally have a positive perception of the aging population; however, certain opinions and behaviors toward service delivery are negative. For this reason, activities must be planned to impart education on the aging process, to change the negative perceptions and attitudes toward aging and aged individuals, and to create awareness among health professionals (nurses) and in the society.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara Yıldırım Beyazıt University (31.03.2017/06).

Informed Consent: All participants received oral information on all aspects of the study and verbal informed consent was obtained from students who participated in this study.

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Determining the Level of Nurses' Compliance with the Isolation Precautions Taken for Preventing Healthcare Associated Infections

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BACKGROUND/AIMS
Healthcare-associated infections (HAIs) are a major issue in hospitals worldwide. Isolation precautions are considered necessary to reduce the spread of HAIs. The failure of nurses to comply with isolation precautions may have a negative impact on both nursing care and the psychological and social lives of patients and their families. Therefore, this study aims to identify the level of nurse compliance with isolation precautions taken to prevent HAIs and to develop suggestions in line with the results obtained.

MATERIAL and METHODS
This work consisted of a cross-sectional descriptive study. The study population was 180 nurses working in a private hospital in Nicosia, the Turkish Republic of Northern Cyprus. Although it aimed to reach the entire population, the study sample consisted of 110 nurses. Data were collected between May and June 2017, using an Information Form and the Compliance with Isolation Precautions Scale.

RESULTS
Nearly all the nurses had adequate knowledge about HAIs and isolation precautions. The study results showed that nurses had a high level of compliance with isolation precautions for preventing hospital infections.

CONCLUSION
These results suggest that it may be advisable to increase the number of continuous education programs that encourage nurses and healthcare professionals to comply with infection control measures and isolation precautions at the highest level and to raise their awareness about the importance of hand hygiene habits and immunization against HAIs.

Keywords: Nurse, infection, healthcare, prevention, isolation, compliance

INTRODUCTION

The Centers for Disease Control and Prevention (CDC) and the World Health Organization define healthcare-associated infections (HAIs) as the most important source of mortality and morbidity worldwide (1, 2). The term HAIs is often used to define hospital or healthcare-related infections and is described through phrases, such as hospital-acquired infection or hospital infection (3). HAIs negatively affect the recovery of patients who are hospitalized or have received treatment in a hospital, and may lead to an increase in morbidity and mortality rates, cause epidemics, and place additional financial burden on both patients and governments (4-8). These infections pose an serious problem for the effective provision of modern hospital services. The rate of hospital infections is considered one of the most important indicators of hospital quality. Furthermore, the prevention and control of the development of infection are among the issues that are increasingly important within the framework of patient safety (9).

HAIs are defined as infections that develop after admission to a hospital, were not in an incubation period at the time of admission, or that sometimes occur after discharge despite having developed in a hospital. They usually occur 48-72 hours after hospitalization and within 10 days of discharge (6, 10). HAIs–of which there is a greater than 10% incidence, particularly in multi-bed large hospitals–prolong hospital stay; increase medical costs by requiring additional treatment interventions; cause loss of labor and productivity; decrease quality of life; and increase disease types, emotional stress, drug use, functional disorders, and mortality rates (11, 12).

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One of the main strategies to control HAIs is to take isolation precautions. Isolation precautions are preventive methods defined as "the prevention of transmission of microorganisms from infected patients to other patients, visitors and healthcare personnel, the separation of individuals with infectious diseases for protective purposes and the restriction on their movements" (13-15). The isolation precautions taken for preventing HAIs are applied as standard measures (handwashing; use of gloves, hand antiseptics, aprons, and face protectors; sterilization and disinfection, medical waste management, and environmental control) and measures against modes of transmission (tight contact isolation; droplet isolation measures; and the use of face protectors, aprons, gloves, and hand sanitizer) (5, 6, 8, 16). Isolation precautions are widely applied in many health institutions and considered necessary to reduce the spread of HAIs (17). Compliance with the infection control measures set by the CDC has a significant effect on the prevention of HAIs, and healthcare professionals implementing these measures reduce the incidence of these infections by 30% (1). Rosenthal et al. (8) reported that the rate of HAIs significantly decreased only by adapting to hand hygiene practices. Contrary to this, the failure of healthcare professionals to comply with all infection control measures has also been found to negatively affect the quality of patient care and safety, increasing the risk of morbidity and mortality (6). Studies conducted in Turkey report that HAIs cause a significant additional budget cost, prolonging the length of hospital stay by 4.3–33.5 days, and nurses allocate an additional 28.73 minutes to patients who develop HAIs (12, 18).

The failure of nurse to comply with isolation precautions may have a negative impact on both nursing care and psychological and social lives of patients and their families (17). In previous studies, the factors that prevent nurses' compliance with standard isolation measures are defined as follows: emergencies, lack of equipment, negative effects of protective materials, patients' discomfort with healthcare professionals wearing masks and aprons, lack of commitment from institutional management, heavy workloads, low number of nurses, the time needed to fully comply with guidelines, effects of protective equipment on physical appearance, professional knowledge and experience, nurses thinking that nothing would happen to them, negative role modeling from head nurses at clinics, and being influenced by the working style of physicians who do not obey the rules (14, 16, 19). It is extremely important, in terms of providing safe and qualified healthcare, that nurses–who spend a lot of time with patients, establish close relationships during the care process, and are responsible for patient care processes–comply with infection control measures (20). Therefore, this study determined the importance of the level of nurse compliance with isolation precautions taken to prevent HAIs, developed suggestions by determining the factors affecting nurse compliance, and created resources meant particularly for health institutions and organizations.

Main Points:

- With regard to patient safety, healthcare-associated infections (HAIs) are the most common global health problem, and their consequences may be related to morbidity, mortality, prolonged hospitalization, and negative effects on the economic welfare of patients and nations. Therefore, health managers and government policies and interventions should pay greater attention to this subject. This study provides valuable data about nurses' knowledge, skills, and attitude regarding the isolation precautions taken to prevent HAIs.
- Our findings highlight the importance of isolation precautions taken to prevent HAIs. They have implications for nurses worldwide who are responsible for taking care of patients while using infection prevention practices.
- Management departments of hospitals should strive to create an organizational atmosphere in which adherence to the recommended isolation precautions taken to prevent HAIs is considered an integral part of providing high-quality care.
- Modern-day understanding treats hospital infections as a patient safety and public health problem. If hospitals seek to reduce infection rates, they must create awareness about the importance of isolation precautions and develop/implement innovative continuous and motivational programs according to the needs of all healthcare professionals.

MATERIALS and METHODS

Design and Sampling

This work was planned as a cross-sectional descriptive study. The study population consisted of 180 nurses working in a private hospital in Nicosia, the Turkish Republic of Northern Cyprus. Although it aimed to reach the whole population, the final study sample consisted of 110 nurses because 25 nurses were on leave and 45 nurses did not volunteer to participate in the research. In the study, 61.1% of the targeted population was reached.

Data Procedure and Instruments

Data were collected between May and June 2017 using an Information Form and the Compliance with Isolation Precautions Scale (CIPS). The Information Form, prepared by the researchers considering related literature, consisted of questions about the sociodemographic characteristics of the nurses and questions on whether they received any training on the isolation precautions taken to prevent HAIs, had adequate knowledge about HAIs, had been immunized against HAIs, and whether they and other hospital personnel complied with the isolation precautions taken to prevent HAIs (5, 10, 13, 15, 20, 22, 26, 28). The CIPS was developed by Tayran and Ulupınar (13) to determine the level of nurse compliance with the isolation precautions; validity and reliability studies were conducted on it, and the Cronbach's alpha reliability coefficient was found to be 0.85. In this study, the Cronbach's alpha reliability coefficient of the scale was found to be 0.91. The scale is a five-point Likert-type scale consisting of 18 items and the following 4 factors: route of infection (items 3, 8, 9, 10, and 11), practitioner-patient safety (items 2, 5, 12, 14, 16, and 17), environmental safety (items 1, 13, 15, and 18), and hand hygiene/glove use (items 4, 6, and 7). Items 5, 7, 12, and 17 were scored in reverse. The lowest and highest scores on the scale are 18 and 90, respectively. Higher scores indicate better the compliance with isolation precautions (13).

Ethical Considerations

The approval and permission necessary to conduct the study were obtained from the hospital and ethics committee (YDU/2017/47-411). The nurses who voluntarily accepted to par-

ticipate in the study signed a consent form after they were informed about the purpose of the study and the confidentiality of the records.

Statistical Analysis

The data were evaluated using the Statistical Package for the Social Sciences 24.0 statistical analysis program (IBM SPSS Corp.; Armonk, NY, USA) and descriptive statistics (arithmetic mean, standard deviation, frequency, and percentage). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine whether the data were normally distributed. The independent sample *t*-, Mann-Whitney U, and Kruskal-Wallis tests were used to determine the significance of the differences between the groups (2I).

RESULTS

The mean age of the nurses who participated in the study was 30.54±9.87, and 40.91% (n=45) were≤25 years of age. A total of 82.73% of the nurses (n=91) were female, 59.09% (n=65) were single, 66.37% (n=73) had no children, 79.09% (n=87) had a Bachelor's or Master's degree, 85.45% (n=94) worked as a nurse, and 41.82% (n=46) had professional experience of ≥ 6 years. The mean working experience was 7.59±8.94 years. In addition, 94.55% of the nurses (n=104) received training on isolation precautions and 53.85% (n=56) received this training from an infection control nurse. A total of 91.82% of the nurses (n=101) had adequate knowledge about HAIs and isolation precautions, 68.18% (n=75) thought HAIs could be controlled through training, and 93.64% (n=103) emphasized that hand hygiene was important in preventing infections. Furthermore, 66.36% of the nurses (n=73) were not immunized against HAIs; only 33.64% (n=37) were. A total of 54.06% (n=20) and 2.70% (n=1) of the nurses who were immunized against HAIs had anti-hepatitis B virus (HBV) and anti-human immunodeficiency virus vaccines, respectively; however, 43.24% of the nurses (n=16) who were immunized against HAIs did not respond to the question on immunization. Finally, 79.09% of the nurses (n=87) stated that healthcare personnel influenced the development and spread of HAIs and 50.91% (n=56) reported that hospital employees did not adequately comply with isolation precautions (Table 1).

