ISSN 1302-0072

The Medical Bulletin of Haseki

2022

Volume 60

Issue
January 1

www.hasekidergisi.com

The Medical Bulletin of Haseki

Editorial Board

Galenos Publishing House Owner and Publisher
Derya Mor
Erkan Mor

Publication Coordinator
Burak Sever

Web Coordinators
Fuat Hocalar
Turgay Akpinar

Graphics Department
Ayda Alaca
Cigdem Birinci
Gulay Saday
Gulsah Ozgul

Finance Coordinator
Sevinc Cakmak

Project Coordinators
Aysel Balta
Duygu Yildirim
Gamze Aksoy
Gulay Akin
Hatice Sever
Melike Eren
Ozlem Celik Cekil
Pinar Akpinar
Rabia Palazoglu

Research&Development
Nihan Karamanli
Melisa Yigitoglu

Digital Marketing Specialist
Umit Topluoglu

Publisher Contact
Address: Molla Gurani Mah. Kacamak Sk. No: 21/1
34093 Istanbul, Turkey
Phone: +90 (212) 621 99 25
Fax: +90 (212) 621 99 27
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr
Publisher Certificate Number: 14521

Online Publishing Date: January 2022

ISSN: 1302-0072 **E-ISSN:** 2147-2688
International scientific journal published quarterly.

The Medical Bulletin of Haseki

Scientific Advisory Board

The Medical Bulletin of Haseki

Scientific Advisory Board

The Medical Bulletin of Haseki

Aims and Scope

The Medical Bulletin of Haseki is the official scientific journal of the University of Health Sciences Turkey, Istanbul Istanbul Haseki Training and Research Hospital. It covers subjects on general medicine, published both in Turkish and English, and is independent, peer-reviewed, international periodical and is published quarterly (January, March, June, September and November).

The aim of the Medical Bulletin of Haseki is to publish original research papers of the highest scientific and clinic value on general medicine. Additionally, educational material reviews on basic developments, editorial short notes and case reports are published.

The Medical Bulletin of Haseki is indexed in **Emerging Sources Citation Index (ESCI), Index Copernicus, EBSCO Database, Turkish Medline-National Citation Index, Excerpta Medica/EMBASE, SCOPUS, TÜBİTAK/ULAKBİM Türk Tıp Dizini, CINAHL, DOAJ, Hinari, GOALI, ARDI, OARE, AGORA, ProQuest, ROOT INDEXING, British Library, J-Gate, IdealOnline ve Türkiye Atıf Dizini** databases.

Open Access Policy

This journal provides immediate open access to its content on the principle that making research freely available to the public supports a greater global exchange of knowledge.

Open Access Policy is based on rules of Budapest Open Access Initiative (BOAI) http://www.budapestopenaccessinitiative.org/.

By "open access" to [peer-reviewed research literature], we mean its free availability on the public internet, permitting any users to read, download, copy, distribute, print, search, or link to the full texts of these articles, crawl them for indexing, pass them as data to software, or use them for any other lawful purpose, without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. The only constraint on reproduction and distribution, and the only role for copyright in this domain, should be to give authors control over the integrity of their work and the right to be properly acknowledged and cited.

Subscription Information

The Medical Bulletin of Haseki is distributed free of charge to the subscribers at the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital. All notices of change of address should be sent to the editorial officer as immediate as possible. Subscribers, who did not receive an issue within the related period, should inform the editorial officer accordingly. All published volumes in full text can be obtained free of charge at www.hasekidergisi.com. Nonmembers who wish to subscribe to the journal should apply to the secretariat of The Medical Bulletin of Haseki, University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital.

Address
University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital
Secretariat of The Medical Bulletin of Haseki
Adnan Adivar Caddesi, 34906 Haseki-Aksaray-Istanbul-Turkey
Phone: +90 212 529 44 00/1874
Fax: +90 212 530 84 23
Web Page: www.hasekidergisi.com
E-mail: hasekidergisi@gmail.com

Permissions
Request for permission for reproduction of the published materials should be made to the editorial office.
Editor in Chief: Akif Erbin
University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Nephrology
Phone: +90 212 529 44 00/1133
Fax: +90 212 530 84 23
Web Page: www.hasekidergisi.com
E-mail: hasekidergisi@gmail.com

Advertisement
Applications concerning advertisement should be addressed to the Associate Editor.
University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital
Secretariat of The Medical Bulletin of Haseki
Adnan Adivar Caddesi, 34906 Haseki-Aksaray-Istanbul-Turkey
Phone: +90 212 529 44 00/1874
Fax: +90 212 530 84 23
Web Page: www.hasekidergisi.com
E-mail: hasekidergisi@gmail.com

Publisher Corresponding Address
Galenos Yayinevi Tic. Ltd. Şti.
Molla Gurani Mahallesi Kacamak Sokak No: 21 34093
Findikzade - Istanbul - Turkey
Phone: +90 212 621 99 25
Fax: +90 212 621 99 27
E-mail: info@galenos.com.tr

Instructions for Authors
Instructions for authors are published in the journal and may be obtained from www.hasekidergisi.com

Material Disclaimer
The opinions and reports published in The Medical Bulletin of Haseki are those of the author(s), and not of the Editor, Editorial Publishing Directors or the publisher. The author(s) is (are) responsible from the articles published in the Haseki Medical Bulletin. The Editor, Editorial Board and the Publisher do not accept any responsibility.

OPEN ACCESS

The Medical Bulletin of Haseki

Instruction to Authors

The Medical Bulletin of Haseki publishes papers on all aspects of general medicine. In addition to original articles, review articles, original case reports, letters to the editor and announcements of congress and meetings are also published. The scientific board guiding the selection of the papers to be published in the journal consists of elected experts of the journal and if necessary, is selected from national and international authorities.

Turkish language Institution dictionary and orthography guide should be taken as a basis for the literary language. Papers written in English language are particularly supported and encouraged.

Ethical committee approval may be requested by the Editor or Associate Editors for clinical research studies. Authors are responsible for the contents of the manuscripts and for the accuracy of the references.

The authors should guarantee that the manuscripts have not been previously published and/or are under consideration for publication elsewhere. Only those data presented at scientific meetings in form of abstract which do not exceed 200 words may be accepted for consideration, however, the date, name and place of the meeting in which the paper was presented should be stated. The signed statement of scientific contributions and responsibilities of all authors, and statement on the absence of conflict of interests are required. All manuscripts are reviewed by the editor, related associate editor and at least three experts/referees. The authors of the accepted for publication manuscripts should agree that the editor and the associate editors can make corrections on condition that there are no changes in the main text of the paper. Manuscript format should be in accordance with Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication (available at http://www.icmje.org/)

The Medical Bulletin of Haseki does not charge any article submission or processing charges.

The journal should be abbreviated as Med Bull Haseki when referenced.

General Guidelines

Manuscripts are accepted only online and can be submitted electronically through web site (http://hasekitip.dergisi.org) after creating an account. This system allows online submission and review.

The ORCID (Open Researcher and Contributor ID) number of the correspondence author should be provided while sending the manuscript. A free registration can create at http://orcid.org.

The manuscripts gathered with this system are archived according to ICMJE-www.icmje.org, Index Medicus (Medline/PubMed) and Ulakbim-Turkish Medicine Index Rules. Rejected manuscripts, except artworks are not returned.

Articles sent to the editor for publication should be written single-sided on A4 pages, double-spaced in 12-point, arial/times, new roman font and with 2.5 cm margins. Abbreviations must be explained clearly in parentheses in their first instance within the text and custom abbreviations should not be used. Numbers 1 to 10 should be given as text (In the two treatment groups the second day) and numbers 11 or bigger given as numbers. However, numbers 1-10 with a descriptive suffix should be given with numbers (1 year) while numbers that start sentences (Fifteen-year-old female patient) should be given as text.

The manuscript should not exceed 5000 words in total. All pages of the manuscript should be numbered at the top right-hand corner, except for the title page. Papers should include the necessary number of tables and figures in order to provide better understanding.

The rules for the title page, references, figures and tables are valid for all types of articles published in this journal.

Patients have a right to privacy. When not essential, identifying information, patient names and photographs should not be published, unless the written informed consent of the patient (parent or guardian) has been given.

The patient should, therefore, be given a draft of the paper in order to obtain written informed consent. When not necessary, any identifying details of the patient should not be published. Complete anonymity is difficult to attain, however, informed consent should be obtained if any doubt exists. For example, masking the eye region of a patient's photograph provides incomplete anonymity.

For the experimental, clinical and drug studies having the obligation of being approved by ethical committee and being sent in order to be published in The Medical Bulletin of Haseki, ethical committee approval report being in accordance with the international agreements with Helsinki Declaration revised 2013 is required (http://www.wma.net/en/30publications/10policies/b3/). In experimental animal studies, the authors should indicate that the procedures followed were in accordance with animal rights (Guide for the care and use of laboratory animals. (https://oacu.oir.nih.gov/regulations-standards) and they should obtain animal ethics committee approval. The approval of the ethical committee including approval number and the fact that the "informed consent" is given by the patients should be indicated in the "Methods" section. Authors should declare the conflict of interest concerning their articles and the financial supports.

Original Articles

1) Title Page: This page should include the titles of the manuscripts, information about the author(s), key words and running titles.

For papers n Turkish language, a title in English should be included. Similarly, articles in English should include a title in Turkish. Key words in English and Turkish, and running titles should also be included in the title page.

The names, affiliated institutions and full addresses of the authors should be given. The author to whom correspondence is to be addressed should be indicated separately. As e-mail addresses will be used preferentially for communication, the e-mail address of the corresponding author should be stated. In addition, telephone and fax numbers must be notified.

If the content of the paper has been presented before, and if the summary has been published, the time and place of the conference should be denoted on this page.

If any grants or other financial support has been given by any institutions or firms for the study, information must be provided by the authors.

2) Summary: In the second page, summaries of the manuscripts (maximum 200 words for each) and the key words in Turkish and English language should be given.

The Summary Should Consist of the Following Sub Sections: Aim, Methods, Results, Conclusion. Separate sections are not used in the summaries of the review articles, case reports and educational articles. For these articles, the summaries should not exceed 200 words and include the scope and aims of the study, the salient findings and conclusions.

The references should not be cited in the summary section. As far as possible, use of abbreviations are to be avoided. Any abbreviations used must be taken into consideration independently of the abbreviations used in the text.

3) Text (From the according to the length of the summaries)

Please follow the instructions in "general guidelines."

The Main Headings of the Text Should be as Follows: Introduction, Methods, Results, Discussion, Study Limitations and Conclusion.

The introduction should include the rationale for investigation and the background of the present study. Results of the study should not be discussed in this part.

"Materials and methods" section should be presented in sufficient details to permit the repetition of the work. The statistical methods used should be clearly indicated.

Results should also be given in detail to allow the reproduction of the study.

The Discussion section should provide a correct and thorough interpretation of the results. The references should be directly related to the findings of the authors.

Study Limitation should be detailed in the section.

Conclusion section should provide highlighted and interpreted with the study's new and important findings.

Acknowledgements should be as brief as possible. Any support should be acknowledged in this section. (Acknowledgements should be only send with the "Cover Page".)

The excessive use of abbreviations is to be avoided. All abbreviations should be defined when first used by placing them in brackets after the full term. Abbreviations made in the abstract and in the text are taken into consideration separately. Abbreviations of the full terms stated in the abstract must be re-abbreviated after the same full term in the text.

4) References: Accuracy of reference data is the author's responsibility.

References should be numbered according to the consecutive citation in the text. References should be indicated in brackets in the text.

Personal communications, unpublished data and submitted manuscripts must be cited, not in this section, but in the text as "(name(s), unpublished data, 19)."

The reference list should be typed on a separate page at the end of the manuscript. If there are more than 6 authors, abbreviation of "et al." should be used for the authors out of the first three. Journal titles should be abbreviated according to the style used in the Index Medicus. All the references should be written according to the Vancouver system as follows:

a) Standard Journal Article: Intiso D, Santilli V, Grasso MG, Rossi R, Caruso I. Rehabilitation of walking with electromyographic biofeedback in foot-drop after stroke. Stroke 1994;25:1189-92.

b) Book: Getzen TE. Health economics: fundamentals of funds. New York: John Wiley & Sons; 1997.

c) Chapter of a Book: Porter RJ, Meldrum BS. Antiepileptic drugs. In: Katzung BG, editor. Basic and clinical pharmacology. 6th ed. Norwalk, CN: Appleton and Lange; 1995. p. 361-80.

If more than one editor: editors.

d) Conference Papers: Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Reinhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10;Geneva, Switzerland: North-Holland; 1992. p. 1561-5.

e) Journal on the Internet: Morse SS. Factors in the emergence of infectious disease. Emerg Infect Dis [serial online] 1995 1(1):[24 screens]. Available from:s URL:http://www/cdc/gov/ncidoc/EID/eid.htm. Accessed December 25, 1999.

f) Thesis: Kaplan SI. Post-hospital home health care: the elderly access and utilization (thesis). St. Louis (MO): Washington Univ; 1995.

5) Tables, Graphics, Figures and Pictures: All tables, graphics or figures should be presented on a separate sheet. All should be numbered consecutively according to their place in the text and a brief descriptive caption should be given. Abbreviations used should be explained further in the figure's legend. The text of tables especially should be easily understandable and should not repeat the data of the main text. Illustrations already published are acceptable if supplied by permission of the authors for publication. Photographs should be printed on glossy paper. Figures should be done professionally and no grey colors should be used.

Special Sections

1) Reviews: All reviews within the scope of the journal will be taken into consideration by the editors; also the editors may solicit a review related to the scope of the journal from any specialist and experienced authority in the field.

2) Case Reports: Case reports should present important and rare clinical experiences. They should consist of the following parts: introduction, case, discussion.

3) Letters to the Editor: These are views about articles published in this journal. The editor may request responses to the letters. There are no separate sections in the text.

Correspondence

For all correspondence with the editorial board, mail or e-mail addresses given below may be used.

Editor of The Medical Bulletin of Haseki
University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Department of Nephrology
Adnan Adivar Caddesi, 34906 Haseki-Aksaray-Istanbul-Turkey
Phone: +90 212 529 44 00/1874
Fax: +90 212 530 84 23
Web Page: www.hasekidergisi.com
E-mail: hasekidergisi@gmail.com

The Medical Bulletin of Haseki

Contents

Original Articles

1 **A Large-scale Pilot Breast Cancer Screening Program Undertaken in Turkey: Findings and Recommendations for National Screening Programs**
Abdullah Emre Guner, Aral Surmeli, Guven Turan, Kemal Kural, Engin Ersin Simsek,Isil Maral; Istanbul, Turkey

7 **The Relationship between Intracardiac Atrial Sensing Values and Atrial High-rate Episodes in Patients with Permanent Pacemakers Implanted due to Sick Sinus Syndrome**
Sukru Arslan, Betul Balaban Kocas, Omer Dogan, Selim Tanyolac, Isil Uzunhasan; Istanbul, Turkey

13 **Monocyte/High Density Lipoprotein Ratio in Patients with Symptomatic Carotid Artery Stenosis and Its Relationship with Stenosis Degree**
Fettah Eren, Aydin Talip Yildogan, Gozde Ongun, Gokhan Ozdemir, Serefnur Ozturk; Konya, Gaziantep, Mus, Turkey

20 **Comparison of the Urodynamic Patterns of the Disorders Frequently Encountered in the field of Pediatric Urology**
Hasan Demirkan, Mehmet Ozgur Kuzdan; Istanbul, Turkey

26 **Evaluation of the Relationship Between Janus Kinase 2 Mutational Burden and Clinical Findings in Adult Myeloproliferative Neoplasm Patients**
Cigdem Yuce Kahraman, Gulden Sincan, Abdulgani Tatar; Erzurum, Turkey

33 **A Comparative Study of the Effectiveness of Serum C-reactive Protein and Serum Pentraxin-3 Levels in the Diagnosis and Follow-up of Neonatal Sepsis**
Tugrul Atay, Kamil Sahin, Murat Elevli, Ala Ustyol, Demet Oguz, Emel Ataoglu, Hatice Nilgun Duru; Istanbul, Turkey

40 **Relationship between Maternal Serum Calcium and Magnesium Levels and Isolated Fetal Echogenic Intracardiac Focus Encountered During Second-trimester Ultrasound Screening**
Filiz Yarsilikal Guleroglu, Aliye Balkan Ozmen, Murat Ekmez, Ali Cetin; Istanbul, Bursa, Turkey

45 **Multifidus Muscle Stiffness in Single-level Unilateral Lumbar Disc Herniation: Comparison of Two Shear-wave Elastography Methods**
Tuba Selcuk Can, Behice Kaniye Yilmaz, Sevim Ozdemir; Istanbul, Turkey

52 **Investigation of the Relationship between Wrist Ganglion Cysts and the Ulnar Variance using 3-tesla Magnetic Resonance Imaging**
Murat Bayav; Eskisehir, Turkey

57 **The Relationship Between Nutritional Status and Early- and Mid-term Mortality of Geriatric Patients Admitted to the Emergency Internal Medicine Unit**
Arzu Cennet Isik, Ali Karagoz, Asli Ocal, Seydahmet Akin, Banu Boyuk, Ozcan Keskin; Istanbul, Turkey

64 **Efficacy of Prothrombin Complex Concentrate versus Fresh Frozen Plasma in Patients with Bleeding in the Emergency Department**
Burak Demirci, Abuzer Coskun; Istanbul, Turkey

72 **Evaluation of the Demographic and Clinical Data of Psoriasis Patients: A Detailed Analysis of a Big Series**
Tugba Ozkok Akbulut, Filiz Topaloglu Demir, Ayşe Nur Tufan, Nazli Caf, Baran Cayhan, Senay Agirgol, Zafer Turkoglu; Istanbul, Turkey

Case Series

78 **Evaluation of Postoperative Symptom Relief With Styloidectomy Procedure For Eagle Syndrome: A Case Series From A National-Accredited Center**
Semih Usaklioglu, Gokhan Gurbuz, Onur Ustun, Yagmur Barcan; Istanbul, Turkey

Case Reports

84 **A Turkish Family with Loeys-Dietz Syndrome and a Report of a Homozygous Patient with SMAD3 Pathogenic Variation**
Betul Okur Altindas, Ayse Gul Zamani, Mehmet Burhan Oflaz, Muhammed Gunes, Mahmut Selman Yildirim; Konya, Turkey

89 **Acute Segmental Testicular Infarction caused by COVID-19 Disease: A Case Report and Current Literature Review**
Murat Demir, Ilyas Dundar; Van, Turkey

Original Article

DOI: 10.4274/haseki.galenos.2021.7793
Med Bull Haseki 2022;60:1-6

A Large-scale Pilot Breast Cancer Screening Program: Findings and Recommendations for National Screening Programs

Abdullah Emre Guner*, Aral Surmeli**, Guven Turan***, Kemal Kural****, Engin Ersin Simsek*****, Isil Maral***

*Istanbul Health Directorate, Public Health Services, Istanbul, Turkey

**HERA INC., Boston, United States of America

***Istanbul Medeniyet University Faculty of Medicine, Department of Public Health, Istanbul, Turkey

****Istanbul Health Directorate, Monitoring, Evaluation and Statistics, Istanbul, Turkey

*****University of Health Sciences Turkey, Istanbul Kartal Dr. Lutfi Kirdar Health Application and Research Center, Istanbul, Turkey

Abstract

Aim: Breast cancer is the most prevalent cancer diagnosed in women. Screening programs to diagnose breast anomalies increase the likelihood of early diagnosis and survival. This study describes the most extensive breast cancer screening program in Istanbul/Turkey between 2018 and 2019 and offers recommendations for nationwide programs.

Methods: We collected data from the Istanbul Health Directorate's cancer surveillance database from May 2018 to December 2019. We analyzed data on patients referred for further investigation due to suspicion of possible tumors in their screening radiography. The database included socio-demographic information and further examination details (tests, outcomes, and planned treatment).

Results: The mean age of the 3,577 women who were invited for further examination was 52.3 [standard deviation (SD): 7.5]. The age group with the highest percentage of further investigation invitations was between 50 and 54. The mean time between the results of screening mammography was 16.2 days (SD: 15.3). 5.1% of the women referred were diagnosed with some sort of cancer. Women who went to the place of scheduled appointments, instead of getting an appointment in another place of their choosing, were diagnosed and treated earlier.

Conclusion: For a breast screening program to reach the entirety of the target population, a comprehensive approach to every step of the process (screening, diagnosis, treatment) needs to be considered together.

Keywords: Breast cancer screening, imaging, mammography, screening

Introduction

Breast cancer is the most prevalent cancer in women, with 2.08 million yearly cases and 626,000 fatal cases (1). Breast cancer data from Turkey is also similar. One in every four cancer diagnoses in women is breast cancer (2). Survival rates of localized spread stages and metastatic stages are 85.7% and 28.1%, respectively (3). While the disease is a type of progressive cancer, early diagnosis and treatment provide to decreased mortality and morbidity (4).

Recommended methods for early detection of breast cancer include breast self-examination, clinical examination, and breast mammography, the latter being the gold standard for complete cancer screening (5). Screening for breast cancer decreases breast cancer mortality if implemented for the appropriate age group and recommended frequencies (6-8). While consensus on the frequency of mammography has not been established, the American Cancer Society recommends yearly screening between the ages of 45 to 55 and

Address for Correspondence: Aral Surmeli,
HERA INC., Boston, United States of America
Phone: +90 535 314 01 79 E-mail: a.surmeli@medak.org.tr ORCID: orcid.org/0000-0002-5173-3867
Received: 29.09.2021 **Accepted:** 24.12.2021

every two years after the age of 55 (9). However, the Turkish Ministry oh Health starts screening procedures at age 40.

In light of the evidence, the Turkish Ministry of Health planned to undertake a nationwide screening program through these 15 centers in Istanbul as a pilot. During the implementation of this program, there were 2,529.072 women in the target age group (10). This study presents the initial results of the pilot program involving forty-seven thousand women living in Turkey.

This screening protocol is implemented by Cancer Diagnosis, Screening, and Education Center [Erken Teşhis, Tarama ve Eğitim Merkezleri (KETEM)] and their mobile services, which are overseen by the Ministry of Health. These centers were open to the public, and anyone in the target group could come in for screening without the need for an appointment, free of charge. If the findings necessitate further investigation, the women would be contacted by family physicians, who are assigned to each individual in Turkey. Physicians contact the person via calls, emails, or short message services and are invited for voluntary screening.

The aim of this study is to evaluate the screening process, discuss the feasibility of large-scale screening programs, and produce insights for implementation for nationwide uptake of such a program.

Methods

An Internal Review Board approval was received from Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee (date: 27.01.2021 and approval number: 2021/0055). No informed consent was sought as the study only used data from the existing databases.

This is a cross-sectional study that enrolled data already collected by Istanbul Municipal Health Directorate Public Health Services in National Breast Cancer Screening Program. The program started collecting data in May 2018. This study includes all the data available from May 2019 to December 2019. For the purposes of this study, all available data from the database was used. Variables included socio-demographic information, details of appointments, diagnostic choices, diagnosis, and treatment.

Screening Procedure

Mammography of invited participants is done through either the KETEM or their two mobile units. Diagnostic results of mammography are evaluated and decided by Hacettepe University Medical School Radiography Department. Results are directed to Municipal Health Directorates then to the district health directorate or primary care centers. Screened women with positive (or suspected) results are called to inform the participant and schedule further tests by either their primary care physicians or the Cancer Screening Department of the district health directorate. Simultaneously, data from the women who accepted further tests is entered into a shared database. Further data collection and input are done by the hospital personnel where the participant chooses to go. If the participant rejects further testing, the data collected stays in the district health directorate level for calling again at a later date. This algorithm is summarized in Figure 1.

Data collected includes contact information, date of birth, dates, and details of each test, district name, diagnosis, and treatment details. For the purposes of this study, all variables except planned/ongoing treatment details are used.

Statistical Analysis

We analyzed the data with SPSS version 22.0. Descriptive statistics are presented as percentages, frequencies, means, medians, and standard deviations (interquartile range). We compared medians with the Student's t-test and paired t-test after assumptions were affirmed. The statistical difference was set as $p<0.05$. Statistical tests done are presented as a separate table (Table 1).

Results

The screening program included 47,698 women. 3,577 of the screened participants (7.5%) were referred for further investigation. Health Directorate personnel were able to reach 97.7% (3,490 women) of them to refer them for further testing. Efforts to reach 2.4% were unsuccessful. In total, 3,086 women (86.3%) accepted the invitation to set up a referral appointment. Enrollment and follow-up of participants are summarized in Figure 2. Information on the people who did not accept an appointment but then made an appointment by themselves was added later.

Of the women referred for further investigation (3,577), the mean age was 52.3 [Standard deviation (SD):7.5]. Final diagnosis and further investigation results were available

Table 1. Statistical test variables, measured outcome and p-value

Group 1	Group 2	Measured outcome	Test	p-value
Persons who went to the set appointment	Persons who did not go to the set appointment	Completeness of outcome data (%)	Chi-squared	>0.001
Persons who went to the set appointment	Persons who did not go to the set appointment	Days between the result of initial mammography test and further testing appointment	Paired t-test	0.005

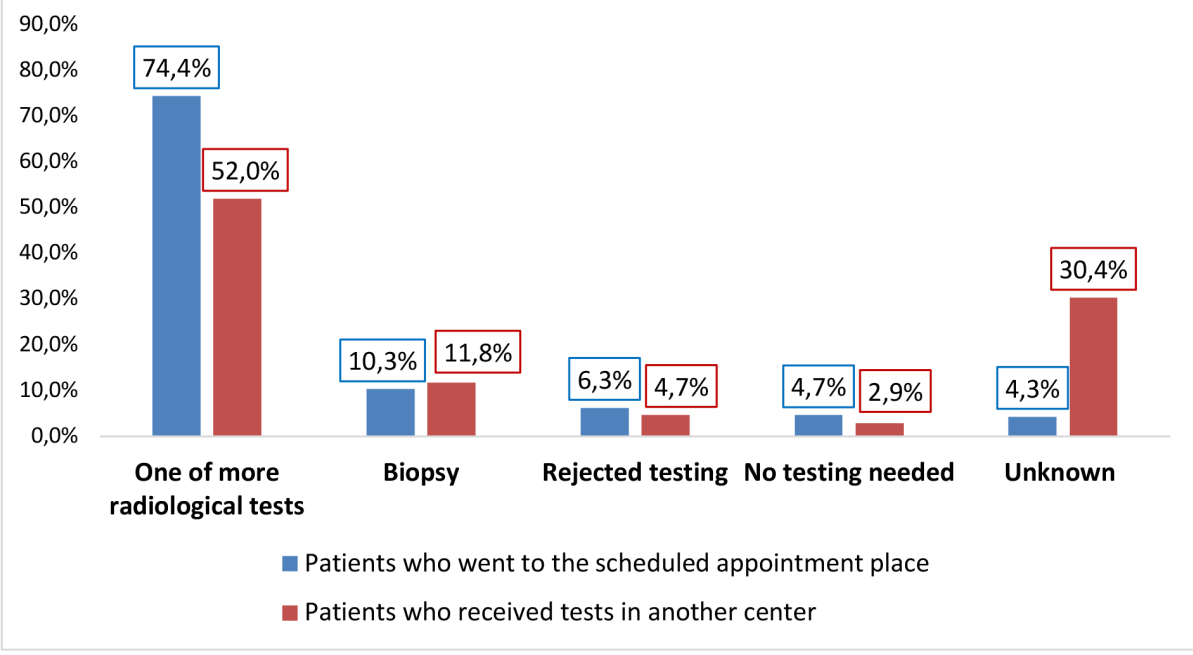
Table 2. Age groups and follow-up percentages of women referred for further testing		
		n (%)
Age groups	40-44	488 (13.6%)
	45-49	1,084 (30.3%)
	50-54	748 (20.9%)
	55-59	591 (16.5%)
	60-64	368 (10.3%)
	65+	298 (8.3%)
	Total	3,577 (100%)
Appointment place of further investigation	Unreachable	85 (2.4%)
	In the appointment center	2,832 (81.1%)
	Another center	519 (14.9%)
	Appointment not made	54 (1.6%)
	Total	3,490 (100%)
Method of investigation	One or more radiological test	2,758 (82.3%)
	Biopsy	353 (10.6%)
	No further testing	15 (0.4%)
	Further testing rejected	85 (2.5%)
	Unknown or ongoing process	140 (4.2%)
	Total	3,351 (100%)
Diagnosis	Normal	2,295 (68.5%)
	Cancer	191 (5.7%)
	Unknown or ongoing process	865 (25.8%)
	Total	3,351 (100%)

for 2,486 people. Age groups, further investigation, and diagnostic procedure details are presented in Table 2.

Out of 3,490 women who had their appointment set, 81.1% (2,832 women) went to the scheduled appointment, while the rest went to another health center of their choosing (14.9%) or did not receive the appointment (Table 2). The mean number of days between the results of screening mammography and scheduling the further testing appointment is 16.2 (SD: 15.3) and the mean day between the results and the actual day of the appointment is 27.1 (SD: 37.2). There was a statistical difference between the number of days from the results of the initial mammography to the day of the further testing appointment between people who went to the place of appointment (mean: 26.6, SD: 37.1 days) and people who went to another place of their choice (mean: 39.9, SD: 43.4 days), (paired t-test, p=0.0052).

Among further testing methods, 82.3% of the patients received one or more radiological tests, and 10.3% received a biopsy (Table 2). There was a marked difference in the completeness of diagnostic methods between the data of patients who went to the place of appointment (4.3% incomplete data) and patients who went to another place (30.4% incomplete data) (chi-squared test p<0.001). Diagnostic tests done are summarized in Graph 1.

In total, there were 191 diagnoses of any kind of breast cancer in the population for which data was available (2,486 women). The mean age of women who received a cancer diagnosis of cancer was 55.2 (SD: 8.0), older than



Graph 1. Diagnostic tests done by place of appointment

the whole screened group. While only 56% of the women screened were over the age of 50, the ratio was 69% in the group that received a breast cancer diagnosis.

Discussion

This study aims to describe a large-scale breast cancer screening program, the first of its kind in Istanbul, Turkey. We hope the findings on screening and follow-up will be beneficial in implementing similar interventions through primary care services. In the program's scope, 47,698 women were screened, 3,577 (%) were referred for further testing, and 191 (5% among those referred and 0.4% among the screened) received a diagnosis and treatment.

Four out of five women whose mammography was done are over 45 years of age. While guidelines in the U.S. and Europe typically recommend screening at least 45-50 years of age, the Turkish screening program starts at forty (11,13). There is existing local literature that finds similar breast cancer rates between the ages of

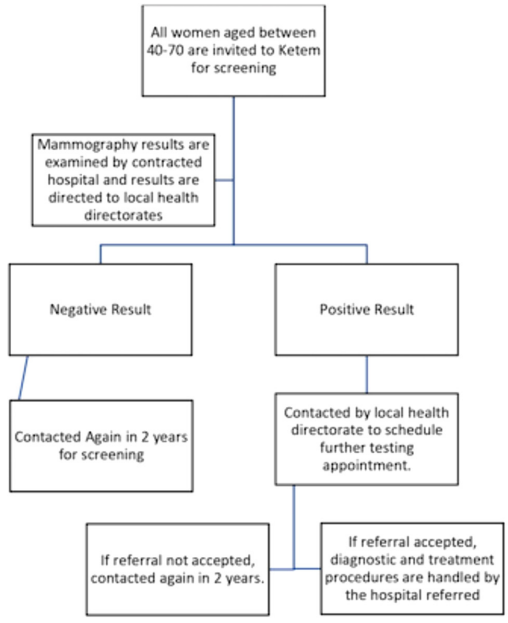


Figure 1. Breast cancer screening algorithm

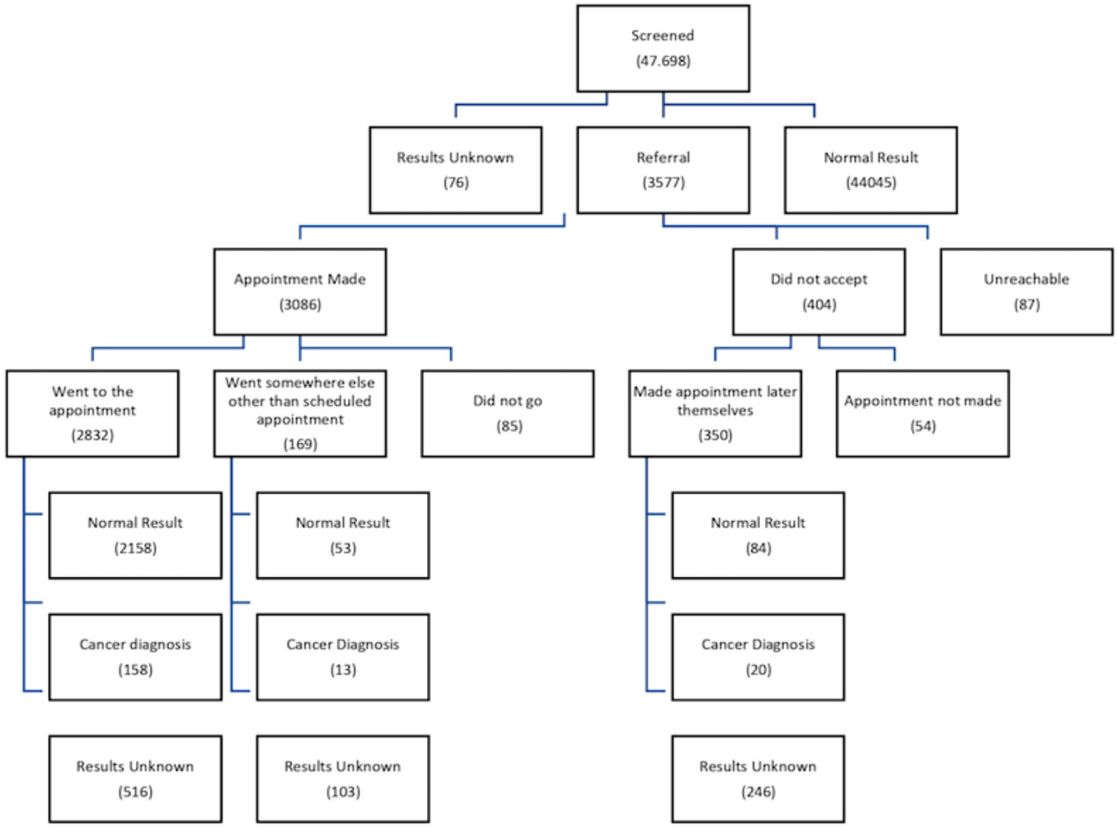


Figure 2. Summary of screening program enrollment and follow-up

Appointment made: These are the women who were contacted for further testing and scheduled their appointments. Went to the appointment: This group includes participants who went to the scheduled appointments. Went somewhere else: These participants had a scheduled appointment, but decided to go somewhere else, in a different time. Did not accept: These refer to the participants who declined the offer of scheduling an appointment. Made appointment later themselves: these women, who had previously declined to schedule an appointment, made their own appointments later on.

50-59 and 40-49 (14). In addition, we found that one-third of all those diagnosed with some sort of cancer were under fifty (31%). Considering the fact that the sensitivity of mammography is lower in the age groups below 50 (15), this ratio could also be higher in reality. This finding suggests screening programs may benefit from starting at an earlier age. Similarly, literature from developed countries suggests starting mammography screenings at an earlier age is associated with mortality rates of up to 23% (7). Starting the screening programs at age 40, long-term follow-up randomized protocols from the UK also provided supporting evidence of benefits (11).

Our study found that for women who received further testing and treatment in the center where they scheduled the appointment, the time between testing, diagnosis, and eventual treatment was earlier. This is also partly due to reaching out to individuals and making scheduling easier by phone. This practice is known to increase the uptake of follow-up services and also timeliness of interventions (16). This could result in less early detection and, as a result, a higher chance of survival.Mobile screening programs, such as this pilot, also increase access to diverse and rural populations that might otherwise be overlooked (12). In addition, the levels of follow-up were much higher when the patient went to the scheduled appointment rather than a place of their choosing instead.

Study Limitations

This screening program only used mammography as a screening tool. However, other radiological methods could have higher sensitivity and specificity for the detection of masses in younger women. In the younger age groups, the results may be skewed. However, the literature suggests mammography is still the best option considering logistics, costs, and the need for specialized personnel (13).

Participation in the screening program was open to everyone passing by the KETEM and there was no sampling used in this pilot study. It is hard to stipulate the breast cancer levels in the target population without actual sampling methods for participant selection being used. In addition, our sample was among the 2,529.072 women living in Istanbul at that time. While the screening was done on almost 3500 women, data on only 2400 was completed after the follow up time. While there is no information on people who did not respond, some were added to the database afterwards to alleviate this issue. Nonetheless, this could have skewed the results due to factors related to non-responsiveness.

The follow-up time was short in this study, focusing on the diagnosis as the end point. Mortality rates are not discussed, and further studies could benefit from looking at the 5 or 10-year survival rate in this population.

However, this study also has several strengths. Primarily, this screening program was the largest of its kind in Turkey, a country with free access to screening and breast cancer treatment. In addition, a centralized electronic medical records keeping system allowed for high levels of follow-up during the data collection phase. As a pilot program, this study provides insights for nationwide scale-up programs.

Conclusion

This study focuses on the procedure of the screening program. However, successful implementation also requires more profound insight into referrals of screening invitations. Understanding the reasons behind the refusal or possible barriers is essential for population-wide impact.

We recommend the following considerations before implementing a nationwide screening program:

- The process needs to be planned as a continuity of care, not in silos such as “screening” or “treatment”. A central database and authority on screening and follow-up could be beneficial in implementing the analysis of data (deaths averted, costs saved) and policy development.

- Standardization of screening, diagnosis, and data collection is a vital part of successful programs.

- Sensitization and an overall increase in “demand” for preventive care should be part of such programs to increase uptake.

- Novel follow-up methodologies could be cost-effective alternatives to prevent loss in follow-up, such as automated calls or short message service reminders.

- To increase uptake of screening by the target population, further actions are needed that focus on understanding the reasons for rejecting being screened, or scheduling appointments. These follow-up procedures on people who reject them should be incorporated into the initial implementation.

Ethics

Ethics Committee Approval: The study was approved by the Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee (date: 27.01.2021, approval number: 2021/0055).

Informed Consent: No informed consent was sought as the study only used data from the existing databases.

Authorship Contributions

Concept: A.E.G., A.S., Design: A.S., G.S., Data Collection or Processing: A.E.G., K.K., Analysis or Interpretation: I.M., E.E.S., Literature Research: G.T., K.K., Writing: A.S., I.M.

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

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

References

1. IARC, age-standardized (World) Incidence Rates, Breast, All ages, International Agency for Research on Cancer, WHO. 2018. Available from:http://gco.iarc.fr/today
2. T.C. Sağlık Bakanlığı, Türkiye kanser İstatistikleri 2016, Türkiye Cumhuriyeti Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü. 2019. Available from: https://hsgm.saglik.gov.tr/depo/birimler/kanser-db/istatistik/Trkiye_Kanser_statistikleri_2016.pdf
3. Howlader N, Noone AM, Krapcho M et al. SEER Cancer Statistics Review, 1975-2017, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2017/, based on November 2019 SEER data submission, posted to the SEER web site, April 2020.
4. American Cancer Society. Breast cancer facts & figures 2017-2018. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and figures-2017-2018.pdf.
5. Selda S. Meme Kanseri Taraması : Son Yenilikler Neler ? TSK Koruyucu Hekim Bülteni 2011;10:193-200.
6. Bjurstam NG, Björneld LM, Duffy SW. Updated results of the Gothenburg Trial of Mammographic Screening. Cancer 2016;122:1832-5.
7. Armstrong K, Moye E, Williams S, Berlin JA, Reynolds EE. Screening mammography in women 40 to 49 years of age: A systematic review for the American College of Physicians. Ann Intern Med 2007;146:516-26.
8. Moss SM, Wale C, Smith R, Evans A, Cuckle H, Duffy SW. Effect of mammographic screening from Age 40 years on breast cancer mortality in the UK Age trial at 17 years follow-up: a randomized controlled trial. Lancet Oncol 2015;16:1123-32.
9. American Cancer Society, Breast Cancer Early Detection and Diagnosis, Recommendations for the Early Detection of Breast Cancer, 2016. Available from: https://www.cancer.org/content/dam/CRC/PDF/Public/8579.00.pdf
10. Türkiye İstatistik Kurumu, Adrese Dayalı Nüfus Kayıt Sistemi Sonuçları, 2019 https://data.tuik.gov.tr/Bulten/Index?p=Adrese-Dayali-Nufus-Kayit-Sistemi-Sonuclari-2019-33705
11. Duffy SW, Vulkan D, Cuckle H, et al. Effect of mammographic screening from age 40 years on breast cancer mortality (UK Age trial): final results of a randomised, controlled trial. Lancet Oncol 2020;21:1165-72.
12. Stanley E, Lewis MC, Irshad A, et al. Effectiveness of a mobile mammography program. AJR Am J Roentgenol 2017;209:1426-9.
13. Siu AL; U.S. Preventive Services Task Force. Screening for breast cancer: U.S. Preventive services task force recommendation statement. Ann Intern Med 2016;164:279-96.
14. ECIBC, European guidelines on breast cancer screening and diagnosis, The European Commission's science and knowledge service. 2020 Available from:https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines
15. Kerlikowske K, Grady D, Barclay J, Sickles EA, Ernster V. Effect of age, breast density, and family history on the sensitivity of first screening mammography. JAMA 1996;276:33-8.
16. Schapira MM, Barlow WE, Conant EF, et al. Communication practices of mammography facilities and timely follow-up of a screening mammogram with a BI-RADS 0 assessment. Acad Radiol 2018;25:1118-27.

Original Article

DOI: 10.4274/haseki.galenos.2021.7732
Med Bull Haseki 2022;60:7-12

The Relationship between Intracardiac Atrial Sensing Values and Atrial High-rate Episodes in Patients With Permanent Pacemakers Implanted due to Sick Sinus Syndrome

Sukru Arslan*, Betul Balaban Kocas**, Omer Dogan*, Selim Tanyolac*, Isil Uzunhasan*

*Cardiology Institute of Istanbul University-Cerrahpasa, Department of Cardiology, Istanbul, Turkey

**Istanbul Prof. Dr. Cemil Tascioglu City Hospital, Clinic of Cardiology, Istanbul, Turkey

Abstract

Aim: An increase in fibrosis and collagen in the atrium and sinus node tissues constitutes the basic pathophysiology of sick sinus syndrome (SSS). We aimed to investigate the relationship between P-wave sensing values and atrial high rate episodes (AHRE) in patients with dual-chamber (DDDR) pacemakers implanted due to SSS.

Methods: Patients with DDDR pacemakers implanted due to SSS between 2011 and 2019 were included in our retrospective cohort study. The patients were called for a visit and pacemaker controls were performed. The study population was divided into two groups according to the development of AHRE.

Results: At least one AHRE episode was detected in 51.7% of participants. Left atrial (LA) diameters were increased in the AHRE+ group (p<0.01). P-wave sensing values were significantly lower in the AHRE+ group (p=0.01). LA diameter [hazard ratio (HR): 1.10, 95% (1.04-1.18), p<0.01] and P-wave sensing values [HR: 0.74, confidence interval 95% (0.57-0.95) p=0.02] were determined as independent predictors of AHRE.

Conclusion: Our study demonstrated that LA diameter and P-wave sensing values were found to be independent predictors of AHRE development. Lower initial P-wave sensing values seem to be an important risk factor for AHRE development in this patient group.

Keywords: Sinoatrial node, permanent pacemakers, cardiac arrhythmias

Introduction

Sick sinus syndrome (SSS) is an important clinical condition presenting as isolated sinus bradycardia, sinusal arrest, sinus bradycardia and atrial arrhythmias. An increased amount of collagen and fibrosis in the sinoatrial node and atrium tissue constitutes the basic pathophysiology of SSS (1,2). Most studies reported that increased fibrosis in the atrial tissue may both cause prolongation of atrial conduction time and increase the frequency of atrial arrhythmias (3,4). In addition, some studies have reported that low atrial sensing values may be associated with increased volume load and scarring in the atrial tissue, thereby causing atrial arrhythmias (4-6).

Dual-chamber (DDDR) pacemaker implantation is the main treatment strategy to improve symptoms in this patient group. Although permanent pacemakers provide improvement in symptoms in SSS, their impact on mortality is still controversial (1,7,8). Since these patients are mostly of advanced age, it is important to follow them in terms of atrial arrhythmias (9). Therefore, we aimed to investigate the relationship between the initial intracardiac P-wave sensing values and the development of atrial high rate episodes (AHRE) in patients with DDDR permanent pacemakers implanted due to SSS.

Address for Correspondence: Sukru Arslan
Cardiology Institute of Istanbul University-Cerrahpasa, Department of Cardiology, Istanbul, Turkey
Phone: +90 212 459 20 00 E-mail: sukru.arslan@istanbul.edu.tr ORCID: orcid.org/0000-0003-0962-0540
Received: 01.09.2021 **Accepted:** 10.10.2021

Methods

Ethical Approval and Study Population

All patients gave their written informed consent, and the study was approved by the local ethics committee (Ethics Committee of Cardiology Institute of Istanbul University-Cerrahpasa, 2.İ.Ü.E.50.0.05.00/4). Patients with DDDR pacemakers implanted due to SSS between 2011 and 2019 were included in our single-center retrospective cohort study. Patients with pacemaker implantation for atrioventricular node disease, non-optimal atrial lead location, ejection fraction (EF) <40%, persistent or permanent atrial fibrillation (AF), patients with implantable cardioverter-defibrillator (ICD), severe organ failure (chronic liver, chronic renal failure, etc.), active malignancy, prior radiotherapy, and systemic rheumatic disease were excluded from the study. A total of 118 patients were analyzed after excluding the patients with one of the exclusion criteria and those who could not be reached. The flow chart of the study is given in Figure 1.

Study Protocol

SSS is defined for patients who present with syncope, presyncope, effort dyspnea, fatigue, or palpitation with no other underlying cause, and sinus bradycardia, sinusal arrest, sinoatrial block, and/or accompanying atrial arrhythmias are detected in the examinations (10). Initial demographic characteristics, laboratory parameters and baseline pacemaker measurements of the study group were recorded by the electronic hospital system. In addition, the atrial lead position of the patients was examined from the hospital database; the right atrium appendix and the anterior and lateral areas close to this region were determined as the optimal lead locations. Only the data of patients whose recent pacemaker control data and event records were available in the hospital system for the last 6 months were recorded.

Patients with no recent data were called for a control visit, pacemaker measurements were performed, and events were recorded. Pacemaker controls were performed by two experienced physicians. Patients with AHRE episodes that exceeded 175/min and lasted longer than 30 seconds were included in the AHRE (+) group (11). Patients who did not have AHRE episodes or whose attacks were less than the specified criteria constituted the AHRE (-) group.

