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Address: Büyükdere Cad. No: 105/9 34394 Mecidiyeköy, Şişli-İstanbul
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com

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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).

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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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Phone: +90 212 217 17 00
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Web page: avesyayincilik.com
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Instruction to Authors

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Editorial And Publication Process
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2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
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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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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
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Title page: A separate title page should be submitted with all submissions and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, highest academic degree(s), and ORCID IDs of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number), and 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 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.

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

Data Sharing

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

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

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 1 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.

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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

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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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 I 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 I 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)"

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.
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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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Editorial

Dear readers,

I don't know how to begin with, but I can tell that we are very sad and sorry for those that are suffering of those who died from the new Coronavirus Covid-19 infection all over the world. We are also very sorry for our colleagues who lost their lives on duty. For us, they are heroes. While I am writing this, the number of infected people has come close to 800.000, and the death toll has risen to 38.000. As we also feel in our country, there is a danger of shortages of medical supplies. It could be disastrous for the economy, which has already been affected.

We can imagine from this pandemic that in the future, the diseases that will threaten people's health very seriously will be infectious diseases. All countries must have gotten a lesson from this outbreak, and they will probably design their health systems and strategies according to this.

Cyprus Journal of Medical Sciences, like all other journals, will be very welcome to publish any type of manuscripts related to the Covid-19 infectious disease.

We have to remember that apart from fighting the disease, we should sit and think where we made wrong. Hopefully, we will recover soon, but if we don't change ourselves and our strategies of life, this might recur. Solidarity is important. Peace is important. Respect for nature, animals, and plants is important. They have the same rights as us to live in this world.

As the Editor-in-Chief of the Cyprus Journal of Medical Sciences, I wish a healthier and peaceful life for everyone. I hope that all countries recover soon. I also wish good luck to my colleagues, who are working to find a vaccine or medicine for the treatment of the disease.

Best regards,

Sonuç Büyük
Editor-in-Chief

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Original Article

DOI: 10.5152/cjms.2020.866

The Prevalence and Patient Characteristics of Primary Antibody Deficiencies in a Tertiary Care Setting in North Cyprus

Özel Yürüker[1], Burçin Şanlıdağ[2], Nerin Nadir Bahçeciler[2]

[1]Department of Immunology, University of Kyrenia School of Medicine, Kyrenia, Cyprus
[2]Department of Pediatrics, Near East University School of Medicine, Nicosia, Cyprus

ORCID IDs of the authors: O.Y. 0000-0002-9770-076I; B.S. 0000-0003-I0II-475X; N.B. 0000-0003-I337-204I.

Cite this article as: Yürüker O, Şanlıdağ B, Bahçeciler NN. The Prevalence and Patient Characteristics of Primary Antibody Deficiencies in a Tertiary Care Setting in North Cyprus. Cyprus J Med Sci 2020; 5(I): I-6.

BACKGROUND/AIMS
Primary antibody deficiencies (PADs) are the most common group of primary immunodeficiency disorders that present with a wide range of clinical features. We conducted this study to evaluate the frequency and characteristics of patients with PADs.

MATERIAL and METHODS
The medical records of I60 children (M:F 99:6I, mean age 42.39±28.44 months) were retrospectively reviewed from the Near East University Hospital database. Children who had PADs were then compared according to their demographic, clinical, and laboratory findings.

RESULTS
A total of 97 children were diagnosed with PADs (49 THGI, 3I IgGD, I SIgAD, 8 CVID, 6 IgMD, and 2 PHGI)*. Patients with THGI had the youngest age at the time of diagnosis (27±I6.40 months), and those with CVID had the oldest age at the time of diagnosis (8I.62±49.9 months old) compared with children in other PAD groups. In the HGG group, 63.9% of children presented with both recurrent wheezing/cough and infections, 22.7% had only recurrent infection, I3.4% of them had only recurrent wheezing/cough, and 7I.7% of the children were atopic. At the end of the 2-year follow-up period, 8 patients (5 THGI and 3 IgGSD) out of 70 with HGG recovered.

CONCLUSION
PADs generally present with recurrent infections and/or recurrent bronchoconstriction unresponsive to standard asthma treatment. Evaluation of the immune system is important to increase the quality of life of these patients and also decrease the healthcare costs.

Keywords: Allergy, hypogammaglobulinemia, immunoglobulin, recurrent infections

INTRODUCTION

Primary immunodeficiency disorders (PID) are defined on the basis of the component of the body's immune system that is missing or not functioning properly (I). These disorders are caused due to hereditary genetic defects. Approximately 300 single gene disorders have been reported with underlying symptoms, including recurrent infections, allergy, autoimmunity, and malignancy (2). Hypogammaglobulinemia (HGG) is one of the major groups of PIDs that is caused due to various defects in the B-cell lineage or B-cell function resulting in low levels of immunoglobulins in the blood circulation. This affects the body's immune response and causes a broad spectrum of clinical features ranging from asymptomatic diseases to severe and recurrent infections, chronic inflammation, and autoimmunity (3). Major B-cell immunodeficiencies include transient hypogammaglobulinemia of infancy (THGI), IgM deficiency (IgMD), Bruton agammaglobulinemia, selective IgA deficiency (SIgAD), IgG subclass deficiency (IgGSD), and common variable immunodeficiency (CVID) (4).

The majority of patients can lead normal lives by taking prophylactic antibiotics. However, those with severe infections require intravenous immune serum globulin (IVIG) treatments (5).

***Abbreviations:** CVID, common variable immune deficiency; THGI, transient hypogammaglobulinemia of Infancy; PHGI, protracted hypogammaglobulinemia of infancy; IgMD, IgM deficiency; SIgAD, selective IgA deficiency; IgGSD, IgG subclass deficiency.

Corresponding Author: Özel Yürüker
E-mail: ozel.yuruker@yahoo.com

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Epidemiological studies have reported geographical and racial variations in both the prevalence and pattern of immunodeficiencies (6). In adults, IgA deficiency is the most common disorder (1:400–800). Bruton (X-linked) agammaglobulinemia affects 1 in 10,000–200,000 males, whereas females do not manifest any clinical symptoms as they are only carriers (7). The incidence rate of CVID is 1:10,000–50,000 depending on particular race (1).

The national registry for incidence and prevalence rates of PID diseases is currently not available in North Cyprus. Early diagnosis of hypogammaglobulinemia is important to prevent fatal results and complications during the follow-up period of their current symptoms.

In the present study, we aimed at determining the rate of any humoral PID diseases among children who were admitted to our hospital, which is a tertiary care setting in North Cyprus.

MATERIAL AND METHODS

Ethical Approval
This study was approved by the Institutional Ethics Evaluation Board (2017/43-359) on January 18, 2017.

Informed Consent
Informed consent was not necessary as this was a retrospective study.

Study Population
This investigation was designed as a single-center retrospective study including those children who were under follow-up in the Division of Paediatric Allergy and Immunology in the tertiary hospital in Cyprus for a 3-year interval.

Children who had recurrent infection (8-10) and/or recurrent wheezing/cough and were unresponsive to standard asthma medications (11) were investigated for HGG.

Children who did not apply to the Division of Paediatric Allergy and Immunology and/or had secondary immunodeficiencies, e.g., HIV, were excluded based on a commercially available ELISA test combo reagent kit for detecting HIV Ag/Ab (Architect System, Abbott, Wiesbaden, Germany).

Study Design
The demographic, clinical, and laboratory data of the children included in this study were collected from the hospital's database retrospectively.

Main Points:

- The admission to the hospital of PAD patients were mainly, recurrent infections and/or recurrent bronchiolitis unresponsive to standard asthma treatment.
- THGI had been found to be the major subgroup of PAD in which 10% of them recovered in a 2 year follow up period.
- Early diagnosis and the follow up period of PAD are important in order to increase the quality of life of the patients as well as to decrease the healthcare costs.

Details regarding gender, age, family history of immunodeficiency, allergy, recurrent infections, follow-up period, remission of hypogammaglobulinemia, initial and final treatments, serum Ig levels, IgG subgroup levels, lymphocyte subset percentages, specific antibody responses, skin prick test, or allergen-specific IgE results were recorded.

Follow-up Period and Treatment
Patients who had fewer than six mild infections in a year were not given prophylactic treatment.

Patients who had more than six infections such as upper respiratory tract infections, otitis media, sinusitis, and gastroenteritis requiring antibiotic treatment were administered an oral prophylactic treatment with trimethoprim-sulfamethoxazole (Trim-Sulf).

Those who failed to respond to the oral antibiotic prophylaxis and those who required hospitalization two or more times a year due to severe infections such as pneumonia, bronchopneumonia, and cellulitis were administered IVIG at a dosage of 0.5 g/kg every 21 days.

For the treatment of asthma, inhaled corticosteroids (ICSs) were used as a first-line medication. The dosage of ICSs was adjusted according to the severity of symptoms based on GINA guideline recommendations (11). The patients were examined every 2 months to adjust the ICS dosage.

The immune system was evaluated by measuring the serum Ig and IgG subclass levels. Further tests such as determination of the lymphocyte subset percentages and the specific antibody responses were performed if indicated by the clinician.

Laboratory Studies

Atopy
For the determination of the presence of atopy, skin prick tests were performed using 21 common aeroallergens, including *Dermatophagoides farinae, D. pteronyssinus, Alternaria, Aspergillus mix, Penicillium* mix, *Candida albicans,* Betulaceae, *Aesculus hippocastanum, Olea europaea, Plantago, Artemisia, Parietaria, Secale cereale, Triticum vulgaris, Acacia dealbata,* and a mixture of five grasses, feathers, cat hair, dog hair, and cockroach (Stallergenes, Antony, France). Histamine and saline were used as positive and negative controls, respectively. A drop of each allergen extract was placed on the volar surface of the left forearm and penetrated using a staller point. After 15 min, the wheal reaction was measured as the mean of the longest diameter and the diameter perpendicular to it. A wheal diameter of at least 3 mm greater than that in the negative control was considered as positive.

Immunological Tests
All the equipment used for laboratory analyses are calibrated routinely in the laboratory of our hospital. Furthermore, negative and positive control samples were used before analyzing the patient's serum samples.

Assessment of Immunoglobulin Levels
Peripheral venous blood samples of the patients were centrifuged at 2000× g for 10 min to obtain serum.

Serum IgG, IgA, and IgM levels were measured by the turbidimetric method using Roche Cobas c311 and commercially available kits (Roche Diagnostics, Mannheim, Germany).

Serum IgE levels were measured by fully automated ELISA, Roche Cobas e411 using commercially available kits (Roche Diagnostics, Mannheim, Germany).

Serum IgG subclasses (IgG1, IgG2, and IgG3) were evaluated by nephelometry using commercially available kits.

All Ig results were evaluated according to the normal±2SD values based on the levels of healthy Turkish children according to age (12). Values lower than 2SD were accepted as low.

Lymphocyte Subset Analysis

Lymphocyte subpopulation analysis was performed by flow cytometry (BD FACS Calibur, BD Biosciences, San Jose, CA, USA). Lymphocyte subsets derived from peripheral blood were counted by fluorescence-activated cell sorting (FACS), including total lymphocytes (CD45+), total T cells (CD3), helper T cells (CD3+/CD4+), cytotoxic T cells (CD3+/CD8+), B cells (CD19+), NK cells (CD16/56+), and active T cells (CD3/anti-HLA DR). The results were evaluated according to the normal±2SD values based on the age of Turkish children (13). Values lower than 2SD were accepted as low.

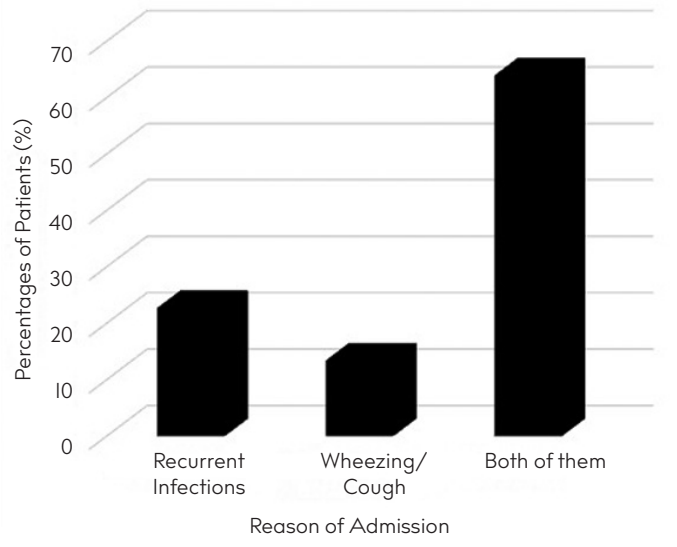

FIGURE 1. Number of patients with HGG according to the reason of admission
HGG: hypogammaglobulinemia

Antigen-specific Antibody Response

Antigen-specific antibody responses were evaluated by anti-tetanus toxoid IgG antibody levelEuroImmune IgG ELISA (catalog no: EI 2060-9601 G) Pneumococcus IgG, ELİZEN/ ZenTech (catalog no: E-DG-96), and anti-Hbs, fully automated ELİSA Roche Cobas e411 (catalog no: EI 2060-9601 G) using commercially available kits (Roche Diagnostics, Mannheim, Germany).

Statistical Analysis

Statistical analyses were performed using the IBM SPSS software package for Windows (release 20.0.0, SPSS Inc., Chicago, Ill, USA). In the descriptive statistics, prevalence rates were expressed as mean (SD) and percentages. Chi-square, Kruskal–Wallis, and Mann–Whitney U tests were used for analyses. P values <0.05 were considered to be statistically significant.

RESULTS

A total of 160children, including 61 (38.1%) females and 99 (61.9%) males, who met the inclusion criteria were enrolled in this study. Of these children, 35 (21.9%) were admitted with recurrent infections, 25 (16.6%) had with recurrent cough/wheezing, and 100 (62.5%) children had both recurrent infections and recurrent cough/wheezing. After further laboratory investigations, 97 (60.6%) children were diagnosed with humoral PID and defined as the hypogammaglobulinemia (HGG) group (mean±SD age: 43.07±30.67 months, male/female: 66/31). The number, gender, and mean age of these patients were presented according to the type of PID that they had at the time of diagnosis The most frequently diagnosed immune deficiency diseases among the children with HGG were THGI 49 (50.5%) and IgG subclass deficiency 31 (32%). The mean age at the time of diagnosis was 27 months for patients with THGI, 57.35 months for those with IgGSD, 49 months for those with SIgAD, 81.62 months for children with CVID, 40.50 months for those with IgMD, and 66 months for children with protracted hypogammaglobulinemia (PHGI) (Table 1).

In the HGG group, the majority of children (63.9%) had both recurrent wheezing/cough and infections, 22.7% of them had only recurrent infection, and 13.4% of the children presented with only recurrent wheezing/cough that was unresponsive to standard asthma treatment (Figure 1).

Among the 49 children who were diagnosed with THGI, 29 were admitted to the hospital with both recurrent cough/wheezing and recurrent infections, of whom 14 had only recurrent infections and 6 had recurrent wheezing/cough.

Among the majority of children who were diagnosed with IgG subgroup deficiency, 20 (64.5%) had recurrent infection togeth-

TABLE 1. Patients' demographic data according to their PADs

	THGI	IgGSD	SIgAD	CVID	IgMD	PHGI
Number						
n (%)	49 (50.5)	31 (32)	1 (1)	8 (8.2)	6 (7.9)	2 (2.1)
Gender (Male/Female)	37/12	16/15	1/0	5/3	5/1	2/0
Age at the time of Diagnosis (months±SD)	27.00±16.40	57.35±29.05	49.00±0.00	81.62±49.96	40.50±18.45	66.00±7.07

PAD: primary antibody deficiency; CVID: common variable immune deficiency; THGI: transient hypogammaglobulinemia of Infancy; PHGI: protracted hypogammaglobulinemia of infancy; IgMD: IgM deficiency; SIgAD: selective IgA deficiency; IgGSD: IgG subclass deficiency.

er with wheezing/cough, 6 (19.3%) had only recurrent infection, and 5 had only wheezing/cough.

Patients who were admitted to the Division with complaints of only asthmatic symptoms belonged to the THGI, Ig subgroup deficiency, PHGI and IgM deficiency groups, 6 (12.2%), 5 (16.1%), 1 (100%), and 1 (100%) in numbers respectively (Table 2).

TABLE 2. Reasons of admission among patients with PAD

	Diagnosis at admission n (%)		
PADs (n=97)	**Recurrent Infection**	**Recurrent wheezing/ cough**	**Both of them**
THGI (n=49)	14 (28.6%)	6 (12.2%)	29 (59.1%)
IgGSD (n=31)	6 (19.4%)	5 (16.1%)	20 (64.5%)
SIgAD (n=1)	0 (0.0%)	0 (0.0%)	1 (100%)
CVID (n=8)	1 (100%)	0 (0.0%)	7 (87.5%)
IgMD (n=6)	0 (0.0%)	1 (100%)	5 (83.3%)
PHGI (n=2)	1 (100%)	1 (100%)	0 (0.0%)

PAD: primary antibody deficiency; CVID: common variable immune deficiency; THGI: transient hypogammaglobulinemia of Infancy; PHGI: protracted hypogammaglobulinemia of infancy; IgMD: IgM deficiency; SIgAD: selective IgA deficiency; IgGSD: IgG subclass deficiency.

TABLE 3. Family history of allergic diseases, PADs, and consanguineous marriage for patients with PAD

	Family History		
	Allergic Diseases	**PAD**	**Consanguineous Marriage**
PADs (n=97)	**No of cases (%)**		
THGI (n=48)	18 (37.5)	1 (2.0)	2 (4.2)
IgGSD (n=30)	19 (63.3)	2 (6.7)	0 (0.0)
SIgAD (n=1)	0 (0.0)	0 (0.0)	0 (0.0)
CVID (n=7)	4 (57.14)	1 (14.3)	0 (0)
IgMD (n=6)	3 (50)	2 (33.3)	1 (16.7)
PHGI (n=1)	0 (0.0)	0 (0.0)	0 (0.0)

PAD: primary antibody deficiency; CVID: common variable immune deficiency; THGI: transient hypogammaglobulinemia of Infancy; PHGI: protracted hypogammaglobulinemia of infancy; IgMD: IgM deficiency; SIgAD: selective IgA deficiency; IgGSD: IgG subclass deficiency.

TABLE 4. Medications that were given to patients with PAD

Diagnosis (n)	**Trim-sulf n (%)**	**IVIG n (%)**	**Trim-sulf + IVIG n (%)**	**No. of patients requiring treatment n (%)**
THGI (n=49)	16 (32.7)	1 (2)	-	17 (17)
CVID (n=8)	6 (75)	1 (12.5)	-	7 (87.5)
IgGSD (n=31)	9 (29)	-	-	9 (29)
IgMD (n=6)	-	-	1 (16.7)	1 (16.7)

PAD: primary antibody deficiency; CVID: common variable immune deficiency; THGI: transient hypogammaglobulinemia of Infancy; PHGI: protracted hypogammaglobulinemia of infancy; IgMD: IgM deficiency; SIgAD: selective IgA deficiency; IgGSD: IgG subclass deficiency; Trim-Sulf: Trimethoprim/sulfamethoxazole; IVIG: Intravenous immunoglobulin.

Among the HGG group, 71.7% of patients were sensitive to at least one allergen. Atopy was present in 53.1% of children in the non-HGG group (Figure 2).

The highest rate of atopy was observed in patients with Ig subgroup deficiency [17/23 (73.9%)], followed by patients with THGI [17/25 (68%)].

Among the group with primary antibody deficiencies (PADs; 97 patients), 60 patients were evaluated for atopy, and it was detected in 43/60 (71.7%) children with PADs. Among these patients, 17/25 (68%) had THGI, 17/23 (73.9%) had IgGSD, 5 (83.3%) had CVID, and 2 (50%) had IgMD.

Children in the HGG group were further evaluated based on the family history of allergic diseases, PADs, and consanguineous marriage of parents, whose prevalence rates were found to be 48.4%, 6.4%, and 3.2%, respectively.

Children who were diagnosed with IgMD had the highest prevalence of positive family history for both allergic diseases (50%) and PADs (33.3%) and also for the presence of consanguineous marriage among their parents (16.7%) (Table 3).

Treatment Follow-up

Patients with HGG were followed up for 2–48 months, with a mean follow-up period of 13 months.

Among patients with HGG, 3 (3.1%) were under IVIG treatment, 31 (32%) were under Trim-Sulf prophylaxis, and 25 (26.9%) were followed up without any medication.

Medications that were administered to the patients are summarized in (Table 4).

A total of 70 patients who had hypogammaglobulinemia were followed up for 2 years. During this period, eight patients had recovered, including five in the THGI group and three in the IgG3 subgroup deficiency group, indicating recovery rates of 4/40 (12.5%) and 3/17 (17.6%), respectively, during the 2-year follow-up.

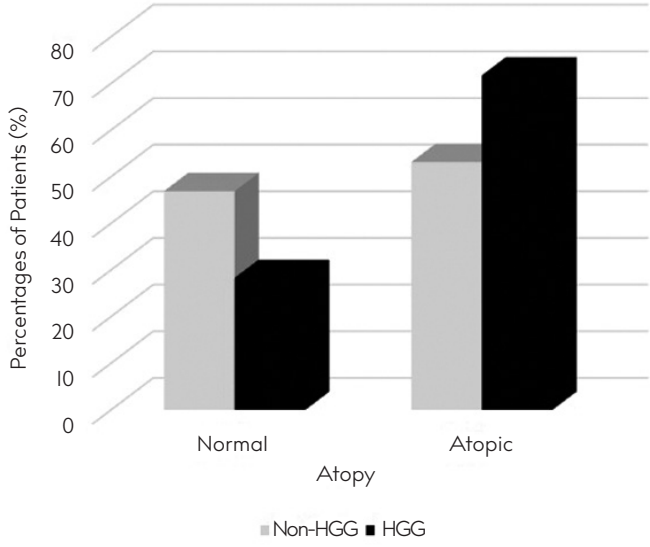

FIGURE 2. Presence of atopy in the non-HGG and HGG groups
HGG: hypogammaglobulinemia

DISCUSSION

Among the 160 children evaluated for PADs who had presented with recurrent infections and/or recurrent wheezing/cough, 97 (60.6%) were identified as having HGG.

THGI was the most frequently diagnosed group of HGG that affected approximately half of our study population. This result was in accordance with a study performed in Turkey (6) reporting THGI as the most frequently detected PAD with a prevalence rate of 7/100,000. On the other hand, studies from Europe, Australia, and Japan reported SIgAD as the most common type of PAD (3, 14-16). In addition, CVID was reported as the most frequently diagnosed PAD in Ireland, Norway, and Egypt (17-19).

Especially in CVID cases, high prevalence of consanguineous marriage and autosomal recessive trait were claimed to be the reason for the high prevalence (3). In a study reported from Turkey, the rate of consanguineous marriage among the parents of children with PAD was found to be 9.7% (8), which was higher than that in our study population (3%).

In our study, males (61.9%) were more affected with PADs than females (38.1%), which was consistent with studies from Turkey, Europe, Iran, Kuwait, Israel, and Australia (8, 20-24).

IgG subgroup deficiency was the second most common type of PAD in our study population. The majority of cases belonged to the IgG3 deficiency group (96.77%), and one patient belonged to the IgG2 deficiency group (3.2%). In a previous study, the prevalence of IgG subgroup deficiency was reported to be 4.6/100,000, making it the third most common type of antibody deficiency (8). Karaca et al. (25) reported that IgG3 deficiency was the most common IgG subgroup deficiency with a prevalence rate of 77%, whereas isolated IgG2 deficiency was detected in 9% of the patients. In another study, IgG2 deficiency was reported as the leading IgG subgroup deficiency (25).

In our study, patients with THGI had the youngest age at the time of diagnosis (27±16.40 months), and those with CVID had the oldest age at the time of diagnosis (81.62±49.9 months old) compared with children in other PAD groups. These results were consistent with those of previous studies, e.g., 16.8 months for THGI cases and60 months for CVID cases at the time of diagnosis (26) and45.12±31.08 months for THGI cases and87.96±58.44 months for CVID cases (27). In general, the majority of patients with CVID are diagnosed in late adolescence (28), which may be one of the reasons for the lower prevalence in our study.

In our study, recurrent infection was the most common presenting clinical feature in children with PADs (86.6%), which was consistent with the studies done in Turkey (58%) (6), Iran (89.6%) (3), Taiwan (54.5%) (29), and USA (87%) (30).

Among patients with PADs, 13 (13.4%) were admitted to the Division with only recurrent bronchoconstriction and wheezing. Among the PAD group of patients, six (4.6%) had THGI, five (3.8%) had IgG subgroup deficiency, 1 (7.7%) had PHGI, and 1 (7.7%) had IgM deficiency who presented with only asthmatic symptoms. In different studies, 5.4% (3) and 36.4% (26) of patients with PAD were reported to have asthmatic symptoms. In addition, 7%–8% of children with sIgMD were reported to have allergic diseases and asthma (31). In our study, despite the high atopy rates among patients with IgMD (50%), 16.6% of them had allergic asthma. Karaca et al. (25) reported 15% of atopy in Turkish children with IgG subgroup deficiency, and Chong et al. (25) reported 40% of allergic cases. In our study, 23 of the 31 patients were evaluated for atopy, and 17 (73.9%) were found to be atopic. Atopy was much more common in our patients with PAD compared to that in other studies.

In addition to infections, it has been reported that allergic symptoms occur as the first clinical manifestations of PADs (4.2%) (3), as also found in our study. The tendency to develop allergy among patients with SIgAD (22.2%) has been reported to be higher than that of other types of PADs (32, 33). However, in our study, children with IgGSD (73.9%), followed by those with THGI (68%), had higher rates of atopy. A dysregulation in the immune response contributing to defective antigen elimination in early childhood has been postulated to be a critical risk factor for the development of allergy (31).

The treatment given to these patients depends on the severity and frequency of symptoms. Mild cases with PAD can be observed without any treatment. Ig replacement is one of the important treatments in PAD. Three (8.8%) patients had received IVIG therapy.

Regarding the study limitations, larger number of patients could be included and the follow-up period could be extended to decide the number and type of certain PADs more clearly. Another limitation was that some of the patients had stopped coming for follow-up to our hospital according to their own will, so that we could not analyze any data obtained during the follow-up period, which reduced the amount of obtained information about the patients after the long-term follow-up.

In conclusion, early diagnosis and treatment of PAD are important for decreasing the morbidity and increasing the quality of life of those patients. Appropriate and early treatment would also decrease the healthcare costs. PADs have the highest prevalence among PIDs in several countries. In our study, the THGI and IgG subgroup deficiencies were the most common antibody deficiencies that may present not only with recurrent infections but also with recurrent bronchoconstriction unresponsive to standard asthma treatment. Evaluation of the immune system should be considered in children presenting with these types of clinical symptoms.

Creating a successful registry of PADs in North Cyprus would provide authorities adequate information for developing strategies for both diagnosis and treatment of patients with PADs.

Ethics Committee Approval: Ethics committee approval was received for this study from the Near East University Scientific Research Ethics Evaluation Board (Approval Date: 18.01.2017, Approval Number: YDU/2017/43-359).

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

Peer-review: Externally peer-reviewed.

Author contributions: Concept - N.B., B.S.; Design - B.S., O.Y.; Supervision - N.B.; Resource - B.S., O.Y.; Materials - N.B.; Data Collection and/or Processing - B.S., O.Y.; Analysis and/or Interpretation - B.S., O.Y.; Literature Search - B.S., O.Y.; Writing - B.S., O.Y.; Critical Reviews - N.B.

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

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Original Article

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Top 100-Cited Articles in Tinnitus: A Bibliometric Analysis

Seyit Mehmet Ceylan

Department of Otolaryngology, Sanko University School of Medicine, Gaziantep, Turkey

ORCID ID of the author: S.M.C. 0000-0002-8908-3345.

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BACKGROUND/AIMS
This study aimed to identify and analyze the top 100 cited articles about tinnitus research.

MATERIAL and METHODS
Using the Web of Science database, we searched the term "tinnitus" from 1900 to date and ordered the articles sequentially based on the highest to the lowest total number of citation. Then, we listed the top 100 cited articles and further analyzed them in terms of author, publication year, research category, journal, institution, and country. All data are reported as tabulated values, bar graph, and percentage. No statistical analysis was performed.

RESULTS
The most cited article received 726 citations. With 12 articles, the Hearing research journal published the highest number of articles. Moreover, 51 out of 100 articles originated from the USA. Southern Illinois University with 18 articles ranked the first in the list, followed by the University of Antwerp with 10 articles. Furthermore, 45% and 42% of these articles were categorized under the fields of neuroscience and otorhinolaryngology, respectively.

CONCLUSION
This bibliometric analysis identified the top 100 cited research articles about tinnitus and provided a track record of the historical development and trends in tinnitus research.

Keywords: Article, bibliometric analysis, the most cited, tinnitus

INTRODUCTION

Tinnitus is the phantom sensation of hearing sound without any external acoustic stimulation (1, 2). It is classified as objective tinnitus (observer/doctor can hear the sound during the examination) and subjective tinnitus (only patient can hear the sound) (3). In adult population, the most common type of tinnitus is idiopathic subjective tinnitus (3). While 10% to 15% of the adult population experiences tinnitus, only one in five patients seeks professional treatment (4-6).

The experimental and clinical studies on tinnitus contribute significantly to understanding the pathology and developing an effective strategy for the treatment. However, most of these studies and their impacts are inadequately known by clinicians. In fact, clinical decision to the treatment relies mostly on evidences from high-quality studies. The most important methodological factors to determine a high-quality study are the number of citations received and the impact factor of a journal where the article is published (7-9). In recent years, several articles aiming to analyze the top cited articles in breast cancer (10), septicemia (11), melanoma (12), pancreatitis (13), pulmonary diseases (14), and psychology (15) have been published. For clinicians, such articles involving bibliometric analysis are important to easily access the literature on a specific research field, thereby tracking easily the historical progression of the field. Therefore, identifying the top cited studies on tinnitus would be useful. Accordingly, this study aimed to identify and analyze the top 100 cited articles about tinnitus.

MATERIAL and METHODS

On April 6, 2018, we obtained the data used in this study from the Science Citation Index Expanded (SCI-Expanded) database of Web of Science (WOS) (Clarivate Analytics, USA) without using any restriction on time (1900 to date) and on journals (8500 major journals were included). Using the term "tinnitus," we searched the articles pub-

Corresponding Author: Seyit Mehmet Ceylan
E-mail: drmehmetceylan@hotmail.com

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lished from 1900 to date. Any article that is irrelevant to tinnitus was excluded from the study. A total of 4126 articles published from 1980 to date (April 6, 2018) were found. We then arranged these 4126 articles in a descending order by the number of citation and identified the top 100 cited articles. We analyzed the top 100 cited articles by publication year, country, institution, authors, journals, and research field through the WOS analysis tool. The total number of citation of the identified articles was also cross-checked using the Scopus database. We did not request for an approval from the ethics committee because this study was a retrospective evaluation of publicly available data. Nevertheless, the study was conducted in accordance with the Declaration of Helsinki. No statistical analysis was performed, considering that the results were reported as tables.

RESULTS

When the top 100 cited articles were listed in a descending order according to the number of citation, the most frequently cited article received 726 citations, whereas the least frequently cited article received 105 citations (Table 1). These most cited articles were published between 1980 and 2014 in 25 high-impact journals, and 77 out of these 100 articles were published within 15 years between 1999 and 2014. In 2011, the number of most cited articles peaked with 10 publications (Figure 1). With 12 publications, the *Hearing Research* was the most frequently chosen journal by the authors to publish their articles (Table 2); in particular, 51% of the articles originated in the USA, followed by Germany and then England (Table 3). When analyzing the centers where the articles were published, Southern Illinois University ranked the first, with 18% of all articles, followed by the University of Antwerp with 10% (Table 4). Furthermore, 45% and 42% of these articles were categorized under the fields of neuroscience and otorhinolaryngology, respectively (Table 5). Among the authors who published these articles, de Ridder D. was the most cited author, with 10 articles, followed by Langguth B. with 8 articles (Table 6).

TABLE I. The top 100 cited articles in tinnitus research

Rank	Articles	Citation density	No. of Citations WOS	No. of Citations Scopus
1	Jastreboff PJ. Phantom auditory perception (tinnitus): mechanisms of generation and perception. Neurosci Res. 1990; 8 (4): 221-54.	25,03	726	880
2	Newman CW, Jacobson, GP, Spitzer JB. Development of the tinnitus handicap inventory. Archives of Otolaryngology-Head&Neck Surgery. 1996; 122(2): 143-148	27,65	636	788
3	Jos J. Eggermont, Larry E. Roberts. The neuroscience of tinnitus. Trends in Neurosciences. 2004; 27 (11): 666-682	41,27	619	701
4	Muhlnickel W, Elbert T, Taub E, Flor H. Reorganization of auditory cortex in tinnitus. Proc. Natl. Acad Sci. USA. 1998; 95 (11): 10340–10343	20,33	427	503
5	Lockwood AH, Salvi RJ, Coad ML, Towsley ML, Wack, DS, Murphy BW. The functional neuroanatomy of tinnitus - Evidence for limbic system links and neural plasticity. Neurology. 1998; 50 (1): 114-12	18,38	386	454
6	Jastreboff, PJ; Hazell, JWP. A Neurophysiological Approach to Tinnitus - Clinical Implications. British Journal of Odiology. 1993; 27 (1): 7-17	13,15	342	444
7	Shargorodsky, J; Curhan, GC; Farwell, WR. Prevalence and Characteristics of Tinnitus among US Adults. American Journal of Medicine. 2010; 123 (8): 711-718	36,88	332	365
8	Schaette, R; McAlpine, D. Tinnitus with a Normal Audiogram: Physiological Evidence for Hidden Hearing Loss and Computational Model. Journal of Neuroscience. 2011; 31 (38): 13452-13457	36,5	292	332
9	Lockwood, AH; Salvi, RJ; Burkard, RF. Current concepts: Tinnitus. New England Journal of Medicine. 2002; 347 (12): 904-910	17,11	291	348

Main Points:

- Bibliometric analysis of the top cited articles about tinnitus can provide a platform that allows the researchers to access such articles easily and analyze the studies.
- When analyzing the article list, a significant number (n=52) of paper is about the underlying mechanism of tinnitus.
- The effects of technological developments have been crucial in the advancement of tinnitus research. For example. neuroimaging by functional magnetic resonance imaging and positron emission tomography provides important data for pathophysiology-oriented studies.
- In tinnitus research, the top cited treatment-oriented articles are about repetitive transcranial magnetic stimulation.

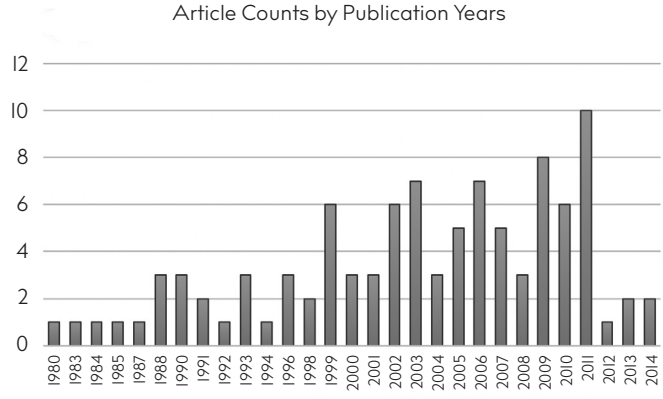

FIGURE I. Distribution of articles by years of publication

TABLE I. The top 100 cited articles in tinnitus research (continued)

Rank	Articles	Citation density	No. of Citations WOS	No. of Citations Scopus
10	Henry, JA; Dennis, KC; Schechter, MA. General review of tinnitus: Prevalence, mechanisms, effects, and management. Journal of Speech Language and Hearing Research. 2005; 48 (5): 1204-1235	20,64	289	320
11	Norena, AJ; Eggermont, JJ. Changes in spontaneous neural activity immediately after an acoustic trauma: implications for neural correlates of tinnitus. Hearing Research. 2003; 183 (1-2): 137-153	17	272	294
12	Heller, AJ. Classification and epidemiology of tinnitus. Otolaryngologic Clinics of North America. 2003; 36 (2): 239-+	16,87	270	317
13	Rauschecker, JP; Leaver, AM; Muhlau, M. Tuning Out the Noise: Limbic-Auditory Interactions in Tinnitus. Neuron. 2010; 66 (6): 819-826	29,88	269	304
14	De Ridder, D; Elgoyhen, AB; Romo, R; Langguth, B. Phantom percepts: Tinnitus and pain as persisting aversive memory networks. Proceedings of The National Academy of Sciences of The United States of America. 2011; 108 (20): 8075-8080	33,37	267	301
15	Brozoski, TJ; Bauer, CA; Caspary, DM. Elevated fusiform cell activity in the dorsal cochlear nucleus of chinchillas with psychophysical evidence of tinnitus. Journal of Neuroscience. 2002; 22 (6): 2383-2390	29,33	264	277
16	Roberts, LE; Eggermont, JJ; Caspary, DM; Shore, SE; Melcher, JR; Kaltenbach, JA. Ringing Ears: The Neuroscience of Tinnitus. Journal of Neuroscience. 2010; 30 (45): 14972-14979	28,44	256	302
17	Tyler, RS; Baker, LJ. Difficulties Experienced by Tinnitus Sufferers. Journal of Speech and Hearing Disorders. 1983; 48 (2): 150-154	6,5	234	284
18	Wilson, JP. Evidence For a Cochlear Origin For Acoustic Re-Emissions, Threshold Fine-Structure and Tonal Tinnitus. Hearing Research. 1980; 2 (3-4): 233-252	5,97	233	227
19	Kuk, FK; Tyler, RS; Russell, D; Jordan, H. The Psychometric Properties of A Tinnitus Handicap Questionnaire. Ear and Hearing. 1990; 11 (6): 434-445	7,90	229	283
20	Hallam, RS; Jakes, SC; Hinchcliffe, R. Cognitive Variables In Tinnitus Annoyance. British Journal of Clinical Psychology. 1988; 27 (3): 213-222	7,26	225	256
21	Norena, A; Micheyl, C; Chery-Croze, S; Collet, L. Psychoacoustic characterization of the tinnitus spectrum: Implications for the underlying mechanisms of tinnitus. Audiology and Neuro-Otology. 2002; 7 (6): 358-369	12,59	214	236
22	Muhlau, M; Rauschecker, JP; Oestreicher, E; Gaser, C; Rottinger, M; Wohlschlager, AM; Simon, F; Etgen, T; Conrad, B; Sander, D. Structural brain changes in tinnitus. Cerebral Cortex. 2006; 16(9): 1283-1288	16,31	212	240
23	Goebel, G; Hiller, W. The Tinnitus Questionnaire (TQ) - A Standardized Instrument For Grading The Severity of Tinnitus - Results of A Multicenter Study Using The TQ. HNO. 1994; 42 (3): 166-172	8,48	212	222
24	Wilson, PH; Henry, J; Bowen, M; Haralambous, G. Tinnitus Reaction Questionnaire - Psychometric Properties of A Measure of Distress Associated With Tinnitus. Journal of Speech and Hearing Research. 1991; 34 (1): 197-201	7,54	211	273
25	Baguley, D; McFerran, D; Hall, D. Tinnitus. Lancet. 2013; 382 (9904): 1600-1607	34,66	208	226
26	Dobie, RA. A review of randomized clinical trials in tinnitus. Laryngoscope. 1999; 109 (8): 1202-1211	10,2	204	251
27	Weisz, N; Moratti, S; Meinzer, M; Dohrmann, K; Elbert, T. Tinnitus perception and distress is related to abnormal spontaneous brain activity as measured by magnetoencephalography. Plos Medicine. 2005; 2 (6): 546-553	13,79	193	239
28	Vanneste, S; Plazier, M; van der Loo, E; Van de Heyning, P; Congedo, M; De Ridder, D. The neural correlates of tinnitus-related distress. Neuroimage. 2010; 52 (2): 470-480	21	189	207
29	Turner, JG; Brozoski, TJ; Bauer, CA; Parrish, JL; Myers, K. Gap detection deficits in rats with tinnitus: A potential novel screening tool. Behavioral Neuroscience. 2006; 120 (1): 188-195	14,54	189	198
30	Leaver, AM; Renier, L; Chevillet, MA; Morgan, S; Kim, HJ; Rauschecker, JP. Dysregulation of Limbic and Auditory Networks in Tinnitus. Neuron. 2011; 69 (1): 33-43	23,25	186	191
31	Melcher, JR; Sigalovsky, IS; Guinan, JJ; Levine, RA. Lateralized tinnitus studied with functional magnetic resonance imaging: Abnormal inferior colliculus activation. Journal of Neurophysiology. 2000; 83 (2): 1058-1072	9,79	186	214
32	Meikle, MB; Henry, JA; Griest, SE; Stewart, BJ; Abrams, HB; McArdle, R; et al. The Tinnitus Functional Index: Development of a New Clinical Measure for Chronic, Intrusive Tinnitus. Ear and Hearing. 2012; 33 (2): 153-176	26,29	184	198
33	Guitton, MJ; Caston, J; Ruel, J; Johnson, RM; Pujol, R; Puel, JL. Salicylate induces tinnitus through activation of cochlear NMDA receptors. Journal of Neuroscience. 2003; 23 (9): 3944-3952	11,5	184	204
34	Jastreboff, PJ; Brennan, JF; Coleman, JK; Sasaki, CT. Phantom Auditory Sensation in Rats - An Animal-Model For Tinnitus. Behavioral Neuroscience. 1988; 102 (6): 811-822	5,90	183	209
35	Kleinjung, T; Eichhammer, P; Langguth, B; Jacob, P; Marienhagen, J; Hajak, G; Wolf, SR; Strutz, J. Long-term effects of repetitive transcranial magnetic stimulation (rTMS) in patients with chronic tinnitus. Otolaryngology-Head and Neck Surgery. 2005; 132 (4): 566-569	13	182	205
36	Moller, AR. Pathophysiology of tinnitus. Otolaryngologic Clinics of North America. 2003; 36 (2): 249-+	11	176	208

TABLE I. The top 100 cited articles in tinnitus research (continued)