The nurses' total mean score on the CIPS was 3.75±1.01. The nurses definitely agreed with 14 items but definitely disagreed with four items. The nurses received the highest scores on the items "If the patient undergoing isolation is examined in another unit, I would warn the relevant unit supervisor to continue to apply the isolation precautions." (4.45±1.02) and "I wash my hands before contact with the patient." (4.42±1.17). The nurses received the lowest scores on the items of "I do not need to wash or scrub my hands when I remove gloves." (1.84±1.19) and "I do not mind touching a wound of the patient with naked hands." (1.58±1.24). The nurses' total mean score indicates that they have a high level of compliance with isolation precautions (Table 2).

The mean CIPS score of nurses who received training on the isolation precautions taken to prevent HAIs was 76.81±14.99, whereas those without such training had a mean score of 62.50±15.64, which was a statistically significant difference (p≤.05) in favor of those with the training (Table 3).

The mean CIPS score of the nurses who having adequate knowledge about isolation precautions taken to prevent HAIs was 77.35±14.42, whereas those without such knowledge had a mean score of 61.22±17.98; this is a statistically significant difference (p≤.01) in favor of those with adequate knowledge (Table 3).

The mean CIPS score of the nurses who believed that HAIs could be controlled by giving relevant training was 78.71±13.64, whereas the mean score of those who did not believe that HAIs can be controlled in this manner was 51.88±17.63, indicating a statistically significant difference between the mean scores (p≤.01) in favor of the former (Table 3).

The mean CIPS score of the nurses who were immunized against HAIs was 70.78±18.14, whereas the mean score of those who

TABLE I. Nurses' Training and Immunization Status Regarding HAIs and Isolation Precautions (n=110)

Training and immunization	n	%
Being trained on isolation precautions		
Yes	104	94.55
No	6	5.45
Trainer/training place (n:104)		
Infection control nurse	56	53.85
In-service training	15	14.42
Undergraduate education	26	25.00
Congress/Symposium	7	6.73
Having adequate knowledge about HAIs		
Yes	101	91.82
No	9	8.18
Whether HAIs can be controlled through training		
Yes	75	68.18
No	8	7.27
Partially	27	24.55
Whether hand hygiene is important in preventing HAIs		
Yes	103	93.64
No	3	2.73
Partially	4	3.64
Immunization		
Yes	37	33.64
No	73	66.36
Immunization type (n:37)		
No response	16	43.24
Anti HBV	20	54.06
Anti HIV	1	2.70
Whether healthcare personnel affect the development and spread of HAIs		
Yes	87	79.09
No	1	0.91
Partially	22	20.00
Whether hospital staff adequately comply with isolation precautions		
Yes	20	18.18
No	56	50.91
Partially	34	30.91

TABLE 2. Distribution of Items Regarding Nurses' Compliance with Isolation Precautions (n=110)

Items	I definitely agree		I agree		No idea		I disagree		I deefinitely disagree		$\bar{X}$	s
	n	%	n	%	n	%	n	%	n	%		
1. I believe that nosocomial infections can be controlled by implementing isolation precautions.	65	59.09	31	28.18	1	0.91	1	0.91	12	10.91	4.24	1.26
2. I will be a strict follower of the continuous implementation of isolation precautions.	62	56.36	27	24.55	9	8.18	5	4.55	7	6.36	4.20	1.17
3. If the pathogenic microorganism is transmitted to the patient through more than one route, I apply isolation precautions together.	68	61.82	23	20.91	7	6.36	5	4.55	7	6.36	4.27	1.17
4. I wash my hands before contact with a patient.	78	70.91	20	18.18	1	0.91	2	1.82	9	8.18	4.42	1.17
5. Sometimes I do not use gloves during the care and treatment of the patient undergoing contact isolation.	10	9.09	20	18.18	7	6.36	26	23.64	47	42.73	2.27	1.41
6. I remove the gloves before leaving the patient's room.	64	58.18	31	28.18	4	3.64	4	3.64	7	6.36	4.28	1.13
7. I do not need to wash or scrub my hands when I remove the gloves.	9	8.18	2	1.82	10	9.09	30	27.27	59	53.64	1.84	1.19
8. I wear a protective apron in the implementation of strict contact insulation.	61	55.45	33	30.00	5	4.55	3	2.73	8	7.27	4.24	1.15
9. I take care to change the protective mask when it is wet.	71	64.55	24	21.82	3	2.73	4	3.64	8	7.27	4.33	1.17
10. I provide the necessary barrier measures during the transfer of the patient.	75	68.18	21	19.09	3	2.73	3	2.73	8	7.27	4.38	1.16
11. If the patient undergoing isolation is examined in another unit, I would warn the relevant unit supervisor to continue to apply the isolation precautions.	75	68.18	23	20.91	4	3.64	3	2.73	5	4.55	4.45	1.02
12. I do not mind touching a wound of the patient with naked hands.	10	9.09	3	2.73	2	1.82	11	10.00	84	76.36	1.58	1.24
13. I do not allow the patient, to whom isolation precaution is applied, to walk outside his/her room.	60	54.55	29	26.36	5	4.55	5	4.55	11	10.00	4.11	1.29
14. I restrict visits of the patient who is isolated.	67	60.91	25	22.73	6	5.45	4	3.64	8	7.27	4.26	1.19
15. I ensure that patient toilets and the surfaces more frequently touched in the isolation room are cleaned more frequently than the surfaces less touched in the isolation room.	72	65.45	21	19.09	3	2.73	4	3.64	10	9.09	4.28	1.26
16. I take care that the medical waste formed in the isolation room is disposed of in accordance with the relevant rules.	65	59.09	24	21.82	7	6.36	6	5.45	8	7.27	4.20	1.23
17. I do not want to give care to the patient who is undergoing isolation because of the risk of infection.	7	6.36	8	7.27	20	18.18	22	20.00	53	48.18	2.04	1.24
18. I take care that the cleaning materials used in the insulation room are not used in other patient rooms.	61	55.45	23	20.91	11	10.00	5	4.55	10	9.09	4.09	1.29
Overall Average											3.75	1.01

TABLE 3. The Relationship between Some Socio-Demographic Characteristics of Nurses and the Level of Their Compliance with Isolation Precautions (n=110)

Some Socio-Demographic Characteristics		n	$\bar{x}$	SD	Z, X^2	p
Being trained on the isolation precautions taken for preventing HAIs	Yes	104	76.81	14.99	Z= -2.442	0.015*
	No	6	62.50	15.64		
Having adequate knowledge about HAIs and isolotion precautions	Yes	101	77.35	14.42	Z= -2.822	0.005**
	No	9	61.22	17.98		
Whether HAIs can be controlled by giving relevant training on HAIs and isolation precautions	Yes	75	78.71	13.64	X2=14.058	0.001**
	No	8	51.88	17.63		
	Partially	27	75.74	12.97		
Being immunized against HAIs	Yes	37	70.78	18.14	Z= -2.008	0.045*
	No	73	78.68	12.98		

* $P < .05$, ** $P < .01$

were not immunized against HAIs was 78.68±12.98, indicating a statistically significant difference between the mean scores ($p \leq .05$) in favor of those who were not immunized (Table 3).

No statistically significant difference was found between the nurses' mean CIPS scores in terms of their age, sex, education level, employment status and professional experience, whether they believe in the importance of hand hygiene in preventing HAIs, whether they think healthcare personnel directly or indirectly affect the development and spread of HAIs, or whether they think hospital staff sufficiently comply with isolation precautions. These results may suggest that the aforementioned variables do not affect the level of nurse compliance with isolation precautions.

DISCUSSION

Most of the nurses received training on the isolation precautions taken to prevent HAIs, and more than half of them received this training from an infection control nurse. This result is consistent with the results of studies conducted by Zencir et al. (15), Aytaç et al. (22), Erden et al. (20), Özden and Özveren (12), in which 82.7%, 63.3%, 79.0%, and 78.4% of participating nurses, respectively, reported taking part in a training program related to HAIs and isolation precautions. Other studies emphasize that the level of knowledge that healthcare professionals/nurses have on HAIs and relevant isolation precautions play a decisive role in preventing HAIs that prolong hospital stay and increase morbidity and mortality rates and medical costs (3, 4, 6, 16). In this respect, these results–which show that most nurses have participated in training programs on HAIs and isolation precautions–are pleasing. In addition, the result indicating that the majority of the nurses received this training from an infection control nurse suggests that hospital staff training is given due emphasis in line with universal measures and nursing practices set by the CDC, and that infection control nurses are aware of their duties and responsibilities (1, 23).

Most nurses had knowledge about HAIs. This result is consistent with the results of other studies conducted by Mankan and Kaşıkçı (10) and Aytaç et al. (22), in which 81.1% and 78.1% of participating nurses, respectively, correctly identified HAIs and knew their types and the time intervals at which they occurred. When evaluated with the previous result, this result is considered satisfactory because the knowledge level of healthcare professionals and nurses plays a decisive role in preventing HAIs.

More than half the nurses stated that HAIs were controllable through relevant training. This result is consistent with the results found by Coopersmith et al. (4) regarding the effects of training programs on reducing HAIs; in that study, the rate of HAIs decreased by 66% as a result of relevant training given to healthcare professionals (39 nurses, 1 doctor, and 2 intensive care unit [ICU] personnel). This result suggests that nurses understood the role of training nurses in the prevention and control of HAIs and were consciously aware of this issue.