Clinical Outcomes

The primary endpoints of the study were defined as death, myocardial infarction, cerebrovascular events, and

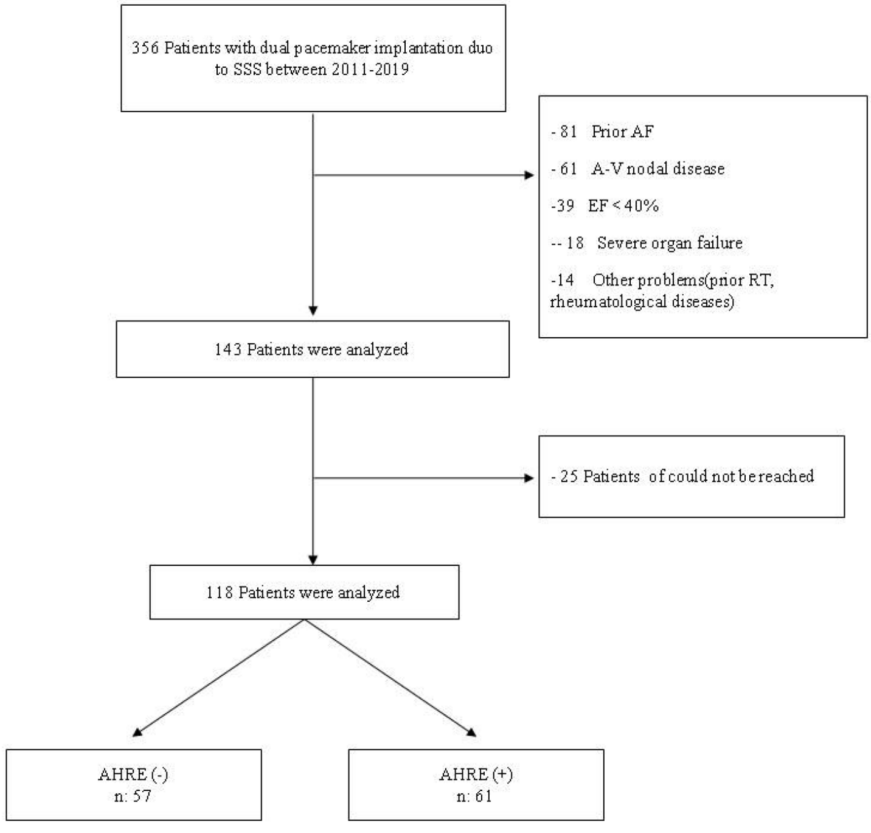


Figure 1. Trial flow diagram
AHRE: Atrial high rate episodes, AF: Atrial fibrillation, EF: Ejection fraction, SSS: Sick sinus syndrome

pacemaker-related complications. The information related to the primary endpoints was obtained from the hospital database and patient visits.

Statistical Analysis

The SPSS version 21.0 (SPSS Inc., Chicago, Illinois) packet program was used for analysis. Normal distribution analysis of the data was performed by analytical methods such as the Kolmogorov-Smirnov and Shapiro-Wilks tests. Continuous variables were presented as means followed by standard deviation, and categorical variables as frequency and percentage. Continuous variables between the AHRE (+) and AHRE (-) groups were compared using Student's t-tests for normally distributed data and the Mann-Whitney U test for abnormally distributed data. Categorical parameters were evaluated by Pearson's chi-square test. A model of AHRE predictors was devised using Cox proportional multivariable analysis. A p-value <0.05 (2 tailed) was considered statistically significant.

Results

Clinical and Demographical Features and Laboratory Parameters

An AHRE was developed in 51.7% of the study group during a mean follow-up time of 49.4±8 months. The mean age of the patients was 57.9±16 years. In addition, 54.2% of the patients were female. The mean age of the AHRE+ group was significantly higher (p=0.03). From the initial echocardiographic parameters, left atrium (LA) and right ventricular end-diastolic (Rvd) diameters were significantly higher in the AHRE+ group (p<0.01 and p=0.04; respectively). Tricuspid annular plane systolic excursion (TAPSE) values were significantly lower in the AHRE+ group (p<0.01). In addition, alanine transaminase, leukocyte, total cholesterol, and low-density lipoprotein cholesterol levels were significantly lower in the AHRE+ group (p<0.01, p<0.01, p=0.02, p<0.01, respectively). According to the initial pacemaker and lead parameters, P-wave sensing values were significantly lower in the AHRE+ group (p=0.01). Atrial and ventricular pacing rates, lead impedances and atrial threshold levels were similar between the groups (p=0.64, p=0.52, p=0.44, p=0.31, respectively). Demographic and biochemical parameters of the groups were given in detail in Tables 1 and 2.

Clinical Outcomes

The rates of primary outcomes, such as death, myocardial infarction, cerebrovascular accident, and pacemaker-related complications, at a mean follow-up of 49.4±8 months were given in Table 3. Primary outcomes were significantly higher in the AHRE+ group (p<0.01).

Multivariable Analysis

Predictors of AHRE were determined by a cox-regression multivariable analysis model (Table 4). This model consisted of age, diabetes mellitus, LA, left ventricular end-diastolic diamater and Rvd, TAPSE, leukocyte and P-wave sensing values. LA diameter [hazard ratio (HR): 1.10, confidence interval (CI) 95% (1.04-1.18), p<0.01] and P-wave sensing value [HR: 0.74, CI 95% (0.57-0.95), p=0.02] were determined as independent predictors for the development of AHRE.

Discussion

Our results demonstrated that initial LA and RVd diameters were significantly higher in the AHRE+ group. Initial P-wave sensing values were lower in the positive AHRE group, but there was no significant difference in atrial and ventricular pacing rates. In addition, LA diameter and P wave sensing values were defined as independent predictors of AHRE development.

SSS is a clinical condition that mostly occurs at advanced ages (2). Degeneration caused by increased fibrosis as a result of ischemia, collagen and fat deposition in the sinoatrial node is the most common cause of SSS (1,12,13). Likewise, similar changes are expected to occur in the atrium. It has been reported that these changes cause deterioration of electrical homogeneity and prolongation of conduction times in the atrium that may lead to atrial arrhythmias (14-17). Also, increased fibrosis in the atrial tissue may also decrease the electrical activity of the atrium. The hypothesis that initial P-wave sensing values obtained from the atrial lead in sinus rhythm may be predictive of AHRE, especially in patients with permanent pacemakers, formed the basis of our study. In a cohort study of patients with low EF and an ICD, low atrial sensing values were associated with atrial arrhythmias. It has been documented that initial atrial sensing values below 1.5 mV are a strong predictor of AHRE (5). Nielsen et al. (4) showed that an initial long P-Q interval predicts atrial arrhythmias in patients with DDDR pacemakers implanted due to HSS. In addition, they found lower atrial sensing values in patients with AF. The main difference between this study and ours was the inclusion of patients with AF. Healey et al. (18) reported that LA diameter and LA volume were defined as the predictors of AHRE. Similarly, Mathen and Chase (19) and Wu et al. (20) demonstrated that LA diameter was higher in the AHRE+ group and LA diameter was found as an independent predictor of AHRE. Unlike in these studies, in a study conducted with 109 patients with permanent DDDR pacemakers implanted for SSS, there was no relationship between P-wave interval and P-wave dispersion and atrial arrhythmias (21). Conversely, some studies demonstrated that prolonged

Table 1. Baseline demographic characteristics of study groups			
	AHRE (-) (n=57)	**AHRE (+) (n=61)**	**p-value**
Age (years)	54.9±15	60.8±17	**0.025**[b]
Female, n (%)	33 (57.9%)	31 (50.8%)	0.441
Hypertension, n (%)	24 (42.1%)	31 (50.8%)	0.343
Diabetes mellitus, n (%)	13 (22.8%)	13 (21.3%)	0.850
Hyperlipidemia, n (%)	12 (21.1%)	12(19.7%)	0.852
Active smoking, n (%)	23 (40.4%)	31 (50.8%)	0.254
Previous MI, n (%)	5 (8.8%)	5 (8.2%)	0.911
Previous CABG, n (%)	7 (12.3%)	5 (8.2%)	0.463
BB, n (%)	17 (29.8%)	23 (37.7%)	0.366
CCB, n (%)	6 (10.5%)	10 (16.4%)	0.352
Amiodarone, n (%)	0	4 (6.6%)	*
Propafenon, n (%)	10 (17.5%)	15 (24.6%)	0.349
Statin, n (%)	15 (26.3%)	18 (29.5%)	0.699
LVEF %	59.3±2	59.6±2	0.450
LA (mm)	35.6±6	39.9±5	**<0.001**[c]
LVd (mm)	47.6±5	48.5±5	0.256
RVd (mm)	22.8±3	23.6±2	**0.044**[c]
IVS (mm)	9.8±1	10.3±1	0.116
TAPSE (mm)	23.7±3	22.1±3	**0.002**[c]
Initial lead measurements			
P-wave sensing (mV)	3.07±1.4	2.40±1.1	**0.016**[c]
Atrial threshold (V)	0.8±0.2	0.8±0.3	0.310
Atrial impedance (ohm)	627.6±176	594.3±139	0.489
Total AP, %	69.4±23	63.3±29	0.635
Total VP, %[a]	8 (1-99)	10 (1-100)	0.519
Follow-up time (month)	49.8±8	48.9±8	0.648

[a]: Median (min-max), [b]:Mann-Whitney U test, [c]: Student's t-test
The mean age and LA diameter were considerably larger in the AHRE+ group, whereas the TAPSE and P wave sensing values were significantly lower.
AP: Atrial pacing, BB: Beta blocker, CCB: Calcium channal blocker, CABG: Coronary artery bypass grafting, LA: Left atrium, LVd: Left ventricular diastolic diamater, RVd: Right ventricular diastolic diameter, IVS: Interventricular septum thickness, TAPSE: Tricuspid annular plane systolic excursion, LVEF: Left ventricular ejection fraction, MI: Myocardial infarction, VP: Ventricular pacing, AHRE: Atrial high rate episode

P-wave duration before pacemaker implantation was an independent predictor of worsening atrial fibrillation burden after pacemaker implantation (22,23).

Likewise, LA diameter was higher in the AHRE+ group, and it was found to be an independent predictor of AHRE. In addition, atrial lead sensing values in initial sinus rhythm were found to be predictive of AHRE in patients with DDDR pacemaker implanted due to SSS. No other study regarding this subject was encountered in the literature. In this respect, we believe that our study may contribute to the source data.

Study Limitations

There were some limitations to be reported in our study. First of all, it was a single-center, retrospective study, and the number of patients was relatively low. Secondly, because of the retrospective nature of the study, we could not obtain the initial electrocardiograms. Despite these limitations, evaluation of the lead positions and pacemaker controls by two independent physicians, and obtaining records from cardiac devices, thereby providing subclinical atrial arrhythmias detection, were the superior aspects of our study.

Conclusion

Our results showed that higher initial LA and RVd diameters were reported in patients with DDDR pacemakers implanted due to SSS and who developed AHRE during follow-up. Also, initial P-wave sensing values were lower in patients who developed AHRE. Baseline LA diameter and P-wave sensing values were found to be independent predictors of AHRE development. In conclusion, initial low P-wave sensing values may be considered as a risk factor

Table 2. Baseline biochemical characteristics of study			
	AHRE (-) (n=57)	**AHRE (+) (n=61)**	**p-value**
Glucose (mg/dL)	97.2±18	97.9±16	0.716
HbA1c (%)	5.8±1	5.9±1	0.240
Kreatinine (mg/dL)	0.8±0.2	0.9±0.2	0.392
ALT*	20 (7-89)	15 (5-33)	**0.003[a]**
Hemoglobin (mg/dL)	12.9±1.3	13.2±0.7	0.571
Leukocytes (/mm^3)	7629.8±2103	6681.9±1735	**0.009[b]**
Lymphocytes (/mm^3)	1989.5±1030	1898.4±597	0.771
Platelets (10^3/mm^3)	223.9±8	218.7±65	0.436
Total cholesterol (mg/dL)	196.3±41	181.3±35	**0.020[b]**
LDL cholesterol (mg/dL)	135.1±38	118.7±33	**0.006[b]**
HDL cholesterol (mg/dL)	50.5±13	52.2±14	0.509
Triglycerides (mg/dL)	125.1±39	112.9±52	0.068
CRP *	6 (1-28)	5 (1-48)	0.273

*Median (min-max), [a]:Mann-Whitney U Test, [b]: Student's t-test.
ALT, leukocyte, total cholesterol and LDL cholesterol levels were significantly lower in the AHRE+ group.
ALT: Alanine aminotransferase, CRP: C-reactive protein, HbA1c: Hemoglobin A1c, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, AHRE: Atrial high rate episode

Table 3. Clinical events at long-term follow-up			
	AHRE (-) (n=57)	**AHRE (+) (n=61)**	**p-value**
Death, n (%)	0	5 (8.2%)	*
MI, n (%)	0	0	*
CVA, n (%)	0	7 (11.5%)	*
PAC, n (%)	1 (1.8%)	0	*
All events	1 (1.8%)	12 (19.7%)	**0.002[a]**

[a]: Chi-square test.
Primary outcomes were significantly higher in the AHRE+ group.
CVA: Cerebrovascular accident, MI: Myocardial infarction, PAC: Pacemaker associated complication, AHRE: Atrial high rate episode

Table 4. Multivariable predictors of AHRE occurance			
	HR	**%95 CI**	**p-value**
Age	1.01	(0.99-1.03)	0.281
DM	0.85	(0.43-1.71)	0.652
LA	1.10	(1,04-1,18)	**0.003[a]**
LVd	0.94	(0.88-1,01)	0.059
RVd	1.05	(0.91-1.22)	0.504
TAPSE	0.95	(0.88-1.03)	0.217
WBC	0.99	(0.97-1.03)	0.107
P-wave sensing	0.74	(0.57-0.95)	**0.020[a]**

[a]: Cox proportional multivariable analysis.
Analysis Model: Omnibus Test Model-2 likelihood: 482,3; Chi-square 28,8; p<0,001.
LA diameter and P-wave sensing value were determined as independent predictors for development of AHRE.
CI: Confidence interval, DM: Diabetes mellitus, LA: Left atrium, LVd: Left ventricular end-diastolic diamater, RVd: Right ventricular end-diastolic diamater, TAPSE: Tricuspid annular plane systolic excursion, WBC: White blood cell, HR: Hazard ratio, AHRE: Atrial high rate episode

for AHRE development in patients with DDDR pacemakers implanted due to SSS. In this context, further prospective studies with a large number of patients are warranted.

Ethics

Ethics Committee Approval: The study was approved by the local ethics committee (Ethics Committee of Cardiology Institute of Istanbul University-Cerrahpasa 2.İ.Ü.E.50.0.05.00/4).

Informed Consent: All patients gave their written informed consent.

Authorship Contributions

Concept: S.A., Design: S.A., O.D., Data Collection or Processing: S.T., Analysis or Interpretation: O.D., Literature Research: S.A., I.U., Writing: S.A., B.B.K.

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

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

References

1. Wahls SA. Sick sinus syndrome. Am Fam Physician 1985;31:117-24.
2. Lamas GA, Lee K, Sweeney M, et al. The mode selection trial (MOST) in sinus node dysfunction: design, rationale, and baseline characteristics of the first 1000 patients. Am Heart J 2000;140:541-51.
3. Schwartzman D, Chang I, Michele JJ, Mirotznik MS, Foster KR. Electrical impedance properties of normal and chronically infarcted left ventricular myocardium. J Interv Card Electrophysiol 1999;3:213-24.

4. Nielsen JC, Thomsen PE, Højberg S, et al. Atrial fibrillation in patients with sick sinus syndrome: the association with PQ-interval and percentage of ventricular pacing. Europace 2012;14:682-9.
5. Zecchin M, Solimene F, D'Onofrio A, et al. Atrial signal amplitude predicts atrial high-rate episodes in implantable cardioverter defibrillator patients: Insights from a large database of remote monitoring transmissions. J Arrhythm 2020;36:353-62.
6. Li C, Ju W, Gu K, et al. Atrial involvement and progression of sinus node dysfunction in non-senile patients: evidences from electroanatomic mapping and long-term follow-up. J Interv Card Electrophysiol 2021;60:365-73.
7. Andersen HR, Nielsen JC, Thomsen PE, et al. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. Lancet 1997;350:1210-6.
8. McComb JM, Gribbin GM. Effect of pacing mode on morbidity and mortality: update of clinical pacing trials. Am J Cardiol 1999;83:211-3.
9. Yang PS, Kim D, Jang E, et al. Risk of sick sinus syndrome in patients diagnosed with atrial fibrillation: A population-based cohort. J Cardiovasc Electrophysiol 2021;32:2704-14.
10. AdanV, Crown LA. Diagnosis and treatment of sick sinus syndrome. Am Fam Physician 2003;67:1725-32.
11. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021;42:373-498.
12. Rodriguez RD, Schocken DD. Update on sick sinus syndrome, a cardiac disorder of aging. Geriatrics 1990;45:33-6.
13. Tierney LM, McPhee SJ, Papadakis MA. Heart conduction disturbances: sick sinus syndrome. In: Papadakis MA, Tierney LM, McPhee SJ, editors. Current medical diagnosis & treatment, 39th ed. New York, N.Y: Lange Medical Books/ McGraw-Hill; 2000. p. 412.
14. Brachmann J, Karolyi L, Kübler W. Atrial dispersion of refractoriness. J Cardiovasc Electrophysiol 1998;9(Suppl 8):35-9.
15. Liu Z, Hayano M, Hirata T, et al. Abnormalities of electrocardiographic P wave morphology and their relation to electrophysiological parameters of the atrium in patients with sick sinus syndrome. Pacing Clin Electrophysiol 1998;21:79-86.
16. Centurion OA, Isomoto S, Shimizu A, et al. Supernormal atrial conduction and its relation to atrial vulnerability and atrial fibrillation in patients with sick sinus syndrome and paroxysmal atrial fibrillation. Am Heart J 1994;128:88-95.
17. Centurion OA, Isomoto S, Fukatani M, et al. Relationship between atrial conduction defects and fractionated atrial endocardial electrograms in patients with sick sinus syndrome. Pacing Clin Electrophysiol 1993;16:2022-33.
18. Healey JS, Martin JL, Duncan A, et al. Pacemaker-detected atrial fibrillation inpatients with pacemakers: prevalence, predictors, and current use of oral anticoagulation. Can J Cardiol 2013;29:224-8.
19. Mathen PG, Chase D. Pacemaker detected prolonged atrial high rate episodes - Incidence, predictors and implications; a retrospective observational study. J Saudi Heart Assoc 2020;32:157-65.
20. Wu Z, Chen X, Ge J, Su Y. The risk factors of new-onset atrial fibrillation after pacemaker implantation. Herz 2021;46(Suppl 1):61-8.
21. Kristensen L, Nielsen JC, Mortensen PT, et al. Sinus and paced P wave duration and dispersion as predictors of atrial fibrillation after pacemaker implantation in patients with isolated sick sinus syndrome. Pacing Clin Electrophysiol 2004;27:606-14.
22. Murase Y, Imai H, Ogawa Y, et al. Usefulness of P-wave duration in patients with sick sinus syndrome as a predictor of atrial fibrillation. J Arrhythm 2021;37:1220-6.
23. Nishinarita R, Niwano S, Oikawa J, et al. Novel Predictor for New-Onset Atrial High-Rate Episode in Patients With a Dual-Chamber Pacemaker. Circ Rep 2021;3:497-503.

Original Article

DOI: 10.4274/haseki.galenos.2021.7578
Med Bull Haseki 2022;60:13-19

Monocyte/High Density Lipoprotein Ratio in Patients with Symptomatic Carotid Artery Stenosis and Its Relationship with Stenosis Degree

Fettah Eren*, Aydin Talip Yildogan**, Gozde Ongun***, Gokhan Ozdemir*, Serefnur Ozturk*

*Selcuk University Faculty of Medicine, Department of Neurology, Konya, Turkey

**Ersin Arslan Training and Research Hospital, Clinic of Neurology, Gaziantep, Turkey

***Mus State Hospital, Clinic of Neurology, Mus, Turkey

Abstract

Aim: Monocyte/high-density lipoprotein (HDL) ratio (MHR) is an inflammatory marker associated with vascular diseases. The aim of this study is to evaluate the MHR in patients with symptomatic carotid artery stenosis and to examine its relationship with the degree of stenosis.

Methods: The study was conducted as a case-control study, with data obtained from patients' files between January 2020 and May 2021. Ninety patients with symptomatic carotid stenosis and 40 healthy controls were included in the study. For vascular imaging, computed tomography angiography and/or digital subtraction angiography were used. Carotid artery stenosis was grouped according to North American Symptomatic Carotid Endarterectomy Trial criteria. Tests for monocyte and HDL cholesterol were performed, and the MHR was calcu-lated.

Results: There were 67 male and 23 female patients with a mean age of 65.10±12.26 years in the study. In 46 (51.1%) of the patients, there was 50% or more carotid artery stenosis. The HDL cholesterol level was lower, and the MHR was higher in the patient group (p=0.042, p=0.041, respectively). Monocyte and MHR levels were higher in patients with 50% or more carotid stenosis (p=0.04).

Conclusion: The MHR is a predictive biomarker for the degree of symptomatic stenosis in the carotid artery.

Keywords: Ischemic attack, carotid stenosis, monocyte/HDL ratio, monocytes, cholesterol

Introduction

An acute ischemic stroke describes a focal or global cerebral injury that develops suddenly and has no apparent cause other than vascular. Ischemia is the most common etiological cause of strokes, and carotid artery disease is the cause in approximately one-third of them. It occurs especially with atherosclerosis (1-3). There is evidence that the inflammatory process associated with atherosclerosis and vascular stenosis is important in the development and prognosis of ischemic stroke (4).

Macrophages and monocytes have critical roles in the release of proinflammatory cytokines and the modulation of inflammation (5,6). Activated monocytes play a role in the etiology of cardiovascular diseases by modulating inflammatory cytokines (7). High-density lipoprotein (HDL) tries to prevent the occurrence of endothelial damage. It does this by inhibiting the oxidation of low-density lipoprotein (LDL). HDL cholesterol exerts its anti-inflammatory effect in this way (8). The monocyte/HDL cholesterol ratio (MHR) is an indicator of atherogenic and antiatherogenic balance, and its higher level is associated with the degree of atherosclerosis. Recent studies show that MHR may be a new predictive factor in predicting cardiovascular disease prognosis (9,10). There are quite a few studies in the literature evaluating the role of MHR in the process or prognosis of ischemic stroke, but there is no study to evaluate the relationship between symptomatic carotid stenosis and MHR (11).

Address for Correspondence: Fettah Eren
Selcuk University Faculty of Medicine, Department of Neurology, Konya, Turkey
Phone: +90 505 860 41 46 E-mail: dreren42@hotmail.com ORCID: orcid.org/0000-0001-6834-0827
Received: 25.06.2021 **Accepted:** 20.11.2021

This study aims to evaluate MHR in patients with symptomatic carotid artery stenosis and to reveal its relationship with the degree of stenosis.

Methods

Ethical Approval and Field of Study

Ischemic stroke patients hospitalized in the neurology clinic were included in the study, which was planned as a case-control and retrospective study. The data were obtained with patients file from January 2020 to May 2021. Since this study was retrospective, an informed consent form was not required. Prior to the study, approval was obtained from the local ethics committee of Selcuk University (date: 21.04.2021, decision number: 2021/221). The study process adhered to the Helsinki Declaration and good clinical practice guidelines.

Participants

A total of 800 ischemic stroke patients were evaluated. Patients with temporary or permanent carotid region stroke symptoms within the last 6 months were evaluated. Ninety stroke patients and 40 control patients who were found to have stenosis in the carotid location consistent with the present symptom on vascular imaging were included in the study. Age, gender and chronic diseases [hypertension, diabetes mellitus (DM)] were evaluated. Patients were grouped as under 65 years old, 66-79 years old and over 80 years old. The control patients included in the study were healthy individuals of similar age and gender as the patient group. In addition, these patients did not have the exclusion criteria and stroke history. The study design and exclusion criteria were determined (Figure 1). It was thought that these factors might change monocytes and HDL cholesterol levels. They were pregnancy, active systemic infection, hematological disease and antihyperlipidemic treatment history. Patients with other stroke risk factors were excluded. They were vertebrobasilar and intracranial stenosis, mechanical prosthetic valve, severe mitral stenosis, atrial fibrillation, intracardiac thrombus, endocarditis, dilated cardiomyopathy and atrial myxoma.

Brain Computed Tomography Angiography

CTA was used to determine the degree and location of carotid artery stenosis and was performed with 64

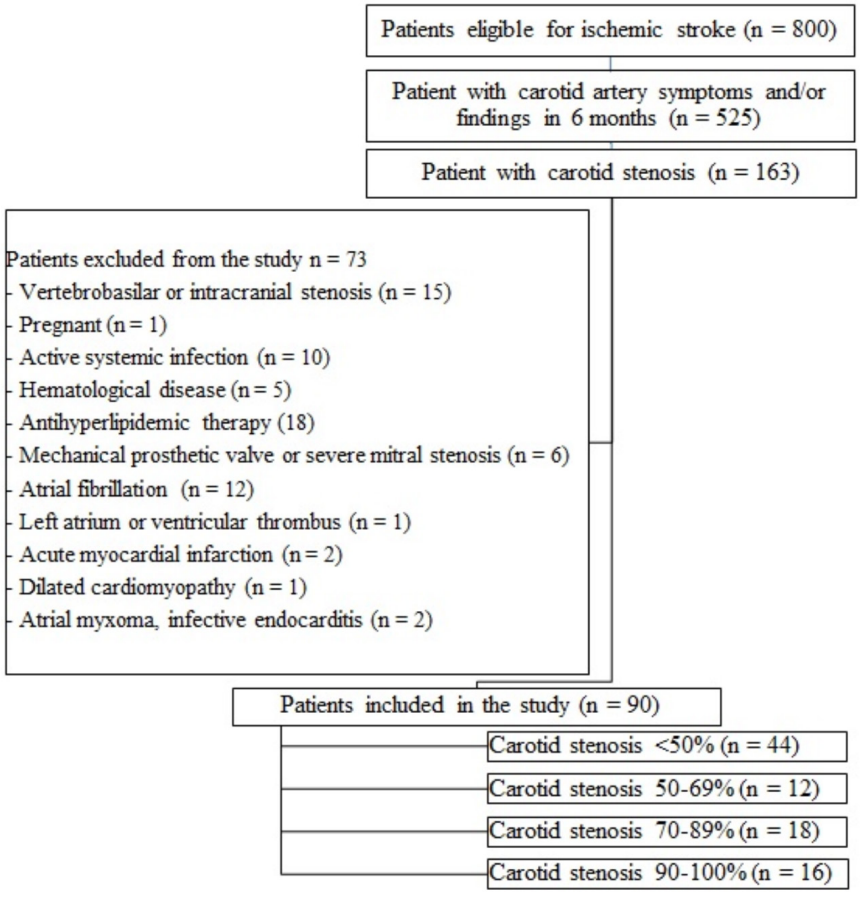


Figure 1. Study design and exclusion criteria

MDCT (Toshiba, Japan). The arcus aorta and the sphenoid wing are scanned in the upper section. The scanning area is determined, and the recording is made by giving contrast material via the venous route. Various programs and reconstructions were obtained by volume rendering techniques. Calcifications and stenosis degrees are determined with various window settings.

Digital Subtraction Angiography

Digital subtraction angiography (DSA) was used in addition to computed tomography angiography in patients whose stenosis degree and localization in the carotid artery could not be determined decisively. The Axiom Artis FA (Siemens, Germany) brand device was used for DSA and the femoral artery was utilized for intervention. Sheaths were placed in sizes varying between 6F-8F. Aortography was performed first with a 6F pigtail from the aortic arch. In cases where both carotid arteries (AP and lateral) were required, images were taken obliquely. Non-ionic contrast material was used to obtain the images.

Evaluation of Images

The stenosis degrees of the patients included in the study were determined by tomography angiography and/or DSA. The degree of carotid artery stenosis was calculated according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. The degree of stenosis was calculated using the formula: (1-narrowest segment/distal normal segment) x 100 (12,13). According to the NASCET, the results were divided into 4 groups: less than 50%, 50-69, 70-89, and 90 and above. The localization of carotid artery stenosis was determined (right and/or left).

Blood Test Parameters

Monocyte and HDL levels were detected at any time point within six months after stroke symptoms. The MHR was calculated with these levels. Blood samples were taken on hospitalization, in the morning hours after fasting for at least 8 hours. Serum was taken into gel tubes with a separator and blood samples were taken into tubes with potassium-ethylenediaminetetraacetic acid. The samples obtained (5000 rpm) were centrifuged and sera were separated. HDL cholesterol spectrophotometry, the parameter used in the study, was measured using hemogram (monocyte) fluorescence flow cytometry and was calculated using the formula MHR=Monocyte (K/uL)/ HDL cholesterol (mg/dL) x 1000.

Statistical Analysis

SPSS 16.0 Package Software (Statistical Package for the Social Sciences Inc.; Armonk, NY, USA) was used to analyze the collected data. Normality analysis was performed using the Kolmogorov-Smirnov test. The demographic data obtained were expressed as a number, percentage, mean standard deviation, or median (minimum-maximum) based on the results of the normality analysis. Normally distributed data was compared with the Student's t-test. Data that was not normally distributed was analyzed using the Kruskal-Wallis test. Post-hoc analysis was performed using the Mann-Whitney U test and Bonferroni correction. The chi-square, or Fisher's exact test, was used to compare categorical data. The MHR cut-off points were calculated according to the receiver operating characteristic (ROC) curve. The cut-off point was determined according to the sensitivity and specificity values. The area under the curve (AUC) was calculated with confidence intervals (CI). The relationship between the numerical data was evaluated using Spearman's correlation test. A logistic regression analysis was used to predict the factors affecting carotid artery stenosis. The results were considered significant at $p<0.05$ with a 95% CI.

Results

In the study, there were 90 carotid artery stenosis patients with a mean age of 65.10±12.26 (38-86) years and 40 healthy volunteers with a mean age of 64.03±9.481 (50-78) years. Twenty-three (25.6%) of the patients with carotid stenosis were female and 67 (74.4%) were male. Patients and healthy controls were comparable in terms of age and gender (p=0.098). The patients had lower HDL cholesterol levels (p=0.042) and higher MHR levels (p=0.041) compared with the control group. Clinical and laboratory parameters in patients with symptomatic carotid artery stenosis and the control group are summarized in (Table 1).

There was no difference in monocyte, HDL cholesterol, and MHR levels between the age groups (under 65 years old, 66-79 years old and over 80 years old) (p=0.33, p=0.60, and p=0.39, respectively). When the patients were grouped according to their gender, it was found that there was no difference in the levels of monocyte, HDL cholesterol and MHR (p=0.05, p=0.39, and p=0.06, respectively). No relationship was found between the presence of hypertension or DM and the level of monocytes, HDL cholesterol, and MHR. There was no correlation between stenosis localization (right or left) and serum MHR level. When the degree of stenosis was examined by dividing into 4 groups (less than 50%, 50-69%, 70-89%, 90% and above), no difference was found between the groups in terms of monocyte, HDL cholesterol and MHR levels. However, when the groups were divided into 2 groups (50% and more, 50% below), the monocyte and MHR levels were significantly higher in patients with 50% and more stenosis (p=0.04) (Table 2). The monocyte cut-off level was calculated as 0.5285 with 68% sensitivity

Table 1. Clinical and laboratory parameters in patients with symptomatic carotid artery stenosis and control group			
	Patient group (n=90)	**Healthy individuals (n=40)**	**p-value**
Age (years), mean ± SD	65.10±12.26	64.03±9.48	0.065
Female, n (%) **Male, n (%)**	23 (25.6) 67 (74.4)	16 (40.0) 24 (60.0)	0.098
Hypertension, n (%)	58 (64.4)	3 (7.5)	0.001*
Diabetes mellitus, n (%)	34 (37.8)	5 (12.5)	0.004*
Monocyte (K/uL), median (minimum - maximum)	0.595 (0.01-1.23)	0.490 (0.20-1.32)	0.069
HDL (mg/dL), median (minimum - maximum)	36.50 (17.00-65.00)	39.500 (21.0-66.0)	0.042**
MHR, median (minimum - maximum)	15.48 (0.36-41.38)	12.24 (3.57-38.93)	0.041**
Stenosis localization **Right, n (%)** **Left, n (%)**	 26 (57.8) 18 (21.1)	 - -	 - -
Stenosis degree, n (%) **0-50%** **50-69%** **70-89%** **90-100%**	 44 (48.9) 12 (13.3) 18 (20.0) 16 (17.8)	 - - - -	 - - - -
*/**: Statistical significant value, *: Fisher's exact test, **: Student's t-test SD: Standard deviation, n: Number, %: Percentage, HDL: High density lipoprotein, MHR: monocyte/low-density lipoprotein ratio			

and 55% specificity for stenosis above and below 50% (p=0.037, 95% CI: 0.511-0.745, AUC: 0.628) (Figure 2). The MHR cut-off level was calculated as 15.22 with 66% sensitivity and 58% specificity for stenosis above and below 50% (p=0.46, 95% CI: 0.503-0.741, AUC: 0.622) (Figure 3).

As a result of the Spearman correlation test, no correlation was found between the age of the patients and the monocyte, HDL cholesterol and MHR levels (p=0.188, p=0.910, p=0.191, r=0.140, r=-0.012, r=0.139). There was also no correlation between monocyte, HDL cholesterol and MHR levels with increased stenosis levels in stenosis above 50% (p=0.119, p=0.546, p=0.186, r=0.233, r=-0.091, r=0.186).

A logistic regression model was created with hypertension, DM, monocyte, HDL cholesterol and MHR level to predict 50% or more carotid stenosis. The model achieved a good fit (Hosmer-Lemeshow=0.382, Nagelkerke R^2=0.128). Monocyte had an effect on carotid artery stenosis. Carotid artery stenosis (50% or more) risk increased 2.8 times when monocytes increased by one unit (p=0.013).

Discussion

The first step in the development of atherosclerosis is endothelial dysfunction. Macrophages and monocytes have an important role in the development of this step and the progression of atherosclerosis. Monocytes lead to the progression of the inflammatory reaction, transforming into macrophages and then into foam cells with oxidized lipids (10). Foam cells that turn into fatty streaks contribute to local inflammation and the secretion of proinflammatory cytokines. Local tissue factors induce intravascular coagulation (14,15). The increase in monocytes and macrophages, which are the sources of foam cells and atherosclerosis, is a predictor of atherosclerosis and plaque formation (16-22). Monocytes

Table 2. Monocyte/high-density lipoprotein ratio in patients with symptomatic carotid artery stenosis. The data were presented as a median (minimum-maximum)		
	MHR-value	**p-value**
Age 18-65 (n=43) 66-79 (n=36) 80-92 (n=11)	 15.25 (2.11-32.63) 16.09 (4.29-39.68) 13.88 (0.36-41.38)	0.39
Male (n=67) Female (n=23)	16.0 (6.13-41.38) 13.95 (0.36-23.46)	0.06
Hypertension None (n=32) Yes (n=58)	 15.51 (6.13-32.63) 15.46 (0.36-41.38)	0.95
DM None (n=56) Yes (n=34)	 15.26 (0.36-41.38) 15.71 (4.29-39.68)	0.84
Localization Right (n=52) Left (n=38)	 15.93 (2.68-39.68) 15.21 (0.36-41.38)	0.34
Stenosis degree 0-50% (n=44) 50-69% (n=12) 70-89% (n=18) 90-100% (n=16)	 14.65 (0.36-32.63) 15.91 (9.50-39.68) 18.77 (10.67-23.46) 14.56 (10.26-23.46)	0.07
Stenosis degree 0-50% (n=44) 50-100% (n=46)	 14.65 (0.36-32.63) 16.03 (9.50-41.38)	0.04*
*: Statistical significant value, *: Mann-Whitney U test n: Number, %: Percent, MHR: Monocyte/low-density lipoprotein ratio, DM: Diabetes mellitus		

also have an important role in thrombus formation and the development of the ischemic area. Asymptomatic carotid artery stenosis and non-stenotic ischemic stroke have been linked to monocyte levels, degree of stenosis, stroke development, and prognosis (11,18,23). Our study is also built on this etiopathogenetic process. Monocyte levels in the patient group were similar to those in the control group. The monocyte/high-density lipoprotein ratio, which is considered to be a more sensitive marker, was significantly higher in the patient group. However, it may also be related to the higher frequency of comorbid diseases in the patient group. The monocyte serum level and MHR were higher in symptomatic 50% and more severe carotid artery stenosis. This suggests that the presence and degree of stenosis in stroke may be associated with inflammation.

Many studies have shown that HDL cholesterol has anti-inflammatory, antithrombotic, and antioxidant effects (9,10). HDL cholesterol is classically known to have anti-atherogenic effects. It performs this function, especially through lipid-loaded macrophages. In this way, the transport of cholesterol to the artery wall is prevented. It also inhibits the signaling of HDL cholesterol adhesion molecules. Thus, inflammatory cells, especially monocytes, are prevented from adhering to the vascular wall. It may also limit the inflammatory response through its direct effect on monocytes (9). Thanks to these mechanisms of action, HDL cholesterol has also been shown to be resistant to atrial myocyte cells (10,24). At the time of ischemia, HDL cholesterol tries to limit inflammation with its anti-inflammatory and antioxidant activity. However, monocytes try to shift the process towards inflammation with their pro-inflammatory properties. Many studies have shown that inflammation can negatively affect the process of ischemia and vascular stenosis (4,5,25). In our study, serum HDL cholesterol levels were lower in patients with carotid artery stenosis, supporting the anti-atherogenic effect of HDL cholesterol.

The monocyte/high-density lipoprotein ratio, a marker obtained by dividing the serum level of monocyte and HDL cholesterol, is an inflammatory indicator that was recently identified. Used more commonly for cardiovascular diseases initially, this marker was later shown to be associated with cerebrovascular disease and peripheral artery disease (9,11,26). In a recent study, Bolayir et al. (11) showed that acute ischemic stroke patients with high MHR on hospitalization had higher mortality rates within 30 days. In the same study, the results of the ROC curve analysis demonstrated that the value of 17.5 was the cut-off value for 30-day mortality (11). Yurtdaş et al. (17) have shown that MHR levels were higher in stenosis than 50% in asymptomatic carotid artery stenosis. In this study, the MHR cut-off point was determined as 11.0, with 75% sensitivity and 70% specificity based on 50% stenosis. In our study, the MHR level was significantly higher in patients with 50% and more symptomatic carotid stenosis. The MHR cut-off point was calculated as 15.22 with 66% sensitivity

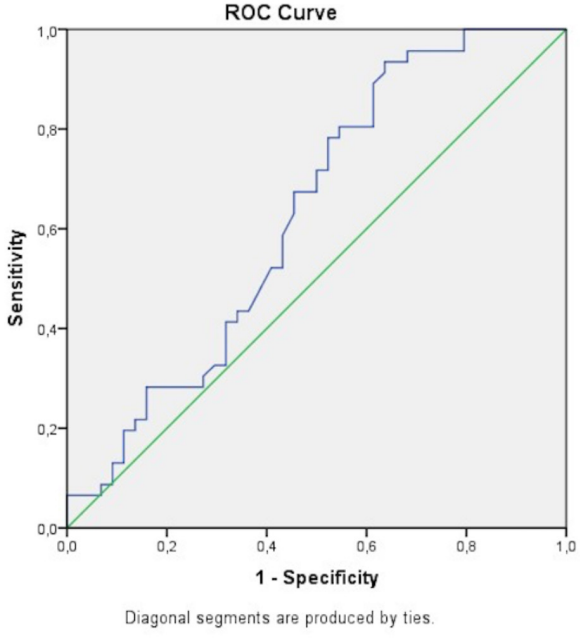


Figure 2. Monocyte: The receiver operating characteristic (ROC) curve analysis for carotid artery stenosis

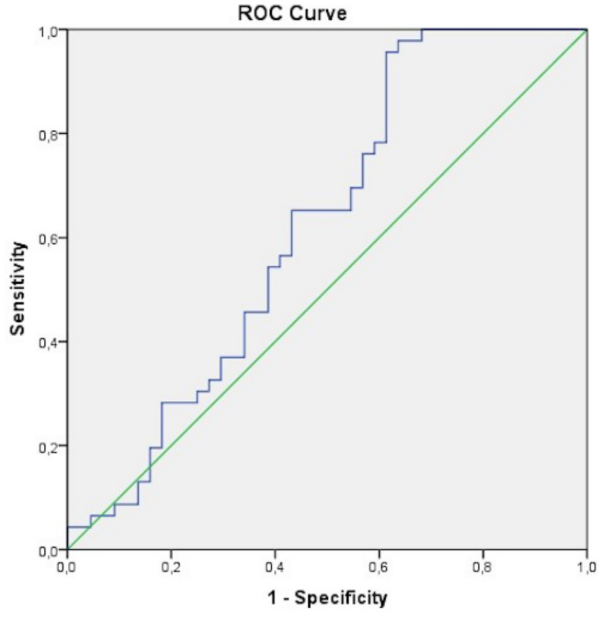


Figure 3. Monocyte/high-density lipoprotein (HDL) ratio (MHR): The receiver operating characteristic (ROC) curve analysis for carotid artery stenosis

and 58% specificity, demonstrating a relationship between the degree of stenosis and MHR level.

Study Limitations

This was a case-control and retrospective study with relatively few patients. The difference in the frequency of comorbid chronic diseases (such as hypertension and DM) between groups may affect the results. In addition, the relationship between MHR and symptom time has not been evaluated. Many factors affect monocyte and HDL cholesterol levels. Although diseases affecting these parameters were excluded, these parameters are also influenced by many local and/or systemic processes. Therefore, larger and multi-center studies are needed on this subject. Despite these limitations, to our knowledge, this is the first study to evaluate the MHR level in patients with symptomatic carotid artery stenosis. In addition, risk factors that may affect monocytes and HDL cholesterol levels were excluded from the study.

Conclusion

Previous studies have shown that monocyte and HDL cholesterol have direct and/or indirect effects on the vascular system, especially through inflammatory mechanisms. In our study, it was observed that HDL cholesterol and MHR levels were lower in patients with carotid artery stenosis. It was also demonstrated that monocyte and MHR levels were higher in patients with 50% or more symptomatic carotid stenosis. MHR is a predictive biomarker for the degree of symptomatic stenosis in the carotid artery.

Ethics

Ethics Committee Approval: Prior to the study, approval was obtained from the local ethics committee of Selcuk University (date: 21.04.2021, decision number: 2021/221).

Informed Consent: Since this study was retrospective, informed consent form did not required.

Authorship Contributions

Concept: F.E., A.T.Y., G.O., Gok.O., S.O., Design: F.E., A.T.Y., G.O., Data Collection and/or Processing: F.E., A.T.Y., G.O., Analysis and/or Interpretation: F.E., Gok.O., S.O., Literature Research: F.E., Gok.O., S.O., Writing: F.E., A.T.Y.

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

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

References

1. Dharmakidari S, Bhattacharya P, Chaturvedi S. Carotid artery stenosis: Medical therapy, surgery, and stenting. Curr Neurol Neurosci Rep 2017;17:77.
2. Orrapin S, Rerkasem K. Carotid endarterectomy for symptomatic carotid stenosis. Cochrane Database Syst Rev 2017;6:CD001081.
3. Meschia JF, Klaas JP, Brown RD Jr, Brott TG. Evaluation and management of atherosclerotic carotid stenosis. Mayo Clin Proc 2017;92:1144-57.
4. Taleb S. Inflammation in atherosclerosis. Arch Cardiovasc Dis 2016;109:708-15.
5. Hansson GK, Libby P, Schönbeck U, Yan ZQ. Innate and adaptive immunity in the pathogenesis of atherosclerosis. Circ Res 2002;91:281-91.
6. Kazmierski R, Guzik P, Ambrosius W, Ciesielska A, Moskal J, Kozubski W. Predictive value of white blood cell count on admission for in-hospital mortality in acute stroke patients. Clin Neurol Neurosurg 2004;107:38-43.
7. Olivares R, Ducimetière P, Claude JR. Monocyte count: a risk factor for coronary heart disease? Am J Epidemiol 1993;137:49-53.
8. Murphy AJ, Westerterp M, Yvan-Charvet L, Tall AR. Anti-atherogenic mechanisms of high density lipoprotein: effects on myeloid cells. Biochim Biophys Acta 2012;1821:513-21.
9. Yakar HI, Kanbay A. Could monocyte level/HDL cholesterol ratio predict cardiovascular diseases in patients with COPD? Niger J Clin Pract 2020;23:450-5.
10. Chen SA, Zhang MM, Zheng M, et al. The preablation monocyte/ high density lipoprotein ratio predicts the late recurrence of paroxysmal atrial fibrillation after radiofrequency ablation. BMC Cardiovasc Disord 2020;20:401.
11. Bolayir A, Gokce SF, Cigdem B, et al. Monocyte/high-density lipoprotein ratio predicts the mortality in ischemic stroke patients. Neurol Neurochir Pol 2018;52:150-5.
12. Dix JE, McNulty BJ, Kallmes DF. Frequency and significance of a small distal ICA in carotid artery stenosis. AJNR Am J Neuroradiol 1998;19:1215-8.
13. Wilterdink JL, Feldmann E. Carotid stenosis. A neurologist's perspective. Neuroimaging Clin N Am 1996;6:831-41.
14. Steinberg D, Witztum JL. Is the oxidative modification hypothesis relevant to human atherosclerosis? Do the antioxidant trials conducted to date refute the hypothesis? Circulation 2002;105:2107-11.
15. Moreno PR, Purushothaman KR, Fuster V, O'Connor WN. Intimomedial interface damage and adventitial inflammation is increased beneath disrupted atherosclerosis in the aorta: implications for plaque vulnerability. Circulation 2002;105:2504-11.
16. Ma Y, Mouton AJ, Lindsey ML. Cardiac macrophage biology in the steady-state heart, the aging heart, and following myocardial infarction. Transl Res 2018;191:15-28.
17. Yurtdaş M, Yaylali YT, Özdemir M. The role of monocyte to HDL ratio in predicting clinically significant carotid stenosis in patients with asymptomatic carotid artery disease. Rev Assoc Med Bras 2020;66:1043-8.

18. Jin R, Yang G, Li G. Inflammatory mechanisms in ischemic stroke: role of inflammatory cells. J Leukoc Biol 2010;87:779-89.

19. Riksen NP, Netea MG. Immunometabolic control of trained immunity. Mol Aspects Med 2021;77:100897.

20. V M, Raveesha. Relation between Monocyte/High dansity lipoprotein(HDL) ratio in acute ischemic stroke severity. J Assoc Physicians India 2020;68:67.

21. Oh SW, Yi HJ, Lee DH, Sung JH. Prognostic significance of various inflammation-based scores in patients with mechanical thrombectomy for acute ischemic stroke. World Neurosurg 2020;141:710-7.

22. Fotakis P, Kothari V, Thomas DG, et al. Anti-inflammatory effects of HDL (High-Density Lipoprotein) in macrophages predominate over proinflammatory effects in atherosclerotic plaques. Arterioscler Thromb Vasc Biol 2019;39:253-72.

23. Schumski A, Ortega-Gómez A, Wichapong K, et al. Endotoxinemia accelerates atherosclerosis through electrostatic charge-mediated monocyte adhesion. Circulation 2021;143:254-66.