Rank	Articles	Citation density	No. of Citations WOS	No. of Citations Scopus
37	Lanting, CP; de Kleine, E; van Dijk, P. Neural activity underlying tinnitus generation: Results from PET and fMRI. Hearing Research. 2009; 255 (1-2): 1-13	17,5	175	181
38	Kaltenbach, JA; Afman, CE. Hyperactivity in the dorsal cochlear nucleus after intense sound exposure and its resemblance to tone-evoked activity: a physiological model for tinnitus. Hearing Research. 2000; 140 (1-2): 165-172	9,16	174	189
39	Arnold, W; Bartenstein, P; Oestreicher, E; Romer, W; Schwaiger, M. Focal metabolic activation in the predominant left auditory cortex in patients suffering from tinnitus: A PET study with [F-18]deoxyglucose. ORL-Journal For Oto-Rhino-Laryngology and Its Related Specialties. 1996; 58 (4): 195-199	7,43	171	203
40	Stouffer, JL; Tyler, RS. Characterization of Tinnitus by Tinnitus Patients. Journal of Speech and Hearing Disorders. 1990; 55 (3): 439-453	5,76	167	203
41	Langguth, B; Kreuzer, PM; Kleinjung, T; De Ridder, D. Tinnitus: causes and clinical management. Lancet Neurology. 2013; 12 (9): 920-930	26,66	160	183
42	Schlee, W; Hartmann, T; Langguth, B; Weisz, N. Abnormal resting-state cortical coupling in chronic tinnitus. BMC Neuroscience. 2009; 10 (11): 1-11	16	160	172
43	Kaltenbach, JA; Zacharek, MA; Zhang, JS; Frederick, S. Activity in the dorsal cochlecar nucleus of hamsters previously tested for tinnitus following intense tone exposure. Neuroscience Letters. 2004; 355 (1-2): 121-125	10,66	160	167
44	Norena, AJ. An integrative model of tinnitus based on a central gain controlling neural sensitivity. Neuroscience and Biobehavioral Reviews. 2011; 35 (5): 1089-1109	19,75	158	173
45	Weisz, N; Hartmann, T; Dohrmann, K; Schlee, W; Norena, A. High-frequency tinnitus without hearing loss does not mean absence of deafferentation. Hearing Research. 2006; 222 (1-2): 108-114	12,15	158	171
46	Andersson, G; Stromgren, T; Strom, L; Lyttkens, L. Randomized controlled trial of Internet-based cognitive behavior therapy for distress associated with tinnitus. Psychosomatic Medicine. 2002; 64 (5): 810-816	9,29	158	191
47	Arndt, S; Aschendorff, A; Laszig, R; Beck, R; Schild, C; Kroeger, S; Ihorst, G; Wesarg, T. Comparison of Pseudobinaural Hearing to Real Binaural Hearing Rehabilitation After Cochlear Implantation in Patients With Unilateral Deafness and Tinnitus. Otology & Neurotology. 2011; 32 (1): 39-47	19,62	157	200
48	Levine, RA. Somatic (Craniocervical) tinnitus and the dorsal cochlear nucleus hypothesis. American Journal of Otolaryngology. 1999; 20 (6): 351-362	7,85	157	188
49	Yang, G; Lobarinas, E; Zhang, LY; Turner, J; Stolzberg, D; Salvi, R; Sun, W. Salicylate induced tinnitus: Behavioral measures and neural activity in auditory cortex of awake rats. Hearing Research. 2007; 226 (1-2): 244-253	12,92	155	163
50	De Ridder, D; Verstraeten, E; Van der Kelen, K; De Mulder, G; Sunaert, S; Verlooy, J; Van de Heyning, P; Moller, A. Transcranial magnetic stimulation for tinnitus: Influence of tinnitus duration on stimulation parameter choice and maximal tinnitus suppression. Otology & Neurotology. 2005; 26 (4): 616-619	11	154	170
51	Landgrebe, M; Langguth, B; Rosengarth, K; Braun, S; Koch, A; Kleinjung, T; May, A; de Ridder, D; Hajak, G. Structural brain changes in tinnitus: Grey matter decrease in auditory and non-auditory brain areas. Neuroimage. 2009; 46 (1): 213-218	15,3	153	166
52	Coles RRA; Baskill JL; Sheldrake JB. Measurement and management of tinnitus Part II. Management. The Journal of Laryngology and Otology. 1985; 99 (1): 1-10	4,5	153	11
53	McCombe, A; Baguley, D; Coles, R; McKenna, L; McKinney, C; Windle-Taylor, P. Guidelines for the grading of tinnitus severity: the results of a working group commissioned by the British Association of Otolaryngologists, Head and Neck Surgeons, 1999. Clinical Otolaryngology. 2001; 26 (5): 388-393.	7,55	151	165
54	Langguth, B; Goodey, R; Azevedo, A; Bjorne, A; Cacace, A; Crocetti, A; et al. Consensus for tinnitus patient assessment and treatment outcome measurement: Tinnitus Research Initiative meeting, Regensburg, July 2006. Tinnitus: Pathophisiology and Treatment.Book Series: Progress in Brain Research. 2007; 166: 525-536	12,42	149	156
55	Mirz, F; Pedersen, CB; Ishizu, K; Johannsen, P; Ovesen, T; Stodkilde-Jorgensen, H. Positron emission tomography of cortical centers of tinnitus. Hearing Research. 1999; 134 (1-2): 133-144	7,4	148	180
56	Jastreboff, PJ; Gray, WC; Gold, SL. Neurophysiological approach to tinnitus patients. American Journal of Otology. 1996; 17 (2): 236-240	6,30	145	202
57	Van der Loo, E; Gais, S; Congedo, M; Vanneste, S; Plazier, M; Menovsky, T; Van de Heyning, P; De Ridder, D. Tinnitus Intensity Dependent Gamma Oscillations of the Contralateral Auditory Cortex. Plos One. 2009; 10 (4): 1-5	14,2	142	152
58	Gu, JW; Halpin, CF; Nam, EC; Levine, RA; Melcher, JR. Tinnitus, Diminished Sound-Level Tolerance, and Elevated Auditory Activity in Humans With Clinically Normal Hearing Sensitivity. Journal of Neurophysiology. 2010; 104 (6): 3361-3370	15,55	140	151
59	Giraud, AL; Chery-Croze, S; Fischer, G; Fischer, C; Vighetto, A; Gregoire, MC; Lavenne, F; Collet, L. A selective imaging of tinnitus. Neuroreport. 1999; 10 (1): 1-5	7	140	155
60	Plewnia, C; Reimold, M; Najib, A; Brehm, B; Reischl, G; Plontke, SK; Gerloff, C. Dose-dependent attenuation of auditory phantom perception (tinnitus) by PET-guided repetitive transcranial magnetic stimulation. Human Brain Mapping. 2007; 28 (3): 238-246	11,58	139	159

TABLE I. The top 100 cited articles in tinnitus research (continued)

Rank	Articles	Citation density	No. of Citations WOS	No. of Citations Scopus
61	Fregni, F; Marcondes, R; Boggio, PS; Marcolin, MA; Rigonatti, SP; Sanchez, TG; Nitsche, MA; Pascual-Leone, A. Transient tinnitus suppression induced by repetitive transcranial magnetic stimulation and transcranial direct current stimulation. European Journal of Neurology. 2006; 13 (9): 996-1001	10,69	139	154
62	Bauer, CA; Turner, JG; Caspary, DM; Myers, KS; Brozoski, TJ. Tinnitus and inferior colliculus activity in chinchillas related to three distinct patterns of cochlear trauma. Journal of Neuroscience Research. 2008; 86 (11): 2564-2578	12,54	138	146
63	Mirz, F; Gjedde, A; Ishizu, K; Pedersen CB. Cortical networks subserving the perception of tinnitus - a PET study. Acta Oto-Laryngologica Supplement. 2000; 543: 241-243	8,56	137	144
64	Plewnia, C; Bartels, M; Gerloff, C. Transient suppression of tinnitus by transcranial magnetic stimulation. Annals of Neurology. 2003; 53 (2): 263-266	8,19	131	153
65	Moller, AR; Moller, MB; Yokota, M. Some Forms of Tinnitus May Involve The Extralemniscal Auditory Pathway. Laryngoscope. 1992; 102 (10): 1165-1171	4,85	131	157
66	Moller, AR. Pathophysiology of Tinnitus. Annals of Otology Rhinology and Laryngology. 1984; 93 (1): 39-44	3,71	130	157
67	Schlee, W; Mueller, N; Hartmann, T; Keil, J; Lorenz, I; Weisz, N. Mapping cortical hubs in tinnitus. BMC Biology. 2009; 7 (80):-	12,9	129	131
68	Vermeire, K; de Heyning, PV. Binaural Hearing after Cochlear Implantation in Subjects with Unilateral Sensorineural Deafness and Tinnitus. Audiology and Neuro-Otology. 2009; 14 (3): 163-171	12,9	129	147
69	Dobie, RA. Depression and tinnitus. Otolaryngologic Clinics of North America. 2003; 26 (2): 383-+	8	128	153
70	Tonndorf, J. The Analogy Between Tinnitus And Pain - A Suggestion For A Physiological-Basis of Chronic Tinnitus. Hearing Research. 1987; 28 (2-3): 271-275	4	128	144
71	Kaltenbach, JA; Zhang, JS; Finlayson, P. Tinnitus as a plastic phenomenon and its possible neural underpinnings in the dorsal cochlear nucleus. Hearing Research. 2005; 206 (1-2): 200-226.	9	126	141
72	Plewnia, C; Reimold, M; Najib, A; Reischl, G; Plontke, SK; Gerloff, C. Moderate therapeutic efficacy of positron emission tomography-navigated repetitive transcranial magnetic stimulation for chronic tinnitus: a randomised, controlled pilot study. Journal of Neurology Neurosurgery And Psychiatry. 2007; 78 (2): 152-156.	10,33	124	138
73	Schaette, R; Kempter, R. Development of tinnitus-related neuronal hyperactivity through homeostatic plasticity after hearing loss: a computational model. European Journal of Neuroscience. 2006; 23 (11): 3124-3138	9,54	124	147
74	Andersson, G. Psychological aspects of tinnitus and the application of cognitive-behavioral therapy. Clinical Psychology Review. 2002; 22 (7): 977-990	7,29	124	145
75	Yang, S; Weiner, BD; Zhang, LS; Cho, SJ; Bao, SW. Homeostatic plasticity drives tinnitus perception in an animal model. Proceedings of The National Academy of Sciences of The United States of America. 2011; 108 (36): 14974-14979	15,37	123	139
76	Sullivan, MD; Katon, W; Dobie, R; Sakai, C; Russo, J; Harropgriffiths, J. Disabling Tinnitus - Association With Affective-Disorder. General Hospital Psyhiatry. 1988; 10 (4): 285-291	3,93	122	134
77	Kaltenbach, JA. Tinnitus: Models and mechanisms. Hearing Research. 2011; 276 (1-2): 52-60	15	120	131
78	Wang, H; Brozoski, TJ; Turner, JG; Ling, L; Parrish, JL; Hughes, LF; Caspary, DM. Plasticity at Glycinergic Synapses in Dorsal Cchlear Nucleus of Rats With Behavioral Evidence of Tinnitus. Neuroscience. 2009; 164 (2): 747-759	12	120	120
79	Tunkel DE; Bauer CA; Sun GH, at al. Clinical Practice Guideline: Tinnitus. Otolaryngol Head Neck Surg. 2014; 151 (2 Suppl): 1-40	23,8	119	129
80	Smits, M; Kovacs, S; de Ridder, D; Peeters, RR; Van Hecke, P; Sunaert, S. Lateralization of functional magnetic resonance imaging (fMRI) activation in the auditory pathway of patients with lateralized tinnitus. Neuroradiology. 2007; 49 (8): 669-679	9,83	118	134
81	Middleton, JW; Kiritani, T; Pedersen, C; Turner, JG; Shepherd, GMG; Tzounopoulos, T. Mice with behavioral evidence of tinnitus exhibit dorsal cochlear nucleus hyperactivity because of decreased GABAergic inhibition. Proceedings of The National Academy of Sciences of The United States of America. 2011; 108 (18): 7601-7606	14,62	117	131
82	Folmer, RL; Griest, SE; Meikle, MB; Martin, WH. Tinnitus severity, loudness, and depression. Otolaryngology-Head and Neck Surgery. 1999; 121 (1): 48-51	5,85	117	142
83	Hickox, AE.; Liberman MC. Is noise-induced cochlear neuropathy key to the generation of hyperacusis or tinnitus? Journal of Neurophysiology. 2014; 11 (3): 552-564	23,2	116	122
84	Van de Heyning, P; Vermeire, K; Diebl M; et al. Incapacitating unilateral tinnitus in single-sided deafness treated by cochlear implantation. Annals of Otology Rhinology and Laryngology. 2008; 117 (9): 645-652.	10,45	115	195
85	Norena, AJ; Eggermont, JJ. Enriched acoustic environment after noise trauma abolishes neural signs of tinnitus. Neuroreport. 2006; 17 (6): 559-563	8,85	115	126
86	Bauer, CA; Brozoski, TJ. Assessing tinnitus and prospective tinnitus therapeutics using a psychophysical animal model. JARO 2001; 2 (1): 54-64	6,39	115	131

TABLE 1. The top 100 cited articles in tinnitus research (continued)

Rank	Articles	Citation density	No. of Citations WOS	No. of Citations Scopus
87	Hesser, H; Weise, C; Westin, VZ; et al. A systematic review and meta-analysis of randomized controlled trials of cognitive-behavioral therapy for tinnitus distress. Clinical Psychology Review. 2011; 31 (4): 545-553	14,25	114	125
88	Lockwood, AH; Wack, DS; Burkard, RF; Goad, ML; Reyes, SA; Arnold, SA; Salvi, RJ. The functional anatomy of gaze-evoked tinnitus and sustained lateral gaze. Neurology. 2001; 56 (4): 472-480	6,33	114	132
89	Sullivan, M; Katon, W; Russo, J; Dobie, R; Sakai, C. A Randomized Trial of Nortriptyline For Severe Chronic Tinnitus - Effects on Depression, Disability, And Tinnitus Symptoms. Archives of Internal Medicine. 1993; 153 (19): 2251-2259	4,38	114	124
90	Halford, JBS; Anderson, SD. Anxiety And Depression In Tinnitus Sufferers. Journal of Psychosomatic Research. 1991; 35 (4-5): 383-390	4,07	114	143
91	Langguth, B; Landgrebe, M; Kleinjung, T; Sand, GP; Hajak, G. Tinnitus and depression. World Journal of Biological Psychiatry. 2011; 12 (7): 489-500	13,87	111	129
92	De Ridder, D; De Mulder, G; Walsh, V; Muggleton, N; Sunaert, S; Moller, A. Magnetic and electrical stimulation of the auditory cortex for intractable tinnitus - Case report. Journal of Neurosurgery. 2004; 100 (3): 560-564	7,33	110	126
93	Andersson, G; Lyttkens, L. A meta-analytic review of psychological treatments for tinnitus. British Journal of Audiology. 1999; 33 (4): 201-210	5,5	110	137
94	Moller, MB; Moller, AR; Jannetta, PJ; Jho, HD. Vascular Decompression Surgery For Severe Tinnitus - Selection Criteria And Results. Laryngoscope. 1993; 103 (4): 421-427	4,23	110	131
95	Haller, Sven; Birbaumer, Niels; Veit, Ralf . Real-time fMRI feedback training may improve chronic tinnitus. European Rdiology. 2010; 20 (3): 696-703	12	108	114
96	Adjamian, P; Sereda, M; Hall, DA. The mechanisms of tinnitus: Perspectives from human functional neuroimaging. Hearing Research. 2009; 253 (1-2): 15-31	10,8	108	119
97	Koenig, O; Schaette, R; Kempter, R; Gross, M. Course of hearing loss and occurrence of tinnitus. Hearing Research. 2006; 221 (1-2): 59-64	8,31	108	133
98	Baguley, DM. Mechanisms of tinnitus. British Medical Bulletin. 2002; 63: 195-212	6,29	107	124
99	Eichhammer, P; Langguth, B; Marienhagen, J; Kleinjung, T; Hajak, G. Neuronavigated repetitive transcranial magnetic stimulation in patients with tinnitus: A short case series. Biological Psychiatry. 2003; 54 (8): 862-865.	6,62	106	115
100	Roberts, LE; Moffat, G; Baumann, M; Ward, LM; Bosnyak, DJ. Residual Inhibition Functions Overlap Tinnitus Spectra and the Region of Auditory Threshold Shift. JARO-Journal of The Association For Research In Otolaryngology. 2008; 9 (4): 417-435	9,54	105	112

TABLE 2. Journals in which the top 100 cited articles were published

Field: Source Titles	Record Count	% of 100	Bar Chart
HEARING RESEARCH	12	12.000	
JOURNAL OF NEUROSCIENCE	4	4.000	
PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	4	4.000	
JOURNAL OF NEUROPHYSIOLOGY	3	3.000	
LARYNGOSCOPE	3	3.000	
OTOLARYNGOLOGIC CLINICS OF NORTH AMERICA	3	3.000	
OTOLARYNGOLOGY HEAD AND NECK SURGERY	3	3.000	
ANNALS OF OTOLOGY RHINOLOGY AND LARYNGOLOGY	2	2.000	
AUDIOLOGY AND NEURO OTOLOGY	2	2.000	
BEHAVIORAL NEUROSCIENCE	2	2.000	
BRITISH JOURNAL OF AUDIOLOGY	2	2.000	
CLINICAL PSYCHOLOGY REVIEW	2	2.000	
EAR AND HEARING	2	2.000	
JARO JOURNAL OF THE ASSOCIATION FOR RESEARCH IN OTOLARYNGOLOGY	2	2.000	
JOURNAL OF SPEECH AND HEARING DISORDERS	2	2.000	
NEUROIMAGE	2	2.000	
NEUROLOGY	2	2.000	

TABLE 2. Journals in which the top 100 cited articles were published (continued)

Field: Source Titles	Record Count	% of 100	Bar Chart
NEURON	2	2.000	
NEUROREPORT	2	2.000	
OTOLOGY NEUROTOLOGY	2	2.000	
ACTA OTO LARYNGOLOGICA	1	1.000	
AMERICAN JOURNAL OF MEDICINE	1	1.000	
AMERICAN JOURNAL OF OTOLARYNGOLOGY	1	1.000	
AMERICAN JOURNAL OF OTOLOGY	1	1.000	
ANNALS OF NEUROLOGY	1	1.000	

TABLE 3. Countries of origin of the top 100 cited articles

Field: Source Titles	Record Count	% of 100	Bar Chart
USA	51	51.000	
GERMANY	24	24.000	
ENGLAND	14	14.000	
BELGIUM	11	11.000	
CANADA	8	8.000	
FRANCE	8	8.000	
SWEDEN	5	5.000	
NETHERLANDS	3	3.000	
NEW ZEALAND	3	3.000	
SWITZERLAND	3	3.000	
AUSTRIA	2	2.000	
BRAZIL	2	2.000	
DENMARK	2	2.000	
ITALY	2	2.000	
ARGENTINA	1	1.000	
AUSTRALIA	1	1.000	
COLOMBIA	1	1.000	
MEXICO	1	1.000	
PEOPLES R CHINA	1	1.000	
SOUTH KOREA	1	1.000	
SPAIN	1	1.000	

TABLE 4. Institutions of origin

Field: Source Titles	Record Count	% of 100	Bar Chart
UNIVERSITY OF ANTWERP	10	10.000	
SOUTHERN ILLINOIS UNIVERSITY	9	9.000	
SOUTHERN ILLINOIS UNIVERSITY SYSTEM	9	9.000	
HARVARD UNIVERSITY	8	8.000	
UNIVERSITY OF REGENSBURG	8	8.000	
MASSACHUSETTS EYE EAR INFIRMARY	7	7.000	
VA BOSTON HEALTHCARE SYSTEM	7	7.000	
CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE CNRS	6	6.000	

TABLE 4. Institutions of origin (continued)

Field: Source Titles	Record Count	% of 100	Bar Chart
UNIVERSITY OF KONSTANZ	6	6.000	
STATE UNIVERSITY OF NEW YORK SUNY SYSTEM	5	5.000	
UNIVERSITY COLLEGE LONDON	5	5.000	
UNIVERSITY OF CALGARY	5	5.000	
UNIVERSITY OF LONDON	5	5.000	
UNIVERSITY OF TEXAS SYSTEM	5	5.000	
VETERANS HEALTH ADMINISTRATION VHA	5	5.000	
CLEVELAND CLINIC FOUNDATION	4	4.000	
EBERHARD KARLS UNIVERSITY OF TUBINGEN	4	4.000	
GEORGETOWN UNIVERSITY	4	4.000	
PENNSYLVANIA COMMONWEALTH SYSTEM OF HIGHER EDUCATION PCSHE	4	4.000	
STATE UNIVERSITY OF NEW YORK SUNY BUFFALO	4	4.000	
UNIVERSITY OF CALIFORNIA SYSTEM	4	4.000	
UNIVERSITY OF PITTSBURGH	4	4.000	
HUMBOLDT UNIVERSITY OF BERLIN	3	3.000	
MCMASTER UNIVERSITY	3	3.000	
OREGON HEALTH SCIENCE UNIVERSITY	3	3.000	

TABLE 5. Distribution of the articles according to the Web of Science Categories

Field: Web of Science Categories	Record Count	% of 100	Bar Chart
NEUROSCIENCES	45	45.000	
OTORHINOLARYNGOLOGY	42	42.000	
AUDIOLOGY SPEECH LANGUAGE PATHOLOGY	17	17.000	
CLINICAL NEUROLOGY	10	10.000	
MEDICINE GENERAL INTERNAL	6	6.000	
PSYCHIATRY	6	6.000	
SURGERY	6	6.000	
MULTIDISCIPLINARY SCIENCES	5	5.000	
RADIOLOGY NUCLEAR MEDICINE MEDICAL IMAGING	5	5.000	
NEUROIMAGING	4	4.000	
BEHAVIORAL SCIENCES	3	3.000	
LINGUISTICS	3	3.000	
MEDICINE RESEARCH EXPERIMENTAL	3	3.000	
PHYSIOLOGY	3	3.000	
PSYCHOLOGY CLINICAL	3	3.000	
REHABILITATION	2	2.000	
BIOLOGY	1	1.000	
LANGUAGE LINGUISTICS	1	1.000	
PSYCHOLOGY	1	1.000	
PSYCHOLOGY MULTIDISCIPLINARY	1	1.000	

DISCUSSION

Bibliometric analysis is a frequently applied quantitative method in many areas for different purposes; for instance, it can help track the historical development of a research field and research trends (16). Therefore, bibliometric analysis of the top cited articles about tinnitus can provide a platform that allows the researchers to access such articles easily and analyze the studies. Furthermore, it can provide an opportunity to observe

TABLE 6. Authors who contributed three or more of the top 100 cited tinnitus research articles

Field: Authors	Record Count	% of 100	Bar Chart
DE RIDDER D	10	10.000	
LANGGUTH B	8	8.000	
KLEINJUNG T	6	6.000	
BAUER CA	5	5.000	
BROZOSKI TJ	5	5.000	
HAJAK G	5	5.000	
KALTENBACH JA	5	5.000	
ANDERSSON G	4	4.000	
CASPARY DM	4	4.000	
EGGERMONT JJ	4	4.000	
JASTREBOFF PJ	4	4.000	
MOLLER AR	4	4.000	
RAUSCHECKER JP	4	4.000	
TURNER JG	4	4.000	
TYLER RS	4	4.000	
VAN DE HEYNING P	4	4.000	
WEISZ N	4	4.000	
EICHHAMMER P	3	3.000	
ELBERT T	3	3.000	
GERLOFF C	3	3.000	
HARTMANN T	3	3.000	
HENRY JA	3	3.000	
LANDGREBE M	3	3.000	
LEVINE RA	3	3.000	
LOCKWOOD AH	3	3.000	

the research trend and can give the researchers a clue for future studies.

Our bibliometric analysis showed that 80% of the top 100 cited articles about tinnitus were published within the past 2 decades. The reason may be that published articles have increased overall and have a widespread internet access for literature search within the past 20 years (12, 17). Given the fact that the number of citation is closely proportional to the publishing date (18-21), such as the snowball phenomenon (22), the more recent articles most likely received less citation than the earlier articles. Not surprisingly then, articles published since 2014 could not be part of the list, highlighting the effect of publishing year on receiving more citation. The article entitled "Phantom Auditory Perception (Tinnitus): Mechanism of Generation and Perception," published in 1990 by Jastreboff P.J. is the most cited article in our list. Interestingly, only eight articles published in the 1980s appeared in the list. Among them, the most cited article received 284 citations but only ranked 17th in the list. Two reasons why the earlier studies in the 1980s received less citation are as follows. First, obliteration by incorporation might happen during the development of the field, and certain contents of the earlier studies might become well accepted and commonly used; consequently, their authors were no longer cited (7). Second, parallel to the rapid technological development, the field of tinnitus research may be ever developing.

The articles are not generally cited within 2 years of publication, but they receive more citation 3–10 years after publication (23). After this time period, they still receive citation, but less frequently (23). To overcome this intrinsic problem, we further calculated the average yearly citation for each article in our list. Subsequently, the ranking of the articles slightly changed. For example, Jos J. Eggermont's article entitled "The Neuroscience of Tinnitus," published in 2004 ranked third in the original list, but it ranked first in the list according to the average yearly citation.

The citation number of articles was not analyzed solely by WOS. Google Scholar and Scopus are the other most widely used citation databases (24). However, WOS is the most commonly used citation database for bibliometric analysis, and it provides a user-friendly analyzing tool. In this study, we primarily used WOS and then cross-checked with Scopus. Our findings showed that when analyzing the top 100 cited articles in Scopus, 12 out of 100 articles in the original list generated by WOS did not enter the list generated by Scopus.

To consider an article as a "classic article," it must have at least 100 citations (25). Hence, the articles in our list can be consid-

ered as classic articles because all of them reached at least 100 citations. However, the total citation number of these classic articles about tinnitus remains far below than that of the classic papers identified by other bibliometric analyses in different research fields (10-15). The possible reason for this situation could be that tinnitus is an extremely specific research field that only 4419 articles have been published to date, and this number is dramatically lesser than the article numbers in other bibliometric analyses in various research fields (10, 11).

Except for one article published in German, all articles were published in English. As can also be seen in other bibliometric analyses in various research fields (10-15), most of these articles (N=51) originated from universities or institutions in the USA. As discussed in other bibliometric analyses (26), this situation can be associated with the fact that USA dominates the research on medical science because of a higher federal budget and a higher number of researchers than any country. Furthermore, authors from the USA generally tend to cite articles originated from the USA (17), resulting in a higher citation for USA-based articles.

The top 100 cited articles about tinnitus were published in first-quartile journals (high-impact journals). The journal *Hearing research* (the latest impact factor: 2906; Journal Citation Reports, Clarivate Analytics, 2018) with 12 published articles is the top preferred journal, followed by the *Journal of Neuroscience* (impact factor in 2018: 5988; Journal Citation Reports, Clarivate Analytics, 2018). Most authors thought that publishing in high-impact journals provides more of an advantage to receive higher citations; hence, they tend to publish their articles in these journals, eventually resulting in maintaining the impact factor of these high-impact journals (19). Therefore, following the Bradford's law (27, 28), most of the top cited articles were published in a limited number of selective high-impact journals.

Our bibliometric analysis in tinnitus research also provided the opportunity to identify the authors and their studies. For example, as being the first among three authors, de Ridder D. ranked first in our list, with 10 articles, followed by Langguth B. with 8 articles. Meanwhile, Jastreboff P.J., who is the author of the top cited article in our list, published four articles in which he was regarded as the first author, and two of these articles appeared in the top 10. In addition, Jastreboff and Hazell (5) et al.'s article on the study of the first emotional test on an animal model using rats 30 years ago ranked 34th in the list.

When analyzing each article in our list, a significant number (n=52) of them is about the underlying mechanism of tinnitus. This finding can be associated with the fact that the pathology of tinnitus remains poorly known, and the research is heterogeneous. Hence, an effective classification of the underlying pathophysiological mechanisms of tinnitus symptoms could be an innovative approach toward personalized rehabilitation (29). Therefore, more research on humans and animals that investigates tinnitus pathology is clinically important.

Eleven out of 100 articles in our list are questionnaire studies. *Tinnitus handicap inventory* and *tinnitus functional index* are the two common questionnaires used to evaluate the effects of tinnitus. Considering that the second top cited article in the list was about a commonly used questionnaire, that is, tinnitus handicap inventory, not surprisingly, it received high citations (n=636). Similar to the articles involving commonly used questionnaires, review articles also receive typically high citations because such articles are generally the primary source when writing up a new article to track the past studies in the literature (7). Our findings also support this idea in a way that 16 out of 100 articles in the list are review articles. Moreover, the third top cited article, which also ranks first in the list based on average yearly citation number, is a review article.

The effects of technological developments have been crucial in the advancement of tinnitus research. For example, neuroimaging by functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) provides important data for pathophysiology-oriented studies. For instance, the fMRI study on lateralized tinnitus by Melcher, J.R. et al. showed an abnormally low percent signal change in the inferior colliculus contralateral to the tinnitus percept compared with that in control subjects (30). This study ranked 31st in our list. In addition to this study, four more articles involve the use of fMRI. Meanwhile, PET is another commonly used imaging modality, and nine articles in our list mention the use of PET. Showing the cortical abnormalities except the auditory system, PET using the voxel-based morphometry and magnetoencephalography methods showed changes in cortical activities on subcallosal region including the frontal cortex, parietal lob, mesial posterior regions, and nucleus accumbens. With the roles of central auditory pathway and limbic system on tinnitus pathophysiology revealed tangibly, these studies are among the classic articles about tinnitus.

Another interesting finding of this bibliometric analysis is that most of the classic articles about tinnitus (n=15) involve animal studies/models. Animal models are used, mainly because tinnitus is a subjective phenomenon and its diagnosis in humans relies on self-report. Therefore, animal models have been developed to overcome this problem and to provide a more objective evaluation. However, the common problem with animal tinnitus models is its reliability and validity.

In tinnitus research, the top cited treatment-oriented articles are about repetitive transcranial magnetic stimulation (rTMS). This noninvasive method was first developed in 2003, involving a repetitive short-period ~2 Tesla magnetic stimulus modulated by neuronal activity transcutaneously (31). Considering that this method is expensive, time consuming and used with neuronavigation, it is used limitedly to research, and it is not viable as a routine procedure in clinics. The articles that involved rTMS receive high citations, probably because it is a relatively new technology and its effect mechanism is not still well understood.

Meanwhile, this study has several limitations. First, we did not consider the effect of incomplete station, that is, analyzing the results from systematic reviews, instead of analyzing each article separately. Other intrinsic limitations include self-citation, journal and author bias, in-house bias toward friends or colleagues, language bias toward English, and omission bias toward not purposely referencing competitors (12), which all eventually affect the listing of the top 100 cited articles. Second, we used the WOS database where only major journal article citations are accounted for calculating the total citation number of

an article. However, in Google Scholar, other citations in books and an online platform are also accounted for calculating the total citation number. Therefore, our reported citation numbers can be different from those calculated by Google Scholar (26). Furthermore, the WOS only includes articles published after 1975, whereas earlier studies before 1975 can be found in Scopus database. For example, the earliest study found in Scopus database was published in 1841. Nevertheless, none of the articles published before 1975 appeared in the top 100 list generated by Scopus. Lastly, the time for collecting citation data is another important factor that can also affect the ranking of articles in the list because the total number of citation changes continuously. Especially, the citation numbers of the articles located at the bottom of the list are extremely close to each other. Thus, the ranking of these articles can change swiftly, and/or some of these articles can be out of the list soon after. Moreover, the articles having a higher yearly average citation can claim immediately the top of the list. Thus, our list of top 100 cited articles about tinnitus can change soon afterward when considering tinnitus research as an ever-developing field.

In this study, we identified and analyzed the top 100 cited research articles about tinnitus, with the aim of providing researchers a source to track the historical development and trends of the field. Our analysis indicated that the current tinnitus research trends include finding the objective evolution of tinnitus, revealing specific pathophysiological mechanisms of tinnitus etiology, and developing new treatment methods accordingly. Meanwhile, technological innovations support these efforts critically to provide an opportunity for diagnosing tinnitus objectively.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects". (amended in October 2013).

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Original Article

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Determining the Effects of the Monitoring and Counseling in Addition to Standard Monitoring on the Abstinence after Quit Smoking: A Randomized Controlled Study

Aslı Güleşen[2], Tülay Yavan[1], Hatice Bebiş[3]

[1]Department of Nursing, İzmir University of Economics, İzmir, Turkey
[2]Turkish Armed Forces, Nursing, Ankara, Turkey
[3]Faculty of Nursing, Near East University, Nicosia, Cyprus

ORCID IDs of the authors: T.Y. 0000-0003-3287-1487; H.B. 0000-0001-6217-9753; A.G. 0000-0002-4204-1746.

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BACKGROUND/AIMS
The aim of this study was to determine the effects of supplemental monitoring and counseling in addition to the standard monitoring during the treatment period on the abstinence behavior of smoking cessation center applicants.

MATERIAL and METHODS
The randomized controlled study was conducted in the smoking cessation clinic as an intervention study. The study involved 67 participants. Data collection was implemented using the Descriptive Questions Form, Fagerström Test for Nicotine Dependence, Carbon Monoxide Monitoring Chart, and Self-Efficacy Questionnaire. After routine standard training and tests at the smoking cessation center, a total of six supplemental interviews were conducted in the intervention group by one of the researchers; these interviews were conducted one week before smoking cessation and one week and one, two, three, and six months after quitting. Two interviews were conducted in the control group for evaluation: one week before and six months after quitting.

RESULTS
After six months, 88.2% of the intervention group and 60.6% of the control group had stopped smoking. A statistically meaningful difference was found between the intervention and the control groups in terms of attending the standard monitoring. In the last interview, the self-efficacy score of the intervention group was significantly higher than that in the control group. Compared to the control group, the intervention group was 1.5 times more successful in smoking cessation at the end of the sixth month.

CONCLUSION
Those successful in smoking cessation must be monitored in frequent follow-ups simultaneously supported by physicians, nurses, and other health-care providers.

Keywords: Abstinence, counseling, monitoring, nursing, quit smoking

INTRODUCTION

Nicotine addiction is a very common addiction, and tobacco use has serious negative effects on human health and is one of the most significant preventable public health problems in the world (1). Interventions for smoking cessation include pharmacological and behavioral methods and other alternative approaches (2). Each year approximately two out of every three smokers make an attempt to quit (3). However, quitting is very difficult to achieve without any systemic support or program. Only 3%–5% of self-quitters achieved abstinence after a self-quit effort (4).

The greatest problem in smoking cessation is relapse. The relapse rate for smokers who attempt to quit on their own has been reported as 80% within the first month, with only 3%–5% individuals remaining abstinent at 6 months (5). Relapse generally occurs within the first three months. Although relapse is related to withdrawal symptoms in the early cessation period, psychological factors may play a more crucial role in the long term (6); therefore, a model focusing on cognitive-behavioral relapse prevention has been suggested (7). Interviews intended to prevent relapse and

Corresponding Author: Tülay Yavan
E-mail: tulayyavan@ieu.edu.tr

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approaches to reward positive attitude were very effective in the attempting-to-quit phase. Frequent contact with health-care providers is important to support the abstinence efforts. The clinical guidelines reported a strong relationship between the number of health care providers visits and the length of abstinence (3, 8). Pharmacotherapy, counseling, and behavioral support also increase quitting and abstinence rates (3, 8, 9). In addition, self-efficacy influences behavioral changes in smoking cessation efforts. Self-efficacy represents the self-confidence levels that cause individuals to resist smoking in many high-risk situations (10). The success of the intervention was markedly increased, if it was implemented in specialized smoking cessation clinics with close monitoring and appropriate motivational and psychological support (11).

Nurses are mainly involved in the smoking cessation campaigns and provide preventive and curative services in collaboration with other health-care professionals. There have been successful cessation interventions implemented by nurses in clinics and in other social contexts (12–16). Besides smoking cessation interventions, nurses have been involved in relapse prevention by monitoring smokers, during both the cessation attempt and the continuation phase (17, 18).

The aim of this study was to determine the effects of monitoring and counseling during the cessation period in addition to the routine monitoring performed during the treatment period on the abstinence behavior of smoking cessation center applicants.

MATERIALS AND METHODS

Design and Participants

This study was conducted in the smoking cessation clinic of the Cancer Early Diagnosis, Screening and Education Center (CEDSEC) between December 2012 and November 2013 as an intervention type and randomized controlled study. In Turkey, smoking cessation clinics are incorporated into the CEDSEC. Ethical approval was received from the Institutional Ethics Committee (1491-1323-12/1648-4002). Research application approval was received from the Public Health Institution (Ministry of Health).

Main Points:

- In our study, we studied the effects of supplemental monitoring and counseling in addition to the standard monitoring during the treatment period on the abstinence behavior of smoking cessation center applicants.
- At the end of the six months, the self-efficacy score of the intervention group was significantly higher than that in the control group.
- The intervention group was 1.5 times more successful than the control group in smoking cessation.
- Individuals who have been successful in smoking cessation should be frequently monitored, and in follow-ups simultaneously supported by physicians, nurses, and other health-care providers.
- There is a need for longer-term, randomized controlled studies with larger sample groups.

The participants were individuals admitted to the smoking cessation program who were > 18 years of age. Informed consent was obtained from all individual participants included in the study. Participants were assigned to the intervention or control groups by way of random closed-enveloped lottery. Participants were blinded to their assigned group, each of which consisted of 34 individuals. One individual from the control group was excluded after the first interview because they moved away from the area.

Data were collected by using the following forms:

- Descriptive Questions Form,
- Fagerström Test for Nicotine Dependence (FTND),
- Carbon monoxide (CO) Monitoring Chart, and
- Self-Efficacy Questionnaire (SEQ).

Descriptive Questions Form

This form was developed by the researchers in keeping with the related literature (1, 4, 6, 8, 10, 12-15, 17, 18, 21, 22, 25-27, 31, 34); it elicits individual characteristics and smoking behaviors.

FTND

FTND, developed in 1978 and revised in 1991, indicates the individual's nicotine dependence level (19). Uysal et al. (20) translated the scale into Turkish in 2004. They determined the Cronbach's alpha was 0.59 in a sample of Turkish smokers.

The FTND is composed of six questions, two scored "0–3", and four scored "0–1". Total scores vary from 0 to 10; 0 indicates no dependence, and 10 indicates the highest level of dependence. The FTND was routinely applied by physicians before education on "Effects of Tobacco on Health" to those who applied to the CEDSEC for smoking cessation. These test results were used in our study.

CO Monitoring Chart

CO measurement is used to monitor those undergoing smoking cessation and to diagnose various pulmonary diseases (21). CO levels of CEDSEC applicants for smoking cessation were routinely measured by the physician every monitoring visit. These measurement results have been used in our study.

SEQ

The SEQ, developed by Nicki et al. (10) in 1984, was adapted by Karanci in a Turkish sample of 174 smokers in 1992. Cronbach's alpha value was determined as 0.92. The SEQ assesses the subjects' perceptions of their ability to abstain from smoking in various situations. It contains 25 items, each rated on a five-point scale ranging from "not sure at all: 1" to "very sure: 5". The scale total score varies between 25 and 125 points and a higher score indicates a greater ability to refrain from smoking (10). We obtained permission from Karanci by e-mail to use the SEQ. In our study, Cronbach's alpha value was 0.80.

Application

A total of six interviews were performed with the intervention group members who also received standard care in the clinic. The researchers encouraged their continued participation in the standard monitoring. The individuals in the control group received only standard monitoring in the clinic on a voluntary ba-

sis. For both groups, the measurements were conducted during the first and the last interviews. Participants were asked about their abstinence in the first, third, and sixth month. Figure I shows the application process in detail.

Standard Monitoring:
This monitoring was routinely implemented in the CEDSEC. Participants completed the FTND before education on "Effects of Tobacco on Health". Then, participants had a blood test, breath function test, and lung X-ray performed at the Chest Diseases Clinic. If nothing was amiss, the participants were provided with appropriate pharmacotherapy. Participants were given information about the medicine and cautioned about the early effects of quitting smoking and the importance of avoiding even minimal amounts of smoking. Their first CO measurement was also taken at this time. They were provided with the first three month supply of medicines, and at every control visit, CO levels were measured. During this period, the participants were required to attend a control visit in the first week, and in the first, second, third, sixth, ninth, and twelfth months. For the standard monitoring, there were no attempts to make absent participants attend the control visits, and participants with CO levels >5 were excluded. After 12 months of monitoring, successful participants were no longer required to attend.

Intervention Group
Interviews were conducted as follows: 45 minute sessions of nurse counseling were provided in a quiet and appropriate room in the clinic by a qualified nurse in accordance with the principals of individual counseling.

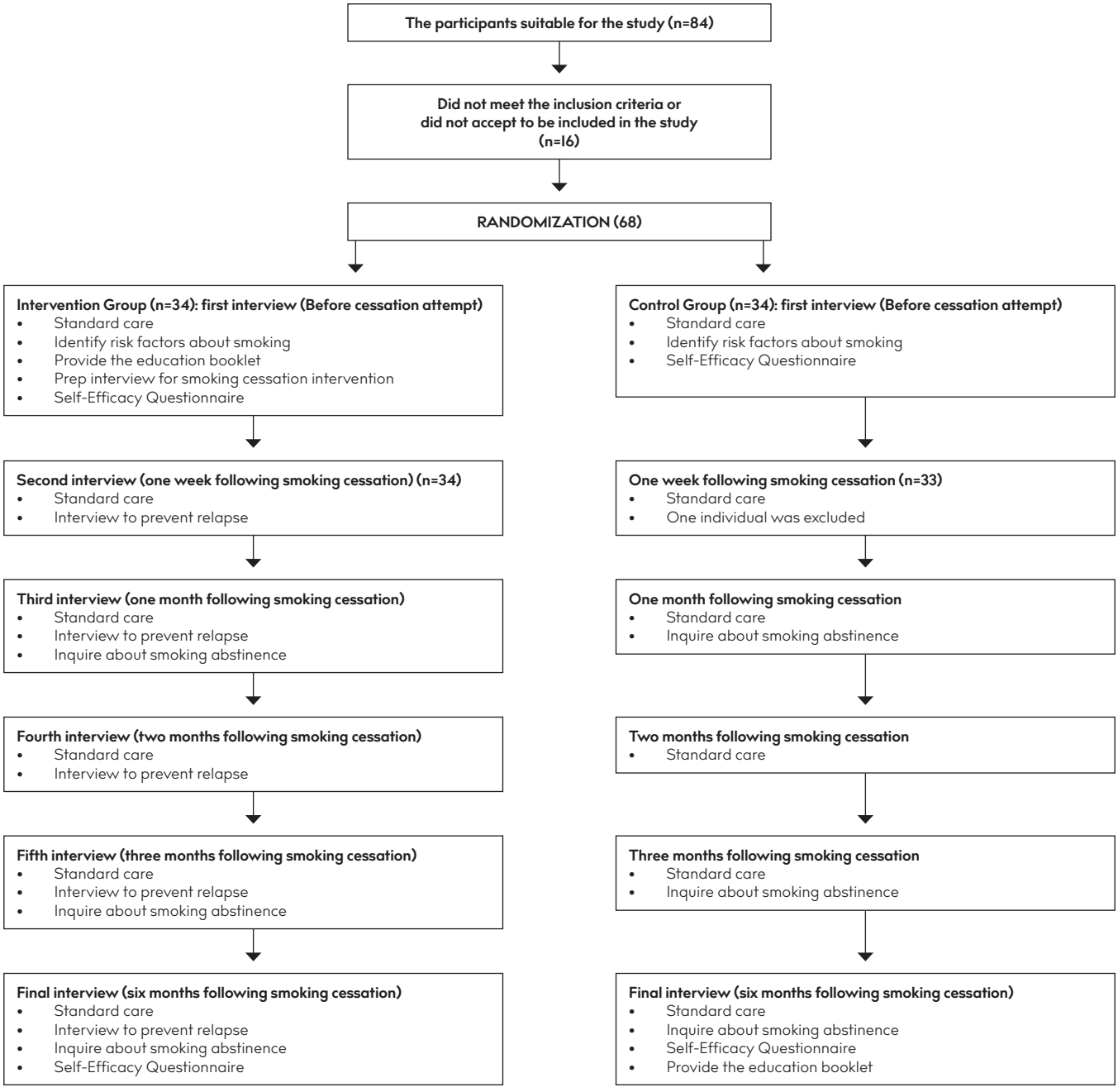

FIGURE I. Flow chart of the Study

Education Booklet
An educational booklet, which provided information on the challenges of cessation, was prepared for those undertaking smoking cessation to support this endeavor. The booklet was provided in the first interview, and participants were asked to complete the "Smoking Cessation Diary" section.

First Interview (Prep Interview)
This was an interview to prepare the individual to quit smoking; it was conducted approximately one week before the smoking cessation date and determined the personal information and risk factors of the individual. Information about the education booklet was provided, and participants completed their "My Smoking Cessation Diary". No statistical analysis was applied to the diary as its aim was only to motivate and support the cessation efforts.

Second Interview (High-Risk Period Monitoring)
The first two weeks of the cessation period carry the greatest risk of relapse (3). Therefore, the second interview took place within a week, in order to prevent relapse.

Third, Fourth, and Fifth Interviews (Relapse Prevention Monitoring):
Interviews to prevent relapse were repeated. In these interviews, participants who missed their control appointments were reminded of the appointments and invited by phone to attend. When participants missed appointments because of forgetfulness, shame, or failure, they were reminded that:

- Smoking one or two cigarettes did not mean that they had resumed smoking,
- This was a learning process, and
- They should not smoke even the smallest amount.

Last Interview (Evaluation Interview)
Participants' smoking cessation statuses were evaluated. In this period, those who managed to quit were in the cessation phase. They were reminded of the continuing danger of relapse. Those in relapse risk were supported with cessation help and counseling.

Control Group
In the first interview, personal information and risk factors were determined for the control group. In the second and final interview, the smoking cessation status of the participants was evaluated. For ethical reasons, an educational booklet was also provided for this group at the end of the study.

Statistical Analysis
Statistical Package of Social Sciences 16.0 (SPSS, Inc., Chicago, IL, USA) was used for the data analysis. The results were assessed at the 95% confidence interval, with significance at $p<0.05$. For the descriptive statistics, variables determined by counting were stated as numbers and percent, and measured variables were stated as median (±) standard deviation, and "minimal"–"maximal". Normal distribution suitability of the continuous variables was evaluated with the one-sample Kolmogorov-Smirnov test. In analyzing the differences between the groups, for the normal distribution variables, Student *t* test was used, and for the others, Mann-Whitney U test was used. In analyzing the differences within a group for the normal distribution variables, Paired samples *t* test was applied, and for others, Wilcoxon test. Pearson chi-square test was used for the analysis of intermittent variables.

TABLE I. Sociodemographic characteristics

	Intervention (n=34)		Control (n=33)			
Characteristics	**n**	**%**	**n**	**%**	**X^2**	**p**
Age						
≤45 years	14	41.2	12	36.4	0.163	0.686
>45 years	20	58.8	21	63.6		
Gender						
Female	18	52.9	17	51.5	0.014	0.907
Male	16	47.1	16	48.5		
Marital Status						
Married	27	79.4	29	87.9	0.875	0.350
Single/Widow	7	20.6	4	12.1		
Education level						
≤Primary education	9	26.5	15	45.5	2.625	0.269
Secondary education	7	20.6	5	15.2		
≥Higher education	18	52.9	13	39.4		
Working status						
Working	10	29.4	10	30.3	1.185	0.553
Not working	13	38.	16	48.5		
Retired	11	32.4	7	21.2		

X^2=Pearson Chi-Square

RESULTS
No statistically meaningful differences in demographics and smoking behavior were observed between the intervention and the control groups at the first interview ($p>0.05$) (Table 1).