In addition, the result that 66.36% of the nurses (n=73) were not vaccinated against HAIs, that only 33.64% (n=37) were immunized with anti-HBV vaccine, and that 43.24% (n=16) did not respond to the relevant question is consistent with the results of the study by Aytaç et al. (22), in which 90.5% of the nurses stated that receiving HBV vaccine was important to preventing HAIs. These results suggest that nonvaccinated nurses do not have conscious awareness of protecting themselves against infections. Of the nurses, 79.09% (n=87) believed that healthcare personnel influenced the development and spread of HAIs and 50.1% (n=56) thought that hospital staff did not adequately comply with isolation precautions. These results suggest that nurses are aware of the importance and key role of healthcare personnel in the prevention of HAIs.

The nurses' total mean CIPS score was 3.75±1.01. This is a positive result, indicating that the nurses had a high level of compliance with isolation precautions, and parallels the results of many studies that used the CIPS and found that nurses had a high level of compliance with isolation precautions (12, 15, 20). However, this result does not agree with the results of the study by Pettinger and Nettleman (9), in which the level of nurses' compliance with isolation precautions was found to be insufficient. Halcomb et al. (17) reported that nurse failure to comply with isolation precautions negatively affected both nursing care and psychological and social lives of patients and their families. Accordingly, the results of this study also suggest that a high level of compliance of nurses with isolation precautions positively affects both nursing care and psychological and social lives of patients and their families.

No statistically significant difference was found in the levels of nurse compliance with isolation precautions in terms of their education level ($P > .05$). However, Özden and Özveren (12) stated that the education level of nurses did influence the level of their compliance with isolation precautions, reporting that nurses with a Bachelor's degree had a much higher mean compliance score than the nurses who graduated from a vocational health high school. Zencir et al. (15) also found that the nurses' education level influenced the level of their compliance with isolation precautions, reporting that those with a Master's degree had a higher mean compliance score than those with a Bachelor's or Associate's degree and those who graduated from vocational health high schools. Similarly, this study found that the mean CIPS scores of the nurses with Bachelor's or postgraduate degrees were higher than the mean scores of the nurses with vocational health high school or Associate's degrees. The literature emphasizes that undergraduate education is very important in terms of informing health personnel and leading to positive behavioral changes (12). This result can be attributed to the fact that the level of knowledge and awareness of nurses increases as their level of education increases.

No statistically significant difference was found in the levels of nurse compliance with isolation precautions in terms of work experience ($P > .05$). However, the mean CIPS score of the nurses with ≥ 6 years of work experience was higher than the mean scores of nurses with less experience. This result is consistent with the results of studies conducted by Zencir et al. (15) and Özden and Özveren (12), which reported that as nurses' work experience increased, so did the level of their compliance with isolation precautions. A study conducted in Nigeria found that nurses with professional experience of ≥ 10 years had a high level of compliance with isolation precautions.[24] This suggests that the length of professional experience and in-service training programs have a positive effect on the level of nurse compliance with isolation precautions taken to control HAIs. The literature notes that professional experience and experience-induced learning reflect positively on the professional practices of nurses (5, 12).

A statistically significant difference was found in the mean CIPS scores of nurses who received training on the isolation precautions taken to prevent HAIs and those who did not receive such training. The difference favored those with the training ($P < .05$). This result is consistent with those of a study by Helder et al. (25), in which the level of compliance with hand hygiene increased among health professionals who participated in a training program; this led to a decrease in HAIs. The result is also in agreement with those of a study by Pekuslu et al. (26), in which the level of compliance with isolation precautions among doctors and nurses who received training on the issue was found to be higher than among those who did not receive that training. However, many other studies found no statistically significant relationship between the level of compliance with isolation precautions and the training received in this regard (10, 12, 15, 20, 22). Training has a vital role in ensuring that healthcare professionals comply with isolation precautions. Jeffe et al. (27) found that training positively improved nurse knowledge and attitudes. In this context, periodically repeating the training on isolation precautions in a way that includes all healthcare professionals who provide healthcare services and putting into practice the solutions suggested to determine what factors are preventing compliance with isolation precautions may increase compliance with isolation precautions. The literature emphasizes support–via trainings, audits, and feedback–particularly for nurses who comply with infection control measures as a way to increase the quality of healthcare given (16, 23).

There was a statistically significant difference between the mean CIPS scores of nurses who reported having adequate knowledge about HAIs and isolation precautions and those who reported not having such knowledge ($P < .01$). Considering that the majority of the nurses (94.55%) who participated in our study were trained on HAIs and isolation precautions, this result may be considered a satisfactory result supporting the fact that relevant training programs positively affect nurses' knowledge, attitudes, and behaviors regarding HAIs and isolation precautions.

A statistically significant difference was found between the mean CIPS scores of the nurses who reported believing that HAIs can be controlled through relevant training and isolation precautions and those who did not ($P < .01$). This result is consistent with those of a study by Helder et al. (25), in which levels of compliance with hand hygiene increased among healthcare professionals who participated in a training program, thereby decreasing HAIs. This result is also consistent with those of a study by Kanouff et al. (28), which reported that HAIs in ICUs can be prevented through training and strict control. The result is also in agreement with those of a study by Coopersmith et al. (4), which asserted that a training program was found to be very effective in reducing HAIs in surgical ICUs; the rate of HAIs decreased by 66% as a result of relevant training given to healthcare professionals. Çetinkaya Şardan (29) concluded that hand hygiene and antiseptics were the most important measures controlling the spread of HAIs. The result of this study suggests that training programs are key to preventing/controlling HAIs.

There was no statistically significant difference between the mean CIPS scores of the nurses who reported believing in the importance of hand hygiene in preventing HAIs and those who did not believe this ($P > .05$). Özden and Özveren (12) found that healthcare professionals received low mean scores on the patient safety, hand hygiene, and use of gloves subscales on the CIPS. The CDC emphasizes the necessity of handwashing before and after providing care for each patient to prevent HAIs (1). In addition, Boyce and Pittet (11) emphasized that poor hand hygiene–either washing or using an antiseptic hand rub–is a major contributor to infection. According to the results of this study, nurses' beliefs that hand hygiene is important for preventing HAIs is considered a variable that does not affect the level of their compliance with isolation precautions. Furthermore, the effect of hand hygiene and related subjects/concepts should be investigated in detail through future qualitative studies that should be carried out with larger samples.

No statistically significant difference was found between the mean CIPS scores of nurses who reported believing that healthcare professionals directly or indirectly affect the development and spread of HAIs and those who did not ($p>.05$). Although this result suggests that nurses' belief that healthcare professionals directly or indirectly affect the development and spread of HAIs is a variable that does not affect the level of their compliance with isolation precautions, different studies report that the attitudes and behaviors of healthcare professionals constitute the most important factor in the development of HAIs. HAIs are controllable and preventable. The failure of nurses and physicians to comply with all isolation precautions, including hand hygiene as a basic isolation precaution and other infection control measures, causes the proliferation of microorganisms and the spread of infections (11, 13, 30, 31). The transmission of microorganisms usually occurs during medical care and intervention. Nurses and physicians are expected to comply with necessary measures to control infection in the delivery of healthcare and to exercise due diligence during diagnosis, treatment, and care (18, 31, 32). Nurses who are frequently in contact with patients to meet their care and treatment needs, as well as other healthcare professionals, have an important role in preventing the development and spread of HAIs (6, 31, 32).

In conclusion, the results of this study showed that nurses had a high level of compliance with the isolation precautions taken to prevent HAIs. Given these results, the following advice is offered:

1. Increase the number of continuous education programs to encourage nurses and healthcare professionals to comply with infection control measures and isolation precautions at the highest level.
2. Create studies and activities to raise the awareness of all healthcare professionals about the importance of hand hygiene habits.
3. Ensure that all healthcare professionals cooperate in putting isolation compliance measures into practice.
4. Conduct further qualitative studies with larger samples.

This study has limitations. This study was conducted at only one university hospital in Nicosia. The results reflect only the practices of nurses at this hospital and cannot be generalized to all nurses.

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Original Article

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Interobserver Variability and Stiffness Measurements of Normal Lacrimal Gland in Healthy People Using Shear Wave Elastography

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BACKGROUND/AIMS
To determine a reference data set for stiffness values of normal lacrimal gland using shear wave elastography and to evaluate the interobserver variability of these measurements.

MATERIAL and METHODS
A total of 50 participants (bilaterally 100 glands) comprising 25 females and 25 males, aged between 19 and 58 years, were included in this prospective study. For each participant, we evaluated both lacrimal glands using grayscale and shear wave elastography, and the relationships with sex, age, and body mass index were determined. All lacrimal glands were evaluated by 2 independent observers blinded to each other.

RESULTS
The mean stiffness values of lacrimal glands for the 2 observers were 6.17±2.94 kPa and 6.00±3.10 kPa, respectively. In terms of stiffness values, there were no significant differences between the left and right lacrimal glands and between sexes ($p>.05$). Age exhibited a weak correlation with stiffness values ($r=0.280$, $p=.005$; $r=0.284$, $p=.004$). The intraclass correlation coefficient for the interobserver variability of the shear wave elastography measurements was 0.948 (95% confidence interval: 0.924-0.965).

CONCLUSION
The lacrimal gland can be quantitatively evaluated using shear wave elastography. Normal shear wave elastography values for the lacrimal gland in the healthy population included in this study were estimated to be 6.17±2.94 kPa. Operator dependency of this method is low, and interobserver compliance is high. The standard stiffness values of the normal lacrimal gland obtained using shear wave elastography in this study may be used as reference data to distinguish the healthy tissues from the pathological tissues.