24. Bonacina F, Pirillo A, Catapano AL, Norata GD. HDL in immune-inflammatory responses: Implications beyond cardiovascular diseases. Cells 2021;10:1061.

25. Libby P. Inflammation in atherosclerosis-no longer a theory. Clin Chem 2021;67:131-42.

26. Ceyhun G, Engin MÇ. The monocyte/high density lipoprotein cholesterol ratio (MHR) as an indicator of the need for amputation in patients with peripheral artery disease developing critical limb ischemia. Angiology 2021;72:268-73.

Original Article

DOI: 10.4274/haseki.galenos.2021.7771
Med Bull Haseki 2022;60:20-25

Comparison of the Urodynamic Patterns of the Disorders Frequently Encountered in the Field of Pediatric Urology

Hasan Demirkan*, Mehmet Ozgur Kuzdan**

*University of Health Sciences Turkey, Kanuni Sultan Suleyman Training and Research Hospital, Clinic of Pediatric Urology, Istanbul, Turkey

**University of Health Sciences Turkey, Kanuni Sultan Suleyman Training and Research Hospital, Clinic of Pediatric Surgery, Istanbul, Turkey

Abstract

Aim: There is still a lack of sufficient evidence-based data on the standardized urodynamic patterns of urological disorders worldwide, particularly in the childhood age group. With this study, we sought to investigate the outcomes of urodynamic studies of common disorders frequently encountered in pediatric urology practice.

Methods: Children who underwent urodynamic studies in a pediatric urology unit between March 2019 and September 2020 were included in the study. A retrospective review of data on demographic characteristics and cystometrogram findings of 266 children from the urodynamic laboratory database was performed.

Results: The diagnoses of the patients were vesicoureteral reflux (VUR) (n=120), spinal dysraphism (SD) (n=94) and day-time incontinence (DI) (n=28). Twenty-four patients who had other than these diagnoses were excluded. While there was no statistically significant difference between VUR-DI cases (p=0.31) and DI-SD cases (p=0.1) regarding bladder compliance, it was noteworthy that bladder compliance was diminished in the SD group when compared to the VUR group (p<0.001). The presence of idiopathic detrusor contraction (IDC) suggesting overactive bladder was also compared and no significant difference was found between the groups (p=0.084).

Conclusion: The results of our study contribute the literature for urodynamic manifestations that are still challenging to standardize in children with urologic disorders because of the variety of outcome measures and multitude of urodynamic parameters used. We also announce that the IDC is a noteworthy pattern of neurogenic as well as non-neurogenic urological disorders.

Keywords: Incontinence, spinal dysraphism, urodynamics, vesicoureteral reflux

Introduction

Urodynamic or video-urodynamic studies are widely used technical contrivances for monitoring voiding dysfunction in children with lower urinary tract (LUT) symptoms (1,2). The standard urodynamic test consists of four main parts: the uroflow test, cystometrogram, electromyelogram, and voiding pressure study (3). They all at once assist in identifying the underlying urological condition in cases with LUT symptoms by making precise and objective measurements for muscle/nerve function, pressure in/around the vesica, urinary flow rates, and several other parameters (4). The recent Cochrane analysis, including seven trials, has argued that the management of children with LUT symptoms according to urodynamic investigations leads to better clinical outcomes compared to treatment based on history and physical examination (1). Subsequently, in 2015, the International Children's Continence Society (ICCS) established a standardization report on urodynamic studies of LUT in children (5). It aimed to create a uniform guideline on the measurement and documentation of urodynamic investigations in children. According to

Address for Correspondence: Hasan Demirkan
University of Health Sciences Turkey, Kanuni Sultan Suleyman Training and Research Hospital, Clinic of Pediatric Urology, Istanbul, Turkey
Phone: +90 533 422 17 29 E-mail: drhdemirkan@gmail.com ORCID: orcid.org/0000-0002-8930-6692
Received: 16.09.2021 **Accepted:** 21.11.2021

the report, invasive urodynamic studies are indicated in cases of non-invasive investigation suggests obstruction, genitourinary abnormalities, neuropathic detrusor-sphincter dysfunction, profound non-neuropathic detrusor-sphincter dysfunction [children with high-grade vesicoureteral reflux (VUR) and recurrent febrile urinary tract infection], or prominent post-voiding residue of undefined cause (5,6).

To date, various studies have been carried out by clinicians to establish reference values for urodynamic parameters in children of various age groups (7,8). However, the small number of studies, the fact that they were mostly conducted in healthy groups, and the wide age range of the participants prevent the generalization of the obtained reference values to the whole population (9). This difficulty is also due to the diversity of measurement methods in each laboratory, and hence the difficulties in standardizing and creating a universal nomogram of urodynamic outcomes. Therefore, data on the distribution of urodynamic patterns in children is still insufficient and further research is needed (3,6,10).

Invasive urodynamic studies are frequently preferred in children with LUT dysfunction depending on VUR, day-time incontinence (DI), spinal dysraphism (SD), or posterior urethral valve. Therefore, we aimed to investigate the distribution of urodynamic patterns of the three diseases that are the most common indications for urodynamic studies in pediatric urology practice.

Methods

Study Design and Ethical Consideration

Following local institutional review board approval (from University of Health Sciences Turkey, Kanuni Sultan Suleyman Training and Research Hospital local ethical committee, with a number of 2020.11.205 and the date of 16/11/2020), a total of 266 children under 18 years of age who underwent urodynamic study in a pediatric urology clinic from March 2019 to September 2020 were enrolled in the study. Written informed consent was obtained from all subjects and their parents or guardians. The age, gender and diagnosis were recorded from hospital automation system. Analyses of the urodynamic patterns of patients with DI, VUR, or SD were performed retrospectively using the urodynamic laboratory database. Patients who had to receive any medication at the time of the study and refused to participate in the study were excluded. Even if any patient had to take a drug that could affect the outcome of the study, the drug was interrupted at least one week before the examination if it did not harm the patient. Before the procedure, urine culture negativity was verified.

Diagnosis of Primary Diseases

Diagnosis of primary VUR was established by voiding cystourethrography, and the severity of VUR was determined using the International Reflux Study Classification (11). Patients with secondary VUR were excluded.

The diagnosis of SD was made in the newborn period and the patients with SD underwent reconstructive surgery for the defect.

According to a report by ISSC on the standardization of terminology for LUT function, DI was defined as the leakage of urine in discrete amounts while awake intermittently (12). Patients with DI had no organic disease in their medical history.

Urodynamic Procedure

Urodynamic examinations were performed in the urodynamics laboratory by a nurse, and the results were interpreted by a pediatric urologist. A supine position on a urological table was used for each subject. The patients were monitored during the procedure. The bladders of patients were emptied by a 6 Fr, 2 lumen catheter that was placed in the urethra. Thereafter, the bladder was filled continuously at a filling rate of 10% of the expected bladder capacity with room temperature sterile saline. The expected bladder capacity was estimated according to the following formula: (age+1) x 30 (5). The procedure was stopped if the patient needed to void, the presence of significant urine leakage, or 40 cm H_2O of intravesical pressure was detected. The residual urine volume of more than 20 mL at the end of the voiding phase marked the emptying disorder. The detrusor type and compliance, voided urine volume, expected bladder capacity for children, maximum value of cystometric capacity, and residual urine volume in the bladder were analyzed. Detrusor activity was characterized as normoactive, overactive, or underactive (13). Hypocompliance of the detrusor muscle was evaluated quantitively. The outcomes in the filling and voiding phases identified the storage and emptying disorders. Uroflow was performed after the procedure. Consequently, electromyography activities during micturition were measured. Urodynamic investigations were performed by a licensed urodynamic measurement system (Aymed-Locum Wireless Urodynamics System).

Statistical Analysis

Urodynamic test results were evaluated and compared based on age, gender, and etiologies. The SPSS software Version 22.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Among the descriptive statistics, mean ± standard deviation was used for normally distributed variables, median [interquartile range (IQR)] was used for non-normally distributed variables, and percentage

(%) was used for categorical variables. For non-normally distributed values, non-parametric tests were used to compare the groups. T-test for independent samples was used in the comparison of descriptive statistics, the chi-square test or Fischer's exact test was used in the comparison of categorical parameters, and ANOVA was used to compare the means among three or more groups, Post-hoc evaluations were made with the Games-Howell test. P<0.05 was considered statistically significant.

Results

There were 104 (39.1%) boys and 162 (60.9%) girls among the 266 patients who underwent urodynamic testing. Among the group; 120 (45.1%) patients had VUR, 28 (10.5%) had DI, 94 (35.3%) had SD, and 24 (9%) had other disorders. The mean age of the patients was 7.69±3.86 years. Demographic features and the comparisons of the urodynamic findings of the patients with VUR, DI, and SD are summarized in Table 1.

A comparison of median maximum cystometric capacities revealed that while there was no significant difference between VUR and DI patients (p=0.31), patients with SD had a lower maximum cystometric capacity than VUR and DI cases (p<0.001, p=0.031, respectively).

While mean bladder compliance was lower in the SD group than in the VUR group (p<0.001), there was no statistically significant difference between VUR-DI cases (p=0.31) and DI-SD cases (p=0.1).

Residual urine volume comparison revealed that significant residue was present in patients with SD compared with those patients with VUR or DI (p<0.001). However, cases with VUR and DI showed no statistically significant difference regarding residual urine volume (p=0.03).

The presence of idiopathic detrusor contraction (IDC) suggesting overactive bladder (OAB) was also compared and there was no significant difference between the groups (VUR-DI: p=0.089; VUR-SD: p=0.095; SD-DI: p=0.66).

The mean maximum detrusor pressure was significantly higher in children with SD than in children with DI and VUR (p<0.001). It did not, however, show a difference in subjects with VUR and DI (p=0.35).

Voiding patterns of the study group are summarized in Figure 1. The flow patterns identified in those diagnosed with SD were no micturition in 59 (62.7%) patients, staccato in two (2.1%), interrupted in 14 (14.8%), plato in 14 (14.8%), and bell-shaped in five (5.3%).

Discussion

Urodynamic studies are invaluable diagnostic modalities widely used in the fields of urology and pediatric urology (14). In the last quarter century, urodynamic testing has been preferred increasingly in children to reveal the underlying causes of LUT symptoms and for accurate and effective management of several urinary tract abnormalities resistant to therapy (15). Therewithal, uniform and standardized patterns of urodynamic results based on real-life data couldn't be established previously, as well as for ultrasonography or voiding cystourethrography. This study aimed to describe and compare the urodynamic parameters of the three most common pediatric urologic disorders.

OAB is defined as urgency and increased daytime frequency of micturition with or without urinary incontinence according to the definition of the ICCS (12). As an abnormality in urodynamics, OAB is characterized by IDC during the filling phase of the micturition cycle, which can be spontaneously or provoked (16). In a study by Xing et al. (17), an investigation of the prevalence of OAB in Chinese children was reported as 9.01 % (913/10 133). In a review by Franco (18,19), they revealed that OAB is a common problem affecting up to 12% of children. In our study, 42.1% of the group had IDC suggesting

Table 1. Demographics and urodynamic patterns of the patients

	VUR	DI	SD	p-value
Patient number (n)	120	28	94	
Age (years), median (minimum-maximum)	8 (1-16)	7 (4-17)	7 (1-19)	0.53
Gender, n (%) Male/female	38 (31.7%)/82 (68.3%)	12 (42.9%)/16 (57.1%)	43 (45.7%)/51 (54.3%)	0.096
Mean expected bladder storage capacity (%)	90.8	81.6	74.1	
Mean bladder compliance (mL/cm H_2O)	18.1±11.7	14.9±12.6	10.8±11.1	0.001*,a
Residual urine volume (mL), IQR (minimum-maximum)	40 (0-400)	30 (0-330)	115 (0-500)	<0.001*,b
Presence of idiopathic detrusor contraction (n)	46 (38.3%)	16 (57%)	50 (53.1%)	0.084
Mean maximum detrusor pressure (cm H_20)	17±11.4	14.7±12.8	48.6±31.8	<0.001*,c

*One-Way ANOVA test was used for comparison, post-hoc evaluations were made with the Games-Howell test.
[a]: SD<VUR; [b]: SD>VUR, DI; [c]: SD>VUR, DI
VUR: Vesicoureteral reflux, DI: Daily incontinence, SD: Spinal dysrpahism, IQR: interquartile range

OAB in accordance with symptoms. This inconsistency was attributed to the fact that the study was conducted on a patient group having an organic pathology. In a recent cross-sectional study from China, 232 children with urotherapy-resistant OAB were evaluated to assess the relationship between urodynamic study findings and urotherapy treatment response. Ultimately, it was shown that decreased cystometry bladder capacity in urodynamic investigation may suggest a poorer treatment response to urotherapy than in patients with normal bladder capacity, although urodynamic verification of overactivity is not a prerequisite for response to urotherapy treatment (20). Among the pathological findings in urodynamics, OAB evaluation is an important finding that should be investigated in many diseases and in healthy children.

In 2011, researchers from Bambino Gesu` Children's Hospital of Rome suggested that urodynamic evaluation may be beneficial in the management of children with VUR by identifying those with bladder dysfunction secondary to abnormal voiding habits (21). According to their data, detrusor hyperactivity was present in 10.8% of the whole group, whereas it was significantly higher in symptomatic patients (24%) than in the non-symptomatic group (6%) ($p<0.05$). In our study, despite comparing the patients with or without symptoms, we found IDC in 38.3 % of patients with VUR. This high rate was in roughly concordance with the rate of %44.7 that is in the study of Batinic et al. (22) comparing the grade of reflux and urodynamic findings of children with VUR. They revealed that children with lower VUR grades (I and II) had a higher percentage of pathological urodynamic findings than children with higher VUR grades (III and IV) (77.5 vs. 66.6%) (22). In our cohort, data on reflux grade was not obtained.

In a study conducted with 240 patients with DI, IDC was found in 12 patients who did not respond to treatment. Since the information about the pre-treatment urodynamic studies of these patients was not provided, information about the detrusor muscle activity of all the incontinent patients in the group is not available. In a study by Elmissiry et al. (4), IDC was reported in 45% of 56 pediatric patients with refractory enuresis, which is consistent with our study. In our study, IDC was present in 57% of the subjects with DI, and there was no significant difference between the groups. The fact that there was no significant difference in the presence of IDC in neurogenic and non-neurogenic urologic disorders provides invaluable information for clinicians in terms of their clinical approach.

Musco et al. (23) published a systematic review of all the available evidence on urodynamics predicting upper urinary tract damage in patients with neurogenic LUT dysfunction. No authors reported data on the duration of IDC in neurogenic detrusor overactivity children. In 2020, Solakhan et al. (24) evaluated the course of urinary problems in children with SD. They found the differences between bladder capacity, bladder pressure at maximal capacity, compliance, and detrusor hyperactivity at first admission and post-treatment were statistically significant ($p<0.05$). They suggested that early follow-up of

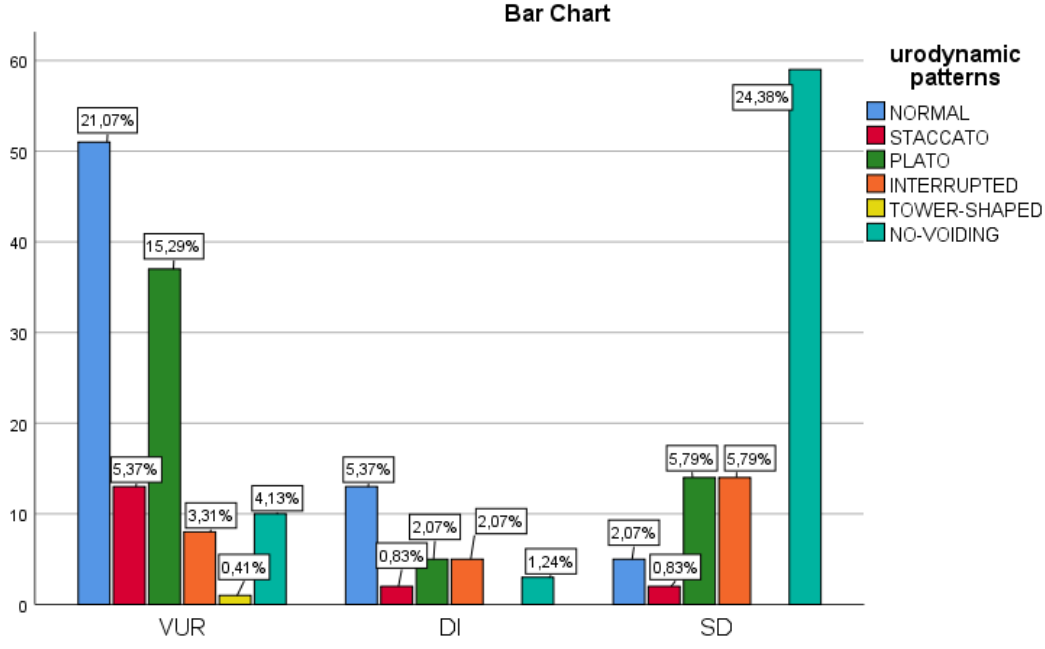


Figure 1. Micturition patterns of the groups
VUR: Vesicoureteral reflux, DI: Daily incontinence, SD: Spinal dysrpahism

urodynamics should be performed, and treatment should be carried out if necessary (24). Although our study does not discuss pre-and post-treatment urodynamic findings, it is valuable as it provides IDC frequency data for both SD and non-neurogenic patients.

Worldwide, uroflowmetry is often the sole tool performed during the initial evaluation of children with LUT symptoms. Various alterations in flow patterns are thought to indicate particular types of LUT disorders, specifically staccato flow indicating dysfunctional voiding and interrupted flow indicating detrusor underactivity. Assessing patients with uroflowmetry is of utmost importance in advancing diagnostic certainty and thereby leading to choosing the most accurate therapy (25). Because available data is limited and varied it is not entirely clear what the normal course of urinary flow in children is (26). In the literature, one of the largest series in healthy children evaluating urinary flow parameters generated uroflowmetry nomograms (27). The staccato pattern was the most common pattern seen in children with LUT dysfunctions in several studies (25,28). In contrast with them, the interrupted pattern was the most common in all patient groups in our study.

Overall, urodynamic testing is a well-tolerated, invasive procedure commonly used to evaluate LUT function in children (29). However, standardization of urodynamic patterns is still a challenging issue in this age group. This is the first study in terms of revealing and simultaneously comparing the urodynamic patterns of the most frequently encountered diseases in pediatric urology daily practice. In view of our results, we suggest that IDC is worth considering in both neurogenic and non-neurogenic urologic disorders in children.

Study Limitations

Missing data on urodynamic findings of patients limits the study. In addition, analyses with larger sample groups and detailed data from urodynamic studies will be more effective for making meaningful comparisons. Since there were not an equal number of patients from each disease group in the study, homogeneity could not be achieved and statistical interpretations could only be limitedly made. Despite these limitations, the study is very valuable in terms of revealing the urodynamic patterns in common urological pathologies in children compared to adults.

Conclusion

Our findings suggest that urodynamic evaluation may play an important role in the management of children with urologic disorders by identifying those with bladder dysfunction. We think this study contributes to the literature regarding the comparison of IDC frequency for the most common disorders in pediatric urology since normal urodynamic parametric data in pediatric patients is limited. Larger, definitive randomized trials are still required to standardize the findings of urodynamic studies to determine the place for urodynamics in both the routine and individualized clinical care of pediatric patients with urologic disorders.

Ethics

Ethics Committee Approval: The ethical approval was obtained from University of Health Sciences Turkey, Kanuni Sultan Suleyman Training and Research Hospital local ethical committee, with a number of 2020.11.205 and the date of 16/11/2020.

Informed Consent: Written informed consent was obtained from all subjects and their parents or guardians.

Authorship Contributions

Concept: H.D., M.O.K., Design: H.D., M.O.K., Data Collection or Processing: H.D., M.O.K., Analysis or Interpretation: H.D., M.O.K., Literature Research: H.D., M.O.K., Writing: H.D., M.O.K.

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

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

References

1. Clement KD, Lapitan MC, Omar MI, Glazener CM. Urodynamic studies for management of urinary incontinence in children and adults: A short version Cochrane systematic review and meta-analysis. Neurourol Urodyn 2015;34:407-12.
2. Li X, Wen JG, Xie H, et al. Delayed in toilet training association with pediatric lower urinary tract dysfunction: A systematic review and meta-analysis. J Pediatr Urol 2020;16:352.
3. Jackson EC. Urodynamics in the Pediatric Patient: When to Order, How to Interpret. Curr Treat Options Pediatr 2018;4:151-73.
4. Elmissiry M, Abdelkarim A, Badawy H, Elsalmy S, Ali GA. Refractory enuresis in children and adolescents: how can urodynamics affect management and what is the optimum test? J Pediatr Urol 2013;9:348-52.
5. Bauer SB, Nijman RJ, Drzewiecki BA, Sillen U, Hoebeke P; International Children's Continence Society Standardization Subcommittee. International Children's Continence Society standardization report on urodynamic studies of the lower urinary tract in children. Neurourol Urodyn 2015;34:640-7.
6. Arlandis S, Morán E, Martínez-Cuenca E, Bonillo MÁ, Martínez-García R, Rosier P. Adaptation to Spanish of the ICS Good Urodynamic Practices. Actas Urol Esp (Engl Ed) 2018;42:625-31.
7. Chang SJ, Chiang IN, Hsieh CH, Lin CD, Yang SS. Age-and gender-specific nomograms for single and dual post-void residual urine in healthy children. Neurourol Urodyn 2013;32:1014-8.

8. Chang SJ, Tsai LP, Hsu CK, Yang SS. Elevated postvoid residual urine volume predicting recurrence of urinary tract infections in toilet-trained children. Pediatr Nephrol 2015;30:1131-7.
9. Meister MR, Zhou J, Chu H, et al. Non-invasive bladder function measures in healthy, asymptomatic female children and adolescents: A systematic review and meta-analysis. J Pediatr Urol 2021;17:452-62.
10. El Desoky SM, Banakhar M, Khashoggi K, Zaher ZF, Kari JA. Voiding dysfunction in children causes, management, and prognosis: A single-center retrospective study. Saudi Med J 2021;42:869-77.
11. Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen-Möbius TE. International system of radiographic grading of vesicoureteric reflux. International Reflux Study in Children. Pediatr Radiol 1985;15:105-9.
12. Austin PF, Bauer SB, Bower W, et al. The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the standardization committee of the International Children's Continence Society. Neurourol Urodyn 2016;35:471-81.
13. de Jong TP, Klijn AJ. Urodynamic studies in pediatric urology. Nat Rev Urol 2009;6:585-94.
14. Tekgul S, Stein R, Bogaert G, et al. EAU-ESPU guidelines recommendations for daytime lower urinary tract conditions in children. Eur J Pediatr 2020;179:1069-77.
15. Drzewiecki BA, Bauer SB. Urodynamic testing in children: indications, technique, interpretation and significance. J Urol 2011;186:1190-7.
16. Fuentes M, Magalhães J, Barroso U Jr. Diagnosis and Management of Bladder Dysfunction in Neurologically Normal Children. Front Pediatr 2019;7:298.
17. Xing D, Wang YH, Wen YB, et al. Prevalence and risk factors of overactive bladder in Chinese children: A population-based study. Neurourol Urodyn 2020;39:688-94.
18. Franco I. Overactive bladder in children. Nat Rev Urol 2016;13:520-32.
19. Franco I. Functional bladder problems in children: pathophysiology, diagnosis, and treatment. Pediatr Clin North Am 2012;59:783-817.
20. Wei C, Gao J, Kou L, Liu X, Lin T, He D. Can Urodynamic Findings of Overactive Bladder Determine the Treatment Effect of Urotherapy in Children? J Coll Physicians Surg Pak 2020;30:41-5.
21. Altobelli E, Buscarini M, Nappo SG, Nguyen HT, Caione P. Urodynamics investigation on children with vesicoureteral reflux identifies overactive bladder and poor compliance in those with voiding dysfunction. Pediatr Surg Int 2011;27:517-22.
22. Batinic D, Miloševic D, Topalovic-Grkovic M, et al. Vesicoureteral reflux and urodynamic dysfunction. Urol Int 2013;90:480-3.
23. Musco S, Padilla-Fernández B, Del Popolo G, et al. Value of urodynamic findings in predicting upper urinary tract damage in neuro-urological patients: A systematic review. Neurourol Urodyn 2018;37:1522-40.
24. Solakhan M, Oktay K, Guzel E, Bayrak O, Guzel A. Course of Urological Problems in Children with Spinal Dysraphism: Long-Term Follow-Up Results. Pediatr Neurosurg 2020;55:101-5.
25. Wenske S, Combs AJ, Van Batavia JP, Glassberg KI. Can staccato and interrupted/fractionated uroflow patterns alone correctly identify the underlying lower urinary tract condition? J Urol 2012;187:2188-93.
26. Wilcox DT aRK. Clinical and Urodynamic Evaluation of Lower Urinary Tract Dysfunction in Children. In: AW P, editor. Campbell-Walsh-Wein Urology, 12th ed. Elsevier; 2021. p. 473-88.
27. Gupta DK, Sankhwar SN, Goel A. Uroflowmetry nomograms for healthy children 5 to 15 years old. J Urol 2013;190:1008-13.
28. Wenske S, Van Batavia JP, Combs AJ, Glassberg KI. Analysis of uroflow patterns in children with dysfunctional voiding. J Pediatr Urol 2014;10:250-4.
29. Finkelstein JB, Cahill D, Graber K, et al. Anxiety, distress, and pain in pediatric urodynamics. Neurourol Urodyn 2020;39:1178-84.

Original Article

DOI: 10.4274/haseki.galenos.2021.7530
Med Bull Haseki 2022;60:26-32

Evaluation of the Relationship between Janus Kinase 2 Mutational Burden and Clinical Findings in Adult Myeloproliferative Neoplasm Patients

Cigdem Yuce Kahraman*, Gulden Sincan**, Abdulgani Tatar*

*Ataturk University Faculty of Medicine, Department of Medical Genetics, Erzurum, Turkey

**Ataturk University Faculty of Medicine, Department of Hematology, Erzurum, Turkey

Abstract

Aim: Philadelphia-negative chronic myeloproliferative neoplasms (Ph-negative MPNs) are associated with various genetic abnormalities. The *JAK2* V617F mutation is the most common one and plays a crucial role in diagnosis. We aimed to evaluate the relationship between *JAK2* mutational burden and clinical parameters of MPN patients.

Methods: The present cross-sectional study was conducted on patients with MPN referred to our clinic for *JAK2* mutation screening between January 2019 and December 2020. The clinical information of the patients was obtained from the hospital automation system and records in the hematology and medical genetics departments. We evaluated 143 *JAK2* positive patients diagnosed with polycythemia vera, primary myelofibrosis (PMF) and essential thrombocythemia.

Results: The mean age of the patients was 60.29 (standard deviation:14.81). The mutational burden was correlated with spleen size and lactate dehydrogenase (LDH) level, particularly in PMF (p=0.002, p=0.003, respectively). There was no significant difference in age, gender, mutation burden and laboratory findings in patients with and without thrombosis and bleeding.

Conclusion: Clinical parameters and *JAK2* mutational burden are related, but this relationship differs based on the MPN types. The spleen size in MPN, particularly massive splenomegaly and high LDH levels, may be correlated with the *JAK2* mutational burden. This relationship is more pronounced for PMF. There is no significant relationship between *JAK2* mutational burden and vascular complications such as thrombosis and bleeding.

Keywords: Myeloproliferative disorders, Janus kinaz 2, primary polycythemia, essential thrombocythemia, primary myelofibrosis

Introduction

Philadelphia-negative chronic myeloproliferative neoplasms (Ph-negative MPNs) consist mainly of polycythemia vera (PV), primary myelofibrosis (PMF) and essential thrombocythemia (ET) (1). Ph-negative MPNs are associated with various genetic abnormalities. One of these abnormalities is Janus kinase 2 (*JAK2*), a protein tyrosine kinase gene. It is associated with cellular growth and proliferation. The most common genetic mutation found in Ph-negative MPNs is the *JAK2* V617F mutation, wherein phenylalanine replaces valine due to a point mutation in Codon 617. The *JAK2* gene is located on the short arm of chromosome 9. This mutation increases tyrosine phosphorylation activity, resulting in hypersensitivity of hematopoietic progenitor cells to growth factors (2,3). Treatment options for MPN patients include acetylsalicylic acid (ASA), phlebotomy, and hydroxyurea. Where hydroxyurea cannot be used due to its side effects, interferon-alpha (IFN-α), *JAK2* inhibitors (ruxolitinib) or busulfan are recommended (4). *JAK2* inhibitors such as ruxolitinib are more effective for splenomegaly and clinical symptoms than clonal effects. Studies on target molecules except *JAK2* are ongoing (5).

The *JAK2* V617F mutation occurs in approximately half of ET and PMF patients and in 90% of PV patients. Other common genetic abnormalities in MPNs include mutations in *CALR* and *MPL*. *JAK2*, *CALR* and *MPL* mutations have been listed under World Health Organization's MPN diagnostic criteria (6). With the NGS (next-generation

Address for Correspondence: Cigdem Yuce Kahraman
Ataturk University Faculty of Medicine, Department of Medical Genetics, Erzurum, Turkey
Phone: +90 542 3671419 E-mail: cigdem.kahraman@atauni.edu.tr ORCID: orcid.org/0000-0003-1957-9596
Received: 09.06.2021 **Accepted:** 23.11.2021

sequencing) technique, all of these mutations can be viewed at once (7). Testing for the *JAK2* V617F mutation in MPN needs to be performed routinely for diagnosis as well as for prognosis. In addition, it is opined that the mutation burden may be associated with complications related to the disease (8). The clinical course of myeloproliferative diseases is known to be quite heterogeneous. It has been stated that *JAK2* V617 positivity is associated with clinical heterogeneity (9-11). Thrombosis risk in MPN patients is considered to be in low- and high-risk groups. Patients over 60 years of age and/or the presence of arterial or venous vascular complications are considered to be a high-risk group in PV. *JAK2* positivity for ET is also a factor for the high-risk category (12). MPN and clonal hematopoiesis are clinical conditions that may evolve into each other, and *JAK2* positivity is also seen in clonal hematopoiesis. There is a correlation between the burden of *JAK2* and other genomic changes and clinical severity (13). In the literature, the clinical findings of MPN patients with and without *JAK2* mutations were evaluated.

In this study, we aimed to evaluate the relationship between *JAK2* mutational burden and clinical parameters of the MPN patients referred to our clinic. We evaluated the laboratory findings, spleen size, thrombosis status and treatment options of the patients.

Methods

Study Design

Written informed consent was obtained from the participants. Our study complies with the principles of the Helsinki Declaration. This study was approved by the Ataturk University Clinical Research Ethic Committee (decision number: B.30.2.ATA.0.01.00/129).

The present cross-sectional study was conducted on patients with MPN referred to our clinic for *JAK2* mutation screening between January 2019 and December 2020. We identified 143 (16.94%) *JAK2* positive patients among the 844 patients who were examined. The clinical information of the MPN patients was obtained from the hospital automation system and records in the hematology and medical genetics departments.

We evaluated the laboratory parameters, clinical follow-up, thrombotic complications and *JAK2* mutational burden of these *JAK2* positive patients.

JAK2 Genetic Analysis

DNA isolation from patient blood samples was performed using the EZ1 DNA Blood 200 µL (Qiagen) kit. DNA quality was standardized through measurement with nanodrop technology. A real-time polymerase chain reaction (PCR) study was performed with 25 ng of purified DNA. The Ipsogen *JAK2* MutaQuant Kit (Qiagen) was used for the detection and quantification of the *JAK2* V617F/G1849T somatic mutation in the Rotor Gene-Q PCR system. Mutation analysis was performed with PCR software.

Statistical Analysis

The statistical analysis of laboratory results and patients' data was carried out using SPSS version 20.0. Categorical data was compared using the Pearson chi-square test. To determine the distribution of continuous variables, the Kolmogorov-Smirnov and Shapiro-Wilk tests were used; normally distributed data were presented as the mean and SD, while non-normally distributed data were presented as the median and interquartile range. The Mann-Whitney U test and the Kruskal-Wallis H test were performed for independent samples. The threshold for statistical significance was set at p=0.05.

Results

There were 90 (62.9%) PV, 34 (23.8%) ET and 19 (13.3%) PMF patients among a total of 143 patients. Demographic features were presented in Table 1.

When laboratory findings were evaluated according to the diagnosis, white blood cell (WBC), red blood cell (RBC), hemoglobin (Hgb), hematocrit (Htc), neutrophil (neu), erythropoietin and *JAK2* mutational burden showed

Table 1. *JAK2* mutational burden and patient demographics

	Diagnosis			Total	
	PV	ET	PMF		
***JAK2* (1-49%)**	53 (58.9%)	30 (88.2%)	9 (47.4%)	92 (64.3%)	
***JAK2* (50-100%)**	37 (41.1%)	4 (11.8%)	10 (52.6%)	51 (35.7%)	
Total	90 (100%)	34 (100%)	19 (100%)	143 (100%)	
	Diagnosis			**Total**	**Mean age (SD)**
	PV	**ET**	**PMF**		
Male	56 (62.2%)	14 (41.2%)	13 (68.4%)	83 (58%)	59.47 (SD: 14.99)
Female	34 (37.8%)	20 (58.8%)	6 (31.6%)	60 (42%)	60.37 (SD: 15.78)
Total	90 (100%)	34 (100%)	19 (100%)	143 (100%)	60.29 (SD: 14.81)

PV: Polycythemia vera, ET: Essential thrombocythemia, PMF: Primary myelofibrosis, SD: Standard deviation, JAK2: Janus kinase 2

significant differences between groups (Table 2). The *JAK2* mutational burden was significantly different in terms of diagnosis (p<0.05) (Figure 1).

Based on *JAK2* mutational burden, two groups were formed: ≥50% and <50%. When laboratory findings were evaluated based on these groups, WBC, Hgb, neu, platelet (plt), and lactate dehydrogenase (LDH) values showed significant differences between groups. WBC, neu, LDH levels (Figure 2), spleen size (Figure 3) and median age were higher in the high mutational burden group (p<0.05). Gender was not a significant factor (p>0.05) (Table 3). In addition, we compared the laboratory parameters according to *JAK2* mutational burden in three different MPN diagnosis groups. However, when divided into subgroups, the number of samples was unevenly insufficient and significant results could not be obtained. Significant differences in WBC, Hgb, neu, LDH, uric acid, and spleen size were detected only in the PV group because of the relatively higher sample number (p<0.05). Thrombosis occurred in 26 (18.2%) patients out of 143, while gastrointestinal bleeding occurred in three (2.1%) patients. Among the patients with thrombosis, four had cerebrovascular events, two had pulmonary thromboembolism, ten had myocardial infarction, four had pulmonary vein thrombosis, two had splenic vein thrombosis, one had deep vein thrombosis and one had digital arterial thrombosis. When the groups with and without thrombosis were compared, there was

Table 2. Laboratory findings, demographics and diagnosis

	PV	ET	MF	p-value
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	
Hgb (g/dL)	16.10 (3.67)	15 (3.38)	13.90 (9.30)	0.000*
Htc (%)	50.15 (11.38)	44.65 (10.53)	38.40 (4.8)	0.000*
RBC (x10^{12}/L)	6.26 (2.19)	5.32 (1.49)	4.60 (0.95)	0.000*
WBC (x10^{9}/L)	12.44 (8.70)	10.15 (3.38)	13.90 (9.30)	0.018*
Neu (x10^{9}/L)	9.06 (7.88)	7.08 (3.08)	9.69 (9.86)	0.002*
Plt (x10^{9}/L)	570 (452.25)	641 (242)	288 (354)	0.000*
Lymp (x10^{9}/L)	2.01 (1.23)	2.25 (0.85)	1.70 (0.94)	0.068
Uric asid (mg/dL)	6.10 (2.30)	5.60 (2.08)	5.75 (3.18)	0.159
LDH (U/L)	350 (207)	286 (153)	461 (352)	0.248
Erythropoietin (mU/mL)	3.03 (3.65)	4.89 (2.83)	20.31 (36.20)	0.000*
JAK2%	33.50 (35)	22.50 (18)	50 (45)	0.000*
Spleen size (mm)	136.5 (51)	140 (51)	184.5 (80)	0.009*
Age	64 (24)	61 (23)	65 (13)	0.473
	N (%)	**N (%)**	**N (%)**	**Total**
Patients	90 (62.9%)	34 (23.8%)	19 (13.3%)	143 (100%)
Female	34 (37.8%)	20 (58.8%)	6 (31.6%)	60 (42%)
Male	56 (62.2%)	14 (41.2%)	13 (68.4%)	83 (58%)

Htc: Hhematocrit, Hgb: Hemoglobin, RBC: Red blood cell, WBC: White blood cell, neu: Neutrophilia, plt: Platelet, lymp: Lymphocyte, LDH: Lactate dehydrogenase, IQR: Interquartile range
*significant p-values, detected by the Kruskal-Wallis test

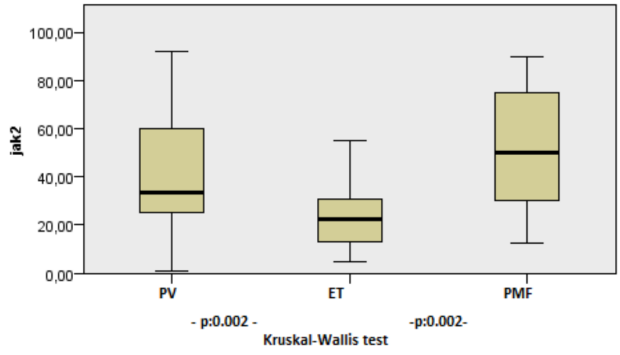


Figure 1. *JAK2* mutational burden in terms of diagnosis
PMF: Primary myelofibrosis, PV: Polycythemia vera, ET: Essential thrombocythemia, *JAK2*: Janus kinase 2

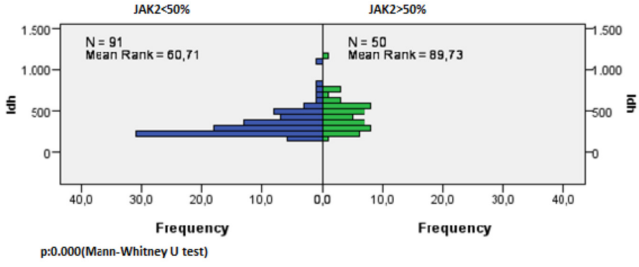


Figure 2. LDH levels in terms of *JAK2* mutational burden
JAK2: Janus kinase 2, LDH: Lactate dehydrogenase

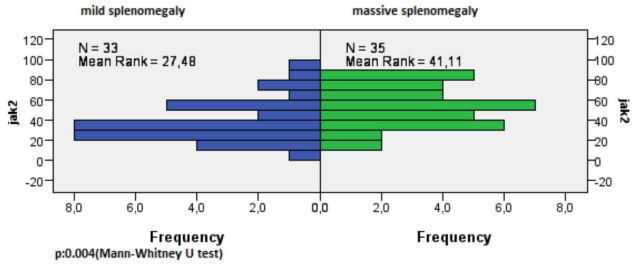


Figure 3. *JAK2* mutational burden in terms of splenomegaly category
JAK2: Janus kinase 2

no statistical difference in age, *JAK2* mutational burden, spleen size and laboratory findings. Only the lymphocyte count was lower ($p<0.05$). Gender was not a significant factor ($p>0.05$). Eighteen PV, seven ET patients, and one PMF patient were part of the thrombosis group.

Cases with a spleen size ≥160 mm in the ultrasonography were considered as massive splenomegaly (SM) and those with a spleen size of 130-160 mm were considered as mild splenomegaly. Laboratory findings were evaluated according to mild and massive SM groups (Table 4). The SM rate was 57.1% in the group having a *JAK2*≥50% mutation burden. Splenomegaly was found to be associated with *JAK2* mutation burden ($p=0.002$) (Table 2). The SM rates were 48.7% in PV, 35.3% in ET and 83.3% in PMF patients. The PMF group was significantly different from the other groups ($p=0.009$).

We also evaluated the treatment protocols of the patients. Most of the patients were treated with ASA+hydroxyurea (59.4%); 64.7% of the patients using this treatment were PV patients, 22.4% were ET, and 12.9% were PMF patients. The second most common treatment options were ASA (14.7%) and ASA+phlebotomy (14.7%). 71.4% of those treated with ASA were ET patients, 23.8% were PV patients, and 4.8% were PMF patients. 100% of the patients treated with ASA+phlebotomy were PV patients. The other treatment protocols included ASA+ruxolitinib in 4.2%, ASA+IFN-α in 3.5%, ruxolitinib in 1.4%, clopidogrel+hydroxyurea in 0.7%, hydroxyurea in 0.7% and allogenic bone marrow transplantation in 0.7% of the patients. Htc and lymph levels were significantly higher in lower-aged patients treated with ASA+phlebotomy than in patients treated with ASA+hydroxyurea. The *JAK2* mutational burden, mean age and LDH level were significantly higher in patients treated with ASA+hydroxyurea than in those treated with ASA alone. The patients treated with ASA+hydroxyurea were older than the patients treated with ASA and ASA+phlebotomy. Twenty-one thrombosis patients were treated with ASA+hydroxyurea, three with ASA+IFN-α, one with ASA+ruxolitinib, and one with clopidogrel+hydroxyurea.

Table 3. Laboratory findings in terms of JAK2 mutational burden

	JAK2% (1-49)	JAK2% (50-100)	p-value
	Median (IQR)	Median (IQR)	
Hgb (g/dL)	15.65 (3.20)	13.50 (4.60)	0.005*
Htc (%)	49.30 (9.60)	47.10 (16.10)	0.141
RBC (x10^{12}/L)	5.82 (1.63)	5.15 (3.11)	0.677
WBC (x10^9/L)	10.325 (4.98)	16.130 (10.52)	0.000*
Neu (x10^9/L)	7.26 (4.28)	12.54 (8.87)	0.000*
Plt (x10^9/L)	644 (397.5)	439. (364)	0.001*
Lymp (x10^9/L)	2.11 (1.03)	2.14 (1.25)	0.066
Uric asid (mg/dL)	5.72 (1.84)	6.76 (2.50)	0.3
LDH (U/L)	287 (159)	436.5 (241))	0.003*
Eritropoetin (mU/mL)	4.31 (4.54)	3.34 (4.37)	0.5
Age	61 (22)	65 (16)	0.003*
Spleen size (mm)	133 (48)	162 (76)	0.002*
	N (%)	N (%)	
Patients	92 (64.3%)	51 (35.7%)	0.8
Female	38 (63.3%)	22 (36.7%)	
Male	54 (65.1%)	29 (34.9%)	

Htc: Hematocrit, Hgb: Hemoglobin, RBC: Red blood cell, WBC: White blood cell, neu: Neutrophil, plt: Platelet, lymp: Lymphocyte, LDH: Lactate dehydrogenase, IQR: Interquartile range
*significant p-values, detected by the Mann-Whitney U test and means the distrubution of the parameters was not the same across categories of *JAK2* mutational burden

Discussion

Based on laboratory findings, thrombosis status, and treatments, we evaluated the *JAK2* V617F positive MPN patients. There have been studies evaluating MPN patients with and without *JAK2* V617F mutation in only

Table 4. Laboratory findings in terms of splenomegaly groups

	Spleen size (130-159 mm)	Spleen size (≥160 mm)	p-value
	Median (IQR)	Median (IQR)	
Hgb (g/dL)	15.30 (4.05)	12.60 (4.30)	0.003*
Htc (%)	48.40 (11.90)	40.20 (13.20)	0.006*
RBC (x10^{12}/L)	5.91 (2.20)	4.80 (2.22)	0.008*
WBC (x10^9/L)	11.02 (8.14)	11.46 (12.43)	0.830
neu (x10^9/L)	7.67 (7.39)	8.80 (8.38)	0.480
Plt (x10^9/L)	623 (304.5)	391 (336)	0.005*
Lymp (x10^9/L)	2.19 (1.18)	1.41 (1.00)	0.018*
Uric asid (mg/dL)	5.90 (2.60)	6.60 (2.85)	0.299
LDH (U/L)	315 (216)	504 (224.75)	0.007*
Eritropoetin (mU/mL)	3.65 (3.55)	4.04 (4.31)	0.716
JAK2 %	30 (29)	52 (40)	0.004*
Age	64 (17)	64 (25)	0.917
Spleen size (mm)	138.30 (14)	180 (54)	0.000*
	N (%)	N (%)	
Patients	33 (48.53%)	35 (51.47%)	

Htc: Hematocrit, Hgb: Hemoglobin, RBC: Red blood cell, WBC: White blood cell, neu: Neutrophil, plt: Platelet, lymp: Lymphocyte, LDH: Lactate dehydrogenase, IQR: Interquartile range
*significant p-values, detected by the Mann-Whitney U test and means the distrubution of the parameters was not the same across categories of spleen size

PV (11), in only ET (9,14-17), both in PV and ET (18-20), in ET and PMF (1), and in PV, ET and PMF (21). In these studies, within the *JAK2* positive group, Hgb (18,22), Htc (1,14,15,19), RBC (20) levels were significantly higher, and plt (1,14,15,18,20) levels were significantly lower. In various other studies, WBC (1,18-20,22) and neu (9) were also significantly higher. In our study, we evaluated PV, ET and PMF patients who already had the *JAK2* mutation.

There are studies evaluating the *JAK2* mutational burden in MPN patients, which are similar to our study. In a study by Tefferi et al. (11), *JAK2* heterozygous and homozygous PV patients were compared, and no statistical difference was found in age, gender, leukocyte or platelet counts, or thrombosis or bleeding cases, at the time of diagnosis. However, in homozygous patients, a significantly higher hemoglobin level at the time of diagnosis, increased pruritus, and a higher rate of fibrotic transformation were found (11). In the study by Zhou et al. (20), the *JAK2* V617F mutational burden was found to be significantly higher in PV compared to ET and PMF patients, similar to our study. It was reported that the *JAK2* mutational burden was positively correlated with WBC and plt counts in ET patients, and with WBC and RBC counts in PV patients (20). In the study by Liu et al. (21), high to low *JAK2* mutation burden was determined in patients with PV, PMF and ET, respectively. Patient age and WBC in PV, WBC in ET, and Hgb, WBC, and plt count in PMF were significantly correlated with higher mutation burden (21). In our study, Htc, Hgb, and RBC were significantly higher in the PV group compared to the ET and PMF groups, which is consistent with previous studies (18,20,23); while WBC, neu were significantly higher in the PV group compared to the ET group. In contrast to our study, Vannucchi et al. (19), indicated that age, Htc, and WBC levels were not different in terms of the diagnosis of PV or ET. In some studies, LDH levels were not different in *JAK2* mutant patients (1,9,17,24), while in other studies, LDH was different, consistent with our study (25).

In the study by Kittur et al. (14), it was stated that *JAK2* mutational burden was associated with splenomegaly and male gender in ET patients. Several studies have found a link between splenomegaly and *JAK2* mutations in ET patients (1,15,18,19). In our study, SM and *JAK2* mutational burden were related, but gender was not related, as in various other studies (16,26). According to our study, patients with SM may have a higher *JAK2* mutational burden.