The percent of participants who began smoking before age 18 years was 52.9% in the intervention group and 45.5% in the control group; 55.9% of the intervention group and 63.6% of the control group reported smoking for >30 years, and 38.2% of the intervention group and 42.4% of the control group reported smoking more than a pack per day. No previous attempts at smoking cessation were reported by 32.4% of the intervention group and 18.2% of the control group; 61.8% of the intervention group and 60.6% of the control group reported previously trying to quit by themselves. According to the FTND, 29.4% of the intervention group and 24.2% of the control group were in the very high dependence group (Table 2).

The intervention group attended an average of 5.47±1.16 standard monitoring sessions, whereas the control group attended an average of 4.12±1.56 ($p<0.01$).

An increase in the self-efficacy scores of all subjects in the study was found. At the last interview, the self-efficacy score of the intervention group was significantly higher than that in the control group ($p<0.05$) (Table 3).

The intervention group stated that their desire to smoke was strongest "postprandial" and "when stressed" before cessation and "when stressed" and during "arguments" after cessation. The control group also stated that before cessation, their desire was strongest "postprandial" and "when stressed". Except for "Coffee" and "popular smoking places", no statistically significant differences were determined between the groups after cessation attempt (p>0.05).

At the end of the study, it was observed that 88.2% of the intervention group and 60.6% of the control group had ceased smoking, and a statistically significant difference was determined (p<0.05). The intervention group was 1.5 times more successful compared to the control group at the end of the sixth month. Among participants who had not tried any previous cessation attempts, the intervention group was 5.5 times more successful than the control group. Among participants who had tried previous cessation attempts, the intervention

TABLE 2. Smoking behavior characteristics

	Intervention (n=34)		Control (n=33)			
Characteristics	**n**	**%**	**n**	**%**	**X^2**	**p**
Beginning age for smoking						
≤17 years	18	52.9	15	45.5	0.376	0.540
≥18 years	16	47.1	18	54.5		
Cigarettes per day						
≤1 pack (20 pieces)	21	61.8	19	57.6	0.122	0.727
>1 pack (20 pieces)	13	38.2	14	42.4		
Smoking years						
<15	6	17.6	3	9.1	1.085	0.581
15–29	9	26.5	9	27.3		
≥30	19	55.9	21	63.6		
Pack - years						
≤20	19	55.9	13	39.4	1.825	0.224
>20	15	44.1	20	60.6		
Previous cessation attempts						
Yes	23	67.6	27	81.8	1.776	0.183
No	11	32.4	6	18.2		
Method used in the previous attempt						
No Intervention	11	32.4	6	18.2	5.681	0.128
Self-willed	21	61.8	20	60.6		
With drug support	2	5.9	3	9.1		
Other (Acupuncture etc.)	0	0	4	12.1		
Encouragement of close friends in the cessation attempt						
They encourage	16	47.1	20	60.6		
Do not encourage	11	32.4	7	21.2	1.396	0.498
Partially encourage	7	20.6	6	18.2		
Fagerström Nicotine Dependence Test (FNDT)						
Very low (0–2 p.)	1	2.9	3	9.1	6.730	0.151
Low (3–4 p.)	9	26.5	2	6.1		
Medium (5 p.)	4	11.8	6	18.2		
High (6–7 p.)	10	29.4	14	42.4		
Very high (8–10 p.)	10	29.4	8	24.2		

X^2=Pearson Chi-Square

TABLE 3. Self-efficacy Questionnaire (SEQ) scores at first and last interviews

	Intervention (n=34)	Control (n=33)	t	p
SEQ scores (X±SD)				
First Interview (SEQ1)	59.94±17.17	62.93±14.94	-0.762	0.449
Last Interview (SEQ2)	113.82±19.37	101.06±14.94	2.356	0.021
Score Differences (SEQ2-SEQ1)	53.88±27.50	38.12±24.03	2.495	0.015

t=Independent samples t test

TABLE 4. Smoking Abstinence Statuses of the Intervention and Control groups at the 1st, 3rd, and 6th month periods

	Ceased Smoking %			
Characteristics	**Intervention**	**Control**	**RE**	**%95 CI**
All the Participants				
At the end of 1st month	97.1	90.9	1.068	0.944-1.207
At the end of 3rd month	97.1	84.8	1.144	0.979-1.336
At the end of 6th month	88.2	60.6	1.456	1.077-1.968
Previous Cessation Attempt Exists				
At the end of 1st month	95.7	92.6	1.033	0.900-1.186
At the end of 3rd month	95.7	88.9	1.076	0.918-1.262
At the end of 6th month	87.0	70.4	1.236	0.923-1.654
Previous Cessation Attempt Does Not Exist				
At the end of 1st month	100	83.3	1.200	0.839-1.716
At the end of 3rd month	100	66.7	1.500	0.852-2.641
At the end of 6th month	90.9	16.7	5.455	0.903-32.963
Cigarettes per day ≤1 pack (20 pieces)				
At the end of 1st month	95.2	84.2	1.131	0.910-1.405
At the end of 3rd month	95.2	73.7	1.293	0.972-1.719
At the end of 6th month	85.7	52.6	1.629	1.027-2.582
Cigarettes per day >1 pack (20 pieces)				
At the end of 1st month	100	100	-	-
At the end of 3rd month	100	100	-	-
At the end of 6th month	92.3	71.4	1.292	0.896-1.865
FNDT ≤5				
At the end of 1st month	92.9	72.7	1.277	0.864-1.886
At the end of 3rd month	92.9	72.7	1.277	0.864-1.886
At the end of 6th month	92.9	45.5	2.043	1.052-3.966
FNDT ≥6				
At the end of 1st month	100	100	-	-
At the end of 3rd month	100	90.9	1.100	0.964-1.255
At the end of 6th month	85.0	63.6	1.336	0.927-1.925

RE: Relative effectiveness; CI: Confidence Interval; FNDT: Fagerström Nicotine Dependence Test

group was 1.2 times more successful than the control group. Among the individuals who smoked less than a pack per day, the intervention group was 1.6 times more successful than the control group. All participants in both groups who smoked more than a pack per day managed to avoid smoking at the end of the first and third months. But at the end of the sixth month, the intervention group was 1.3 times more successful than the control group. Among the individuals with a dependence score of 5 or less, it was observed that the intervention group was 2 times more successful than the control group at the end of the sixth month. Among the individuals with a dependence score of 6 or more, the intervention group was 1.3 times more successful than the control group at the end of the sixth month (Table 4).

DISCUSSION

Nicotine is a challenging addiction, and relapse is one of the biggest problems in smoking cessation. Relapse prevention interventions and smoking cessation interventions are different, but they cannot be separated from one another. Smoking cessation interventions focus on cessation, whereas relapse interventions focus on prevention, especially of smoking resumption (22). Although data about relapse prevention indicate a wide variation, in a systematic review, it was stated that pharmacotherapy and written materials were effective in the short term, and behavioral interventions were effective in the long term (23). In the literature, a combination of behavioral counseling and pharmacotherapy have been found to produce the best results (3, 8). The likelihood of success increased by between 10% and 25% when the level of behavioral support increased (9). In our study, participants who decided to quit received supplemental monitoring and counseling along with pharmacotherapy and routine monitoring in the smoking cessation clinic. At the end of the sixth month, it was determined that 88.2% of the intervention group and 60.2% of the control group ceased smoking ($p<0.05$). In studies in Turkey that evaluated data from smoking cessation therapies, cessation rates were reported as 36%–65% after three months and 22%–45% after the first year (24–26). In our study, the intervention group's cessation rates were higher than those rates. In a study conducted in 2010 at a smoking cessation clinic, Önen et al. (27) observed that behavioral therapy applied with pharmacologic treatments was more effective than other therapies, and they recommended routine monitoring and support with behavioral treatments.

According to randomized trials, there is a strong dose-response relationship between the duration of counseling and abstinence rates (3, 28). Intensive counseling is more effective if there are at least four sessions longer than 10 minutes (3). Joseph et al. (29) stated that intensive counseling providing long-term social support was effective in smoking cessation and relapse prevention. In our study, the intervention group attended an average of 5.5 follow-ups and the control group an average of 4; the results were significantly different. Argüder et al. (25) stated that the low success rate in their clinic may have been because of the failure of participants to attend follow-ups after the first interview.

It is important to identify factors that may increase the risk of smoking or relapse. These factors include stressful conditions, spending time with other smokers, alcohol consumption, and smoking triggers (e.g., drinking coffee and after a meal) (3). In our study, risk factors were identified during the first interview, and coping strategies were determined based on individual needs. Individuals in the intervention group stated that they most desired to smoke "postprandial" and "when stressed" before the cessation attempt and "when stressed" and "when in arguments" after cessation. In the previous interviews, participants were asked to note smoking triggers and coping strategies in a "smoking diary" in order to identify and manage their own triggers. Similarly, Sağlam (26) determined the "eating" factor was a key trigger. Joseph et al. (29) investigated high-risk situations for relapse and planned interventions that were designed to cope with them.

It is important to practice coping skills to deal with the dangerous situations once these have been defined. Appropriate encouragement and support should be given to maintain healthy practices (3). In our study, participants in the intervention group who relapsed were advised to regard the relapse cigarette as their last, to consider this as a learning experience, and to continue their visits. At the end of the sixth month, the greater effectiveness in the intervention group compared to the control group was noticeable. The greater rate of relapse in the control group was attributed to the lack of this support. Similarly, Joseph et al. (29) stated that intensive follow up resulted in greater success compared to standard follow up in the long term. Deiches et al. (30) determined that in the first eight weeks of smoking cessation, the relapse rate was as high as 63%, and that 78% of those who relapsed in the early period restarted smoking within about six months.

According to Bandura, self-efficacy was one of the most important criteria for quitting smoking (10). Studies also showed that there was a positive correlation between self-efficacy scores and the time after quitting (10, 31–33). In our study, increases in the self-efficacy scores were greater in the intervention group than those in the control group.

In the literature, it has been reported that long-term smokers who started smoking early are more prone to failure in smoking cessation (4). According to the Global Adult Tobacco Survey, approximately half of all smokers attempted to quit, but only 15.8% succeeded (34). Önen et al. (27) stated that unsuccessful cessation attempts do not adversely affect the success rates of future cessation attempts, but in our study, the intervention was 1.2 times more effective in participants with a history of cessation attempts but 5.5 times more effective in those without a history when compared to results for the control group. When the intervention group rates compared to rates for similar groups of participants in the control group, the cessation success rates of intervention group were 1.6 times greater for individuals smoking a pack or less a day; 1.3 times greater for individuals smoking more than a pack a day; 2 times greater for those with a dependence score of 5 or less, and 1.3 times greater for those with a dependence score of 6 or more.

Conclusion and Practice Implications

In our study, we studied the effects of supplemental monitoring and counseling in addition to the standard monitoring during the treatment period on the abstinence behavior of smoking cessation center applicants. At the end of the six months, the

self-efficacy score of the intervention group was significantly higher than that in the control group. The intervention group was 1.5 times more successful than the control group in smoking cessation. Individuals who have been successful in smoking cessation should be frequently monitored, and in follow-ups simultaneously supported by physicians, nurses, and other healthcare providers. There is a need for longer-term, randomized controlled studies with larger sample groups.

Study Limitations

Individuals who were successful in smoking cessation were monitored for only six months. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ethics Committee Approval: Ethics committee approval was received for this study from Ethics committee approval received for this study from Gulhane Military Medical Academy (Approval Date: May, 2012, Approval Number: 1491-1323-12/1648-4002)

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

Peer-review: Externally peer-reviewed.

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Delirium Awareness and Treatment Approach in Orthopedics Clinic

Özhan Pazarcı[1], Seyran Kılınç[1], Fatma Bekmez[1], Burhanettin Çiğdem[2], Zekeriya Öztemur[1]

[1]Department of Orthopaedics and Traumatology, Cumhuriyet University School of Medicine, Sivas, Turkey
[2]Department of Neurology, Cumhuriyet University School of Medicine, Sivas, Turkey

ORCID IDs of the authors: Ö.P. 0000-0002-2345-0827; S.K. 0000-0003-0144-0916; F.B. 0000-0001-5839-6974; B.Ç. 0000-0003-4941-9497; Z.Ö. 0000-0003-2134-8797.

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BACKGROUND/AIMS
Orthopedic clinics are among the leading clinics in hospitals that request consultation for patients with delirium. However, delirium is often missed by nurses and physicians, resulting in an incorrect diagnosis. This study aimed to identify patients with delirium in the orthopedic clinics and describe our approach for these patients.

MATERIAL and METHODS
After forming a strategy for the diagnosis, treatment, and follow-up of patients with delirium, prospective follow-up was performed for patients hospitalized in the orthopedic ward. High-risk patients were screened using the Nursing Delirium Screening Scale, and patients diagnosed with delirium were evaluated using a prepared form. This approach was used to determine the risk factors for delirium, ensure patient safety, and treat the symptoms of delirium.

RESULTS
Total 988 patients were evaluated, and 34 (2.44%) were diagnosed with delirium. The mean age of the patients was 66.17±22.68 years. The mean duration of delirium was 2.88±0.84 days. An age group-based comparison showed that the duration of delirium in older patients was significantly longer than that in younger patients (3.08±0.9 vs. 2.45±0.52 d, p=0.042). Further, delirium duration was more among men than among women (3.0 vs. 2.2 d, p=0.031).

CONCLUSION
Rapid identification of delirium and determination of the etiological cause allows timely and appropriate correction of the condition Identification of delirium by the medical team and the use of a systemic approach are important in treatment. The duration of delirium is longer in men and the elderly; further, most delirious patients have more than one risk factor for delirium.

Keywords: Approaches, delirium, orthopaedics, treatment

INTRODUCTION

Delirium is an acute organic brain syndrome (1). In preoperative or postoperative patients in orthopedic clinics, a delirium table may be seen; a delirium table is a clinical disease characterized by acute onset and fluctuating course of attention, cognitive function, and mood disorders. Delirium is an important geriatric syndrome (2); although it may be present in young patients as well as in the elderly, it is usually overlooked or neglected (3). Delirium is important because it causes severe morbidity and even mortality; however, in the absence of awareness regarding this condition, diagnosis is difficult. There are established diagnostic criteria for delirium, and when it is diagnosed, its complications can be prevented. However, the diagnosis is missed out in 30%–60% of all cases. The development of delirium in patients prolongs their hospital stay, reduces their functional capacity, and increases the healthcare costs (4). In addition, it can result in permanent cognitive disorder, pressure sores, falls, pneumonia, increased mortality, and increased rate of moves to residential care homes. Worldwide, the rates of delirium are accepted as a marker of the quality of healthcare services.

Majority of hospital consultations requested because of delirium are from orthopedic clinics (5). The reported frequency of delirium cases encountered in orthopedic clinics varies. Elderly patients with hip fracture constitute the highest-risk group among all orthopedic patients, and the reported delirium rates among this patient group are 6%–61% (6, 7). The

Corresponding Author: Özhan Pazarcı
E-mail: dr.pazarci@gmail.com

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wide variation in these rates is largely attributable to the frequent overlooking and misdiagnosis of delirium by nurses and physicians (8). The approach to delirium and its treatment show variations in the literature (9). Therefore, this study aimed to identify patients with delirium in the orthopedic clinics and describe our approach strategy for these patients.

MATERIAL and METHODS

A team comprising an orthopedic-ward nurse, an orthopedist, and a neurologist was informed about delirium and received training about this condition. A treatment and follow-up strategy was formed for these patients. Thereafter, patients admitted and treated at the orthopedic and traumatology clinic from January 1 to December 31 2018 were enrolled in the study.

Approval for the study was granted by the local ethics committee. Patient data were collected prospectively. According to the approach strategy for patients with delirium that has been defined in Figure 1, for each patient with acute onset of distraction and cognitive function disorder, the Nursing Delirium Screening Scale (Nu-DESC) was used. Those with a Nu-DESC score of ≥2 were evaluated for delirium. A neurological consultation was requested for the patients. Delirium was diagnosed based on the DSM-V diagnosis criteria, and those diagnosed with delirium were examined to understand the etiology, as shown in Table 1. The causes of delirium that were determined were then treated.

Patients were excluded from the study if they were day-case patients; were < 18 y old; had a history of dementia, depression, or other psychiatric disorders; had metastatic cancer; or had a life expectancy of <6 months. Total 988 patients were examined, and for 38, a neurological consultation was requested with a pre-diagnosis of delirium. According to the DSM-V, 4 patients were not diagnosed with delirium. Thus, 34 patients were diagnosed with delirium and were followed up using the prepared form (Table 1).

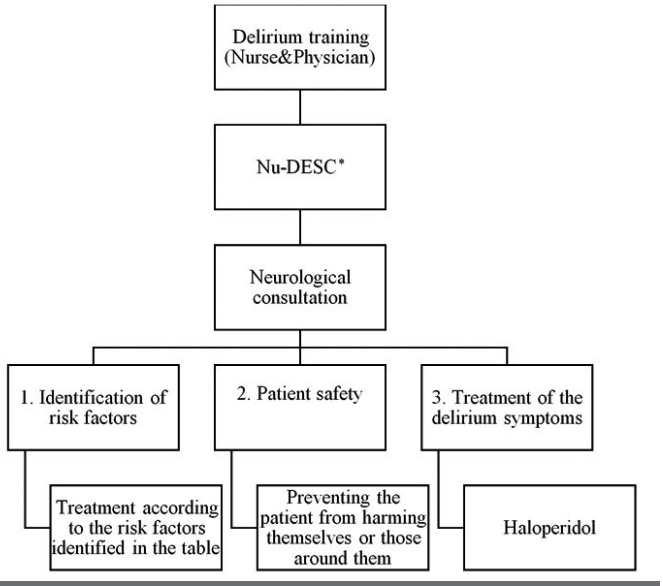

FIGURE 1. Schematic diagram of the approach to patients with delirium in the orthopedic clinic
*Nu-DESC: The Nursing Delirium Screening Scale

Main Points:

- A timely and early diagnosis of delirium is important.
- A team approach is important for delirium treatment.
- The duration of delirium is longer in men and the elderly.
- Most patients have more than one risk factor for delirium.

The diagnoses and demographic data of the patients were recorded. The patients were compared in terms of the duration of delirium, sex, age (classified as young if <65 years old and elderly if aged ≥65 years old), and risk factors.

Statistical Analyses

Data obtained in the study were analyzed statistically using IBM Statistical Package for the Social Sciences version 22 software (SPSS IBM Corp.; Armonk, NY, USA). Conformity of the data to normal distribution was assessed using the Shapiro-Wilk test. For the comparison of 2 independent groups, the t-test was applied to parametric data and the Mann Whitney U-test was used for the non-parametric data. Data obtained from counts were evaluated using the Chi-square test. A p value <0.05 was accepted as statistically significant.

RESULTS

Of the 988 patients evaluated in the study, 34 (3.44%) were diagnosed with delirium. The mean patient age was 66.17±22.68 y. When the patients were classified as per age group, the mean age of the "young" group (those aged <65 y) was 37.36±15.88 y, while that of the "elderly" group (those aged ≥65 y) was 79.95±6.59 y.

The patients were classified as per their diagnosis as follows: 26 (76.5%) had hip fracture, 5 (14.7%) had multiple trauma, and 3 (8.8%) had fractures in other regions. Fewer than 4 risk factors

TABLE 1. Delirium Patient Etiology Evaluation Form

Patient information	Day 1	Day 2	Day 3
1. Vital signs			
2. Blood glucose level			
3. Need for control of falling			
4. Intracranial bleeding			
5. Pain score			
6. Infection			
7. Dehydration			
8. Withdrawal syndrome			
9. Urinary retention			
10. Constipation			
11. Cardio/Pulmonary problems			
12. Electrolyte imbalance			
13. Immobilization			
14. Vision impairment			
15. Insomnia			
16. Inappropriate drug use			
17. Disorientation			
18. Physical restraint			

for delirium were determined in 19 (55.9%) patients and more than 4 in 15 (44.1%) (Figure 2).

TABLE 2. Delirium Evaluation Parameters

		N	%
1. Sex	Male	29	85.3
	Female	5	14.7
2. Diagnosis	Hip fracture	26	76.5
	Multiple Trauma	5	14.7
	Other region fractures	3	8.8
3. Age	<65 y	11	32.4
	≥65 y	23	67.6
4. Problems in vital signs	Absent	20	58.8
	Present	14	41.2
5. Blood glucose level	Normal	26	76.5
	High	8	23.5
6. Need for control of falling	Absent	15	44.1
	Present	19	55.9
7. Intracranial bleeding	Absent	33	97.1
	Present	1	2.9
8. Infection	Absent	31	91.2
	Present	3	8.8
9. Dehydration	Absent	25	73.5
	Present	9	26.5
10. Withdrawal syndrome	Absent	32	94.1
	Present	2	5.9
11. Urinary retention	Absent	33	97.1
	Present	1	2.9
12. Constipation	Absent	23	67.6
	Present	11	32.4
13. Cardiopulmonary problem	Absent	32	94.1
	Present	2	5.9
14. Electrolyte imbalance	Absent	15	44.1
	Present	19	55.9
15. Immobilization	Absent	23	67.6
	Present	11	32.4
16. Vision impairment	Absent	32	94.1
	Present	2	5.9
17. Insomnia	Absent	22	64.7
	Present	12	35.3
18. Inappropriate drug use	Absent	32	94.1
	Present	2	5.9
19. Disorientation	Absent	0	0
	Present	34	100
20. Physical restraint	Absent	19	55.9
	Present	15	44.1
21. Pain	Normal/moderate	17	50.0
	Severe	17	50.0

Severe pain, elevated blood glucose level, and the presence of > 4 risk factors influenced the duration of delirium (p: 0.627, p: 0.113, and p: 0.851, respectively). The mean blood glucose level was 151.67±58.57 mg/dL. The findings are shown in Table 2.

The mean duration of delirium was 2.88±0.84 d. An age-group based comparison showed that the duration of delirium was significantly longer in the older patients than in the younger patients (3.08±0.9 vs. 2.45±0.52 d, p=0.042). Further, men had significantly longer duration of delirium than women (3.0 vs. 2.2 d, p=0.031).

DISCUSSION

This study can be considered valuable because it presents an approach for the treatment of delirium that is frequently observed in patients in orthopedic clinics. Early diagnosis is crucial in the prevention of delirium and its effects (10). Considering the increase in the elderly population and the prevalence of hip fracture, it can be predicted that there will be an increase in the incidence of delirium (8). Therefore, awareness regarding delirium and good management are important. In this study, the prevalence of delirium in the orthopedic patients was 3.44%. In the literature, the incidence rates of delirium are reported to be increasing, with higher rates in the elderly. The reported incidence rate of postoperative delirium in patients who have undergone hip surgery is 4%–61% (11).

According to the neuroinflammatory hypothesis, delirium represents the central nervous system manifestation of a systemic disease state that has crossed the blood-brain barrier. Inflammation has been recognized as a trigger for episodes of delirium, particularly in older adults, with a correlation between the severity of the patient's underlying medical problem and the development of delirium. Systemic inflammatory events trigger the release of inflammatory mediators by tissue macrophages and brain vascular endothelial cells. These mediators may have a direct effect on the neuronal function or indirect effect via the activation of microglial cells that have become primed by neurodegenerative disease or aging. Inflammatory mediators may cause reversible disruption of neuronal function, as in the case of delirium; they may be irreversible and contribute to long-term cognitive decline or may cause neuronal death, contributing to the accumulating damage and neuropathological burden (12).

A team approach was adopted for the patients in the current study; the team comprised an orthopedist, a nurse, and a neu-

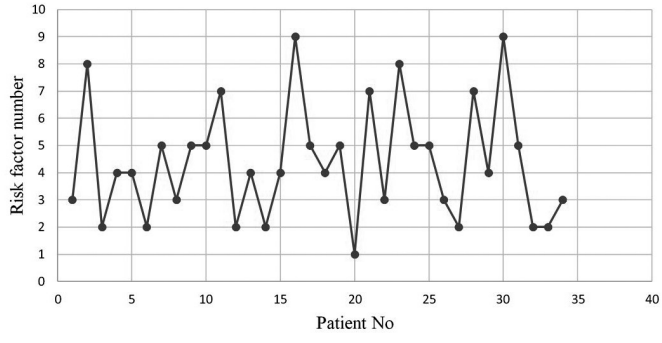

FIGURE 2. Number of risk factors determined in each patient

rologist. The importance of a multidisciplinary team approach for patients with delirium has been emphasized in the literature (8, 13). There are 3 goals in the treatment of delirium, as follows: i) to determine the etiological cause, ii) to ensure patient safety, and iii) to treat the symptoms of delirium. The training of physicians, particularly nurses, who are working in the clinic, is important for timely and accurate diagnosis and management of delirium (8). The use of the Nu-DESC enables rapid screening of delirium (14).

Different studies have reported varying duration of delirium (4). In the current study, the mean duration of delirium was 2.88±0.84 d, and the duration was longer in men and the elderly. Previous studies have also shown that delirium lasted longer in men and that there was a correlation of delirium duration with age (15). Several studies have shown that the delirium duration can be <1 wk or >1 wk (16). Daily follow-up and evaluation of the patient is crucial for delirium of short delirium, as in the current study (15).

Recent trials support the approach for delirium patients recommended in this study. It has been emphasized in the literature that geriatric multimodal consultation has reduced the rates of delirium among the elderly (17). Disruptions in the electrolyte levels in the body, changes in the blood glucose levels, cardiopulmonary problems, and drug or substance withdrawal syndromes, are predisposing factors for delirium. In addition, the inappropriate use of drugs, such as polypharmacy with the use of >4 different drugs or the initiation of >3 new drugs in the previous 24 h is also implicated as a risk factor. Patients presenting with a delirium table must be investigated for infection focus. Delirium rarely has a single cause and is usually multifactorial (18). On the follow-up form used in the current study, in addition to age, sex, and diagnosis data, 18 etiological parameters were evaluated (Table 1). The delirium risk factors that were determined were treated. It has been frequently emphasized in the literature that the identification of risk factors is the critical first step in the prevention and rapid treatment of delirium (18). However, the present results showed no significant difference in the delirium duration, irrespective of the number of risk factors present. Various drugs are used in the treatment of delirium and its symptoms (9). The use of Haloperidol is supported by previous reports in studies for a rapid effect in delirium treatment (8). Therefore, Haloperidol was used in the current study approach for treating delirium symptoms, as emphasized in the literature. In addition to pharmacological treatment, the non-pharmacological treatment approach is a part of delirium treatment. This is implemented with methods that will provide time and spatial orientation for the patient, such as staying in a quiet room, being accompanied by a family member or known caretaker, and the presence of a clock and television in the room (19). In the current study, a non-pharmacological approach constituted a part of the treatment for delirium patients.

There are certain limitations to this study. Although it was a prospective study, the relatively lower sample size precluded the formation of a control group. Thus, further multi-center prospective studies are warranted to support the use of the treatment approach presented here.

In conclusion, timely diagnosis of delirium and identification of the etiological cause allows the delirium table to be quickly and properly corrected. There is no single recommendation for the treatment and management of patients with delirium; however, a team approach is important for the awareness of delirium and a systematic approach to treatment. The duration of delirium is longer in men and the elderly, and most patients have more than one risk factor for delirium.

Ethics Committee Approval: Ethics committee approval was received for this study from the Local Ethics Committee (Date: 02.01.2019, No: 2019-01/06)

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

Peer-review: Externally peer-reviewed.

Author contributions: Concept – O.P.; Design – O.P., S.K.; Supervision – Z.O., B.C.; Resource – O.P., F.B.; Materials – O.P.; Data Collection and/or Processing – F.B., O.P., S.K.; Analysis and/or Interpretation – S.K., B.C.; Literature Search – O.P., S.K., B.C.; Writing – O.P., Z.O.; Critical Reviews –Z.O., B.C.

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

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Original Article

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Demographic and Clinical Analysis and Outcome of Critically Ill Patients in a Northern Cyprus Hospital

Atalay Arkan[1], Nedim Çakır[2], Kaya Süer[2], İlker Gelişen[3], Selin Bardak-Özcem[2], İlker Etikan[3]

[1]Department of Anesthesiology and Reanimation, Near East University School of Medicine, Nicosia, Cyprus
[2]Department of Infectious Diseases and Clinical Microbiology Near East University School of Medicine, Nicosia, Cyprus
[3]Department of Pharmacy, Near East University School of Medicine, Nicosia, Cyprus

ORCID IDs of the authors: A.A. 0000-0001-5317-6200; N.Ç. 0000-0002-3632-5187; K.S. 0000-0002-2565-3425; İ.G. 0000-0001-5945-9447; S.B.Ö. 0000-0002-7393-8062; İ.E. 0000-0001-9171-8269.

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BACKGROUND/AIMS
Depending on the demographic and clinical characteristics of patients, mortality rate is an indicator of the quality of community health and hospital-based healthcare. This study aimed to determine the mortality rate and basic demographic and clinical characteristics of critically ill patients in Northern Cyprus.

MATERIAL and METHODS
We retrospectively investigated the hospital records of critically ill patients who were admitted to the 14-bedded general intensive care unit of a university hospital in Northern Cyprus between August 2015 and July 2018.

RESULTS
In total, 734 patients were admitted to our hospital during the study period. The overall mortality rate of these critically ill patients was 27.11%. The mean patient age was 59.67±22.47 years. The average length of hospital stay was 16.33±38.20 days. The mortality rate was higher among men than among women although the average age of the female patients was higher than that of the male patients. The mean age of deceased patients was more than that of the survivors. There was no sex-based difference in this statistic. Patients accumulated between 60–79 years of age. Although most of the patients were transferred from the department of chest diseases, with most experiencing internal diseases, except for those in the age group of 20–29 years.

CONCLUSION
To our knowledge, this is the first study to report the mortality rate of critically ill patients in Cyprus. Our results indicate that our mortality rates are lower than those of many low-income countries.

Keywords: Age distribution, critical care, length of stay, mortality

INTRODUCTION

Critically ill patients (CIPs) are usually those that need to be managed and monitored in intensive care units (ICUs). The demographic and clinical characteristics as well as mortality rates (MRs) of these patients vary from those of other patients admitted to other wards of the hospital owing to several multifactorial variables. Usually, ICUs have higher MRs than other hospital wards. These higher MRs in ICUs are mainly because these units have patients with greater disease severity, longer length of stay (LOS) in the ICU, resistance of causative agents to anti-infectives in case of infections, and the presence of co-morbid factors, such as age, obesity, chronic heart disease, diabetes, and others (1, 2).

Many countries and institutions calculate their own MRs for CIPs to measure the improvement efforts rather than to compare with other medical facilities. Generally, calculation methods of MRs are described by the rules and regulations of medical authorities. However, no such regulations exist for the Turkish Republic of Northern Cyprus (TRNC); therefore, the MRs of CIPs are calculated for the entire Cyprus island, not for the country.

This study aimed to detect the MRs as well as demographic and clinical characteristics of CIPs who were admitted to tertiary care ICU in a hospital at the TRNC.

Corresponding Author: Kaya Süer
E-mail: kaya.suer@neu.edu.tr

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MATERIALS and METHODS

Patients and Study Design: Necessary permissions were obtained from the hospital ethics committee. Patient consent was not required owing to the retrospective nature of the study. The official hospital records of CIPs admitted to tertiary care ICU between August 1, 2015 and July 31, 2018 were collected and analyzed retrospectively. A university teaching hospital provides tertiary care general ICU with 14 well-designed and equipped beds.

Clinical outcomes; demographic characteristics, such as age and sex; and LOS were recorded. The mean and standard deviation values as well as median values and interquartile ranges (IQR) were calculated for these data.

Age, mortality rate-LOS correlations and clinical distributions of all ages and 20–29 years, monthly MRs, and 28 days in-hospital mortality records were calculated and analyzed.

Exclusion Criteria

Patients admitted to the pediatric unit, newborn infants, premature children, and patients who were admitted to the ICU after cardiovascular surgery were excluded from the study because of their completely different demographic and clinical characteristics.

Statistical Analyses

The data were entered into Statistical Package for the Social Sciences version 3.0 (SPSS Inc., Chicago, IL, USA) statistical analyses software program; the t-test and Mann–Whitney U-test were used to assess the differences between the groups.

RESULTS

In total, 734 patients were enrolled in the study. The average ICU stay was 11.991 days. The occupancy rate of the ICU beds was 78.21% during the study period, and approximately 20.53 new CIPs were admitted to our ICU each month.

TABLE I. General characteristics of the study population

Total patients	734
Mean age of the study population (±SD)	59.67±22.47
Median age and IQR of the study population	66 (78-44=34)
Minimum and maximum age of the study population	7–96
Total LOS*	16.33±38.20
Total median of LOS and IQR*	7 (15-3=12)
Minimum and maximum LOS of the study population*	1–722

(*): In days. LOS: Length of stay; IQR: Interquartile ranges

Main Points:

- It is observed that the overall mortality rate in our hospital's ICU patients is not higher than the countries mentioned in the literatures.
- The average age of the patients who applied to our service was around 60 years old. These patients stayed in the ICU for an average of 16 days. 27% of these patients lost their lives.
- Although our male patients were more than women, there was no difference between mortality rates.

The total mean, median, and minimum-maximum ages and total LOS as well IQR values have been outlined in Table I.

The correlation between the age distribution of patients and clinical outcomes is presented in Figure 1. The most prevalent group was 70–79 years old at total and dead patients (24.1% and 33.65% respectively); while the majority of surviving patients were 80–89 years old (17.5%). Another remarkable result was that the higher rates in total and living patients in 20–29-year-old patients among less than 60-year-old age patients.

We classified the patients according to their sex; the clinical outcomes, mean ages, median ages, and LOS were analyzed and compared. Results have been outlined in Table 2.

The correlation of the clinical outcomes with patient sex, age, and LOS is presented in Table 3.

Figure 2 shows that majority of the subjects had been transferred from clinics of chest diseases, internal medicine, neurology, and neurosurgery (30%, 25% 17%, and 16% respectively). The difference in the outcome of those in the age group of 20–29 years led us to evaluate their clinical origin. We have outlined these results in Figure 3. The majority of these patients were re-

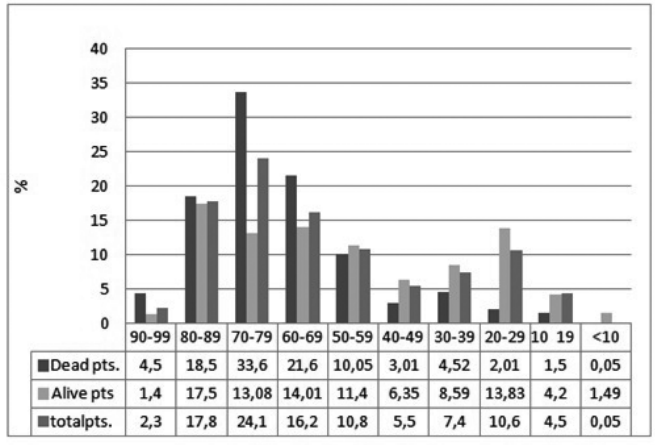

FIGURE I. The correlation between the age distribution of patients and clinical outcomes

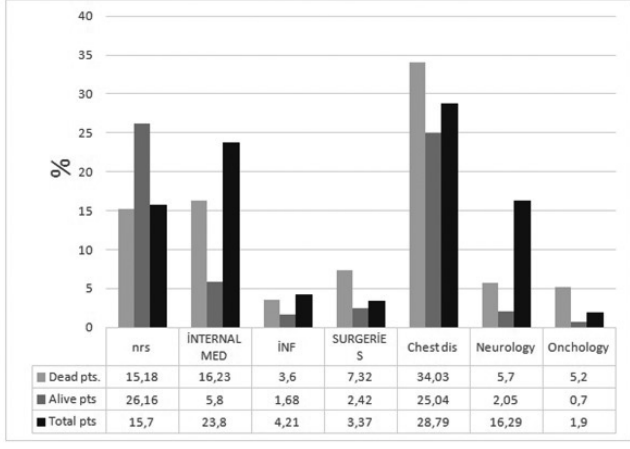

FIGURE 2. The clinical classification of the patients

ferred from internal medicine and neurology clinics rather than from chest diseases clinics, and the latter group of patients dramatically decreased down to 8% (the second lowest group of total patients).

The monthly monitoring of MRs is essential to maintain the quality of hospital care, and regular monitoring and supervision is necessary. We calculated the MRs of our hospital during the study period, and the results are outlined in Figure 4.

The average, maximum, and minimum monthly MRs were 27.11%, 44%, and 5%, respectively.

We also detected a correlation between MR and total LOS; the results are shown in Figure 5. Fourteen percent of the total deaths occurred on the first day of ICU stay, and nearly 40% of the deaths occurred within the first week of admission.

DISCUSSION

ICUs are the most critical units of hospitals because they cater to patients with greater morbidity and higher mortality risk; further, patients with different clinical diagnoses, treatments, and follow-up procedures are admitted to the ICU. MRs are the most important outcomes of these units and should be monitored continuously. These rates may vary for each hospital and

TABLE 2. Sex-based differences in the clinical outcomes, age, and LOS of the subjects

	Male	Female	p
Patient sex n (%): 734	10 (55.8%)	324 (44.2%)	0.0019*
Dead patients n (%): 199	112 (56.28)	87 (46.72)	0.1821
Surviving patients n (%): 535	298 (55.70)	237 (44.3011)	0.0091*
Mean age of the study population (±SD)	56.46±23.52	67.85±17.14	≤0.0001*
Mean age of the study population (±SD)	68.58±19.30	68.21±15.47	0.7788
Mean age of surviving patients	55.29±3.119	58.21±23.85	0.0144*
Median age of the study population (and IQR)	64 (77-42=35)	69 (78-48=30)	
Median age of dead patients (and IQR)	70 (79-62=17)	74 (71-58=13)	
Median age of surviving patients (and IQR)	60 (75-37=38)	65 (78-36=42)	
LOS* of the study population (±SD)	17.78±45.6	14.23±25.73	0.2113
Mean LOS* of dead patients (±SD)	20.53±71.08	15.71±26.83	0.2476
Mean LOS*of surviving patients (±SD)	16.75±31.44	13.69±25.35	0.1549
Median LOS* of the study population (and IQR)	7 (15-3=12)	7 (16-3=13)	
Median LOS* of dead patients (and IQR)	6 (18-2=16)	8 (19-2=17)	
Median LOS* of surviving patients (and IQR)	7 (15-3=12)	7 (15-3=12)	

(*): In days. LOS: Length of stay; IQR: Interquartile ranges

TABLE 3. Different characteristics and clinical outcomes of the study population

	Dead patients	Live patients	p
Total patients n (%): 734	n=199 (27.11)	n=535 (72.89)	p<0.0001
Male n (%): 410	112 (27.31)	298 (72.69)	
Female n (%): 324	87 (26.85)	237 (83.15)	
Mean age of the study population (±SD)	68.3±16.54	56.58±23.43	p<0.0001
Mean age of male patients (±SD)	68.58±19.30	55.29±3.119	p<0.0001
Mean age of female patients (±SD)	68.21±15.47	58.21±23.85	p<0.0001
Median age of the study population (and IQR)	72 (78-61=17)	62 (77-35=42)	
Median age of male patients (and IQR)	70 (79-62=17)	60 (75-37=38)	
Median age of female patients (and IQR)	74 (71-58=13)	65 (78-36=42)	
Mean LOS* of the study population (±SD)	18.66 (±56.02)	15.47 (±28.93)	0.3149
Mean LOS of male patients (±SD)	20.53 (±71.08)	16.75 (±31.44)	0.3194
Mean LOS* of female patients (±SD)	15.71 (±26.83)	13.69 (±25.35)	0.3453
Total Median LOS* (and IQR)	7 (18-2=16)	7 (15-3=12)	
Median LOS* of male patients (and IQR)	6 (18-2=16)	7 (15-3=12)	
Median LOS* of female patients (and IQR)	8 (19-2=17)	7 (15-3=12)	

(*): In days

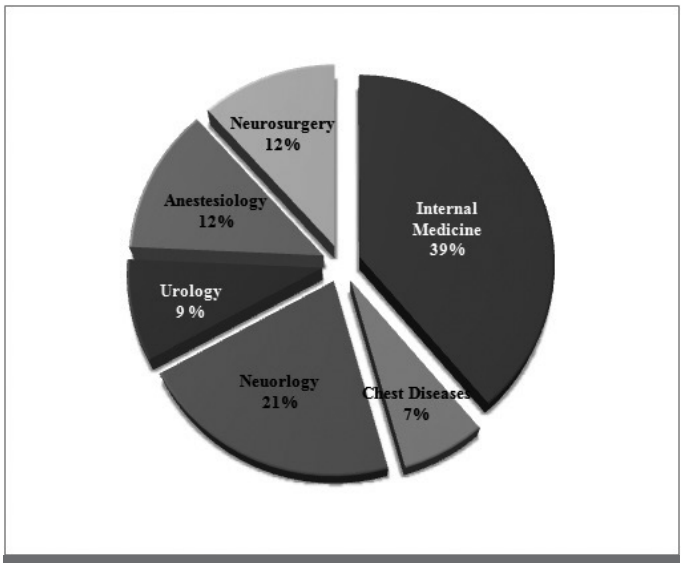

FIGURE 3. The distribution of the MR, age, and clinical characteristics of the patients

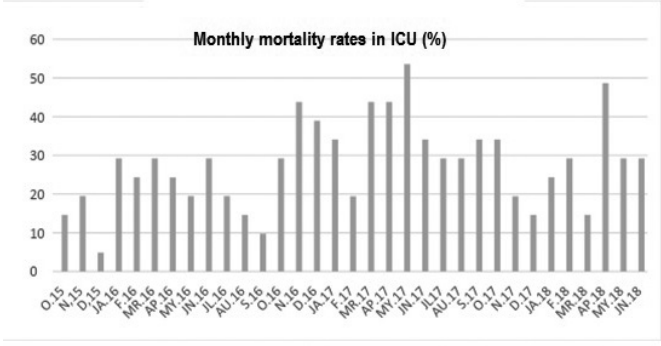

FIGURE 4. Calculation of monthly MRs during the study period

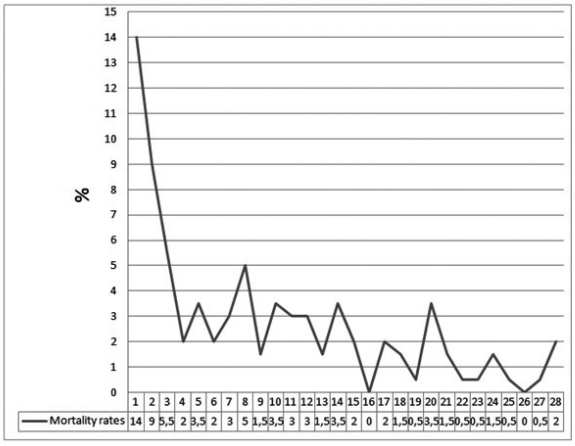

FIGURE 5. Correlation between MR and total LOS
MR: mortality rates; LOS: longer length of stay

among countries. Generally, lower-income countries tend to have higher MRs as compared to their well-developed counterparts. The total MR of our CIPs was 27.11%. Bonkoungou et al. (3) reported a MR of 43.7% at a university hospital in Burkino-Faso. Similar results have been reported by other authors in their countries (2-6). The MRs are lower in well-developed countries. Cook et al. (7) reported an MR of 17% in the USA.

Total MRs of 25.6% and 52.3% have been reported in two independent Turkish studies (8, 9). The MR reported in the second study is significantly higher than that determined in our study.

We have summarized the general characteristics of our study population in Table 1. The average ICU LOS was 16.33±38.20 days in our study. The minimum LOS was 1 day, while the maximum LOS was 722 days (only one patient stayed for an extraordinarily long time). The median LOS and IQR (days) were 7 (15-3=12) days. The median LOS and IQR show the variation in the LOS. The mean age of our patients was 59.67±22.47 years (range: 7–96 years), with more subjects belonging to the elderly age group.

As shown in Table 2, significantly more male than female patients were admitted (55.8% vs. 44.2%, p=0.0019); however, there was no difference in their MRs. More male subjects survived compared to female subjects (p=0.0091). A meta-analysis revealed dominance of male sex at 63.6% (10).