Keywords: Lacrimal gland, elastography, interobserver variability, ultrasound imaging

INTRODUCTION

The function of the lacrimal gland includes moistening of the cornea by producing tears. As the lacrimal gland contains both epithelial and lymphoid tissue, various pathologies are observed. However, the clinical presentation of lacrimal gland pathologies is nonspecific, and exophthalmos, palpebral enlargement, or deviation of the eye are common clinical findings (1). Inflammatory disease of the lacrimal gland can manifest as acute and chronic dacryoadenitis and as an inflammatory pseudotumor (2). Acute dacryoadenitis may be of bacterial or viral origin, is more common in children than in adults, and may develop in young people owing to trauma. Chronic dacryoadenitis can develop after an acute infection. It has been reported in sarcoidosis, Mikulicz syndrome, sclerosing pseudotumors, thyroid ophthalmopathy, and Wegener granulomatosis. In Sjögren syndrome, the lacrimal glands increase in size owing to lymphocytic infiltration of the gland tissue. In half of the patients with Sjögren syndrome, the development of connective tissue diseases, such as rheumatoid arthritis, systemic lupus erythematosus, scleroderma, or polymyositis, has been reported (3, 4). Additionally, the development of various benign or malignant neoplasms has also been documented.

The clinical history, symptoms, radiological imaging, and histopathological evaluation should be considered in combination for the diagnosis and treatment of lacrimal gland lesions (4). Computed tomography (CT) or magnetic resonance

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imaging (MRI) provides clear information by localizing ambiguous clinical features of the lacrimal gland and by aiding the precise determination of the extent and nature of the disease (1). Although several diseases affecting the lacrimal gland and fossa can be diagnosed specifically by adopting imaging methods, it is often difficult to distinguish each disease individually based on imaging features (2). Compared to CT and MRI that demonstrate higher sensitivity in a detailed assessment of the lacrimal gland, performance of sonography, which is cost-effective and requires a shorter duration, may be more practical in daily clinical practice. Owing to the superficial anatomy of the lacrimal gland, ultrasonography (US) can be conducted reasonably with simplicity and efficiency. Nevertheless, US is an operator-dependent technique, and intraobserver and interobserver variabilities remain a typical issue (5). Lacrimal gland US is less conducted in clinical practice. The superficial location in the superolateral part of the orbit permits the evaluation under favorable conditions, as the gland is recognized as a small hypoechoic, homogenous area (6).

Ultrasound elastography is a noninvasive method utilized to evaluate the stiffness of soft tissue, and it aids the determination of elastic properties of different tissues. Shear wave elastography (SWE) is performed to evaluate tissue elasticity in a quantitative manner. In recent years, the usage of SWE has gained considerable attention owing to the ease of applicability and less operator dependence. The elasticity is defined as elasticity modulus (or Young's modulus), measured in kilopascals (kPa), or as shear wave velocity, measured in meters per second (m/s). For the diagnosis and treatment of a variety of diseases, measurements of tissue elasticity may be performed (7, 8).

Consequently, normal elastic values for the lacrimal gland may be an indicator for the diagnosis of inflammatory diseases such as Sjögren syndrome, infectious diseases such as dacryoadenitis, and neoplastic diseases such as pleomorphic adenoma (9). Various values may be provided by conducting measurements using different equipment and techniques (10, 11). Furthermore, with respect to age or body mass index (BMI), the reference values for the same tissue may differ (12, 13). In the existing literature, there are studies documenting the reference values of different tissues (e.g., thyroid, breast, muscle, tendon, liver, spleen, and kidney) using various technologies that use acoustic radiation force impulse, strain elastography or SWE techniques (14-18). The applicability of SWE in evaluating the lacrimal gland remains unclear, mainly owing to the availability of insufficiently reported data**.** To the best of our knowledge, thus far, normal 2-dimensional (2D)-SWE elasticity values for the lacrimal gland in healthy people were recently published in a single study (19). As SWE measurements can be used to demonstrate variabilities among vendors, the measurement of the elasticity of lacrimal glands using devices obtained from different vendors will be useful (20).

Main Points:

- Shear wave elastography (SWE) is a reproducible imaging method for the assessment of lacrimal gland elasticity.
- The SWE measurements of the normal lacrimal gland may be used as reference data to discern healthy from abnormal parenchyma.
- In terms of stiffness values, there were no significant differences between the left and right lacrimal glands and between sexes.

The primary aim of our study was to define elasticity values using SWE for the lacrimal glands in healthy adults and to evaluate the impact of several factors, such as sex, age, BMI, and the laterality on SWE measurements. Additionally, the study was aimed to evaluate the interobserver variability for SWE measurements.

MATERIAL and METHODS

Study Design

This prospective study was approved by a local clinical research ethics committee. Informed consent was obtained from all individuals who agreed to participate in the study. A total of 50 normal healthy adults (age range: 19-58 years; mean age: 35.26±10.05 years) who agreed to participate in the study, comprising 25 men and 25 women, were included in the study. B-mode US followed by SWE was used for investigation of the lacrimal gland of all participants. Adults with no lacrimal gland pathology, with no medical history, and without inflammatory diseases that might influence the lacrimal gland were included in the study. Exclusion criteria were as follows: the presence of heterogeneous gland parenchyma as per grayscale US evaluation; age <18 years; refusal to adequately cooperate; refusal to participate in the study; presence of thyroid ophthalmopathy; occurrence of fever during the assessment; presentation of trauma, tumor, and a history of chronic inflammatory disease; usage of contact lenses; and a history of lacrimal gland surgery. Of the 53 normal healthy individuals who agreed to participate in the study, a total of 3 patients with heterogeneous gland parenchyma, a history of ocular surgery, and a history of trauma were excluded from the study. Demographic data (age, sex, weight, and height) were noted. BMIs of all participants were calculated (kg/m^2). For all cases included in the study, images of appreciable quality were obtained and techniques were performed appropriately.

Ultrasonography and Shear Wave Elastography Examination

SWE measurements were performed on the same day by 2 radiologists possessing 5 and 6 years of elastography experience, respectively. Observer I performed a B-mode US and used the 2D-SWE imaging technology to quantify the stiffness values (kPa) of all participants consecutively. Immediately after completion of the first evaluation, observer 2 performed only an elastographic assessment of all lacrimal glands. All measurements were obtained using LOGIQ S8 (GE Healthcare Systems, Waukesha, WI, USA) with a 9-MHz linear probe. The observers were blinded to their measurement results. All participants were assessed in the supine position, with their heads turned to the opposite side. The participants were advised to breathe normally with eyes closed. The glands were assessed in longitudinal and transverse scans, but the measurements were performed in the transverse plane (Figure 1). To better evaluate the area of the lacrimal glands, the ultrasound focus was adjusted. For conducting 2D-SWE evaluation, an adequate quantity of ultrasound gel was used, and no pressure was applied on the ex-

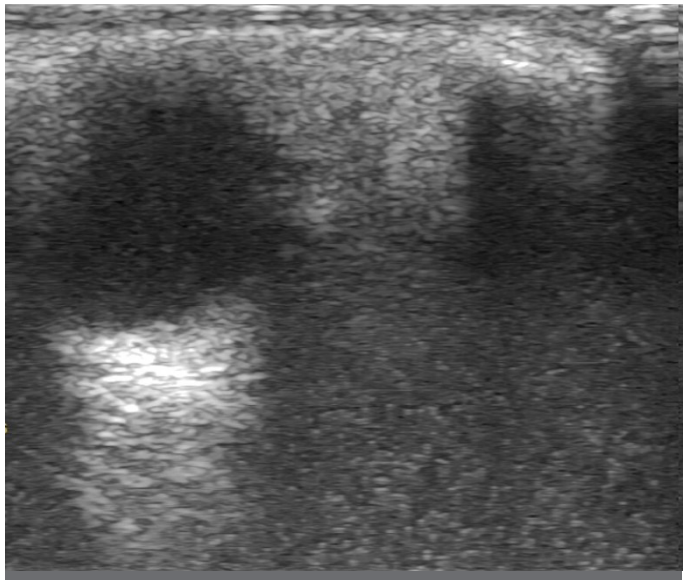

FIGURE 1. Grayscale ultrasound image of the lacrimal gland in the axial plane

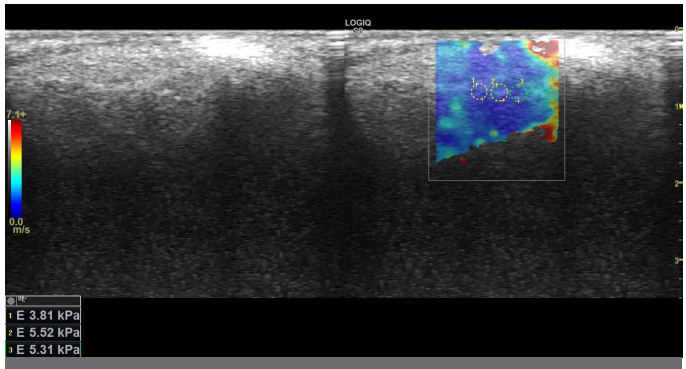

FIGURE 2. SWE measurements of the lacrimal gland were completed using a circular ROI that focused on the homogeneous parenchyma. The 2D-SWE map (right side) and grayscale image (left side) are shown. A total of 3 valid measurements were obtained. 2D-SWE: 2-dimensional shear wave elastography; ROI: region of interest

TABLE 1. The Demographic Characteristics of the Participants

Variables	Participants (n=50)
Age (years)	32.5 (min-max: 19-58)
Gender (female/male)	25/25
Body mass index (kg/m^2)	24.77±3.08 (18.6-30.9)

Data are expressed as mean±standard deviation (for normal distributions) or median (min-max) (for non-normally distribution). Max: maximum; min: minimum.