There is conflicting information in the literature about the relationship between the *JAK2* mutation and thrombosis. Several studies have found that *JAK2* mutations are linked to thrombosis in MPN patients (9,14,16,19,27,28). According to another study, MPN patients with an allele burden of ≥50% *JAK2* patients had an increased risk of vascular complications, and they account for the majority of PV and a small proportion of ET (27). Thrombosis or bleeding risk, on the other hand, was not found to be associated with the *JAK2* mutation in myeloproliferative diseases in various studies (1,11,17,22,29). In our study, there was no significant difference between the groups with and without thrombosis, in terms of age, gender, *JAK2* mutational burden and laboratory parameters except lymph count. The lymph count was significantly higher in the group without thrombosis. This result may be due to the small number of patients with thrombosis. Across studies, low/high-risk of thrombosis groups are defined for PV (30) and ET patients (12,30). ASA is recommended in low-risk patients to prevent venous and arterial thrombosis. Phlebotomy is performed in both high and low-risk groups to keep the hematocrit values below 45% (12). Low-dose ASA, phlebotomy and hydroxyurea are recommended for patients in the high-risk category. Hydroxyurea regulates the plt count and reduces the risk of vascular complications. IFN-α, *JAK2* inhibitor or Busulfan are used when hydroxyurea cannot be used due to its side effects (4). In our study, consistent with the literature, ASA+hydroxyurea, ASA+phlebotomy and ASA were the common treatment options and early preventive treatments may be protective for thrombosis.

Study Limitations

Although our total number of patients was sufficient, when we evaluated the three different groups of MPNs, the number of samples was low in the ET and PMF groups, in particular. When the subgroups were classified according to *JAK2* mutational burden, a strong comparison could not be made because the numbers were further reduced. This is the limited aspect of our study. Despite these limitations, there have been few articles on the effects of *JAK2* mutational burden in all three MPNs, and we believe that this article will contribute to the literature.

Conclusion

Clinical parameters and *JAK2* mutational burden are related but this relationship differs based on the MPN types. The spleen size in MPN, particularly SM and high LDH level may be correlated with the *JAK2* mutational burden. This relationship is more pronounced for PMF. There is no significant relationship between *JAK2* mutational burden and vascular complications such as thrombosis and bleeding.

Ethics

Ethics Committee Approval: This study was approved by Ataturk University Clinical Research Ethic Committee (decision number: B.30.2.ATA.0.01.00/129).

Informed Consent: Retrospective study.

Authorship Contributions

Concept: C.Y.K., G.S., A.T., Design: C.Y.K., G.S., A.T., Data Collection or Processing: C.Y.K., G.S., Analysis or Interpretation: C.Y.K., G.S., A.T., Literature Research: C.Y.K., G.S., Writing: C.Y.K., G.S.

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

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

Acknowledgements

This manuscript was reviewed as a preprint in Research Square, a research communication platform. Research Square preprints are published under a CC-BY 4.0 license, meaning the author retains full copyright for their work. When the paper is accepted and published in a journal, a link to the final version of record can be placed on the preprint, guiding readers to the published paper (https://www.researchsquare.com/article/rs-305849/v1).

References

1. Yönal İ, Dağlar-Aday A, Akadam-Teker B, et al. Impact of JAK2V617F Mutational Status on Phenotypic Features in Essential Thrombocythemia and Primary Myelofibrosis. Turk J Haematol 2016;33:94-101.
2. Kralovics R, Passamonti F, Buser AS, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med 2005;352:1779-90.
3. Lee E, Lee KJ, Park H, et al. Clinical Implications of Quantitative JAK2 V617F Analysis using Droplet Digital PCR in Myeloproliferative Neoplasms. Ann Lab Med 2018;38:147-54.
4. Hintermair S, Zwickl-Traxler E, Pecherstorfer M, et al. Evaluation of vascular events in patients with myeloproliferative syndromes and mutations of either the januskinase-2 or calreticulin gene at the university hospital Krems from 2008 to 2015. Oncotarget 2018;9:8450-62.
5. Brkic S, Meyer SC. Challenges and Perspectives for Therapeutic Targeting of Myeloproliferative Neoplasms. Hemasphere 2021;5:e516.
6. Tefferi A. Primary myelofibrosis: 2021 update on diagnosis, risk-stratification and management. Am J Hematol 2021;96:145-62.
7. Kearney L, Lee Tokar L, Flynn C, Mykytiv V, Murphy K, Langabeer SE. Repeat JAK2 V617F testing in patients with suspected essential thrombocythaemia. J Clin Pathol 2020;73:772.
8. Borowczyk M, Wojtaszewska M, Lewandowski K, et al. The JAK2 V617F mutational status and allele burden may be related with the risk of venous thromboembolic events in patients with Philadelphia-negative myeloproliferative neoplasms. Thromb Res 2015;135:272-80.
9. Campbell PJ, Scott LM, Buck G, et al. Definition of subtypes of essential thrombocythaemia and relation to polycythaemia vera based on JAK2 V617F mutation status: a prospective study. Lancet 2005;366:1945-53.
10. Nielsen C, Birgens HS, Nordestgaard BG, Bojesen SE. Diagnostic value of JAK2 V617F somatic mutation for myeloproliferative cancer in 49 488 individuals from the general population. Br J Haematol 2013;160:70-9.
11. Tefferi A, Lasho TL, Schwager SM, et al. The clinical phenotype of wild-type, heterozygous, and homozygous JAK2V617F in polycythemia vera. Cancer 2006;106:631-5.
12. Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2021 update on diagnosis, risk-stratification and management. Am J Hematol 2020;95:1599-613.
13. Moliterno AR, Kaizer H. Applied genomics in MPN presentation. Hematology Am Soc Hematol Educ Program 2020;2020:434-9.
14. Kittur J, Knudson RA, Lasho TL, et al. Clinical correlates of JAK2V617F allele burden in essential thrombocythemia. Cancer 2007;109:2279-84.
15. Palandri F, Ottaviani E, Salmi F, et al. JAK2 V617F mutation in essential thrombocythemia: correlation with clinical characteristics, response to therapy and long-term outcome in a cohort of 275 patients. Leuk Lymphoma 2009;50:247-53.
16. Bayram M, Özkocaman V, Özkalemkaş F, et al. Esansiyel Trombositoz Tanısıyla İzlenen Olgularda JAK-2 Gen Mutasyonu ve Komplikasyonlarla İlişkisi. Uludağ Üniversitesi Tıp Fakültesi Dergisi 2011;37:13-6.
17. Antonioli E, Guglielmelli P, Poli G, et al. Influence of JAK2V617F allele burden on phenotype in essential thrombocythemia. Haematologica 2008;93:41-8.
18. Karkucak M, Yakut T, Ozkocaman V, et al. Evaluation of the JAK2-V617F gene mutation in Turkish patients with essential thrombocythemia and polycythemia vera. Mol Biol Rep 2012;39:8663-7.
19. Vannucchi AM, Antonioli E, Guglielmelli P, et al. Clinical profile of homozygous JAK2 617V>F mutation in patients with polycythemia vera or essential thrombocythemia. Blood 2007;110:840-6.
20. Zhou J, Ye Y, Zeng S, et al. Impact of JAK2 V617F mutation on hemogram variation in patients with non-reactive elevated platelet counts. PLoS One 2013;8:e57856.
21. Liu Y, Liu C, He N, et al. [JAK2 V617F mutation burden and its clinical implications in 415 patients with myeloproliferative neoplasm]. Zhonghua Xue Ye Xue Za Zhi 2015;36:191-5.
22. Lieu CH, Wu HS, Hon YC, et al. Prevalence of the JAK2-V617F mutation in Taiwanese patients with chronic myeloproliferative disorders. Intern Med J 2008;38:422-6.
23. Cetin G, Ozkan T, Turgut S, et al. Evaluation of clinical and laboratory findings with JAK2 V617F mutation as an independent variable in essential thrombocytosis. Mol Biol Rep 2014;41:6737-42.

24. Campbell PJ, Griesshammer M, Döhner K, et al. V617F mutation in JAK2 is associated with poorer survival in idiopathic myelofibrosis. Blood 2006;107:2098-100.

25. Alvarez-Larrán A, Cervantes F, Bellosillo B, et al. Essential thrombocythemia in young individuals: frequency and risk factors for vascular events and evolution to myelofibrosis in 126 patients. Leukemia 2007;21:1218-23.

26. Cheung B, Radia D, Pantelidis P, et al. The presence of the JAK2 V617F mutation is associated with a higher haemoglobin and increased risk of thrombosis in essential thrombocythaemia. Br J Haematol 2006;132:244-5.

27. Carobbio A, Finazzi G, Antonioli E, et al. JAK2V617F allele burden and thrombosis: a direct comparison in essential thrombocythemia and polycythemia vera. Exp Hematol 2009;37:1016-21.

28. Zhang Y, Zhou Y, Wang Y, et al. Thrombosis among 1537 patients with JAK2(V617F) -mutated myeloproliferative neoplasms: Risk factors and development of a predictive model. Cancer Med 2020;9:2096-105.

29. Ayer M, Menken İ, Yamak M, Ayer FA, Kırkızlar O, Burak Aktuğlu M. The Impact of Mean Platelet Volume (MPV) and JAK-2 Mutation on Thrombosis in Chronic Myeloproliferative Diseases. Indian J Hematol Blood Transfus 2017;33:181-7.

30. Iurlo A, Cattaneo D, Bucelli C, Baldini L. New Perspectives on Polycythemia Vera: From Diagnosis to Therapy. Int J Mol Sci 2020;21:5805.

Original Article

DOI: 10.4274/haseki.galenos.2021.7308
Med Bull Haseki 2022;60:33-39

A Comparative Study of the Effectiveness of Serum C-reactive Protein and Serum Pentraxin-3 Levels in the Diagnosis and Follow-up of Neonatal Sepsis

Tugrul Atay, Kamil Sahin, Murat Elevli, Ala Ustyol, Demet Oguz, Emel Ataoglu, Hatice Nilgun Duru

University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Pediatrics, Istanbul, Turkey

Abstract

Aim: Neonatal sepsis is a disease with multisystemic involvement accompanied by bacteremia in the first 28 days of life and in which the pathogen micro-organism spreads to different systems via the blood. Laboratory tests with high sensitivity and specificity are needed for the early diagnosis of neonatal sepsis. The purpose of this study was to investigate the effectiveness of pentraxin 3 in neonatal sepsis.

Methods: This prospective clinical study was performed between November, 2015, and March, 2016, with 49 newborns diagnosed with sepsis and under monitoring at the neonatal intensive care unit and with Tollner sepsis scores of 5 or above and with 35 healthy neonates. Blood was collected from every patient diagnosed with sepsis for complete blood count, C-reactive protein, blood culture and pentraxin 3 measurements.

Results: No significant difference was determined between the patient and control groups in terms of birth weight or gender. C-reactive protein, leukocyte, and pentraxin 3 levels were found to differ significantly between the healthy newborns in the control group and the septic patients. A significant correlation was observed between pentraxin 3 levels and serum C-reactive protein levels ($r=0.44$, $p<0.05$). The area under the curve was statistically significant at logistic regression analysis (area: 0.782).

Conclusions: The data from our study show that pentraxin 3 may represent a valuable marker in the differential diagnosis of neonatal sepsis.

Keywords: C-reactive protein, newborn, pentraxin, sepsis

***This manuscript have presented as oral presentation in "5. Çocuk Dostları Kongresi İstanbul-Türkiye," on 6-8 March 2017.**

Introduction

Although sepsis in neonates is increasingly less prevalent in developed countries, it continues to represent a cause of significant mortality and morbidity (1). Neonatal sepsis is seen in 1-10/1000 live births. Despite the advances made in antibiotherapy in neonatal sepsis, there are still vital problems for both term and premature newborns (2). Neonatal sepsis is classified as early-onset sepsis (ENS) (0-3 days) or late-onset sepsis (LNS) (4-28 days), depending on the time of onset of symptoms and findings, and as unproved (presence of bacterial growth in hemoculture) or clinical sepsis (no bacterial growth in hemoculture), depending on whether or not a microbiological agent is isolated (3).

The gold standard in the diagnosis of sepsis is the growth of one or more microbial agents in blood culture. However, this is not always possible. The main assistant techniques in diagnosis involve inflammatory markers such as white cell count and C-reactive protein (CRP), procalcitonin, fibrinogen, ceruloplasmin, haptoglobin, interleukin-6 (IL-6), serum amyloid-A (SAA), and pentraxin-3 (PTX-3) (4). PTX-3 is an endothelium and

Address for Correspondence: Kamil Sahin
University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Pediatrics, Istanbul, Turkey
Phone: +90 532 405 97 06 E-mail: drkamil_sahin@hotmail.com ORCID: orcid.org/000-0002-0443-2148
Received: 22.04.2021 **Accepted:** 25.05.2021

macrophage-derived inflammatory marker and has been used as such in several studies, particularly in cardiovascular diseases (5).

The purpose of this study was to investigate the role of PTX-3 in the diagnosis and treatment of neonatal sepsis.

Methods

Approval for the study was also granted by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Ethical Committee (approval number: 271/2015, date: 16.12.2015). Written consent to participate was obtained from the parents of all the babies enrolled before the study commenced.

This study was performed between October, 2015, and April, 2016, with 49 neonatal patients being monitored and treated with a preliminary diagnosis of sepsis in our hospital neonatal intensive care unit and with 35 healthy newborn babies born without complications. The sepsis group and the control group were weighed using a SEGA digital. Babies born before 37 gestational weeks were regarded as preterm. Those born after 40 weeks were regarded as post-term. Babies weighing less than 2500 g were regarded as low birth weight, and neonates with a rectal temperature above 38 °C were regarded as febrile.

In addition to risk factors such as urogenital infection in the mother, peripartum fever, presence of early membrane rupture, home birth, early birth and low birth weight, diagnosis of neonatal sepsis was made by excluding other diseases that might cause these conditions in newborns with findings such as reducing sucking in the newborn, reduced or low newborn reflexes, cyanosis, retraction, grunting, respiration, tachypnea, tachycardia, hypothermia, hyperthermia, vomiting, diarrhea, lethargy, hypotonia, irritability, jaundice, bulging fontanelle, cutis mormarata, and cutaneous eruptions.

All patients treated with a diagnosis of neonatal sepsis were scored according to the Tollner system, and patients scoring between 5 and 15 were included in the study. Under this method, which permits a clinical approach to cases of suspected sepsis, a score below shows an absence of sepsis (negative), scores of 5-10 indicate suspected sepsis, and scores above 10 show the presence of sepsis (6) (Table 1).

Blood samples were collected from the patient group before the start of antibiotic therapy for blood count, blood culture, CRP and PTX-3 study. One-milliliter venous blood specimens were placed in a pediatric BACTEC broth medium and stored for 7 days in a hemoculture device (Becton Dickinson, Phoenix 100). During this time, those exhibiting growths were gram stained and identification was performed.

Cord bloods were placed into gel separator tubes without additives immediately after birth. Blood specimens from patients with early and late sepsis were placed into gel separator tubes without additives once the diagnosis had been made and were centrifuged for 10 min at 1500 g. Venous specimens for complete blood count were placed into EDTA tubes. CRP and complete blood count were investigated on the same day. Specimens for PTX-3 were set aside and immediately placed in a deep freeze at -80 °C until assay.

CRP was investigated using the immunoturbidimetric method on a Beckman Coulter AU2700 biochemistry autoanalyzer (Beckman, California, USA). Complete blood count parameters were studied on a Mindray BC-3000 (Mindray, Shenzhen, China) hematology analyzer. PTX-3 values were studied manually with the help of a Biotek ELX800 (Biotek, Winooski, VT, USA) ELISA reader. PTX-3 was investigated with a Bioassay commercial ELISA kit (Stegmann Systems GmbH, Germany).

Statistical Analysis

Statistical analyses were performed on SPSS Version 20.0 (For Windows, SPSS Inc., Chicago, IL, USA) software. Descriptive statistics were expressed as number and percentage for categorical variables and mean, standard deviation and minimum and maximum values for numerical variables. The normality of data was analyzed using the Kolmogorov-Smirnov test. Intergroup comparisons were performed using Student's t-test when numerical variables were normally distributed and using the Mann-Whitney U test when not normally distributed. Comparisons between more than two groups were performed using ANOVA in case of normal distribution and with the Kruskal-Wallis test when normal distribution was not established. Differences between categorical variables were assessed using the chi-square test. Correlations between variables were evaluated using the Spearman test. Receiver operating characteristic analysis was performed to determine the highest PTX-3 value with the highest sensitivity and specificity in predicting sepsis. Alpha significance was accepted <0.05.

Results

The patient newborns' chronological ages ranged between 0 and 28 days, gestational weeks between 35 and 39, and birth weights between 2400 g and 3900 g. Control group birth weights were 2300-4550 g and their birth weeks ranged between 36 and 39. There was no statistically significant difference between the groups in terms of gestational weeks or weight distributions (Table 2). No significant difference was observed between the early and late-sepsis groups and control groups.

Significant differences were observed in leukocyte, PTX-3 and CRP values between the study and control groups ($p<0.05$). No significant difference was observed in platelet values (Table 3, Figure 1).

Table 1. Tollner scoring				
Score	**0**	**1**	**2**	**3**
Change in skin color	None		Moderate	**Marked**
Peripheral circulation impairment	None		Impaired	**Marked**
Hypotonia	None	Moderate	Marked	
Bradycardia	None	Present		
Apnea	None	Present		
Respiratory distress	None	Present		
Hepatomegaly	None	> 4cm		
Gastrointestinal finding	None	Present		
Leukocyte count	Normal	Leukocytosis		**Leukopenia**
Band/segmented neutrophil	None		Moderate	**Marked**
Thrombocytopenia	None		Present	
Metabolic acidosis (pH)	**None**	**>7.2**	**<7.2**	

Examination of the study group revealed a significant correlation between serum PTX-3 and serum CRP levels and Tollner sepsis scores (p=0.001 and p<0.05, respectively) (Table 4).

No statistically significant difference was determined in the PTX-3 and CRP values, leucocyte and platelet count between the early and late-neonatal sepsis groups. No statistically significant difference was determined in the parameters (PTX-3, CRP, leucocyte, and platelet) investigated in the sepsis patient group in terms of gender.

At a cut-off value of 3.26 ng/ml for PTX-3, sensitivity was 81% and specificity 69%, while positive predictive value was 78.4% and negative predictive value (NPV) 72.7% (Table 5) (Figure 2).

Table 2. Comparison of the study groups' gestational week and birth weight			
	Sepsis group	**Control group**	**P[1]**
	Mean ± SD	**Mean ± SD**	
Week	34.45±4.26	35.32±2.69	0.564
Weight (gram)	3211.2±425.7	3342.2±558.7	0.226

[1]Mann-Whitney U test.
There was no statistically significant difference between the groups in terms of gestational weeks or weight
SD: Standard deviation

Discussion

Difficulties may sometimes be experienced in the diagnosis of neonatal sepsis, for reasons such as subtle clinical findings, late emergence of results for growth in cultures such as blood, urine and cerebrospinal fluid and the absence of a rapid specific and sensitive inflammatory biomarker for neonatal sepsis (7).

Gürsu et al. (8) reported that sepsis in the neonatal period was twice as common in males as in females. The male-female ratio in the patient group in our study was 0.96, compared to 1.18 in newborns in the control group. In Katar and Devecioğlu (9) study, male and female incidence levels in cases of sepsis were approximately equal.

No significant difference was determined between gestational weeks in the newborns In the study group (35-39 weeks) and those in the control group (36-39 weeks) (Table 2). Various studies have shown that gestational weeks affect CRP levels. Only limited information is

Table 3. Comparison of laboratory values between the groups			
	Sepsis group	**Control group**	**P[1]**
Leukocyte	25,901±4923.9	17.872.2±6941.1	<0.05
Platelet	238,020.4±103,616.9	269,257.14±85,692.7	0.148
Pentraxin-3	8.1 (2.04-37.2) 14.07±11.4	1.79 (0.75-49.8) 7.8±12.7	<0.05
C-reactive protein	31.7±19.8	1.42±1.6	<0.05

[1]Mann-Whitney U test.
Significant differences were observed in leukocyte, PTX-3 and CRP values between the study and control groups
PTX-3: Pentraxin-3, CRP: C-reactive protein

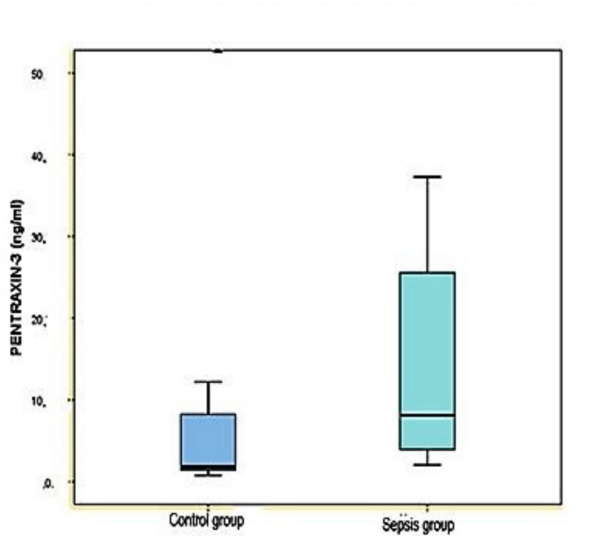


Figure 1. Patient and control group serum pentraxin-3 levels

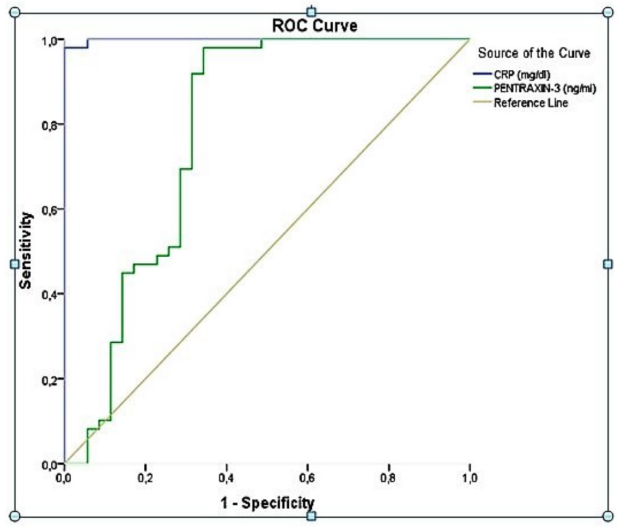


Figure 2. ROC curve analysis of Pentraxin-3 and CRP values
ROC: Receiver operating characteristic, CRP: C-reactive protein

available in the literature concerning how PTX-3 changes with age in the neonatal period. PTX-3 levels, the main subject of investigation in our study, varied depending on gestational weeks. In a study from Turkey, Akin et al. (10) reported that PTX-3 levels rose as gestational week decreased. Due to the low numbers in our study group and the fact that gestational weeks were close to one another, we were unable to analyze how PTX-3 changes with age on the basis of our own data. No significant relation was determined between sex and PTX-3 levels (p>0.05). No significant difference was determined between the birth weights of patients diagnosed with and treated for sepsis (2400 and 3900 g) and those of the babies in the control group (2300 and 4550 g) (Table 2).

Blood culture growth rates in the identification of neonatal sepsis and the pathogen micro-organism involved range between 6% and 82%. This rate did not exceed 80% even in newborns with very severe sepsis (11). In our study, growth in culture was determined in eight (16%) of the 49 patients under monitoring for sepsis in our study. We think that the low growth rates in culture may have been caused by factors such as technical errors during specimen collection and addition to culture, the small amount of material collected for blood culture and antibiotics being given before culture was taken. Different results have been reported in publications from Turkey concerning growth in blood culture. Growth rates of 66.75% were reported by Bulut et al. (12) and of 50-80% by Satar et al. (13).

The bacteria responsible for neonatal sepsis vary from country to country *Staphylococcus aureus* and *Escherichia coli* are most commonly isolated, while group B streptococci (GBS) are less frequently identified, in developing countries. Gram-negative bacteria have been isolated twice as frequently as gram-positive bacteria (14). GBS is more common in ENS in developing countries, followed by gram-negative bacilli and staphylococci. *Klebsiella pneumonia* was the most commonly isolated pathogen micro-organism in early-sepsis in our study, in three of the eight cases. In Perk's (15) study from 2010, *Klebsiella spp.* were most commonly isolated in ENS, followed by *S. epidermidis*, and by GBS in third place.

No difference was determined between the sepsis patient group with growth and the sepsis patient group without growth in terms of parameters investigated

Table 4. Analysis of correlation between Pentraxin-3 and C-reactive protein, leukocyte count and Tollner sepsis scores

	R	p
C-reactive protein	0.44	0.001
Tollner	0.62	<0.05
Leukocyte	-0.42	0.774
Platelet	-0.144	0.324

Spearman correlation analysis, Examination of the study group revealed significant correlation between serum PTX-3 and serum CRP levels and Tollner sepsis scores.
PTX-3: Pentraxin-3, CRP: C-reactive protein

Table 5 . ROC results for PTX-3 levels (area under the curve)

			95% confidence interval	
Area	Standard error	Asymptomatic indicator	Lower limit	Upper limit
0.782	0.059	>0.05	0.666	0.898

PTX-3: Pentraxin-3, ROC: Receiver operating characteristic

(leukocyte count, platelet count, CRP, PTX-3, and Tollner sepsis scores). The absence of any difference between the two groups in terms of clinical (Tollner scoring) and laboratory data and the inability to determine growth in cultures of patients with a clinical diagnosis of sepsis may be attributed to a deficiency in identifying the agent micro-organism.

Leukocytosis and leukopenia may be seen at complete blood count in neonatal sepsis. This may be due to infection in the newborn, and factors such as asphyxia, stress burden during birth, various congenital diseases deriving from the baby, diseases in the mother capable of affecting the baby (preeclampsia, eclampsia and chorioamnionitis) may also be involved in changes in the leukocyte count. Differing results have been obtained concerning leukocyte count in neonatal sepsis in various studies (16). Aygün et al. (17) reported a mean leukocyte count of 16,500±10,000. In our study, the mean leukocyte count in newborns with sepsis was 25,901±4923, and the mean count in the control group was 17,872.29±6941.161. We determined a significant difference between the patient and control groups ($p<0.05$). No significant difference was determined when leukocyte counts were compared between newborns monitored and treated for sepsis with growth and newborns monitored and treated for sepsis but without growth. Platelet count is not regarded as a particularly reliable parameter for the diagnosis of neonatal sepsis (18). Thrombocytopenia may persist for approximately a week, and neonatal sepsis appears as a non-specific, late finding (19). Although thrombocytopenia is a late-emerging finding and is not a specific finding for neonatal sepsis, it may still be indicative of neonatal sepsis when evaluated together with other parameters. Platelet count is therefore included among the parameters examined under the Tollner sepsis scoring system. Berger et al. (20) determined the sensitivity of 57% and specificity of 65% for thrombocytopenia in the diagnosis of neonatal sepsis. Prevalences of thrombocytopenia between 10% and 60% have been determined in different studies (21).

Thrombocytopenia is monitored due to platelet destruction occurring by way of immune mechanisms and the pathogen micro-organism or products from the pathogen micro-organism increasing aggregation and adhesion by impairing platelets and the vascular endothelium (18). No relation has been determined in terms of the bacterium giving rise to sepsis being gram-negative or gram-positive and thrombocytopenia (12). Shyamala et al. (22) reported that gram-negative bacteria were statistically significantly more responsible for the development of thrombocytopenia than gram-positive bacteria. Seven (14.28%) patients with thrombocytopenia were under observation in our study. No significant difference was determined between the sepsis patient group and the healthy control group in terms of platelet counts (Table 3).

CRP and SAA constitute members of the short PTX family. CRP is synthesized in the liver, particularly with the effect of IL-6. Secretion commences 4-6 h after the start of the inflammatory process and peak serum levels are reached after approximately 24-48 h (23). CRP's late response to the inflammatory process, serum levels peaking after 24-48 h and the fact that it cannot be synthesized in liver function disorders or multiorgan failures have encouraged researchers to seek a new inflammatory marker. Infection is not the sole cause of increases in CRP. Elevation in serum may also be determined due to tissue damage in conditions such as EMR, difficult birth, vacuum extraction, maternal chorioamnionitis, perinatal asphyxia and similar (23). The fact that CRP does not only rise due to infection restrict its use alone in the diagnosis of neonatal sepsis; the sensitivity of CRP in the diagnosis of neonatal sepsis ranges between 35% and 94% in different studies, and the specificity between 60% and 96% (20). The sensitivity and specificity of CRP increase in serial measurements. CRP levels below 1.0 mg/dL in two consecutive measurements increase its NPV to up to 99%. Berger et al. (20) investigated CRP and leukocyte count in the diagnosis of sepsis and determined sensitivity of 75% and specificity of 86% for CRP monitored in the first three postnatal days (19). For leukopenia, the sensitivity of 67% and specificity of 90% were determined. While CRP and leukopenia in the first three days are important diagnostic parameters for ENS, CRP becomes more dominant after the first three days. Indeed, the sensitivity and specificity of CRP after the first three days increase to 86% and 87%, respectively (19). Since only low levels of CRP are able to pass into the placenta, CRP in cord blood and infant blood is fetal in origin and may indicate a potential pathology (24).

A statistically significant difference was observed in our study between the septic patient group and the healthy control group in terms of serum CRP levels (Table 3). No difference was determined between serum CRP levels in babies with ENS and LNS.

PTXs are components of the natural immune system that, together with the complement system and macrophages, neutralize pathogen micro-organisms and scavenge metabolic wastes (25).

CRP release begins in 4-6 h after the inflammatory process, and peak serum values are reached in 24-48 h, while PTX-3 levels in serum increase up to 100-fold 6-h after the start of synthesis. PTX-3 is produced independently of liver functions (25). For reasons such as PTX-3 being produced independently of liver functions and

reaching peak serum levels more quickly, the view that it will reflect infection better than traditionally used markers has emerged. Data obtained from patients in septic shock with meningococcal disease in adults and children confirm this (26).

PTX-3 has become the subject of research in numerous different areas; for example, it has been investigated in the diagnosis of cardiovascular diseases in adults in several studies. PTX-3 levels in the diagnosis and monitoring of treatment of pediatric vasculitis and adult and pediatric patients with septic shock, and its relations with prognosis, mortality and morbidity in these diseases have also been examined (27,28).

Data concerning PTX-s in the neonatal period are limited. In a study from Turkey published in 2014, Akin et al. (10) measured and compared serum PTX-3 levels of neonates born to mothers with early membrane ruptures and of those mothers. No correlation was determined between maternal and baby serum PTX-3 levels in this study (24). In the light of that information, we think that PTX-3 (long pentraxin) may also be unable to cross the placenta. We also examined PTX-3 values in cord blood in 20 healthy neonates. Serum PTX-3 elevation in cord blood may indicate a probable pathology deriving from the baby. Akin et al. (10) determined an inverse correlation between a gestational week and PTX-3 levels and a direct correlation in subjects with intraventricular bleeding and mortality. High serum PTX-3 levels were determined in subjects with a low Apgar score, respiratory distress syndrome, clinical sepsis, intraventricular hemorrhage, necrotizing enterocolitis and prolonged hospitalization in the neonatal intensive care unit. Higher proportions of neurological and cardiac problems were determined in patients with PTX-3 elevation. High PTX-3 levels have been observed in newborns with hypoxic-ischemic diseases and low ejection fraction at simultaneous echocardiography (29). Myocardial depression initiates a response in the central nervous system in association with impairment of tissue blood supply as a result of hypo- and hypertension, and PTX-3 may start being released from neurons. Other long pentraxins, such as neuronal PTX-1 and human neuronal PTX-2 are released in the event of neuron damage and can reach high levels in the blood (30). In the study of Duman et al. (31), They found 72.97% sensitivity and 88% specificity values for PTX 9.3 ng/mL in the diagnosis of appendicitis. In coronavirus diseases-2019 (COVID-19) patients, a strong relationship was found between early death and PTX-3 values (32). PTX-3 was found to be lower in patients with COVID-19 pulmonary sepsis than in patients with other pulmonary sepsis (33).

A significant difference was determined in our study in terms of PTX-3 levels between septic and normal newborns. Very limited information is available in the literature concerning the normal serum PTX-3 level in newborns. Our review of the literature elicited no information for recommended cut-off values for PTX-3 in sepsis. A cut-off value of 3.2 ng/mL for PTX-3 in our own patient study resulted in a sensitivity for sepsis of 81% and a specificity of 69%. This value of 3.2 ng/ml elicited an NPV and PPV for PTX-3 in sepsis of 78.4% and 72.7%, respectively. We think that the value we recommend for PTX-3 can be used in future studies.

Study Limitations

The small number of patients in our study is an important limitation of the study. However, our study, which reveals important results for PTX-3, which can be an important marker in the diagnosis of neonatal sepsis, is important.

Conclusion

The data elicited from our study shows that PTX-3 can be used as a valuable marker in the differential diagnosis of neonatal sepsis. Determination of normal levels in newborns with values obtained in serial measurements in more comprehensive and multi-center studies and greater experience in this area are now needed.

Ethics

Ethics Committee Approval: This study was performed following approval from the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Ethical Committee (no: 271, approval date: 16.12.2015).

Informed Consent: Written consent to participate was obtained from the parents of all the babies enrolled before the study commenced.

Authorship Contributions

Concept: T.A., M.E., D.O., Design: D.O., A.U., Data Collection and/or Processing: T.A., E.A., Analysis and/or Interpretation: M.E., K.S., Literature Research: T.A., K.S., H.N.D., Writing: T.A., D.O., K.S.

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

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

References

1. Dağoğlu T, Ovalı F, Samancı N. Neonatoloji: Yenidoğanın Muayenesi. 1.baskı. İstanbul: Nobel Tıp Kitabevleri Ltd Şti; 2000:81-8.
2. Stoll BJ, Hansen NI, Sánchez PJ, Faix RG, Poindexter BB, Van Meurs KP, et al. National Institute of Child Health and Human Development Neonatal Research Network. Early onset neonatal sepsis: the burden of group B streptococcal and E. coli disease continues. Pediatrics 2011;127:817-26.

3 Odabaşı İO, Bülbül A. Neonatal sepsis. Sisli Etfal Hastan Tip Bul 2020;54:142-58.

4. Ng PC, Lam HS. Diagnostic markers for neonatal sepsis. Curr Opin Pediatr 2006;18:125-31.

5. Jaillon S, Bonavita E, Gentile S, et al. The long pentraxin PTX3 as a key component of humoral innate immunity and a candidate diagnostic for inflammatory diseases. Int Arch Allergy Immunol 2014;165:165-78.

6. Töllner U. Early diagnosis of septicemia in the newborn. Eur J Pediatr 1982;138:331-7.

7. Köksal N, Harmanci R, Çetinkaya M, Hacimustafaoglu M. Role of procalcitonin and CRP in diagnosis and follow-up of neonatal sepsis. Turk J Pediatr 2007;49:21-9.

8. Gürsu HA, Vitrinel A, Cömert S, et al. Neonatal Sepsisli Olgularımızın Prospektif Değerlendirilmesi. Med J Bakirkoy 2007;3:89-93.

9. Katar S, Devecioğlu C. Dicle Üniversitesi Yenidoğan Bakım Ünitesi'nde izlenen çok düşük doğum ağırlıklı bebeklerin değerlendirilmesi. Dicle Tıp Dergisi 2006;33:248-51.

10. Akin MA, Gunes T, Coban D, Ozgun MT, Akgun H, Kurtoglu S. Pentraxin 3 concentrations of the mothers with preterm premature rupture of membranes and their neonates, and early neonatal outcome. J Matern Fetal Neonatal Med 2015;28:1170-5.

11. Edwards MS. Part 2: Postnatal bacterial infections. Fanaroff and Martin's neonatal-perinatal medicine: Diseases of the fetus and newborn. 9th ed. St Louis; 2011. p. 793-829.

12. Bulut MO, Bulut İK, Büyükkayhan D, et al. Neonatal sepsisli olguların retrospektif olarak değerlendirilmesi. Cumhuriyet Üniversitesi Tıp Fakültesi Dergisi 2005;27:63-8.

13. Satar M, Engin Arısoy A, Çelik İH. Turkish Neonatal Society guideline on neonatal infections - diagnosis and treatment. Turk Pediatri Ars 2018;53(Supll 1):88-100.

14. Zaidi AK, Thaver D, Ali SA, Khan TA. Pathogens associated with sepsis in newborns and young infants in developing countries. Pediatr Infect Dis J 2009;28(Suppl 1):10-8.

15. Perk Y. Yenidoğan Sepsisinde Antibiyotik Direncinin altı (2002-2007) yıllık Cerrahpaşa tıp faültesi deneyimi. istanbul üniversitesi Cerrahpaşa tıp faküktesi Çocuk sağlığı ve Hastalıkları Anabilim Dalı Uzmanlık (Tezi). İstanbul; 2010.

16. Kordek A, Łoniewska B, Podraza W, Nikodemski T, Rudnicki J. Usefulness of estimation of blood procalcitonin concentration versus C-reactive protein concentration and white blood cell count for therapeutic monitoring of sepsis in neonates. Postepy Hig Med Dosw (Online) 2014;68:1516-23.

17. Aygün C, Oran O, Portakal O. Yenidoğanlarda Prokalsitonin düzeyleri ve sepsis tanısındaki yeri. Çocuk Sağlığı ve Hastalıkları Dergisi 2003;46:83-9.

18. Ovalı F. Yenidoğan enfeksiyonları. 1.baskı. İstanbul: İstanbul Medikal Yayıncılık; 2006:107-60.

19. Ng PC. Diagnostic markers of infection in neonates. Arch Dis Child Neonatal Ed 2004;89:229-35.

20. Berger C, Uehlinger J, Ghelfi D, Blau N, Fanconi S. Comparison of C-reactive protein and white blood cell count with differential in neonates at risk for septicaemia. Eur J Pediatr 1995;154:138-44.

21. Barman M, Das B. A Study of Validity of Haematological Parameters in the Diagnosis of Neonatal Sepsis. Indian J Appl Res 2016;6.532-5.

22. Shyamala K, Subbalakshmi N, Raghuveera K. Role of platelet count and CRP level in Gram negative versus Gram positive bacterial sepsis in low birth weight neonates. Journal of Chinese Clinical Medicine 2010;5:474-9.

23. Benitz WE. Adjunct laboratory tests in the diagnosis of early-onset neonatal sepsis. Clin Perinatol 2010;37:421-38.

24. Pizzini C, Mussap M, Plebani M, Fanos V. C-reactive protein and serum amyloid A protein in neonatal infections. Scand J Infect Dis 2000;32:229-35.

25. Agrawal A, Singh PP, Bottazzi B, Garlanda C, Mantovani A. Pattern recognition by pentraxins. Target Pattern Recognition in Innate Immunity: Springer; 2009. p. 98-116.

26. Lannergård A, Rosenström F, Normann E, Larsson A. Serum pentraxin 3 concentrations in neonates. Ups J Med Sci 2014;119:62-4.

27. Ge W, Wang HL, Sun RP. Pentraxin 3 as a novel early biomarker for the prediction of Henoch-Schönlein purpura nephritis in children. Eur J Pediatr 2014;173:213-8.

28. Ketter PM, Guentzel MN, Schaffer B, et al. Severe Acinetobacter baumannii sepsis is associated with elevation of pentraxin 3. Infect Immun 2014;82:3910-8.

29. Sciacca P, Betta P, Mattia C, et al. Pentraxin-3 in late-preterm newborns with hypoxic respiratory failure. Front Biosci (Elite Ed). 2009;2:805-9.

30. Polentarutti N, Bottazzi B, Di Santo E, et al. Inducible expression of the long pentraxin PTX3 in the central nervous system. J Neuroimmunol 2000;106:87-94.

31. Duman L, Cesur Ö, Kumbul Doğuç D, Çelik S, Karaibrahimoğlu A, Savaş MÇ. Diagnostic value of serum pentraxin 3 level in children with acute appendicitis. Ulus Travma Acil Cerrahi Derg 2020;26:699-704.

32. Brunetta E, Folci M, Bottazzi B, et al. Macrophage expression and prognostic significance of the long pentraxin PTX3 in COVID-19. Nat Immunol 2021;22:19-24.

33. Protti A, Meessen J, Bottazzi B, et al. Circulating pentraxin 3 in severe COVID-19 or other pulmonary sepsis. Eur J Clin Invest 2021;51:e13530.

Original Article

DOI: 10.4274/haseki.galenos.2021.7841
Med Bull Haseki 2022;60:40-44

Relationship between Maternal Serum Calcium and Magnesium Levels and Isolated Fetal Echogenic Intracardiac Focus Encountered During Second-trimester Ultrasound Screening

Filiz Yarsilikal Guleroglu*, Aliye Balkan Ozmen**, Murat Ekmez*, Ali Cetin*

*Sultangazi University of Health Sciences Turkey, Istanbul
Haseki Training and Research Hospital, Clinic of Gynecology and Obstetrics, Istanbul, Turkey
**Bursa City Hospital, Clinic of Gynecology and Obstetrics, Bursa, Turkey

Abstract

Aim: As a frequent finding of prenatal second trimester ultrasound screening, echogenic intracardiac focus (EIF) may have a relationship with serum calcium and magnesium levels instead of major fetal abnormalities. This study was conducted to assess the relationship between the EIF and serum calcium and magnesium levels in women who had undergone mid-trimester screening ultrasound and had no other soft markers or fetal malformations.

Methods: This cross-sectional study was performed in a tertiary center experienced in maternal, fetal, and neonatal care, and included 206 patients who had undergone prenatal screening at 18-25 weeks of pregnancy with isolated EIF or without other laboratory abnormalities from July 2020 to June 2021. Serum calcium and magnesium levels were collected from the electronic health records of our institution.

Results: Overall, although there were remarkable changes in some of the clinical characteristics of patients with or without EIF, in general, the study groups were found comparable in terms of these variables. No significant differences were found between the study groups regarding serum calcium and magnesium levels.

Conclusions: Serum calcium and magnesium levels did not show a significant increase in cases with EIF. Therefore, measurement of serum calcium and magnesium levels in EIF cases was not found to be explanatory of the cause.

Keywords: Fetal heart, muscle, papillary, ultrasonography, prenatal, calcium, magnesium

Introduction

Echogenic intracardiac focus (EIF) is recognized when a bright spot is observed in the heart muscle during fetal ultrasound examination and is accepted as due to calcium deposition in the heart tissue. EIFs can be determined as single or multiple echogenic structures as bright as bone seen in the papillary muscle of the ventricles on routine four-chamber images that move synchronically with the atrioventricular valves (1,2). In fetuses with EIF, mineralization in the papillary muscles can be demonstrated histologically (3). In 90% of cases, microcalcification of papillary muscles is found in the left ventricle. Because the sensitivity of the EIF is low, further investigations, as well as counseling and information, are necessary to address parental anxiety (2). Although the pathogenesis of this finding is unclear, its presence does not cause structural or functional cardiac problems.

Although EIF is seen in 3% to 5% of healthy pregnancies and in 15% to 30% of trisomy 21 fetuses in mid-trimester ultrasound, they do not pose a problem when isolated. The presence of EIF increases the risk of chromosomal abnormality in the fetus, but most

Address for Correspondence: Filiz Yarsilikal Guleroglu
Sultangazi University of Health Sciences Turkey, Istanbul, Haseki Training and Research Hospital, Clinic of Gynecology and Obstetrics, Istanbul, Turkey
E-mail: filizyarsilikal@gmail.com ORCID: orcid.org/0000-0003-4577-3368
Received: 07.11.2021 **Accepted:** 30.12.2021

often increases the risk of trisomy 21 (4). Based on this finding, follow-up ultrasound, fetal echocardiography, and postpartum evaluation are not recommended in pregnant women with isolated EIF with negative serum or cell-free DNA screening results, as EIF diagnosed prenatally is not associated with childhood cardiac dysfunction (5,6).

Magnesium and calcium are essential for fetal development. A number of physiological changes occur during pregnancy for maternal adaptation and to meet fetal nutritional needs. Maternal serum calcium levels change with gestational age during pregnancy. Many studies have reported that total serum calcium levels are significantly reduced in normal pregnancy, especially in the third trimester of pregnancy (7).

There was a lack of information regarding serum calcium and magnesium levels and an isolated EIF during mid-trimester screening ultrasound. Since in the pathogenesis of EIF, the role of microcalcifications is considered, the knowledge about the status of serum calcium and magnesium in the development of EIF needs to be clarified. The finding of EIF, which is known as a soft marker for congenital anomalies, is associated with serum calcium and magnesium, which may increase alertness to accompanying electrolyte metabolism disorders in these infants. The aim of this study was to assess the relationship between the EIF and serum calcium and magnesium levels in women who had undergone mid-trimester screening ultrasound and had no other soft markers or fetal malformations.

Methods

Compliance with Ethical Standards and Study Design

The Local Ethics Committee for Human Research approved the study protocol (Bursa City Hospital, approval no: 2021-13/6 and date: 2021). Written informed consent forms were obtained from all participants. This was a cross-sectional study of women, including 206 patients with singleton pregnancies examined for prenatal care from July 2020 to June 2021. The participants included all pregnant women resorting to a tertiary care hospital for the second trimester ultrasonic analysis.

Patient Evaluation

These mothers were examined for ultrasound markers of chromosomal abnormalities, including EIF in the intraventricular spaces of the fetus through second trimester ultrasound screening. A diagnosis of EIF (Figure 1) was made when a discrete area of echogenicity that is as bright as bone, noted in the heart. Fetal ultrasound examinations during the second trimester were performed by one (A.B.O) of the perinatologists using a 3.5-5 MHz probe on a Voluson E8 ultrasound machine (GE Healthcare, USA). Pregnancies with assisted reproductive technology, other soft markers for aneuploidy, and known chromosomal and major congenital anomalies were excluded from the study. Medical records for this study were retrospectively reviewed for baseline clinical, obstetric, and detailed obstetric ultrasound reports.

Five milliliters of venous blood were collected from the antecubital fossa of each woman. The corrected calcium level was calculated by measuring serum calcium, in addition to measurements of serum magnesium and albumin. All tests were performed using standard procedures of a biochemistry laboratory. Corrected calcium was calculated in mg/dL using the following formula: corrected calcium=serum calcium + 0.8 x (4-serum albumin) (http://www.perinatology.com/calculators/Corrected Calcium). In the second trimester, serum total calcium and magnesium levels ranged from 8.2-10.6 mg/dL and 1.5-2.2 mg/dL, respectively, in healthy subjects (8).

Statistical Analysis

The clinical data was analyzed using IBM SPSS Statistics v23 (IBM SPSS, USA). The Kolmogorov-Smirnov test was used to determine the normality of the data. For parametric and non-parametric analyses of variables, t-test and Mann-Whitney U tests were used, respectively. A categorical variable was analyzed using a chi-square test. The statistical difference was set as $p<0.05$.