More elderly females were admitted as compared to elderly male subjects (mean age of female patients vs. that of male patients: 67.85±17.14 vs. 56.46±23.52 and p<0.0001). Although female survivors were older than male survivors, there was no sex-based difference in those who died (p=0.0144). These results were supported by the data regarding median age and IQR difference studies. Similar results have been reported by other studies (5, 6, 11). There were no significant sex-based differences in studies analyzing the LOS.

We have also compared the main characteristics of both the outcomes in Table 3. The total MR was 27.11% (p<0.0001) in our ICU. The MRs of the male and female patients were similar to that of the total study population (comparison of deaths vs. survivals: men: 27.31% vs. 72.69%, women: 26.85% vs. 83.15%). There were no sex-based differences in the outcome; however, those who died were older than those who survived (all p<0.0001). Median ages of patients were also similar. However, all three IQRs were quite different. The IQR of age for those who died was 13–17, while that for the survivors was 38–42. These results indicate that the variability in the median age of the survivors was about three times more than that for those who died. There were no differences in the mean, median, and IQR for LOS based on the outcomes.

As stated in Figure 1, the age distribution study pointed out a reciprocal curve between 79 and 20 years of ages both in total and survivor groups, while mortal cases continuously decrease in same age period. In total, 64% of the study population was aged >60 years. Age distribution sharply increased after 50 years. In this distribution, 71.2% of the patients were older than 50 years.

The clinical classification of the patients has been summarized in Figure 2. Those with chest diseases formed the majority, followed by those transferred from the internal medicine clinic.

The distribution of the MR, age, and clinical characteristics of the patients in this study has been outlined in Figure 3; these

findings prompted us to further evaluate the distribution of the clinical characteristics among those aged 20–29 years. It is noteworthy that internal medicine patients comprised the majority (40%) rather than chest diseases patients, followed by neurology patients (22%). The number of chest diseases patients decreased in the second least group.

We also calculated the monthly MRs during the study period; the results have been highlighted in Figure 4. This was the most important quality indicator of the hospital and ICU settings. This indicator should be calculated periodically. There are no mandatory regulations to detect this indicator in the TRNC. We studied these indicators in our ICU among CIPs. The average number of patients admitted to our ICU every month was 20.53, with the minimum MR being 4.87% and the maximum MR being 53.58%.

The LOS is one of the most important indicators of ICU care. Longer LOS may be related to both the patient's medical condition and the quality of medical services provided; however, this does not influences the increase in MRs.

We classified the patient's outcome according to their LOS. The highest number of deaths occurred on the day of admission (14% of the total deaths). As seen in Figure 5, 40% of the deaths in our ICU occurred within the first 15 days. Similar results were reported by Williams et al. (12) and Santamaria et al. (13). It is noteworthy that we could not detect any correlation between higher MR and longer LOS.

Study Limitations

The measurement of disease severity in the admitted patients and 28-day follow-up after discharge were not possible due to technical limitations.

In conclusion, to our knowledge, this is the first study to report on the MR of CIPs in Cyprus. Our results showed that our MRs are lower than those in many low-income countries. This basic study will be an indicative reference for further studies. The results will enable hospital authorities to enhance and improve their quality of care.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of the Near East University Medical Research Ethics Committee. (Approval Date: 14.09.2018, Approval Number: NEU/2018/59/618).

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

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

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Original Article

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Discriminating Borderline Ovarian Tumors from Ovarian Cancer: Focus on Systemic İnflammatory Response Markers

Gulin Feykan Yegin, Emre Erdem Taş, Gökhan Kılıç, Hüseyin Levent Keskin, Ayşe Filiz Yavuz

Department of Gynecology and Obstetrics, Yıldırım Beyazıt University Ataturk Training and Research Hospital, Ankara, Turkey

ORCID IDs of the authors: G.F.Y. 0000-0001-8006-5055; E.E.T. 0000-0001-6043-2700; GK 0000-0002-9940-7139; H.L.K. 0000-0002-2268-3821; A.F.Y. 0000-0003-3699-7757.

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BACKGROUND/AIMS
This study aims to investigate the preoperative diagnostic accuracy of systemic inflammatory response (SIR) markers, including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), in discriminating borderline ovarian tumors (BOTs) from malignancy and, thereby, prevent over- or underdiagnosis in the management of BOTs and ovarian malignancy.

MATERIAL and METHODS
Medical records of 99 patients who underwent surgical treatment and had confirmed histopathologic diagnosis of primary malignant or BOT were retrospectively analyzed. The recommended cut-off values for preoperative NLR and PLR were determined using receiver operating characteristic. The associations of NLR and PLR with tumors' malignancy potentials were analyzed using the Chi-square test or the Fisher's exact test.

RESULTS
The mean NLR and PLR were significantly lower (p=0.002 and p=0.006, respectively) in BOTs group than in the epithelial ovarian carcinoma (EOC) group. Optimal cut-off points of NLR and PLR for discriminating BOTs and EOC group was 2.42 and 169.2, respectively. The likelihood of malignancy increased in group with NLR values >2.42 (p<0.001; OR, 2.36, 95%; CI, 1.19–4.68) and PLR values >169.2 (p<0.001; OR, 3.6, 95%; CI, 1.48–8.76). Most importantly, both NLR and PLR values were above the cut-off point, and the malignancy risk had a 12-fold increase (p<0.001; OR, 12.15, 95%; CI, 1.78–82.6).

CONCLUSION
This data will strengthen the discrimination of malignant tumors from BOTs and facilitate the decision-making on surgical radicality and may also be used in combination with imaging strategies, tumor markers, and frozen section to increase diagnostic accuracy.

Keywords: Borderline ovarian tumor, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic inflammatory response

INTRODUCTION

Epithelial ovarian cancer is the most lethal gynecologic cancer; it is a major cause of cancer-related death in women (1, 2). The high mortality is associated with difficulties regarding early diagnosis, development of resistance to chemotherapeutic agents in advanced stage, and high recurrence rates (1). Currently, about 60%–65% of patients are being diagnosed with stage III ovarian carcinoma, which explains the high mortality of this neoplasm (3, 4). The five-year survival for patients diagnosed with stage I ranges from 80% to 90%; whereas for patients with stages III–IV, it ranges from 5% to 50% (4). Though great efforts had been made in decades, the abilities of predicting malignancy potential of ovarian tumors are inadequate, and there is still no well-established screening tool for ovarian cancer (5, 6).

Borderline tumors of the ovary (BOTs), also called tumors of low-malignant potential, are a heterogeneous group of lesions histologically defined by atypical epithelial proliferation without stromal invasion (7). The behavior of these noninvasive neoplasms is distinct from low-grade ovarian carcinoma, and they are considered a distinct clinical entity (7). BOTs account for 14%–15% of all primary ovarian neoplasms (8). The disease has a good prognosis (stage I five-year survival is 99%), and unilateral salpingo-oophorectomy (USO) appears to be an option for women with unilateral disease (9). Com-

Corresponding Author: Gülin Feykan Yegin
E-mail: gulin_yegin@hotmail.com

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plete staging with total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) is required for women with stage II or higher disease. The efficacy of conservative surgery in early-stage diseases was best illustrated in a systematic review and meta-analysis of 120 mostly retrospective studies (10). For women with stage I ovarian borderline tumors treated with either USO or ovarian cystectomy, with an average follow-up of three to six years, the borderline recurrence rate was 13%, recurrence with malignant disease was 1.6%, and the death rate was 0.5% (10, 11). According to recent data, for women with an apparent unilateral stage I BOT, unilateral salpingo-oophorectomy, pelvic washing, or omental and peritoneal biopsy is suggested rather than complete staging surgery (1, 5). The ability to preoperatively distinguish borderline tumors from early-stage carcinoma considerably influences surgical treatment and allows improved counseling of patients.

Systemic inflammatory response (SIR) are closely associated with cancer initiation, progression, and metastasis, and thus, inflammatory markers, including the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have been studied and found to be related to cancer mortality and employed as useful prognostic indications in many solid tumors (12, 13). Studies associated with BOTs are exactly limited, and to the best of our knowledge, the cut-off values of NLR and PLR to discriminate BOTs from malignant tumors have not been clarified yet. Thus, we conducted the current study to compare preoperative diagnostic accuracy of SIR markers, including NLR and PLR, in BOTs and malignant tumors, and thereby prevent over- or underdiagnosis in the management of BOTs and ovarian malignancy.

MATERIAL and METHODS

Subjects

A retrospective analysis was performed with data gathered from 99 patients who underwent surgical treatment and were histopathologically diagnosed with primary malignant or BOT between 2007 and 2017. The indication criteria for surgical treatment (laparotomy/laparoscopy) was determined as anechoic cysts with a maximum diameter more than 7 cm; persistence of change more than six months; altered CA 125, CA 15-3, CEA, alpha-fetoprotein, and CA 19.9; presence of intracystic vegetation; ovarian masses with septation and/or solid component; and resistance index by color Doppler less than or equal to 0.4. On the other hand, the exclusion criteria suggests the presence of acute inflammatory disease, myeloproliferative disorders, concomitant gynecological and other cancers, autoimmune disease, and usage of any drug that affects CBC parameters, including anticoagulants or hormonal contents, or reported smoking. According to inclusion and exclusion criteria, 99 patients were enrolled in the study. All participants submitted a written informed consent. The study was approved by the Ethical Review Board of our institution. This research was conducted in accordance with the World Medical Association Declaration of Helsinki (and the 2000 revision).

Main Points:

- The mean neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were significantly lower (p=0.002 and p=0.006, respectively) in borderline ovarian tumors (BOTs) groups than in the epithelial ovarian cancer (EOC) group.
- Most importantly, the malignancy risk had a 12-fold increase in cases whom NLR and PLR values were both above the cut-off point(p<0.001; OR, 12.15, 95%; CI, 1.78–82.6).
- NLR and PLR can be used to strengthen the diagnostic accuracy on discriminating borderline ovarian tumors (BOTs) from ovarian cancer.

Demographic and pathologic characteristics (age, gravidity, parity, histological type, FIGO stage) and data regarding preoperative SIR markers, including NLR and PLR, were retrieved from patients' medical files and hospital records. Blood samples were collected from patients during their admission at the hospital for surgery and before receiving any medications (Sysmex XE-2100 Automated CBC Analyzer, Sysmex, Nürnberg, Germany).

After grouping patients according to malignancy potential (i.e., borderline vs malignant epithelial ovarian tumors), the groups were compared in terms of the examined parameters.

Data Extraction

Preoperative blood samples were drawn 7–10 days prior to surgery. NLR was defined as absolute neutrophil count divided by absolute lymphocyte count, and PLR was defined as absolute platelet count divided by absolute lymphocyte count. Patients were then classified into low- and high-risk groups according to the cut-off values determined by the Youden index to examine the correlation between those markers and malignancy potential of epithelial ovarian tumors, preoperatively.

Statistical Analyses

The Kolmogorov–Smirnov assesses the normality of the data. Normally distributed data were expressed as means and standard deviations. Nonparametric data were expressed as medians and interquartile ranges. The groups were compared using independent sample t-tests and Mann–Whitney U tests. Variables with a $p<0.05$ were included in the receiver operating characteristic (ROC) curve analysis which determines the cut-off values. The biggest Youden index (sensitivity+specificity-1) was selected as the optimal cut-off point. The associations of NLR and PLR with tumor malignancy potentials were analyzed using the Chi-square test or the Fisher's exact test.

Statistical analyses were conducted using the Statistical Package for the Social Sciences software for Windows version 21.0 (IBM Corporation, Armonk, NY, USA). Odds ratios and 95.0% confidence intervals were determined. A $p<0.05$ was considered statistically significant.

RESULTS

The cases involved in the present study include a total of 99 patients; 79 (79.8) patients manifested epithelial ovarian carcinoma (EOC) and 20 (20.2%) patients with borderline ovarian tumor (BOTs). In the BOTs group, 10 (10.1%) of the neoplasms were serous and 10 (10.1%) were musinous. Demographic and pathologic characteristics and examined parameters of patients were summarized in Table 1.

TABLE 1. Demographic and surgical characteristics and preoperative SIR markers including NLR and PLR of patients

Characteristic	BOTs	EOC	p
Demographic and surgical, mean ± SD (range)			
Age (years)	47.4±14.5	57.1±14.5	0.740
Gravidity	4.24±2.86	2.75±1.9	0.042*
Parity	2.00±1.30	3.29±2.20	0.002*
FIGO stage, n (%)			
Low stage (IA-IB)	14 (14.1%)	3 (3%)	<0.001*
High stage (IC- II-III-IV)	6 (6.1%)	76 (76.8%)	<0.001*
SIR markers, mean±SD (range)			
NLR (%)	2.23±0.83	3.89±2.16	0.002*
PLR (%)	151.714±75.210	249.153±139.010	0.006*

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; BOT, borderline ovarian tumors; EOC, epithelial ovarian cancer; OR: odd ratio; CI: confidence interval

TABLE 2. Demographic and surgical characteristics and preoperative SIR markers including NLR and PLR of patients

		<cut-off	>cut-off	p	OR	95% CI
NLR	EOC	23 (29.1%)	56 (70.9%)	<0.001	2.36	1.19–4.68
	BOT	14 (70%)	6 (30%)			
PLR	EOC	22 (27.8%)	57 (72.2%)	<0.001	3.6	1.48– 8.76
	BOT	16 (80%)	4 (20%)			
NLR & PLR	EOC	31 (39.2%)	48 (60.8%)	<0.001	12.15	1.78– 82.6
	BOT	19 (95%)	1 (5%)			

NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; BOT: borderline ovarian tumors; EOC: epithelial ovarian cancer; OR, odd ratio; CI, confidence interval

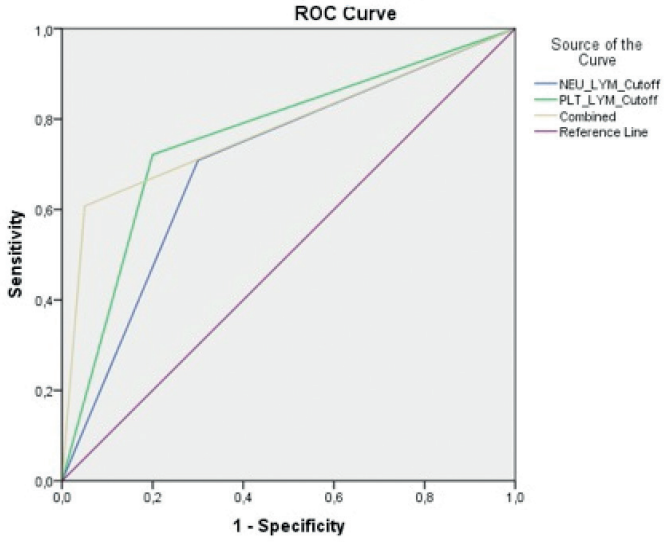

FIGURE 1. The receiver operating characteristic curve analysis of the relationship between only NLR, only PLR, and both NLR and PLR values
NEU_LYM : neutrophil-to-lymphocyte ratio
PLT_LYM: platelet-to-lymphocyte ratio
Combined: both neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in discriminating borderline ovarian tumors (BOTs)

There was no significant difference in the demographic characteristics (age, gravidity, and parity) between the BOTs and EOC groups (all p>0.05).

The mean NLR and PLR were significantly lower (p=0.002 and p=0.006, respectively) in BOTs group than in the EOC group.

ROC curve analyses revealed that the optimal cut-off points of NLR and PLR for discriminating BOTs and EOC group was 2.42 and 169.2, respectively (Figure 1).

Finally, when the groups (i.e., BOTs and EOC) were subdivided according to NLR, PLR, and NLR-PLR cut-off values (NLR≤2.42 vs. NLR>2.42 and PLR≤169.2 vs. PLR>169.2), the ratio of patients whose NLR, PLR, and NLR-PLR were above the cut-off value were high in EOC group than BOTs group, and significant differences were observed (p<0.001) (Table 2).

DISCUSSION

Our study demonstrated that in the group of patients with NLR values >2.42, the likelihood of malignancy increased by 2.3-fold (p<0.001; OR, 2.36, 95%; CI, 1.19–4.68), and the likelihood of malignancy of the ovarian tumor increased by 3.6-fold in the patient group with PLR values >169.2 (p<0.001; OR, 3.6, 95%; CI, 1.48–8.76). Most importantly, both NLR and PLR values were above the cut-off point, and a 12-fold increase in the malignancy risk was observed (p<0.001; OR, 12.15, 95%; CI, 1.78–82.6).

The increasing evidences focus on the importance of inflammation in the initiation, promotion, invasion, and metastasis periods of cancer. Increased neutrophil, platelet, C-reactive protein, and fibrinogen concentration in cancer process have been discussed in many studies (14). In addition, neutrophil-to-platelet ratio (NLR) and platelet-to-lymphocyte ratio have also been suggested to be useful in discriminating malignant and benign ovarian tumors (15-19). Numerous studies have demonstrated the association of PLR and NLR with ovarian cancers (20-22). In this study, the cut-off values of these markers discriminate BOTs from malignancy, preoperatively, to prevent higher morbidity and mortality due to radical or second-look surgeries.

In a published meta-analysis, NLR and PLR were found to be significant predictors for solid tumors originating from several tissues (23). However, there is no consensus on predictive values of NLR and PLR in gynecologic cancers. Additionally, data pertaining to BOTs is limited (24).

Current tools used in the management of adnexal masses are gynecologic examination, tumor markers, and imaging methods. However, there are no sonographic features strongly suggestive of borderline histology, and sonographic appearance ranges from unilocular cysts to masses with solid components. Tumor markers have been demonstrated as useful in identifying malignancy, but these parameters are also found to be elevated in 25%–60% of BOTs (25-28). In current literature, CA 125, CEA, and CA 19–9 were targeted to identify the prognosis of borderline tumors but are not considered to be a diagnostic tool (29). Consequently, we are still unable to anticipate malignancy potential and invasion status of ovarian tumors, preoperatively.

Intraoperative frozen section plays the most critical role in the management of these cases. However, the sensitivities for detection of BOTs are 50%–85%. A previous study was designed with patients who underwent surgery due to an adnexal mass. Among these patients, 17.5% were preliminarily diagnosed as a BOT. The final pathology was reported as benign. More importantly, in 17.5% of patients diagnosed with ovarian carcinoma in frozen section, the final pathology was reported as BOT (24). All under- and overdiagnosis of these patients will undoubtedly cause mismanagement and increased morbidity and mortality due to overtreatment or recurrent surgeries.

Parameters that increase the frozen section's accuracy have also been studied, and the most favorable marker in literature was determined to be CA 125, especially in serous malignancies (25-27). Conversely, numerous studies showed no remarkable effect of CA 125 in increasing frozen section diagnostic potential (30). It has been reported that simple indices, such as NLR and PLR, have high sensitivity for detection of early-stage invasive ovarian cancer (31). Additionally, the NLR value was found to be useful in increasing frozen section accuracy (24).

Although studies focus on the discrimination of malignant tumors from benign masses, it is also important to classify a tumor as borderline/malignant tumor especially in a fertility-preserving surgery and manage operation in an optimal way by decreasing morbidity and mortality.

In a reported study, a statically significant impact for both preoperative NLR and PLR in distinguishing BOTs from simple ovarian serous cysts was suggested (17). In another study designed on a patient group with benign and malignant ovarian tumors, preoperative PLR and platelet count were statistically found to be significant between groups, but there was no association detected with NLR (20). Similarly, in another study, preoperative NLR, PLR, and monocyte were established to be higher in malignant cases. It was also stated by authors that NLR and PLR combined with CA 125 can be useful for the differentiation of ovarian tumors, whether it's benign or malignant (32). PLR was also found to be correlated with low survival rates in ovarian cancers (19). In a study regarding discrimination of BOTs from malign tumors by using NLR and PLR, authors stated that these SIR markers are predictors of malignant tumors but not borderline tumors, even in case of tumor invasion less than 5 mm (33).

The current research is limited to its retrospective and single-centered design; thus, prospective randomized studies with larger sample sizes are required to verify our results.

In conclusion, this data will strengthen the elimination of malignant tumors from BOTs and may also be used in combination with imaging strategies, tumor markers, and frozen section to increase diagnostic accuracy before radical surgical interventions.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Yıldırım Beyazit University Faculty of Medicine Clinical Research Ethics Committee. (Approval date: 21.12.2018, approval no: 2367996/ i32).

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

Peer-review: Externally peer-reviewed.

Author contributions: Concept-N.B., B.S.; Design- B.S.,O.Y.; Supervision-N.B.; Resource:- B.S.,O.Y.; Materials- N.B.; Data Collection and/or Processing- B.S.,O.Y.; Analysis and/or Interpretation- B.S.,O.Y.; Literature Search- B.S.,O.Y.; Writing- B.S.,O.Y.; Critical Reviews- N.B.

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Original Article

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Childhood and Adolescence Vitiligo: Clinicoepidemiological Profile and Its Impact on Quality of Life

Nermin Karaosmanoğlu[1], Pınar Özdemir Çetinkaya[2], Işıl Göğem İmren[1], Esra Kıratlı Nalbant[1], Engin Karaaslan[3]

[1]Department of Dermatology and Venereology, Ankara Training and Research Hospital, Ankara, Turkey
[2]Department of Dermatology and Venereology, Nazilli State Hospital, Aydın, Turkey
[3]Department of Dermatology and Venereology Nusaybin State Hospital, Mardin, Turkey

ORCID IDs of the authors: N.K. 0000-0002-3462-1628; P.Ö.Ç. 0000-0001-5286-3260; İ.G.İ. 0000-0002-9574-3231; E.K.N. 0000-0002-1154-0219; E.K. 0000-0003-2911-5082.

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BACKGROUND/AIMS
Vitiligo is an acquired, idiopathic, generally progressive pigmentation disorder of an unknown etiology. Vitiligo usually begins during childhood or adolescence. This study aimed to evaluate the clinical and demographic characteristics of this disease as well as understand its impact on patient quality of life (QoL).

MATERIAL and METHODS
Thirty-one vitiligo patients aged 5–16 years who visited the outpatient dermatology clinic were included in the study. The demographic information of all the patients was collected. A complete clinical examination was performed, and the disease-related features were recorded. Moreover, all the patients completed the children's dermatology life quality index (CDLQI).

RESULTS
Of the 31 patients, 20 were girls (64.5%), and 11 were boys (35.5%). The mean patient age was 10.33±4.19 years. Vitiligo vulgaris was the most common (51.6%) clinical type of vitiligo. The most commonly involved areas were the trunk (54.9%), face (54.9%), and extremities (41.7%). In the study group, 32.3% of the patients (10 of 31) had an accompanying autoimmune disease. The median CDLQI score of the patient group was 6 (min–max: 0–22). There was a significant correlation between patient age and CDLQI score (r=0.369, p=0.041).

CONCLUSION
Vitiligo has a different clinicoepidemiological profile in children and adolescents. This disease significantly lowers the patient's QoL. Our study found a significant correlation between patient age and CDLQI score. In clinical practice, it is important to remember that vitiligo is not only a cosmetic disorder; it may negatively affect multiple aspects of the patient's QoL.

Keywords: Epidemiology, quality of life, vitiligo

INTRODUCTION

Vitiligo is generally an acquired, progressive pigmentation disorder of an unknown etiology (1, 2). The onset of vitiligo is usually during childhood or adolescence (3), with the prevalence being 0.04%–2.2% in children (2). The disease does not cause a physical disturbance; however, its clinical manifestations may have negative psychosocial effects and decrease the patient's quality of life (QoL), especially when the onset is during childhood or adolescence (1).

The Children's Dermatology Life Quality Index (CDLQI) is used for children aged 5–16 years and evaluates the influence of skin diseases on the QoL considering the findings during last week. It was first created by Lewis-Jones and Finlay (4). Balcı et al. (5) then translated the scale into the Turkish language and conducted validation studies.

This index has been used for many childhood dermatological diseases (6); however, few studies have used this index for vitiligo (1, 2, 7-11). Limited information is available about the influence of vitiligo on the QoL of children; therefore, we decided to conduct research on this topic with the patients managed at the outpatient clinic.

Corresponding Author: Pınar Özdemir Çetinkaya
E-mail: pinarozdemir44@gmail.com

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This study aimed to evaluate the clinical and demographic characteristics of the disease and the effects on the QoL of children and adolescents.

MATERIALS and METHODS

Total 31 vitiligo patients aged 5–16 years who visited the outpatient dermatology clinic were included in the study. The research protocol was approved by the institutional ethics committee. All the participants and their parents were informed about the study, and informed consent form was obtained.

Diagnoses were established by dermatologists in charge of the study and were based on the clinical symptoms. Demographic details of all the patients, including the age, sex, body mass index, age of onset, duration of disease, presence of associated autoimmune and endocrine diseases, family history, and story of previous treatments were recorded. The patients were questioned about the daily duration of sun exposure, use of sunscreen, seasonal exacerbation, as well as symptoms, such as pruritus and erythema. A complete clinical examination was performed and information about the sites, percentage of the body surface area involved, presence of leukotrichia and Koebner phenomenon was recorded from the clinic notes. The status of the disease was defined as active and stable. If there was emergence of new lesions and/or enlargement in the size of existing lesions during the previous 3 months, the disease was recorded as active. The standard working classification system was used to determine the clinical types of vitiligo, and the patients were divided into the following six groups: focal, segmental, vulgaris, acrofacial, mucosal, and universal (12).

The 10-question CDLQI is often used in dermatology practice to assess how a skin disease has affected a patient's daily life activities during the previous week. The validated CDLQI was the instrument mainly used in this study. It has a Likert scale scored from 0–3 (0=not at all, 1=only a little, 2=quite a lot, and 3=very much) and consists of 7 parts that help evaluate different characteristics as follows: "symptoms/feelings," "leisure," "school/holidays," "daily activities," "personal relationships," "sleep," and "treatment." The maximum possible score was 30 and the lowest possible score was 0. Higher the score, lower the QoL (4). The children completed the CDLQI themselves. Few younger children could not read or write; for these children, the parents were asked to read out the questions and record their answers without directing the children in their point of view.

Main Points:

- Vitiligo does not cause a physical disturbance; however, its clinical manifestations may have negative psychosocial effects and decrease the patient's quality of life, especially when the onset is during childhood or adolescence.
- Of the 31 patients, 20 were girls (64.5%), and 11 were boys (35.5%). There is a female preponderance in the present study.
- Ten (32.3%) patients had accompanying autoimmune and endocrine diseases such as autoimmune tiroiditis, celiac disease, alopecia areata, type 1 diabetes mellitus, and halo nevus.
- The median children's dermatology life quality index (CDLQI) score of the patient group was 6 (range: 0–22). There was a significant correlation between patient age and CDLQI scores.
- Vitiligo is common in children and adolescents and has a different clinicoepidemiological profile.

Statistical Analyses

All the analyses were performed using the Statistical Package for the Social Sciences, version 16.00 (SPSS Inc., Chicago, USA) and a p value <0.05 was considered statistically significant. Normality of the data was tested. The qualitative variables were described as absolute and relative frequencies. Mean and standard deviation values were calculated for normal quantitative variables, while median and minimum-maximum values were calculated for the non-normal variables. Non-normally distributed quantitative variables were compared using the Mann-Whitney U test in the presence of two variables and the Kruskal Wallis test in the presence of more than two variables; Spearman's Rho analyses was used for correlations between two variables.

RESULTS

Of the 31 patients, 20 were girls (64.5%), and 11 were boys (35.5%). The mean patient age was 10.33±4.19 years. Twenty patients were children (<12 years old) and 11 were adolescent (12–16 years old).

The mean body mass index was 20.62±3.50 kg/m^2. The average age at disease onset was 8.89±3.84 years. The median disease duration was 12 months (range: 1–72) (Table 1).

Eleven patients (35.5%) had focal, 16 (51.6%) had vulgaris, 2 (6.5%) had acrofacial, and 2 (6.5%) had segmental vitiligo. Nobody had mucosal or universal types of vitiligo (Table 2). Most patients (17, 54.9%) had lesions on the trunk; further, 17 (54.9%) had lesions on the face (Figure 1). The detailed distribution of the lesions is presented in Figure 2. The percentage of the involved body surface area is shown in Figure 3. Twenty-two (71%) patients complained of itching, and 27 (87.1%) had erythema. Eight (25.8%) reported seasonal exacerbation of the disease. Twenty-two patients (71%) had an active and progressive disease course, while 9 (29%) had a stable course. Eight patients (25.8%) had a positive Koebner phenomenon. Leukotrichia was found in 6 (19.4%) of the patients. None had a mucosal lesion (Table 3).

Total 23 patients (74.2%) had a sun exposure of <5 hours per day, 5 (16.1%) had 5–10 hours of exposure, and 3 (9.7%) had >10 hours of exposure per day. Of the 31 patients, only 4 (12.9%) reported using sunscreen regularly.

Twenty-one (67.7%) patients had no accompanying autoimmune and endocrine diseases, while 4 (12.9%) had autoimmune tiroiditis, 2 (6.5%) had celiac disease, 2 (6.5%) had alopecia areata, 1 (3.2%) had type 1 diabetes mellitus, and 1 (3.2%) had halo nevus. Seven patients (22.6%) had a family history of vitiligo. Seventeen patients (54.8%) had not undergone any treatment previously, while 5 (16.1%) used topical steroids, 3 (9.7%) used topical pimecrolimus, 3 (9.7%) used topical tacrolimus, and 3 (9.7%) underwent narrow-band ultraviolet UVB therapy.

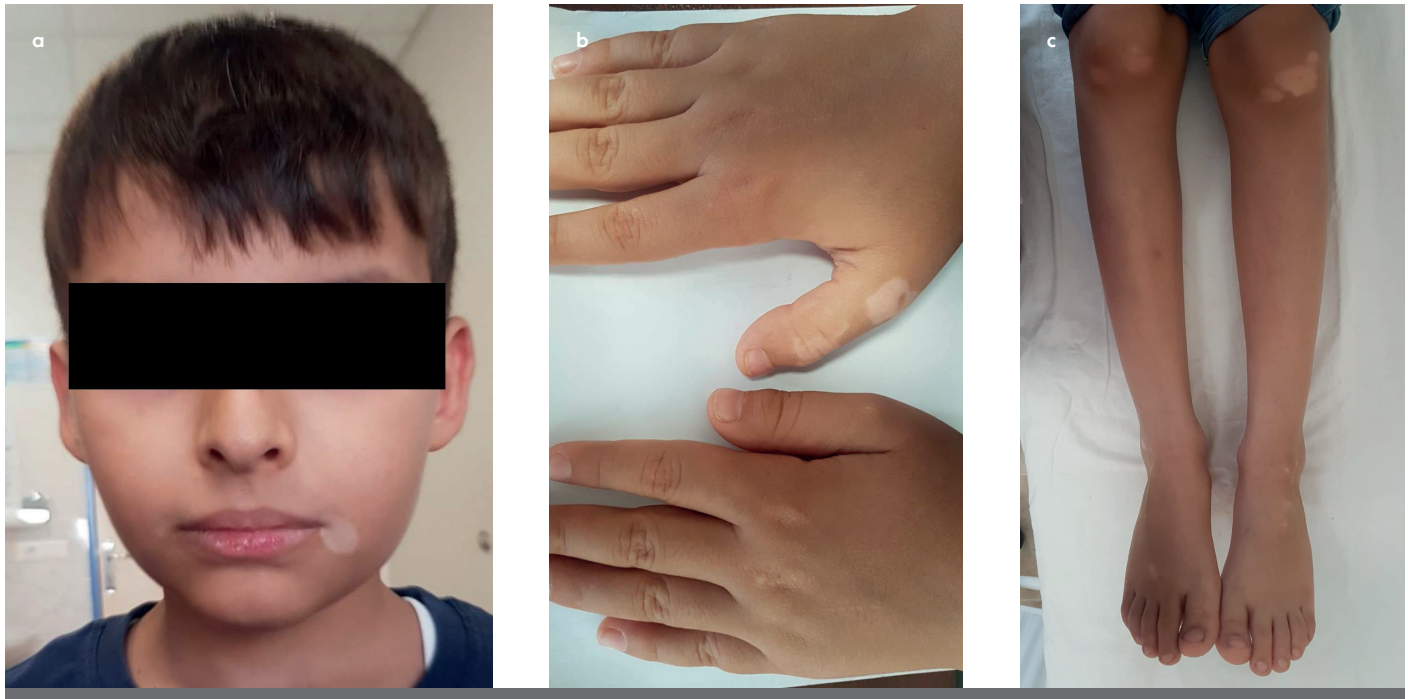
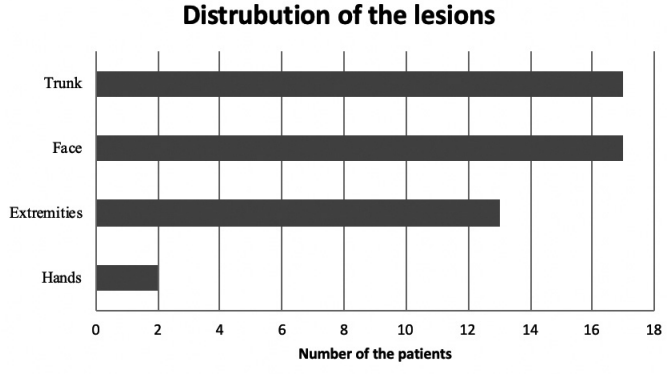


FIGURE 1. a-c. Depigmented macules and patches involving the face, hands, knees and feet in a patient with vitiligo vulgaris. (a) Face involvement. (b) Hand involvement. (c) Knee and feet involvement

TABLE I. Demographic characteristics of the vitiligo patients

Demographic characteristics			
Sex	Female (n/%)	Male (n/%)	Total (n/%)
	20 (64.5%)	11 (35.5%)	31 (100%)
Age	Mean±SD (years)	Min (years)	Max (years)
	10.33±4.19	2	16
Body Mass Index	Mean±SD (kg/m^2)	Min (kg/m^2)	Max (kg/m^2)
	20.62±3.50	13	27
Age at Disease Onset	Mean±SD (years)	Min (years)	Max (years)
	8.89±3.84	1.5	16
Duration of the Disease	Median (months)	Min (months)	Max (months)

Max: Maximum, Min: Minimum, SD: Standard deviation



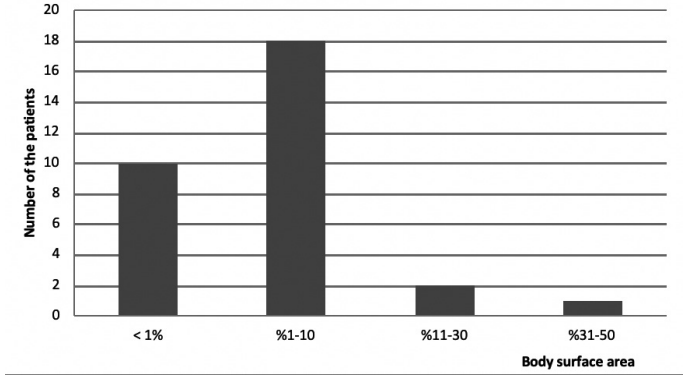


FIGURE 2. Distribution of the lesions

FIGURE 3. The percentage of the involved body surface area

TABLE 2. Distribution of the types of vitiligo among the patients

Types of Vitiligo	n	%
Focal Vitiligo	11	35.5
Vitiligo Vulgaris	16	51.6
Acrofacial Vitiligo	2	6.5
Segmental Vitiligo	2	6.5
Mucosal Vitiligo	-	-
Universal Vitiligo	-	-

TABLE 3. Clinical features of the vitiligo patients

Clinical Features	Present (n/%)	Absent (n/%)
Itching	22 (71)	9 (29)
Erythema	27 (87.1)	4 (12.9)
Seasonal exacerbation	8 (25.8)	23 (74.2)
Active and progressive course	22 (71)	9 (29)
Koebner phenomenon	8 (25.8)	23 (74.2)
Leukotrichia	6 (19.4)	25 (80.6)

TABLE 4. Evaluation of the correlation between the CDLQI scores of children and adolescents as well as the correlation of patient age with the CDLQI scores

	CDLQI score median/(min–max)	p
Children (n=20)	6 (3–20)	0.233
Adolescents (n=11)	4 (0–22)	
	Correlation coefficient	**p**
Age	r=0.369	0,041*
CDLQI score		

CDLQI: Children's Dermatology Life Quality Index

Effect of vitiligo on the CDLQI scores

The median CDLQI score of the patient group was 6 (range: 0–22). There was no significant difference in the CDLQI scores of boys and girls (p=0.917) as well as those of children and adolescents (p=0.233). There was a significant correlation between patient age and CDLQI scores (r=0.369, p=0.041) (Table 4). As the age of the patients increased, the CDLQI scores also increased, and thus, the QoL decreased. There was no significant correlation between age at disease onset and the CDLQI scores (p=0.123). There was no significant difference in the CDLQI scores as per vitiligo subtypes (p=0.350). There was no significant correlation between disease duration and the CDLQI scores (p=0.137) or between the percentage of the involved body surface area and the CDLQI scores (p=0.321).

DISCUSSION

Vitiligo is the most commonly encountered disease among disorders of depigmentation. It usually starts during childhood or early adulthood (3). This study aimed to describe the clinical spectrum and epidemiological data of vitiligo in children and adolescents. Moreover, we attempted to determine the effect of vitiligo on their QoL, using the CDLQI.

In >60% of the patients in our study group, the age of disease onset was 4–12 years (mean age: 8.89±3.84 years). In 10 out of the 31 patients (32.3%), the disease developed at 4–8 years of age, and in 10 (32.3%) subjects, the first symptoms of the disease occurred at 9–12 years of age. The reported disease onset varied greatly across studies; however, most authors have concluded that vitiligo is acquired in the early stages of life, especially at 4–12 years of age (13). When the age at presentation was studied, the mean age was 10.33±4.19 years, and most patients (35.5%) were 9–12 years old. This disparity and delay between the age of onset and age of presentation shows the progressive course of the disease and the need for long-term treatment and follow-up.

A female preponderance of (63% vs. 57%) in childhood vitiligo has been reported by most studies, in accordance with our results that showed a higher incidence (64.5%) of vitiligo in girls (14-16). However, some other studies have reported an almost equal incidence for boys and girls (17, 18). The higher incidence in girls could be attributed to overrepresentation in childhood and adolescence because of the cosmetically disfiguring, de-pigmenting nature of the disease.

In agreement with previous reported (3, 14), vitiligo vulgaris was the most common (51.6%) clinical type of vitiligo in children and adolescents in our study. Focal vitiligo was the second most common (35.5%) presentation in this study similar to the result published by Halder et al (14). Segmental type of vitiligo is a special clinical type for children because it has been reported more frequently in children. In most studies, the frequency is >16%, ranging from 4.6%–32.5% (14-18). However, in our patients, segmental vitiligo accounted for only 6.5% of all cases. We did not observe universal vitiligo, mucosal vitiligo, or mucosal involvement related to other clinical types of vitiligo in our patient group.

The three most commonly involved areas were the trunk (54.9%), face (54.9%) and extremities (41.7%). In the present study, 22.6% of the patients had a family history of vitiligo. Various studies have reported that patients with vitiligo have higher rates of positive family history, ranging from 3.3%–35% (3, 14, 17, 19, 20).

The incidence of leukotrichia was 19.4% in the present study. In the literature, the incidence of leukotrichia is known to range from 3.7%–25% (3, 14, 19). The Koebner phenomenon was present in 25.8% of our patients, similar to that reported in a previous trial (19).

Vitiligo may be associated with several endocrinopathies and other autoimmune disorders; however, in various studies, the frequency of autoimmune disorders in vitiligo patients was less than that observed in our study (21-23). In our study group, 32.3% of the patients (10/31) had an accompanying autoimmune disease. Four (12.9%) had autoimmune tiroiditis, 2 (6.5%) had celiac disease, 2 (6.5%) had alopecia areata, 1 (3.2%) had type I diabetes mellitus, and 1 (3.2%) had halo nevus.

Handa et al. (15) reported an incidence of 1.3% (7/625) for autoimmune disorders in children with vitiligo. Jaisankar et al (3) reported that none of their patients was diagnosed with autoimmune disorders, while Halder et al. (14) reported that 2.4% of their patients had alopecia areata (2/82). Schallreuter et al. (23) reported that all of the diseases thought to be associated with

vitiligo were coincidental except for thyroid diseases and vitiligo patients were susceptible to thyroid diseases withimpaired thyroidal function tests. Alopecia areata is frequently reported in children with vitiligo, with the rate ranging from 0.32%–2.4%. Thus, our rate of 6.5% was higher than that reported in the literature (14, 15).

Vitiligo is a disorder of skin color that causes emotional and functional deterioration that leads to a decreased QoL. In the present study, the median CDLQI score of the patient group was 6 (range: 0–22). The QoL was found to be severely impaired in 19.35% (n=6) of the subjects (scores>10). The literature includes several studies that have assessed the dermatology life quality index in children and adolescents with vitiligo. Dertlioğlu et al (1) evaluated the CDLQI scores in vitiligo patients, atopic dermatitis patients, and controls. The CDLQI scores were significantly elevated in the vitiligo patient group (mean±standard deviation: 11.68±6.54) compared to that in the atopic dermatitis group (7.74±4.59) and control group (0.62±0.77). Kruger et al (2) evaluated 74 patients, including children and adolescents, and a control group to compare their disease-related QoL scores. They reported that there was no significant severe impairment in the QoL in most patients. However, the mean score of CDLQI in the patient group was 2.8 (median: 1.5) and that in the control group was 0.6 (median: 0.0), representing a statistically significant difference (p=0.004). Silverberg et al (11) found that the median CDLQI score was 3.0 (interquartile range 5.0) in children and adolescent subjects with vitiligo. Furthermore, Lewis-Jones and Finlay (4) investigated the effect of cutaneous diseases of childhood on the CDLQI scores in a group of pediatric patients to find that the mean CDLQI scores were 5.4±5.0 in psoriasis patients, 7.7±5.6 in atopic dermatitis patients, and 5.6±3.8 in vitiligo patients. Although the scores varied across the studies, they usually remained <10. Thus, vitiligo usually lowers the QoL in children and adolescents significantly; however, but usually does not cause a severe impact.

In this study, neither disease duration nor percentage of the involved body surface area influenced the CDLQI scores. Although there was no significant difference in the CDLQI scores of children and adolescents, there was a significant correlation between patient age and CDLQI scores. Thus, as patient age increased, the CDLQI scores increased and the QoL decreased. This finding was consistent with that reported by Silverberg et al (11) who reported that the QoL in adolescents with a disease onset age of 10 years or older further deteriorated, suggesting that disease onset during the developmental stages of ego causes the greatest QoL impairment. Adolescence is a developmental period that includes physical, social, emotional, and cognitive development. Owing to the physical changes associated with puberty, adolescent patients were assumed to be more concerned with their physical symptoms. Thus, it was understandable that the quality of life decreased with disturbing dermatological findings that appeared on their bodies during this process of establishing a sense of identity. In more detail, the psychological findings in vitiligo can be explained by the interaction of cytokines and neuropeptides at the cellular level. Vitiligo is assumed to be an autoimmune disease. However, in the recent years, the concept of psycho-neuro-endocrine-immune system has been established. This system defines a bidirectional connection among stress, neuropeptides, cytokines, and the skin and claims that alterations in the levels of various cytokines and neuropeptides result in development of skin diseases, including vitiligo and neuropsychiatric findings (24).

In conclusion, this study presents the sociodemographic and clinical characteristics of patients with vitiligo aged <16 years old from Turkey as well as the effects of this disease on the patient QoL. Our study reveals that vitiligo is common in children and adolescents and has a different clinicoepidemiological profile. There is a female preponderance in the present study. Vitiligo vulgaris was the most common clinical type of vitiligo. Frequency of associated autoimmune disorders is more common. The median CDLQI score of the patients was 6 (range: 0–22), and there was a significant correlation between patient age and CDLQI score. In clinical practice, it is important to remember that vitiligo is not just a cosmetic disorder; it also has a considerable impact on multiple aspects of the patient's QoL.

Ethics Committee Approval: Ethics committee approval was received for this study from Instutional Ethics Committe of Ankara Training and Research Hospital Approval No: 4/2019 Date: 30.05.2019

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

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Original Article

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Comparison of Platelet-Rich Plasma and Hyaluronic Acid for Treatment of Early Stage Gonarthrosis

Yunus Emre Bektaş[1], Ortaç Güran[2], Nihat Demir Demirkıran[3], Ramadan Ozmanevra[4]

[1]Department Orthopaedics and Traumatology, Kilis State Hospital, Kilis, Turkey
[2]Department of Orthopaedics and Traumatology, Van Özalp State Hospital, Van, Turkey
[3]Department of Orthopaedics and Traumatology, Dumlupınar University, Evliya Çelebi Education and Research Hospital, Kütahya, Turkey
[4]Department of Orthopaedics and Traumatology, University of Kyrenia School of Medicine, Kyrenia, North Cyprus

ORCID IDs of the authors: Y.E.B. 0000-0001-5551-6475; O.G. 0000-0001-6485-5807; N.D.D. 0000-0002-0724-9672; R.Ö. 0000-0003-0515-4001.