amined tissues. We used the presetting for examination of small sections. For obtaining measurements, we used the elasticity modulus (Young's modulus E). As the lacrimal gland is a small, lobulated, tear-shaped organ, the middle of the lacrimal gland was selected as the region of interest (ROI) to ensure that no measurements were acquired from extraglandular structures. A 2-mm diameter circular ROI was used, and three valid measurements were obtained (Figure 2) (19). All images were saved for further analysis. Participants were divided into 2 subgroups according to their ages (<40 and ≥40 years)

Statistical Analysis

The Statistical Package for the Social Sciences, version 22.0, software for Windows (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analyses. The descriptive statistics of the data are presented as mean, standard deviation, median, minimum, and maximum values. The distribution of variables was analyzed using the Kolmogorov-Smirnov test. Owing to the non-normal distribution of lacrimal gland stiffness values, the stiffness values were compared by performing the Mann-Whitney U test. For correlation analysis, Spearman's coefficient (with a 2-tailed test) was used. The numerical values obtained by using Spearman's correlation coefficient were evaluated as follows: r of 0-0.19 was regarded as very weak, r of 0.2-0.39 was regarded as weak, r of 0.40-0.59 was regarded as moderate, r of 0.6-0.79 was regarded as strong, and r of 0.8-1 was regarded as a very strong correlation. α=0.05 was set as the significance level. Interobserver variability was evaluated using Bland-Altman plots; the mean difference between the 2 observers and the 95% limits of agreement were analyzed. Paired *t*-test was used to determine the absolute values for interobserver variability. Interobserver variability was also evaluated by using the intraclass correlation coefficient (ICC). The numerical values obtained by using ICC were evaluated as follows: <0.5 indicating poor, 0.5-0.75 indicating moderate, 0.75-0.90 indicating good, >0.9 indicating excellent agreement (21). A *P*-value <.05 was considered significant.

RESULTS

Table 1 presents the demographic data of the participants. The mean age of the participants was 35.41 (range: 19-58) years. All lacrimal glands exhibited normal homogeneous parenchyma with flat contours. Pathological sonographic findings suggestive of inflammatory diseases were not obtained for any participant. The mean stiffness values of lacrimal glands as assessed by the 2 observers were estimated to be 6.17± 2.94 kPa and 6.00±3.10 kPa, respectively.

SWE measurements of the lacrimal gland according to laterality, sex, and age groups are presented in Table 2. Comparison of the SWE parameters revealed no significant differences between the left and right lacrimal glands between sexes (p>.05). For observer 1, the median stiffness values of lacrimal glands for participants aged <40 years and those aged ≥40 years were 6.89 (minimum-maximum values: 1.54-13.50) kPa and 3.79 (minimum-maximum values: 1.56-13.05) kPa, respectively. For observer 2, the median stiffness values of lacrimal glands for participants aged <40 years and those aged ≥40 years were 6.75 (minimum-maximum values: 1.43-12.93) kPa and 4.08 (minimum-maximum: 1.51-15.20) kPa, respectively. There was a significant difference in stiffness measurements between participants aged <40 years and those aged above 40 years (observer 1: p=.006; observer 2: p=.007).

In the assessment conducted by both observers, BMI showed no significant correlation with parenchyma stiffness (observer 1: p=.607; observer 2: p=.570). Age exhibited a weak negative correlation with parenchyma stiffness (observer 1: r= -.280, p=.005; observer 2: r= -.284, P=.004) (Figure 3).

The ICC for the interobserver variability of the SWE measurements was 0.948 (95% confidence interval: 0.924-0.965). Figure 4 presents Bland-Altman plots of pairs of SWE measurements showing the 95% limits of agreement and the median of dif-

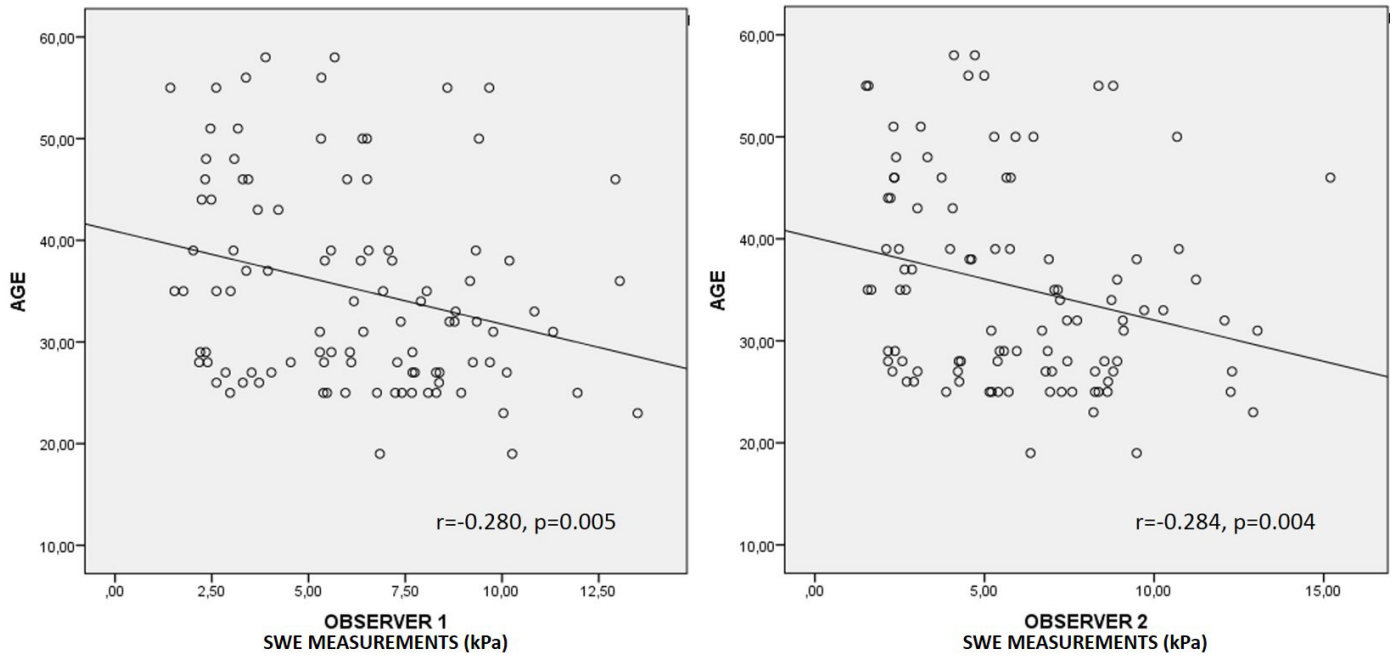

FIGURE 3. Scatterplots showing a weak negative correlation between shear wave elastography measurements and age

TABLE 2. Shear Wave Elastography Measurements of Lacrimal Gland According to Laterality, Gender, and Age Groups

	Right (n=25)	Left (n=25)	p
Observer I	6.14 (1.43-13.50) kPa	6.21 (2.20-10.84) kPa	.815
Observer 2	5.24 (1.56-15.20) kPa	5.86 (1.51-12.30) kPa	.942
	Female (n=50)	**Male (n=50)**	
Observer I	6.66 (1.54-13.50) kPa	5.53 (1.43-11.32) kPa	.363
Observer 2	5.76 (1.56-15.20) kPa	5.34 (1.51-13.05) kPa	.420
	Aged <40 years (n=74)	**Aged ≥40 years (n=26)**	
Observer I	6.89 (1.54-13.50) kPa	3.79 (1.43-12.93) kPa	.006
Observer 2	6.75 (1.56-13.05) kPa	4.08 (1.51-15.20) kPa	.007

*P<.05 has been considered statistically significant (two-tailed test)

ferences for interobserver variability. The mean interobserver difference of SWE measurements was 0.17. The range of measurement error expressed as 95% limits of agreement was ±1.88. There was no significant difference between absolute values of SWE measurements (P=.081).

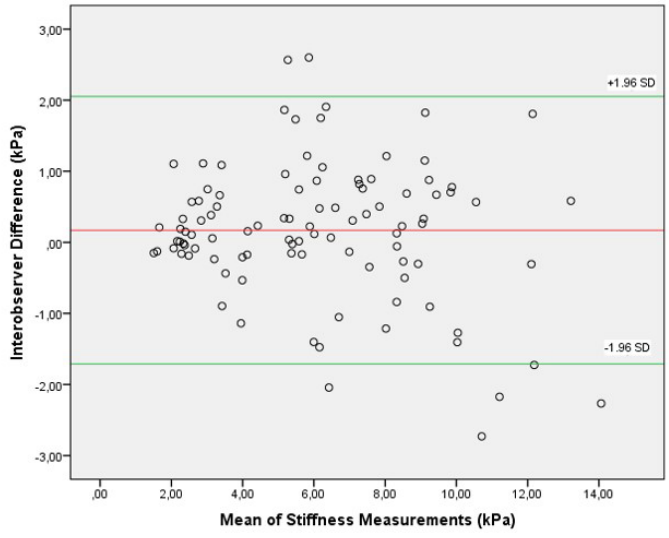

FIGURE 4. Bland-Altman plots of stiffness measurements conducted and obtained by 2 observers. The difference in stiffness values between observers I and 2 is plotted against the mean stiffness values obtained by 2 observers. The red line represents the mean difference of all measurements (n=100), and the green lines represent 95% Bland-Altman limits of agreement (mean±1.96 SD). SD: standard deviation

DISCUSSION

In this study, we defined normal values for lacrimal gland stiffness measurements by performing SWE in adult healthy participants, and we evaluated the influence of several factors, such as sex, age, BMI, and the laterality on SWE-based imaging values. In terms of SWE measurements, there were no significant differences between the left and right lacrimal glands and between sexes. Age exhibited a weak correlation with stiffness values. Additionally, we assessed the interobserver variability of SWE measurements, and excellent interobserver reliability was demonstrated.