Results

Table 1 presents the baseline clinical characteristics of the study population. In the study population, there were 105 participants with EIF and 101 participants without EIF. The median age of the women with and without EIF was found to be similar (p=0.583). The study groups were found to be comparable regarding the median gravidity value (p=0.770). There was no significant difference in the median parity of study groups (p=0.382). The mean body

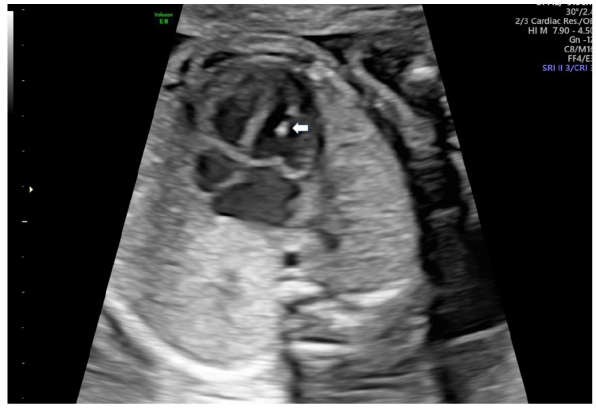


Figure 1. A representative ultrasound image of fetal echogenic intracardiac (arrow) focus in the left ventricle

mass index of the women with and without EIF was found to be similar (p=0.325). The median gestational age of the study groups was found to be comparable (p=0.786). There was no significant difference regarding the median birth weight (p=0.710). Regarding the location of EIF, the rate of being on the right side and bilateral was 4.8% and 1.9%, respectively. Considering the number of EIF, 2 and 3 focuses were found to be 10.5% and 1%, respectively.

Figure 2 displays the serum calcium and magnesium levels of study groups. No significant differences were found between the study groups regarding the serum calcium and magnesium levels (p=0.793 and p=0.938, respectively).

Discussion

In the current study, we aimed to determine the relationship between EIF and the status of serum calcium and magnesium in pregnant women who had undergone mid-trimester screening ultrasound and had no other soft markers of fetal malformations. In accordance with relevant literature, the EIF finding was present mostly on the left side and as a singularity. Serum calcium and magnesium levels had no meaningful relationship with the development of EIF.

Table 1. Baseline clinical characteristics of the study population

	EIF (n=105)	No EIF (n=101)	p-values
Age (years), median (IQR 25-75)	28 (18-43)	29 (17-41)	0.583
Gravidity (n), median (IQR 25-75)	2 (1-7)	2 (1-5)	0.770
Parity (n), median (IQR 25-75)	1 (0-4)	1 (0-4)	0.382
BMI (kg/m2), mean ± SD	26.8±3.9	26.2±4.4	0.325
Gestational age (week), median (IQR 25-75)	21 (18-24)	21 (18-25)	0.786
Female gender (n, %)	48 (46%)	48 (48%)	0.819
Birth weight (g), median (IQR 25-75)	3,240 (1,300-4,295)	3,217 (2,700-4,200)	0.710
Location (n, %)			
Left	98 (93.3%)		
Right	5 (4.8%)		
Bilateral	2 (1.9%)		
Number of EIF (n, %)			
1	93 (88.5%)		
2	11 (10.5%)		
3	1 (1%)		

Data are expressed as mean with standard deviation, median with interquartile range, and count with percentage as appropriate. Statistical analyses were performed with t, Mann-Whitney, and chi-square tests.
EIF: echogenic cardiac focus, BMI: Body mass index, IQR: Interquartile range, SD: Standard deviation

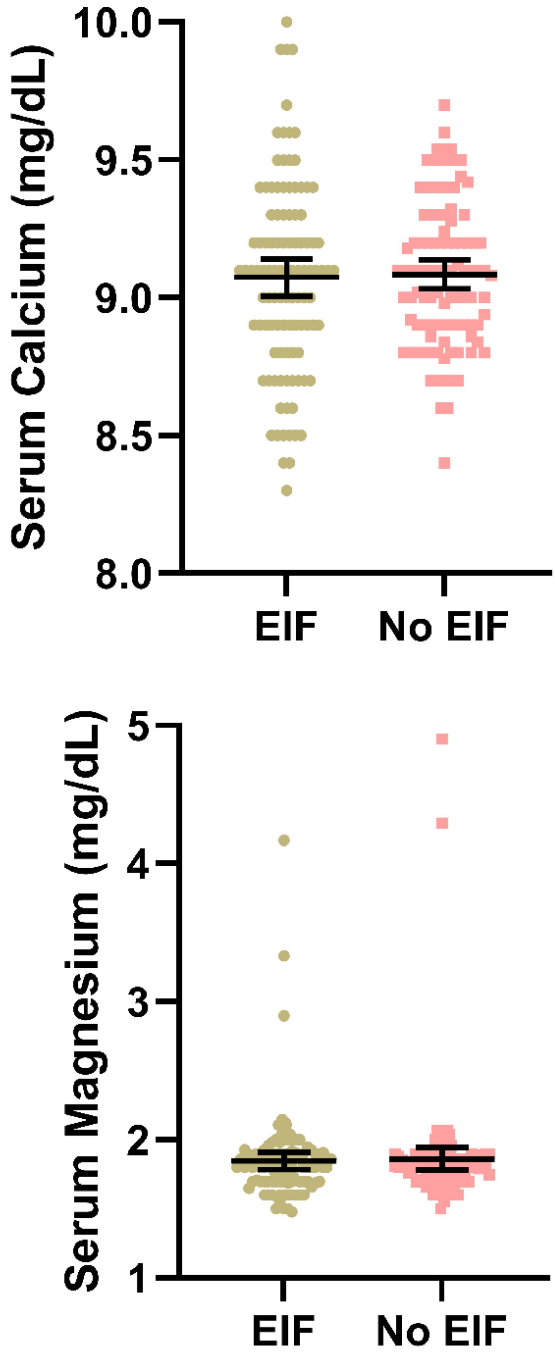


Figure 2. Serum calcium and magnesium levels of the study population. The data are expressed as a median with an interquartile range, and the Mann-Whitney test revealed no significant differences between study groups (p>0.05).
EIF: Echogenic intracardiac focus

During pregnancy and lactation, specific regulatory systems regulate mineral homeostasis according to the needs of the pregnancy trimesters. Intestinal calcium absorption is doubled to meet fetal calcium needs. In comparison, besides calcium release from the skeletal system, renal calcium conservation is also evident. While calcium supplementation during pregnancy causes greater calcium absorption, the effect of calcium supplements on the amount of bone lost during breastfeeding is minimal (7). During the entire pregnancy, the fetus accumulates about 30 g of calcium, 20 g of phosphorus, and 0.8 g of magnesium for mineralization of the skeletal system and for its normal physiological events. Approximately 50% of the total magnesium in the body is found in the bones, the other 50% intracellularly and approximately 1% intravascularly (1). The level of the intravascular compartment is tightly controlled. Serum magnesium levels are between 1.5-2.1 mg/dL (9). Magnesium acts as a cofactor for various enzymatic processes. In some studies, it has been observed that serum magnesium levels decrease with advancing gestational age (10).

The presence of an EIF, when seen isolated in a normal pregnancy, is considered a benign variant that can be interpreted by considering maternal risk factors and other sonographic anomalies, and some authors do not consider karyotyping necessary in mid-trimester fetuses (4,11,12). The finding of an incidental EIF in high-risk pregnancies may increase the risk of echogenic foci of aneuploidic anomalies. Classified as a soft marker for aneuploidic anomalies, there is no recognized direct association with congenital heart disease for an EIF per se (unless there is an aneuploidic anomaly). These are found to have disappeared in the follow-up of infants (13).

Because the presence of an isolated EIF is not associated with a cardiac abnormality, fetal echocardiography is not considered necessary and no specific follow-up is recommended for these pregnancies (14). Index pregnancy should be followed up according to the presence of other clinical indications or the results of the patient's prenatal screening and/or diagnostic tests.

Pavlíček et al. (14) conducted a retrospective study to determine the status of echogenic foci in the fetal heart during prenatal screening and to determine their value for the outcome of offspring. Their findings revealed that the isolated EIF was detected in 3% of the participants. The EIF was located in the left ventricle in 93%, 5%, and 2% of the subjects, mainly in the valvular apparatus of the mitral valve, in both of the ventricles, and in the right ventricle, respectively. No genetic abnormalities were present in the study population. The authors suggested that in their large series, EIF needs to be considered as a meaningfully less important finding without serious consequences in the offspring.

In another study investigating the EIF status, the authors examined the impact of an EIF on the risk of fetal trisomy 21 in a large population. EIF was found in 3.6% of participants and trisomy 21 was diagnosed in 0.4% of fetuses. When EIF, along with other markers, is present, it is associated positively with the presence of trisomy 21. An isolated EIF was not a valuable finding to consider trisomy 21 in patients younger than 35 years old without abnormal serum screening results for aneuploidy (15).

It is possible that the EIF decreases or even disappears with the progression of the gestational week. Huang et al. (11) followed all fetuses with isolated EIF and did not detect any serious disease or symptoms. They stated that these findings were not compatible with the results of previous studies (11,16). The authors noted that their results indicated a low rate of chromosomal abnormalities in fetuses with isolated EIF; however, they pointed to the benefit of performing chromosomal microarray analysis in fetuses with cardiac echogenic focus when other fetal anomalies are found, which facilitates the prediction of fetal outcome during genetic counseling and definitive assessment of prognosis (11).

Study Limitations

Some limitations of the current study also merit consideration before determining the implications of the study results. Although the EIF data were obtained from a single ultrasound examination between weeks 18 and 25, serial ultrasound screening of the EIF after week 25 would be more informative.In the literature, there is no previous study that examined serum calcium and magnesium in terms of the status of EIF. Our results can increase the awareness of serum electrolytes with congenital abnormalities. We think that this aspect of our current work can be considered the strength of this study, and this increases the reliability of our conclusions.

Conclusions

The presence of isolated EIF in the second trimester ultrasound scan causes a serious concern in mothers, and additional laboratory tests and research requests are encountered in this regard. Due to the nature of EIF, the first laboratory tests that come to mind include serum calcium and magnesium measurements. The results of this study revealed that in cases with EIF, serum calcium and magnesium levels did not show a significant increase. Therefore, measurement of serum calcium and magnesium levels in EIF cases was not found to be explanatory of the cause. There is a need to elucidate the pathogenesis of

EIF development with studies examining a wider range of biochemical measurements.

Ethics

Ethics Committee Approval: The Local Ethics Committee for Human Research approved the study protocol (Bursa City Hospital, approval no: 2021-13/6 and date: 2021).

Informed Consent: Written informed consent forms were obtained from all participants.

Authorship Contributions

Concept: F.Y.G., A.B.O., M.E., A.C., Design: F.Y.G., A.B.O., Data Collection or Processing: M.E., A.C., Analysis or Interpretation: F.Y.G., A.B.O., M.E., A.C., Literature Research: F.Y.G., A.B.O., M.E., A.C., Writing: F.Y.G., A.B.O., M.E., A.C.

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

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

References

1. Djagbletey R, Darkwa EO, deGraft-Johnson PK, et al. Serum Calcium and Magnesium Levels in Normal Ghanaian Pregnant Women: A Comparative Cross-Sectional Study. Open Access Maced J Med Sci 2018;6:2006-11.
2. Koutras A, Fasoulakis Z, Halil A, Kontomanolis EN. Echogenic intracardiac focus - existence in the first trimester and the role of microRNAs. Folia Med (Plovdiv) 2021;63:142-7.
3. Brown DL, Roberts DJ, Miller WA. Left ventricular echogenic focus in the fetal heart: pathologic correlation. J Ultrasound Med 1994;13:613-6.
4. He M, Zhang Z, Hu T, Liu S. Chromosomal microarray analysis for the detection of chromosome abnormalities in fetuses with echogenic intracardiac focus in women without high-risk factors. Medicine (Baltimore) 2020;99:e19014.
5. Society for Maternal-Fetal Medicine (SMFM). Electronic address: pubs@smfm.org, Prabhu M, Kuller JA, Biggio JR. Society for Maternal-Fetal Medicine Consult Series #57: Evaluation and management of isolated soft ultrasound markers for aneuploidy in the second trimester: (Replaces Consults #10, Single umbilical artery, October 2010; #16, Isolated echogenic bowel diagnosed on second-trimester ultrasound, August 2011; #17, Evaluation and management of isolated renal pelviectasis on second-trimester ultrasound, December 2011; #25, Isolated fetal choroid plexus cysts, April 2013; #27, Isolated echogenic intracardiac focus, August 2013). Am J Obstet Gynecol 2021;225:2-15.
6. Wax JR, Donnelly J, Carpenter M, et al. Childhood cardiac function after prenatal diagnosis of intracardiac echogenic foci. J Ultrasound Med 2003;22:783-7.
7. Kovacs CS, Feingol KR, Anawalt B, et al. Calcium and Phosphate Metabolism and Related Disorders During Pregnancy and Lactation. Endotext [Internet], 2021.
8. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. Obstet Gynecol 2009;114:1326-31.
9. Hantoushzadeh S, Jafarabadi M, Khazardoust S. Serum magnesium levels, muscle cramps, and preterm labor. Int J Gynaecol Obstet 2007;98:153-4.
10. Takaya J, Yamato F, Kaneko K. Possible relationship between low birth weight and magnesium status: from the standpoint of "fetal origin" hypothesis. Magnes Res 2006;19:63-9.
11. Huang H, Cai M, Liu L, Xu L, Lin N. Effectiveness of Chromosomal Microarray Analysis for Prenatal Diagnosis of Fetal Echogenic Intracardiac Focus: A Single-Center Experience. Int J Gen Med 2021;14:1991-7.
12. Song Y, Xu J, Li H, et al. Application of Copy Number Variation Detection to Fetal Diagnosis of Echogenic Intracardiac Focus During Pregnancy. Front Genet 2021;12:626044.
13. Liu HH, Lin MT, Chang CC, et al. Postnatal outcome of fetal cardiac echogenic foci. J Formos Med Assoc 2002;101:329-36.
14. Pavlíček J, Klásková E, Kaprálová S, et al. Echogenic foci in fetal heart from a pediatric cardiologists point of view. Ces Gynekol 2019;84:190-4.
15. Shanks AL, Odibo AO, Gray DL. Echogenic intracardiac foci: associated with increased risk for fetal trisomy 21 or not? J Ultrasound Med 2009;28:1639-43.
16. Chiu G, Zhao A, Zhang B, Zhang T. Intracardiac echogenic focus and its location: association with congenital heart defects. J Matern Fetal Neonatal Med 2019;32:3074-8.

Original Article

DOI: 10.4274/haseki.galenos.2021.1673
Med Bull Haseki 2022;60:45-51

Multifidus Muscle Stiffness in Single-level Unilateral Lumbar Disc Herniation: Comparison of Two Shear-wave Elastography Methods

Tuba Selcuk Can, Behice Kaniye Yilmaz, Sevim Ozdemir

University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Radiology, Istanbul, Turkey

Abstract

Aim: The suitability of shear-wave elastography (SWE) analysis in muscle tissue has been demonstrated previously. There are no studies that have applied the two SWE methods to evaluate the multifidus muscle in patients with lumbar disc herniation. We aimed to evaluate multifidus muscle stiffness in patients with single-level unilateral lumbar disc herniation via two SWE methods.

Methods: This cross-sectional study was carried out by examining the hospital records of patients who underwent lumbar MRI in July 2019. A total of 22 patients with single-level unilateral lumbar disc herniation underwent bilateral multifidus stiffness assessment via the two-dimensional SWE (2D-SWE) and point-SWE (p-SWE) methods.

Results: The only measurement that demonstrated a significant difference between normoweight and overweight subjects was the hernia-side p-SWE value. On the hernia side, 2D-SWE and p-SWE were correlated. Age was determined to be an independent factor that significantly altered results for the hernia and non-hernia sides of both techniques, while weight was an independent factor for the hernia and non-hernia results of only the p-SWE technique.

Conclusion: Lower muscle stiffness determined via 2D-SWE or p-SWE may have value in the diagnosis, follow-up, or management of patients with one-sided unilateral lumbar disc herniation. Age and weight appear to be important variables to consider when evaluating multifidus muscle stiffness values.

Keywords: Body mass index, height, multifidus muscle, shear-wave elastography, weight

Introduction

Chronic low back pain is a common condition since it may be associated with a variety of underlying pathologies, including lumbar disc herniation, facet joint degeneration, paraspinal muscle problems, and ligament injury (1,2). It is estimated that approximately one out of every four people has chronic low back pain and that it recurs at certain intervals (3).

With the use of ultrasound elastography (USE) in the musculoskeletal system over the last decade, promising results have been achieved in the diagnosis and management of muscle disorders (4,5). The working principle of USE in muscle evaluation is based on the testing methods utilized to identify the mechanical features of tissues. Meaning that the deformation caused by an outside force is recorded by the measurement of temporal shift in ultrasound (US) echo (6,7). However, strain elastography is operator-dependent and provides semi-quantitative values; conversely, shear-wave elastography (SWE) is considered to be a quantitative method that yields objective results. There are three different methods of SWE: transient elastography (TE), two-dimensional (2D) SWE, and point (p-) SWE. In TE, there are no B-mode anatomical images, while the other two methods can provide better data. In 2D-SWE, tissue stiffness can be determined via multiple measurements on 2D colored velocity maps of regions of interests (ROIs) determined by the operator. The third method, p-SWE, allows for multiple measurements on B-mode US images from the same area with a fixed ROI (8,9).

The suitability of SWE analysis in muscle tissue has been demonstrated previously (10,11). Moreover, studies

Address for Correspondence: Tuba Selcuk Can
University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital, Clinic of Radiology, Istanbul, Turkey
Phone: +90 532 784 34 77 E-mail: drtubas@gmail.com ORCID: orcid.org/0000-0002-2388-1715
Received: 04.08.2021 **Accepted:** 06.12.2021

by Murillo et al. (12) and Alis et al. (13) have utilized SWE to assess the multifidus muscle in patients with low back pain and lumbar disc herniation, respectively. There are no studies that have applied two SWE methods to evaluate the multifidus muscle in patients with lumbar disc herniation. In this study, we aimed to compare multifidus muscle elasticity on the herniated-side and non-herniated side of patients with unilateral lumbar disc herniation by using the 2D-SWE and p-SWE techniques and to compare the results obtained with each technique.

Methods

Ethical Consideration

Approval was received from the Ethics Committee of University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, (no: 2019-38, date: 27.11.2019). After providing verbal information concerning the conduct of the study, written informed consent forms were signed by each volunteer patient.

Study Design and Patient Population

This cross-sectional study was carried out by examining the hospital records of patients who underwent lumbar magnetic resonance imaging (MRI) in July 2019. We included 22 patients who were found to have a unilateral paramedian (posterolateral) hernia at a single level through lumbar MRI. All subjects that underwent MRI had been admitted with lower back pain complaints and were found to have one-sided compression-related pain, suggesting a preliminary diagnosis of lumbar disc herniation. Patients with multiple hernias or bilateral hernias, spondylolisthesis, and spinal canal stenosis, as well as those with a history of trauma, rheumatologic disease, malignancy, infection, or back surgery, were excluded from the study.

MRI

All lumbar MRI images were performed according to the standard lumbar MRI protocol (axial T2-weighted fast spin-echo; TR: 3000-4000, TE: 100, sagittal T2-weighted fast spin-echo; TR: 2500-3000, TE: 100, Sagittal T1-weighted spin-echo TR: 500, TE: 10) with a 1.5 Tesla Philips Achieva MRI device (Philips Healthcare, Best, The Netherlands). The images were evaluated at a workstation (SYNAPSE PACS, Fujifilm Medical Systems, U.S.A.) by a single radiologist with 7 years of spinal imaging experience. The observer first detected the presence of hernia from sagittal T2W images and then confirmed the presence of hernia on axial T2W images. Focal bulging of the intervertebral disc towards the lateral recess was considered a paramedian hernia (14). In the cases of nerve root contact in the lateral recess, compression and deviation in the nerve root were considered as the presence of nerve root contact in the relevant segment, and patients without nerve root contact were excluded from the study at this stage (15). Furthermore, the multifidus muscle areas were determined on both sides by drawing muscle borders with a free-hand ROI (Figure 1).

SWE

Two radiologists, different from the one that conducted MRI analysis, who had 12 years of experience with US and 4 years of experience with USE performed USE evaluations. The device used for SWE was an Esaote MyLab 9 device equipped with QElaXto 2D and QElaXto-pSWE with an L4-15 MHz linear probe. The evaluation of SWE was carried out in the following manner: before beginning the

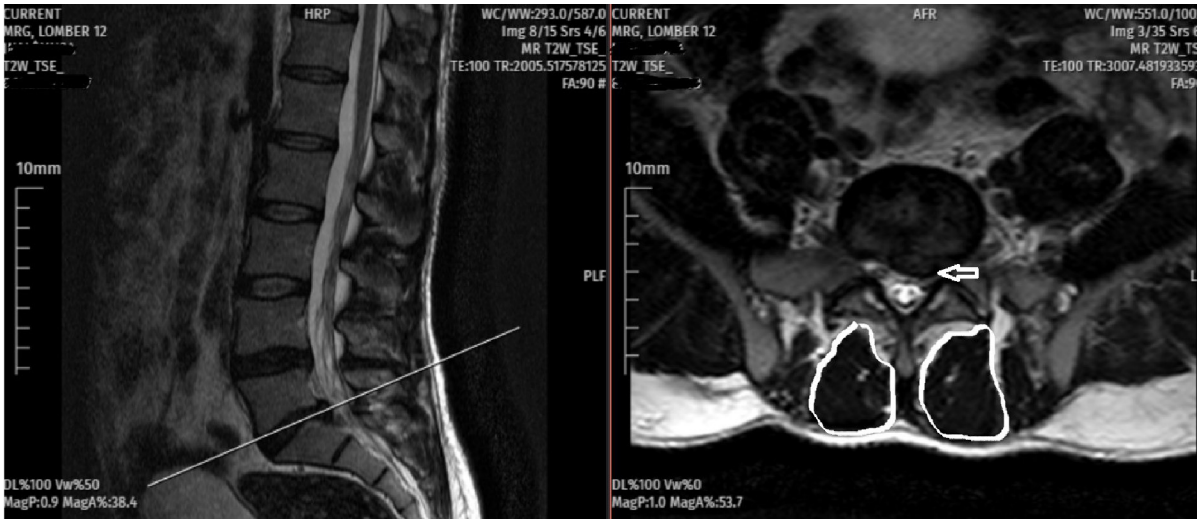


Figure 1. Sagittal T2W images are shown on the left and axial T2W images are shown on the right. A left paramedian hernia is seen at the level of L5-S1 in the axial view (arrow). Left S1 nerve compression is present in the left lateral recess. At this level, the borders of the bilateral multifidus muscle were drawn

procedure, the first radiologist was immediately informed about the hernia level, but not the side of the hernia. The patients were brought into the prone position with their hands supporting the head in the forehead area and arms in approximately 120° of abduction at normal room temperature (24 °C) (16-19). Rolled towels were placed under the abdominal area (to reduce lumbar lordosis) and under the ankles (for support) (16-19). The SWE measurement was performed appropriately for each level. For instance, in the presence of disc herniation at the L4-L5 level, the L5 vertebra spinous process was identified in B-mode and the probe was shifted 2 cm laterally for imaging of the multifidus muscle. The probe was then switched from longitudinal orientation to transverse orientation, and the probe was rotated about 10° (with the superior section moving medially) to enable a parallel position to muscle fibers (13). For the 2D-SWE measurement, a color-coded map was created by pressing the related button. Tissue stiffness was coded with colors varying between red and blue (high to low). After this stage, the patient was warned not to breathe deeply. A total of 3 ROIs, each with a diameter of 7 mm (13), were placed at different points in the color-coded area, followed by 2D-SWE measurements. After completing the measurements, the radiologist left the room and was replaced by the second radiologist who would carry out the p-SWE measurements. The second radiologist entered the room when the patient was lying down in the same position, and without changing the position of the patient, brought the probe into the appropriate position at the hernia level that he had been informed about immediately before entering the room. After necessary adjustments to confirm positioning, the radiologist performed 5 consecutive measurements in the image area with the fixed ROI by selecting the "point SWE (QElaXto)" mode on the device (Figure 2).

Statistical Analysis

A statistically significant difference in effect size difference (effect size dz=0.80) in the dependent group sampling was predicted to be 95%. With power analysis, the total number of subjects necessary for comparison was determined to be 19 patients, for an alpha error of 0.05 (13).

The Statistical Package for Social Sciences software, version 15.0, was used for statistical analysis in the evaluation of all the data obtained from the study. Descriptive statistical results (mean, standard deviation, minimum, maximum, frequency, percentage) were reported with regard to the quantitative and qualitative characteristics of each variable. The Mann-Whitney U test was used for the analyses comparing the means between two groups, the Wilcoxon test was implemented for right-left comparisons, and the Pearson correlation coefficient was calculated to assess relationships between variables. The results were accepted and evaluated at a confidence interval of 95% and significance was identified as $p<0.05$.

Results

Twenty-two patients with unilateral lumbar disc herniation were included in the study. The age of the patients ranged between 32 and 52 years, and the mean age was 44.23±5.49 years. Twelve patients (54.5%) were female, and 10 patients (45.5%) were male. With respect to age and body mass index (BMI), there were no statistically significant differences between females and males. The patients' mean height was found to be 1.69±0.11 m (range: 1.52-1.90 m), their mean weight

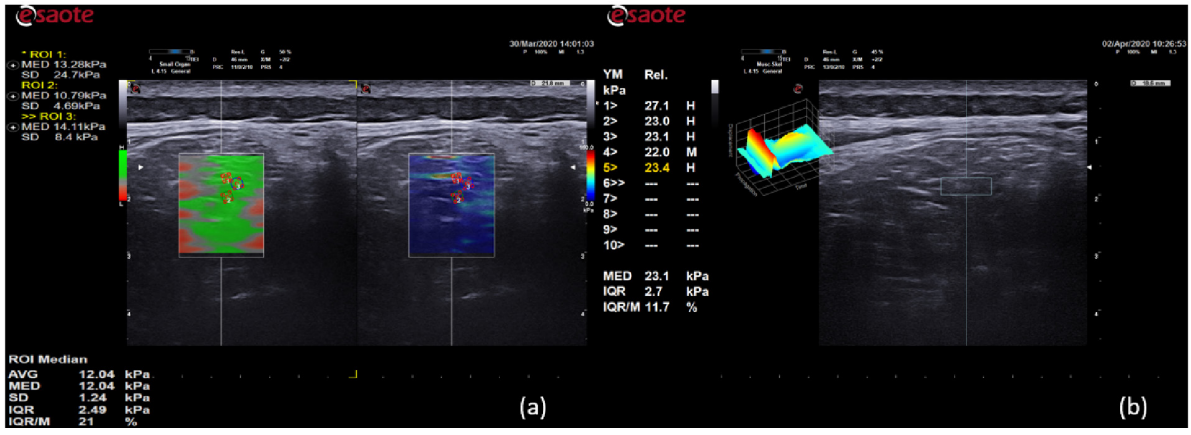


Figure 2. Elastography images, a: 2D-SWE measurement sample. This image consists of two images and is known as a "confidence map" with a green background, which shows that the measurement was made at the right place. It was necessary to do it from where it is homogeneous. The blue next to it shows three different measurements made from the field that we confirmed from the ie confidence map b: point-SWE measurement. The grayscale shows five different measurements made from the area in the ROI that we placed in the anatomical area we determined on the US image
US: Ultrasound, SWE: Shear-wave elastography, ROI: Regions of interest

Table 1. Comparison of p-SWE and 2D-SWE values on the hernia side and opposite side

	Hernia side		Non-hernia side		p-value*
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
p-SWE (kPa)	8.5±3.9	7.7 (4.6-21.4)	11.6±3.3	11.3 (6.3-21.2)	**0.002**
2D-SWE (kPa)	10.7±6.9	8.5 (3.1-28.2)	13±6.8	11.6 (3.2-33.6)	**0.020**
p-SWE vs. 2D-SWE p-value*	0.239		**0.016**		

*Related-samples Wilcoxon signed-rank test: It shows difference between the herniated and non-herniated sides of the same cases
SD: Standard deviation, min: Minimum, max: Maximum, SWE: Shear-wave elastography

Table 2. The results of p-SWE and 2D-SWE according to BMI category

	Normoweight (BMI<25)		Overweight (BMI≥25)		p-value*
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
Hernia p-SWE (kPa)	10.7±4.8	9.8 (4.6-21.4)	6.7±1.5	6.3 (5-9.2)	**0.014**
Non-hernia p-SWE (kPa)	13.1±3.7	12.4 (8.5-21.2)	10.3±2.2	10.7 (6.3-13.5)	0.059
Hernia 2D-SWE (kPa)	13.7±8.8	13.1 (3.3-28.2)	8.3±3.9	8.1 (3.1-17.2)	0.180
Non-hernia 2D-SWE (kPa)	15.1±9.8	12.6 (3.2-33.6)	11.4±2.3	11.4 (7.2-16.2)	0.418

**Independent samples, Mann-Whitney U test: it shows a difference between the normoweight and overweight cases
SD: Standard deviation, min: Minimum, max: Maximum, SWE: Shear-wave elastography, BMI: Body mass index

Table 3. Linear regression results showing parameters that were independently influential on different measurements of multifidus muscle stiffness

	Age	Weight	Height	BMI
Hernia p-SWE	ß=-0.552, P=0.008	ß=-0.648, P=0.043	ß=0.751, P=0.019	NS
Non-hernia p-SWE	ß=-0.651, P=0.007	ß=-0.454, P=0.038	NS	NS
Hernia 2D-SWE	ß=-0.598, P=0.004	NS	NS	NS
Non-hernia 2D-SWE	ß=-0.688, P=0.002	NS	NS	NS

NS: Not significant, BMI: Body mass index, SWE: Shear-wave elastography

was 71.91±10.14 kg (range: 50-92 kg), and their mean BMI was 25.25±2.27 kg/m^2 (range: 20.03-29.69 kg/m^2).

The level of hernia was L3-L4 in 13.6% (n=3), L4-L5 in 31.8% (n=7) and L5-S1 in 54.5% (n=12) of the subjects. The side of the hernia was distributed 50:50 between right and left. In terms of age and BMI, no statistically significant difference was found between those with a hernia on the right side and those with a hernia on the left side.

The p-SWE and 2D-SWE values were found to be significantly lower on the hernia side compared to the non-hernia side (p=0.002 and p=0.020, respectively) (Table 1). Although the p-SWE and 2D-SWE results were in agreement for the hernia side (p=0.239), there was a significant difference between the two tests in terms of the results obtained for the non-hernia side (p=0.016). Correlation analyses confirmed this, revealing a significant relationship on the hernia side (r=0.811, P<0.001) but no correlation on the non-hernia side (p=0.078).The cross-sectional areas of the multifidus muscle on the hernia side were found to be significantly smaller compared to the non-hernia side (p=0.002).

The results showed that the hernia-side p-SWE values were significantly lower among overweight subjects (n=12) compared to normoweight subjects (n=10) (p=0,014) (Table 2).

Finally, we performed linear regression to assess the effects of various variables on the results obtained from the tests. All four parameters of muscle stiffness were defined as dependent variables in separate regression analyses, with age, weight, height, and BMI included as factors. In all analyses, age was identified as a significant factor. Weight was identified as a significant factor for both p-SWE results, while height was only significant for hernia-side p-SWE results. Interestingly, the BMI value was not significant for any of the measurements (Table 3).

Discussion

Our results with two SWE techniques show that multifidus muscle stiffness is significantly decreased on the hernia side (compared to the non-hernia side) in patients with unilateral lumbar disc herniation. The comparison of the two techniques showed that p-SWE may result in lower stiffness values compared to 2D-SWE on the

side of the hernia. The results showed that age was a significant parameter that affected measurement results for both sides in both methods, whereas weight was only significant for p-SWE results. These results suggest that age should always be considered when performing multifidus stiffness evaluation, while weight should be taken into account when using p-SWE. It is also remarkable that BMI was not found to be effective on stiffness results.

In their MRI evaluation of L5 radiculopathy, Campbell et al. (17) described isolated atrophy and fatty change in the multifidus muscle on the ipsilateral side at the L5 level. In the following years, the multifidus muscle drew the attention of researchers since it had unisegmental innervation from a single root compared to multisegmental innervation in other paraspinal muscles. Studies were conducted on the cross-sectional area and fatty degeneration of the multifidus muscle in patients with radiculopathy (18-20). As a result of denervation, Hyun et al. (18) discovered muscle atrophy and a decrease in the cross-sectional area of the multifidus muscle. However, Battié et al. (19) discovered a larger fatty change in the hernia-side muscle, with a greater cross-sectional area than the non-hernia side. Although this difference can partially be explained by the fact that the duration of symptoms in the study of Battié et al. (19) was shorter compared to other studies, this finding still leads to questions regarding the use of multifidus muscle atrophy as a criterion in radiculopathy evaluation.

With the use of US elastography, SWE has drawn the attention of authors researching this topic due to its ability to provide quantitative data about muscle stiffness in addition to the changes in cross-sectional area and tissue structure. In a study where Creze et al. (1) evaluated SWE features at the L3 level of the paraspinal muscles in asymptomatic volunteers, *in vivo* results of 5.4±1.6 kPa and *ex vivo* results of 5.1±1.7 kPa stiffness were obtained for the multifidus muscle (1). In a feasibility study with 10 asymptomatic volunteers, Moreau et al. (21) evaluated the SWE features of the multifidus muscle at two different levels (L2-L3 and L4-L5), in the "passive stretching" position and at "rest". Although they worked with a small number of volunteers, they obtained intraclass correlation coefficient (ICC) values of 0.94 and 0.95 at the L2-L3 level in both positions with three different observers (in rest and passive stretching positions, respectively). They obtained relatively lower ICC values at the L4-L5 level. However, the small difference between repeatability and reproducibility and its independence from the observer were promising for the reliability of the technique. Besides these studies, Koppenhaver et al. (16) evaluated the multifidus muscle in a larger series consisting of 36 patients at three different contraction levels in addition to the rest position. At rest, multifidus SWE values were about 6 kPa and were shown to increase in direct proportion with the amount of contraction. Sadeghi et al. (22) obtained stiffness values of 16.15, 27.28 and 45.02 kPa, respectively, in their study evaluating the SWE features of the multifidus muscle in the prone position, standing and with one arm raised. In our study, the multifidus muscle measurements in the prone position ranged between 11.30 and 11.89 kPa on the non-hernia side. In contrast to the measurements made at one level in the literature, measurements were made at three different levels in our study, and the current differences shown may result from this feature, as well as the difference between the USE devices used. Among the few studies on symptomatic patients, Murillo et al. (12) found higher stiffness values (at the L3 level) in those with low back pain compared to controls. A similar finding was reported by Masaki et al. (23) who performed measurements at the L4 level. Koppenhaver et al. (16) also showed that multifidus stiffness was increased in people with low back pain. In these studies, which were carried out on patients with low back pain without any specific diagnosis, the finding of high stiffness can be explained by the protective mechanism and increased reflex muscle spasm (16).

In the literature on this subject, studies on this subject have almost always been conducted with 2D-SWE. In a similar study to ours by Alis et al. (13) the SWE features of the multifidus muscle were evaluated comparatively with the opposite side in patients with a single unilateral hernia at one of the three different levels. They found a mean stiffness value of 13.70±4.05-14.08±3.57 kPa on the affected side. In our study, the mean 2D-SWE value on the affected side was 10.7±6.9 (median: 8.5) kPa, and comparisons showed the hernia side had significantly lower values compared to the non-hernia side. They also identified a negative correlation between the duration of symptoms and multifidus stiffness (13). In addition, Wan et al. (24) found a similar correlation between the duration of symptoms and fatty change in patients with low back pain. Although the correlation between the duration of symptoms and multifidus stiffness was beyond the scope of our study, we did not include symptom duration as a parameter. We found that age was independently influential on stiffness analysis with both techniques. Although advanced age does not equate to an increased duration of symptoms in most patients, it is possible that this factor may be confounding for our regression analysis. Having said this, when we consider the difference between the affected and unaffected sides in terms of the cross-sectional area of the multifidus muscle, it seems apparent that the subjects in our study had a symptom duration that made atrophy possible. On

the other hand, regarding the changes in muscles due to denervation, Wen et al. (25) showed a decrease in muscle stiffness arising from the increase in extracellular fluid in the early period of denervation in a rabbit model; whereas, there was an increase in stiffness in the latter period (depending on increased collagen fibers despite a decrease in the cross-sectional area of the muscle). As a result, they hypothesized that the reduction in stiffness was an early sign of denervation. Rosskopf et al. (26) in their study in patients with supraspinatus tendon rupture, they found increased shear-wave velocities in stage IV patients, which were compatible with greater fatty atrophy in MRI, despite the decrease in muscle shear wave velocities up to Goutallier stage III. Although providing some insight, histological confirmation was not performed in this study, and it is also possible that these results were associated with the injury characteristics and the fact that they had applied the probe perpendicular to the muscle fibers (unlike other studies). In our study, the smaller size of the muscle areas on the hernia side can be explained by early denervation according to the hypothesis of Wen et al. (25) However, more data is required to draw conclusions since symptom duration was not evaluated in our study.

Study Limitations

Our study has some limitations. First, the presence of unilateral hernia was decided according to MRI and clinical data, and there was no electromyography verification in this study. Additionally, although the cross-sectional areas of the multifidus muscle were compared between the sides with and without hernia in the patients who were included in the study, the correlation between SWE values and symptom duration could not be evaluated since the symptom duration in the patients was not investigated. The relatively small number of people is an important limitation of the study. Finally, the changes in the multifidus muscle could not be verified histopathologically. Despite these limitations, being one of the rare studies on this subject and offering an alternative to clinicians were the important strengths of the study.

Conclusion

Our results demonstrate that two different SWE methods, 2D-SWE and p-SWE, measured lower stiffness values on the hernia side in patients with lumbar disc herniation. Moreover, we discovered that the cross-sectional areas of the multifidus muscle were smaller on the hernia side compared to the opposite side. It is also important to note that age and weight may be variables that independently affect multifidus stiffness in patients with unilateral lumbar disc herniation. In line with our results, we think that SWE methods have the potential for clinical utilization in the management of patients with lumbar disc herniation. Future studies that take into account the aforementioned points and limitations should be performed to assess these methods, and more comprehensive data should be obtained to determine the utility of SWE in the clinical setting.

Ethics

Ethics Committee Approval: Approval was received from the Ethics Committee of University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, (no: 2019-38, date: 27.11.2019).

Informed Consent: Written informed consent forms were signed by each volunteer patient.

Authorship Contributions

Concept: T.S.C., B.K.Y., Data Collection or Processing: B.K.Y., S.O., Analysis or Interpretation: S.O., Investigation: T.S.C., S.O., Methodology: B.K.Y., Project Administration: T.S.C., Supervision: T.S.C., Writing: T.S.C., B.K.Y., S.O.

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

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

References

1. Creze M, Nyangoh Timoh K, Gagey O, Rocher L, Bellin MF, Soubeyrand M. Feasibility assessment of shear wave elastography to lumbar back muscles: A Radioanatomic Study. Clin Anat 2017;30:774-80.
2. Al Qaraghli MI, De Jesus O. Lumbar Disc Herniation. Treasure Island: StatPearls Publishing; 2021.
3. Peck J, Urits I, Peoples S, et al. A Comprehensive review of over the counter treatment for chronic low back pain. Pain Ther 2021;10:69-80.
4. van Holsbeeck M, Soliman S, Van Kerkhove F, Craig J. Advanced musculoskeletal ultrasound techniques: what are the applications? AJR Am J Roentgenol 2021;216:436-45.
5. Demarco PJ. Advanced Ultrasound Applications: Elastography and Contrast-Enhanced Ultrasound. Musculoskeletal Ultrasound in Rheumatology Review: Springer; 2021. p. 529-60.
6. Brandenburg JE, Eby SF, Song P, et al. Ultrasound elastography: the new frontier in direct measurement of muscle stiffness. Arch Phys Med Rehabil 2014;95:2207-19.
7. Zúñiga LDO, López CAG, González ER. Ultrasound Elastography in the Assessment of the Stiffness of Spastic Muscles: A Systematic Review. Ultrasound Med Biol 2021;47:1448-64.
8. Kishimoto R, Kikuchi K, Koyama A, et al. Intra-and inter-operator reproducibility of US point shear-wave elastography in various organs: evaluation in phantoms and healthy volunteers. Eur Radiol 2019;29:5999-6008.
9. Mackintosh S, Young A, Lee A, Sim J. Considerations in the application of two dimensional shear wave elastography in muscle. Sonography 2020;7:13-21.

10. Saeki J, Ikezoe T, Nakamura M, Nishishita S, Ichihashi N. The reliability of shear elastic modulus measurement of the ankle plantar flexion muscles is higher at dorsiflexed position of the ankle. J Foot Ankle Res 2017;10:18.
11. Hug F, Tucker K, Gennisson JL, Tanter M, Nordez A. Elastography for Muscle Biomechanics: Toward the Estimation of Individual Muscle Force. Exerc Sport Sci Rev 2015;43:125-33.
12. Murillo C, Falla D, Rushton A, Sanderson A, Heneghan NR. Shear wave elastography investigation of multifidus stiffness in individuals with low back pain. J Electromyogr Kinesiol 2019;47:19-24.
13. Alis D, Durmaz ESM, Alis C, et al. Shear Wave Elastography of the Lumbar Multifidus Muscle in Patients With Unilateral Lumbar Disk Herniation. J Ultrasound Med 2019;38:1695-703.
14. Fardon DF, Williams AL, Dohring EJ, Murtagh FR, Gabriel Rothman SL, Sze GK. Lumbar disc nomenclature: version 2.0: Recommendations of the combined task forces of the North American Spine Society, the American Society of Spine Radiology and the American Society of Neuroradiology. Spine J 2014;14:2525-45.
15. Pfirrmann CW, Dora C, Schmid MR, Zanetti M, Hodler J, Boos N. MR image-based grading of lumbar nerve root compromise due to disk herniation: reliability study with surgical correlation. Radiology 2004;230:583-8.
16. Koppenhaver S, Kniss J, Lilley D, et al. Reliability of ultrasound shear-wave elastography in assessing low back musculature elasticity in asymptomatic individuals. J Electromyogr Kinesiol 2018;39:49-57.
17. Campbell WW, Vasconcelos O, Laine FJ. Focal atrophy of the multifidus muscle in lumbosacral radiculopathy. Muscle Nerve 1998;21:1350-3.
18. Hyun JK, Lee JY, Lee SJ, Jeon JY. Asymmetric atrophy of multifidus muscle in patients with unilateral lumbosacral radiculopathy. Spine (Phila Pa 1976) 2007;32:598-602.
19. Battié MC, Niemelainen R, Gibbons LE, Dhillon S. Is level- and side-specific multifidus asymmetry a marker for lumbar disc pathology? Spine J 2012;12:932-9.
20. Kang JI, Kim SY, Kim JH, Bang H, Lee IS. The location of multifidus atrophy in patients with a single level, unilateral lumbar radiculopathy. Ann Rehabil Med 2013;37:498-504.
21. Moreau B, Vergari C, Gad H, Sandoz B, Skalli W, Laporte S. Non-invasive assessment of human multifidus muscle stiffness using ultrasound shear wave elastography: A feasibility study. Proc Inst Mech Eng H 2016;230:809-14.
22. Sadeghi S, Quinlan K, E Eilertson K, et al. Changes in Shear Modulus of the Lumbar Multifidus Muscle during Different Body Positions. J Biomech Eng 2019.
23. Masaki M, Aoyama T, Murakami T, et al. Association of low back pain with muscle stiffness and muscle mass of the lumbar back muscles, and sagittal spinal alignment in young and middle-aged medical workers. Clin Biomech (Bristol,Avon) 2017;49:128-33.
24. Wan Q, Lin C, Li X, Zeng W, Ma C. MRI assessment of paraspinal muscles in patients with acute and chronic unilateral low back pain. Br J Radiol 2015;88:20140546.
25. Wen J, Wang Y, Jiang W, et al. Quantitative Evaluation of Denervated Muscle Atrophy with Shear Wave Ultrasound Elastography and a Comparison with the Histopathologic Parameters in an Animal Model. Ultrasound Med Biol 2018;44:458-66.
26. Rosskopf AB, Ehrmann C, Buck FM, Gerber C, Flück M, Pfirrmann CW. Quantitative Shear-Wave US Elastography of the Supraspinatus Muscle: Reliability of the Method and Relation to Tendon Integrity and Muscle Quality. Radiology 2016;278:465-74.

Original Article

DOI: 10.4274/haseki.galenos.2022.7788
Med Bull Haseki 2022;60:52-56

Investigation of the Relationship Between Wrist Ganglion Cysts and the Ulnar Variance Using 3-Tesla Magnetic Resonance Imaging

Murat Bayav

Eskisehir City Hospital, Clinic of Radiology, Eskisehir, Turkey

Abstract

Aim: A ganglion cyst is the most common soft tissue mass in the wrist and although the etiology of ganglion cysts remains unclear, the commonly accepted theory is that they are due to acute or chronic stress in the joint, which may be also caused by ulnar variance. The study aims to evaluate the relationship of ulnar variance in the wrist with ganglion cysts in this region using magnetic resonance imaging (MRI).

Methods: In this cross-sectional study, patients aged 18 years and over who underwent wrist MRI between January 1, 2019 and December 31, 2019 were evaluated. The MR images and patient demographic data were obtained from a hospital database. The presence and size of the ganglion cyst and the amount of ulnar variance were assessed using the MR images. The ulnar variance was classified into negative, positive, and neutral groups to compare ganglion cyst presence between these groups.

Results: A total of 216 wrists from 206 patients were included in the study. The ulnar variance was negative in 100 (46.3%) wrists, neutral in 99 (45.8%), and positive in 17 (7.9%). One or more ganglion cysts were observed in 130 (60.2%) wrists, and no ganglion cyst was found in 86 (39.8%). Compared to the neutral group, the patients with negative ulnar variance had a six-fold increased risk, and those with positive ulnar variance had a 12-fold increased risk of having a ganglion cyst.

Conclusion: The presence of positive or negative ulnar variance increases the risk of having a ganglion cyst in the wrist. This may be related to soft tissue trauma caused by joint instability due to ulnar variance. MRI can be performed to evaluate the presence of ganglion cysts in patients with positive or negative ulnar variance detected on direct radiography.

Keywords: Wrist joint, ganglion cysts, ulna, magnetic resonance imaging

Introduction

Ulnar variance is the relative length of the distal articular surface of the ulna to the radius (1). Ulnar variance measurement is generally performed in the neutral position using postero-anterior radiographs. However, the soft tissue resolution of radiographs is low. A recent study shows that ulnar variance on wrist magnetic resonance imaging (MRI) can be measured reliably (2). Another recent study shows positive ulnar variance increases pathologies of the triangular fibrocartilage complex (TFCC) and longitudinal carpal instability using MRI (3).

A ganglion cyst is the most common benign soft tissue mass in the wrist. It is diagnosed based on imaging with sonography or MRI (4). Although the etiology of ganglion cysts remains unclear, the commonly accepted theory is that due to acute or chronic stress in the joint, the fluid in the joint leaks between the tissues, creating an inflammatory reaction (5). It is known that both negative and positive ulnar variances cause carpal instability (1). However, there is not sufficient information in the literature concerning the relationship between ulnar variance and ganglion cysts located in the wrist.