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BACKGROUND/AIMS
This study aimed to compare the outcomes of platelet-rich plasma (PRP) and hyaluronic acid (HA) injections in early-stage gonarthrosis.

MATERIAL and METHODS
Radiographs were examined retrospectively, and 60 patients with Kellgren Lawrence Stage I, 2, and 3 were included in the study. Twenty-eight patients were administered HA, and 32 patients were administered PRP. PRP injections were administered three times in total with two-week intervals, while the HA injection was used once. The initial, 1-month, and 6-month follow-up records were obtained. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (pain, stiffness, physical function) and Visual Analog Scale (VAS) scores were evaluated.

RESULTS
No statistically significant difference was observed between the HA and PRP groups. When the WOMAC scores were evaluated, it was seen that the function, joint stiffness, and overall WOMAC scores were positively affected in both the groups; however, there was no difference between the two groups.

CONCLUSION
PRP is a novel treatment option in knee osteoarthritis (OA) management, and an increasing number of clinical studies have shown promising results. Both PRP and HA have positive effect in patients with early gonarthrosis; however, the results indicated no superiority in the PRP group.

Keywords: Gonarthrosis, hyaluronic acid, osteoarthritis, platelet-rich plasma

INTRODUCTION

Knee osteoarthritis is a very common chronic degenerative disease that can impose significant costs on the health systems (1). This disease is recognized as one of top 10 causes of disability around the world (2). The most common symptoms of knee osteoarthritis are pain and physical limitations that have a significant effect on the individual's quality of life and his/her social and economic activities (3).

Today, drugs, including painkillers, corticosteroids, glucosamine, chondroitin sulfate, and non-steroid anti-inflammatory drugs, are used along with viscosupplementation to relieve pain and symptoms as well as to slow the progression of the arthritis (3). Moreover, intra-articular injections are used as an effective option for the drug therapy of arthritis (4).

Hyaluronic acid (HA) and platelet-rich plasma (PRP) are two treatment methods are currently used in patients with early-stage gonarthrosis and have shown promising results. The present study aimed to compare the outcomes of PRP and HA injections in early-stage gonarthrosis.

Corresponding Author: Ramadan Ozmanevra
E-mail: rozmanevra@gmail.com

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MATERIALS AND METHODS

Radiographs were examined retrospectively, and 60 patients with Kellgren Lawrence Stage I, 2, and 3 were included in the study. Patients who had undergone PRP and HA therapy from April 2017 to November 2017 at the Dokuz Eylül University Hospital were enrolled in the study. The study protocol was approved by the Ethics Committee at the Dokuz Eylül University. Informed consent was obtained from the patients before the injections were administered, and the WOMAC and VAS scores at follow-ups were used.

The exclusion criteria included previous lower extremity surgery, systemic disorders (diabetes, rheumatic diseases, severe cardiovascular diseases, hematological diseases, and infections), generalized OA, ongoing anticoagulant, or antiaggregant therapy, use of NSAIDs in the 5 days before the injection, hemoglobin values <II g/dL, and platelet values <I50,000/mm^3.

Twenty-eight patients were administered HA, and 32 were administered PRP.

PRP injections were administered three times in total with two-week intervals, while HA was administered as a single, 4-mL injection. For PRP preparation, about 40 mL of venous blood was centrifuged for I5 min, giving two different layers of red blood cell sediment and plasma. Then, the plasma was separated to the sediment containing platelets. Finally 4–6 mL PRP was obtained.

The injection site on the skin was cleaned with povidone iodine. PRP was injected using a 22-gauge needle while the knee was at 90° flexion in the sitting position. The inferolateral approach was used and after I5 min of rest, the patients were asked to flex and extend their knees. HA was administered as a single injection with a prepared needle in the same procedure as that used for administering PRP. The initial WOMAC and VAS scores were obtained from the patients' medical records. The initial scores were saved before starting each procedure. No restrictions were placed on the patients, and no complications were observed after the applications.

The initial, I-month, and 6-month follow-up records were obtained. The WOMAC score and VAS scores were evaluated. The WOMAC index consists of 27 questions for three parameters, including pain, stiffness, and physical function. Each question is scored from 0 (none) to 4 (extreme). The sum of the scores of the subscales is the total WOMAC score (ranging from 0–I08). Higher scores indicated worse conditions. The VAS index was also evaluated. VAS scores range from 0 (no pain) to I0 (worst possible pain).

Data were analyzed by using Statistical Package for the Social Sciences (IBM SPSS Corp.; Armonk, NY, USA) I8.0 Mann Whitney U and Wilcoxon tests were used for the statistical analyses.

Main Points:

- PRP has been accepted as an intra-articular treatment method such as hyaluronic acid in the treatment of knee osteoarthritis especially in the last I0 years.
- There are studies reporting that PRP treatment has satisfactory results, as well as studies concluding that there may be a placebo effect.
- The PRP treatment is considered practically harmless and is being increasingly used. However, higher cost of PRP should be kept on mind and indications should be revised.
- Randomized controlled clinical studies are essential to determine its indications more clearly and to confirm its efficacy and safety.

RESULTS

There were 6 men and 22 women in the HA group and 6 men and 26 women in the PRP group. The mean patient age was 63.53 y in the HA group and 63.43 y in the PRP group. The body mass index was 3I.48 kg/m^2 in the HA group and 33.I5 kg/m^2 in the PRP group (Table I). The initial, I-month, and 6-month WOMAC scores in the HA group were 83.96, 66.89, 58.53, respectively.

The initial, I-month, and 6-month WOMAC scores for the PRP group were 79.84, 67.8I, and 64.62, respectively (Table 2).

The initial, I-month, and 6-month VAS scores in the HA group were 6.45, 4.66, and 4.04, respectively. The initial, I-month, and 6-month VAS scores in the PRP group were 6.0, 4.2I, and 3.83, respectively (Table 3).

There was no difference between the groups in terms of sex and Kellgren Lawrence staging. However, the duration of the complaints in the PRP group was significantly longer than that in the HA group.

In both the HA and PRP groups, pain was reduced significantly in the subsequent measurements. Thus, HA and PRP applications

TABLE I. Demographic features of the patients

	Male	Female	Age (Mean)	BMI (Mean)
Group HA	6	22	63.53	3I.48
Group PRP	6	26	63.43	33.I5

BMI:Body Mass Index, HA: Hyaluronic acid, PRP:Platelet-rich-plasma

TABLE 2. Mean WOMAC scores of the patients

	WOMAC score (initial)	WOMAC score (at I mon)	WOMAC score (at 6 mon)
Group HA	83.96	66.89	58.53
Group PRP	79.84	67.8I	64.62

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, HA: Hyaluronic Acid, PRP:Platelet-Rich Plasma

TABLE 3. Mean VAS scores of the patients

	VAS score (initial)	VAS score (at I mon)	VAS score (at 6 mon)
Group HA	6.45	4.66	4.04
Group PRP	6.0	4.2I	3.83

VAS: Visual Analog Scale, HA: Hyaluronic Acid, PRP: Platelet-Rich Plasma

were associated with a decrease in pain over time. However, no statistically significant difference was observed between the HA and PRP groups (p>0.05). When the WOMAC scores were evaluated, the function, joint stiffness, and overall WOMAC score were positively affected in both the groups of patients; however, there was no difference between the two groups (p>0.05).

DISCUSSION

PRP and HA are both effective in knee osteoarthritis treatment and improve the patients' functionality and quality of life.

Chang et al (5) reviewed the effects of intra-articular PRP injection in knee OA compared to that of HA in a systematic review performed in 2014. The study demonstrated that PRP caused significantly functional improvement in patients with knee cartilage pathology, where the effects lasted for at least 12 mon. Compared to patients receiving HA, those receiving PRP had more and longer-lasting improvement. Moreover, better results were observed among patients with milder forms of OA than those whose condition was advanced.

Similar results were obtained in a 2013 meta-analysis by Khoshbin et al. (6) wherein PRP was more efficient than HA and normal saline in mild-to-moderate OA.

Another systematic review conducted in 2014 stated that evidence often supported the use of PRP in knee OA. Different studies have shown that PRP has an effect in causing pain relief and reducing the clinical symptoms in 6 months. However, there is no evidence advocating PRP efficiency in traumatic or degenerative chondral pathology. Therefore, high-quality randomized controlled trial studies are warranted to compare PRP with placebo and surgical treatments supplemented by PRP with operative management alone (7).

In a meta-analysis conducted by Merchan in 2013 (8), the efficiencies of steroids, HA, and PRP were reviewed. The researchers suggested 3–5 weekly HA injections in the OA knee before performing surgical treatment. They concluded that steroid injections had very short-term effects; however, PRP injections needed to be further investigated to determine the grade and duration of the efficiency.

In another study by Vaquerizo et al. (9) in 2013, 96 patients in two groups received three therapy injections of plasma rich in growth factors (PRGF) or a single injection of HA and were followed up for 48 wk. The efficiency of PRGF in terms of pain and stiffness decrement and physical performance improvement was greater than that of HA. In addition, the patients' responses to PRGF in all scores, including those for pain, stiffness, and physical performance in the WOMAC, Lequesne, and Outcome Measures in Rheumatology Osteoarthritis Research Society International were more meaningful than those for HA; this result is contradictory to our finding.

Filardo et al (10) conducted a study in 2012 to compare PRP and HA in the treatment of knee OA. Total 109 patients (55 in the HA group and 54 in the PRP group) participated in the study. They were evaluated at the beginning and at 2, 6, and 12 months after the treatment using the Knee injury and Osteoarthritis Outcome Score, International Knee Documentation Committee (IKDC), and EuroQol (EQ)-VAS questionnaires. PRP/HA were injected thrice with one-week intervals. At the end of the follow-up, significant improvements were observed in all the parameters in both the groups. However, there were no meaningful differences between the groups in terms of the EQ-VAS and IKDC scores. The authors concluded that PRP should not be given priority over HA in middle-aged patients with moderate OA and should not be applied as the first-line treatment.

Filardo et al. (11) evaluated the benefits provided by PRP and HA injections in the treatment of knee-joint degeneration. They concluded that PRP does not provide a superior clinical improvement than HA. In a similar manner, in our study, when the WOMAC scores were evaluated, the function, joint stiffness, and overall WOMAC scores were positively affected in both the groups; however, there were no between-group differences.

A meta-analysis by Sadabad et al. (12) investigated the efficiency of PRP and HA in the treatment of knee osteoarthritis. Seven studies on 722 subjects (364 in the PRP group and 358 in the HA group) were analyzed. The results of this meta-analysis two years after the PRP injection showed the efficacy of PRP versus that of HA.

Cerza et al (13) compared the clinical response of HA and PRP treatment in the two groups of patients affected by gonarthrosis. They conclude that treatment with HA did not seem to be effective in patients with grade III gonarthrosis.

The limitations of this study include the absence of a placebo control group, lack of blinding, and the lack of objective evaluation of the treatment effects on the morphology of the cartilage, soft tissue, and other intra- and peri-articular structures of the knee. Furthermore, considering the higher cost of PRP than that of other injection therapies, such as HA, and the need for special kit and a centrifuge devise for using PRP, the administration of this therapy should be carefully considered (cost-effectiveness and availability).

In addition, this study was performed retrospectively. Long-term prospective studies may be helpful to consider more detailed knowledge about this topic.

CONCLUSION

PRP is a novel option in knee OA management, and an increasing number of clinical studies have shown promising results. Both PRP and HA have positive effects in early gonarthrosis; however the results indicated no superiority in the PRP group.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of of Dokuz Eylul University, 2017.

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - Design-Y.E.B., O.G, N.D.D.; Supervision - Y.E.B, N.D.D.; Resource - Y.E.B, O.G.; Materials - Y.E.B, O.G, N.D.D.; Data Collection and/or Processing - Y.E.B, O.G, N.D.D.; Analysis and/or Interpretation - Y.E.B, O.G., N.D.D.; Literature Search-Y.E.B, O.G, N.D.D, R.Ö.; Writing - Y.E.B, N.D.D, R.Ö; Critical Reviews - N.D.D, R.Ö.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Original Article

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Knowledge and View of Mothers Whose Babies in Newborn Intensive Care Units About Breast Milk Banking in Turkey

Reyyan Gürel[1], Ayten Şentürk Erenel[2]

[1]Başkent Universty Faculty of Health Sciences, Ankara, Turkey
[2]Gazi University Faculty of Health Sciences, Ankara, Turkey

ORCID IDs of the authors: R.G. 0000-0003-1217-1002; A.Ş.E. 0000-0002-0841-2099.

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BACKGROUND/AIMS
This study aimed to assess the knowledge, awareness, and attitudes of mothers whose babies were in the newborn intensive care units about breast milk banking.

MATERIALS and METHODS
The participants of this descriptive research were 102 mothers who provided their oral and written consent for study participation and whose newborns were in the intensive care units during June to August 2016 (n=102). A p value <0.05 was considered to indicate statistical significance.

RESULTS
We found a statistically significant relationship of the "Request to Benefit from Breast Milk Banking" with the educational background, working status, and the place where the mothers had spent most of their lives. In addition, there was a statistically significant relationship of the "Request to Donate Breast Milk to the Breast Milk Banks" with the place where the mothers had spent most of their lives, breast-feeding experience, and the institution from which they had received care before the delivery (p<0.05).

CONCLUSION
Although a considerable proportion of the mothers have positive thoughts about breast milk banking, they were hesitant about feeding their babies donor milk when needed.

Keywords: Breastfeeding, human milk banking, milk banking, Turkey.

INTRODUCTION

Feeding newborns with breast milk is a fundamental element of healthy growth and development (1, 2). The World Health Organization (WHO) and many international organizations recommend that infants should be fed only breast milk for the first 6 months; thereafter, liquid and solid supplements should be started. Furthermore, it is also recommended that breast-feeding be continued until the baby gives it up (1, 3). In addition to being the optimum exclusive source of nutrition for the infants, breast milk provides several benefits to human health both in the early years and beyond (1). Therefore, the United Nations International Children's Emergency Fund (UNICEF), the WHO, and many international health organizations emphasize the importance of breast milk for newborns (1, 3). The UNICEF has stated that the practice of breast-feeding can save the lives of approximately 1.5 million infants annually (4). Thus, it has been pointed out that it is the human right of each infant to be fed breast milk to allow the achievement of optimal health. Studies have shown that breast-feeding is crucial for infants who are treated in newborn intensive care units for various reasons, and the most suitable approach involves the use of donor milk in situations where the infant cannot be fed its own mother's milk (3, 5, 6).

Breast milk banks are the most suitable and important source of breast milk for babies who cannot be fed its own mother's milk for various reasons (7). Donor milk undergoes a rigorous health-screening process. Breast milk banks are institutions that provide breast milk to infants who need it by sourcing it from mothers who produce more milk than that needed

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Corresponding Author: Reyyan Gürel
E-mail: reyyan_guney@hotmail.com

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by their own children or from those who donate their milk for some other reasons, such as death of their own child. Donor milk is subjected to pasteurization and a health-screening process. Milk banking first began in the 1900s in Boston and continues to function in many countries of the world (8). In Turkey, several initiatives have been undertaken to establish a breast milk bank; however, there has not been any milk banks in Turkey. In addition, when the literature regarding this subject is examined, few studies were found that involved both healthcare personnel and the general public; thus, limited information is available regarding this subject (9). Consequently, this study aimed to inform mothers whose babies were in the newborn intensive units about breast milk banking and to contribute to the literature about the subject, given the importance of breast milk for neonates in the newborn intensive care units.

MATERIALS AND METHODS

This descriptive research was performed to observe and collect information about knowledge and attitudes regarding breast milk banking among mothers whose neonates were in the newborn intensive care units of a public hospital in Ankara, the capital city of Turkey, from June to August 2016. The researchers included a short and standard information note that was prepared based on the information in the literature about breast milk banks on the header of the data collection form; this note provided information regarding the fact that there were no breast milk banks in Turkey and limited research has been conducted on the subject. Within this scope, information about where the first breast milk bank was established; the qualifications of donor milk; as well as the analysis, pasteurization, and storage conditions of donor milk were included. Following this, the form consisted of 32 questions that aimed to determine the mothers' observations regarding breast milk banks and the personal characteristics of their babies; the survey was conducted using face-to-face interviews. Study participation was purely voluntary for the mothers. The study was conducted on 102 mothers who willingly provided their written and oral consent for study participation and whose babies were in the incentive care unit during the research period.

Main Points:

- Breast milk banking has great importance for mothers whose babies are in intensive care and do not have milk secretion.
- In spite of fact that there is no milk banks in Turkey, it is determined that the majority of mothers support the milk bank.
- It has been established that there is a significant relationship between "Request to Benefit from Breast Milk Banking" and mother's educational background, working status, and the place where the mothers spent most of their lives.
- In addition, it has been found that there is significant relationship between "Request to Donate Breast Milk to the Breast Milk Banks" and mother's breast-feeding experience, the institution from which they had received care before the delivery and the place where the mothers spent most of their lives.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences software version 17.0 (SPSS Inc., Chicago, IL, USA). Frequency tables and descriptive statistics were used for data analyses. $\chi 2$-cross tab was created according to the expected value levels to examine the relationship between two quantitative variables.

Research questions

1. What are the views of mothers whose babies are hospitalized in the neonatal intensive care unit about breast milk banking?
2. Do mothers want to take advantage of the milk bank in the newborn intensive care unit?

Ethical Aspect of Research

Before initiating data collection, written ethical approval was obtained from the Ethics Board of the hospital (23 May 2016; 2016-054). At each step of the research, the principles of "the Declaration of Helsinki" were followed.

RESULTS

In Table 1, some descriptive characteristics of the mothers are shown. Their average age was 28.34±6.45 y, and 44.1% of the mothers were 26–33 y old. Total 51% of all mothers had graduated primary school; 81.4% were housewives; for 67.6%, their income was equivalent to their expenses; and 87.3% belonged to elementary families. Total 56.9% of the newborns were male infants, and 74.5% were term infants. Further, 38.2% of the newborns are fed only breast milk, while 56.9% were fed supplementary formula along with breast milk. Although not included in the table, 56.9% of the mothers had a vaginal birth, 42.2% had been pregnant at least 3, and 39.2% had given birth twice. Total 41.2% of the mothers had 2 living children, and 79.4% of them did not have any previous experience of breast-feeding.

Table 2 shows the data on the mothers' information and observations regarding breast milk banks. Total 95.1% of the mothers had never heard about the breast milk banks before, and 77.5% supported the establishment of breast milk banks in Turkey. The most common reason for not supporting the establishment of breast milk banks was that pertaining to religious beliefs (73.9%). We found that 50% of the mothers asked to be benefited from the services provided by breast milk banks when needed, and 64.7% said that they could donate their breast milk if there was a breast milk bank in Turkey. The reason stated by 50% of the mothers who were willing to donate was the provision of breast milk for infants whose mothers could not provide it. In contrast, 36.1% of those who were unwilling to donate did so because they believed that they only produced enough milk for their own child. While 55% of the mothers stated that they did not want to benefit from the breast milk bank even if they needed, 56.9% of them believed that there would be a demand for breast milk banks in Turkey.

The distribution of mothers who wanted and did not want to avail the services of breast milk banks when needed are shown in Table 3, according to their some characteristics. There was no significant difference in the age, monthly income, and family type of mothers who request to benefit from breast milk bank-

ing (p>0.05). However, there was a significance difference between those who requested to be benefited from breast milk banking in terms of the educational background, working status, and the place where they spent most of their life (p<0.05). Mothers who were educated up to high school level or lower had similar attitudes toward breast milk banking; however, the attitudes of those who were postgraduates were different. Housewives were more reluctant to benefit from breast milk banking than those who had jobs. The place where the mother had spent most of her life influenced the willingness to benefit from breast milk banking; a difference was observed in those who had lived in city centers for a long time.

Table 4 shows the distribution of the characteristics of mothers who were and were not willing to donate breast milk. There was a significant difference based on the place where they had spent most of their life, breastfeeding experience, and the place where they received care before delivery (p<0.05). It has been established that the place where they spent most of their life influenced their willingness to donate breast milk, and this difference arose from living in the city centers for a long time. More mothers who had no experience about breast-feeding were willing to donate their milk than the ones with experience. Most mothers who were willing to donate their milk had received care from the public hospitals before delivery.

Table 5 shows the distribution of the characteristics of mothers with respect to their information about breast milk bank. There was no significant difference between mothers who did and did not have

TABLE I. Distribution of the descriptive characteristics of mothers and newborns

Characteristic (n=102)	n	%
Age [$\bar{X}$±SD→28.34±6.45 (y)]		
18–25 y	33	32.4
26–33 y	45	44.1
≥34 y	24	23.5
Educational Background		
Literate	3	2.9
Primary school graduate	52	51.0
High school graduate	30	29.4
Postgraduate	17	16.7
Working Status		
Housewife	83	81.4
Civil servant	11	10.8
Freelancer	8	7.8
Monthly income		
Income less than expenditure	7	6.9
Income equal with expenditure	69	67.6
Income more than expenditure	26	25.5
Types of Family		
Elementary family	89	87.3
Extended family	13	12.7
Place where the most of life spent		
Village or Small town	8	7.8
District	24	23.6
City Center	70	68.6
Gender of Newborn		
Female	44	43.1
Male	58	56.9
Type of Feeding		
Breast Milk	39	38.2
Formula	5	4.9
Breast milk and Formula as supplementary food	58	56.9

SD: Standard Deviation

TABLE 2. Distribution of the mothers' information and observations regarding breast milk banks

Characteristics (n=102)	n	%
Heard before about breast milk bank		
Heard	5	4.9
Not heard	97	95.1
Giving support to breast milk bank in Turkey		
Supporter	79	77.5
Not supporter	23	22.5
Reasons not giving support to breast milk bank in Turkey (n=23)		
Religious reasons	17	73.9
Unreliability on records	4	17.4
Unknown grantor	2	8.7
Request to benefit from the milk bank when needed		
Requestor	51	50.0
Non-requestor	51	50.0
Willing to donate breast milk if available in Turkey		
Willing	66	64.7
Unwilling	36	35.3
Donate reason (n: 66)		
To give milk to infants whose mothers cannot	33	50.0
To provide that all infants be fed by breast milk	17	25.8
Having extra breast milk	16	24.2
Reason for unwilling to donate breast milk (n: 36)		
In the belief that her breast milk is enough only for her own baby	13	36.1
Her spouse will not allow	9	25.0
Cannot find time since she **will** be giving care to her own baby	9	25.0
Religious reasons	5	13.9
Request to benefit from breast milk bank when needed		
Requestor	45	44.1
Non-Requestor	57	55.9
Mothers who think that there will be demand to breast milk bank in Turkey		
Yes	58	56.9
No	44	43.1

information about breast milk banking in terms of willingness to donate, requesting for milk from breast milk banks when needed, and willingness to benefit from the breast milk bank (p>0.05).

DISCUSSION

Breast milk is crucial for at-risk infants in the newborn intensive care units as well as infants and newborns because of its high nutrition content. Therefore, it is recommended that for infants, feeding should be started with their own mothers' milk. If this is unavailable, they should be fed donor milk; formula feeding should be the last resort (1, 3). Few studies have assessed the awareness and information of mothers and health care personnel about breast milk banking (2, 9, 10, 11). To our knowledge, no study has been conducted on mothers whose children are in the newborn intensive care units.

In our study, although most mothers (95.1%) stated that they had no information about breast milk banking, they were able to provide some information about breast milk banking, showing a positive attitude. Similarly, a significant number of women had never heard about breast milk banking (10, 12). However, Ekşioğlu and her colleagues reported that a high percentage of mothers had information about breast milk banking (2); this result is believed to be attributable to the fact that there was ongoing work for the establishment of breast milk banks in the city where this study was conducted. In our study, ¾ of the women support the establishment of breast milk banks. Although there is considerable evidence in favor of the benefits of breast milk banking, religious reasons are the most commonly cited cause for unwillingness to support breast milk banking in Turkey. In Islam, sharing of breast milk is considered virtuous; however, it is believed that children who share the breast milk of the same mother become siblings although they are not related by blood (13, 14, 15) and thus cannot marry each other. Despite these beliefs, at least 50% of the women have a positive attitude toward the benefits of breast milk banking and >50% may donate and receive donor milk from the breast milk bank.

It is noteworthy that 77.5% of the mothers whose children were in the newborn intensive care unit supported breast milk banking in Turkey; however, overall, 50% women do and 50% do not support breast milk banking. According to the study (2) by Ekşioğlu and his colleagues, most mothers (71.3%) request the establishment of breast milk banks; however, only 52.5% reported that they would request donor milk when needed. Mackenzie et al. (10) state that breast milk is the most important source of nutrition for infants and should be preferred over formulas; they support breast milk banking. However, we found that while most mothers were willing to donate their milk, the number of mothers who wanted to receive donor milk when needed was low. In a similar manner, studies (2, 12) have shown that the number of mothers who are willing to donate is higher than that of those willing to use donor milk from these banks. Thus, we conclude that mothers are unwilling to feed their children donor milk owing to religious reasons; however, they are willing to help other infants who need breast milk and are unable to receive it from their own mother.

TABLE 3. Distribution of the characteristics of mothers who did and did not request to be benefited from the services of the breast milk banks

	Request to benefit from breast milk bank		
Characteristics (n=102)	**Requestors (n=51)**	**Non-requestors (n=51)**	**Statistical analyses[a] Possibility**
Age			
18–25 y	12 (23.5%)	21 (41.2%)	$\chi2$=3.710
26–33 y	26 (51.0%)	19 (37.3%)	p=0.156
≥34 y	13 (25.5%)	11 (21.5%)	
Educational background			
Primary school graduate and lower	23 (45.1%)	32 (62.7%)	$\chi2$=11.947
High school graduate	13 (25.5%)	17 (33.4%)	p=0.003
Postgraduate	15 (29.4%)	2 (3.9%)	
Working status			
Housewife	36 (70.6%)	47 (92.2%)	$\chi2$=7.826
Working	15 (29.4%)	4 (7.8%)	p=0.005
Monthly income			
Income lower than or equal to expenditure	35 (68.6%)	41 (80.4%)	$\chi2$=1.858
Income more than expenditure	16 (31.4%)	10 (19.6%)	p=0.173
Type of family			
Elementary family	44 (86.3%)	45 (88.2%)	$\chi2$=0.088
Expended family	7 (13.7%)	6 (11.8%)	p=0.767
Place where the most of life spent			
Village or small town or district	23 (45.1%)	9 (17.6%)	$\chi2$=8.925
City center	28 (54.9%)	42(82.4%)	p=0.003

[a]In interpreting the findings, frequency tables and descriptive statistics were used. $\chi2$-cross tab was created as per the expected value levels in examining the relationship of the two quantitative variables.

TABLE 4. Distribution of the characteristics of mothers who were and were not willing to donate their breast milk to the breast milk bank

	Willing to donate		
Characteristics (n=102)	**Willing (n = 66)**	**Unwilling (n=36)**	**Statistical analyses[a] Possibility**
Educational background			
Primary school graduate and lower	33 (50.0%)	22 (61.1%)	$\chi2$=2.876
High school graduate	19 (28.8%)	11 (30.6%)	p=0.237
Postgraduate	14 (21.2%)	3 (8.3%)	
Working status			
Housewife	53 (80.3%)	30 (83.3%)	$\chi2$=0.012
Civil servant/freelancer	13 (19.7%)	6 (16.7%)	p=0.913
Monthly income			
Income lower than or equal to expenditure	51 (77.3%)	25 (69.4%)	$\chi2$=0.396
Income more than expenditure	15 (22.7%)	11 (30.6%)	p=0.529
Type of family			
Elementary family	56 (84.8%)	33 (91.7%)	$\chi2$=1.033
Expended family	10 (15.2%)	3 (8.3%)	p=0.309
Place where most of life spent			
Village/small town or district	28 (42.4%)	4 (11.1%)	$\chi2$=9.204
City center	38 (57.6%)	32 (88.9%)	p=0.002
Breast-feeding experience			
Have experience	47 (71.2%)	34 (94.4%)	$\chi2$=9.044
No experience	19 (28.8%)	2 (5.6%)	p=0.005
Care before giving birth			
Primary care center	26 (39.4%)	28 (77.8%)	$\chi2$=14.610
Public hospital	34 (51.5%)	8 (22.2%)	p=0.001
Private hospital	6 (9.1%)	-	
Delivery method			
Vaginal delivery	39 (59.1%)	19 (52.8%)	$\chi2$=0.165
Cesarean Section	27 (40.9%)	17 (47.2%)	p=0.685

[a]In interpreting the findings, frequency tables and descriptive statistics were used. $\chi2$-cross tab was created according to the expected value levels to examine the relationship between two quantitative variables.

TABLE 5. Distribution of the characteristics of mothers who did and did not have information about breast milk banking

	Having information		
Characteristics (n=102)	**Have (n=5)**	**Not have (n=97)**	**Statistical analyses[a] Possibility**
Request for breast milk bank			
Requestor	5 (100.0%)	74 (76.3%)	$\chi2$=1.531
Non-requestor	-	23 (23.7%)	p=0.216
Willingness to donate			
Willing	5 (100.0%)	61 (62.9%)	$\chi2$=2.868
Unwilling	-	36 (37.1%)	p=0.090
Request for milk from breast milk bank when needed			
Requestor	3 (60.0%)	42 (43.3%)	$\chi2$=0.538
Non-requestor	2 (40.0%)	55 (56.7%)	p=0.463
Request to benefit from breast milk bank			
Requestor	3 (60.0%)	48 (49.5%)	$\chi2$=0.210
Non-requestor	2 (40.0%)	49 (50.5%)	p=0.647

[a]In interpreting the findings, frequency tables and descriptive statistics were used. $\chi2$-cross tab was created according to the expected value levels to examine the relationship between two quantitative variables.

In our study, the most common reason for mothers to not support the establishment of breast milk banks was pertaining to religious beliefs. In contrast, other studies (10, 16-18) have cited reasons other than religious beliefs for this attitude among mothers. Helping each other and meeting the others' legitimate needs are among the fundamental principles of Islam, and this requires giving permission for breast milk banks (13).

It has been established that the mothers who live in city centers who do not have breastfeeding experience before and who received care from public hospitals before delivery have more positive attitudes toward breast milk banking. Thus, the mother's attitudes regarding this issue are closely associated to their social status and easy accessibility to sources such as health facilities and breastfeeding oriented foundations.

The study was conducted at a single hospital, and some mothers refused to participate in the study. These can be considered the limitations of this study.

Consequently, although most mothers supported the establishment of breast milk banks in Turkey, about 50% were unwilling to donate or benefit from the services for certain reasons. Considering the fact that the next-best nutrition source for at-risk children after their own mother's milk is donor breast milk, awareness and responsibilities of nurses are crucial in the popularization of breast milk donation because nurses are health care personnel responsible for the protection and developing the health of the infant and mother. Thus, if nurses, especially those working in postpartum clinics and newborn intensive care units give information to parents about breast milk banks, breast milk donation, and the benefits of donor milk, traditional believes and attitudes may change, and concerns about the safety and nutrition of donor milk would be reduced.

Study Limitations

The research was conducted in a single center. Therefore, it was limited to mothers who met the sampling criteria and agreed to participate in the study. Therefore, the research results can be generalized only to this group.

Based on studies about the breast milk banking, mothers can be informed about the subject, and the demand for breast milk banks can be increased to overcome the obstacles in the establishment of breast milk banks. In addition to all above-mentioned explanations, it is recommended that health care personnel be informed about the breast milk banking and that the mothers be informed about the issue in a fair and impartial manner.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Board of Ankara Paediatrics Haematology-Oncology Training and Research Hospital (23 May 2016; 2016-054).

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

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A Comparative Study on the Effect of Using Three Maternal Positions on Postpartum Bleeding, Perineum Status and Some of the Birth Outcomes During Lathent and Active phase of the Second Stage of Labor

Mehri Rezaie[1], Sheida Dakhesh[2], Leila Kalavani[3], Mahboubeh Valiani[4]

[1]Department of Nursing and Midwifery, Saveh University of Medical Sciences, Markazi, Iran
[2]Department of Medical Sciences, Hamadan University, Hamedan, Iran
[3]Jahrom Universiy of Medical Sciences, Jahrom, Iran
[4]Isfahan University of Medical Sciences, Isfahan, Iran

ORCID IDs of the authors: M.R. 0000-0002-6060-4979; S.D. 0000-0003-1931-5312; L.K. 0000-0002-3377-3996; M.V. 0000-0003-3955-4628.

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BACKGROUND/AIMS
This study aimed to determine the effect of three different positions of delivery on the postpartum bleeding, perineum status, and some birth outcomes.

MATERIALS and METHODS
This clinical trial study was performed on 96 primiparous pregnant women who had voluntarily entered the trial and were randomly assigned to one of the following three groups: lithotomy, sitting, and squatting group in the second stage of labor. Bleeding during the first hour after delivery, postpartum status of the perineum, as well as type and degree of tear were measured. The data were analyzed using Statistical Package for the Social Sciences 17 (SPSS Inc.; Chicago, IL, USA).

RESULTS and CONCLUSION
The mean volume of bleeding in the lithotomy group was significantly lower than those in the other two groups (p=0.016), and there was no significant difference between the sitting and squatting groups. There was no significant difference among the three groups in terms of the perineal status (tear and episiotomy), the height of the uterus, and the neonatal mean Apgar mean scores at 1 and 5 minutes (p>0.05). The use of different delivery positions based on the status of the mother can have different effects on the mother and infant outcomes; further studies are warranted on this subject.

Keywords: Childbirth position, episiotomy and laceration, post partum position

INTRODUCTION

The main goal of the third-millennium development program is to ensure the physical and mental health of mothers, and one of the items is safe pregnancy and childbirth. Childbirth or parturition is an event that has great psychological, social, and emotional impact on the mother and the family. Thus, management of the stages of labor, especially the third and fourth stages, play an important role in maintaining the health of women and children who constitute two-thirds of the population (1). One of the major causes of maternal morbidity and mortality, especially in developing countries, is postpartum hemorrhage, with a reported prevalence of around 1%–5%, as per different criteria. Most bleedings occur in the third and fourth stage of labor (2, 3). The third phase of labor includes the separation and dissection of the placenta. This phase begins with the baby's birth and ends with the extraction of the placenta. The placenta is generally extracted within the third or fourth postpartum contraction. After the birth, the uterus contracts with more intensity and strength, and because of this, the coupling site of the placenta becomes smaller than the size of the placenta itself. Then, the separation, descent, and extraction of the placenta and membranes occur. One hour after the delivery is considered as the fourth stage of labor owing to its importance in bleeding, and it should be carefully monitored. Some practitioners have increased this

Corresponding Author: Mehri Rezaie
E-mail: Mehrangize_rezai@yahoo.com

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time to two hours on consensus. At this stage, rapid healing and restoration of homeostasis are re-established (4).

Typically, postpartum hemorrhage is defined as blood loss of 500 cc or more after the completion of the third stage of labor (5). In fact, about 5% of women who give birth vaginally lose more than 1000 mL of blood. Usually, the estimated blood loss is 50% of the actual blood loss. Therefore, if the bleeding is estimated to be >500 mL, it should be considered as moderate to severe bleeding. Increase in the normal blood volume during pregnancy (usually 30%–60% in women with moderate body mass) is about 1500–2000 mL. During the delivery, blood lossis approximately equivalent to the amount of blood added during pregnancy. At the end stage of the pregnancy, at least 600 mL of blood passes through the space between the villi per minute. Homeostasis at the placental implantation site is initiated via a contraction in the myometrium that causes compression of the arteries. As a result, the formation of a large clot in the uterine myometrium prevent effective myometrium contraction and can disrupt homeostasis in the placental implantation site. Therefore, it is clear that despite the natural coagulation, uterine atony may cause fatal hemorrhage after the delivery (6). Postpartum bleeding may be observed before or after the separation of the placenta. Sometimes, constant bleeding can be observed instead of sudden bulky bleeding. The bleeding may appear moderate, but may persist until signs of hypovolemic shock appear. Some women in the postpartum period may not bleed from the vagina, and the blood will accumulate in their uterus; therefore, a phenomenon could occur wherein 1000 mL or more of blood causes dilation in the uterus. In some cases, during the uterine massage, a sheet of abdominal fat may be massaged instead of the uterus. Thus, it is important care of the uterus in the postpartum period not be allocated to inexperienced practitioners or midwives (7). Multiple factors affect the bleeding and postpartum laceration, including underlying diseases, age, weight of the neonate, and the delivery position of the mother. Maternal position during labor can affect the amount of bleeding during the third and fourth stages and facilitate placenta removal by intervening in the process of uterine contractions (8). Until the mid-eighteenth century, women underwent active labor in the vertical position during childbirth. During the 17th century, a French physician developed the recumbent-in-bed position for the first time. However, in recent years, more attention is being paid to the tendency of many women who want to use more simple methods of labor, such as the vertical position (9). Labor in the sitting position affects the duration of placenta extraction and postpartum hemorrhage. In this position, intra-abdominal pressure and the gravity force facilitate placenta and membrane extraction and accelerate the third stage of the labor. It is believed that vertical position can likely increase the chances of postpartum hemorrhage. It seems that the gravitational force applied during the vertical position is one of the most important factors in the occurrence of excessive bleeding. In the recombinant or supine position, there is a higher chance of developing blood clots in the uterus therefore the real amount of bleeding remains hidden (10).

If the bleeding continues despite a rigid and completely constricted uterus, it is likely to be the consequence of a tear. Presence of bright red blood also indicates the presence of arterial blood resulting from a rupture in the genital duct (11). Perineal tearing may occur following vaginal delivery. The underlying causes of laceration include being in labor for the first time, interruption of the second stage of labor, consistent posterior occipital posture, use of local anesthetic, and median episiotomy (12).

Routine episiotomy is performed to prevent perineal rupture, irregular tears, prevent damage to the fetus, and avoid complications of the pelvic floor; however, its routine use has been questioned (13). One of the disadvantages of episiotomy is the increased incidence of anal and rectal sphincter ruptures that can contribute to the incontinence of the anal sphincter. The incidence of severe rupture is related to the type of episiotomy. Total 20%–50% of women who are repaired due to rupture of sphincter have symptoms of urinary incontinence (14). Problems with the sphincter sometimes manifest 20 years later. Several clinical trials have shown that the limitation of episiotomy is associated with desirable outcomes, such as reduced damage to the posterior perineum, repair complications, stitches, and blood loss. This also leads to faster return to daily activities (15, 16).

Most studies have estimated the amount of postpartum bleeding subjectively. This would increase the error in the estimation of the bleeding amount; thus, contradictory results have been concluded in this regard. Several studies have also been conducted on the status of the perineum and its damages; as per the study methods, different results have been obtained. Thus, conducting a variety of research trials in this field can help understand the application of some of these techniques during delivery. Therefore, this study was planned to perform a comparative evaluation of the effects of three delivery positions on bleeding, perineum status, and some birth outcomes.

Main Points:

- One of the positive points of the present study was that postpartum bleeding was measured objectively. Also, in order to ensure the accuracy of the measurement, bleeding volume was measured in three ways.
- In this study, the volume of bleeding in all three delivery positions was within normal range.
- Postpartum bleeding and perineal tear are likely to be controlled if the delivery goes through its natural and physiological process and using positions according to the mother's circumstances.
- Because of the difficulty of increasing the sample size one limitation of the study was the low sample size.

MATERIAL and METHODS

This research was a clinical trial (Ethics committee approval: 389292) performed on primiparous women in 2010–2011.

Women who were undergoing labor for the first time with a singleton pregnancy between 37 and 42 weeks, had head presentation, and were completing the first phase of delivery via the physiological method without any problems were entered in the trial at 8-cm dilatation.

Mothers who had fetal distress in the first stage of labor, those who gave birth to neonates weighing >4000 g (based on the

Johnson formula) (17), those diagnosed with asynclitism, those with special diseases, and those who took oxytocin were excluded from the study.

The subjects were provided a detailed description of the study design and procedures; thereafter, the willing subjects provided written consent for study participation. The patients were provided individual rooms for their comfort, convenience, and privacy. During all study stages, each patient was provided similar emotional, verbal and non-verbal support.

Based on the mentioned entry and prohibition criteria, 96 eligible women were randomly selected . into the three groups of lithotomy, squatting, and sitting positions. (each group included 32 women). Each subject was immediately placed in the respective position at 10 cm dilatation of the uterus and 100% effacement; they remained in the same position until complete extraction of the placenta.

In order to determine the amount of bleeding in the first hour after childbirth in all the three groups, immediately after the baby was extracted, one basin was placed under the mother's hips. In the lithotomy position, after complete extraction of the placenta and its blood, the basin was removed and immediately thereafter, the pad that was weighed was placed in the perineal and vulva area. If necessary, the pads were replaced. In the sitting and squatting positions, a basin was placed under the hips of the mother. Immediately after the third stage ended and the placenta and its blood were completely extracted, the basin was removed, and the pad was placed in the perineal and vulva area. The mother was moved to a bed near the delivery site, and the pads were replaced if needed. It is noteworthy that for collecting blood in each of the three groups, a draw sheet was weighted and placed under the mother immediately after the basin was removed in the lithotomy position and immediately before moving the mother to the bed (after the third stage ended) in the sitting and the squatting positions. In case of excessive bleeding, uterine massage was applied. If the bleeding was not controlled, syntocinon was injected (30 units of syntocinon per 1000 cc of ringer serum). In the next step, the blood inside the basin was transferred to a container; thereafter, it was measured and recorded. The blood stuck to the basin was placed within the gauzes that were previously weighed in a container. At the end of the first hour after delivery, the pads and gauzes that were weighed before by using a digital scale were weighed again and deducted from the previous weight, and the amount of blood was measured in grams. According to the blood weight (per grams) formula, they were divided by the total blood concentration (total blood concentration is 1.06) (10), resulting in a blood volume per cc, and it was accumulated with the volume of blood measured in the scaled container. The volume of bleeding in the first hour after delivery was obtained and recorded in the questionnaire (in cc). To prevent the error of collecting the lost blood volume, the bleeding volume was calculated using three methods. In method I, as noted, the volume of blood in the scaled container and the volume of blood in the pads were measured. In the second method, the graduated cylinder was weighed with the containing blood; thereafter, the result was weighed out of the cylinder alone and then added to the amount of blood in the pads. Finally, the whole blood volume was measured. In the third method, the clot that had developed in the scaled container was weighed during the next hour after delivery and converted to cc; thereafter, it was added to the rest of the blood in the container and the blood volume in the pads; the final bleeding volume was measured.

In the lithotomy position, the mother rested on her back on a bed at a 30° angle from the horizons with her knees bent.

The sitting posture was a condition in which the mother sat on the delivery chair, with the vertebrae completely flat and the joints of the knee and hip on one level. The squatting condition was a situation wherein the mother sat in the sitting position on the leg so that the palm of the foot was completely on the ground and the knee joint was lower than the hip joint.

The labor stages were controlled by the researcher. Throughout the study, psychological support was continuously provided, and the mother was never left alone.

Perineal tear could occur due to the force applied to the perineum in the middle of the perineal area between the vaginal opening and the anus (median rupture) or the vaginal lateral wall or by a rupture in the median line, extending to the left or right perineal area (medio lateral rupture). The perineal tear was considered to be of first degree if there was tear of the hymen, perineum skin, and mucous membrane of the vagina; it was considered a second-degree laceration if there was laceration of the hymen, perineum skin, and mucosal membrane of the vagina with fascia and muscles. The tear was considered a grade-3 tear if there was tearing of the hymen, perineal skin, mucosal vagina, fascia, muscle, and rectal sphincter. A grade-4 rupture was that which included the rupture of the hymen, perineal skin, vaginal mucosal membrane, fascia, muscle, sphincter, and rectal mucosa (7).

In order to control the condition of the perineum and determine the degree and type of the rupture, immediately after placing the baby on the mother's abdomen for skin-to-skin contact and after completing the extraction of placenta, the presence of rupture and the type and degree of rupture was determined by the researcher. In cases wherein repair was needed, an episiotomy was performed on the area, and the tear was repaired. The status of the uterus contraction was examined by examination of the abdomen and the detection of normal or abnormal contractions of the uterus during the first hour after delivery (when the mother was lying on the bed). In this study, uterine contraction was defined by examining the abdomen and pressing the fingers on the uterus fundus during the first hour after delivery; if the finger did not enter the uterus, it was defined as natural and if the finger entered the uterus area, it was defined as abnormal. Control of the contractile condition of the uterus was investigated by the researcher during the first hour after delivery and then every 15 minutes (four times). The height of the uterus vertex was controlled and recorded by the researcher's assistant by touching the uterus at the umbilical cavity and at the bottom (as normal) and above the umbilicus (as abnormal) at the end of the fourth stage.