Undoubtedly, the presence of reference values for a measured parameter is necessary to discern pathological cases from healthy ones via implementation of a diagnostic method. Identification of reference values is the critical initial process for the determination of a diagnostic technique and for the definition of values for investigation of several types of diseases. This pilot study represents the first attempt to identify the reference values for the lacrimal gland parenchyma in healthy patients. In the study reported by Bădărînză et al. (19), in which the authors measured the 2D-SWE values of the lacrimal gland using Supersonic Imagine Aixplorer Ultimate device in healthy adults, normal values were found to be 9.47±2.1 (4.8-15.9). In contrast, in the

present study conducted using the LOGIQ S8 (GE Healthcare Systems) device, normal 2D-SWE values of the lacrimal gland were estimated to be 6.17±2.94 kPa (observer 1) and 6.00±3.10 kPa (observer 2). The main differences might be attributable to the machines and converters used. It has been reported that shear wave velocities exhibit a dependency on excitation frequencies and that devices obtained from different vendors may operate at different frequencies (7). Moreover, in a phantom study, Shin et al. (23) have shown that shear wave velocities are different among different ultrasound devices and among different transducers. Considering that SWE measurements may demonstrate significant variabilities among the devices manufactured by vendors, the application of different ultrasound devices for the conduction of studies may be the most plausible explanation for the obtainment of discordant results (20). Thus, additional studies are warranted for the establishment of exchangeable normal values.

In this study, factors such as sex, laterality, and BMI, that were hypothesized to affect parenchymal elasticity, exerted no effect on reference SWE values of the lacrimal glands. These results were in line with those reported by a previous study (19) and showed that the reference values for lacrimal glands could be reproducible and might be beneficial for the conduction of future studies.

The age-related alterations of the lacrimal gland comprise improved fat content in epithelial secretory cells and glandular tissue, glandular parenchymal atrophy, and increased interstitial connective tissue (22). In our study, a weak negative correlation was observed between age and elasticity values. Additionally, according to the age groups (<40 years, ≥40 years), the measurement of SWE was found to decrease with the age (P<.05). These results are predictable for the lacrimal gland, whose age-related atrophy is associated with an increase in the fatty component. In a study conducted by Herman et al. (17) involving adults (aged 21-91 years), normal elasticity values were determined for the salivary glands, thyroid gland, cervical lymph nodes, and sternocleidomastoid and masseter muscles, and a mild decrease in elasticity was observed with increasing age (17). However, in the study reported by Bădărînză et al. (19), a statistically significant difference was not found between age groups in terms of 2D-SWE measurements. Studies with a wider age range and more participants are warranted for further clarification.

Interobserver and intraobserver variabilities are an important aspect of radiological evaluations. Additionally, weak reproducibility is one of the traditional limitations in ultrasonographic evaluations. There are several studies in the literature documenting applications of SWE for investigation of the liver, thyroid, breast, prostate, salivary glands, and cervical lymph nodes, and in these studies, limited or negligible limitations were found in technical performance and reproducibility in SWE measurements (16, 24-29). In the present study, as evidenced by both the ICC and the Bland-Altman analysis, the interobserver agreements were high. This study is the first to evaluate interobserver variability in the assessment of lacrimal gland using 2D-SWE, and our results showed that 2D-SWE might be a beneficial, noninvasive diagnostic method with high reproducibility that could be useful for the evaluation of lacrimal glands.

This study has certain limitations. First, one of the most important limitations of this study is that the study cohort was heterogeneous and small. Therefore, the results of this study should be verified through studies using a large-sized cohort. Second, the lack of available software designed and developed specifically for the examination of the lacrimal glands may be considered another drawback of the present study. Third, the intraobserver variability was not assessed. Future studies that will focus on the evaluation of both intra and interobserver variabilities are necessary. Fourth, the lack of histopathological correlation is a limitation of this study. In contrast, a histopathological correlation could not be performed because the study population comprised normal healthy individuals and because the lacrimal gland biopsy was an invasive and challenging procedure. Finally, we were unaware of the time between the participant's last crying and US assessment and did not confirm whether this could have any impact on 2D-SWE results. To the best of our knowledge, no sufficient information is present in the literature on this issue, and comprehensive studies are warranted. Similarly, a lack of control of the potential confounders by variables, such as environmental conditions (climate, moisture, or the prevailing atmospheric conditions) or age-related dry eye development, might have also exerted effects on the lacrimal gland stiffness (30).

SWE is a reproducible imaging method used for the assessment of lacrimal gland elasticity. The SWE measurements of the normal lacrimal gland may be used as reference data to discern healthy parenchyma from abnormal parenchyma. However, further studies are necessary to validate its utility before the application of this technology in routine clinical cases.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gazi University Clinical Research Ethics Committee (Approval Date/Number: 07.12.2020/830).

Informed Consent: Informed consent was obtained from all individuals who agreed to participate in the study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - M.C.; Design - M.C.; Supervision - H.N.Ş.; Resource - M.N.C., H.N.Ş.; Materials - M.C., H.N.Ş.; Data Collection and/or Processing - M.N.C., H.N.Ş; Analysis and/or Interpretation - M.C.; Literature Search - M.C.; Writing - M.C.; Critical Reviews - H.N.Ş.

Conflict of Interest: Authors have no conflicts of interest to declare.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Case Report

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A Case of Antiglutamic Acid Decarboxylase and Voltage-Gated Potassium Channel Antibody-Associated Limbic Encephalitis With Temporal Lobe Epilepsy

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In this report, we present a patient with limbic encephalitis and related temporal lobe epilepsy with antibodies (Abs) against voltage-gated potassium channels complex and glutamic acid decarboxylase. The diagnosis was confirmed after the occurrence of adult-onset partial temporal lobe immune epilepsy accompanying increased T2 signal abnormalities in limbic structures, confirmed by magnetic resonance imaging and positive Abs.

Keywords: Limbic encephalitis, autoimmune epilepsy, anti-GAD antibody, VGKC antibody

INTRODUCTION

Limbic encephalitis (LE) is an autoimmune or paraneoplastic disease. Autoimmune LE is a challenging diagnosis because it is not always included in the typical paraneoplastic/autoimmune panels (1). Autoimmune LE is an immune-mediated inflammation of the limbic system, including the hippocampus, thalamus, hypothalamus, and amygdala (2). Neuropsychiatric symptoms and new-onset seizures are often the presenting symptoms owing to autoimmune damage to limbic structures (3). Specific autoantibodies against neuronal antigens have been defined thus far. The cell surface antigens are the most frequently involved: voltage-gated potassium channel (VGKC) complex is one of them (4).

VGKCs play an important role in the regulation of neuronal excitability controlling cell membrane potential, and the mutations of potassium channel genes are associated with the disturbances of neuronal firing in humans (5).

Anti–glutamic acid decarboxylase (GAD) antibodies (Abs) function against the GAD enzyme, which is essential in the formation of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter found in the brain. The absence or low levels of GABA causes patients to exhibit motor and cognitive symptoms (6).-

The anti-GAD Ab is found in various diseases, including type I diabetes mellitus (DM), and in neurological syndromes, such as stiff person syndrome, paraneoplastic stiff person syndrome, Miller Fisher syndrome, limbic encephalopathy, cerebellar ataxia, eye movement disorders, and epilepsy (6, 7). It affects the medial temporal lobe of the brain, occasionally involving hippocampal atrophy as well (1).

Both VGKC complex and GAD Abs have thus far been implicated in some types of idiopathic and symptomatic epilepsies and refractory seizures (5, 7). Although both the paraneoplastic and nonparaneoplastic LE related to GAD and VGKC complex Abs have been reported, paraneoplastic forms are rare (1, 7). For the most part, the LE associated with VGKC complex and GAD Abs is an immune form of encephalitis responsive to immunotherapy (8).-

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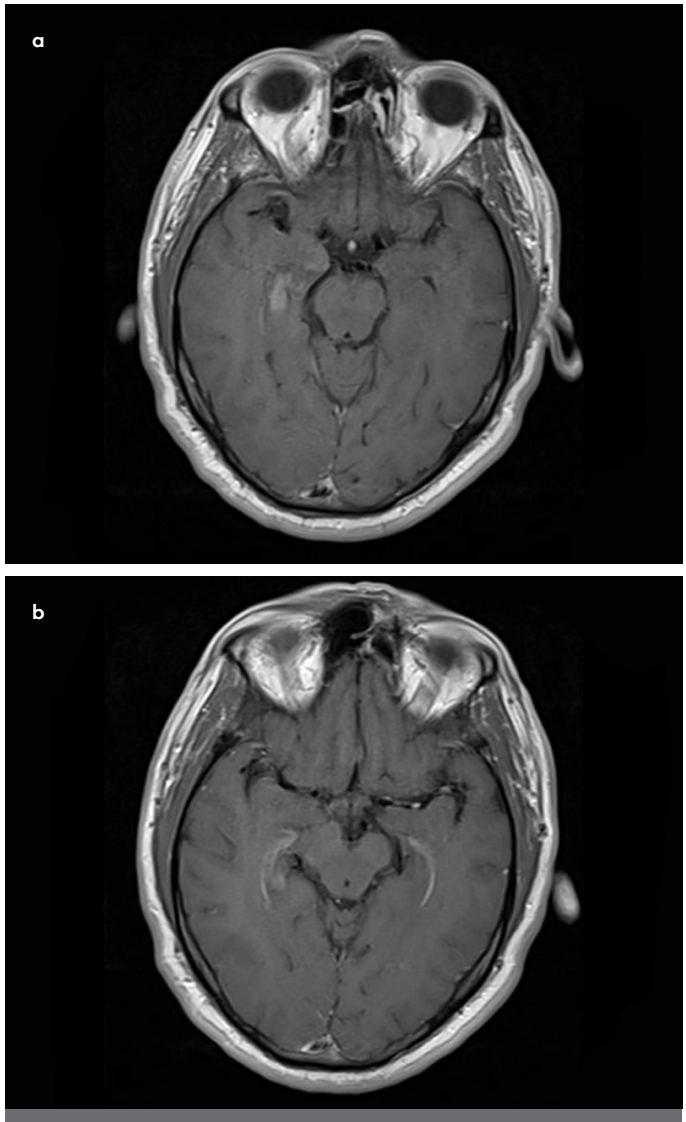

Figure 1. a, b. TI-weighted axial MRI showing hyperintense lesion with contrast enhancement in the right temporal region at disease onset. MRI: magnetic resonance imaging.