This study aimed to evaluate the relationship between ulnar variance in the wrist and ganglion cysts in this region using 3-Tesla MRI.

Address for Correspondence: Murat Bayav
Eskisehir City Hospital, Clinic of Radiology, Eskisehir, Turkey
Phone: +90 535 617 17 47 E-mail: muratbayav@hotmail.com ORCID: orcid.org/0000-0002-8210-4182
Received: 21.09.2021 **Accepted:** 02.01.2022

Methods

Ethical Statement

An ethics committee and institution approval were obtained before starting the study (approved by the ethics committee of Eskisehir Osmangazi University, approval number: 2020/541, date: 12.01.2021). Informed consent was not required by the ethics committee due to the retrospective nature of the study.

Patients

In this retrospective cross-sectional study, patients aged 18 years and over who underwent wrist MRI between January 1, 2019 and December 31, 2019 were retrospectively evaluated. Broad inclusion criteria which cover most of the patients without considering clinical symptoms were used in order to investigate the relationship between ulnar variance and the presence of ganglion cysts in many cases independent of clinical symptoms. The exclusion criteria were MRI images with insufficient diagnostic quality, those that contained congenital or sequelae changes that would disrupt the wrist bone alignment, which makes it impossible to measure ulnar variance, and those that were not obtained in the neutral position. We identified a total of 216 wrist images of 206 patients meeting the study criteria.

Imaging Protocol and Image Analysis

Images were obtained using the Siemens Magnetom Skyra™ (Siemens AG, Muenchen, Germany) 3-Tesla MRI device. The imaging protocol was as follows: axial fat suppressed (FS) turbo spin echo (TSE) proton density-weighted imaging (PD-WI) (TR, 4860 ms; TE, 46 ms; NEX, 1; ETL, 7; section thickness, 2.5 mm; interslice gap, 0.25 mm; flip angle, 150°; matrix size, 320x320; and field of view, 100x100 mm), coronal FS TSE PD-WI (TR, 2340 ms; TE, 37 ms; NEX, 1; section thickness, 3 mm; interslice gap, 0.3 mm; flip angle, 150°; matrix size, 320x320; and field of view, 100x100 mm), coronal TSE T1 WI (TR, 2340 ms; TE, 37 ms; ETL, 9; NEX, 1; section thickness, 3 mm; interslice gap, 0.3 mm; matrix size, 320x320; and field of view, 100x100 mm), 3D TSE T2 WI (TR, 17 ms; TE, 5,67 ms; ETL, 2; NEX, 1; section thickness, 0.4 mm; matrix size, 320x320; and field of view, 100x100 mm), and sagittal FS TSE T2 WI (TR, 3800 ms; TE, 78 ms; NEX, 1; ETL, 9; section thickness, 2.5 mm; interslice gap, 0.25 mm; flip angle, 150°; matrix size, 288x384; and field of view, 90x120 mm).

The images were evaluated by a radiologist with two years of experience in MRI. The presence of ganglion cysts was evaluated from coronal T2 WI and T1 WI together with FS PD-WI in the axial and coronal planes. Ganglion cysts were defined as lesions with low T1 signal and high T2 and PD signals similar to synovial fluid, with a well-demarcated nodular appearance, adjacent to the joint space or tendons (Figure 1). For the patients detected to have ganglion cysts, the size measurement of the cysts was performed using 3D T2 WI due to the thinner section thickness. The longest diameter of the ganglion cyst was accepted as the size. The ulnar variance was evaluated using coronal T1 WI. In this evaluation, the distance between the transverse plane passing through the lunate fossa of the radius and the transverse plane passing through the ulnar head was measured (Figure 2). Positive or negative ulnar variance amounts below 1 mm were considered neutral. A dataset was created by recording the demographic data of the patients with the measurement data obtained.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS version 25 (IBM Corp., Armonk, New York, NY, USA) software package. Mean standard deviation (minimum-maximum) values were used to represent continuous data with a normally distributed distribution, whereas frequency and percentage were used to represent categorical data. The correlation analysis of the amount of ulnar variance and the diameter of the ganglion cysts was performed with the Pearson correlation test. Ulnar variance groups were compared using the chi-square test in terms of categorical data such as the presence of ganglion cysts, while the independent samples t-test was used to compare the mean values of continuous data such as the ganglion cyst diameter between the groups. In addition, for the groups with positive and negative ulnar variances, the odds ratio (OR) for having a ganglion cyst was calculated in comparison with the ulnar neutral variance group. A p-value of 0.05 was considered statistically significant.

Results

Of the 206 patients included in the study, 93 (45.1%) were male and 113 (54.9%) were female. The mean age of the patients was 35.03±12.51 (18-74) years. Of the 216 wrists imaged, 116 (53.7%) belonged to the right wrist and 100 (46.3%) to the left wrist. The most common reasons for imaging indications included trauma in 65 (30.1%) patients, tenosynovitis in 42 (19.4%), pain in 41 (19%), and ganglion cysts and soft tissue masses in 41 (19%). Ulnar variance was negative in 100 (46.3%) wrists, neutral in 99 (45.8%), and positive in 17 (7.9%). The mean amount of ulnar variance was 3.15±1.38 (1.10-9.18) mm for the wrists with negative ulnar variance and 2.02±0.67 (1.16-3.66) mm for those with positive ulnar variance. One or more ganglion cysts were observed in 130 (60.2%) wrists, and no ganglion cyst was found in 86 (39.8%) (Table 1). Among the wrists with ganglion cysts, there was one ganglion cyst in 111 (85.4%), two in 16 (12.3%), and

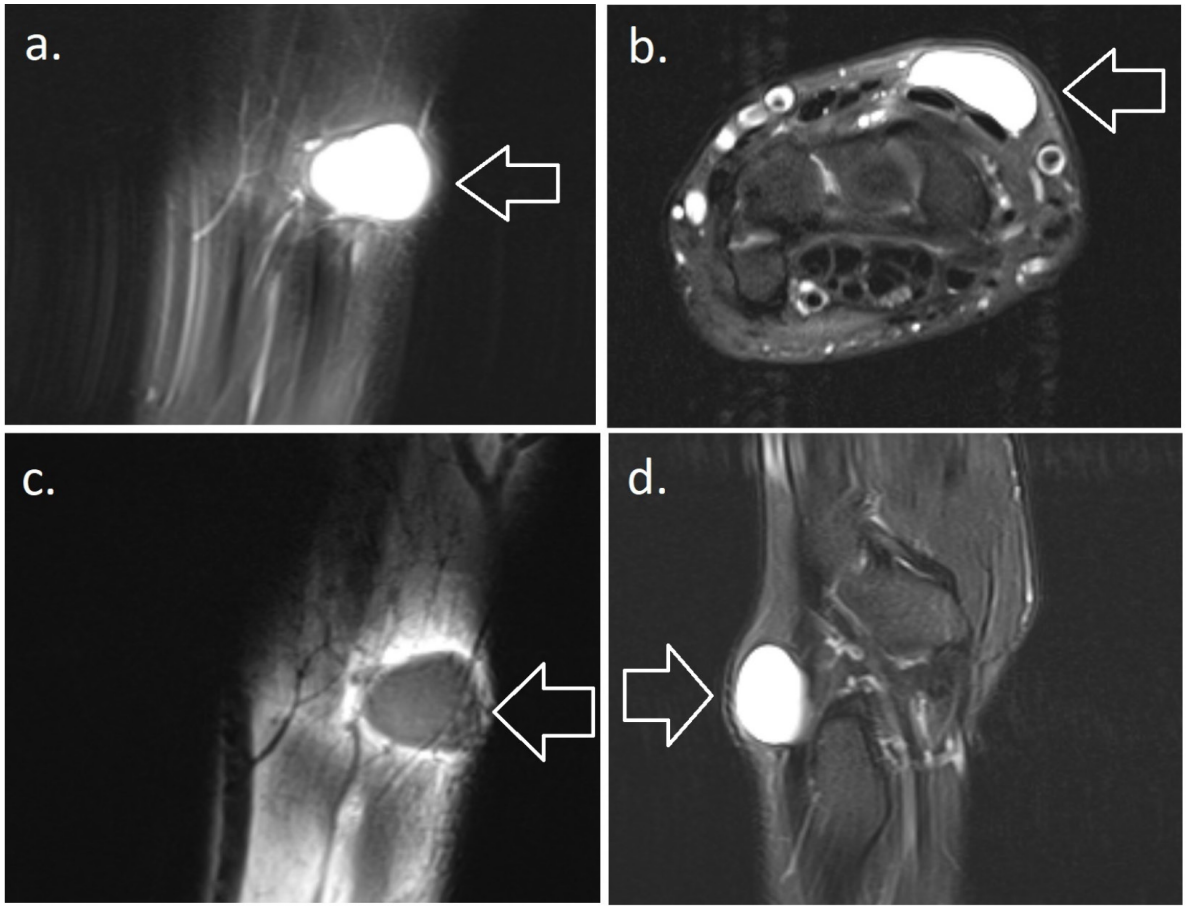


Figure 1. a. Coronal fat-suppressed proton density-weighted and **b.** Axial fat-suppressed proton density-weighted images showing a well-demarcated hyperintense ganglion cyst adjacent to the extensor tendons. **c.** Coronal T1 and **d.** sagittal FS T2-weighted images of the same cyst (white arrows)

three or more in three (2.3%). The female had a ganglion cyst presence ratio of 63.6%, while the male had a ratio of 55.8%. Considering the largest cyst of the cases with more than one ganglion cyst, the location of the cyst was in the palmar area in 70 (53.8%) cases, dorsal in 43 (33.1%), and the interosseous area in 17 (13.1%).

Table 1. Patient characteristics		
Mean age, years	35.03±12.51 (18-74)	
Gender	Male	93 (45.1%)
	Female	113 (54.9%)
Wrist side	Right	116 (53.7%)
	Left	100 (46.3%)
Ganglion cyst	Present	130 (60.2%)
	Absent	86 (39.8%)
Ulnar variance	Negative	100 (46.3%)
	Neutral	99 (45.8%)
	Positive	17 (7.9%)
Data are shown as mean ± standard deviation (min-max) and n (%) Min: Minimum, max: Maximum		

For the patients with ganglion cysts, the mean cyst diameter was 9.04±4.55 (3.3-25.82) mm in those with negative ulnar variance, 8.45±4.11 (2.8-20.44) mm in

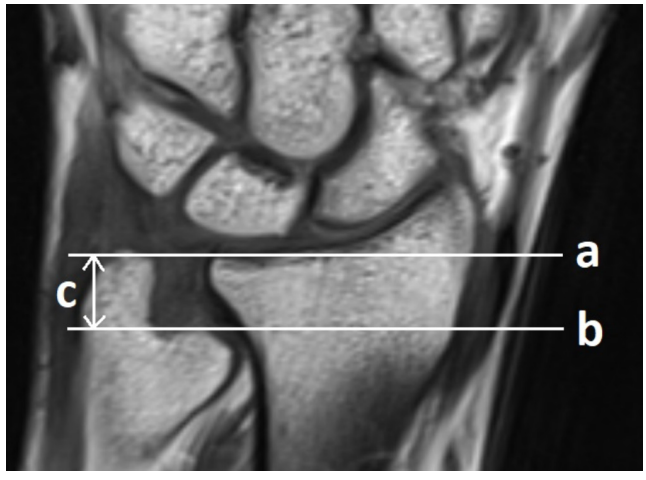


Figure 2. Coronal T1-weighted image. **a.** Transverse plane in the lunate fossa of the radius, **b.** transverse plane passing through the distal ulnar head, and **c.** ulnar variance amount

those with neutral ulnar variance, and 9.77±5.01 (3.59-20.89) mm for those with positive ulnar variance, indicating no statistically significant difference between the negative and positive groups and the neutral group (p=0.49 and p=0.90, respectively). When the ganglion cyst presence according to ulnar variance was examined, compared to the neutral group, those with negative ulnar variance had a six-fold increased risk [OR: 5.95; 95% confidence interval (CI): 3.18-11.11] and those with positive ulnar variance had a 12-fold increased risk of having a ganglion cyst (OR: 12.56; 95% CI: 2.72-58.07) of having a ganglion cyst. Ganglion cysts were statistically significantly more common among the patients with negative or positive ulnar variance (Table 2) (Pearson's χ^2: 40,325, p<0.001).

Discussion

At the end of the study, the risk of having a ganglion cyst was found to be approximately six times greater in the group with negative ulnar variance and 12 times greater in the group with positive ulnar variance compared to the neutral ulnar variance. This reveals that having a ganglion cyst is particularly closely related to having positive ulnar variance. We have not encountered any publication in the literature that demonstrates this relationship. However, Turan et al. (6) showed a relationship between negative ulnar variance and scaphoid bone fractures. In addition, Yoshioka et al. (7) reported that ulnar variance was positively correlated with the TFCC angle and negatively correlated with its thickness. In another study, Roh et al. (8) determined that positive ulnar variance was more common in patients with a symptomatic TFCC tear. These studies reveal the effect of wrist instability caused by positive or negative ulnar variance on bone and soft tissues. Also, shortening of the ulna in positive ulnar variance patients by osteotomy resulted in improved carpal stability outcomes (9). In the etiology of ganglion cysts, there is acute or chronic stress-induced leakage of the joint fluid, which results in an inflammatory reaction as discussed in the introduction (5). This also explains the effect of positive and negative ulnar variance on ganglion cysts observed in our study.

Ghalimah et al. (10) found the negative ulnar variance rate to be 56.2% and the neutral variance rate to be 43.8% in X-ray (plain radiography) examinations performed on the wrist in healthy volunteers, and they did not find any positive ulnar variance. In our study, although the rate of neutral variance was similar, a positive variance was observed at a rate of approximately 8%, and the negative variance rate was 46.3%. This may be associated with the symptomatic nature of the cases with positive variance since we did not exclude patients showing symptoms from our sample. In another study conducted with X-ray examinations, it was revealed that there was excellent agreement between the observers and the maximum inter-observer difference was 1 mm in the assessment of ulnar variance (11). Studies demonstrate the success of X-ray imaging in evaluating ulnar variance. However, the soft tissue resolution of X-ray imaging is low. Due to the low soft tissue resolution of X-ray, Yoshioka et al. (7) chose to use high-resolution gradient echo T2 *MRI images obtained with a 1.5-Tesla device, and Roh et al. (8) used conventional T1 and T2 WI obtained with a 3-Tesla device to evaluate ulnar variance. In the current study, we also obtained images using a 3-Tesla MRI device to evaluate ganglion cysts and used conventional T1 WI to evaluate ulnar variance.

Zhang et al. (12), who evaluated ganglion cysts with sonography, stated that 69% of the ganglion cysts associated with the wrist were seen on the palmar surface and 31% on the dorsal face. In an MRI study, Lowden et al. (13), investigating the presence of ganglion cysts in a healthy volunteer population, reported that 86% of the ganglion cysts originated from the palmar surface, mostly from the opening between the radioscaphocapitate and the long radiolunate ligament. In addition, they found the frequency of ganglion cysts among healthy volunteers to be 51% (13). Similarly, in the current study, although ganglion cysts were mostly seen on the palmar side, the incidence of ganglion cysts was found at a rate of approximately 60%, and this was attributed to the inclusion of symptomatic patients in the sample.

In a study examining the surgical results of ganglion cysts, the recurrence rate of ganglion cysts was found

Table 2. Presence of ganglion cyst according to ulnar variance

		Ganglion cyst		
		Absent	**Present**	
Ulnar variance	Negative	22 (10.2%)	78 (36.1%)	Pearson's χ2: 40,325 (p<0.001)
	Neutral	62 (28.7%)	37 (17.1%)	
	Positive	2 (0.9%)	15 (6.9%)	
	Total	86 (39.8%)	130 (60.2%)	

Data are shown as n (%)
The presence of ganglion cyst is higher in positive and negative ulnar variance groups than in neutral group

to be approximately 10%, and no significant relationship was detected between recurrence and gender, age, wrist side, or cyst localization (14). Ganglion cysts can also be resected arthroscopically with a low rate of complications and recurrence when they are symptomatic (15). Although ganglion cysts have been mostly evaluated surgically in the literature, in an MRI study of wrist ganglion cysts in pediatric cases, Bracken and Bartlett (16) found accompanying imaging findings in those with ganglion cysts, listing them as joint effusion, trauma-related bone marrow edema and fractures, TFCC tears, and negative ulnar variance, in order of frequency. We did not find any study in the literature that directly investigated the relationship between ulnar variance and ganglion cysts.

Study Limitations

The main limitations of the study are the absence of imaging and clinical follow-up of the patients due to the retrospective design. In addition, the results cannot be generalized to the whole population since the study was conducted in a single center. Lastly, only radiological findings were evaluated, and clinical symptoms or surgical findings were not included in the study. On the other hand, this study was the first one evaluating the relationship of ulnar variance in the wrist with ganglion cysts, and further studies that include clinical features of ganglion cysts can provide further information on the relationship.

Conclusion

Ulnar variance can be easily evaluated with direct radiography performed in the first line of imaging undertaken due to wrist pain. As shown in our study, the risk of having ganglion cysts in patients with positive or negative ulnar variance is considerably higher compared to patients with neutral ulnar variance. In this situation, MRI will be useful in revealing accompanying ganglion cysts and other soft tissue disorders among patients with negative or positive ulnar variance.

Ethics

Ethics Committee Approval: The study was approved by the ethics committee of Eskisehir Osmangazi University with approval number: 2020/541, date: 12.01.2021.

Informed Consent: Informed consent was not required by the ethics committee due to the retrospective nature of the study.

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

References

1. Cerezal L, del Piñal F, Abascal F, García-Valtuille R, Pereda T, Canga A. Imaging findings in ulnar-sided wrist impaction syndromes. Radiographics 2002;22:105-21.
2. Serfaty A, Costa HP, Foelker CE, Filho ENK, Souza FF, Bordalo-Rodrigues M. Evaluation of ulnar variance on wrist MR imaging: is it a reliable measure? Skeletal Radiol 2020;49:723-30.
3. Ozer K, Zhu AF, Siljander B, Lawton JN, Waljee JF. The Effect of Axial Loading on Ulnar Variance. J Wrist Surg 2018;7:247-52.
4. Strike SA, Puhaindran ME. Tumors of the Hand and the Wrist. JBJS Rev 2020;8:e0141.
5. Meena S, Gupta A. Dorsal wrist ganglion: Current review of literature. J Clin Orthop Trauma 2014;5:59-64.
6. Turan A, Kose O, Aktan C, Unal M, Acar B, Sindel M. Radiographic analysis of anatomic risk factors for scaphoid fractures; A case-control study. Clin Imaging 2018;51:341-6.
7. Yoshioka H, Tanaka T, Ueno T, et al. Study of ulnar variance with high-resolution MRI: correlation with triangular fibrocartilage complex and cartilage of ulnar side of wrist. J Magn Reson Imaging 2007;26:714-9.
8. Roh YH, Kim S, Gong HS, Baek GH. Prevalence and clinical characteristics of radiographic central triangular fibrocartilage complex tears in symptomatic and asymptomatic individuals younger than 50 years. Arch Orthop Trauma Surg 2018;138:1173-8.
9. Roulet S, Gubbiotti L, Lakhal W, et al. Ulna shortening osteotomy for ulnar impaction syndrome: Impact of distal radioulnar joint morphology on clinical outcome. Orthop Traumatol Surg Res 2021;107:102970.
10. Ghalimah BA, Mimish RL, Khashoggi KG, Hamdi AS. A preliminary exploration of ulnar variance in healthy wrists at a tertiary hospital in Jeddah. Saudi Med J 2016;37:843-6.
11. Goldfarb CA, Strauss NL, Wall LB, Calfee RP. Defining ulnar variance in the adolescent wrist: measurement technique and interobserver reliability. J Hand Surg Am 2011;36:272-7.
12. Zhang A, Falkowski AL, Jacobson JA, Kim SM, Koh SH, Gaetke-Udager K. Sonography of Wrist Ganglion Cysts: Which Location Is Most Common? J Ultrasound Med 2019;38:2155-60.
13. Lowden CM, Attiah M, Garvin G, Macdermid JC, Osman S, Faber KJ. The Prevalence of Wrist Ganglia in an Asymptomatic Population: Magnetic Resonance Evaluation. J Hand Surg Br 2005;30:302-6.
14. Kuliński S, Gutkowska O, Mizia S, Martynkiewicz J, Gosk J. Dorsal and volar wrist ganglions: The results of surgical treatment. Adv Clin Exp Med 2019;28:95-102.
15. d'Ailly PN, Koopman JE, Selles CA, Rahimtoola ZO, Schep NWL. Patient-Related Outcomes of Arthroscopic Resection of Ganglion Cysts of the Wrist. J Wrist Surg 2021;10:31-5.
16. Bracken J, Bartlett M. Ganglion cysts in the paediatric wrist: magnetic resonance imaging findings. Pediatr Radiol 2013;43:1622-8.

Original Article

DOI: 10.4274/haseki.galenos.2021.7876
Med Bull Haseki 2022;60:57-63

The Relationship between Nutritional Status and Early- and Mid-term Mortality of Geriatric Patients Admitted to the Emergency Internal Medicine Unit

Arzu Cennet Isik*, Ali Karagoz**, Asli Ocal*, Seydahmet Akin*, Banu Boyuk*, Ozcan Keskin*

*University of Health Sciences Turkey, Kartal Dr. Lutfi Kirdar City Hospital, Clinic of Internal Medicine, Istanbul, Turkey

**University of Health Sciences Turkey, Kosuyolu Yuksek Ihtisas Training and Research Hospital, Clinic of Cardiology, Istanbul, Turkey

Abstract

Aim: The need for bodily energy in the elderly may decrease due to physical activity limitations, while it may increase with the effects of the disease. The most common screening tool developed for the geriatric population is the Mini Nutritional Assessment, and lower scores are associated with higher mortality predictions. We aimed to correlate the nutritional status of patients admitted to the emergency department with mortality.

Materials and Method: Among the geriatric patients admitted to our emergency internal medicine unit between October 1, 2019, and March 1, 2020, 289 patients were included in this cross-sectional study. The Nutritional Risk Screening-2002 and Mini Nutritional Assessment tests were administered to all patients.

Results: The number of patients at risk of malnutrition was 49.4% (n=143). The median follow-up was 312 days for all patients, and the mortality rate was 42.5% (n=123) for all our patients, and 50.4% (n=72) of the patients who died were male. Diabetes was high in our geriatric patients, as in all age groups, and its effect on mortality was observed, and cancer patients had an almost three-fold higher malnutrition rate. Seventy patients were transferred from the internal medicine service to the intensive care unit, and 61 of these patients (87.14%) died.

Conclusion: The Mini Nutritional Assessment is a non-complex and sensitive method that can be used to predict early and mid-term mortality in geriatric patients admitted to the emergency department.

Keywords: Malnutrition, nutritional assessment, nutritional surveys, emergency medicine

Introduction

The size of the geriatric age group, defined as 65 and over by the World Health Organization, is rapidly increasing in our country and all over the world. By 2050, it is estimated that the global elderly population, which was 900 million in 2015, will reach 2 billion, and in Turkey by 2080, it is predicted to be 25.6% (1,2). This increase will result in rising healthcare service use and costs due to chronic diseases (3,4).

The need for bodily energy in the elderly may decrease due to physical activity limitations, while it may increase with the effect of disease (5). Since malnutrition can occur not only in thin people but also in obese people, it is recommended that all geriatric patients be screened routinely for nutritional evaluation during hospital admissions and followed up regularly (3 months/yearly), depending on the patient's detected nutritional status.

The average minimum energy requirement of a geriatric patient is considered to be between 25 and 30 kcal/kg (5,6). The most common screening tool developed for the geriatric population is the Mini Nutritional Assessment (MNA) (7). An observational study revealed that lower MNA scores are associated with higher mortality predictions (8). Another 5-year mortality study showed that the detection of malnutrition in hospitalized patients

Address for Correspondence: Arzu Cennet Isik
University of Health Sciences Turkey, Kartal Dr. Lutfi Kirdar City Hospital, Clinic of Internal Medicine, Istanbul, Turkey
Phone: +90 505 817 45 19 E-mail: arzukaracelik@gmail.com ORCID: orcid.org/0000-0001-9844-8599
Received: 16.10.2021 **Accepted:** 23.12.2021

with acute causes and different comorbidities effectively predicts all-cause mortality (9). In a study in Portugal, it was determined that the results of 456 patients who underwent short and long MNA tests were compatible, and even by adding two questions, the nutritional status could be better demonstrated (10).

However, the relationship of the MNA with early and mid-term mortality in emergency internal medicine referrals of the geriatric population has not been studied. This study aimed to evaluate the effect of the nutritional status of geriatric patients receiving inpatient treatment in emergency internal medicine clinics on early and mid-term mortality.

Methods

Study Design

The ethics committee of University of Health Sciences Turkey, Kartal Dr. Lutfi Kirdar City Hospital approved the study on 06.12.2019 with the number 2019/514/167/23, and it was performed following the 1964 Declaration of Helsinki and its later amendments. An informed consent form was approved by all patients. Among the geriatric patients admitted to our emergency internal medicine unit between October 1, 2019, and March 1, 2020, 289 hospitalized patients were prospectively included in the study. Clinical and laboratory information was obtained from electronic records, and the patients were evaluated with the MNA following the nutrition risk screening in 2002 (NRS-2002) (11). Body mass index (BMI) is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m^2). A BMI of less than 18.5 means a person is underweight.

A BMI of between 18.5 and 24.9 is ideal. A BMI of between 25 and 29.9 is considered overweight, and over 30 is obese. The detailed study inclusion and exclusion criteria are indicated in Figure 1.

Nutritional Assessment

NRS-2002 aims to identify people who will benefit from nutritional therapy due to increased nutritional needs resulting from malnutrition and/or disease. The screening form includes an initial scan and a final scan. A final screening is performed if the answer to any of the four questions in the first screening is "yes". Patients with a total score of three or more are considered to be at nutritional risk.

MNA was developed as a reliable screening test to determine whether nutrition is adequate in aged people (7). With questions and anthropometric measurements, the nutritional status of patients can be easily estimated even without laboratory data (12). Although the parameters used are not crucial for diagnosis, they are generally essential for follow-up. The first part consists of six questions and is a quick screening test. The total score is obtained by asking in the second part an additional 12 questions of those who scored lower in the first part. A total score of 23.5 and above is considered normal nutritional status, a score between 17 and 23 is a risk of malnutrition, and a score <17 is considered malnutrition. There is not yet a specific laboratory test that can be used to diagnose malnutrition.

The NRS-2002 test and the first part of the MNA were administered to all patients. The long MNA was not applied to those with adequate nutrition, but by evaluating the scores from the first part, those who did not have sufficient nutrition were evaluated with the long MNA.

Chronic disease and malignancy diagnoses of the patients were determined, and the NRS and MNA tests were performed. As per the MNA score, patients with malnutrition and those at risk of malnutrition were evaluated as having nutritional deficiencies, and their nutrition was arranged according to their nutritional status. Within one year after discharge, follow-up and mortality data were provided using hospital and telephone visits or a national registry system.

Statistical Analysis

Numerical variables are represented by median and interquartile-ranges (25^{th}-75^{th}), Wilcoxon rank-sum test used for the comparisons. For the discrete data, frequencies and absolute numbers are given as frequencies. For comparison, Pearson chi-squared was used. For the correlation analysis of numerical variables, the Spearman test was used.

Outcome variable: All-cause mortality until one year of follow-up.

Multivariable Cox regression was used to find all-cause mortality predictors. The plausible predictors of the multivariable regression model were selected according to the literature, and our main variable (MNA). The Kaplan-Meier curve and the log-rank test were used for the group comparison. A two-tailed p-value <0.05 was set as the significance level. The statistical analyses were performed using R version 4.01 software (Vienna, Austria) with the "rms", "survival", "ggplot", and "desctool" packages.

Results

A total of 289 elderly patients who applied to emergency services were included in our study, of whom 48.4% (n=140). The prevalence of malnutrition and patients at risk of malnutrition was 49.4% (n=143), while nutritional deficiency was found in 49.6% (n=71) of this group. The comorbid diseases found were hypertension (72.2%; n=203), ischemic heart disease (50.8%; n=147), diabetes mellitus (35.2%; n=102),

chronic renal failure (32.8%; n=95), malignancy (25.2%; n=73), neuropsychiatric disease (22.8%; n=66), chronic obstructive pulmonary disease (19.03%; n=55), and chronic liver disease (9.6%; n=28) (Table 1). In relation to the reasons for hospitalization, 11.1% (n=32) of the patients were hospitalized for gastrointestinal system diseases, 14.9% (n=43) decompensated heart failure, 26% (n=75) renal diseases, 5.5% (n=16) electrolyte imbalance and diabetic coma, 9.3% (n=27) hematological and rheumatologic diseases, 18% (n=52) upper gastrointestinal bleeding and inflammatory bowel diseases, and 15.2% (n=44) supportive treatment.

The median follow-up was 312 days for all patients, and the mortality rate was 42.5% (n=123) for all our patients, and 50.4% (n=72) of the patients who died were male. Seventy patients were transferred from the internal medicine service to the intensive care unit (ICU), and 61 of these patients (87.14%) died.

When the MNA scores were evaluated, mortality occurred in 67 (72.8%) of 92 people with a score of <17 indicating malnutrition, and in 25 (49.01%) of the 51 people at risk of malnutrition with a score between 17 and 23. These two patient groups were considered to have a nutritional deficiency. The number of patients in the group with good nutrition, i.e., with a score of 23.5 and above, was 146 (50.5%), and 31 (21.2%) of them died. BMI results included six people (4.2%) with a BMI<18.5 kg/m² and 81 people (56.6%) with a BMI in the range of 18.5-25 kg/m², and the mean BMI was lower in the deceased group with a range of 24.2 (22-26) (p<0.001) (Table 2).

Univariable Cox proportional regression analysis showed that the MNA, NRS, C-reactive protein, BMI, and albumin were associated with mortality (Table 3). Multivariable Cox regression analysis revealed that the MNA, the NRS, and albumin were associated with mortality 0 vs. 2, [hazard ratio (HR) 2.64 95% confidence interval (CI) 1.56-4.45], 0 vs. 1 [HR 2.11 (95% CI 1.22–3.68)], 0 vs. 2 [HR 1.56 (95% CI 1-2.44)], 0 vs. 1 [HR 0.54 (95% CI 0.38-0.78)] respectively. The other results are presented in Table 3.

The Kaplan-Meier curve showed higher mortality in the score <17 and score between 17 and 23 groups when compared to the score of 23.5 and above groups, with a p-value <0.0001 in the log-rank test (Figure 2).

Table 1. Baseline clinical and laboratory variables comparison alive and deceased

Variables	Alive (n=166)	Deceased (n=123)	p-value
Age	75 (70-81)	78 (71-84.5)	0.055
Gender n, (%) (female)	72 (43.4)	68 (55.3)	**0.04#**
Diabetes mellitus n, (%)	60 (36.1)	42 (34.1)	0.72
Hypertension n, (%)	131 (78.9)	72 (62.6)	**0.002#**
Coronary artery disease n, (%)	86 (51.8)	61 (49.6)	0.71
Chronic obstructive pulmonary disease n, (%)	30 (18.1)	25 (20.3)	0.63
Malignancy n, (%)	22 (13.3)	51 (41.5)	**<0.001#**
Chronic kidney disease n, (%)	46 (27.7)	49 (38.9)	**0.03#**
Chronic liver disease n, (%)	11 (6.6)	17 (13.8)	**0.004#**
Neuropsychiatric disorders n, (%)	34 (20.5)	32 (26.0)	0.26
Albumin	3.2 (2.9-3.68)	2.7 (2.4-3.05)	**<0.001***
C-reactive protein	20.3 (4.22-76)	47.7 (13.9-101)	**<0.001***
Lymphocyte	1300 (900-1700)	900 (650-1400)	**<0.001***
Intensive care unit stay n, (%)	9 (5.4)	61 (49.6)	**<0.001***
Total cholesterol	168 (136-205)	142 (124-184)	**<0.001***
HbA1c	6 (5.6-6.57)	5.7 (5.2-6.65)	0.08
Follow-up duration	356 (319-396)	48 (17-231)	**<0.001***
Body mass index	25.4 (24.2-26.9)	24.2 (22-26)	**<0.001***
Nutritional risk screening n, (%)	22 (13.3)	56 (45.9)	**<0.001***
Mini nutritional assessment n, (%)			
0 (<17) 1 (17-23) 2 (>23.5)	25 (15.1) 26 (15.7) 115 (69.3)	67 (54.5) 25 (15.3) 31 (25.2)	**<0.001#**

#Chi-square test, * Wilcoxon -signed-rank test; MNA score was worse in deceased group p<0.001.
MNA: Mini Nutritional Assessment

Discussion

Our study showed that the MNA, which calculates malnutrition status, was independently associated with early and mid-term mortality and. In our study, in which the nutrition and survival of 289 geriatric inpatients admitted to the emergency department and followed up were evaluated, nutritional status was a strong determinant of survival. At their 12-month follow-up, mortality was not observed in 51 (35.6%) of 143 people (49.4%) with malnutrition and malnutrition risk. All-cause mortality was high in our patients with nutritional deficiency and malignancy (p<0.001). Mortality occurred in 61 (87.1%) of our patients admitted to the ICU. When concomitant diseases were evaluated, hypertension was the most common, and liver diseases were seen the least.

In a randomized controlled study in Ireland, when 353 elderly patients admitted to the emergency room were evaluated with the MNA test, it was found that more than one third were at risk of malnutrition or malnutrition. This was associated with a longer stay in the emergency department, a decrease in functional capacity and quality of life, and an increased risk of hospitalization. Patients defined as malnourished in the emergency department were more than four times more likely to report a decline in quality of life and mortality was higher than patients defined as having a normal nutritional status (13).

Table 2. Demographic and nutritional data comparison according to MNA status

	MNA (≥23.5)	MNA (≤23.5)	p-value
Age			
65-74 years	68 (46.6%)	58 (40.6%)	0.137
75-84 years	55 (37.7%)	49 (34.3%)	
≥85 years	23 (15.8%)	36 (25.2%)	
Body mass index			
<18.5	0 (0%)	6 (4.2%)	**<0.001#**
19-24.9	30 (20.5%)	81 (56.6%)	
25-29.9	102 (69.9%)	51 (35.7%)	
>30	14 (9.6%)	5 (3.5%)	
Malignancy	29 (19.9%)	44 (30.8%)	**0.03#**
Gender (female)	69 (47.3%)	71 (49.7%)	0.68

#Categoric comparison made with chi-square, MNA (≥23.5) group was higher body mass index than MNA (≤23.5) p<0.001.
MNA: Mini Nutritional Assessment

Malnutrition has emerged as a major problem among the aged. Different mechanisms, such as gastrointestinal and endocrine system disorders, decreased appetite, loss of taste and smell, and malnutrition due to both disease states and psychosocial factors, are involved in the

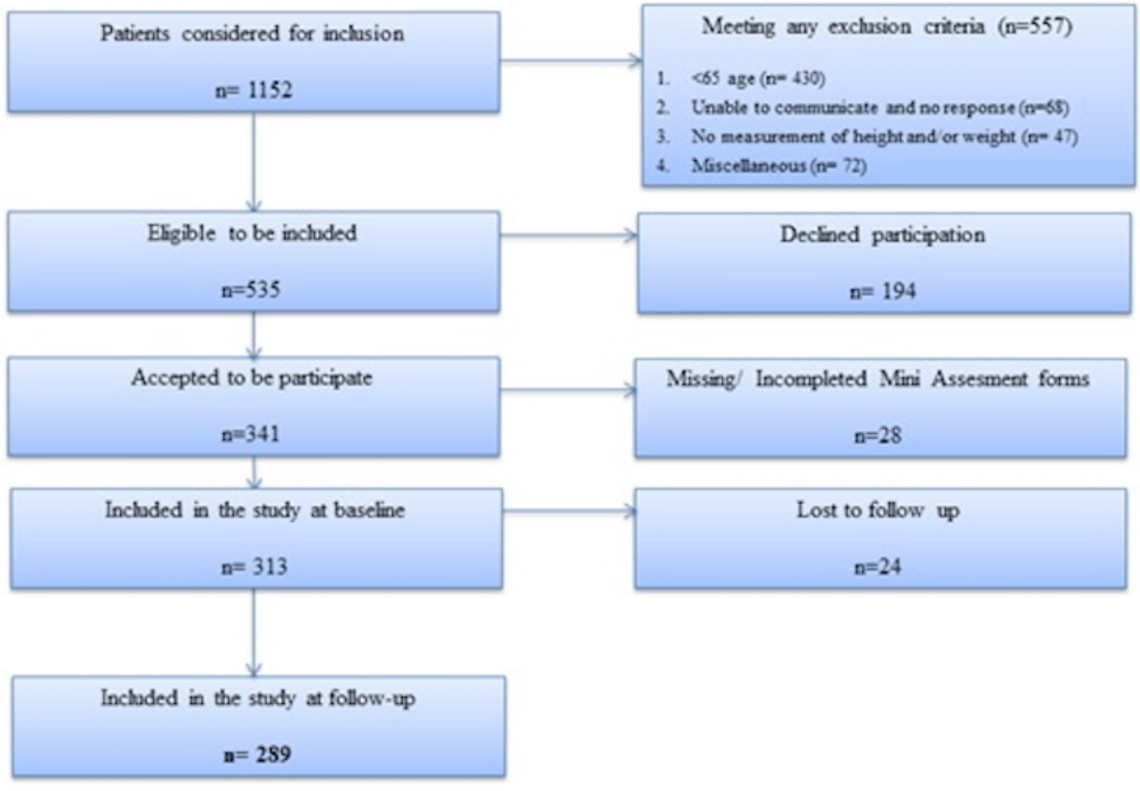


Figure 1. Flow chart of inclusion and exclusion criteria

Table 3. Univariate and multivariable Cox proportional hazard regression analysis				
Variables	**Univariate HR, CI 95%**	**p-value**	**Multivariate HR, CI 95%**	**p-value**
Age (per 1-year increase)	1.02 (1.00-1.05)	0.029	1.00 (0.98-1.03)	0.679
Gender (male reference)	1.41 (0.919-2.01)	0.058	1.67 (1.13-2.47)	**0.01§**
Diabetes mellitus	1.00 (0.69-1.45)	0.98	0.94 (0.67-1.47)	0.796
Hypertension	0.608 (0.42-0.87)	0.006	0.69 (0.43-1.09)	0.111
Coronary artery disease	0.91 (0.64-1.30)	0.600	1.16 (0.76-1.77)	0.505
COPD	1.10 (0.71-1.71)	0.675	1.25 (0.79-1.97)	0.348
Malignancy	2.51 (1.75-3.60)	<0.001	2.46 (1.62-3.73)	**<0.001§**
Chronic kidney disease	1.58 (1.10-2.27)	<0.001	1.94 (1.28-2.94)	**0.002§**
Chronic liver disease	1.77 (1.06-2.95)	0.03	1.61 (0.93-2.78)	0.091
Neuropsychiatric disorders	1.43 (0.96-2.14)	0.082	1.49 (0.96-2.29)	0.072
MNA 0 vs. 2* MNA 1 vs. 2*	5.39 (3.51-8.28) 3.03 (1.79-5.14)	<0.001 <0.001	2.64 (1.56-4.45) 2.11 (1.22-3.68)	**<0.001§** **0.008§**
NRS-2002	3.52 (2.46-5.04)	<0.001	1.56 (1.001-2.44)	0.049§
CRP (per 1 unit increase)	1.001 (1.000-1.002)	0.03	1.00 (0.99-1.001)	0.42
Albumin (per 1 unit increase)	0.39 (0.29-0.52)	0.005	0.54 (0.38-0.78)	**0.001§**
BMI (per 1 unit increase)	0.83 (0.78-0.89)	<0.001	0.86 (0.80-0.93)	**<0.001§**
25-OH D3 (per 1 unit increase)	1.001 (0.99-1.01)	0.70	1.00 (0.99-1.01)	0.34

*MNA 0: Score <17, MNA 1: 18-23, MNA 2: >23.5
§Cox regression analysis significant result. Both MNA 0 and 1 associated worse outcome than MNA 2; [2.64 (1.56-4.45) p<0.001, 2.11 (1.22-3.68) p=0.008 respectively].
COPD: Chronic obstructive pulmonary disease, CRP: C-reactive protein, BMI: Body mass index, MNA: Mini Nutritional Assessment, NRS-2002: Nutritional Risk Screening-2002, CI: Confidence interval, HR: Hazard ratio

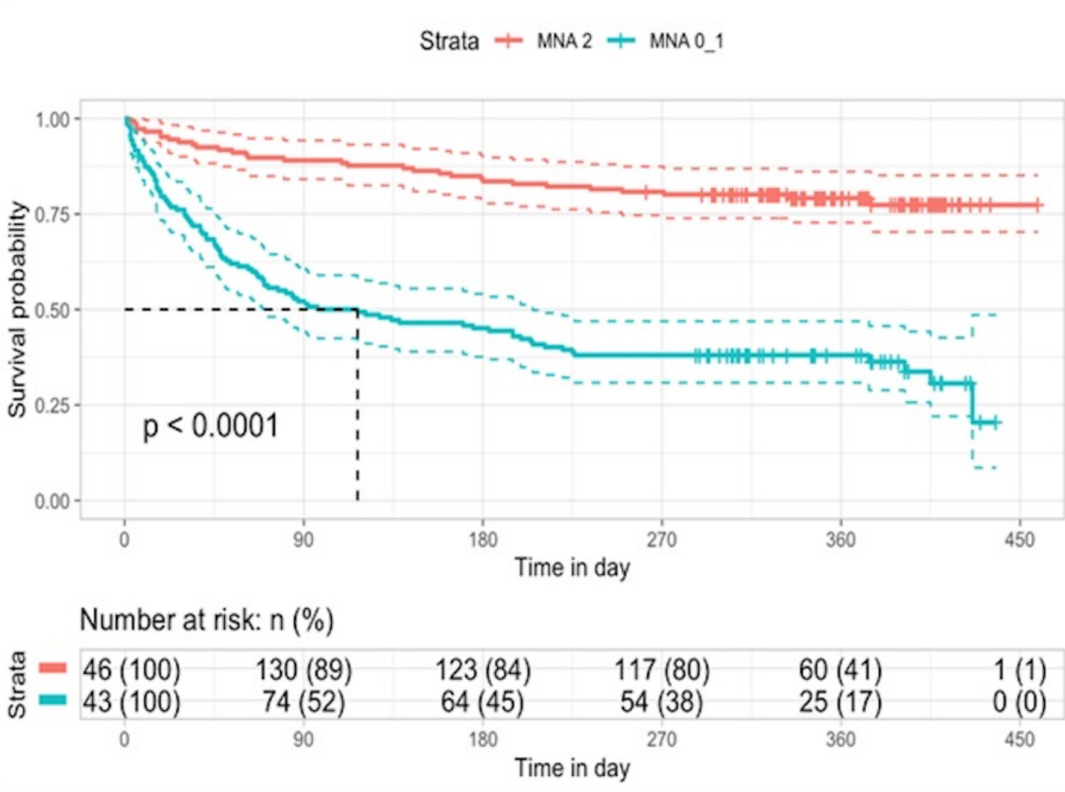


Figure 2. Kaplan-Meier curve comparison between MNA 2 and MNA 0-1
MNA: Mini Nutritional Assessment

development of malnutrition in the elderly (14). Therefore, it is crucial to support a diet containing food and liquid with adequate and appropriate nutrition to prevent and treat malnutrition.

Obesity is an increasing problem in the elderly as well as the general population, and it currently affects 18% to 30% of the world's population aged 65 and over (14). The mean BMI of our patients who did not die was 25.4 (24.2-26.9) kg/m², and as the BMI increased to be in the range of 25-30, a lower risk of death was found compared to the elderly patients with a BMI in the normal range.

In a study conducted by Kaiser et al. (15), the MNA was recommended as a screening test to be used as the basis of nutritional assessment, especially due to its predictive characteristics for early detection and assessment of malnutrition risk in the elderly population and the regulation of nutrition. In their study, the malnutrition rate in the elderly in the community was 5.8%, 13.8% in those living in nursing homes, and 38.7% in hospitalized patients (15). The malnutrition rate was significantly high in our study, with a value of 49.4%; therefore, the elderly population should be evaluated in terms of nutrition and those with malnutrition or at risk of malnutrition should be monitored periodically.

Our study showed a diabetes prevalence of 35.2% and a 41.17% in mortal cases, which is higher than our country's data. In the Turkish Diabetes Epidemiology Study, one of the largest data-based studies, the prevalence of type 2 diabetes was found to be 7.2% in individuals aged 20-60, while it was 20% in individuals over 60 years old (16). Diabetes was high in our geriatric patients, as in all age groups, and its effect on mortality was observed. Malnutrition is considered a hallmark of advanced malignant disease in cancer patients who have an almost three times higher rate of malnutrition (17). Anorexia-cachexia is seen in cancer patients. This situation occurs as a result of complaints such as nausea, vomiting, and early satiety and leads to results such as poor quality of life, poor prognosis, and loss of functional status. In our study, 30.8% (n=44) of the cancer patients had low MNA scores. A recent study found the malnutrition status of geriatric patients followed in the ICU affected the duration of hospital stay, post-discharge care, and mortality. In the study, 331 geriatric patients were followed up, and their nutrition scores with the NRS and the MNA were found to be in the range of 23-34% (18). In our study, mortality (87.14%) was high in those transferred to the ICU, and 32 (52.4%) of these patients had nutritional deficiencies.

Considering the data in our study, age, comorbidities, BMI, and mortality were associated with malnutrition. Various physiological and psychological changes in advanced age lead to decreased hunger, insufficient food intake, metabolic inefficiency, and impaired nutrition. As demonstrated in our study, malnutrition associated with internal emergency diseases is a significant risk factor, especially in terms of mortality. Therefore, it should be kept in mind as an additional evaluation parameter in the elderly population.

Study Limitations

The limitation of the study is the data from a single-center analysis, resulting in the regression analysis's low causal inference. Investigations from different centers are needed to confirm the data. Our study's strength consists of geriatric patients who were followed up, admitted to the tertiary referral and oncology center's emergency room and hospitalized.

Conclusion

Nutritional status in geriatric patients admitted to the emergency internal medicine service was associated with mortality for up to one year regardless of other causes, and age, comorbidities, BMI, and mortality were associated with malnutrition. The MNA is a non-complex and sensitive method that can be used to predict early and mid-term mortality in geriatric patients admitted to the emergency department.

Ethics

Ethics Committee Approval: The ethics committee of University of Health Sciences Turkey, Kartal Dr. Lutfi Kirdar City Hospital approved the study on 06.12.2019 with the number 2019/514/167/23.

Informed Consent: An informed consent form was approved by all patients.

Authorship Contributions

Concept: A.C.I., S.A., Design: B.B., O.K., Data Collection or Processing: A.C.I., A.K., Analysis or Interpretation: A.C.I., A.K., Literature Research: A.C.I., A.K., Writing: A.C.I., A.K., S.A. A.O.