After the full explusion of the baby, five signs of heart rate, respiratory effort, muscle tone, reflexive stimulation, and baby's color were assessed according to the table of Apgar score (each items

with a score of zero, one or two). A total score of 10 indicated that the baby was in optimal health (18). The Apgar score of the infant was determined by the researcher at the first minute and the fifth minute, and it was recorded by the researcher's colleague.

Statistical analysis

In order to analyze the data, Statistical Package for the Social Sciences were used (version 17, IBM, manufacturer is SPSS Inc., 233 South Wacker Drive, Chicago, IL 60606-6412. Patent No. 7,023,453, USA). Significance level was set at $p<0.05$.

RESULTS

The three groups were not significantly different in terms of maternal age and the gestational age based on the first day of menstruation and ultrasonography of the first trimester (Table 1).

Table 2 shows the average bleeding volume during the first hour after delivery (by 3 types of measurement) in the three groups. The mean bleeding volume in the lithotomy group was significantly lower than that in the other two groups; there was no significant difference between the two sitting and squatting groups (p=0.98). The mean volume of postpartum bleeding in the lithotomy group (lying back) was approximately 200 cc less than that in the other two groups.

As shown in Table 2, the mean volume of bleeding in all the groups in the non-rupture and non-episiotomy samples was 589.600±46.377, in episiotomy samples 785.846±235.091 and in tear samples were 770.836±350.131 which were not significantly different (p>0.05).

Table 3 shows that the tear types were not significantly different among the three groups (p>0.05). The frequency distribution of perineal tear degree was not significantly different among the three groups (p>0.05). Perineal status (in terms of rupture and episiotomy) after delivery was not significantly different among the three groups (p>0.05).

Table 4 shows that the contraction status of the uterus in the 1st, 2nd, 3rd, and 4th 15-minute periods after delivery was not significantly different among the three groups (p>0.05). There was no significant difference in the height of the uterus fundus during the first hour after the delivery among the three groups (p>0.05).

The results also indicated that the average Apgar score in the first minute after the birth in the lithotomy group was 8.69±0.59, that in the sitting group was 8.56±1.39, and that in the squatting group was 8.59±0.87. The mean Apgar score in the fifth minute after birth in the lithotomy group was 9.84±0.51, that in the sit-

TABLE 1. Mean age and gestational age in the three groups of lithotomy, sitting, and squatting

Group	Lithotomy		Sitting		Squatting		Test result	
Variable	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	F	P-value
Age	22.31	2.97	23.75	3.90	22.56	4.11	1.38	0.26
Gestational age based on the first day of menstruation	39.22	1.10	38.92	1.26	39.02	0.82	0.57	0.57
Gestational age based on the ultrasonography of the first trimester	38.98	./99	38.95	1.11	38.74	1.20	0.42	0.66

TABLE 2. Comparison of the bleeding volume in the first hour after delivery in the three groups of lithotomy, sitting, and squatting

Group								
Variable	Lithotomy		Sitting		Squatting		Test result	
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	F	P-value
Bleeding volume (measured volume + volume of blood in the pad)	578.91	371.10	796.19	332.84	798.16	321.68	4.33	0.016
Bleeding volume (graded weight of the vessel + volume of blood in the pad)	548.31	360.45	761/.6	334.77	759.31	291.73	4.37	0.015
Clean substance in the container + Container volume + Pad volume	561.9	374.68	779.84	334.77	798.03	333.96	4.56	0.013
Bleeding volume in cases without episiotomy and rupture	461.286	432.420	852.666	679.930	611.400	389.995	1.96	0.35
Volume of bleeding in cases of episiotomy	776	342.471	796.333	105.078	792.750	133.662	0.023	0.98
Bleeding volume in cases of tear	591.625	374.667	812.042	317.639	860.286	332.135	1.184	0.32
Comparing the frequency distribution of bleeding in the three groups of lithotomy, sitting and squatting								
Groups								
Bleeding volume	**Lithotomy**		**Sitting**		**Squatting**		**Test result**	
	number	**percentage**	**number**	**percentage**	**number**	**percentage**	**Chi-square**	**p**
≤ 500 cc	18	56.20	4	12.50	7	21.90	10.51	0.005
501–1000 cc	9	28.10	20	62.50	17	53.10		
> 1000 cc	5	15.60	8	25	8	25		

ting group was 9.81±0.54, and that in the squatting group was 9.88±0.42. The mean Apgar score in the 1st and 5th minutes after birth was not significantly different among the three groups (p>0.05).

DISCUSSION

In the present study, the mean bleeding volume in the first hour after delivery in the lithotomy group was less than that in the other two groups.

A study titled "childbirth in the squatting position" was conducted in 2007 by Aisha Nasir and Korejo (19) in Karachi to examine the advantages and disadvantages of labor in the squatting position in the second stage of labor and compare it with those in the recumbence position. The case-control study was conducted on randomly selected 200 individuals. Both groups were positioned recumbently in the third stage of labor. Nasir (19) reported that in the squatting group, bleeding was <500 cc. However, no significant difference was found between the two groups (p>0.05). These results are not consistent with our findings.

In a review article on 18 clinical trials, Gupta (20) reported that the standing, squatting, and lateral recumbent positions result in >500 cc of blood loss than that in the recumbent position. His study results are consistent with the results of our study.

Bonder et al. (21) reported that the amount of severe bleeding in the two squatting and supine groups was not significantly different (p>0.05).

In a study conducted by Altman et al. (22) in Sweden, the difference in the postpartum hemorrhage between the squatting

TABLE 3. Comparison of the perineum status, type and degree of laceration, and episiotomy in the three groups of lithotomy, sitting, and squatting

	Lithotomy		Sitting		Squatting	
Condition of the perineum after delivery	**Number**	**Percentage**	**Number**	**Percentage**	**Number**	**Percentage**
Without episiotomy and laceration	7	21.86	3	9.40	6	18.75
Episiotomy	6	18.75	3	9.40	3	9.38
Laceration	16	50	24	75	21	65.63
Cyanosis tissue and dead without tear	1	3.13	2	6.30	0	0
Episiotomy + Laceration	2	6.30	0	0	2	6.30
Total	32	100	32	100	32	100
Test result			Chi-square=8.28			
			p=0.41			
Degree of perineal tear						
Degree I	12	37.50	17	53.12	19	59.37
Degree 2	6	18.70	7	21.88	4	12.50
Degree 3	0	0	0	0	0	0
Degree 4	0	0	0	0	0	0
Total	18	100	24	100	23	100
Test result			Chi-square=2.74			
			p=0.25			
Type of laceration						
Median	7	38.90	12	50	11	47.83
Mediolateral	3	16.70	6	25	3	13.04
Lateral	6	33.30	3	12.50	6	26.09
Irregular tear in several areas	2	11.10	3	12.50	3	13.04
Total	18	100	24	100	23	100
Test result			Chi – square=4.88			
			p=0.56			
Condition of type of episiotomy						
Median	0	0	0	0	1	20
Mediolateral	2	25	2	66.7	3	60
Lateral	6	75	1	33.3	1	20
Total	8	100	3	100	5	100
Test result			Chi-square=5.57			
			p=0.23			

and sitting positions was not statistically significant (p=0.7). The mean volume of bleeding in the squatting (kneeling) group was 420±320 mL and that in the sitting group was 480±406 mL. Moreover, there was no significant difference in the prevalence of severe bleeding (bleeding volume>1000 mL) between the two groups (p=0.5). In this study, bleeding volume >500 mLwas considered to be associated with risk factor, such as age of the mother, weight gain of the embryo, prolongation of the second stage of labor, and the use of oxytocin. In the present study, maternal age (range: 20–25 years) and newborn weight (average 3200 g) were not significantly different in the 3 groups. Oxytocin was not used for any subject in any group; however, the duration of the second stage of labor was higher in the sitting group. This may be attributable to an increase in the amount of bleeding in the sitting group because of the prolonged latent phase of the second stage of labor and the active phase of the second stage of labor. Nasir (19) concluded that the cause of increased bleeding in the standing (squatting) position was the increased pressure on the perineum that causes further damage to the perineum. However, collecting lost blood volume in standing position is easier than supine position. Thus, the estimated amount of bleeding may be higher. Possibly, in the sitting and squatting positions, the bleeding volume is overestimated because of the effects of gravity. Collecting, controlling, and calculating the bleeding in the lithotomy position is more challenging; this confirms the reduction in the bleeding volume in this position.

Terry (23) reported a bleeding volume of 295 cc in the standing group and 358 cc in the recumbent group. These research results are not consistent with our findings. In Richard and Terry's study, the bleeding was measured subjectively, while in our study, it was calculated objectively using a graded container and collection on pads.

TABLE 4. The uterine contraction status during the first hour after delivery, every 15 minutes, and the height of the uterus fundus in the three groups of lithotomy, sitting, and squatting positions

Groups / Variable	Lithotomy		Sitting		Squatting	
	Number	Percentage	Number	Percentage	Number	Percentage
Condition of contraction of the uterus during the first 15 minutes after delivery						
Normal	29	90.60	25	78.10	29	90.60
Abnormal	3	9.40	7	21.90	3	9.40
Total	32	100	32	100	32	100
Test result	Chi-square=2.85 p=0.24					
Condition of uterus contraction during the second 15 minutes after delivery						
Normal	30	93.80	31	96.90	31	96.90
Abnormal	2	6.30	1	3.10	1	3.10
Total	32	100	32	100	32	100
Test result	Chi-square=0.52 p=0.77					
Condition of contraction of the uterus during the third 15 minutes after delivery						
Normal	31	96.90	32	100	30	93.80
Abnormal	1	3.10	0	0	2	6.30
Total	32	100	32	100	32	100
Test result	Chi-square=2.07 p=0.36					
Condition of the uterus contraction during the fourth 15 minutes after delivery						
Normal	32	100	32	100	32	100
Abnormal	0	0	0	0	0	0
Total	32	100	32	100	32	100
Height of the uterus in the first hour after delivery						
In the umbilicus and under the umbilicus	32	100	32	100	31	96.90
Above the umbilicus	0	0	0	0	1	3.10
Total	32	100	32	100	32	100
Test result	Chi-square=2.02 p=0.36					

The results of Bamfim's (24) research showed no significant difference in the amount of bleeding in both, the sitting and recumbent groups. The mean weight of the hemorrhage in the recumbent group was 516.5±339.5 gr and that in the sitting group was 334.4±331.6 gr (p=0.52). The results of Bomfim's study are not in line with the present findings.

Reynolds (25) did not report a significant difference in the bleeding volume in the standing (squatting) and recumbent groups in Canada. Postpartum hemorrhage in the recumbent group was 2.3% and that in the standing group was 1.5%. Renolds stated that due to the effects of gravity, a slight increase in the bleeding volume was observed in the standing group; however, the results were not statistically significant (p>0.05).

The mean bleeding volume in cases without episiotomy and tear was significantly less than that in those with an episiotomy or tear (p=0.049). It is obvious that the bleeding volume would increase owing to the bleeding in the episiotomy or tear site. In a study titled, "The relationship between reduced sphincter rupture and restrictions in episiotomy," Jeffrey (14) found that hemorrhage is slightly reduced by limiting episiotomy. There was no significant difference among the three groups in the first, second, third, and fourth 15-minute periods from the aspect of uterus contraction. During the first 45 min postpartum, 6 cases had abnormal contractions of the uterus in the lithotomy and squatting group, and 8 had abnormal uterine contractions in the sitting group. We believe that the prolonged latent phase of the second stage of labor is associated with the abnormal uterus contraction in the sitting position.

There was no significant difference in the height of the uterus fundus during the first hour after delivery in the three groups. As shown in Table 2, only one individual (in the squatting group) has a fundus above the umbilicus. Considering the condition of the uterine contraction and the height of the uterus fundus during the first hour after delivery which are related to the amount of postpartum hemorrhage (if there is a bleeding, contraction of the uterus is disturbed and the height of the uterus fundus will be placed higher than the umbilicus) discussing about these goals was conducted in the form of postpartum hemorrhage. As shown in Table 3, there was no significant difference in the tear type, tear degree, and perineal status of the 3 groups. Nasir (19) did not find any significant difference in the number of episiotomies between the squatting and recumbent groups. However, episiotomy had extended in 7% of the cases from the recumbent group. Grade-2 and grade-3 tears were not observed in the squat group, while 9% of those in the recumbence position had grade-2 and grade-3 tears. A grade-2 tear was reported in 5 cases and grade-3 tear was observed in 4 cases, of which 2 out of 4 children were born with forceps because of their inability to strain.

In our study, 6% of those in the recumbent group and 6% of those in the squatting group had tears after episiotomy. In the sitting group, there was no tear. In the study of Nasir, widespread episiotomy was reported as a rupture, but in our study, first-degree tears and lacerations in other areas of the vulva were considered as a rupture with episiotomy. This study (19) reported no significant difference between grade-2 and grade-3 rupture. In this study, no subject of any group had grade-3 rupture. The results of the study by Nasir showed that given the high rate of episiotomy, the recumbence position should not be used routinely.

Ragnar (26) reported no significant difference in the occurrence of grade-3 tears between the groups with the sitting and crawling positions. The sitting and crawling positions are types of standing positions. In the present study, two groups out of the three compared groups are a subset of standing positions, which they are in agreement with Ragner's study, and there was also no case of grade 3 rupture in either of the three groups.

Hakan (27) concluded that there is a relationship between episiotomy and severe perineal tears. Jeffrey indicated that the risk of rupture of the sphincter is greater with episiotomy. Moreover, restricting the episiotomy will result in reduced perineal damage. In the present study, due to the physiologic process of childbirth and no intervention done during the study , the mother was given the chance to push spontaneously . If there was a possibility of severe tear or prolonged placement of the fetus head on the perineum, episiotomy was conducted. This might be the reason for the absence of grade-3 and grade-4 ruptures.

In the present study, 7 individuals in the group of lithotomy, 3 in the sitting group, and 4 in the squatting group had healthy perineum. Van (28) indicated that more pressure on the perineum in the standing position causes more damage to the perineum.

A study conducted in 2003 by Bonder et al. (21) in Australia reported more perineal tears in the standing group; however, the difference in the prevalence of perineal tears was not significant between the standing and recumbent groups. Furthermore, the number of episiotomies performed for those in the standing group was significantly lower, confirming our findings. Also Bonder et al. (21) reported that grade-3 tears occurred more frequently among patients with the standing positions; however, the difference was not significant. Bonder et al. (21) concluded that not performing the episiotomy in the standing position increased the chances of rupture.

Altman (22) compared the degree of perineal tears that occurred in the sitting group and crawling group (22). There was no significant difference between the two groups regarding the type of rupture; however, in the sitting group, 4 cases of grade-4 ruptures were reported. Richard et al. (23) reported that the level of the perineal tear in the standing positions was significantly lower than that in the recumbent group, and the chances of an intact perineum in the standing group was three times more than that in the recumbent group. The ruptures in the standing group were limited to grade-I; and no grade-3 or grade-4 ruptures were observed, consistent with our findings.

Terry (23) indicated that non-recumbent positions have an intrinsic protective effect on the perineum; this also affects risk factors, such as first birth and neonate weight.

Bamfim (24) conducted a study titled, "Influence of the position of the mother at delivery over some maternal and neonatal outcomes" in Brazil wherein there was no significant difference in the perineal tear and degree of laceration of the sitting and recumbent groups. In women with a history episiotomy, grade-2 rupture was significantly more common (twice as frequent) in

the recumbent group than in the standing group (p=0.02). Bamfim (24) indicated that the open status of thighs in the standing position causes perineal relaxation and reduces damage to the perineum. In the recumbent position, more pressure of the presentation part is applied to the posterior part of vagina due to the inappropriate position of the perineum and leaning it forward, and before the head reaches the vaginal opening, there is a great deal of pressure on the perineum and there may be a rupture due to the excessive stretching. He also believed that the lower prevalence of perineal tears in the standing group was attributable to the lower rate of episiotomy in this group. In our study, episiotomy indications were fully considered in all 3 groups. Further, the study included only primiparous women who had no history of episiotomy or a scar on the perineum.

Renolds (25) reported that the rate of episiotomy was significantly lower in the squatting group than in the recumbent group. Soong (29) in Queensland did not find any significant correlation between perineal rupture and trauma in the sitting, squatting, lithotomy, and crawling positions. Soong stated that the risk of tear and perineal trauma is related to the mother's body position, habits, infant weight, and history of perineal rupture. Eason's study (30) concluded that the mother's position in the second stage of labor does not affect the chances of perineal injury and tear. In addition, the position of the mother and the perineum injuries are not associated with being primiparous; however, a relationship was observed between the risk of perineum injuries and multiparous status.

Sekhavat (31) showed a significant difference between the sitting and recumbent groups in terms of ruptures. During the study, the back of the bed was placed in a vertical position, and the mother was seated in the lithotomy position with her legs placed in the childbirth rack. In this situation, pressure and elasticity on the perineum increases, increasing the rupture rate. In our study, the mother slept on the labor bed, and the top of the bed was raised to 30°; her legs were not bent over the abdomen; further, her buttocks and feet were resting on the bed, so the knees were not too far apart and opened in coordination with the footpads. Perhaps in this situation, too much stretch was not applied to the perineum and vagina; therefore, the tear rate in this situation was comparable to that in the sitting group.

As indicated, there was no significant difference in the Apgar score at 1 and 5 min in the three groups. Sekhavat (31) reported no differences in the Apgar score at 5 min in the sitting and sleeping groups. Delaram and Forozandeh (32) also showed that the maternal position during labor had no effect on the Apgar score of the baby. Ragnar and Altman (22, 26) reported no difference between the Apgar score at 1 and 5 min in the standing and recumbent groups. Terry (23) reported no significant difference in the Apgar scores at 1 and 5 min in the recumbent and non-recumbent positions (sitting and squatting). Nasir (19) indicated no significant difference in the Apgar score at 1 and 5 min. The results of all these studies are in line with our findings. Nasir found no significant difference in the Apgar score of the 2 groups (p>0.05).

Motamedi (33) reported that the Apgar score at 1 min in the combined group (sitting, lateral recumbence, standing, and crawling) was significantly higher than that in the recumbent group.

The Apgar score at 1 min in the standing group was significantly higher than that in the recumbence group in the study by Khavandizadeh (34); moreover, the score at 5 min showed no significant difference.

Reyhani (35) found no difference in the Apgar score at 1 min of the 4 groups (sitting, recumbent, moving, and free groups). However, the score at 5 min in the recumbent group was significantly lower than that in the other 3 groups (including the sitting group). She concluded that the active positions of mothers during labor can improve the Apgar score at 5 min. Bloom (36) indicated that due to uterine pressure on the lower inferior vein and the reduced blood flow to the heart in the recumbent position, the cardiac output would decrease and blood flow to the fetus would be impaired; this may affect the Apgar scores at 1 and 5 min.

One of the positive points of the present study was that postpartum bleeding was measured objectively. Also, in order to ensure the accuracy of the measurement, bleeding volume was measured in three ways. In this study, the volume of bleeding in all three delivery positions was within normal range. Postpartum bleeding and perineal tear are likely to be controlled if the delivery goes through its natural and physiological process and using positions according to the mother's circumstances. Because of the difficulty of increasing the sample size one limitation of the study was the low sample size

CONCLUSION

The use of these three positions can have effects on the postpartum bleeding in normal range. It is noteworthy that each birth position should be selected based on the situation of the mother. Finally, more studies should be conducted to identify the postpartum bleeding of these positions.

Ethics Committee Approval: Ethics committee approval was received for this study from Isfahan University of Medical Sciences Code of Ethics Committee:389292**.**

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

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Original Article

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Comparison of Transhiatal and Transthoracic Approaches in Esophageal Cancer Surgery

Orçun Yalav, Uğur Topal, Burak Yavuz, Kubilay Dalcı

Department of General Surgery, Çukurova University School of Medicine, Adana, Turkey

ORCID IDs of the authors: O.Y. 0000-0001-9239-4163; U.T. 0000-0003-1305-2056; B.Y. 0000-0002-5262-0346; K.D. 0000-0002-3156-4269.

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BACKGROUND/AIMS
We aimed to compare the efficacy and safety of transthoracic and transhiatal surgical approaches for esophageal cancer in our clinic.

MATERIAL and METHODS
The records of patients who underwent curative resection for esophageal cancer between 2011 and 2019 were retrospectively reviewed. Patients were divided into two groups according to the surgical approach: Group 1, transhiatal esophagectomy (THE); and Group 2, transthoracic esophagectomy (TTE). Demographics, preoperative stages, intraoperative findings, postoperative morbidity, mortality, and mean survival were compared.

RESULTS
Group 1 (THE) had 11 patients and Group 2 (TTE) had 19 patients. The groups were similar in terms of age, sex, and preoperative stage (p=0.5). Surgery duration (p=0.002) and the number of dissected lymph nodes (p=0.048) were significantly higher in the TTE group, but intraoperative blood loss (p=0.801), postoperative hospital stay (p=0.414), postoperative complication rates (p=0.734), postoperative mortality (p=0.393), and mean survival time (p=0.164) were not significantly different between the groups.

CONCLUSION
Comparing the TTE and THE surgical techniques performed for esophageal cancer in our clinic, the surgery time was longer for TTE, which allowed for more lymph node dissection; however, TTE showed similar morbidity and mortality rates as THE, and the type of surgical approach did not affect postoperative mortality, major morbidity rates, anastomosis complications, length of hospital stay, or survival time. We believe that these results are due to the low number of patients in the study, the fact that more experienced surgeons had performed THE in the first 4 years, and that esophagectomy cases were not performed by a single surgical team in our clinic.

Keywords: Esophageal cancer, transhiatal surgery, transthoracic surgery

INTRODUCTION

Esophageal carcinoma is the eighth most common cancer worldwide and the sixth most common cause of cancer-related deaths (1). There are two main subtypes of esophageal cancer, and each have distinct epidemiological and biological characteristics: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). There is a high correlation between ESCC and smoking, alcohol abuse, and chronic inflammation; EAC, however, is typically associated with Barrett's metaplasia, gastroesophageal reflux disease, and obesity (2).

Today, esophageal cancer still has a high mortality rate and a poor prognosis, despite improvements in surgical techniques and improved preoperative and postoperative care and conditions. The 5-year survival rate for all patients is less than 20% (3).

Treatment of esophageal cancer is with surgery, radiotherapy, chemotherapy, or a combination of all three. Today, the most effective treatment of esophageal cancer can be achieved by surgery (2, 4). Various methods are used in the surgical treatment of esophageal cancer, with the Ivor Lewis (transthoracic esophagectomy [TTE]) and Orringer (transhiatal esophagectomy [THE]) methods being the most commonly used.

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Corresponding Author: Uğur Topal
E-mail: sutopal2005@hotmail.com

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Transthoracic Esophagectomy (TTE) is typically performed by laparotomy followed by right thoracotomy and intrathoracic anastomosis (Ivor Lewis procedure), first described in two stages in 1946 (5). THE was first performed by Turner for esophageal carcinoma in 1933 (6). In 1978, Orringer supported THE, claiming that a blunt dissection without thoracotomy was safer and better tolerated than combined transthoracic and abdominal surgery (7).

Although both THE and TTE are accepted surgical techniques for esophageal cancer management, there is controversy in the literature as to which of these techniques is superior (8-10). Unfortunately, there is as yet no evidence-based optimal surgical approach to esophagectomy (11, 12). There has been, and continues to be, important debate regarding the optimal surgical approach (10, 13-15).

Previous studies in the literature have found that neither the transhiatal nor transthoracic approach altered early postoperative mortality, major morbidity rates, hospital stay, or survival in esophageal cancers (16). In addition, the effect of sex, race, and patient comorbidities on postoperative complications was similar for both esophagectomy types (17).

In the light of these studies, we aimed to compare the results of transhiatal and transthoracic approaches to esophageal cancer in our clinic.

MATERIAL AND METHODS

Thirty patients who were diagnosed with EAC and ESCC after the histopathological examination of tissue obtained by endoscopic biopsy, taken between January 1, 2011 and January 1, 2019, were included in the study (Ethics Approval number 86/23, dated 08.03.2019 was obtained from the Ethics Committee). Patients with no diagnosis of malignancy, those who underwent palliative surgical treatment, patients under 18 years of age, and patients whose records could not be accessed were excluded from the study. The depth of tumor invasion was evaluated with endoscopic ultrasound in suspected cases. Contrast-enhanced computed tomography (CT) of the thorax and the upper and lower abdomen were performed for staging and positron emission tomography-CT was added to screening tests in suspicious cases.

Main Points:

- Today, treatment of esophageal cancer needs multidisciplinary treatments, including surgery, radiotherapy, chemotherapy, or a combination of all three. The most effective treatment of esophageal cancer may be achieved by surgery following oncologic treatment.
- The most preferred surgical treatment of esophageal cancer is Ivor Lewis (transthoracic esophagectomy [TTE]) or Orringer (transhiatal esophagectomy [THE]), respectively.
- Thoracotomy is technically difficult, although it provides better oncological results and is superior to the transhiatal approach with higher morbidity.
- The most important determinants of survival are the biological behavior of the tumor and its stage during resection, rather than the type of surgical approach. Therefore, patient treatment should be individualized.

The patients were divided into two groups: Group I, THE; and Group 2, TTE. A common database was created by examining patient files, anesthesia records, and hospital information system records. Using this database, patient information was retrospectively evaluated. Follow-up data were supported by telephone interviews with patients. Demographic characteristics, body mass index (BMI), comorbid diseases, American Society of Anesthesiologists (ASA) score, neoadjuvant treatment status, preoperative laboratory values, tumor localizations (upper 1/3 and cervical esophagus, middle 1/3, lower 1/3, gastroesophageal junction, and cardia), and clinical stage were recorded. Surgical technique (open, laparoscopic), duration of surgery, mean blood loss, intraoperative complications, additional organ resection, tumor diameter, histological type and grade, total and metastatic lymph nodes removed, pathological stage, postoperative complications according to the Clavien–Dindo classification (18), respiratory and cardiac complications, wound infection, anastomotic leakage, postoperative hospital stay, 30-day mortality, 90-day unplanned admission to the hospital, long-term anastomotic stenosis, local recurrence or metastasis, mean follow-up, mean survival, and current clinical conditions (exitus, living with metastasis, living disease-free) were compared between the two groups.

Anastomotic leakage was defined as a deterioration in the integrity of the anastomosis as documented by a combination of clinical, radiological, and operative tools.

Wound infection was defined as superficial or deep incisional surgical site infection in the surgical wound according to the definition of the Centers for Disease Control (19).

Unscheduled hospitalization within the first 90 days after discharge was considered as unplanned readmission to the hospital.

We considered unplanned reoperation as a surgical procedure under general, spinal, or epidural anesthesia within 30 days of the index operative procedure for any reason, except for follow-up procedures based on pathology results, in accordance with the American College of Surgeons National Surgical Quality Improvement Program definition (20).

The tumor-node-metastasis (TNM) 2010 or 2016 system was used for tumor staging (21, 22).

All patients were informed about the surgical options, and written informed consent was obtained. THE is defined as the open resection of the esophagus performed through the esophageal hiatus and thoracic inlet without thoracotomy. TTE is defined as the open resection of the esophagus employing thoracotomy, including all single-, 2-, and 3-stage procedures, using either a right or left thoracotomy or thoracoabdominal incision (4, 23).
The transhiatal or transthoracic approach was used according to the patient's general condition, tumor location, and individual surgeon preference. Both procedures were performed a standard manner as previously described (5, 7).

Statistical Analysis

Data were analyzed using IBM Statistical Package for the Social Sciences for Windows, version 24 (IBM Corp., Armonk, NY, USA). Categorical measurements were summarized as numbers and percentages, and continuous measurements were summarized as means

and standard deviation (median and minimum-maximum where necessary). Chi-squared or Fisher's tests were used to compare categorical variables. In the comparison of continuous measurements between groups, Student's t-test was used for parameters showing a normal distribution according to the number of variables, and the Mann–Whitney U test was used for parameters not showing a normal distribution. Kaplan–Meier and log-rank tests were used for the survival analysis. Statistical significance was set at 0.05 in all tests.

RESULTS

The study included 30 patients: 11 in Group I and 19 in Group 2. The age distribution for Group I was 57.27±13.48 (41-86) and 55.89±10.75 (31-74) for Group 2 (p=0.760). Sex distribution was 5 (45.5%) men and 6 (54.5%) women in Group I, and 10 (52.6%) men and 9 (47.4%) women in Group 2 (p=0.500). In Group I, 3 (27.3%) patients had a score of ASA I, and 8 (72.7%) patients had ASA 2; whereas in Group 2, 6 (31.6%) patients had ASA I, 9 (47.3%) patients had ASA 2, and 4 (21.1%) patients had ASA 3 (p=0.207).

The patients' BMI was calculated as 21.63±2.94 (16–26) in Group I and 26.7±4.4 (21-40) in Group 2 (p=0.005). Neoadjuvant treatment was administered to 1 (9.1%) patient in Group I and 16 (84.2%) patients in Group 2 (p=0.001).

Preoperative hemoglobin levels were 11.5±1.7 (8-15) in Group I and 12.1±1.4 (10-15) in Group 2 (p=0.313). Preoperative carcinoembryonic antigen (CEA) level was 1.0±0.8 (0-2) in Group I and 4.2±5.8 (0-22) in Group 2 (p=0.078). Preoperative albumin level was 3.0±0.4 (2-4) in Group I and 2.9±0.7 (2-4) in Group 2 (p=0.826).

The most common presenting symptom was difficulty swallowing in both groups. Nine (81.1%) patients in Group I and 14 (73.7%) patients in Group 2 presented with this symptom (p=0.170).

The most common concomitant disease was asthma in Group I, with 3 patients (27.3%), and diabetes mellitus was observed in 4 (21%) patients in Group 2 (p=0.078).

The tumor was most commonly located in the lower esophagus in both Group I and Group 2 (54.5% and 68.4%, respectively) (p=0.558).

TABLE I. Demographic Characteristics and Preoperative Findings of the Patients

		THE n: 11	TTE n: 19	p*
Age (min-max)		57.27+13.48 (41-86)	55.89+10.75 (31-74)	0.760
Sex	Male	5 (45.5)	10 (52.6)	0.500
	Female	6 (54.5)	9 (47.4)	
ASA score	I	3 (27.3)	6 (31.6)	0.207
	2	8 (72.7)	9 (47.4)	
	3	0 (0.0)	4 (21.1)	
BMI (min-max)		21.63+2.94 (16-26)	24.68+4.25 (19-33)	0.045
Neoadjuvant CT	CRT	1 (9.1)	16 (84.2)	0.001
	None	10 (90.9)	3 (15.8)	
Preoperative (Hgb)gr/dl(min-max)		11.5+1.7 (8-15)	12.1+1.4 (10-15)	0.313
Preoperative (Cea) (min-max)		1.0+0.8 (0-2)	4.2+5.8 (0-22)	0.078
Preoperative albumin gr/dl (min-max)		3.0+0.4 (2-4)	2.9+0.7 (2-4)	0.826
Symptom	Nausea, vomiting	2 (18.2)	1 (5.3)	0.170
	Dyspepsia	0 (0.0)	4 (21.1)	
	Swallowing difficulty	9 (81.8)	14 (73.7)	
Concomitant Diseases	Asthma	3 (27.3)	0 (0.0)	0.078
	Diabetes	0 (0.0)	4 (21.5)	
	HT	1 (9.1)	0 (0.0)	
	CAD	0 (0.0)	2 (10.5)	
	COPD	0 (0.0)	1 (5.3)	
	Nephrolithiasis	1 (9.1)	0 (0.0)	
	None	6 (54.5)	12 (63.2)	
Tumor localization	LOWER	6 (54.5)	13 (68.4)	0.558
	GEJ	1 (9.1)	2 (10.5)	
	MIDDLE	3 (27.3)	4 (21.1)	
	UPPER	1 (9.1)	0 (0.0)	

THE: transhiatal esophagectomy; TTE: transthoracic esophagectomy; ASA: American Society of Anesthesiologists; BMI: body mass index; HGB: hemoglobin; HT: hypertension; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disorder; GOJ: gastroesophageal junction.

Demographic characteristics and preoperative findings of the patients are shown in Table 1.

In Group 2, 3 (15.8%) patients underwent anastomosis in the cervical region, whereas in Group 1, all patients underwent anastomosis in the cervical region (p=0.000). Laparoscopy-assisted surgery was performed in 1 (9.1%) patient in Group 1 and in 8 (42.1%) patients in Group 2 (p=0.065). Anastomosis was performed with a stapler in 1 (9.1%) patient in Group 1 and in 6 (36.6%) patients in Group 2 (p=0.171). Duration of surgery was 210.0±36.8 min (150-250) in Group 1 and 321.84±101.0 min (140-540) in Group 2 (p=0.002). Mean blood loss was 210.0±111.9 mL (50-350) in Group 1 and 225.2±179.1 mL (10-600) in Group 2 (p=0.801). No additional organ resection was needed in any patient and no intraoperative complication developed. R0 resection was performed in 9 (81.8%) patients in Group 1 and in 15 patients (78.9%) in Group 2 (p=0.737). Intraoperative features are shown in Table 2.

Tumor diameter was calculated as 3.00±2.09cm (0-7.0) in Group 1, and as 2.47±2.34 (0-8.0) in Group 2 (p=0.543). Histological type was most commonly squamous cell carcinoma in both Group 1 and Group 2 (63.6% and 63.2%, respectively) (p=0.383). The most common histologic grade in Group 1 was grade 1, observed in 7 (63.6) patients, and in Group 2 was grade 2, also observed in 7 (36.8%) patients (p=0.197). The most common pathological stage was 3C in Group 1 (3 patients, 27.3%), and 0 (7 patients, 36.8%) in Group 2 (p=0.086). Complete pathologic response was observed in 7 of 16 patients receiving neoadjuvant treatment in Group 2 (43.75%); however, it was not observed in any patients receiving neoadjuvant treatment in Group 1. Our pathological complete response rate was 41.6%. The total number of lymph nodes removed was calculated as 13.27±8.43 (3-27) in Group 1 and as 22.58±10.0 (10-48) in Group 2 (p=0.048). The number of metastatic lymph nodes was 1.45±2.2 (0-6) in Group 1 and 1.05±2.8 (0-11) in Group 2 (p=0.687). Tumor characteristics are shown in Table 3.

Postoperative respiratory complications occurred in 3 (27.3%) patients in Group 1 and 7 (36.9%) patients in Group 2 (p=0.412). Cardiac complications were observed in 2 (10.5%) patients in Group 2, but not in Group 1 (p=0.393). Postoperative anastomotic leakage was detected in 2 (18.2%) patients in Group 1 and in 4 (21.1%) patients in Group 2 (p=0.620). Wound infection occurred in 3 (27.3%) patients in Group 1 and in 2 (10.5%) patients in Group 2 (p=0.245). Vocal cord paralysis did not occur in Group 1, whereas it occurred in 3 (15.8%) patients in Group 2 (p=0.239). The Clavien–Dindo classification was used to categorize postoperative complications (Figure 1); according to this classification, 5 (45.5%) patients in Group 1 had Grade 1, and 6 (31.6%) patients in Group 2 had Grade II complications (p=0.734). Reoperation was performed for anastomotic leakage in 1 (9.1%) patient in Group 1, for anastomotic leakage in 2 of 3 (15.8%) patients in Group 2, and in 1 patient due to chylous fistula (p=0.530). Duration of hospitalization in the postoperative intensive care unit (ICU) was 5.91±4.34 (1-16) days in Group 1 and 9.58±12.5 (1-52) days in Group 2 (p=0.359). Postoperative hospital stay was 18.55±9.44 (8-41) days in Group 1 and 23.42±18.05 (8-90) days in Group 2 (p=0.414). Two patients in Group 2 developed postoperative 30-day mortality, of cardiac and respiratory origin. There was no postoperative mortality in Group 1 (p=0.393). When the number and reasons of 90-day readmissions to the hospital were evaluated, 2 of 3 (27%) patients had anastomotic stenosis and 1 had feeding jejunostomy displacement in Group 1, whereas 1 (5.3%) patient presented with anastomotic stenosis in Group 2 (p=0.126). Anastomotic stenosis occurred in 3 (27.3%) patients in Group 1 and in 5 (26.3%) patients in Group 2 (p=0.637). Reflux esophagitis occurred in 2 (10.5%) patients in Group 2. Local recurrence in oncologic follow-up was 1 (9.1%) in Group 1, and 1 (5.3%) in Group 2 (p=0.607). Distant organ metastasis was detected in 2 (18.2%) patients in Group 1 and in 3 (15.8%) patients in Group 2 (p=0.619). Perioperative and postoperative clinical outcomes and oncological outcomes are shown in Table 4.

Postoperative survival time was 43.44±12.68 (18.579-68.318) months in Group 1 and 36.329±4.84 (26.842-45.817) months in Group 2 (p=0.287). The groups in terms of survival are summarized in Table 5 and Figure 2 (p=0.168).

TABLE 2. Intraoperative Characteristics

		THE n: 11	TTE n: 19	p*
Anastomosis	Intrathoracic	0 (0.0)	16 (84.2)	0.000
	Cervical	11 (100.0)	3 (15.8)	
Surgical technique	Open	10 (90.9)	11 (57.9)	0.065
	Lap assisted	1 (9.1)	8 (42.1)	
Anastomosis technique	Hand	10 (90.9)	13 (68.4)	0.171
	Stapler	1 (9.1)	6 (31.6)	
Operation duration (min-max)	210,0+36,8 (150-250)	321.84+101.0 (140-540)	0.002	
Intraoperative blood loss (min-max)	210,0+111,9 (50-350)	225.2+179.1 (50-600)	0.801	
Intraoperative complications	None	11 (100.0)	19 (100.0)	1.000
Additional organ resection	None	11 (100.0)	19 (100.0)	1.000
Resection	R0	9 (81.8)	15 (78.9)	0.737
	R1	2 (18.2)	3 (15.8)	
	R2	0 (0.0)	1 (5.3)	

THE: transhiatal esophagectomy; TTE: transthoracic esophagectomy; LAP: laparascopic

Degree	Definitions
I	Any deviation from the normal postoperative course without the need of intervention beyond the administration of antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physical therapy*
II	Complications requiring pharmacological treatment with other medicines beyond the ones used for the complications of degree I
III	Complications requiring surgical, endoscopic, or radiological intervention
III-a	Intervention without general anesthesia
III-b	Intervention under general anesthesia
IV	Life-threatening complication requiring admission to intensive care unit
IV-a	Uni-organ dysfunction (including dialysis)
IV-b	Multi-organ dysfunction
V	Death

*This degree also includes drained cutaneous infections without general anesthesia.

FIGURE I. Classification of surgical complications

TABLE 3. Tumor Characteristics

		THE n: 11	TTE n: 19	p*
Tumor diameter cm (min-max)		3.00+2.09 (0-7.0)	2.47+2.34 (0-8.0)	0.543
Histological type	Adenocarcinoma	3 (27.3)	7 (36.8)	0.383
	Granular cell tumor	1 (9.1)	0 (0.0)	
	Squamous cell carcinoma	7 (63.6)	12 (63.2)	
Histological grade	0	0 (0.0)	6 (31.6)	0.197
	I	7 (63.6)	7 (36.8)	
	2	3 (27.3)	4 (21.1)	
	3	1 (9.1)	2 (10.5)	
Pathological T	T0	0 (0.0)	8 (42.1)	0.131
	Tla	0 (0.0)	1 (5.3)	
	Tlb	1 (9.1)	1 (5.3)	
	T2	3 (27.3)	1 (5.3)	
	T3	3 (27.3)	4 (21.1)	
	T4a	4 (36.4)	3 (15.8)	
	T4b	0 (0.0)	1 (5.3)	
Pathological N	N0	6 (54.5)	16 (84.2)	0.075
	Nl	3 (27.3)	0 (0.0)	
	N2	2 (18.2)	2 (10.5)	
	N3	0 (0.0)	1 (5.3)	
Pathological M	M0	11 (100.0)	18 (94.7)	0.633
	Ml	0 (0.0)	1 (5.3)	
Pathological stage	0	0 (0.0)	7 (36.8)	0.086
	Ia	2 (18.2)	2 (10.5)	
	Ib	2 (18.2)	1 (5.3)	
	2b	0 (0.0)	3 (15.8)	
	3a	2 (18.2)	3 (15.8)	
	3b	2 (18.2)	0 (0.0)	
	3c	3 (27.3)	2 (10.5)	
	4b	0 (0.0)	1 (5.3)	
Total dissected lymph nodes (min-max)		13.27+8.43 (3-27)	22.58+10.0 (10-48)	0.048
Metastatic lymph nodes		1.45+2.2 (0-6)	1.05+2.8 (0-11)	0.687

THE: transhiatal esophagectomy; TTE: transthoracic esophagectomy

DISCUSSION

National Comprehensive Cancer Network (NCCN) guidelines for the treatment of esophageal and gastroesophageal cancers (11) and the guidelines of the European Medical Oncology Association (ESMO) for the treatment of esophageal cancer (12) indicate that primary surgical treatment is essential. Evaluation of the resectability of all esophageal tumors by thoracic and abdominal tomography, positron emission tomography, and endoscopic ultrasound should be evaluated by the esophageal surgeon to determine the feasibility of performing esophagectomy (24).

Accepted surgical procedures in the treatment of esophageal cancer vary. Generally, the two main options are a transabdominal or transthoracic approach. The recommended reconstruction is from a gastric canal if possible, followed by the colon or jejunum. Although the NCCN guidelines (11) do not provide specific advice on the type of esophagectomy to be performed, the ESMO guidelines (12) recommend performing a three-site esophagectomy, the Ivor Lewis type.

There is controversy regarding the optimal surgical approach to the treatment of patients with esophageal cancer. Perceptions

TABLE 4. Perioperative and Postoperative Clinical Outcomes, and Oncologic Outcomes

		THE n: 11	TTE n: 19	p*
Respiratory complications	No	8 (72.7)	12 (63.2)	0.412
	Pleural effusion	1 (9.1)	1 (5.3)	
	Pneumonia	2 (18.2)	6 (31.6)	
Cardiac complications	No	11 (100.0)	17 (89.5)	0.393
	Cardiac arrest	0 (0.0)	2 (10.5)	
Anastomosis leak	No	9 (81.8)	15 (78.9)	0.620
	Yes	2 (18.2)	4 (21.1)	
Wound complication	No	8 (72.7)	17 (89.5)	0.245
	Yes	3 (27.3)	2 (10.5)	
Vocal cord paralysis	No	11 (100.0)	16(84.2)	0.239
	Yes	0 (0.0)	3 (15.8)	
Complication based on Clavien–Dindo	1	3 (27.3)	6 (31.6)	0.734
	2	5 (45.5)	5 (26.3)	
	3a	1 (9.1)	2 (10.5)	
	3b	2 (18.2)	4 (21.1)	
	5	0 (0.0)	2 (10.5)	
Reoperation	No	10 (90.9)	16 (84.2)	0.530
	Yes	1 (9.1)	3 (15.8)	
Postoperative intensive care stay duration (min-max)		5,91+4,34 (1-16)	9.58+12.5 (1-52)	0.359
Postoperative hospital stay duration (min-max)		18,55+9,44 (8-41)	23.42+18.05 (8-90)	0.414
30-day mortality	No	11 (100.0)	17 (89.5)	0.393
	Yes	0 (0.0)	2 (10.5)	
90-day readmission	No	8 (72.7)	18 (94.7)	0.126
	Yes	3 (27.3)	1 (5.3)	
Anastomotic stenosis	No	8 (72.7)	14 (73.7)	0.637
	Yes	3 (27.3)	5 (26.3)	
Reflux esophagitis	No	11 (100.0)	17 (89.5)	0.393
	Yes	0 (0.0)	2 (10.5)	
Local recurrence	No	10 (90.9)	18 (94.7)	0.607
	Yes	1 (9.1)	1 (5.3)	
Metastasis	No	9 (81.8)	16 (84.2)	0.619
	Yes	2 (18.2)	3 (15.8)	
Current state	Exitus	7 (63.6)	5 (26.3)	0.131
	Alive without disease	3 (27.3)	11 (57.9)	
	Alive with metastasis	1 (9.1)	3 (15.8)	

THE: transhiatal esophagectomy; TTE: transthoracic esophagectomy

of postoperative morbidity and mortality can sometimes lead to surgical treatment, but surgical technique decisions are often based on personal bias, surgeon experience, and ease of the procedure. The ongoing discussion focuses on whether longer resection with thoracotomy provides oncological outcomes superior to resection with relatively limited morbidity and mortality using a transhiatal approach (14, 23).

Although the mean age of the patients with esophageal cancer in the meta-analyses ranged from 60 to 66 years, the male sex had significant dominance (9, 17, 14). The incidence of esophageal cancer increases with age; in one study, 56% of cases in the UK were patients older than 70 (25). Papenfuss et al. (14) had found the mean age to be greater in patients undergoing the transhiatal approach than those undergoing the transthoracic (66 vs. 63, respectively, p=0.003) (14). In our series, the age range was younger than in the literature, and in contrast to the series in the literature, the mean age was similar in the groups (57 THE vs. 55 TTE). In our study, although the male sex was more common in the TTE group, there was no significant superiority. There was no statistical difference between the sexes (p=0.5).