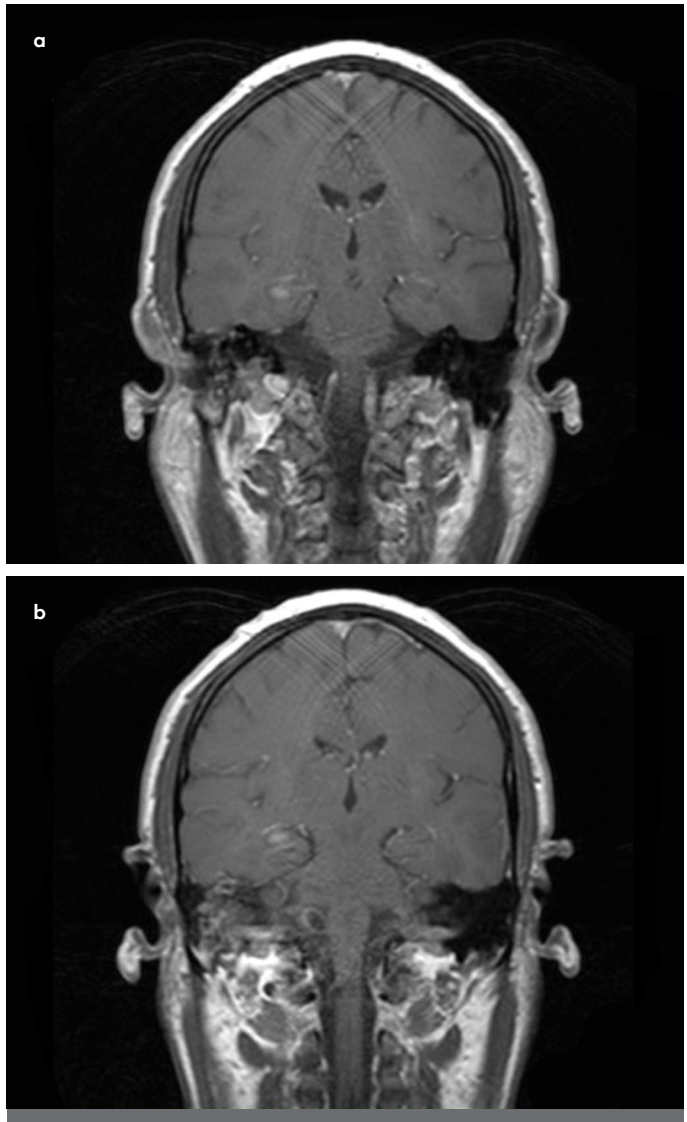

Figure 2. a, b. TI-weighted coronal MRI showing hyperintense lesion and contrast enhancement in the hippocampus. MRI: magnetic resonance imaging.

Neuropsychiatric symptoms, especially anterograde amnesia and new-onset seizures, are often the presenting symptoms owing to autoimmune damage to limbic structures and temporal lobes, as in the case whose details are presented below (3).

CASE PRESENTATION

A 57-year-old man was referred to the neurology department with new-onset complex partial and secondary generalized refractory seizures occurring during the day. A detailed anamnesis revealed a history of confusion, disorientation, agitation, and sleep that had been worsening over a period of 3 weeks. The temporal lobe seizures were typically right-sided faciobrachial dystonic type, involving the ipsilateral face, arm, and leg.

Main Points:

- Antiglutamic acid decarboxylase and voltage-gated potassium channel antibody-associated limbic encephalitis with temporal seizures is an immune cause of epilepsy in adults.
- Paraneoplastic forms are rare.
- The patient had a good recovery after immune treatment.

According to his medical history, he had been recently diagnosed with type 2 DM. On admission, the neuropsychological examination revealed that he was alert and cooperative but disoriented in terms of time and place. The examination did not reveal any lateralizing or focal neurological signs. The Mini-Mental State Examination (MMSE) score was 18 of 30. Laboratory tests, including electrolytes, blood count, infectious markers, and thyroid tests, were all within normal limits. The biochemistry of cerebrospinal fluid (CSF) was normal, and herpes simplex virus types 1 and 2 polymerase chain reactions were also negative. The glucose level was 52 mg/dL, total protein level was 42.69 mg/dL, sodium level was 136 mmol/L, chloride level was 123 mmol/L, and please erase this part as the result is not clear. in the CSF samples. There were no cells in direct cytology, and the CSF culture was negative. The oligoclonal band and immunoglobulin G index were not studied because there was no suspicion of any demyelinating disease. Electroencephalography showed focal sharp waves over the right anteromedial temporal regions.

The brain magnetic resonance imaging (MRI) (1.5T MRI Scanner; Siemens Healthineers, Erlangen, Germany) showed a T2 high-signal change in the hippocampus (bilateral medial temporal lobes), especially from the right temporal region to the hippocampus, with contrast enhancement (Figures 1a and b and 2a and b). Diffusion-weighted imaging and apparent diffusion coefficient values were normal.

VGKC complex Abs were positive with titers of 142 pmol/L in the serum by radioimmunoassay (reference: 100 pmol/L). In addition, GAD Abs showed a level of 82.56 IU/mL (reference: 5-10 IU/mL). Serology for onconeural Abs and NMDA-R, AMPA-R1, AMPA-R2, CASPR2, LGI-1, and GABA-R Abs were negative.

Extensive investigations, including neck ultrasonography, thoracoabdominal computed tomography, serum and urine protein electrophoresis, and immunofixation electrophoresis, did not reveal the presence of any malignancy.

The patient was started on carbamazepine treatment, and he also received a standard 5-day course of intravenous immunoglobulin (IVIG) (0.4 mg/kg/day). Clinical improvement, including seizure control and MMSE scores of 30 of 30, were sustained after a month.

To the best of our knowledge, this is the first case of LE associated with both anti-GAD and VGKC Abs together in the English literature and the first reported case of LE in North Cyprus. Informed consent was obtained from the patient.

DISCUSSION

Patients presenting with amnestic symptoms and newly onset seizures are frequent in neurological practice. Identifying those with possible reversible symptoms is important. Our patient presented with amnestic syndrome and refractory partial secondary generalized seizures. New-onset temporal lobe seizures (according to the old epilepsy classification), particularly when intractable with memory loss and behavioral and psychiatric features, raise the suspicion of autoimmune LE (7). Ab screening should be considered in adult-onset seizures, especially when combined with MRI findings consistent with LE as in this case. Owing to advances in neuroimmunology, several Abs related to immune-mediated encephalitis have been identified so far; therefore, it can be difficult to initially determine which Ab is responsible for the presented case. Hence, IVIG treatment was started with an initial diagnosis of LE rather than waiting for the results of Ab testing, which could take several weeks. Further screenings did not suggest the presence of malignancy, and after anti-GAD and anti-VGKC Abs were found to be positive, the patient was diagnosed with immune-mediated LE. The diagnosis was based on the detection of Abs along with the clinical history, MRI findings, and exclusion of malignancy.

GAD Abs are usually nonparaneoplastic and are typically related to stiff person syndrome and cerebellar ataxia. However, it has been suggested that patients with GAD Abs should be screened for an underlying neoplasm if they develop classical paraneoplastic syndromes such as LE (9).-

In addition, GAD Abs are present in 15% to 35% of patients with newly diagnosed type 2 DM at an age younger than 45 years and only in 7% to 9% of older patients and approximately 80% of newly diagnosed patients with type 1 DM, although at lower titers and against different epitopes from those seen in neurological disease. The presented case had type 2 DM, but we were not able to study different epitopes of GAD (6,10).

Anti-VGKC Ab-associated encephalopathy is a relatively common form of autoimmune and potentially treatable LE and immune epilepsy.

LE, faciobrachial dystonic seizures, and neuromyotonia are the most common neurological phenotypes of the VGKC complex (2). Typical faciobrachial dystonic seizures were detected in the presented case.

Because anti-GAD and anti-VGKC Abs-related LE does not automatically exclude the possibility of malignancy, further investigations are recommended as in our case (11).

There are various Abs defined under the VGKC complex such as LGI-1 and CASPR2. However, there this presented case. Although VGKC complex Abs were positive with titers of 142 pmol/L in the serum by radioimmunoassay (reference: 100 pmol/L), CASPR2, LGI-1, and GABA-R Abs were negative. Therefore, this group of patients may represent a different phenotype (12).

This is a case of immune-mediated LE associated with both anti-GAD and VGKC Abs together. The encephalitis was fully reversible in terms of seizure and memory after treatment.

Informed Consent: Informed consent was obtained from the patient.

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Author contributions: Concept - P.G.; Design - P.G.; Supervision - F.K.; Resource - S.D.; Materials - P.G.; Data Collection and/or Processing - P.G.; Analysis and/or Interpretation - P.G.; Literature Search - S.D.; Writing - P.G., S.D., F.K.; Critical Reviews - F.K., S.D.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Case Report

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Unicentric Retroperitoneal Mass: Castleman's Disease

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Castleman's disease (CD) is a rare cause of lymphadenopathy. Its pathophysiology is unclear. It is usually asymptomatic and is incidentally detected. The treatment of unicentric CD is complete removal of the mass, and its recurrence is very rare. In this study, we present a male patient aged 36 years presenting with dyspepsia and incidentally diagnosed with unicentric CD by reviewing the data from literature.