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

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

References

1. Türkiye İstatistik Enstitüsü. İstatistiklerle Yaşlılar, 2020 [Internet]. 18.03.2021. 2021. p. 1-10. Available from: https://data.tuik.gov.tr/Bulten/Index?p=Istatistiklerle-Yaslilar-2020-37227
2. World Health Organization. Ageing and health [Internet]. 2018. Available from: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health
3. Centers for Disease Control and Prevention (CDC). Trends in aging–United States and worldwide. MMWR Morb Mortal Wkly Rep 2003;52:101-6.

4. Burak C, Süleymanoğlu M, Gümüşdağ A, et al. The effect of nutritional status on long-term mortality in very elderly patients with st segment elevation myocardial infarction. Turkish Journal Geriatris 2021;24:87-94.
5. Gaillard C, Alix E, Sallé A, Berrut G, Ritz P. Energy requirements in frail elderly people: a review of the literature. Clin Nutr 2007;26:16-24.
6. Visvanathan R. Under-nutrition in older people: a serious and growing global problem! J Postgrad Med 2003;49:352-60.
7. Vellas B, Guigoz Y, Garry PJ, et al. The mini nutritional assessment (MNA) and its use in grading the nutritional state of elderly patients. Nutrition 1999;15:116-22.
8. Sheean PM, Peterson SJ, Chen Y, Liu D, Lateef O, Braunschweig CA. Utilizing multiple methods to classify malnutrition among elderly patients admitted to the medical and surgical intensive care units (ICU). Clin Nutr 2013;32:752-7.
9. Balci C, Bolayir B, Eşme M, et al. Comparison of the Efficacy of the Global Leadership Initiative on Malnutrition Criteria, Subjective Global Assessment, and Nutrition Risk Screening 2002 in Diagnosing Malnutrition and Predicting 5-Year Mortality in Patients Hospitalized for Acute Illnesse. JPEN J Parenter Enter Nutr 2021;45:1172-80.
10. Poínhos R, Oliveira BMPM, Sorokina A, Franchini B, Afonso C, de Almeida MDV. An extended version of the MNA-SF increases sensitivity in identifying malnutrition among community living older adults. Results from the PRONUTRISENIOR project. Clin Nutr ESPEN 2021;46:167-72.
11. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M; Educational and Clinical Practice Committee, European Society of Parenteral and Enteral Nutrition (ESPEN). ESPEN guidelines for nutrition screening 2002. Clin Nutr 2003;22:415-21.
12. Buscemi S, Batsis JA, Parrinello G, et al. Nutritional predictors of mortality after discharge in elderly patients on a medical ward. Eur J Clin Invest 2016;46:609-18.
13. Griffin A, O'Neill A, O'Connor M, Ryan D, Tierney A, Galvin R. The prevalence of malnutrition and impact on patient outcomes among older adults presenting at an Irish emergency department: a secondary analysis of the OPTI-MEND trial. BMC Geriatr 2020;20:455.
14. Porter Starr KN, McDonald SR, Weidner JA, Bales CW. Challenges in the Management of Geriatric Obesity in High Risk Populations. Nutrients 2016;8:262.
15. Kaiser MJ, Bauer JM, Rämsch C, et al. Frequency of malnutrition in older adults: a multinational perspective using the mini nutritional assessment. J Am Geriatr Soc 2010;58:1734-8.
16. Satman I, Omer B, Tutuncu Y, et al. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. Eur J Epidemiol 2013;28:169-80.
17. Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME. Nutritional deterioration in cancer: the role of disease and diet. Clin Oncol (R Coll Radiol) 2003;15:443-50.
18. Gündüz E, Eskin F, Gündüz M, et al. Malnutrition in Community-Dwelling Elderly in Turkey: A Multicenter, Cross-Sectional Study. Med Sci Monit 2015;21:2750-6.

Original Article

DOI: 10.4274/haseki.galenos.2021.7639
Med Bull Haseki 2022;60:64-71

Efficacy of Prothrombin Complex Concentrate versus Fresh Frozen Plasma in Patients with Bleeding in the Emergency Department

Burak Demirci, Abuzer Coskun

University of Health Sciences Turkey, Istanbul Bagcilar Training and Research Hospital, Clinic of Emergency Medicine, Istanbul, Turkey

Abstract

Aim: It is important to determine which of the treatment options applied in the emergency department is more effective and usable in coagulation pathologies. In this study, we aimed to evaluate the efficacy and safety of fresh frozen plasma (FFP) and prothrombin complex concentrate (PCC), which are used in the treatment of high hemostasis parameters in the emergency department.

Methods: This retrospective study included 103 patients who were admitted to the emergency department between January 2019 and December 2020. All data were obtained from the hospital automation system. While the patients were divided into two groups (FFP-PCC) according to the treatment option they received, they were also divided into three groups (DED-RSH-ISH) according to hospitalization status. With this data, treatment efficacy and outcomes were analyzed.

Results: The mean age of 103 patients was 67.31±13.17 years, with 58 (56%) females and 45 (44%) males. 51 (49.5%) of the cases received FFP and 52 (50.5%) PCC treatment. While the international normalized ratio (INR)1 value before the treatment was 7.56±4.09 and 2.42±1.01 after the treatment in the FFP group, the INR1 value was 10.12±5.18 and INR2 1.95±0.71 in the PCC group. The percentage of INR decrease was 60.28±19.76 (%) in the FFP group, and 73.41±17.42 (%) in the PCC group (p=0.001). In receiver operating characteristic curve analysis, the sensitivity and specificity of FFP and PCC decreased significantly in INR%.

Conclusion: FFP is preferable in this regard to FFP because it is easier to apply, has a faster effect, and provides better values in coagulation parameters.

Keywords: Emergency departments, fresh frozen plasma, hemostasis, blood coagulation factors, prothrombin complex concentrates

Introduction

In the emergency department, abnormal bleeding can be seen in patients due to defective hemostasis mechanisms. In addition to drug use, conditions such as liver disease and kidney failure can increase the potential for abnormal bleeding (1). In recent years, there has been an increase in the number of patients admitted to the emergency department with warfarin-related complications. Warfarin is important for emergency physicians because it is associated with bleeding complications when the therapeutic range is exceeded and its interactions with drugs are frequent (2). The frequency of emergency department admissions as a result of developing complications is also mentioned. It is also stated that the risk of life-threatening or fatal bleeding is between 1-3% (3,4).

The International Normalized Ratio (INR) is used as a follow-up parameter for warfarin treatment effectiveness. These INR values reflect the extent of anticoagulation that minimizes the risk of serious bleeding while reducing morbidity from thromboembolic disease. For most indications, the INR range of 2-3 is used. Patients with high INR values, asymptomatic or with accompanying bleeding findings, are frequently evaluated in the emergency department (5,6).

To achieve this, fresh frozen plasma (FFP) and prothrombin complex concentrates (PCC) are used today. Both have their advantages and disadvantages. FFP is plasma obtained by separating whole blood from erythrocytes and platelets and freezing within eight hours after collection. FFP is suitable for rapid replacement in

Address for Correspondence: Burak Demirci
University of Health Sciences Turkey, Istanbul Bagcilar Training and Research Hospital, Clinic of Emergency Medicine, Istanbul, Turkey
Phone: +90 (212) 440 40 00 E-mail: drburakdemirci@hotmail.com ORCID: orcid.org/0000-0001-6658-7260
Received: 14.07.2021 **Accepted:** 23.11.2021

multiple coagulation deficiencies such as hepatic failure, warfarin overdose, disseminated intravascular coagulation, and massive transfusion in patients with bleeding. While it has very positive effects when used by its indication, it can also lead to serious complications related to transfusion when used off-label (7). In addition, PCC can be given to patients with high INR to relieve symptoms or in cases where an urgent invasive procedure is required. The use of PCCs containing vitamin K-dependent coagulation factors is also recommended, especially in order to reverse the anticoagulant effect associated with the use of warfarin, due to its advantages such as rapid improvement in INR level, shorter administration time, and higher amount of factors than normal plasma (8-10).

It is seen that the use of PCC has become widespread, especially recently, and accordingly, studies conducted both in isolation and in the form of comparisons with FFP have increased. These studies include trauma or surgical process patients as well as emergency department patients. Both applications are used as treatment options for bleeding disorders, which are a very common reason for admission. Opinions are different about their supply, application times, and ability to provide the desired effectiveness, and the researches continue increasingly. This important and common issue has also encouraged us to work on which treatment is more appropriate (11-14).

In our study, we aimed to evaluate the effects of demographic characteristics, warfarin use, admission complaints, as well as the effects of FFP and PCC treatments on hemostasis values of patients with high INR levels in the emergency department.

Methods

Compliance with Ethical Standards

The study was carried out in the University of Health Sciences Turkey, Istanbul Bagcilar Training and Research Hospital Emergency Medicine Clinic, in accordance with the Helsinki Declaration rules, after the approval of the local ethics committee (decision date and number: 03.05.2021-190).

Study Design and Population

In this retrospective study, 103 patients who were older than 18 years old, had an INR value above 2, were treated with FFP or 4-factor PCC (Cofact®, defined as the third generation) and did not meet any of our exclusion criteria, were admitted to the emergency department between January 2019 and December 2020 (58 women, 45 men; mean age 67.31±13.17 years; range 24-88 years, 56.3% women) were included.

Patients with known chronic liver and kidney disease, severe anemia, and malignancy, in addition to patients with deficiencies in admission and discharge hemostasis parameters and observation data, were excluded from the study.

Patients were divided into 2 groups according to whether they received FFP or PCC treatment in the emergency department. In addition, the patients were divided into 3 groups according to their discharge from the emergency department and hospitalization in the service and intensive care units.

Demographic information of patients from hospital records, comorbidity status, admission complaints, drug use, admission complaints, FFP or PCC treatment status, doses, type of complication if developed (within 24 hours), prothrombin time (PT) before and after treatment, activated Partial Thromboplastin Time (aPTT), INR values, and outcome patterns of the patients (admission, discharge, and death) were recorded. Pre-treatment values were recorded as aPTT1, PT1, INR1, and post-treatment values were recorded as aPTT2, PT2, INR2, according to the results of the sample taken at the 15th minute after treatment. The percentages of decrease in INR were calculated and recorded as "decrease of INR%".

Statistical Analysis

Version 21.0 (released in 2012 by IBM Corp.) of the IBM SPSS Statistics for Windows program (Armonk, NY: IBM Corp.) was used in the analysis. Continuous data were presented as mean standard deviation, while categorical data were presented as a percentage (%). The Shapiro-Wilk test was used to investigate the conformity of the data to the normal distribution. In the comparison of normally distributed groups, an independent sample t-test analysis was used for cases with two groups. The Mann-Whitney U test was used for cases with two groups in the comparison of the groups that did not conform to the normal distribution. For the normally distributed variables, Pearson correlation coefficients were calculated to determine the direction and size of the relationship (correlation) between the variables. Chi-square analyses were used in the analysis of the created cross tables. A receiver operating characteristic (ROC) curve analysis was performed to determine the effectiveness of treatment options. A value of $p<0.05$ was considered significant for statistical significance.

Results

Of the 103 patients with elevated hemostasis parameters, 58 (56%) were female and 45 (44%) were male. Seventy-seven of the patients (74.8%) had a history of warfarin use. 51 (49.5%) of the patients received FFP and 52 (50.5%) PCC treatment. While 47 (45.6%) patients applied due to hemorrhage, this was followed by 13 (12.6%) patients for laboratory follow-up. No treatment-related complications developed in any of the patients. Of

the patients with bleeding, 8 (7.8%) had hematemesis, 9 (8.7%) had melena, 6 (5.9%) had hematochezia, and 8 (7.8%) had hematuria (Table 1).

The mean age of 103 patients who received FFP or PCC treatment was 67.31±13.17 years. INR2 values were 2.42±1.01 in the FFP group and 1.95±0.71 in the PCC group. The correlation of recorded PT and INR values with applied treatment options was significant. The percentages of decrease in INR after treatment were 66.91±19.66 (%) in all groups, 60.28±19.76 (%) in the FFP group, and 73.41±17.42 (%) in the PCC group (p=0.001, Table 2).

According to the hospitalization status of the patients; 47 (45.6%) were discharged from the emergency department (DED), 49 (47.6%) were relevant service hospitalizations (RSH), and 7 (6.8%) were in the intensive care hospitalization group. None of the patients presenting with altered consciousness could be discharged from the emergency department. In the DED group, 20 (42.6%) patients received FFP and 27 (57.4%) patients received PCC treatment (Table 3).

In the correlation analysis of the applied treatment option with the variables, there was a strong positive correlation between the decrease in INR% and the treatment option (p=0.001, Table 4).

In the ROC curve analysis of the INR % change of FFP, the area under curve (AUC): 0.286, with a 95% confidence interval (CI) of 0.187-0.385, sensitivity: 86.5%, specificity: 64.7%, (p=0.001) (Figure 1). In the ROC curve analysis of PCC % change in INR; AUC: 0.714, 95% CI: 0.615-0.813, sensitivity: 96.2%, specificity: 88.2%, (p=0.001) (Figure 2). In addition, the distribution of the percent decrease in INR of FFP and PCC used in the treatment is given in Figure 3.

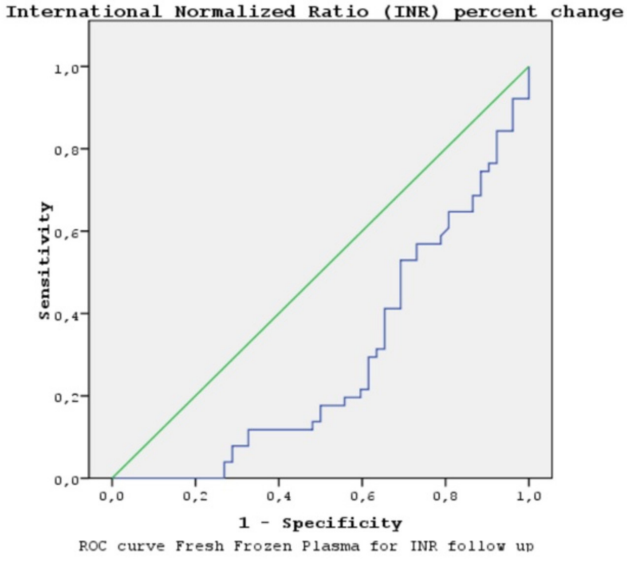


Figure 1. ROC curve analysis of FFP in INR change
ROC curve analysis of INR change of FFP; area under curve 0.286, %95 confidence interval 0.187-0.385, sensitivity: 86.5%, specificity: 64.7%, p=0.001
PCC: Prothrombin complex concentrate, INR: International normalized ratio, FFP: Fresh frozen plasma

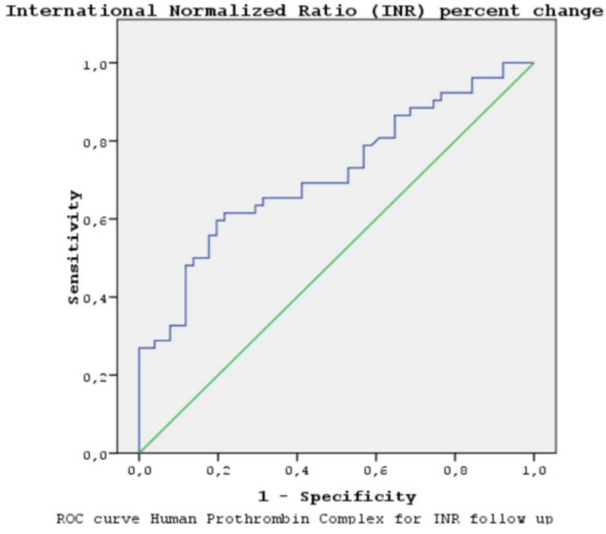


Figure 2. ROC curve analysis of PCC in INR change
ROC curve analysis of PCC's INR change; area under curve 0.714, %95 confidence interval 0.615-0.813, sensitivity: 96.2%, specificity: 88.2%, p=0.001
PCC: Prothrombin complex concentrate, INR: International normalized ratio, FFP: Fresh frozen plasma

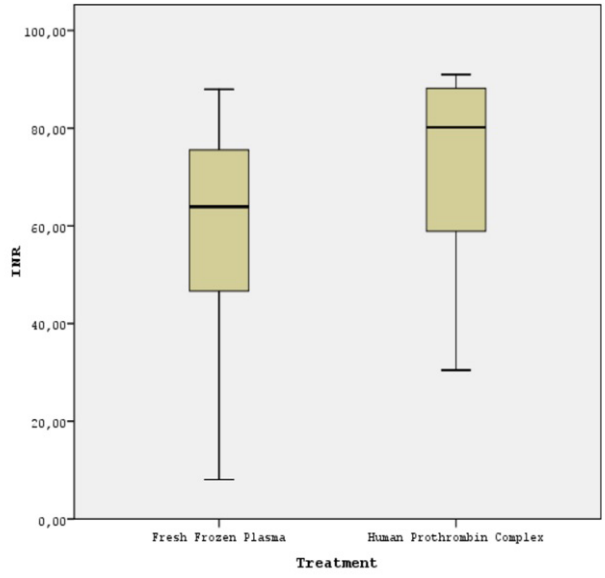


Figure. 3 Percentage of reduction in INR compared to FFP and PCC used in the treatment
PCC: Prothrombin complex concentrate, INR: International normalized ratio, FFP: Fresh frozen plasma

Table 1. Relationship of treatment options with coagulation parameters and other variables				
High INR treatment				
		FFP n (%) 51 (49.5%)	**PCC n (%) 52 (50.5%)**	**ALL n (%) 103 (100%)**
Gender	Female	32 (62.7%)	26 (50%)	58 (56.3%)
	Male	19 (37.3%)	26 (50%)	45 (43.7%)
Use of coumadin	No	12 (23.5%)	14 (26.9%)	26 (25.2%)
	Yes	39 (76.5%)	38 (73.1%)	77 (74.8%)
Complaint	For analysis	7 (13.7%)	6 (11.5%)	13 (12.6%)
	Hemorrhage	25 (49.0%)	22 (42.3%)	47 (45.6%)
	Abdominal pain	7 (13.7%)	2 (3.8%)	9 (8.7%)
	Nausea-vomiting	5 (9.8%)	6 (11.5%)	11 (10.7%)
	Chest pain	4 (7.8%)	2 (3.8%)	6 (5.8%)
	Shortness of breath	2 (3.9%)	4 (7.7%)	6 (5.8%)
	Altered consciousness	1 (2.0%)	2 (3.8%)	3 (2.9%)
	Bad general condition	0 (0%)	8 (15.4%)	8 (7.8%)
Hemorrhage	No	26 (51.0%)	30 (57.7%)	56 (54.5%)
	Hematemesis	7 (13.8%)	1 (1.9%)	8 (7.8%)
	Melena	4 (7.8%)	5 (9.8%)	9 (8.7%)
	Hematochezia	3 (5.9%)	3 (5.8%)	6 (5.9%)
	Hematuria	4 (7.8%)	4 (7.6%)	8 (7.8%)
	Cranial	2 (3.9%)	2 (3.8%)	4 (3.9%)
	Vaginal	3 (5.9%)	1 (1.9%)	4 (3.9%)
	Dermal	2 (3.9%)	3 (5.8%)	5 (4.8%)
	Articulation	0 (0%)	1 (1.9%)	1 (0.9%)
	Eye	0 (0%)	1 (1.9%)	1 (0.9%)
	Nasal	0 (0%)	1 (1.9%)	1 (0.9%)
Complication	No	51 (100%)	52 (100%)	103 (100%)
	Yes	0 (0%)	0 (0%)	0 (0%)

PCC: Prothrombin complex concentrate FFP: Fresh frozen plasma ALL: All patients, INR: International normalized ratio
Percentages were determined by performing the chi-square test

Table 2. Relationship of treatment options with other variables				
High INR treatment				
	FFP	**PCC**	**ALL**	**p-value**
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Age (year)	67.84±13.22	66.79±13.23	67.31±13.17	0.670
APTT-1 (sec)	83.49±37.23	80.44±36.45	81.95±36.69	0.605
PT-1 (sec)	89.29±48.35	113.45±58.39	101.49±54.75	**0.028***
INR-1	7.56±4.09	10.12±5.18	8.85±4.83	**0.009***
APTT-2 (sec)	49.47±16.55	42.98±15.65	46.19±16.35	**0.017***
PT-2 (sec)	30.34±12.35	24.07±9.34	27.17±11.33	**0.005***
INR-2	2.42±1.01	1.95±0.71	2.18±0.90	**0.023***
Decrease of INR (%)	60.28±19.76	73.41±17.42	66.91±19.66	**0.001***

PCC: Prothrombin complex concentrate FFP: Fresh frozen plasma, ALL: All patients, APTT: Activated partial thromboplastin time, PT: Prothrombin time, INR: International normalized ratio, sec: Second, SD: Standard deviation
*:Mann-Whitney U test, p-value of <0.05 was considered statistically significant

Table 3. State of discharge or hospitalization in the variables				
Hospitalization				
		DED n (%) 47 (45.6%)	**RSH n (%) 49 (47.6%)**	**ICH n (%) 7 (6.8%)**
Gender	Female	26 (55.3%)	28 (57.1%)	4 (57.1%)
	Male	21 (44.7%)	21 (42.9%)	3 (42.9%)
Use of coumadin	No	8 (17%)	16 (32.7%)	2 (28.6%)
	Yes	39 (83%)	33 (67.3%)	5 (71.4%)
Complaint	For analysis	10 (21.3%)	3 (6.1%)	0 (0%)
	Hemorrhage	18 (38.3%)	28 (57.1%)	1 (14.3%)
	Abdominal pain	5 (10.6%)	4 (8.2%)	0 (0%)
	Nausea-vomiting	7 (14.9%)	4 (8.2%)	0 (0%)
	Chest pain	4 (8.5%)	2 (4.1%)	0 (0%)
	Shortness of breath	2 (4.3%)	2 (4.1%)	2 (28.6%)
	Altered consciousness	0 (0%)	2 (4.1%)	1 (14.3%)
	Bad general condition	1 (2.1%)	4 (8.2%)	3 (42.9%)
Treatment	FFP	20 (42.6%)	27 (55.1%)	4 (57.1%)
	PCC	27 (57.4%)	22 (44.9%)	3 (42.9%)

PCC: Prothrombin complex concentrate, FFP: Fresh frozen plasma, DED: Discharge from the emergency department, RSH: Relevant service hospitalization, ICH: intensive care hospitalization
*Percentages were determined by performing the chi-square test

Discussion

Today, cases who present with bleeding or other complaints in emergency departments and who have high hemostasis parameters are frequently seen. Although there are partial increases due to metabolic reasons, serious elevations are also detected, especially due to the use of warfarin. The clinical spectrum of patients with elevated hemostasis parameters varies, and it is usually up to emergency clinicians to ensure that the values are in the ideal range. With correct and rapid treatment, it is possible to reduce the mortality and morbidity of patients. FFP and PCC, which are among the treatment modalities applied in an emergency, create a preferred position for the clinician.

FFP is suitable for rapid replacement in multiple coagulation deficiencies such as hepatic failure, warfarin overdose, disseminated intravascular coagulation, and massive transfusion in bleeding patients. FFP can also be used when bleeding is due to a deficiency of coagulation factors. Response to FFP treatment can be monitored by performing coagulation system examinations such as PT, INR, and aPTT (15).

PCC, whose preparations consist of human plasma; contains FII, FVII, FIX, and FX components, is also used in anticoagulant therapy with proven effectiveness. Studies show that PCC offers us not only an effective but also a safe treatment option (16,17). Studies have shown that four-factor PCCs are more effective than three-factor PCCs in the emergency department, but there is no difference with FFP in terms of effectiveness and side effects (18).

Table 4. Correlation of Treatment Options with Variables		
Variables	**Treatmant option (FFP-PCC)**	
	r	**p**
Gender	0.128	0.196
Age	-0.042	0.672
Coumadin use	-0.039	0.695
Complaint	0.166	0.094
Hospitalization	-0.126	0.205
APTT-1 (sec)	-0.051	0.607
PT-1 (sec)	0.217	**0.028***
INR-1	0.260	**0.008***
APTT-2 (sec)	-0.235	**0.017***
PT-2 (sec)	-0.279	**0.004***
INR-2	-0.225	**0.022***
Decrease of INR (%)	0.371	**0.001***

PCC: Prothrombin complex concentrate, FFP: Fresh frozen plasma, APTT: Activated partial thromboplastin time, PT: Prothrombin time, INR: International normalized ratio, sec: Second
*: Pearson correlation test, p-value of <0.05 was considered statistically significant

There are studies evaluating the efficacy, side effects, and prognosis of the use of PCC and FFP in different cases and circumstances. In the study of Karkouti et al. (19), the efficacy of treatment in bleeding during cardiac surgery was investigated, and it was shown that the use of PCC is appropriate because it significantly reduces the need for FFP and can have a hemostatic advantage without increasing the occurrence of adverse events. In trauma patients, a

resuscitation strategy using both PCC and FFP transfusion was associated with reduced mortality compared with a resuscitation strategy involving FFP alone. In addition, PCC reduced the need for RBC transfusions compared to treatment strategies without PCC (20). Although the use of PCC is considered an effective and recommended practice in general, On the other hand, there are researchers who argue that the use of PCC should be avoided in all patients with high INR values caused by vitamin K antagonists and that it can only be used in cases requiring emergency surgery due to serious, life-threatening bleeding (21).

The most important factor for bleeding risk is the INR level, which is above the treatment levels. It has been stated that when the INR level rises from 2-3 to 3-4.5, the risk of bleeding increases 2 times, and when it is between 4.5-6, it increases 4 times. Every 0.5 increase in INR levels increases the risk of major bleeding by 1.43 (22). In a study by Kaya et al. (23) in which they evaluated the use of PCC in an emergency department, the median INR value of the patients was 8.96. In our study, the median INR value of the patients who applied similarly to other studies was 8.85±4.83 and 77 (74.8%) were patients using warfarin for different reasons.

Elderly patients are more susceptible to anticoagulant effects and bleeding than younger patients. In cases over 40 years of age using warfarin, it has been shown that there is a 46% increase in the rate of major bleeding with every 10 years of age. The presence of additional diseases also contributes to this situation (22). Apart from drug efficacy in studies, the condition and comorbid diseases are also important because most of the patients are elderly. It is noteworthy that patients who applied to the emergency department used warfarin, and had high INR values were mostly older. In a similar study, Sarode et al. (4) found the mean age to be 68 years, whereas Barillari et al. (24) reported 76 years. The mean age of the patients in our study was 67 years, which was correlated with the others. Although some studies did not report significant differences in the gender distribution of patients, Keren et al. (25). In their study, the rate of female patients was 56%, similar to our study (26). We think that the important reason for the slightly higher female gender is the incidence of atrial fibrillation and the use of warfarin.

When the complaints of patients who were anticoagulated with warfarin were evaluated, it was shown that the most frequently affected system was the gastrointestinal system (38.5%) (27). In the study conducted by Sayhan et al. (28), it was seen that 16.9% of the patients presented with mostly gastrointestinal bleeding. In our study, bleeding was detected in 47 (45.6%) of all patients, and gastrointestinal system bleeding was found in 23 (31.4%) of them. In addition to the complaints at presentation, nausea and vomiting were present in 11 (10.7%) of the patients. The presence of nausea and vomiting, especially in patients using warfarin, should also suggest an elevated INR.

As a general rule, patients with severe or life-threatening bleeding require a rapid, complete reversal of the effect of warfarin; patients with no bleeding or minor bleeding, especially if the risk of thrombosis is high, can only be followed by discontinuing warfarin. International guidelines recommend the use of PCCs instead of FFP for reversing acute vitamin K antagonism in clinical bleeding (29,30). The risk of bleeding is greatest in the initial phase of treatment. Bleeding rates per year in randomized studies are between 1 and 3%. The most dangerous bleeding for most patients is intracerebral hemorrhage, which can be fatal or cause permanent neurological deficits (31). In the study by Steiner et al. (32), four-factor PCC was found to be superior to FFP in normalizing INR. It has been observed that faster INR normalization leads to smaller hematoma development. The results support the use of PCC instead of FFP in intracranial hemorrhage (32). In our study, PCC was applied to two of the four patients with intracranial hemorrhage, and it was found that success was achieved in terms of more appropriate reference values in INR normalization.

Life-threatening bleeding due to an overdose is relatively low. In his treatment, firstly, stopping warfarin and controlling it by transfusion in the emergency resulted in low hospitalization rates. In some studies, it is recommended that patients in this situation be treated by emergency services and called for necessary controls in order not to increase the cost of the hospital further (33). In our study, 47 (45.6%) patients were successfully treated in the emergency room and discharged. Appropriate dosing was performed, and they were called for control.

PCC was found to be more effective than FFP in normalizing INR and facilitating coagulation. A study of patients with mechanical heart valve disease using warfarin showed that more patients in the PCC group than in the FFP group achieved the ideal INR. The mean INR value before the PCC application was 4.02±1.07 and the mean INR value before the FFP application was 4.88±1.3. However, the mean INR value decreased to 2.51 in the first 48 hours after PCC application (34). In another study, while the mean INR value before PCC was 2.92 (2.54), the mean INR value after PCC was reported as 1.47 (0.44). The mean difference was 1.54 (2.89), which reached statistical significance (p=0.005) (35). In our study, control INR values were 2.42±1.01 in the FFP group and 1.95±0.71 in the PCC group. In addition, the percentage decrease in INR was 60.28±19.76 (%) in the FFP group and 73.41±17.42 (%) in the PCC group. There

were no complications related to the application in both groups. The results of our study showed ideal and safe results in the same direction as other studies in terms of PCC's efficiency and bringing hemostasis parameters to the ideal range.

Compared to the FFP application, fewer thrombotic complications and transfusion reactions were listed as reasons supporting the use of PCC in cases with warfarin overdose. Cruz et al. reported 7.1% thrombotic complications with PCC given after warfarin use (36). In a study using four-factor PCC, the thrombotic complication rate was reported as 1.8% (95% CI 1.0-3.0) (37). In addition, it is recommended to use PCC by considering the benefit-harm balance (26). In our study, no thromboembolic event was detected in any of our cases. The fact that long-term clinical follow-ups were not performed or cases with early-term mortality could not be evaluated for complications may have affected the results.

In a meta-analysis (37), the overall mortality rate due to warfarin overdose was reported as 10.6% (95% CI 5.9-16.6%). In patients who had PCC indications after warfarin use, 30-day mortality was reported as 22.9% (36). In our study, no mortality was observed during follow-up and treatment in the emergency department. This may show that the treatments applied do not have any mortal complications and that the treatment process has developed quite positively in terms of high hemostasis parameters today.

Study Limitations

The retrospective nature of the study was an important limitation. In addition, the limitations of the study are that it is a single-center and the factors that will affect mortality after PCC treatment (additional diseases of the cases, additional drugs used, surgical applications for bleeding control, additional medical treatments given during follow-up). Despite these limitations, clear and efficient analysis of numerical laboratory parameters before and after treatment, and objective interpretation of treatment efficacy are the strengths of the study. In addition, we believe that it contributes positively to the literature in terms of giving an idea about the choice of treatment in these cases, which are frequently encountered and treated in emergency services.

Conclusion

Both FFP and PCC treatments can be safely applied to patients with elevated hemostasis parameters in emergency departments. Recent studies and the result of our study show that PCC is preferable to FFP because it is easier to apply, acts faster, and provides more ideal coagulation parameter levels. Further studies are needed to reveal the cost, efficacy, and safety dimensions of both treatment options.

Ethics

Ethics Committee Approval: The study was carried out in the University of Health Sciences Turkey, Istanbul Bagcilar Training and Research Hospital Emergency Medicine Clinic, in accordance with the Helsinki Declaration rules, after the approval of the local ethics committee (decision date and number: 03.05.2021-190).

Informed Consent: Retrospective study.

Authorship Contributions

Concept: B.D., Design: B.D., A.C., Data Collection or Processing: B.D., Analysis or Interpretation: B.D., Literature Search: B.D., A.C., Writing: B.D., A.C., Supervision and Revision: B.D., A.C.

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

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

References

1. Greaves M, Watson HG. Approach to the diagnosis and management of mild bleeding disorders. J Thromb Haemost 2007;5:167-74.
2. Altunbaş G, Ercan S, Davutoğlu V, Al B. Overview of Warfarin Treatment and Answers to Questions. Eurasian J Emerg Med 2013;12:38-42.
3. Chapman SA, Irwin ED, Beal AL, Kulinski NM, Hutson KE, Thorson MA. Prothrombin complex concentrate versus standard therapies for INR reversal in trauma patients receiving warfarin. Ann Pharmacother 2011;45:869-75.
4. Sarode R, Milling TJ Jr, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation 2013;128:1234-43.
5. Hylek EM, Held C, Alexander JH, et al. Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation):Predictors, Characteristics, and Clinical Outcomes. J Am Coll Cardiol 2014;63:2141-7.
6. Morgan CL, McEwan P, Tukiendorf A, Robinson PA, Clemens A, Plumb JM. Warfarin treatment in patients with atrial fibrillation: observing outcomes associated with varying levels of INR control. Thromb Res 2009;124:37-41.
7. Ozgonenel B, O'Malley B, Krishen P, Eisenbrey AB. Warfarin reversal emerging as the major indication for fresh frozen plasma use at a tertiary care hospital. Am J Hematol 2007;82:1091-4.
8. Gage BF, Eby C, Johnson JA, et al. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. Clin Pharmacol Ther 2008;84:326-31.
9. Carlquist JF, Horne BD, Mower C, et al. An evaluation of nine genetic variants related to metabolism and mechanism of action of warfarin as applied to stable dose prediction. J Thromb Thrombolysis 2010;30:358-64.

10. Tanaka KA, Key NS, Levy JH. Blood coagulation: hemostasis and thrombin regulation. Anesth Analg 2009;108:1433-46.

11. Green L, Roberts N, Cooper J, et al. Prothrombin complex concentrate vs. fresh frozen plasma in adult patients undergoing heart surgery – a pilot randomised controlled trial (PROPHESY trial). Anaesthesia 2021;76:892-901.

12. Kao TW, Lee YC, Chang HT. Prothrombin Complex Concentrate for Trauma Induced Coagulopathy: A Systematic Review and Meta-Analysis. J Acute Med 2021;11:81-9.

13. Bouzat P, Bosson JL, David JS, et al. Four-factor prothrombin complex concentrate to reduce allogenic blood product transfusion in patients with major trauma, the PROCOAG trial: study protocol for a randomized multicenter double-blind superiority study. Trials 2021;22:634.

14. Naeem Z, Allan S, Hernandez A, Galanakis DK, Singer AJ. Clinical utilization of four-factor prothrombin complex concentrate: a retrospective single center study. Clin Exp Emerg Med 2021;8:75-81.

15. Bianco C. Choice of human plasma preparations for transfusion. Transfus Med Rev 1999;13:84-8.

16. Makris M, Van Veen JJ. Three or four factor prothrombin complex concentrate for emergency anticoagulation reversal?. Blood Transfus 2011;9:117-9.

17. Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126(Suppl 3):204-33.

18. Leissinger CA, Blatt PM, Hoots WK, Ewenstein B. Role of prothrombin complex concentrates in reversing warfarin anticoagulation: a review of the literature. Am J Hematol 2008;83:137-43.

19. Karkouti K, Bartoszko J, Grewal D, et al. Comparison of 4-Factor Prothrombin Complex Concentrate With Frozen Plasma for Management of Hemorrhage During and After Cardiac Surgery: A Randomized Pilot Trial. JAMA Netw Open 2021;4:e213936.

20. van den Brink DP, Wirtz MR, Neto AS, et al. Effectiveness of prothrombin complex concentrate for the treatment of bleeding: A systematic review and meta-analysis. J Thromb Haemost 2020;18:2457-67.

21. Sayhan MB, Salt Ö, Demir AM. Prothrombin Complex Concentrates in Life-Threatening Bleeding. Balkan Med J 2016;33:712-3.

22. Baker RI, Coughlin PB, Gallus AS, et al. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. Med J Aust 2004;181:492-7.

23. Kaya FB, Ozakin E, Yüksel GC, Karakılıç ME, Kaya S, Çanakçı ME. Use Of Prothrombın Complex Concentrate In The Emergency Department For Cases With Warfarin Overdose: A Retrospective Study. Ankara Med J 2020;4:1071-81.

24. Barillari G, Pasca S, Barillari A, De Angelis V. Emergency reversal of anticoagulation: from theory to real use of prothrombin complex concentrates. A retrospective Italian experience. Blood Transfus 2012;10:87-94.

25. Keren F, Simşek ET, Balçık ÖŞ, Koşar A. To use prothrombin complex concentrate for reversing the anticoagulant effect depending on warfarin: A single-center study. New Med,ical Journal 2014;31:172. https://app.trdizin.gov.tr/publication/paper/detail/TVRZMU5UTTFOUT09

26. Marcos-Jubilar M, García Erce JA, Martínez-Calle N, Páramo JA, Martínez Virto A, Quintana-Díaz M. Safety and effectiveness of a prothrombin complex concentrate in approved and off-label indications. Transfus Med 2019;29:268-74.

27. Eroğlu S, Denizbaşı A, Özpolat Ç, Akoğlu H, Onur ÖE, Akoğlu EÜ. The Investigation of the Relation Between INR Levels and Risk of Complication in Patients with a History of Warfarin use. Marmara Med J 2015;25:138-42.

28. Sayhan MB, Oğuz S, Yüksel V, Hüseyin S, ayhan ES, Yağcı G. The Analysis of Patients Admitted to the Emergency Department Due to Complications Related to Warfarin Treatment. Eurasian J Emerg Med 2014;13:194-8.

29. Cross-sectional guidelines for therapy with blood components and plasma derivatives: Chapter 7 Procoagulators. Transfus Med Hemother 2009;36:419-36. DOI: 10.1159/000268063

30. O'Shaughnessy DF, Atterbury C, Bolton Maggs P, et al. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. Br J Haematol 2004;126:11-28.

31. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(Suppl 2):152-84.

32. Steiner T, Poli S, Griebe M, et al. Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. Lancet Neurol 2016;15:566-73.

33. Nelson WW, Wang L, Baser O, Damaraju CV, Schein JR. Out-of-range international normalized ratio values and healthcare cost among new warfarin patients with non-valvular atrial fibrillation. J Med Econ 2015;18:333-40.

34. Fariborz Farsad B, Golpira R, Najafi H, et al. Comparison between Prothrombin Complex Concentrate (PCC) and Fresh Frozen Plasma (FFP) for the Urgent Reversal of Warfarin in Patients with Mechanical Heart Valves in a Tertiary Care Cardiac Center. Iran J Pharm Res 2015;14:877-85.

35. Tanaka KA, Szlam F. Treatment of massive bleeding with prothrombin complex concentrate: argument for. J Thromb Haemost 2010;8:2589-91.

36. Cruz JL, Moss MC, Chen SL, Hansen KM, Amerine LB. Retrospective evaluation of the clinical use of prothrombin complex concentrate for the reversal of anticoagulation with vitamin K antagonists. Blood Coagul Fibrinolysis 2015;26:378-82.

37. Dentali F, Marchesi C, Giorgi, et al. Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists. A meta-analysis. Thromb Haemost 2011;106:429-38.

Original Article

DOI: 10.4274/haseki.galenos.2022.7956
Med Bull Haseki 2022;60:72-77

Evaluation of the Demographic and Clinical Data of Psoriasis Patients: A Detailed Analysis of a Big Series

Tugba Ozkok Akbulut*, Filiz Topaloglu Demir*, Ayse Nur Tufan**, Nazli Caf*, Baran Cayhan*, Senay Agirgol*, Zafer Turkoglu*

*University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Dermatology, Istanbul, Turkey

**University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Rheumatology, Istanbul, Turkey

Abstract

Aim: Psoriasis is a chronic disease and requires follow-up settings to manage. The aim of the study is to evaluate the clinical characteristics, disease course, the factors associated with the psoriasis area severity score index (PASI), comorbidities, and treatment of psoriasis in our follow-up psoriasis outpatient clinic.

Methods: Clinical data from patients who were followed in the University of Health Sciences Turkey, Haseki Training and Research Hospital psoriasis outpatient clinic between January 2015 and March 2021 were examined. The relationships between age, age of the disease onset, gender, joint involvement, and nail involvement were analyzed.

Results: In total, 618 patients were included in our study (320 males and 298 females). The median age of the patients was 42 (1-87) years. Family history was present in 25.9% of the patients. The most common clinical type was plaque psoriasis (80.2%). The median value of the PASI was 8.1. The disease course of the patients was progressive (46.4%), remission and exacerbations (37%), and regressive (16.7%). Nail involvement and joint involvement were observed in 58.1% and 24.2% of the patients, respectively. A significant correlation was found between PASI and joint involvement (p=0.009). Onycholysis (a type of nail involvement) was a positive predictive indicator for joint involvement (p=0.004). Comorbidity was present in 34.5% of the patients. Obesity, hypertension, diabetes mellitus, and dyslipidemia were the most common comorbidities. While 19.9% of the patients received only topical treatment, 80.1% underwent systemic treatment.

Conclusions: The socio-demographic and enriched clinical data of psoriasis highlight the features that should be considered, especially in follow-up outpatient clinics. Patients showing an early onset of the disease should be investigated for severe involvement, such as the presence of onycholysis in the nail or evidence of joint involvement. The follow-up and treatment of patients with psoriasis are important in terms of comorbidities.

Keywords: Psoriasis, demographic, plaque, joint

Introduction

Psoriasis is a chronic inflammatory disease that affects 2-3% of people worldwide (1) and can involve the skin, nails, and joints. The prevailing opinion is that psoriasis is a systemic inflammatory disease that occurs due to concomitant hypertension, diabetes, metabolic syndrome, hyperlipidemia, coronary artery disease, and comorbidities such as depression and anxiety (2).

The current recommendation is that patients with psoriasis should be followed up in outpatient clinics to allow for a multidisciplinary approach. Revealing the clinical and socio-demographic characteristics may help to guide treatment approaches and clinical management (3). Patient data for psoriasis follow-up in outpatient clinics in our country is available in various regions (4-11).

In this study, our aim is to examine the socio-demographic and comprehensive clinical data, including

Address for Correspondence: Tugba Ozkok Akbulut
University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Dermatology, Istanbul, Turkey
Phone: +90 554 242 90 26 E-mail: dderm08@hotmail.com ORCID: orcid.org/0000-0001-9995-2543
Received: 14.11.2021 **Accepted:** 01.01.2022

disease course, disease onset, and visual analogue scale (VAS)-pruritus, of the patients followed in the psoriasis outpatient clinic of our hospital.

Methods

The study approval was obtained from the ethics committee of the University of Health Sciences Turkey, Haseki Training and Research Hospital (no: 273, date: 31.10.2019). The follow-up charts of the psoriasis patients admitted to our hospital between January 2015 and March 2021 were retrospectively analyzed. Informed consent was obtained from each patient. Patients with incomplete clinical information were excluded from the study. The patients' data included age, gender, onset age of psoriasis, the type of onset of the disease, disease course, duration of the disease, family history, clinical types, joint involvement, nail involvement, smoking and alcohol use history, concomitant systemic diseases, body mass index (BMI), the psoriasis area and severity index (PASI), VAS-pruritus, VAS-skin pain, and topical and systemic treatments given to the patient. We categorized pruritus and skin pain into three groups using a 0 to 10 cm VAS: <5, mild; 5-7, moderate; and >7-10, severe pruritus and skin pain.

Statistical Analysis

For statistical analysis, SPSS 15.0 for Windows Excel was used for statistical analysis. Descriptive statistics were given as numbers and percentages for categorical variables and numerical variables as the mean, standard deviation, minimum, and maximum. The rates in independent groups were compared using the chi-square test. The statistical significance level of alpha was accepted as $p<0.05$.

Results

A total of 618 patients attending our psoriasis follow-up outpatient clinic were included in the study. The median age was 42 years [interquartile range (IQR) 28-52.3]; 320 (51.8%) were male and 298 (48.2%) were female. The median duration of the disease was 10 years (IQR 3-36). The age of the patients did not differ significantly between the genders ($p>0.05$). The median age of onset was 22.5 years (IQR 14-40) for women and 27 years (IQR 17-40) for men, and this difference was statistically significant ($p=0.014$).

Evaluation of the patients by weight and height characteristics revealed a median BMI of 27 kg/m^2 (IQR 23.7-30.4). The median PASI score was 8.1 (IQR 4.2-13.4). The PASI scores were greater than 10 in 246 patients (41.5%) and less than 10 in 347 patients (58.5%). The disease onset of the patients was sudden in 347 (56.2%) and gradual in 270 (43.8%). The disease course of the patients was progressive in 286 patients (46.4%), remission and exacerbations in 228 patients (37%), and regressive in 103 patients (16.7%). 73.2% of the patients complained of pruritus, varying in severity from 3 to 5, using a VAS (0-10). The median VAS-skin pain was 2 (IQR 1-2) (Table 1).

The smoking rate among the patients was 43.3%, and the alcohol use rate was 7%. The PASI was greater than 10 in 47.4% of the smoking cases and in 36.7% of the non-smoking cases, and this difference was statistically significant ($p=0.009$). No correlation was observed between alcohol consumption and PASI.

Psoriasis history was present in first-degree relatives of 95 (15.4%) patients, in second-degree relatives of 50 (8.1%) patients, and in both first- and second-degree relatives of 15 (2.4%) patients. The median age of the disease onset was significantly lower in patients with a family history of psoriasis [20.5 years (IQR 14.3-30.8)] than in those without a family history [27 years (IQR 17-42)] ($p=0.001$).

A total of 213 patients (34.5%) had comorbidity in the form of concomitant diseases. Obesity was present in 156 (27.0) patients, hypertension in 107 (17.3%), diabetes mellitus in 71 (11.5%), dyslipidemia in 67 (10.8%), thyroid diseases in 37 (6%), and coronary artery diseases in 34 (5.5%).

The most common of the clinical types among the patients were plaque-type (80.2%) (Figure 1) and guttate type (23.4%). The distribution of lesion locations is given in Table 2.

Nail findings were present in 356 (58.1%) of the patients. The most common nail findings were pitting in 293 (47.4%) patients and onycholysis in 135 (21.8%). The rate of nail findings in patients with joint findings was statistically significantly higher [$p=0.009$ OR: 1.62 (95% CI 1.09-2.40)]. The rate of incidence of onycholysis among the nail findings was higher in patients with joint findings than in those without joint findings, and the difference was statistically significant ($p=0.004$ OR: 1.86 95% CI 1.22-2.85) (Table 2).