In the 4053-case series of Schlottmann et al. (17), 79% of the patients in the THE group had an ASA score of 3 or more, and 82% of the TTE group had an ASA score of 3 or more (p=0.07). In the same study, an ASA score ≥3 (odds ratio [OR] 1.37; 95% confidence interval [CI] 1.13-1.68; p=0.002) was independently associated with postoperative complications (17). Our series was in agreement with the literature; patients with ASA scores 2 and 3 were the majority, and there was no statistical difference between the groups (p=0.207).

TABLE 5. Survival Time in Terms of Operation Type (Alive)

		Average (Mean+sd (Min-Max)	p
Operation type	THE	43.44+12.68 (18.579-68.318)	0.164
	TTE	36.329+4.84 (26.842-45.817)	

THE: transhiatal esophagectomy; TTE: transthoracic esophagectomy

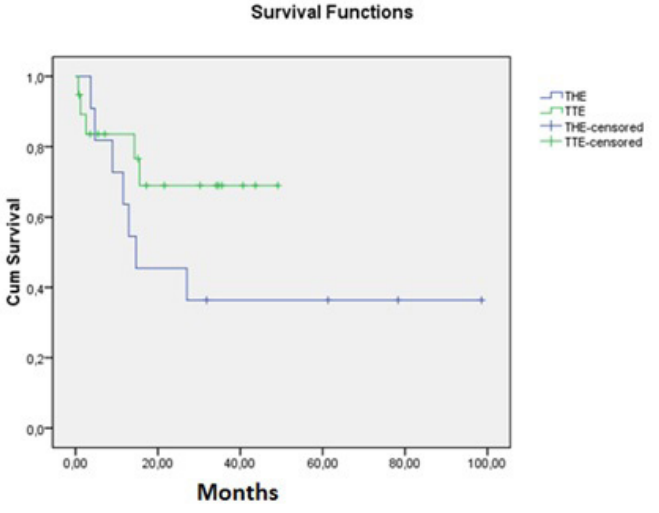

FIGURE 2. Survival duration by group

Although there is not much information in the literature on BMI and surgical method selection, it has been shown that patients with a BMI>23 have better mean survival after esophagectomy, and this parameter is an independent component of predicting survival (26). In our study, BMI was higher in the TTE group compared with the THE group (24 vs. 21, respectively, p=0.045).

It is well known that surgical resection as a monotherapy in esophageal cancer has long been the gold standard, but its usefulness is now being questioned. Neoadjuvant chemotherapy and radiotherapy play an important role in the management of esophageal cancer; in the Chemoradiotherapy for Esophageal Cancer Followed by Surgery Study, patients who underwent surgical treatment after neoadjuvant treatment were compared with patients who only underwent surgical treatment, and a survival advantage was observed in patients receiving neoadjuvant treatment (49.4 vs. 24 months) (27). Esophagectomy is recommended for the initial treatment of patients with TIN0M0 and T2N0M0 tumors, whereas all patients with T3 tumors and some patients with T4a tumors should undergo neoadjuvant chemoradiotherapy (11). In our series, 84% of the patients in the TTE group received neoadjuvant therapy as initial therapy. The neoadjuvant treatment rate was high in the TTE group (p=0.001). Preoperative tumor staging was performed more accurately by using endoscopic ultrasound in tumor staging in our clinic, which led to an increase in neoadjuvant treatment.

Preoperative hemoglobin, albumin, and CEA levels were similar between the groups. Our patients were homogeneous in terms of nutritional status in both groups, as has been previously reported in the literature (16).

Due to the expandable nature of the esophagus, symptoms resulting from an obstructive lesion or stenosis occur only when the tumor has progressed relatively locally or when it reaches a metastatic stage. Warning symptoms include difficulty swallowing, pain during swallowing, and involuntary or progressive weight loss (2). In our series, presenting symptoms were similar between groups, but the most common presenting symptom was difficulty in swallowing.

It is known that patients with higher Charlson Comorbidity Index have a poor prognosis after esophageal cancer surgery, and that comorbid diseases have negative effects on quality of life following esophagectomy (2, 28). In the series by Schlottmann et al. (17), comorbid diseases were found to be similar in the TTE and THE groups, with the most common comorbid diseases hypertension and chronic obstructive pulmonary disease (17). In our series, there was no statistical difference between the groups regarding comorbid diseases, as is reported in the literature.

Esophageal tumors can be located in 4 different regions. The behavior of esophageal cancer, treatment modalities, and surgical intervention methods vary. The resection technique depends on tumor location, the natural course of the cancer, and the personal preference of the surgeon. In addition, esophageal cancers differ according to their histological types in their localization (2). In our series, the tumor site was located in the lower and middle esophagus in both groups and there were no differences between the groups.

In their study comparing cervical and thoracic anastomosis, Biere et al. (29) had found the anastomosis leakage rate and recurrent nerve injury to be higher in patients who underwent esophagectomy with cervical anastomosis (29). In our series, anastomosis was performed in the cervical region in 3 patients in the TTE group.

Minimally invasive esophagectomy has emerged as a viable and safe procedure for esophagectomy in the last few years. It involves hybrid operations that combine laparoscopy with thoracotomy or laparotomy with thoracoscopy and fully minimally invasive procedures or robot-assisted surgeries. A systematic review of 17 studies involving 1598 patients (including minimally invasive surgical combinations) found no difference in long-term survival after minimally invasive surgery compared with open surgery (30). In our series, we performed minimally invasive procedures in 42% of the patients in the TTE group. Minimally invasive access was determined by the surgeon's preference.

In their 416-esophagectomy series, Harustiak et al. (31) had recommended the stapler technique as an intrathoracic esophagogastric anastomosis method, arguing it led to reduced overall anastomosis leakage and anastomotic stenosis rates compared with the hand-sewn technique. Although we used the stapler technique more often in our anastomoses in the TTE group, there were no statistical differences between the groups.

Papenfuss et al. (17) had found that the duration of surgery in the transthoracic group was increased compared with the transhiatal group (364 vs. 298 min, respectively, p<0.001) (14). In our series, the surgery time was longer in the TTE group than in the THE group (321 vs. 210 min, respectively, p=0.002). The factors that prolonged the operation time in the TTE group were patients who underwent thoracotomy and minimally invasive procedures.

Blunt dissection of the esophagus during THE can also cause severe intraoperative bleeding. An important contraindication to THE is the presence of excessive fixation in tissues close to the esophagus, such as the membranous trachea or aorta. In addition, both techniques can cause bleeding due to spleen injury during gastric release. Given managing intrathoracic hemorrhage during THE is difficult, patients might need urgent thoracotomy (32). In the series of Zheng B et al. (33), intraoperative bleeding averages was 218.7 mL in TTE and 202.7 mL in THE (p=0.493). In the meta-analysis by Wei MT et al. (9), no significant difference was found between the two groups (weighted mean difference, 151.17; 95% CI -21.37 to 323.71; p=0.09). In our series, the amount of intraoperative bleeding was similar (225 mL for THE vs. 210 mL for TTE, p=0.801). During transhiatal esophagectomy, there was no bleeding that was unexpected or that required thoracotomy.

In our series, no major intraoperative complications were observed to change the course of the operation, and we did not need additional organ resection. Our R0 resection rate was similar between the groups at approximately 80%.

Tumor size is an independent prognostic factor in esophageal cancer as well as an important prognostic factor in many other cancers (34). Zheng B et al. (33) had found tumor diameters to be similar in the TTE and THE groups (p=0.239). In their series, the rate of patients with a tumor diameter of 3 cm or less was 30%. In our study, the mean tumor diameter was less than 3 cm in both groups, and there was no statistical difference between the groups. Squamous cell carcinoma was the predominant tumor type in both groups. There was no statistical difference between the groups in terms of tumor stage in the studies in the literature (10, 34). In the Khullar OV et al. (10) series, pathological stage 3 was the most common in both techniques. In our series, the most common stage in the THE group was 3 (27.3%) and in the TTE group was 0 (36%) (p=0.086). Our pathological complete response rate was 43%. Pathological complete response has been reported in the literature to be between 19% and 33%, and a higher rate of pathological complete response had been found in squamous cell carcinoma (35). This high rate in our series was attributed to the predominant tumor histology of squamous cell carcinoma.

Regarding lymphadenectomy in esophageal cancer, it is important to consider the ways in which this neoplasm spreads. Local regional growth of esophageal cancer is characterized by spread to the submucosal layer. Initially, it spreads to the regional lymph nodes and then to distant lymph nodes and distant organs (24).

In a retrospective study by Peyre et al. (36), they included 2303 patients (1381 with EAC and 930 with ESCC) diagnosed with esophageal cancer from 9 international centers undergoing R0 esophagectomy. They found that the mean number of resected lymph nodes was 17. Five-year global survival was 40%, and a Cox regression analysis showed that the number of resected lymph nodes was an independent predictor of survival (p<0.0001). In this study, no patient received neoadjuvant therapy.

In the series by Khullar et al. (10), the mean difference between lymphadenectomy performed using 2 different techniques had been analyzed, and TTE (11 lymph nodes) was found to involve 2 more lymph node resections than THE (9 lymph nodes) (p=0.003). Wei et al. (9) had reported 4 articles (2 randomized clinical trials and 2 nonrandomized trials) describing lymphadenectomy in their meta-analysis. They did not find a statistically significant difference in the number of resected nodes in the individualized analysis of both study types (randomized and nonrandomized).

In our study, the number of dissected lymph nodes was statistically higher in the TTE group than in the THE group (22 vs. 12, respectively, p=0.048).

The debate on the effect of the operative approach on surgical complications remains ongoing in the twenty-first century. A randomized controlled trial in the Netherlands had shown that THE was associated with fewer pulmonary complications and involved a shorter hospital stay, but there was no significant difference in hospital mortality rates. In the follow-up study of the same cohort, the 5-year survival for THE and TTE was 34% and 36%, respectively (p=0.71) (37, 38). Boshier et al. (4) had conducted a meta-analysis of 52 studies and reported that the transthoracic group had significantly more respiratory complications and greater early postoperative mortality, and anastomosis leakage was significantly higher in the THE group.

Theoretically, transthoracic resections have the disadvantages of a thoracotomy, which can result in a greater number of pulmonary complications. Transthoracic resections can be associated with a temporary impairment of respiratory function during left-lateral lung ventilation. The incidence of cardiopulmonary complications can be reduced with modern anesthesia techniques and perioperative respiratory care (39). Pulmonary physiotherapy is important in the early postoperative period in patients undergoing esophagectomy. Schlottmann F et al. (17) had found increased postoperative pulmonary complications in patients who underwent TTE compared to those who received THE. (16.8% vs. 13.8%, p=0.001). Although there are studies reporting the rate of postoperative pulmonary complications as similar in the literature (10), the overall rate of pulmonary complications is higher in the TTE group in large metanalyses (9, 17, 39). Although postoperative pulmonary complications were more common in the TTE group, there was no statistical difference in our series.

In the literature, postoperative cardiac complications after esophagectomy were reported in the range of 2%-16%, and there was no difference between TTE and THE groups (9, 10, 17, 39). Our series supports the literature.

The incidence of anastomotic leakage varies widely in the literature (3%-50%), which could be due to a problem with the definition of anastomotic leakage: some authors mention only clinically significant leaks, and some accept both subclinical and clinical leaks (8, 9, 10, 17, 33, 39). The high rate of cervical anastomosis leakage is explained by the reduced blood supply of the proximal gastric area due to the placement of the (tubularized) stomach from the abdomen into the cervical region along a long intrathoracic segment (40). However, it is generally accepted that the mortality rate due to cervical anastomotic leakage is significantly lower than that due to intrathoracic leakages (10). In transthoracic resections, anastomosis can be performed cervically, but it is often performed in the chest. During transhiatal procedures, anastomosis is always performed in the neck.

In their 2001 review, Hulscher et al. (39) had found a significant difference in support of transthoracic approaches in general. Wei MT reported in their meta-analysis in 2014 that there was no significant difference between the two groups according to the aggregated results (OR 1.24; 95% CI 0.80 to -1.94; p=0.34) (9). The effect of the surgical technique on anastomotic leakage has changed over the years. There was no difference between the TTE and THE groups in terms of anastomotic leakage in our series (21.1% vs. 18.2%). In our series, re-exploration was performed in patients with significant leakage, whereas patients with subclinical leakage were followed up medically.

Papenfuss et al. (14) had found in their series that the superficial wound infection rate of the THE group was significantly higher than TTE (11.6% vs. 6.2%, p<0.001). In the Schlottmann F series, the incidence of deep wound infection was significantly higher in THE (3.1% vs. 1.3%, p<0.001) (17). In our series, in line with the literature, wound complications were more frequent in the THE group than in the TTE group (27.3% and 10.5%, respectively), but there was no statistical difference.

Postoperative continuation of voice hoarseness is a symptom of recurrent laryngeal nerve damage. In the case of superior laryngeal nerve injury, the patient can tolerate solid foods better when oral nutrition is initiated, whereas liquid foods tend to be aspirated. The vocal cord is paralyzed on the anastomosis side. After cervical anastomosis in both the transthoracic and transhiatal procedures, the recurrent nerve was reported to be mainly at risk during cervical dissection and anastomosis (39). In the meta-analysis by Boshier PR et al. (4), the occurrence of vocal cord paralysis had been observed significantly less often after TTE (87 of 1541, 5.6%) compared with THE (158 of 1448, 10.9%; OR 0.57; 95% CI 0.38-0.84; p=0.005). In our series, nerve injury developed in 3 patients in the TTE group: 2 during cervical anastomosis and 1 during thoracic anastomosis.

Anastomotic leakage has been reported to be a major cause of reoperations after esophageal cancer surgery. In their series, Schlottmann F, etal. (17) found similar reoperation rates in the THE and TTE groups (12.1% vs. 14.1%, p=0.07). In our series, reoperation rates were similar between the groups. Reoperations were due to anastomotic leakage.

Postoperative hospital stay is often considered representative of perioperative complications and as a measure of surgical quality. In the analysis of National Surgical Quality Improvement Program data, Papenfuss et al. (7) had found no difference between TTE and THE in terms of postoperative hospital stay. However, Boshier et al. (4) had found in their meta-analysis an advantage for THE in which hospital length of stay was less than 4 days on average. In the Khullar OV metanalysis, THE was associated with shorter hospital stay than TTE (11.5 vs. 13.0 days, p<0.006). In the same study, THE was associated with a shorter ICU stay compared with TTE (5 vs. 7 days, p<0.006) (10). In general, it can be concluded that the hospitalization time in the current cohorts is slightly shorter after THE. In our series, the duration of ICU stay and postoperative hospital stay were shorter in THE group, but no statistical difference was observed. We associated this result with the similarity between postoperative complications and the rates of anastomotic leakage that prolonged hospitalization.

Postoperative mortality after esophageal surgery is typically due to pulmonary complications and anastomotic leakage. Improvements in surgical technique and perioperative care, special anesthesia teams, and interventional radiology assisted implementation of drains have contributed to reduced mortality rates over time (17). In three major meta-analyses comparing transthoracic esophagectomy and transhiatal esophagectomy results, a statistically significant difference was found in perioperative mortality (9, 4, 39). There was no statistical difference between the two groups in our series. Our causes of mortality were pulmonary complications and sepsis due to anastomotic leakage.

The rate of hospital admissions following esophagectomy for esophageal cancer has previously been reported to be between 5% and 30% (10, 41).

Admission rates and reoperations after esophageal surgery have a significant impact on hospital costs and quality of care. In addition to mortality, readmission after a surgical procedure is

increasingly viewed as a sign of quality of care (10). The Khullar OV series did not find any difference in readmission between the groups. Our series supports the literature, and there was no difference between the groups. Anastomotic leakage has been reported to be the most important risk factor for readmission after esophageal cancer surgery (17). In our series, the reasons for readmission were anastomotic complications.

Anastomotic leakage is a predisposing pathology for stricture development. Patients typically present with dysphagia in the second and third postoperative months. Anastomosis leakage and manual anastomosis are risk factors for stricture development. The rate of anastomosis stenosis after esophagectomy is reported to be 5%-30% (32). In the Boshier PR meta-analysis, the rate of anastomosis stenosis had been significantly lower in the TTE group than in the THE group (21.8% vs. 25.1%; OR 0.58; 95% CI 0.43–0.79; p<0.001) (4). Although the incidence of anastomotic leakage was higher in cervical anastomosis, benign stricture formation requiring dilatation was not associated with the location of the anastomosis in the meta-analyses (29). In our series, the rate of anastomotic stenosis did not differ between the groups. We preferred endoscopic dilatation for the treatment of anastomotic stenosis.

Local recurrences and distant metastases in esophageal cancer are associated with the tumor's biological structure, histological type, and grade (2). There have been no large meta-analyses comparing the type of surgery with distant metastasis and local recurrence in the literature. In our series, there was no statistical difference between local recurrence and distant metastasis between groups. This result can be explained by the fact that tumor characteristics were similar between groups.

Results after transhiatal and transthoracic surgery showed no difference in overall survival in the meta-analysis of 8 trials (including 3 randomized controlled trials) involving 1155 patients (9). In the series by Khullar OV et al. (10), no difference in 5-year survival was identified (TTE 33.5% vs. THE 36%, p=0.75). In the meta-analysis by Boshier PR et al. (4), an overall analysis of 5-year survival showed no significant difference between the transthoracic (26.6%) and transhiatal (25.8%) groups (OR 1.03; 95% CI 0.80-1.32; p=0.84). Survival in esophageal cancer is affected by many parameters, particularly tumor stage (13). In our series, the overall survival rates were not affected by the type of surgery, supporting the literature.

In conclusion, TTE and THE can be applied with comparable results for esophageal cancer. Although TTE surgical time is longer, it can be performed with morbidity and mortality rates similar to THE. Lymphadenectomy tends to be more common in transthoracic approaches. We have found that the type of surgical approach for esophageal cancers does not affect postoperative mortality, major morbidity rates, anastomosis complications, length of hospital stay, or survival time. We conclude that the most important determinants of survival are the biological behavior of the tumor and its stage during resection, rather than the type of surgical approach. Therefore, patient treatment should be individualized. The most important limitation of our study was its retrospective nature. Of course, the results of this retrospective clinical analysis should be confirmed by large-scale prospective randomized trials.

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Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

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Original Article

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Effects of Acute and Chronic Exercises on Plasma Nesfatin-1 Levels in Young Adults

Şükran Arıkan

Selçuk University, Faculty of Sport Sciences, Konya, Turkey

ORCID ID of the author: Ş.A. 0000-0002-2625-0898.

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BACKGROUND/AIMS
The aim of this study was to investigate the effects of acute and chronic exercise on plasma nesfatin-1 levels in young adults.

MATERIAL and METHODS
Sixteen young adult male university students were recruited to participate in this study. Blood samples were taken from the subjects at the beginning of the study and after the training program both at rest and immediately after acute exhausting exercise. The subjects performed cycling exercises for 40–60 minutes, 3 days a week for 8 weeks at 60%–80% of maximal heart rate. Body weight, body mass index (BMI), body fat percentage (BFP) and maximal aerobic capacity (VO2max) were determined before and after the 8-week training program. Plasma nesfatin-1 levels were determined by enzyme-linked immunosorbent assay (ELISA) using commercial kits. The effects of chronic and acute exercise before and after the training program were examined by analysis of variance with two-factor repeated measures. In this study, SPSS 16.0 statistical program was used to evaluate the data and the level of significance was accepted as <0.05.

RESULTS
Cycling exercises had no impact on body weight, BMI and VO2max ($p>0.05$), but BFP decreased significantly ($p<0.05$). Acute and chronic exercise had no significant impact on plasma levels of nesfatin-1 ($p>0.05$).

CONCLUSION
We observed no significant differences in plasma nesfatin-1 levels in response to acute or chronic exercise among young adult male students. However, chronic exercise had a significant impact on BFP.

Keywords: Acute exercise, chronic exercise, Nesfatin-1

INTRODUCTION

Although the rapid progress and new effort-reducing technologies have had a profoundly positive impact on life in general, among the downsides is a level of inactivity that can result in chronic physical and psychological stress (1). Exercise, defined as regular physical movement, has significant effects on metabolism and energy homeostasis (2). For this reason, physicians and researchers recommend regular exercise as a means to treat and to prevent psychological disorders including aberrant responses to stress and tension; regular exercise may also avert or at least limit the impact of cardiovascular disease, obesity, diabetes, and high cholesterol (1).

The molecular mechanisms underlying the delicate balance between energy consumption and energy intake are not fully understood. Hormonal factors certainly play a role in maintaining this balance (3) and many energy-regulating hormones are synthesized in skeletal muscle and adipose tissue (4). Nesfatin-1 is a regulatory and anorexigenic hormone; its synthesis and release are influenced by nutritional status, energy metabolism and exercise (5). Nesfatin-1 was first discovered by Oh-I et al. (6) and is produced in the hypothalamic nucleus, which is currently understood to be the control center for appetite. When administered to mice, nesfatin-1 results in significantly reduced food intake and body weight. Nesfatin-1 is a 24 amino acid peptide generated by post-translational processing of nucleobindin 2 (NUCB2). The effects of nesfatin-1 are dependent on signaling via the melanocortin-3/4 receptor and are not dependent on the actions of the adipose-derived hormone, leptin.

Corresponding Author: Şükran Arıkan
E-mail: sarikan@selcuk.edu.tr

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Nesfatin-I induces a sense of satiety and suppresses food intake and as such may promote substantial improvements in the health and well-being of overweight and obese individuals (7). Nesfatin-I modulates glucose homeostasis, increases insulin sensitivity, decreases excess body fat and prevents metabolic disorders (8); it may also have profound effects on the cardiovascular system and the release of stress hormones (9, I0).

The results of studies designed the address the impact of exercise on nesfatin-I levels are thus far contradictory. Results from several published studies suggest that exercise has no impact on nesfatin-I levels (5, II, I2). By contrast, other reports suggest that exercise results in either increased (I3-I7) or reduced (I8-20) levels of plasma nesfatin-I. The aim of this study was to determine the effect of acute and chronic exercise on plasma nesfatin-I levels in healthy young adult males.

MATERIAL and METHODS

Subjects: Sixteen males between the ages of 20-27 years who were healthy non-smokers and moderately active were recruited to participate in the study. Prior to the start of the study, all participants received detailed explanations regarding the purpose of the study and each was asked to complete the voluntary participation form. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Selçuk University Faculty of Sports Science Non-interventional Clinical Research.

Determination of Body Composition: Participant height (m) and body weight (kg) were determined using a Seca mechanical weighing scale. Body mass index (BMI) was calculated by dividing body weight (kg) by the height squared (m^2) (2I). For the determination of body fat percentage (BFP), biceps, triceps, subscapularis, suprailiac skinfold thicknesses were measured with a Holtain skinfold caliper which applied I0 g of pressure per mm^2 at each angle while the participants were in anatomical positions. Body densities and BFP were determined with the following mathematical formulas:

Body Density=I.I63I-0.0632×Log (biceps+triceps+subscapularis+suprailiac)

BFP=(4.95/Body Density-4.50)×I00 (22).

Main Points:

- Nesfatin-I, a hormone that has this regulatory effect, is an anorexigenic peptide that functions in many body functions by being influenced by nutritional status, energy metabolism and exercise.
- In this study, the effects of acute and chronic exercises on body composition and plasma nesfatin-I were evaluated in moderately active young adults with normal body mass index.
- It was concluded that the exercises performed significantly decreased only BFP values and had no separate or common effects on Nesfatin-I level.

Acute Exercise test: To determine the maximal aerobic capacities (VO_{2max}), the 20 m shuttle run test was applied according to the protocol described by Leger et al. (23).

Chronic Exercise: Study subjects participated in a cycling exercise program for 8 weeks, 3 days a week, 40-60 minutes a day, at 60%–80% of the maximal heart rate. The maximal heart rate of each subjects was calculated according to the 220-age formula. During the training, a Polar RS800 heart rate monitor watch was used.

Blood Sampling and Biochemical measurements: Blood samples were taken from the participants at the beginning of the study and at the end of the 8 week training program, both at rest and immediately after acute exhausting exercise. Blood samples were drawn into heparinized vacutainer tubes by medical personnel at 8:00 am after overnight fasting. Blood cells were removed by centrifugation at 3000 rpm for 20 minutes at 4°C; the resulting plasma samples were divided into two aliquots which were stored in microcentrifuge tubes at -20°C prior to analysis. Plasma levels of nesfatin-I were determined with a human nesfatin enzyme-linked immunosorbent assay (ELISA) test kit (Elabscience, Houston, TX, USA). Absorbance was measured at 450 nm in a microplate reader (Biotek ELx800) and interpolated to a standard semi-logarithmic curve.

Statistical Analysis

Arithmetic means and standard deviations of all measured variables were calculated. The effects of acute exhausting exercise and chronic exercise before and after the training program were evaluated by analysis of variance using two-factor (2×2; rest-acute exercise x pre-post chronic exercise) repeated measures. In case of significant effect or interaction of factors, t-test was used in dependent groups. In this study, the Statistical Package for the Social Sciences I6.0 (SPSS Inc.; Chicago, IL, USA) was used to evaluate data; the level of significance was accepted as <0.05.

RESULTS

Body weight (t=2.07; p=0.06), BMI (t=2.07; p=0.05I) and maximum oxygen consumption (VO_{2max}; t=-I.24; p=0.23) among the participants did not change significantly from the beginning to completion of the training program. By contrast, BFP decreased significantly (t=3.36; p=0.00). (Table I).

TABLE I. Changes in The Physical and Physiological Properties of the Subjects Before and After the Training Program

		Pre-test	Post-test	
Variables	**N**	**Mean ± SD**	**Mean ± SD**	**t**
Body weight (kg)	I6	68.8±9.3	68.0±8.5	2.07
BMI (kg/m^2)	I6	2I.6±2.6	2I.4±2.3	2.I2
BFP (%)	I6	II.I±3.2	9.8±2.4	3.36*
VO_{2max} (mL/kg/dk)	I6	43.9±5.4	45.3±6.0	-I.24

*p<0.05; SD: Standard Deviation; BMI: Body Mass Index; BFP: Body Fat Percentage; VO_{2max}: Maximum Oxygen Consumption

TABLE 2. Effects of Acute and Chronic Exercise on Nesfatin-1 Levels

		Time	Mean	±	SD	Acute	Chronic	A×C
Nesfatin-1 (ng/mL)	Pre- training program	Rest	40.72	±	12.55	0.28	2.08	1.30
		Exhaustion	40.77	±	17.75			
	Post-training program	Rest	41.54	±	14.76			
		Exhaustion	34.80	±	12.68			

*p<0.05; SD: Standard Deviation; A: Acute exercise; C: Chronic exercise; AxC: Common effect of chronic and acute exercise

Neither the separate nor the common effect ($F_{1,13}$=1.30; p=0.27) of acute exercise ($F_{1,13}$=0.28; p=0.61) or chronic exercise ($F_{1,13}$=2.08; p=0.17) had a statistically significant impact on plasma nesfatin-1 levels (Table 2).

DISCUSSION

In this study, the effects of acute and chronic exercise on body composition and plasma nesfatin-1 were evaluated in moderately active young adult males with normal body mass indices. While the exercise program resulted in significant decrease in BFP, it had no impact on plasma nesfatin-1 levels.

The results of several studies suggest that nesfatin-1 levels and BFP are inversely related. Studies carried out with obese individuals have shown that decreases in BFP were associated with increases in nesfatin-1 levels. Furthermore, significantly more carbohydrate, protein and energy intake was observed among obese individuals with low nesfatin-1 levels (24, 25). While some studies have reported a negative relationship between nesfatin-1 levels and BMI (26, 27), others have concluded that no such relationship exists (28).

The results of the present study are consistent with the latter group of findings. For example, Ghanbari-Niaki et al. (5) explored the impact of an anaerobic sprint test and a kickboxing session in 14 young male athletes; while plasma growth hormone, insulin, glucose, and lactate concentrations increased significantly after the exercise, no changes were observed in plasma concentrations of nesfatin-1. In another study conducted on 30 elderly women with hypertension, aerobic exercise performed three days a week for 12 weeks resulted in a decrease in nesfatin-1 levels, although these findings did not reach statistical significance (29). Similarly, Algül and Özçelik (30) reported a decrease in plasma nesfatin-1 levels among individuals participating in acute exercise although again, the results were not statistically significant. These authors emphasized that plasma nesfatin-1 levels may be affected by other non-exercise-related factors, including anxiety, stress, or nutritional status. Similar results were obtained by Ozdenk (12) who reported an increase in nesfatin-1 levels in samples taken before and after 30 min of aerobic running exercise; these findings also did not reach statistical significance.

By contrast, there are several reports that document significant increases in nesfatin-1 levels in obese subjects (13, 17) or in association with intake of food with high fat content (31). Yazici (14) found that nesfatin-1 levels in young athletes were significantly higher before and after anaerobic exercise than levels determined for a comparatively sedentary group. Among the conclusions, the elevated levels of nesfatin-1 may be due to the degree of metabolic starvation that is encountered both during and immediately after exercise, and/or a neuromuscular stimulus reflex that reestablishes energy balance after excessive energy use during exercise. In a study investigating the effect of resistance exercises (10 weeks and 3 days a week) on the serum levels of nesfatin-1 together with the insulin resistance index, 18 women with type 2 diabetes were randomly divided into two groups, one of which performed resistance exercises while the other did not. After the training, a significant increase in nesfatin-1 levels from baseline levels was identified in the group that performed resistance exercises (15). Algül et al. (16) found that moderate aerobic exercise performed both in the morning and at night significantly increased nesfatin-1 levels in 60 male study participants, but that exercise at night was more effective than exercise in the morning. The study concluded that nesfatin-1 level is a reflex secondary to neuromuscular stimuli that serve to suppress the feeling of hunger caused by the need to maintain energy balance. In contrast to these studies, it has been reported that low-intensity motorized treadmills (20 m/min, 0% slope, 60 min, 8 weeks and 5 days) (18) and high intensity intermittent training (20) decreases nesfatin-1 levels compared to control groups in laboratory rodent studies. Taken together, the research results remain contradictory. Presumably, this may be explained by differences in subjects' baseline nutritional status (26) and the composition of their daily diets (31) as well as stress and thermoregulation (32).

This research has some limitations. The participants in our study were all healthy and moderately active individuals. While the participants were asked not to change their eating habits, they were not maintained on a controlled diet; this could certainly be a significant variable with respect to plasma nesfatin-1 levels. In our study with healthy, moderately active young adult male participants, we detected no significant change in plasma nesfatin-1 levels in response to acute and chronic exercise.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Selçuk University Faculty of Sports Science Non-interventional Clinical Research.

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

Peer-review: Externally peer-reviewed.

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

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Original Article

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Attitudes and Behaviors of Nursing Students towards Caring Nurse-Patient Interaction

Hülya Fırat Kılıç, Bahar Ak

Department of Nursing, Eastern Mediterranean University Faculty of Health Sciences, Famagusta, North Cyprus

ORCID IDs of the authors: H.F.K. 0000-0001-6570-8083; B.A. 0000-0003-3580-4562.

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BACKGROUND/AIMS
This study aimed to determine the attitudes and behaviors of nursing students towards caring nurse-patient interactions.

MATERIAL and METHODS
A total of 177 nursing students, who were enrolled at the undergraduate nursing program of Eastern Mediterranean University in Northern Cyprus in the spring semester of academic year 2018-2019, constituted the sample of this descriptive study. A "Personal Information Form" and "Caring Nurse-Patient Interactions Scale" were used for data collection.

RESULTS
Attitudes and behaviors of nursing students towards caring nurse-patient interactions were positive. Scores obtained regarding the importance aspect of caring nurse-patient interactions were significantly higher than the scores for the competence and realistic aspects. The competence scores of the participants who chose to study nursing because they loved the profession and the importance scores of the participants who had healthcare experience as patients were significantly higher than those of the participants without healthcare experience as patients

CONCLUSION
Our findings suggest that nursing students recognize the importance of caring nurse-patient interactions. However, many do not consider themselves as competent in those interactions and they do not necessarily believe that caring nurse-patient interactions are realistic.

Keywords: Caring, nurse-patient interaction, nursing students

INTRODUCTION

Nursing is a profession that entails important responsibilities related to patient care and health (1-3). Given nurses are primarily concerned with patients, effective interaction and interpersonal communication skills are important. While providing healthcare services, nurses are continuously interacting with patients (4). Caring moments refers to those moments when nurses meet with patients to care for them (5). Since patient needs are the focus of patient-nurse communication, the communication should be patient-centered. The main aim of patient-centered communication is to identify patient needs and plan nursing interventions according to those needs (4, 6).

The "theory of human caring", which was proposed by Watson, focuses on a natural, reliable, compassionate, and sensitive relationship between nurses and patients (7). A "transpersonal caring relationship" is one of the main concepts of the model proposed by Watson (8). Mutual interaction between the patient and the nurse during caregiving is beneficial for the patient. A transpersonal caring relationship is believed to have a healing quality in physical and emotional terms (9, 10). The therapeutic relationship is fundamental to the process of high-quality nurse-patient interactions. As part of the therapeutic relationship, nurses identify patient needs, implement the interventions, and speed up the recovery period. During this relationship, nurses should be trustworthy, helpful, and sensitive to patient needs (11). Factors such as the time needed for institutional procedures, maintaining patient records, and reduced availability of nurses can decrease the time allocated to nurse-patient interactions. A study by Bridges et al. (12) found that the quality of nurse-patient interactions decreased in parallel with the decrease in the number of available nurses.

Corresponding Author: Hülya Fırat Kılıç
E-mail: hulyafirat81@gmail.com

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Most studies that have analyzed the attitudes and behaviors of nurses and nursing students towards caring nurse-patient interactions are based on Watson's theory of human caring (13-15). A study by Kaçmaz and Çam (14) on psychiatric nurses found that the participants scored high on importance aspect, competence aspects and feasibility acpects of the Caring Nurse-Patient Interaction Scale (CNPIS). A study by Bayraktar and Eşer (15) on nurses who worked at a university hospital found that attitudes and behaviors of the participants towards caring nurse-patient interactions were positive. Similarly, studies by Erzincanlı and Yüksel (6) and Yılmaz and Gökdere Çınar (16) found that nursing students had positive attitudes and behaviors towards caring nurse-patient interactions. A study by Nwosu et al (10) found that cordial nurse-patient relationships had a positive impact on patient outcomes. Finally, Lotfi et al. (17) found that most participant patients were dissatisfied with their nursing care, and their dissatisfaction was primarily caused by poor nurse-patient communication.

Nurse-patient interactions constitute the core of a caring relationship. Caring behaviors at the heart of caring relationships should be developed during nursing education. Although nursing education is comprehensive, it is based on the concept of care (18). While developing caring behaviors, communication skills of the nursing students should be improved (19). To this end, the researchers should identify the importance given by nursing students to holistic care, as well as their perceived competence levels in terms of caring nurse-patient interactions and their opinions on the extent to which caring is realistic in nurse-patient interactions. In this way we could attempt to improve nurse-patient interactions among the nursing students and produce information on ways to improve patient care. Within this context, this study aimed to identify the attitudes and behaviors of nursing students towards caring nurse-patient interactions. The research questions included the followings:

1. What are the attitudes and behaviors of nursing students towards caring nurse-patient interactions?
2. Is there a difference between descriptive characteristics of the nursing students and their attitudes and behaviors towards caring nurse-patient interactions?

Main Points:

- Nurse-patient interactions constitute the core of a caring relationship.
- Caring behaviors at the heart of caring relationships should be developed during nursing education.
- Attitudes and behaviors of the nursing students towards the importance aspect of the CNPIS were more positive than those regarding the competence and the realistic aspects.
- The curriculum of undergraduate nursing education should include the development of qualifications and skills in nurse-patient interactions.
- Interventions on the implementation of healthcare should be planned in the curriculum of undergraduate nursing education.

MATERIAL AND METHODS

This descriptive study was conducted with 2nd, 3rd, and 4th year undergraduate students who were studying at the nursing department of the Faculty of Health Sciences of a foundation university located in the Turkish Republic of Northern Cyprus. We excluded first-year students because they had not yet received the basic nursing education courses and did not participate in clinical practice. Some 227 students who were enrolled at the undergraduate nursing program in the spring semester of academic year 2018-2019 were eligible for the study. Three students who refused to participate and 47 students who were absent during the time of data collection did not take part in the study; thus, 177 (78% of the eligible students) who agreed to participate to the study and who were enrolled at the program during the data collection period constituted the final sample.

Data Collection:

Data was collected in the class environment between May 16 and 30, 2019. The students were informed regarding the aim and scope of the research and their written consent was obtained before data collection. Next, we distributed questionnaires to be completed by the participants and returned in the same environment. We used the "Personal Information Form" and CNPIS for data collection.

Personal Information Form

A personal information form was prepared by the researchers by using relevant literature (14-16). The form consisted of 11 questions on the sociodemographic characteristics of the participants, including age, sex, class year, and the reasons they chose to study nursing.

Caring Nurse-Patient Interactions Scale (CNPIS)

The Caring Nurse-Patient Interactions Scale (CNPIS), which was based on Watson's theory of human care, was developed by Cossette et al. (20) to evaluate the attitudes and behaviors of nurses towards care. The validity and reliability of the Turkish version of the scale has been assessed by Atar and Aştı (21), who found that Cronbach's alphas for the importance, competence, and reality aspects of the Turkish version were 0.99, 0.98, and 0.99, respectively. The CNPIS consists of 70 items asking nurses about the extent to which caring nurse-patient interactions are important, competent, and realistic by using a 5-point Likert type scale ranging from never (1) to extremely/always (5) (2). The CNPIS has 10 sub-scales, including humanism, hope, sensitivity, helping relationship, expression of emotions, problem solving, teaching, environment, needs, and spirituality. The subscales for each aspect did not change and the scores on the scales for each aspect ranged between 70 and 350, with higher scores indicating more positive attitudes and behaviors towards caring nurse-patient interactions. In our study, Cronbach's alphas for the impor-

tance, competence and realistic aspects of the CNPIS were 0.988, 0.987 and 0.987, respectively.

Statistical Analysis

The data were analyzed using Statistical Package for the Social Sciences 20.0 version (IBM Corp.; Armonk, NY, USA) software. The One-Sample Kolmogorov-Smirnov test and Shapiro-Wilk test were used for normality of the distribution of numerical variables. Given the analysis revealed that the data were not normally distributed, we used a non-parametric Friedman test. The sociodemographic characteristics of the participants were analyzed using a frequency analysis. The Mann-Whitney U and Kruskal-Wallis H tests were used to compare the scores on the importance, competence, and realistic aspects of the CNPIS with the sociodemographic variables. Correlations between the three aspects of the CNPIS were analyzed by using the Spearman Rho Correlation Coefficient test.

Ethical Considerations

We obtained institutional permission from the chair of the Department of Nursing and ethics permission from the scientific research and publication ethics committee (Decision No. 2019/14-07). Participants were informed about the study and their written voluntary informed consent was obtained.

RESULTS

A total of 48% of the participants were between the ages of 21 and 22 and 66.1% were women. Some 42.37% of the participants were 2nd years students and 71% participated in a clinical practice of medical and surgical nursing course. Some 54.8% of the participants stated that they studied nursing because they loved the profession. The percentages of participants who had no difficulty communicating with the patients and their family members were 88.7% and 90.4%, respectively. Some 77.4% of the participants had healthcare experience as patients, and 52.54% of the nursing students participated in social events.

Scores obtained by the students regarding the importance aspect of the overall CNPIS and its subscales were significantly higher than those obtained for the competence and realistic aspects ($p<0.05$). The scores on the importance, competence, and reality aspects were highest for the "needs" subscale of the CNPIS (Table I).

There was no statistically significant difference between the scores obtained from the importance, competence, and realistic aspects of the CNPIS and the characteristics of the participants, including age, sex, class, clinical practice, difficulties in relating with patients, difficulties in social relations, and participation in social events ($p>0.05$) (Table 2).

There was no statistically significant difference between the scores obtained on the importance and realistic aspects of the CNPIS and the reasons for choosing to study nursing ($p>0.05$). However, we did find a positive correlation between the scores obtained from the competence aspect of the scale and the reason for choosing to study nursing ($p<0.05$). The competence scores of the participants who chose to study nursing because they loved the profession (=300.15±39.26) were higher than the participants who chose to study nursing because of job availability concerns (=279.97±53.94) (Table 2).

In terms of those with previous healthcare experience as patients, we found a statistically significant difference between the scores obtained on the importance aspect of the CNPIS ($p<0.05$), whereas there was no statistically significant difference between the scores obtained on the competence and realistic aspects ($p>0.05$). The scores on the importance of caring nurse-patient interactions among the participants who had previous healthcare experience as patient (=310,24±45.09) were higher than those of the participants without healthcare experience as patients (=307.22±44.28) (Table 2).

TABLE I. Caring nurse-patient interactions scale scores of the participants (n=177)

	Caring Nurse-Patient Interactions Scale				
Subscales	**Importance M±SD**	**Competence M±SD**	**Realistic M±SD**	**p**	**Difference[a]**
Humanism	26.83±4.61	25.29±4.39	25.37±4.8	0.000**	I-C, I-R
Hope	27.33±3.7	25.23±4.52	25.15±5	0.000**	I-C, I-R
Sensitivity	26.62±3.91	24.63±4.63	24.32±5.29	0.000**	I-C, I-R
Helping relationship	31.51±5.23	29.95±5.91	29.92±5.87	0.000**	I-C, I-R
Expression of emotions	26.89±4.7	25.1±4.65	25.02±4.35	0.000**	I-C, I-R
Problem solving	26.59±4.5	24.83±4.73	24.49±4.95	0.000**	I-C, I-R
Teaching	40.18±6.64	38.03±7.19	37.87±7.38	0.000**	I-C, I-R
Environment	31.34±5.31	29.89±5.37	29.85±5.56	0.000**	I-C, I-R
Needs	45.36±6.9	42.73±7.08	42.39±8.42	0.000**	I-C, I-R
Spirituality	26.92±4.43	25.46±4.49	25.73±5.05	0.000**	I-C, I-R
CNPIS	309.56±44.28	291.15±46.83	290.12±50.04	0.000**	I-C, I-R

**p<0.01; a: Bonferoni correction was made for the difference
I=importance; C=competence; R=realistic

TABLE 2. Comparison of the demographic characteristics of the participants with the caring nurse-patient interactions scale scores (n=177)

Variables	Importance $\bar{x}\pm s$	p	Competence $\bar{x}\pm s$	p	Realistic $\bar{x}\pm s$	p
Age						
19-20 years	312.37±35.02	0.148	294.74±37.66	0.943	300.05±37.23	0.566
21-22 years	310.35±51.76		289.52±53.63		287.74±55.07	
23 years and above	306.35±37.3		291.19±41.49		286.89±49.49	
Gender						
Female	307.85±48.85	0.799	291.3±50.04	0.447	288.78±51.36	0.863
Male	312.92±33.77		290.85±40.24		292.75±47.67	
Sınıf						
2nd	312.24±41.39	0.676	296.28±41.23	0.210	293.12±45.07	0.280
3rd	306.96±39.36		281.92±48.65		278.73±57.68	
4th	308.24±52.88		292.82±52.04		297.12±47.8	
Clinical Practice						
Surgical disease nursing	315.63±33.34	0.400	306.31±34.1	0.076	304±36.41	0.177
Pediatric nursing	303.74±40.15		277.26±49.79		274.5±60.17	
Community health nursing	308.91±54.62		293.61±51.35		298.84±43.92	
Medical and surgery nursing	312.38±42.23		295.2±43.04		291.72±47.37	
Reasons for choosing to study nursing						
Job security	304.19±52.51	0.112	279.97±53.94	0.046*	282.46±59.59	0.560
Loves nursing	315.63±37.5		300.15±39.27		296.67±40.94	
Family demand	292±39.34		281.54±48.76		280.77±54.91	
Difficulties relating with the patients						
Yes	306.4±40.97	0.573	283.2±50.23	0.403	279.9±59.77	0.448
No	309.97±44.79		292.16±46.46		291.43±48.73	
Difficulties in social relations						
Yes	292.71±42.91	0.131	274.65±50.26	0.087	266±67.43	0.115
No	311.36±44.17		292.9±46.28		292.69±47.38	
Healthcare experience as a patient						
Yes	310.25±45.1	0.040*	292.44±46.81	0.334	291.55±49.37	0.383
No	307.23±41.81		286.73±47.23		285.23±52.62	
Participation in Social Events						
Yes	308.76±46.04	0.726	290.26±47.85	0.857	294.6±49.5	0.186
No	310.45±42.5		292.13±45.95		285.17±50.46	

*p<0.05; a: Bonferroni correction was made for the difference

TABLE 3. Correlations between the scores obtained from the importance, competence, and realistic aspects of the caring nurse-patient interactions scale (n=177)

		CNPIS		
		Importance	Competence	Realistic
CNPIS (Importance)	r	1		
	p	.		
CNPIS (Competence)	r	0.705	1	
	p	0.000*	.	
CNPIS (Realistic)	r	0.694	0.754	1

*p<0.05; CNPIS: caring nurse-patient interactions scale

Finally, the analysis of the correlation between the scores obtained from the importance, competence, and realistic aspects of the CNPIS revealed a strong, positive, and statistically significant correlation between the three aspects (Table 3).