Keywords: Castleman's disease, dyspepsia, lymphadenopathy

INTRODUCTION

Castleman's disease (CD) is a rare disease characterized by benign lymph node hyperplasia (1, 2). Although this disease may occur anywhere along the lymphatic chain, it has been reported that 7% is retroperitoneal and that 2% is pararenal (1). Unicentric CD (UCD) has a 95.3% survival rate and is usually asymptomatic (1, 3, 4). In this article, we present a male patient aged 36 years who presented with dyspepsia and was incidentally diagnosed with UCD.

CASE PRESENTATION

A male patient aged 36 years who was diagnosed with a mass in the left perirenal area was admitted to our hospital for further examination and treatment. His medical history included hypertension and coronary artery disease. He did not have significant diseases in his family history. On physical examination, no pathological finding was detected except for minimal tenderness in the left colic region. Laboratory findings were normal. On thoracoabdominal computed tomography (CT), a retrocaval, well-circumscribed, homogeneous mass lesion with a size of 60 × 50 mm compressing the vena cava (VC) at the left renal hilum level was observed, and no other pathology was detected in the scans (Figure 1). In clinical evaluation of the patient, soft tissue sarcomas, schwannoma, paraganglioma, retroperitoneal fibrosis, and CD were considered in the differential diagnosis owing to the absence of pathological findings other than isolated retroperitoneal mass. Owing to the mass proximity to the left renal vein and inferior VC inferior, a biopsy could not be taken for tissue diagnosis, and surgery was decided. Written informed consent was obtained from the patient, and elective surgery was planned. On exploration it was found that the mass was invad-

FIGURE 1. Vertical and sagittal section of computed tomography images

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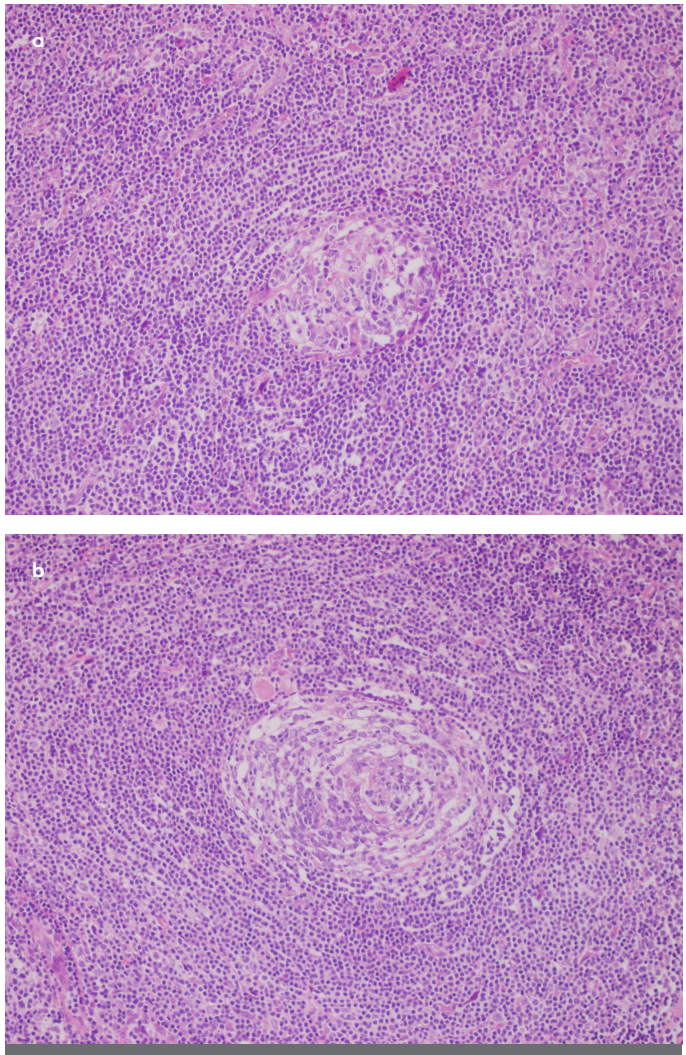

Figure 2. a, b. The microscopic image of the specimen. a) Mantle cells tend to form concentric rings. b) Expanded mantle zone and hypervascular interfollicular region

ing the left renal vein at 360° with a length of 1 cm. Perioperative frozen examination was reported to be compatible with lymphoid tissue, and partial resection was performed owing to renal vein involvement. The patient was discharged on the second postoperative day without any complications. Histopathological diagnosis was hyaline vascular-type CD (Figure 2a and b). There was no change in the size of the mass on the CT performed in the first postoperative year, and no other focus was detected.

DISCUSSION

CD is a rare cause of lymphadenopathy. The pathophysiology has not yet been clarified owing to the lack of large patient studies that allow controlled studies. When it was first described by Castleman in 1956, it was described as a chronic nonspecific inflammatory formation in terms of the histological pattern (5). Owing to systemic symptoms, such as fever, and lymphadenopathy and histopathological features, the etiology of the disease has been focused on viral stimulation. UCD is more benign than multicentric CD and is divided into 2 histological types (1). The hyaline vascular type, which constitutes 90% of the cases, may present with compression symptoms, but they are usually asymptomatic and are incidentally detected (4). The plasma cell type is seen in 10% of the cases, and this type is mostly detected as mesenteric and retroperitoneal (2, 4). Although there is no randomized study, complete excision of the mass is sufficient and is the gold standard method in the treatment of UCD (4). In cases where total surgical excision is not possible, partial removal of the mass has also been reported to be beneficial. Recurrence is very rare and is usually associated with incomplete resection or missed lymph nodes in the first surgery. Systemic symptoms and laboratory abnormalities, if any, are eliminated by total resection (2, 6, 7).

Main Points:

- Castleman's disease (CD) is a rare cause of lymphadenopathy. Its pathophysiology is unclear. It is usually asymptomatic and is incidentally detected.
- The treatment of unicentric CD is complete removal of the mass, and its recurrence is very rare.
- CD should always be kept in mind in the differential diagnosis of retroperitoneal masses.

In conclusion, although UCD is a rare condition, it should always be kept in mind in the differential diagnosis of retroperitoneal masses.

Informed Consent: Written informed consents were obtained from the patients who participated in this study for this study and also to publish photos of the patient.

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Conflict of Interest: Authors have no conflicts of interest to declare.

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Letter to Editor

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Levetiracetam Responsive in Late-Onset Idiopathic Paroxysmal Kinesigenic Dyskinesia

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CASE PRESENTATION

A 70-year-old male patient presented to the neurology department of Burhan Nalbantoglu State Hospital, Nicosia, Cyprus, in April 2014 with subtle abnormal movements of the upper and lower limbs. His dyskinesias were triggered by a sudden movement only while getting in or out of the car. During the initial months, attacks consisted of abrupt choreoathetoid movements of the right arm alone; however, subsequent attacks included choreoathetoid movements of the right leg as well. There was no alteration in the level of consciousness. The events lasted 5 to 10 seconds. General physical and neurological examination of the patient produced unremarkable results. Magnetic resonance imaging of the brain, ictal electroencephalographic study, and laboratory studies (complete blood count, urine screen, comprehensive metabolic panel, thyroid function tests, and antithyroid antibodies, antinuclear antibodies, copper, and ceruloplasmin level tests) were negative or within the normal limits. Because the patient was diagnosed with paroxysmal kinesigenic dyskinesia (PKD), mutation of the PRRT2 gene was investigated and was found negative. The patient was treated with 200 mg carbamazepine twice a day, but he was not episode free. Carbamazepine was stopped owing to hyponatremia, and the patient was switched to 500 mg levetiracetam twice a day. The patient achieved complete resolution of signs with levetiracetam monotherapy. On follow-up, the patient was dyskinesia free, and no side effects were reported thereafter.

DISCUSSION

Paroxysmal dyskinesia (PD) is a rare neurological syndrome characterized by involuntary, intermittent movements manifested by dystonia, chorea, athetosis, ballism, or any combination of these hyperkinetic disorders (1). Demirkiran et al. (2) adopted the term PD and divided it into 4 categories: PKD, paroxysmal nonkinesigenic dyskinesia, paroxysmal exertion-induced dyskinesia, and paroxysmal hypnogenic dyskinesia. Each type has been subdivided into short-lasting (≤5 minutes) and long-lasting (>5 minutes) subtypes, and each subtype has been subdivided into idiopathic and secondary (2). Because PKD is clinically relatively uncommon and because the cases reported in the literature mostly occurred at younger ages (1), we therefore reported a late-onset idiopathic PKD in a male patient aged 70 years and a complete resolution of the symptoms with levetiracetam monotherapy.

The etiopathogenesis of PKD is still unclear. The most common type is familial PKD, which is caused by mutation of the PRRT2 gene (3). In light of abnormal electroencephalography results of some patients and the good response to anticonvulsants, PKD is considered a form of reflex epilepsy. The diagnosis of PKD is based on the clinical history. Carbamazepine and phenytoin are usually considered the first-choice drugs (4, 5). If they are contraindicated or not effective, other anticonvulsants can be administered (5). The right choice of medications decreases the frequency of attacks or even leads to complete resolution, as in our case. The case we described is an exceptional one because the patient had the first symptoms when he was aged 68 years. The only trigger of his attacks was getting in or out of the car. The duration of his attacks was only up to 10 seconds, and he never lost consciousness. None of his relatives had a similar attack, making our patient the only PKD case in his family.

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