DISCUSSION

Care services constitute the basis of the nursing profession. For this reason, students who are candidates for the nursing profession should receive sufficient knowledge and acquire the necessary skills to provide high-quality healthcare services to patients. Acquiring the necessary caring behaviors is among the basic aims of nursing education. In our study, the mean scores obtained by the participant nursing students on the importance, competence, and realistic aspects of the CNPIS were high. The attitudes and behaviors of the participants towards the importance of caring nurse-patient interactions were more positive than those towards the competence and realistic aspects. Similar to our study, two other studies on Turkish nursing students found that the students considered caring nurse-patient interactions important, but they did not consider themselves as competent in such interactions and did not believe that caring nurse-patient interactions were realistic (6, 22). A study of Kaçmaz and Çam on psychiatric nurses also found that the scores obtained by the nurses on the importance aspect of caring nurse-patient interactions were higher (14). Based on these findings, we suggest that nursing students have a more positive attitude towards the importance aspect of caring nurse-patient interaction than towards the competence or realistic aspects. Although the nursing students believed in the importance of caring, they found it difficult to apply this information in practice due to perceived incompetence while interacting with the patient during the delivery of healthcare services. In addition, our findings could be due to the fact that the students were still in the process of learning, so they could not yet use the affective and psychomotor skills in practice (23).

Regarding the importance, competence, and realistic aspects of the CNPIS, the participants obtained the highest scores on the "needs" subscale. Studies by Erzincanlı and Yüksel (6), and Yılmaz and Gökdere Çınar (16) on nursing students also found that the highest scores were obtained from the "needs" subscale of the CNPIS. Based on this finding, we can conclude that the nursing students were sensitive to the physical, emotional, and spiritual needs of the patients to whom they provided healthcare. The sensitivity of the nursing students to the needs of the patients might be related to the fact that nearly half of the participants were sophomore students participating in clinical practice in addition to the classes on medicine and nursing. During clinical practice, the participants probably had a chance to interact with the patients and use their theoretical knowledge in line with their patients' needs. In addition, this finding could also be related to the supportive measures taken by the nursing educators to develop the healthcare behaviors and skills of the nursing students during their clinical practice.

We found that age, sex, and class year of the participants had no impact on their CNPIS scores. Some other studies on nursing students also found that age had no impact on CNPIS scores (6, 16, 22). Regarding the sex aspect, the study by Erzincanlı and Yüksel (6) found that the women scored higher than men on the importance aspect, whereas two other studies found no impact of sex on CNPIS scores (16, 19). The differences in these findings could be related to differences in the sociocultural structures of the samples.

Choosing the nursing profession is a turning point in the life of an individual, with important repercussions on social relations (24). We found that the CNPIS scores obtained on the competence aspect were higher for the participants who chose to study nursing because they loved the profession of nursing, compared with the participants who chose it for job safety. Similar to our findings, another study on nursing students found that the CNPIS scores of the students who chose to study nursing because they loved the profession were higher than those who chose it for job safety (22). Yet another study on nursing students found no statistically significant difference between the reasons for choosing the profession and CNPIS scores (16). According to our findings, choosing to study nursing due to loving the profession led the participants to feel more competent in caring nurse-patient interactions than those who chose the profession for other reasons. As such, we might expect that these students would deliver high-quality healthcare services and contribute to the development of the profession in the future. We believe that nursing students who chose the profession since they loved it might be more successful, leading them to believe themselves more competent in healthcare delivery than those who chose the profession for other reasons.

Having healthcare experience as patients might help nursing students develop their empathy skills. In addition, previous experience as patients might help students understand how patients feel and assess healthcare services from the patients' point of view (25). In our study, we found that nursing students with prior healthcare experience as patients obtained higher scores on the importance aspect of the CNPIS compared to the participants without such experience. The study by Kalender et al. (26) found that the nursing students with previous healthcare experience as patients were more sensitive, humanistic, and that they gave more hope to the patients for whom they cared. The study by Birimoğlu and Ayaz (23) on the perception of caring behaviors of the nursing students found that previous healthcare experience as patients had a positive impact on their caring behaviors. In this sense, our findings are consistent with those of the literature.

Our study found a strong, positive, and statistically meaningful correlation between the importance, competence, and realistic aspects of the CNPIS. The study by Yılmaz and Gökdere Çınar (16) also found a positive and statistically meaningful relationship between the total scores obtained on the importance, competence and realistic aspects of the CNPIS.

The study by Kaçmaz and Çam (14) on psychiatric nurses found a positive and strong correlation between the scores obtained on the importance and competence aspects. Nurses and nursing students might feel more competent if they understand the importance of caring nurse-patient interactions and might apply this understanding while providing healthcare services. Thus, during the patient-nurse interactions, nurses should understand the importance of healthcare, believe in their competence, and prepare to use their competence in practice.

We found that attitudes and behaviors of the participants towards caring nurse-patient interactions were positive. Attitudes and behaviors of the nursing students towards the importance aspect of the CNPIS were more positive than those regarding the competence and the realistic aspects. In addition, the participants obtained the highest scores on the "needs" subscale of the CNPIS. Finally, we found that the competency scores of the participants who chose to study nursing because they loved it and the importance scores of the participants who had previous healthcare experience as patients were significantly higher than the other scores. Based on these findings, we suggest that the curriculum of undergraduate nursing education should include the development of qualifications and skills in nurse-patient interactions. Interventions on the implementation of healthcare should be planned in the curriculum of undergraduate nursing education. Students who love the profession of nursing should be especially encouraged, given those who love the profession believe more in their competence than students who have chosen the profession for other reasons.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Eastern Mediterranean University Research and publication ethics committee. / 7 May 2019. Decision No. 2019/14-07.

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

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Evaluation of the Psychosocial Effects of Long-Term Genital HPV Infection

Ali Şahan[1], Nermin Karaosmanoğlu[2], Erol Koç[3]

[1]Department of Dermatology, Doctor Al-Sa Aesthetic & Cosmetic Dermatology Clinic, Ankara, Turkey
[2]Department of Dermatology, Ankara Training and Research Hospital, Ankara, Turkey
[3]Department of Dermatology, Medical Park Hospital, Ankara, Turkey

ORCID IDs of the authors: A.Ş. 0000-0003-0821-1710; N.K. 0000-0002-3462-1628; E.K. 0000-0003-4147-2015.

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BACKGROUND/AIMS
Genital human papillomavirus (HPV) infection is one of the most common sexually transmitted diseases. This study purposed to evaluate the psychosocial effects of long-term genital HPV infection.

MATERIAL and METHODS
Overall, 77 male patients with genital HPV infection were included. The Dermatological Life Quality Index (DLQI), State-Trait Anxiety Inventory scales (STAI I-2), and the Beck Depression Inventory (BDI) were used to assess the psychological burden of patients. In addition, they were evaluated by a psychiatrist.

RESULTS
The mean age was 37.68±11.67. The mean duration of the disease was 9.74±7.76 months. Overall, 51 patients (66.2%) had more than five lesions. The mean score of the DLQI scale was noted to be 4.58±4.42. Most patients (26; 33.8%) were classified as "small effect on patient's life," at a score of 2-5. STAI-I mean score was 41.74±11.77. Thirty-eight patients (49.4%) were noted to be highly anxious. According to the STAI-2 scale, the mean score was 42.69±9.71, and most patients (40; 51.9%) were noted to be highly anxious. The mean score of BDI was 16.43±11.929, and 27 patients (35.1%) were noted to be moderately depressive. The psychiatrist assessed 14 patients (18.2%) as needing psychiatric medication.

CONCLUSION
Generally, patients suffering from genital HPV for longer than 3 months are affected negatively psychosocially. Therefore, physicians should approach the patient with kindness, compassion, and patience. In addition, an expert psychiatrist's support should be sought if necessary.

Keywords: Dermatology life quality index, human papillomavirus, psychosocial effects

INTRODUCTION

Genital human papillomavirus (HPV) infection is a viral infection that is one of the most common sexually transmitted diseases in humans (1). HPVs are DNA viruses belonging to the *Papillomaviridae* family that can cause benign skin and mucosal lesions on the genital, anal, or oral mucosa, or may cause malignant lesions in various organs (2).

Patients with anogenital warts feel uncomfortable and are often ashamed of these lesions. They may resist consulting a physician, leading to delayed diagnosis. Furthermore, these patients may feel anxious or depressed (3, 4). Patients are consistently worried and anxious about developing anogenital cancers and its negative effects on their sex lives (5). Moreover, patients may have concerns regarding disease transmission and self-image, besides being embarrassed by the disease (4, 6).

This study evaluated the psychosocial effects of long-term genital HPV infection in men using the anxiety-depression tests, as well as a psychological evaluation by an expert psychiatrist.

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Corresponding Author: Nermin Karaosmanoğlu
E-mail: nermin_kara@yahoo.com

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MATERIAL AND METHODS

This study included 77 male patients with genital HPV infection, lasting longer than 3 months, admitted to the outpatient clinic between December 2013 and May 2014. Patients over 18 years of age were included. The local ethics committee approved the study (November 12, 2013, 50687469-1491-2338-13/1648-2499). All participants were informed regarding the study, and written consent was obtained.

All participants were evaluated by a dermatologist and a psychiatrist. Sociodemographic information, including age; smoking, alcohol, and drug use history; marital status; the number of sexual partners; educational status; working status; and the duration of the disease were recorded. A detailed anamnesis was obtained, and a careful dermatological examination was performed. Anamnesis included a history of genital warts, the existence of any extragenital warts, any co-existing sexually transmitted disease, or any medical treatments. Three validated questionnaires, namely the Dermatological Life Quality Index (DLQI), State-Trait Anxiety Inventory scales (STAI 1-2), and Beck Depression Inventory (BDI), were used to assess patients' psychological burden. Patients were individually evaluated by an expert psychiatrist and were assessed using the Structured Clinical Interview for DSM-III-R (SCID 1-2).

The Dermatological Life Quality Index (DLQI) is the first dermatology-specific quality-of-life instrument developed in 1994. It is a simple 10-question validated questionnaire. These 10 questions examine a patient's perception of the impact of skin diseases on different aspects of their health-related quality of life over the preceding week. The test is validated for adult dermatology patients aged 16 years and above.

Each question is scored on a 4-point Likert scale as follows: not at all or not relevant=0; a little=1; a lot=2; and very much=3. Scores of individual items (0-3) are added to yield a total score (0-30), wherein higher scores represent a greater impairment in patient's quality of life (7).

The Beck Depression Inventory (BDI) is an inventory including 21 items designed to assess the symptoms of depression as specified in the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition. The 21 items are scored on a 4-point Likert scale ranging from 0 (absent) to 3 (severe). The total score ranges from 0 to 63. The Turkish version of this test was developed by Hisli (8).

The State-Trait Anxiety Inventory (STAI) is a commonly used measure of trait and state anxiety. It can be used in clinical settings to diagnose anxiety and distinguish it from depressive syndromes. Moreover, it is commonly used in research as an indicator of caregiver distress. All items are rated on a 4-point scale from "almost never" to "almost always." It contains 40 items, and for each subtest, scores range from 20 to 80, with a higher score representing significant anxiety (9).

This test is a semi-structured interview to assess major axis I DSM-III-R diagnoses and is administered by a mental health professional. It is used to ensure that the major DSM-5 diagnoses are systematically evaluated. In addition, it can be used to characterize a study population in terms of current and previous psychiatric diagnoses (10).

Main Points:

- Genital human papillomavirus (HPV) infection is one of the most common sexually transmitted diseases in humans.
- Patients with anogenital warts may feel uncomfortable, anxious or depressed. This study evaluated the psychosocial effects of long-term genital HPV infection in men using the anxiety-depression tests, as well as a psychological evaluation by an expert psychiatrist.
- Based on our results, HPV infections may affect a patient's quality of life, cause anxiety and depression, and may even cause psychosocial stress, thereby necessitating treatment.
- These patients should be approached with kindness, compassion, and patience to achieve treatment success. In addition, an expert psychiatrist's support can be pursued if necessary.

Statistical Analysis

Statistical analyses were performed using the statistical software package Statistical Package for the Social Sciences for Windows 15.0 (SPSS Inc., Chicago, IL, USA). The normal distribution of data was assessed using the Kolmogorov–Smirnov test. Continuous and normally distributed variables were presented as means±standard deviations, and intra-group differences were investigated using the student's t-test. Continuous variables with non-normal distribution were expressed as medians (minimum–maximum), and differences between variables were analyzed using the Mann–Whitney U test. Categorical variables were expressed in percentages.

RESULTS

All the 77 patients were men with a mean age of 37.68±11.67 years. Overall, 54 patients (70.1%) had a history of smoking. Only 2 patients (2.6%) had a history of drug abuse, whereas 33 patients (42.9%) had a history of alcohol use, and 33 patients (42.9%) described a history of extramarital sexual intercourse. Overall, 30 patients (39%) were single, whereas 47 (61%) were married. In addition, 76 patients (98.7%) graduated from at least high school, and 58 (75.3%) had a job, whereas 19 (24.7%) did not work. Eight patients (10.4%) had a history of genital warts. Extragenital warts were observed in 21 (27.3%) patients. None of the patients had any other sexually transmitted diseases. The mean duration of the disease was 9.74±7.76 months. Overall, 51 patients (66.2%) had more than five lesions, and 68 patients (88.3%) had a history of taking medications for the disease. Nine patients (11.7%) had no history of treatment.

Upon review, no previous studies had explored the extent of lesion prevalence and the length of lesion duration. Therefore, we defined the term 'diffuse lesion' as those having more than five lesions and the term 'long-term lesion' as those having disease longer than 3 months.

The mean score of the DLQI scale was 4.58±4.42. The scores of the scale are presented in Table I. Most patients were classified as a "small effect on patient's life" at a score of 2–5 (26 patients,

33.8%). The STAI-1 mean score was 41.74±11.77, and overall, 38 patients (49.4%) were highly anxious. The STAI-2 mean score was 42.69±9.71, with most patients (40; 51.9%) being highly anxious. Detailed STAI 1-2 scores are illustrated in Table 2. The mean BDI score was 16.43±11.929, and 27 patients (35.1%) were moderately depressed, whereas most patients (37; 48.1%) had a normal mood. The BDI scores are presented in Table 3. Overall, 7.8% of patients had a history of psychiatric medication, and 9.1% were still taking psychiatric medication during the study. Finally, after evaluating all patients with the help of an expert psychiatrist and testing them by using the SCID 1-2 tests, 63 patients (81.8%) were noted to have a normal mood and required no medication, whereas 14 (18.2%) required psychiatric medication.

Patients with a history of genital warts were noted to have a higher rate of worsening mental health compared with patients who had no history of genital warts (p=0.001). On the other hand, patients with a history of extragenital warts had less worsening of their mental health than patients with no history of extragenital warts (p=0.006). The mental health of patients with more than five lesions was worse than that of patients with fewer than five lesions (p=0.02). The mental health of patients with a history of any psychiatric medication use was worse than that of patients with no history of psychiatric mediation use (p=0.005). Moreover, patients with a history of extragenital warts had a higher rate of having more than five lesions (p=0.027).

Patients with more than five lesions had a longer duration of lesions (p=0.00048). Patients with a history of psychiatric medication use had a higher rate of extensive lesions (more than five) compared with patients not taking psychiatric medication (p=0.048). Patients with a history of extragenital warts had a longer duration of lesions compared with patients with no history of extragenital warts (p=0.06).

We observed that DLQI scores decreased with the increase in the duration of time with lesions (p=0.005). Patients with multiple sexual partners had higher BDI scores than those having one sexual partner (p=0.032). Patients with a history of extragenital warts had higher STAI-2 scores than those having no history of extragenital warts (p=0.015). The increase in STAI-1 and DLQI scores were similar (p=0.043).

TABLE 1. The scores of DLQI

DLQI	Frequency	Percentage	Valid Percentage	Increasing percentage
Unaffected	25	32.5	32.5	32.5
Little effect	26	33.8	33.8	66.2
Moderate effect	16	20.8	20.8	87.0
Very much affected	10	13.0	13.0	100.0
Total	77	100.0	100.0	

DLQI: Dermatology Life Quality Index

TABLE 2. STAI 1-2 scores of patients

STAI-1	Frequency	Percentage	Valid Percentage	Increasing percentage
No anxiety	21	27.3	27.3	27.3
Little anxious	18	23.4	23.4	50.6
Highly anxious	38	49.4	49.4	100.0
Total	77	100.0	100.0	
STAI-2				
No anxiety	20	26.0	26.0	26.0
Little anxious	17	22.1	22.1	48.1
Highly anxious	40	51.9	51.9	100.0
Total	77	100.0	100.0	

STAI: State-Trait Anxiety Inventory

TABLE 3. BDI scores of patients

STAI-1	Frequency	Percentage	Valid Percentage	Increasing percentage
Normal	37	48.1	48.1	48.1
Little mental disorder	7	9.1	9.1	57.1
Borderline clinical depression	1	1.3	1.3	58.4
Moderate depression	27	35.1	35.1	93.5
Severe depression	5	6.5	6.5	100.0
Total	77	100.0	100.0	

BDI: Beck Depression Inventory

DISCUSSION

Genital Human Papillomavirus (HPV) —one of the most common sexually transmitted infections globally—might negatively affect patients psychosocially (11). The disease may cause feelings of depression, anger, or shame, as well as a loss of sexual desire or transformation of sexuality into an unpleasant experience (11, 12).

Based on our results, HPV infections may affect a patient's quality of life, cause anxiety and depression, and may even cause psychosocial stress, thereby necessitating treatment. Previous reports have revealed that the disease may cause a decrease in the quality of life and lead to psychosocial or sexual problems (1, 4, 11-22). Even though the results of these studies are partially consistent with the present study, comparing these results is difficult because of the use of different evaluation tools. To the best of our knowledge, this is the first study evaluating the dermatological quality-of-life index, patient anxiety, and depression status with internationally validated tests, as well as consulting a psychiatrist to assess the patient's mental state. Therefore, our results are of merit to clinicians and can be used to improve patient care.

No significant relationship was observed between the extensiveness and duration of the lesions and a history of smoking, drug abuse, or alcohol abuse. The test scores were not affected by a history of smoking, drug, or alcohol abuse. However, no control group was available for comparison of these results.

Worsening mental health in patients with a history of genital warts could be due to the infection becoming more resistant to treatment modalities over time and limited patient understanding of the disease severity over time. Hence, the experience of each patient varies.

We noted that a history of extragenital warts protected against a decrease in mental health compared with patients with no history of extragenital warts. Probably these patients become accustomed to having extragenital warts and are not distressed when the same lesions occur in the genital region; thus, their mental health is not affected.

Our results indicated that having more than five lesions may affect mental health compared with having fewer lesions. This finding suggests that more extensive lesions may cause more anxiety, concern, and psychological stress in patients. Patients with a history of psychiatric medication use were more inclined to mental distress. This possibility could be because these patients are not as well equipped to deal with new problems as their healthy counterparts.

Patients with a history of extragenital warts were prone to having more than five lesions in the genital region. This finding could be explained by the autoinoculation of warts. Moreover, because the immune system does not tolerate this condition, more extensive lesions may occur in the genital region.

Patients with more than five lesions were observed to have a longer lesion duration. Notably, lesion prevalence increases with more resistant disease. Moreover, an increase in lesion duration increases the disease resistance.

Notably, patients with a history of psychiatric medication use had more extensive lesions than other patients. This result could be interpreted as patients with susceptibility to depression having more disease-related distress, with the intensive distress causing the disease to spread rapidly.

Furthermore, a history of extragenital warts increases lesion duration. In addition, an immune system prone to HPV infection may have difficulties clearing the infection. We showed that DLQI scores decreased as the duration of the lesions increased. This can be interpreted as the patient adjusting to the disease over time or that the patient lacks information on the disease.

Patients with a history of multiple sexual partners had higher BDI scores. This result suggests that depression can lead the patient to polygamy as an escape mechanism. In addition, it can be concluded that having multiple sexual partners can cause distress, leading to patient depression.

A history of extragenital warts results in increased STAI-2 scores. This result suggests that when the patient is familiar with the disease, the concern and anxiety of the individual increases.

Notably, only one previous study had used DLQI to evaluate the effects of genital and extragenital warts on the quality of life of patients (19). The authors observed that the overall DLQI scores of patients with extragenital warts were higher than those of patients with genital warts, and extragenital warts can negatively affect a patient's life. Nevertheless, the scores of patients in this study were lower than those in the present study, and generally, the disease was noted to have a small effect on the patient's quality of life.

Nonetheless, the fact that 14 patients (18.2%) in the present study required psychiatric medication is a significant observation. However, further studies with large patient groups, including both men and women, as well as control groups, should be conducted to confirm our study results.

Conclusively, patients suffering from genital HPV for longer than 3 months are negatively affected psychosocially. Therefore, these patients should be approached with kindness, compassion, and patience to achieve treatment success. In addition, an expert psychiatrist's support can be pursued if necessary.

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Review

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Current Approaches to Bone-Drilling Procedures with Orthopedic Drills

Yunis Torun[1], Özhan Pazarcı[2], Ahmet Öztürk[1]

[1]Department of Electrical and Electronics Engineering, Sivas Cumhuriyet University School of Medicine, Sivas, Turkey
[2]Department of Orthopedics and Traumatology, Sivas Cumhuriyet University School of Medicine, Sivas, Turkey

ORCID IDs of the authors: Y.T. 0000-0002-6187-0451; Ö.P. 0000-0002-2345-0827; A.Ö. 0000-0002-2102-0276.

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In order to minimize complications during orthopedic surgery, the important of research in this field is gaining importance and more studies are being conducted. The use of robotics and autonomous systems is gaining importance to achieve the aims reducing complications, lowering operation times, and increasing the surgical reliability and effectiveness in bone drilling operations that constitute a sub-set of the Computer-Aided Orthopedic Surgery (CAOS) issue. In this study, signal processing-based approaches for breakthrough detection during bone drilling operations, robotic autonomous systems that optimize optimal plunge and drilling speed while drilling, most effective drilling parameters that affect bone perforation, and studies conducted to improve the safety and efficiency of surgical operations, such as radiological imaging, were investigated. A systematic review of recent studies on bone drilling was performed and potential research topics were proposed for possible future studies.

Keywords: Bone Drilling, breakthrough detection, computer-aided orthopedic surgery, optimal drilling parameters.

INTRODUCTION

Bone drilling is performed in many surgical procedures in orthopedic surgery as well as in the fields of neurosurgery, plastic surgery, and otorhinolaryngology (1). During surgery to fixate fractured bones after a trauma, implants like nails, plates, screws, and wire are used (2, 3). These implants are inserted into holes made by drilling cylindrical tunnels into the bone with an appropriate drill bit, using orthopedic drills (1). Risks during the drilling procedure, include harm caused to the bone, muscle, nerves, and venous tissues by the drill bit if the rapidly rotating drill is wrapped by the surrounding tissue in an uncontrolled manner or if the drill bit does not stop immediately after it exits the second cortex of the bone (Figure 1). Identification of the moment when the drill bit exits the second cortex is called *"breakthrough detection"*. During orthopedic surgery, when bones are drilled manually, a large pushing force is applied to the drill bit with the drill bit advance varying with changes in the force applied. Currently, the speed of drill bit advance is controlled manually by the surgeon. The performance during the drilling procedure is strongly linked to the surgeon's technical skills, based on "drilling by feel" (4) or "drilling by sound" based on sound information (5). The drilling forces perceived by the surgeon are a relative concept. The entry speed of the drill bit is linked to the health/status of the bone and the type of drill used (6). In orthopedic trauma surgery, it is necessary to obtain efficiency and accuracy in the surgical operations using robots for bone-drilling procedures (7). Two types of approaches are used to overcome this issue in scientific studies. The first approach is the computer-supported orthopedic surgery approach that uses medical imaging, localization of the musculoskeletal system, and surgical tools in three-dimensional (3D) space, combined with a semi-robotic system for orthopedic surgery operations (8). The other approach involves the addition of the integrated bone breakthrough algorithms to the available orthopedic drills (9, 10). This study aimed to investigate the current approaches used for the drilling procedure using orthopedic drills and perform a literature review to create an easily accessible resource for future researchers.

Corresponding Author: Özhan Pazarcı
E-mail: dr.pazarci@gmail.com

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Breakthrough detection

Brett et al. (11) Proposed a method to perceive bone breakthrough during the bone drilling procedure. They proposed that sudden changes in the force data represented breakthrough in this method. They used the derivative property of force data for the identification algorithm. They completed breakthrough identification with the limit value determined using this derivative information. Wen-Yo Lee and Ching-Long Shih (12) designed an autonomic robot that perceived bone breakthrough without harming the vital organs. In this proposed robotic system, robot position control used a fuzzy controller and force control used a proportional-derivative control for advanced speed. The breakthrough perception algorithm was designed using drill moment, advance velocity, thrust force data, and changes in these data. They confirmed their proposed technique by drilling pig bones (12). Kotev et al. (13) Designed a hand-type medical drill called the Orthopaedic Bone Drilling Robot (ODRO) preventing bone breakthrough. The designed drill can be operated in two modes with or without presetting. In non-presetting mode, the drill tip stops after passing through the bone marrow or tissue. In preset mode, the drilling procedure continues until the determined bone thickness; thereafter, the drill stops, and the drill bit pulls back to leave the bone. With this system, time, linear velocity, drill speed, force resistance, breakthrough distance, and temperature data are visualized (13, 14). Lin Qi et al. (15) Proposed an algorithm to perceive bone breakthrough during the bone drilling procedure. This algorithm is based on the wavelet transformation of force data. The results of the transformation used a modulus maxima method to perceive breakthrough. In the experiments, pig bones were drilled with the algorithm; breakthrough was found and perceived, and the system stopped. After the system stopped, a very thin bone layer remained at the end of the drill route (15). Ying Hu et al. (16) suggested the performance of a robotic spinal surgery system (RSSS) to aid pedicle screw insertion during surgery. The developed RSSS balances the effects of gravity and ensures better compliance to spinal surgery requirements. They developed a real-time algorithm using a force sensor for the breakthrough perception procedure with medical drills. The algorithm used the mean value of the force signal and the mean amplitude value as characteristics. With the algorithm, they identified the initial cortex, first cortex, spongiosa bone, and second cortex status. They succeeded in breakthrough perception and stopped the procedure with a 2-mm error (16). Yu Wang et al. (17) Proposed a system defining the drill situation with multiple sensor fusion. They used the support vector machine classification method for the definition procedure and used the force mean value and derivative, advance speed, rotation speed, and robot arm angles and derivatives as properties. At the end of the classification, they defined four different drilling stages for cortical, cortical-spongiosa, tissue transition, spongiosa tissue, and almost exit from the second cortex. They identified the most important drilling stage of almost exit from the second cortex with 76.5% success (17). Yunqing Li et al. (18) suggested a method that perceived circulation in the tissues and bone breakthrough for milling procedures in ear surgery. They included flow and 2-axis force data during the milling procedure in their method. They created a mathematical correlation between the radial force and flow. They performed a status perception procedure with the radial force and determined limit values calculated with this equation. At the end of the experiments, bone breakthrough perception was provided with 93% success, and mistaken bone breakthrough was predicted in 2% of the normal milling operations. When cotton tissue was wrapped around the drill bit, an average success rate of 92% was achieved, and in the normal milling operations, 2% was mistakenly perceived with cotton tissue wrapping (18).

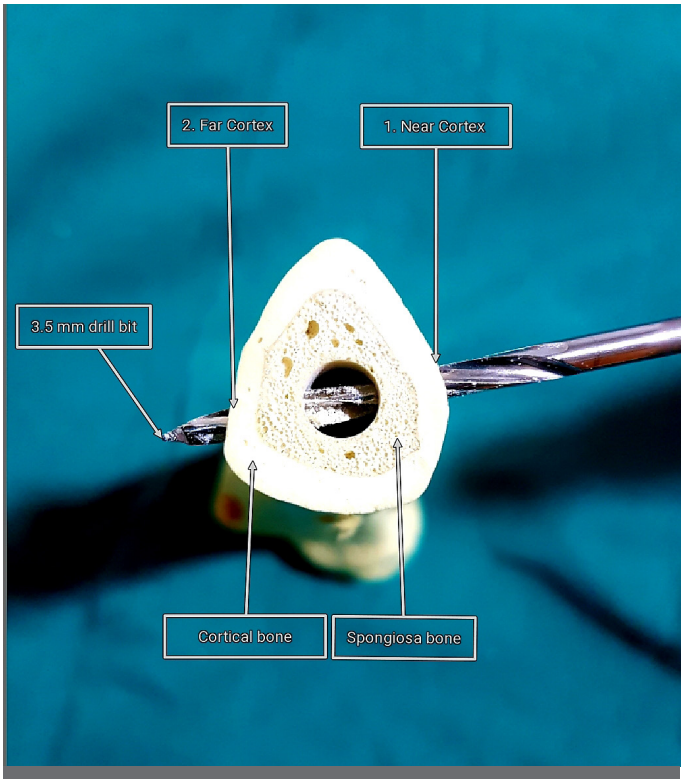

FIGURE I. Explanation of the drilling procedure with 3.5-mm drill in the artificial tibia bone
Drill moves from the proximal cortex (Ist cortical bone surface), to the spongiosa bone, the medullar cavity, and the distal cortex (2nd cortical bone surface)

Autonomy and robotic drilling:

Vishnu et al. (19) proposed a new control technique by setting the power control based on the online prediction of environmental parameters for force control in unknown environments with the available robot systems. The contact of a robotic tip holder with an object was modeled with a mass spring model. Using the environmental conditions of location and force measurements, the elasticity (K) and friction coefficient (B) were estimated with an auto-regressive with exogenous input (ARX) model. Using these estimated parameters, they used an artificial neural network (ANN) method to calculate the proportional integral control (PO + I) parameters used to control impedance force. They showed the efficiency and compatibility of the proposed controller in unknown and variable environments with the interaction involved (19). José Feio et al. (20) Designed a high-sensitivity controller for to-

tal hip surface renewal for use in orthopedic surgery. For the drilling procedure, they designed a controller that allowed "partial control" of the robot movements by the surgeon. They designed a system that ensured surgeon-robot cooperation with sufficient sensitivity. They provided a feeling of impedance to aid surgery in the robot handler (20). Kotev et al. (21) Developed their previously designed ODRO robot that perceived breakthrough during bone drilling and aided the surgeon using modifications. The new robot was lighter and smaller than the previous one and had a linear movement module. They reduced the drill developed for the previous robot ODRO (350 mm) to a smaller size (210 mm). They made the study field (120 mm) longer than that in the previous robot (105 mm) (21). Vijayabaskar Kasi et al. (22) Used two robots to design a system to overcome misalignment. They designed a system with a 6-axis robot linked to the surgical drill and a 5-axis robot holding the bone. To ensure accurate alignment, they used force control for alignment by setting the force intervals determined by position control and applied forces. They succeeded in returning the drill bit to the ideal alignment during every misalignment of the drilling access using the robot holding the bone with this method (22). The greatest disadvantage of the system is that a larger skin-opening procedure is required for the robot to hold the bone. This situation lengthens the healing process and makes it difficult. Haiyang Jin et al. (23) Developed a system to increase the operation success and reliability of spinal surgery. To limit the robot movements in the developed system, they used guided virtual fixtures (GVF) and forbidden region virtual fixtures (FRVF). They used a damping region virtual fixture (DRVF) to prevent the robot from passing the boundary regions and harming the patient's body during surgery. To perceive bone breakthrough during the robotic drilling procedure, they used the mean values for force data and the difference between the mean value and previous value as attributes. At the end of the experiments, the system stopped with maximum 0.86 mm and minimum 0.55 mm remaining bone thickness (23). Zahari et al. (24) used a robot in orthopedic surgery to drill patient bones and proposed a system to automatically identify bone breakthrough during bone drilling. This proposed system reduces noise in the force data with a low-pass filter. Before the drilling procedure, force information was accepted as the limit value, and bone breakthrough perception was based on the limit value. They tested the system with sheep bones. To improve the quality of the drilling procedure, they proposed that the bone drilling procedure be managed by a robot (24). Azeddien Kinsheel (25) presented the design steps and practice outcomes of a hybrid force/position controller (HPF) for drilling procedures with a robot arm. HPF control used an advanced linear position control in the position control cycle and a multi-stage infinite impulse response (IIR) filter with combined proportional derivative control (PD control). They used a steady speed force control scheme to enable force control. They tested the system performance experimentally with a Kflop-based controller on a CRS robot arm. They provided drilling procedure control as per the reference force and speed. With the results on position error and force control, they concluded that the system could be used efficiently for critical robot drilling applications, such as robot-supported orthopedic surgical procedures (25). Markus Hessinger et al. (26) Developed a wearable seven-axis robotic system to help the power and accuracy for the human body. The user increased the accuracy of the target position and ensured fixed thrust force during drilling. They used an inverse kinematic algorithm linked to the joint speed to minimize location error. They perceived the user's movement intentions with moment sensors found in the system. They used a hybrid force position control for fixed thrust force and position control during the drilling procedure. Experiments with the developed system found maximum 1.27 mm position error and maximum 1 N force error (26). George et al. (27) Developed an orthopedic robot for automatic drilling procedures based on the previous ODRO. They proposed a new mechanical structure design with smallest possible robot size and weight for surgery requirements. With the new design, the linear actuator axis and rotation axis were parallel. They used a new micro regulator, new linear movement driver, and new force sensor for the control system. The developments provided less signal noise, better signal processing, and 40% reduction in robot weight (27).

Force parameter imaging and ideal drilling

JuEun Lee et al. (28) Presented a mechanical model to estimate thrust forces and moments formed during bone drilling. The model determined the material and friction properties experimentally using a certain energy formulation; thereafter, it analytically combined it with radially varying drill bit geometry and cutting conditions. They completed the confirmation tests with different advance speed and drill speeds. They proposed the use of the model for the selection of the appropriate drill conditions, to aid robotic surgery, and to design the most appropriate orthopedic drill bits (28). Haiyang Jin et al. (29) Combined a force sensor and optical monitoring system to develop a system that can identify the drilling status during bone drilling and check whether drill procedures occurred in the correct position. They used mean amplitude, short-term energy, gradient, and energy gradient properties of force data to perceive the drilling status. They created boundaries for the drilling status based on the properties defined because of the drilling experiments. The distance from the stop position was determined by measuring the bone thickness with previous bone imaging and then using an imaging and optical monitoring system. They determined the drilling status as a hybrid result of properties formed by forces and properties formed by optical imaging and determined the stop position in relation to this status. They stated that the developed system increased the reliability of the drilling procedure (29). Mohd Hazny Aziz et al. (30) Designed a force control-based algorithm that perceived bone breakthrough during drilling operations in orthopedic surgery and stopped the drilling process, bringing it to a safe location. Bone breakthrough identification was identified based on variations in the force data (30). For algorithms that identified breakthrough based on the force data from a 3-axis force sensor with variation in force above or below a certain threshold value, sensor noise lowers the success of the algorithm. Wen-Yo Lee et al.

(3I) used drill motor moment and advanced speed to control force in a drilling operation. Motor moments were calculated as per the reference moment value, desired force reference value, and drill radius. They developed an algorithm that perceived breakthrough with thrust force, advance velocity, and determined limit values. The proposed technique was experimentally confirmed by drilling pig bones (3I). Markus et al. (32) Proposed a system that used optic monitoring and force sensor to support surgeons during orthopedic drilling procedures. They designed and created an inexpensive system that had a new force sensor with a 0–20-N measurement interval. At the end of the experiments, they stated that the force data obtained from the force sensor was sufficient to perceive the breakthrough (32). Singh AP et al. (33) Proposed a system to prevent damage created during drilling in laminated composites. Velocity and force data obtained by drilling laminated composites at different velocities used Matlab system identification to obtain a first-degree mathematical model. Using this model, they performed force control with PID. They created the PID parameters with Simulink using the Ziegler-Nichols method. They proposed that the drilling procedure controlled with PID had better performance in terms of preventing damage compared to the drilling procedures at fixed velocity (33). Wei Tian et al. (34) Presented a surgical robot that can automatically perceive the drilling status with force and image data for spinal surgery and can stop potential cortical penetration. They created a hybrid property using the mean value and the derivative of force data. They determined the drilling status with these features. They used a navigation and optical monitoring system to drill in the correct location and to perceive breakthrough (34). Zhen Deng et al. (35) Designed fuzzy logic force control for vertebral milling. The system calculated the control parameters in real-time with fuzzy logic to set the force control parameters. Moreover, in order to address security concerns, they proposed a status identification method based on energy consumption during the vertebral lamina milling procedure. They developed a method that could identify three different milling stages and stop the milling procedure. They stated that experiments with the identification method developed based on energy consumption left a bone thickness of <2 mm at the end of milling (35). Xi-sheng L et al. (36) Developed a modified orthopedic drill with current, voltage, and force sensor fusion for manual bone drilling operations. They estimated moment with the current sensor and identified drilling status by training an ANN with voltage and force data. They determined status as normal drilling, drill bit sliding, breaking through the bone tissue wall, and wrapping with cotton-like structures. The mean percentages were 72.625% for identification of normal drilling, 68.575% for drill bit slide, 70.5% for breakthrough of bone tissue wall, and 8I.3% for wrapping with a soft tissue. They calculated that the duration after which the drill should be stopped was 0.2–0.3 s with the developed system (36).

Environmental parameters and drilling different bone density

Koyo et al. (37) Developed a method to estimate the CT value using a quantitative assessment method for bone density. They proposed a method to estimate the CT value by modeling the correlation between the cut-off value and the CT value. They calculated the cut-off force, linear motor thrust force, and motor moment. They completed the experiments with a main robot that gave advanced commands and a second dependent robot that completed the drilling procedure. At the end of the experiments, the CT value estimation error was ± 9I HU, and the estimation accuracy was 84% (37). Fernando et al. (38) Performed experiments to analyze the correlations among the rotational speed, applied force, and bone age in bone drilling procedures. They performed bone-drilling experiments with an orthopedic drill that they had previously developed and a CNC machine. The results of the experiments performed with fixed advance velocity in the fixed bone at different rotational speeds revealed that high rotational speeds required low applied force, while low speeds required high applied force. They concluded that with the same advance and rotational speeds, young bones needed less force, while older bones required greater force (38).

Correlation of radiologic imaging and drilling

Haiyang Jin et al. modeled thrust force in the drilling procedure with an accurate 3D bone model created using micro-CT images. Considering resistance and flexibility of the bone tissue, they theoretically modeled thrust force. Theoretical model parameters were defined with the least squares method. They used peak force in the first and second cortexes, mean force for the spongy layer, and the thickness of each layer to support identification of drilling status. They designed a system that could identify bone breakthrough and could stop the system using the determined parameters (39).

Temperature control

Kais I. Abdul-lateef Al-Abdullah et al. (40) Proposed that there was lack of information about bone milling for spongy tissue in the available literature. Using an ANN and based on real experimental measurement data for bone milling in artificial tissues with spongy features, they determined the appropriate force and temperature models. They modeled the force and temperature that formed as a result of advance velocity and drill speed with the model. They found that the correlation coefficient was 0.996 in the model between force with thrust speed and drill speed. They proposed that increasing the advance speed increased the applied force, while increasing the applied force raised the temperature, because of experiments and models. They stated that the models could be useful for optimization and control of real-time bone milling (40).

CONCLUSION

Research in bone drilling procedures with orthopedic surgical drills is progressing every day. This helps reduce drilling complications and increases the use of robotic and autonomic drilling processes. All these processes indicate that more reliable orthopedic surgical procedures will be available in the future. A systematic review of the current studies for bone drilling was performed and potential research subjects were proposed for possible future studies. Sensorless approach-

es that involve signal processing of only the existing signals in conventional drills for breakthrough detection are potential new research areas. Research can be used to integrate breakthrough detection capability and prevent thermal necrosis. Optimal drilling parameters applicable while drilling different bone densities can be extracted with the available signals, such as motor current, drilling sound, and vibration. We believe that our study will be a useful resource for future researchers.

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Letter to the Editor

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Burning Questions of Treating Addiction in Middle Europe – The German situation

Tamás Józsa

Pedagogical Assistance Service of Budapest, Institution of the 22nd District; University of Debrecen, Human Sciences PhD School, Psychology Program, Budapest, Hungary

ORCID ID of the author: T.J. 0000-0002-3858-4094.

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The World Health Organization has delayed time and time again on publishing any conclusive data on video game addiction (VGA). This could be because they have not yet acquired sufficient scientific data about VGA from the whole of the European Union (UN) to verify its significance in public health. In the United States, spending too much time playing video games was classified as an addiction by the American Psychiatric Association in 2013 (1). In the Far East, a type of mental disorder, termed "hikikomori," was first described at the beginning of the century, where electronics effectively replace all social function. Specifically, it describes the phenomenon of teenagers and young adults substituting their interpersonal relationships with electronic devices and living in total social isolation (2). It is time for European decision makers to take a stand and announce that they will not wait any longer to emphasize this issue because VGA will officially be included in the international classification of diseases from 2022 (3).

Regarding many new psychological diagnoses, initially there was a pushback from the public toward the VGA diagnosis in early stages. However, as smart devices became more ingrained in our everyday life, the time spent on them has exponentially increased. Some experts believed that it was a growing problem when just PCs and and video game consoles were the primary source; however, with the advent of smart devices, there seems to be no end to the number of games and apps available. Virtually everyone, child, adolescent, and adult, owns a smart device—even those from economically challenged countries. Additionally, outsiders have little to no influence on what others do on their smart device. Identifying where useful or relaxing activities end and harmful, socially crippling activities begin is not easy. American researchers have demonstrated that an astounding 99% of boys and 94% of girls, aged 2–17 years, regularly play video games. The numbers are also high for American adults, with 50% of men and 40% of women engaging in video game activity on a regular basis (4). A recent international daily news source reports that in the Far East, treatment camps for teenagers with electronic device addiction are being organized since 2007 (5). Studies in the EU show 5%–6% prevalence, but Austria and Germany are naturally at a greater risk owing to their technical and economic development (6). Interactive entertainment is a wildly successful international industry. In 2016, both China and North America topped the list of countries providing revenue to this burgeoning industry and Germany was the top country in the EU (7).

Behavioral addictions, such as VGA or gambling) and their financial factors have an economic significance. For instance, they can increase the number of absences from work, and this can impact the financial resources of the addict; this problem is not restricted to the United States; it is also noted in Austria and Germany (8). The ratio of German patients with VGA is 6% in pre-puberty and puberty (10-18 year olds) and 8% over the age of 18 (9). . However, these data do not include those at risk in the sub-clinical stage. Additionally, a study with 12,000 participants showed that 70% of subjects admit to lying about the time spent on gaming, highlighting an issue of self-administered questionnaires and their potential of including underestimated data (10).

It is obvious that this phenomenon is a modern, globally spreading challenge of the 21st century that we have to face. It is clear that we need to take action; prevention, early treatment, and improvements in educating medical personnel regarding these novel mental health issues are needed. In 2008, 99% of German households had a mobile phone, 99% had a

Corresponding Author: Tamás Józsa
E-mail: tamasjozsa2@gmail.com

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computer, and 96% had access to the internet (11). It is clear that electronic media will most likely continue to play a huge part in our lives and those of future generations.

Lastly, the growth of cyberbullying (an online form of harassment) is an important factor worldwide. A recent study showed that 600,000 of 12.3 million German students were victims of cyberbullying (12). In Germany, mostly classmates are bullies; however, this stays hidden from the teachers and others as a great part of bullying happens through electronic devices and video games; thus, extra attention is needed when it comes to electronic media usage (13). Another study in Germany shows that victims of cyberbullying have high rates of suicide and can be virtual outcasts online and many of the individuals have negative experiences with online communities (14). It is cardinal because being at risk of cyberbullying has a connection to time spent video gaming: as the level of addiction to virtual reality increases the negative feedback becomes more important and has a greater influence to children's self-representation.

The author is a Clinical Child Psychologist, Marriage and Family Therapist, PhD candidate at the University of Debrecen, Human Sciences PhD School, Psychology Program; currently works at the Pedagogical Assistance Service of Budapest, Institution of the 22nd District in Budapest.

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"The best of people are those that bring most benefit to the rest of mankind."

Koşulsuz destekleri için KKTC Cumhurbaşkanlığı ve Kıbrıs Vakıflar İdaresi Müdürlüğü'ne teşekkür ederiz.