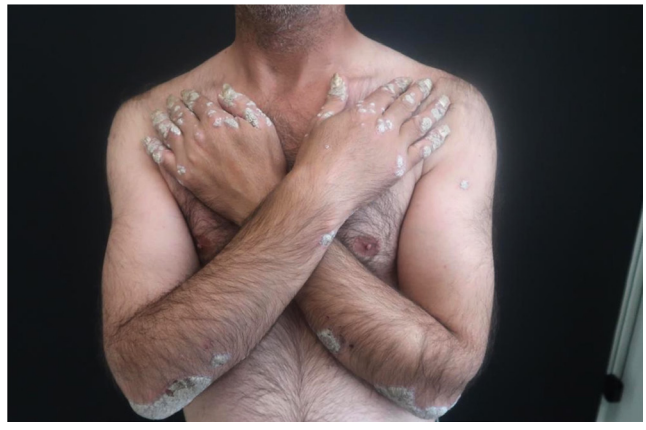


Figure 1. Plaque-type psoriasis

Arthritis was detected in 24.2% of the patients (149 patients). The rate of joint involvement was higher in patients with PASI scores greater than 10 (30.1%) than in those with PASI scores less than 10 (20.9%) (p=0.010).

In total, 123 of the patients (19.9%) were only receiving local treatments, 197 (32%) were treated with phototherapy, and 425 (68.8%) were receiving systemic treatments. Methotrexate (53.1%) was the most common systemic treatment. The distribution of systemic treatments is given in Table 2.

Table 1. Baseline demographics of the patients

Sex, n (%)	**Female**	**298 (48.2)**
	Male	**320 (51.8)**
Age, years, median (IQR)		42 (28-52.3)
Age, years, n (%)	<18	59 (9.5)
	18-64	510 (82.5)
	≥65	49 (7.9)
BMI, kg/m², median (IQR)		27 (23.7-30.4)
BMI, n (%)	<20 kg/m²	44 (7.6)
	20-25 kg/m²	163 (28.2)
	25-30 kg/m²	215 (37.2)
	≥30 kg/m²	156 (27.0)
DLQI, median (IQR)		12 (5-19)
PASI, median (IQR)		8.1 (4.2-13.4)
PASI	<10	347 (58.5)
	≥10	246 (41.5)
Pruritus		450 (73.2)
VAS-pruritus, median (IQR)		4 (3-5)
VAS-skin pain, median (IQR)		2 (1-2)
Disease onset, n (%)	Gradual	270 (43.8)
	Sudden	347 (56.2)
Disease course, n (%)	Progressive	286 (46.4)
	Regressive	103 (16.7)
	Remissions and exacerbations	228 (37.0)
Disease onset age, years, median (IQR)		25 (16-40)
Duration of psoriasis, years, median (IQR)		10 (3-36)
Smoker, yes, n (%)		274 (43.3)
Alcohol insumption, yes, n (%)		43 (7.0)
Family history of psoriasis		
	First-degree	95 (15.4)
	Second-degree	50 (8.1)
	Both	15 (2.4)
Comorbidities, yes, n (%)		213 (34.5)
	Obesity	156 (27.0)
	Hypertension	107 (17.3)
	Diabetes	71 (11.5)
	Dyslipidemia/ hyperlipidemia	67 (10.8)
	Thyroid disease	37 (6)
	Coronary artery disease	34 (5.5)

BMI: Body mass index, VAS: Visual analogue scale, IQR: Interquartile range, DLQI: Dermatology life quality index, PASI: Psoriasis area severity score index

Table 2. Clinical characteristics and treatment modalities of the patients

Clinical type, n (%)		
	Plaque	493 (80.2)
	Guttate	144 (23.4)
	Palmoplantar	58 (9.4)
	Inverse	41 (6.7)
	Generalized pustular	16 (2.6)
	Localized pustular	14 (2.3)
	Erythrodermic	7 (1.1)
Involvement		
Scalp		437 (71.1)
Dorsum of hand		312 (50.7)
Face		206 (33.5)
Nail		356 (58.1)
	Pitting	293 (47.4)
	Onycholysis	135 (21.8)
	Subungual hyperkeratosis	114 (18.4)
	Discoloration	89 (14.4)
	Oil drop sign	83 (13.4)
	Splinter hemorrhage	34 (5.5)
	Leukonychia	17 (2.8)
	Beau's lines	11 (1.8)
Psoriatic arthritis		149 (24.2)
Phototherapy		197 (32.0)
Systemic conventional treatments		425 (68.8)
	Methotrexate	328 (53.1)
	Acitretin	240 (38.8)
	Cyclosporine	72 (11.7)
Biologics		127 (20.6)
	Adalimumab	44 (7.1)
	Ustekinumab	42 (7.0)
	Etanercept	33 (5.3)
	Secukinumab	29 (4.7)
	Ixekizumab	9 (1.5)
	Infliximab	8 (1.3)
	Certolizumab	6 (1)

Discussion

Psoriasis is a systemic inflammatory disease that occurs in 2% of the population, with a more common incidence in Europe and America than in East Africa and Asia (3). Its prevalence was 1.18% in the study by Yaylı et al. (9). Psoriasis has been reported equally frequently in men and women, in general (1); for example, Ferrándiz et al. (12) found a female-male ratio of 1.12/1 in a large patient cohort; Kundakci et al. (4) found a ratio of 1.5/1, and Rifaioglu and Özarmağan (8) found a ratio of 0.95/1. In our study, the female-to-male ratio was 1.07/1, in agreement with the literature.

Psoriasis can occur at any age, with the most common onset in the second and third decades, although it may start at an earlier age in women (1-3). One study conducted in Spain reported the age of onset of psoriasis at 28.2 years in women and 31.8 years in men (12). Topal et al. (10) found an onset of psoriasis at age 27.1 in women and 28.4 in men. In the present study, psoriasis also started at an earlier age in women (22.5 years) than in men (27 years) (p=0.014).

Previous studies have reported a family history of psoriasis in 17.9% and 44% of the patients (13,14). The risk of the disease is 63% in monozygotic twins and 15% in dizygotic twins (15). A study of 444 patients in our country established a family history of psoriasis in 31.9% of the patients (16). Family history was reported in 27.9% of the patients in the study by Aksoy and An (11), and in 24.9% in the study by Topal et al. (10). Similarly, a family history was present in 25.5% of the patients in our study. Solmaz et al. (16) determined that the presence of a family history was also associated with an earlier onset of the disease. Similarly, in our study, the disease started earlier in patients with a family history of psoriasis than in those without a family history of psoriasis (p=0.001).

Some patients experience chronic, persistent lesions for many years, while others experience short- or long-term remissions (17). The course of the disease is generally different in patients, and this is unpredictable (14). Similarly, in this study, the disease progressed progressively in almost half of the patients, with remissions and exacerbations in one-third.

Smoking, as this leads to an increase in free radicals that activate the signaling pathways that are important in psoriasis pathogenesis (18). Being a smoker has been identified as an independent risk factor for the development of psoriasis, and smoking habits are observed twice as often in psoriasis patients (19,20). Aksoy and An (11) found a smoking rate in their psoriasis patients of 28.9%, whereas Rifaioglu and Özarmağan (8) found a rate of 42.3%. In our study, 43.3% of the patients were smokers. Smoking has also been associated with more severe diseases (20); a study conducted in our country also reported a similar association between smoking and disease severity (21). In agreement with the literature, the severity of the disease in our study was significantly higher in patients with psoriasis who smoked (p=0.009).

The results of studies on the effects of alcohol use on psoriasis have been contradictory (8,11,22). For example, Aksoy and An (11) reported alcohol use in 1.3% of their psoriasis patients, based on a conservative cohort representation. By contrast, Rifaioglu and Özarmağan (8) found an alcohol use rate of 19.2%. In our study, 7% of the patients were using alcohol.

Psoriasis is a clinically heterogeneous disease. Plaque psoriasis (23) and lichen planopilaris (24) are the most common clinical types, accounting for 70-80% of cases. In our study, most patients had the plaque-type. Topal et al. (10) reported the plaque-type in 74% of their patients, the guttate type in 23.5%, the generalized pustular type in 3%, and the palmoplantar type in 2%. Turan et al. (7) reported the plaque-type in 73.7% of their patients, the guttate type in 14.5%, the palmoplantar type in 7.6%, the inverse type in 2.8%, and the generalized pustular type in 0.4%. In our study, 80.2% of the patients had plaque-type lesions, 23.4% had guttate lesions, 9.4% had palmoplantar lesions, and 6.7% had inverse involvement, in conformity with the literature.

Joint involvement has been reported in 4.1-40% of patients with psoriatic skin lesions (5,6,22,25,26). Turan et al. (7) found joint involvement in 14.5% of their patients, whereas Gamonal et al. (24) found joint involvement in 24.3% of their patients. In our study, joint involvement accompanied skin lesions in 24.2% of the patients, and the presence of joint involvement was verified by rheumatology consultation. Topal et al. (10) reported a higher frequency of joint involvement in patients with PASI scores greater than 10 (16.1%) than in those with PASI scores less than 10 (8%) (p=0.024). In our study, joint involvement was more common in patients with severe disease, as reported in the literature (p=0.010).

Nail involvement has been reported at rates between 16% and 62.1% in studies conducted in our country (4-11). In our study, nail involvement occurred in 58.1% of the patients, in accordance with the literature. Rifaioglu and Özarmağan (8) found nail involvement in 55.9% of their patients, whereas Kundakci et al. (4) found a rate of 16%. Ferrándiz et al. (12) reported a significant relationship between nail involvement and joint involvement. In our study, the rate of nail findings was higher in patients with joint findings than in those without joint findings, and the difference was statistically significant [p=0.009 OR: 1.62 (95% CI 1.09-2.40)]. In the literature, the most common nail finding was reported as pitting (17.7-20.8%) and the

second as onycholysis (15.3%) (7,8). In our study, 47.4% of the patients had pitting and 21.8% had onycholysis, which is in agreement with the literature. The nail finding associated with joint involvement was onycholysis in this study (p=0.004, OR: 1.86, 95% CI 1.22-2.85).

Psoriasis is a systemic inflammatory disease and can be accompanied by several comorbidities, such as hypertension, diabetes, dyslipidemia, coronary artery disease, and metabolic syndrome. A large-scale study conducted in the USA reported that 27% of patients with psoriasis also had dyslipidemia and 25% had hypertension (25). Cohen et al. (26) compared 12,502 patients with psoriasis with 24,285 control participants and found hypertension in 38.8% (p<0.01) of the psoriasis group. Turan et al. (7) reported comorbidities in 30.6% of their patients, and Aykol et al. (6) found comorbidities in 11.8% of their patients. In our study, 34.7% of the patients had a comorbid disease, in agreement with previous studies.

Another striking finding of our study was that 6% of the patients had comorbid thyroid diseases, which are typically reported at a rate of 3.2% in the general population (27). A previous study also indicated a high prevalence of thyroid diseases in psoriasis patients, at 9.1%. This situation was especially attributed to the production of IL-17 and IL-23 cytokines, which play an important role in the pathogenesis of both psoriasis and autoimmune thyroiditis (28).

Systemic treatment options for patients who fail to respond adequately to topical or phototherapy treatments can include methotrexate, acitretin, cyclosporine, and biological therapies. Topal et al. indicated that the most common systemic drugs used by patients with psoriasis were acitretin (18%), methotrexate (15.7%), and cyclosporine (5.2%) (10). Aksoy and An (11) reported that methotrexate (24.5%) was the most frequently administered systemic treatment. In our study, 53.3% of the patients received methotrexate, whereas only 19.7% received biological treatments. The more frequent preference for methotrexate, one of the conventional agents, in our country may be related to the lack of acitretin or cyclosporine as treatments in the market in 2018-2019.

Study Limitations

One limitation of our study was its retrospective design, as some data was missing. Another was that, since the comorbidities consisted of file data filled in by reviewing the patient's history, concomitant but not diagnosed diseases could have been missed. Confirming this possibility will require further studies in which patients are prospectively investigated for a wide range of possible accompanying diseases.

The strengths of our study are that it includes the current rates of use of biological treatments, detailed analysis of the relationship between subdistribution of nail findings and joint involvement, and includes extensive file data of psoriasis patients.

Conclusion

Since psoriasis is a chronic disease, real-life experience data takes on great importance. In this study, we presented the general demographics and clinical characteristics of patients with psoriasis. We observed that thyroid diseases are not uncommon in psoriasis patients. Our results also indicate that psoriasis starts earlier in women and in patients with a family history of psoriasis. The risk of joint involvement appears to be higher in patients with a PASI value of over 10, as well as in patients with nail involvement, especially with signs of onycholysis. It is seen that the course of the disease is progressive in approximately half of the patients, and that it progresses with remissions and exacerbations in more than one third of the patients.

Ethics

Ethics Committee Approval: The study approval was obtained from the ethics committee of the University of Health Sciences Turkey, Haseki Training and Research Hospital (no: 273, date: 31.10.2019).

Informed Consent: Informed consent was obtained from each patient.

Authorship Contributions

Concept: T.O.A., S.A., A.N.T., Design: T.O.A., A.N.T., Data Collection or Processing: T.O.A., F.T.D., S.A., N.C., B.C., Analysis or Interpretation: T.O.A., F.T.D., N.C., B.C., Z.T., Literature Research: T.O.A., Z.T., Writing: T.O.A.

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

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

References

1. Campanati A, Marani A, Martina E, Diotallevi F, Radi G, Offidani A. Psoriasis as an Immune-Mediated and Inflammatory Systemic Disease: From Pathophysiology to Novel Therapeutic Approaches. Biomedicines 2021;9:1511.
2. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM; Identification and Management of Psoriasis and Associated ComorbidiTy (IMPACT) project team. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol 2013;133:377-85.
3. Mehrmal S, Uppal P, Nedley N, Giesey RL, Delost GR. The global, regional, and national burden of psoriasis in 195 countries and territories, 1990 to 2017: A systematic analysis from the Global Burden of Disease Study 2017. J Am Acad Dermatol 2021;84:46-52.

4. Kundakci N, Türsen U, Babiker MO, Gürgey E. The evaluation of the socio-demographic and clinical features of Turkish psoriasis patients. Int J Dermatol 2002;41:220-4.
5. Tekin NS, Koca R, Altınyazar HC, Çınar S, Muhtar Ş, Aslaner NN. Zonguldak bölgesindeki psoriasis hastalarının sosyodemografik ve klinik özelliklerinin değerlendirilmesi. Turkiye Klinikleri J Dermatol 2005;15:141-6.
6. Aykol C, Mevlitoğlu İ, Özdemir M, Ünal M. Konya Yöresindeki Psoriasis Hastalarinin Klinik ve Sosyodemografik Özelliklerinin Degerlendirilmesi. Turk J Dermatol 2011;5:71-4.
7. Turan H, Acer E, Aliağaoğlu C, Uslu E, Albayrak H, Özşahin M. Psoriazisli Hastalarin Klinik ve Sosyodemografik Özelliklerinin Degerlendirilmesi. Turk J Dermatol 2013;7:76-80.
8. Rifaioglu EN, Özarmağan G. Clinical and demographic characteristics of 626 patients with moderate and severe psoriasis. J Clin Anal Med 2014;5:9-14.
9. Yaylı S, Topbaş M, Arıca DA, Tuğcugil S, Çapkın E, Bahadır S. The prevalence of psoriasis in Trabzon. Turkderm-Turk Arch Dermatol Venereol 2016;50:141-4.
10. Topal İO, Değirmentepe E, Cüre K, Kızıltaç U, Hökenek NB, Kocatürk E. Psoriasisli Hastaların Klinik ve Sosyodemografik Özelliklerinin Retrospektif Analizi. Eur Arc Med Res 2017;33:199-205.
11. Aksoy M, An İ. Psöriazis tanılı 298 hastanın klinik ve demografik özelliklerinin incelenmesi. Harran Üniversitesi Tıp Fakültesi Dergisi 2019;16:385-8.
12. Ferrándiz C, Pujol RM, García-Patos V, Bordas X, Smandía JA. Psoriasis of early and late onset: a clinical and epidemiologic study from Spain. J Am Acad Dermatol 2002;46:867-73.
13. Kavanaugh A, Papp K, Gottlieb AB, et al. Demography, baseline disease characteristics, and treatment history of psoriasis patients with self-reported psoriatic arthritis enrolled in the PSOLAR registry. BMC Rheumatol 2018;2:29.
14. Özkesici Kurt B, Dönmez L, Nazlım B, et al. Defining the natural course of psoriasis: A single-center cohort study of 100 patients. Turk J Dermatol 2018;12:33-7.
15. Brandrup F, Holm N, Grunnet N, Henningsen K, Hansen HE. Psoriasis in monozygotic twins: variations in expression in individuals with identical genetic constitution. Acta Derm Venereol 1982;62:229-36.
16. Solmaz D, Bakirci S, Kimyon G, et al. Impact of Having Family History of Psoriasis or Psoriatic Arthritis on Psoriatic Disease. Arthritis Care Res (Hoboken) 2020;72:63-8.
17. Osborne JE, Hutchinson PE. Demographic and clinical correlates of extent of psoriasis during stable disease and during flares in chronic plaque psoriasis. Br J Dermatol 2008;158:721-6.
18. Armstrong AW, Harskamp CT, Dhillon JS, Armstrong EJ. Psoriasis and smoking: a systematic review and meta-analysis. Br J Dermatol 2014;170:304-14.
19. Herron MD, Hinckley M, Hoffman MS, et al. Impact of obesity and smoking on psoriasis presentation and management. Arch Dermatol 2005;141:1527-34.
20. Lipa K, Zając N, Owczarek W, Ciechanowicz P, Szymańska E, Walecka I. Does smoking affect your skin? Postepy Dermatol Alergol 2021;38:371-6.
21. Kayıran N, Korkmaz S, Özgöztaşı O. Impact of smoking on disease severity in patients with plaque type psoriasis. Turkderm-Turk Arch Dermatol Venereol 2015;49(Suppl 1):19-22.
22. Zou L, Lonne-Rahm SB, Helander A, Stokkeland K, Franck J, Nordlind K. Alcohol intake measured by phosphatidylethanol in blood and the lifetime drinking history interview are correlated with the extent of psoriasis. Dermatology 2015;230:375-80.
23. Alpsoy E. Tüm yönleriyle psoriasis. İstanbul: Galenos Yayınevi; 2020.
24. Gamonal SBL, Gamonal ACC, Brandão MAF, Junqueira LA, Assis PM, Raposo NRB. Prevalence of psoriatic arthritis among patients with plaque psoriasis: a Brazilian retrospective study. Sao Paulo Med J 2021;139:476-80.
25. Kimball AB, Guérin A, Tsaneva M, et al. Economic burden of comorbidities in patients with psoriasis is substantial. J Eur Acad Dermatol Venereol 2011;25:157-63.
26. Cohen AD, Weitzman D, Dreiher J. Psoriasis and hypertension: a case-control study. Acta Derm Venereol 2010;90:23-6.
27. Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, Galofré JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. J Clin Endocrinol Metab 2014;99:923-31.
28. Borges AS, Valejo Coelho MM, Brasileiro A. A possible association between psoriasis and thyroid dysfunction. Eur J Dermatol 2018;28:715-6.

Case Series

DOI: 10.4274/haseki.galenos.2021.7482
Med Bull Haseki 2022;60:78-83

Evaluation Of Postoperative Symptom Relief With Styloidectomy Procedure For Eagle Syndrome: A Case Series From A National-Accredited Center

Semih Usaklioglu, Gokhan Gurbuz, Onur Ustun, Yagmur Barcan

University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Otorhinolaryngology, Istanbul, Turkey

Abstract

Aim: Eagle syndrome is a very rare disease that manifests with a styloid process longer than normal. The aim of this study is to evaluate the characteristic features of Eagle syndrome and postoperative regression of the existing complaints.

Methods: This study is a retrospective case series study. Data of 17 patients who had styloidectomy operation due to Eagle syndrome between 2015 and 2019 in a national accredited center are presented. Radiological findings, physical examination results and medical history were evaluated retrospectively according to the medical records of the hospital. Preoperative and postoperative visual analogue scale (VAS) and verbal response scale (VRS) scoring systems were used for pain scoring.

Results: The most common symptoms were throat pain on the same side (88.2%), neck pain (82.3%), and otalgia (70.5%). Less common symptoms were jaw pain (41.1%), dysphagia (35.2%), facial pain (29.4%), headache (23.5%), and foreign body sensation (23.5%). VAS pain scoring showed that 64.7% of the patients' pain completely regressed. The results of VRS were also similar to the results of postoperative VAS and they had a significant correlation in a negative way ($p<0.001$).

Conclusion: The procedure of styloidectomy is more successful for the regression of neck, throat, jaw, and ear pain than for the headache and facial pain for patients who had Eagle syndrome.

Keywords: Eagle syndrome, partial styloidectomy, transoral, styloid process, stylohyoid ligament

Introduction

Dr. Watt Eagle first described Eagle syndrome (ES) in 1937 as a disease which can be characterized by sore throat, dysphonia, dysphagia, otalgia and foreign body sensation (1). ES is a rare disease that occurs by elongation of the styloid process (SP) (>25 mm) with or without calcification of the stylohyoid ligament (2). This anatomical elongation causes inflammation due to traumatic irritation of the glossopharyngeal nerve (3). The prevalence of the elongated SP is approximately 4-8 cases per 10,000 people in the general population, but only 4-10% of the population has symptoms (4).

The diagnosis of ES is based on anamnesis, physical examination and radiological examination. In physical examination, palpation of the SP in the tonsillary fossa of a patient who has cervicofacial symptoms is one of the most important findings for the elongated SP. These symptoms tend to increase after the palpation of the elongated SP (2). However, in the literature, some of the studies also indicate that if SP is shorter than 7.5 cm, it can't be palpated (5).

The most commonly used techniques for radiological imaging are panoramic radiography (PR) and computed tomography (CT). Three-dimensional reconstructive imaging computed tomography (3D-CT) is the gold standard for evaluating the anatomy of the region and deciding the type of surgery (6). In the radiological examination, the first parameter to evaluate is the length of the SP. Positional variations of SP, mediolateral angulation, anteroposterior angulation and presence of a fracture are the other radiological parameters to be considered as causing the symptoms (7,8).

Address for Correspondence: Yagmur Barcan
University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Otorhinolaryngology, Istanbul, Turkey
Phone: +90 212 453 20 00 E-mail: yagmurbarcan@hotmail.com ORCID: orcid.org/0000-0002-3751-166X
Received: 28.05.2021 **Accepted:** 14.10.2021

The differential diagnosis for the elongated SP includes facial neuralgia, oral diseases and temporomandibular joint problems (9,10). These diseases have many common symptoms with ES, but the main distinction is made by the radiological findings.

The aim of this study is to evaluate the data and postoperative results of the patients who have been diagnosed with ES according to the literature.

Materials and Methods

The Ethics Committee of University of Health Sciences Turkey, Haseki Training and Research Hospital approved this study with file number 2020-63 on May 14th, 2020. In this study, 17 patients who underwent surgery for ES between 2015 and 2019 were included. This study is a retrospective case series review.

Study Design

Data of the patients who underwent styloidectomy procedures were collected from the medical records of the hospital. Data about the patients like age, gender, initial symptoms, physical examination information, location (right/left), unilaterality/bilaterality, SP length, presence of fracture, prior tonsillectomy, surgical approach, postoperative complications, complaints that still remain and follow up time accessed from the patient files.

Operation Technique

The transoral approach was applied to 16 patients, and the transcervical approach was applied to 1 patient. Of the transoral surgery patients, 14 of them were operated unilaterally and 2 of them were operated bilaterally. In this study, bilateral cases were counted as a single case for the determination of demographic factors, number of operations and symptoms. All styloidectomy procedures were performed by an experienced otorhinolaryngologist.

Preoperative and Postoperative Evaluation

The intensity of pain was evaluated with the visual analogue scale (VAS) preoperatively and sixth months after surgery (11). Visual analogue scale is a 10 point visual scale which the patients choose a number according to their pain severity (0=no pain, 10=very severe-unbearable pain). Also at the sixth month after surgery, Verbal Response Scale (VRS) was applied to the patients to assess how much relief they felt after the surgery (1=no relief at all, 2=moderate relief, 3=full recovery).

Three-dimensional computed tomography was used in preoperative imaging (Figure 1). This imaging provided the predictions in terms of SP length, angulation, presence of fracture, evaluation of region anatomy and surgical planning. The SP thickness was measured in axial sections while its length was measured in sagittal sections.

Statistical Analysis

SPSS 15.0 program for Windows was used for the statistical analysis. Descriptive statistical methods were given the number and percentage for categorical variables; mean, standard deviation, minimum, maximum, interquartile range for numerical variables. Paired samples analysis was performed with Wilcoxon analysis since the differences of numerical variables did not provide normal distribution conditions. The statistical significance level was accepted as $p<0.05$.

Results

Fifty eight point eight percent (n=10) of the cases were female and 41.2% (n=7) of the cases were male. The mean age of our patients was 45.7 (minimum-maximum: 22-66). Five point eight percent (n=1) of the patients were under the age of 30, 82.5% (n=14) of the patients were between 40-60 years old, 11.7% (n=2) of the patients were over 60 years old (Table 1).

According to the physical examination and scanning results, 52.9% (n=9) of the patients on the left side, 35.2% of the patients (n=6) on the right side, and 11.9% (n=2) of the patients on both sides had the elongated SP. The length of SP was between 25-30 mm in 23.5% (n=4), 30-40 mm in 47% (n =8), 40-50 mm in 11.7% (n=2), and more than 50 mm in 17.6% (n=3) of them (Figure 2). It was observed that 29.4% (n=5) of the styloid processes were fractured in the radiological examination.

Eigthy eight point two percent (n=15) of the patients had throat pain on the same side, 82.3% (n=14) had neck pain, 70.5% (n=12) had otalgia, 41.1% (n=7) had

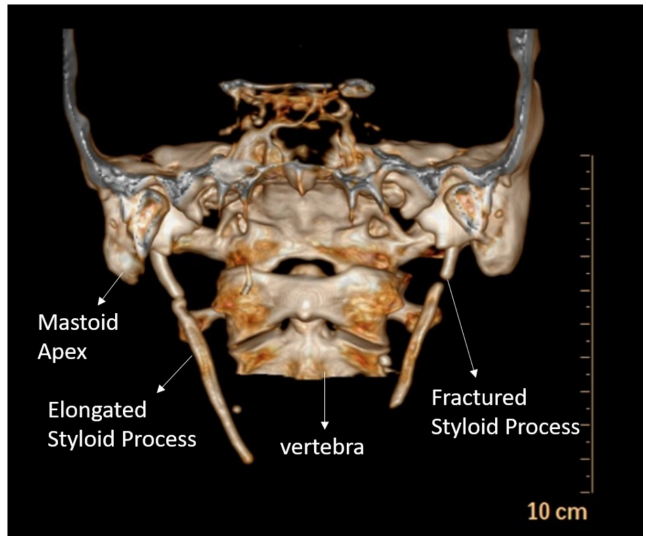


Figure 1. Preoperative 3D-CT scan being used to evaluate styloid process length, thickness and fracture features
3D-CT: Three-dimensional reconstructive imaging computed tomography

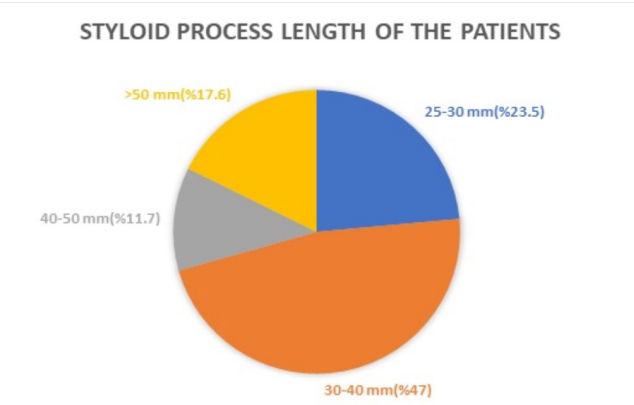


Figure 2. Styloid process length of the patients

jaw pain, 35.2% (n=6) had disphagia, 29.4% (n=5) had facial pain, 23.5% (n=4) had headache and 23.5% (n=4) had foreign body sensation while less frequently only 1 (5.8%) patient had periorbital pain and 1 (5.8%) patient had stinging sensation in the neck (Figure 3).

During the physical examination, the severity of the pain was high in all patients with palpation of the tonsillary fossa. Seventy-six point five percent (n=13) of the patients had continuous pain while 23.5% (n=4) of them had intermittent pain. The severity of the pain increased when lying down in 29.4% (n=5) of the patients while 70.6% (n=12) of them did not describe any changes in pain with the position.

In the preoperative VAS evaluation, 47% (n=8) of the patients gave 10 points, 23.5% (n=4) of the patients gave 8 points, 17.6% (n=3) of the patients gave 7 points, and lastly, 11.7% (n=2) of the patients gave 5 points for their pain. Sixty-four point seven percent (n=11) of the patients experienced complete pain relief following surgery. Eleven percent (n=2) of the patients did not describe regression (Table 2).

In postoperative evaluation, VRS scores were 1 in 11.7% (n=2), 2 in 23.5% (n=4), 3 in 64.7% (n=11) of the patients. The results of VRS correlated with the postoperative VAS scores in a negative way (p<0.001) (Table 3).

None of the patients had a prior tonsillectomy. Three patients underwent tonsillectomy preoperatively. Five-point eight percent (n=1) of the patients had postoperative wound infection in a total of 17 patients, and this patient was just treated with oral antibiotherapy without surgical drainage. Eleven percent (n=2) of the patients had mild symptoms of first bite syndrome. The symptoms of these patients disappeared in a short time. Also, 23% (n=4) of the patients had numbness in the surgical field after surgery, but these symptoms disappeared in the follow-ups.

Table 1. Demographic features of the patients	
Age	
<30	1 (5.8%)
31-60	14 (82.5%)
>61	2 (11.7%)
Gender	
Female	10 (58.8%)
Male	7 (41.2%)

Discussion

The styloid process is a needle-like projection of the temporal bone that has close proximity to the jugular foramen and carotid canal (12). ES can cause different symptoms depending on the irritation of the neural and vascular structures by either an elongated styloid process or a calcified stylohyoid ligament during swallowing and chewing. The most common symptoms are throat pain, otalgia, neck pain, and less often, dysphagia, tinnitus, and foreign body sensation (1,3). Many different theories have been considered for the occurrence of pain; a fracture in the ossified stylohyoid ligament with a sudden move, irritation of the glossopharyngeal nerve, trigeminal nerve or chorda tympani, degeneration and inflammation in the attachment point of the stylohyoid ligament, irritation of the pharyngeal mucosa, carotid artery compression and irritation of sympathetic nerves around the arterial wall caused by the elongated SP (13). In our study, similar to the literature, the most frequent symptoms were throat pain, otalgia, and jaw pain, and less often headache and facial pain.

There are two well-defined subgroups of ES; classical type and vascular/carotid artery syndrome type. In classical type, the irritation of the cranial nerve V (trigeminal), VII (facial), IX (glossopharyngeal) and X (vagus) by the elongated SP causes the symptoms; while the symptoms of vascular/carotid artery syndrome type arise from the affected carotid artery and sympathetic nerves (14-17). In recent studies, the internal jugular vein has also been added to these structures (14). In this second subtype, symptoms can vary from just the compression of the vessels and causing carotidynia (a headache which is spreading

Table 2. The evaluation of preoperative and postoperative pain severity

VAS	n	Mean ± SD	Min. - max.	Median (IQR)	p
Preoperative	17	8.41±1.75	5-10	8 (7-10)	**0.001***
Postoperative	17	1.77±2.68	0-7	0 (0-4.5)	

*Wilcoxon Analyse
The decrease in postoperative pain scores compared to preoperative pain scores was statistically significant (p=0.001)
VAS: Visual analogue scale, SD: Standard deviation, Min: Minimum, Max: Maximum, IQR: Interquantile range

Table 3. Control of the regression in pain symptoms with VAS and VRS

VAS scale				Verbal response scale
Patient number	Preoperative	Postoperative	Pain relief	
1	10	0	100%	3
2	8	5	37.5%	2
3	10	0	100%	3
4	10	0	100%	3
5	5	0	100%	3
6	8	5	37.5%	2
7	10	0	100%	3
8	7	4	42.8%	2
9	10	0	100%	3
10	7	7	0%	1
11	10	0	100%	3
12	7	7	0%	1
13	8	0	100%	3
14	5	0	100%	3
15	8	2	75%	2
16	10	0	100%	3
17	10	0	100%	3
Mean	8.41	1.76	76.04%	

VAS: Visual analogue scale, VRS: Verbal response scale

through the occipital pole to the eye) or dissection of the carotid artery which leads to stroke or transient ischemic attack (5,12). Sveinsson et al. (18) reported a case with ES and internal carotid artery dissection which is one of the few cases about carotid artery pathologies with ES (19). According to the literature all patients in our study were found to be compatible with the classical type of ES.

ES is an idiopathic disease, but it was thought that prior tonsillectomy may be one of the etiological factors. The fibrosis developing after the tonsillectomy operation can cause the symptoms by compression of the neural structures beside the SP (20). However, none of the further studies supported that hypothesis (21,22). In our study, none of the patients had a prior tonsillectomy or trauma history. We accepted the etiology of all patients as idiopathic similar to the literature (23).

The main and long-lasting treatment of ES is styloidectomy operations (24). In surgical treatment, there are two different approaches: transoral and transcervical. As a third approach for some rare cases; those two procedures can be combined. Short hospital stay and absence of external scar are some of the advantages of the transoral approach, while the disadvantages of this procedure include operating in a small area with no good vision, postoperative infection risk and in some cases perioperative tonsillectomy need (25). Muderris et al. (26) compared transoral and transcervical approaches in 2014. They operated 4 patients with the transoral approach while the other 4 patients were operated with the transcervical approach. In postoperative follow-ups, all patients in the transoral group had satisfying recovery except one patient. In the transcervical group, only one patient complained about the external scar. They concluded that both of the approaches were successful and short operation time, absence of external scar and less surgical trauma were the advantages in the transoral approach (26). In our study, we preferred to apply the transoral approach mostly and the results were similar to the literature.

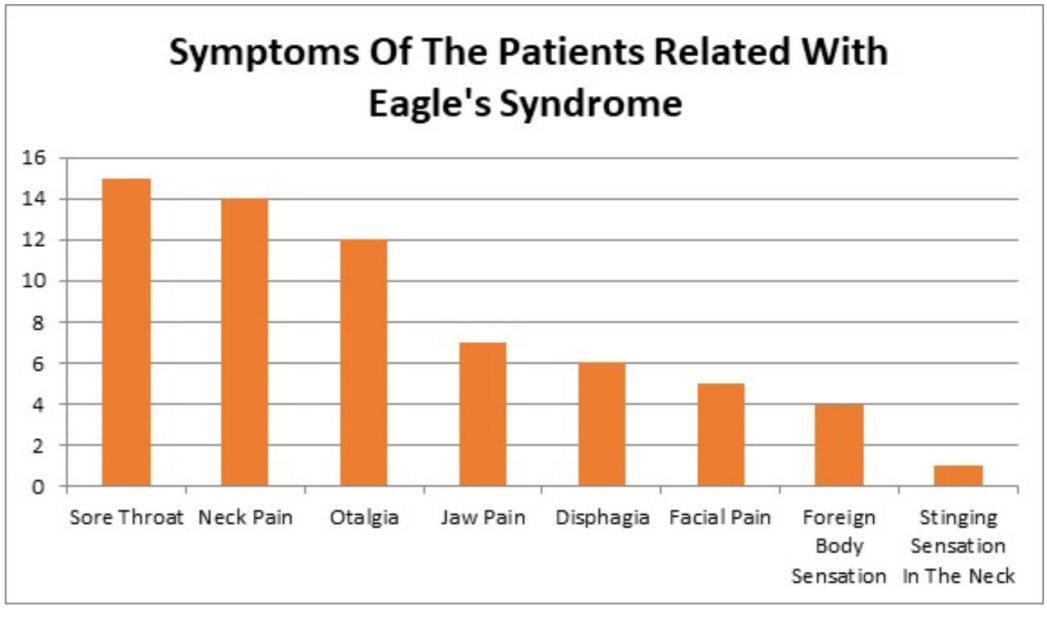


Figure 3. Symptoms of the patients related with Eagle syndrome

A new technique, called transoral robotic surgery (TORS), has been developed in recent years. Kim et al. (27) operated on four patients with this technique, and all four patients had a full recovery without any postoperative complications in follow-ups (27). Rizzo-Riera et al. (28) operated 6 patients with TORS and except one patient who had discomfort by chewing in specific moments; all of the patients had total relief in symptoms. There were no complications except one which was presented with suture dehiscence 4 days after the operation (28).

Fitzpatrick et al. (29) conducted a study with 21 patients and 6 of them were operated with TORS while the rest of the patients were operated with a transcervical approach. As a result, they didn't find a significant difference on symptom reduction between the two approaches. In the same study, there was no difference between perioperative estimated blood loss, operation duration and postoperative hospital stay. Ninety percent of their patients had symptom regression while only 55% of them had a significant recovery. In a study of 133 patients that underwent endoscopic assisted styloidectomy with retroauricular incision by Chen et al. (30), all operations were successful and there was no need to change the technique. Eighty point five percent of their patients had a full recovery, while 15% of them had moderate recovery. They suggested that this is a safe and feasible method in terms of effectiveness, few complications and advantage of cosmetic results. Mevio et al. (31) operated a patient with 3D endoscope-assisted anterior tonsillar fossa approach. They conclude that it's a good alternative for surgical management of ES in terms of high-quality magnification of tonsillar fossa and safe manipulation of the instruments which avoids damage to healthy tissues (31).

The other treatment options are anti-inflammatory, anti-convulsive, anti-psychotic and other analgesic drugs besides surgical intervention (32). However, the disadvantages of these conservative treatments are that the regression of the symptoms is not permanent and there are many possible side effects (16,33).

In our study, we mostly preferred the transoral approach in surgical treatment. The transcervical approach was only used for one patient due to the preoperative 3D-CT scan results and limited mouth opening. Unlike literature, in our study postoperative infection developed in this patient. When we evaluate the other complications in all patients, 2 patients (11.2%) developed first bite syndrome with mild symptoms. First bite syndrome is a clinical diagnosis which is a potential complication of parapharyngeal space operations causing severe pain with the first bite of the meal. There are limited studies of styloid process excision for this complication (25,34). In our study, the prevalence of this complication is much lower compared to the former studies. The first bite syndrome is a very rare complication, but the operation of ES is related with the parapharyngeal space and always should be kept in mind. In our study, we had complications like postoperative wound infections, numbness around the operation field and first bite syndrome.

The decrease in postoperative headache and facial pain complaints was less than neck and jaw pain in the literature (25). In our study, less regression was observed in the head and face pain similar to the literature.

Study Limitations

The main limitation of the study is the small number of patients. Further studies involving multicentric, large series of cases are needed to generate more data about this disease. Also, another limitation is that there was a significant difference between the transcervical and transoral approach groups in terms of patient number. More patients who were operated with a transcervical approach must be added to further studies to be able to compare these two groups and have more reliable results. In the literature, mostly case reports are present and this study is one of the few studies about ES which is a case series.

Conclusion

The surgical excision of the symptomatic elongated styloid process is a successful treatment option in ES. Dramatic recovery is observed especially in neck, throat, jaw, and ear pain; while the regression of head and facial pain is lower.

Ethics

Ethics Committee Approval: The Ethics Committee of University of Health Sciences Turkey, Haseki Training and Research Hospital approved this study with the file number 2020-63 on 14th May 2020.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Authorship Contributions

Concept: S.U., O.U., G.G., Y.B., Design: S.U., O.U., G.G., Y.B., Data Collection or Processing: S.U., O.U., G.G., Y.B., Analysis or Interpretation: S.U., O.U., G.G., Y.B., Literature Research: O.U., G.G., Y.B., Writing: S.U., O.U., G.G.

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

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

References

1. Eagle WW. Elongated styloid processes: report of two cases. Arch Otolaryngol Head Neck Surg 1937;25:584-7.

2. Galletta K, Siniscalchi EN, Cicciù M, Velo M, Granata F. Eagle syndrome: a wide spectrum of clinical and neuroradiological findings from cervico-facial pain to cerebral ischemia. J Craniofac Surg 2019;30:424-8.
3. Eagle WW. Elongated styloid process; symptoms and treatment. AMA Arch Otolaryngol 1958;67:172-6.
4. Kawasaki M, Hatashima S, Matsuda T. Non-surgical therapy for bilateral glossopharyngeal neuralgia caused by Eagle's syndrome, diagnosed by three-dimensional computed tomography: a case report. J Anesth 2012;26:918-21.
5. Saccomanno S, Quinzi V, D'Andrea N, Albani A, Coceani Paskay L, Marzo G. Traumatic Events and Eagle Syndrome: Is There Any Correlation? A Systematic Review. Healthcare (Basel) 2021;9:825.
6. Beder E, Ozgursoy OB, Karatayli Ozgursoy S, Anadolu Y. Three-dimensional computed tomography and surgical treatment for Eagle's syndrome. Ear Nose Throat J 2006;85:443-5.
7. Ramadan SU, Gokharman D, Tunçbilek I, Kacar M, Koşar P, Kosar U. Assessment of the stylohoid chain by 3D-CT. Surg Radiol Anat 2007;29:583-8.
8. Onbas O, Kantarci M, Murat Karasen R, et al. Angulation, length, and morphology of the styloid process o the temporal bone analyzed by multidetector computed tomography. Acta Radiol 2005;46:881-6.
9. Aral IL, Karaca I, Güngör N. Eagle's syndrome masquerading as pain of dental origin. Case report. Aust Dent J 1997;42:18-9.
10. de Barros JF, Rodrigues MV, Barroso LA, Amado IC. Eagle Syndrome: an underdiagnosed cause of orofacial pain. BMJ Case Rep 2021;14:e238161.
11. Shafshak TS, Elnemr R. The visual analogue scale versus numerical rating scale in measuring pain severity and predicting disability in low back pain. J Clin Rheumatol 2021;27:282-5.
12. González-García N, Porta-Etessam J, García-Azorín D. Eagle syndrome: Toward a clinical delimitation. Neurología (Engl Ed) 2021;36:412-7.
13. Buono U, Mangone GM, Michelotti A, Longo F, Califano L. Surgical approach to the stylohyoid process in Eagle's syndrome. J Oral Maxillofac Surg 2005;63:714-6.
14. Westbrook AM, Kabbaz VJ, Showalter CR. Eagle's syndrome, elongated styloid process and new evidence for pre-manipulative precautions for potential cervical arterial dysfunction. Musculoskelet Sci Pract 2020;50:102219.
15. Mendelsohn AH, Berke GS, Chhetri DK. Heterogeneity in the clinical presentation of Eagle's syndrome. Otolaryngol Head Neck Surg 2006;134:389-93.
16. Kim E, Hansen K, Frizzi J. Eagle syndrome: case report and review of the literature. Ear Nose Throat J 2008;87:631-3.
17. Bafaqeeh SA. Eagle syndrome: classic and carotid artery types. J Otolaryngol 2000;29:88-94.
18. Sveinsson O, Kostulas N, Herrman L. Internal carotid dissection caused by an elongated styloid process (Eagle syndrome). BMJ Case Rep 2013;2013:bcr2013009878.
19. Jarrar E, Naija S, Grissa O, Amor SB. Eagle Syndrome: a Rare Etiology of Ischemic Stroke. Clin Neuroradiol 2021. doi: 10.1007/s00062-021-01096-0
20. Leong SC, Karkos PD, Papouliakos SM, Apostolidou MT. Unusual complications of tonsillectomy: a systematic review. Am J Otolaryngol 2007;28:419-22.
21. Fusco DJ, Asteraki S, Spetzler RF. Eagle's syndrome: embryology, anatomy, and clinical management. Acta Neurochir (wien) 2012;154:1119-26.
22. Fritz M. Elongated styloid process: a cause of obscure throat symptoms. Arch Otolaryngol 1940;31:911-8.
23. Bahgat M, Bahgat Y, Bahgat A. Eagle's syndrome, a rare cause of neck pain. BMJ Case Rep 2012;2012:bcr2012006278.
24. Mortellaro C, Biancucci P, Picciolo G, Vercellino V. Eagle's syndrome: importance of a corrected diagnosis and adequate surgical treatment. J Craniofac Surg 2002;13:755-8.
25. Hardin FM, Xiao R, Burkey BB. Surgical management of patients with Eagle syndrome. Am J Otolaryngol 2018;39:481-4.
26. Müderris T, Bercin S, Sevil E, Beton S, Kırıs M. Surgical management of elongated styloid process: intraoral or transcervical? Eur Arch Otorhinolaryngol 2014;271:1709-13.
27. Kim DH, Lee YH, Cha D, Kim SH. Transoral robotic surgery in Eagle's syndrome: our experience on four patients. Acta Otorhinolaryngol Ital 2017;37:454-7.
28. Rizzo-Riera E, Rubi-Oña C, García-Wagner M, et al. Advanced Robotic Surgery of the Parapharyngeal Space: Transoral Robotic Styloidectomy in Eagle Syndrome. J Craniofac Surg 2020;31:2339-41.
29. Fitzpatrick TH 4th, Lovin BD, Magister MJ, Waltonen JD, Browne JD, Sullivan CA. Surgical management of Eagle syndrome: A 17-year experience with open and transoral robotic styloidectomy. Am J Otolaryngol 2020;41:102324.
30. Chen R, Liang F, Han P, Cai Q, Yu S, Huang X. Endoscope-assisted resection of elongated styloid process through a retroauricular incision: a novel surgical approach to eagle syndrome. J Oral Maxillofac Surg 2017;75:1442-8.
31. Mevio N, Achena A, Pilolli F, et al. Eagle Syndrome: 3D endoscope-assisted anterior tonsillar fossa approach to styloid process. Am J Otolaryngol 2021;42:102979.
32. Montevecchi F, Caranti A, Cammaroto G, Meccariello G, Vicini C. Transoral robotic surgery (TORS) for bilateral Eagle syndrome. ORL J Otorhinolaryngol Relat Spec 2019;81:36-40.
33. Wong ML, Rossi MD, Groff W, Castro S, Powell J. Physical therapy management of a patient with Eagle syndrome. Physiother Theory Pract 2011;27:319-27.
34. Cernea CR, Hojaij FC, De Carlucci D Jr, et al. First-bite syndrome after resection of the styloid process. Laryngoscope 2007;117:181-2.

Case Report

DOI: 10.4274/haseki.galenos.2021.7730
Med Bull Haseki 2022;60:84-88

A Turkish Family with Loeys-dietz Syndrome and a Report of a Homozygous Patient with SMAD3 Pathogenic Variation

Betul Okur Altindas*, Ayse Gul Zamani**, Mehmet Burhan Oflaz**, Muhammed Gunes**, Mahmut Selman Yildirim*

*Necmettin Erbakan University, Department of Medical Genetics, Konya, Turkey

**Necmettin Erbakan University, Department of Pediatrics, Division of Pediatric Cardiology, Konya, Turkey

Abstract

Loeys-Dietz syndrome (LDS) is a rare autosomal dominant connective tissue disorder with multisystemic involvement caused by pathogenic genetic variations in the transforming growth factor- β pathway. Here, we report a homozygous case with LDS. A newborn male patient who had congenital diaphragmatic hernia, aortic dilatation and talipes equinovarus was referred to our medical genetics polyclinic. After clinical evaluation, next generation sequencing analysis showed a homozygous c.859C>T pathogenic missense variation [R287W (p.Arg287Trp)] in the *SMAD3* gene. It was confirmed that the parents harbor the variant heterozygously. Due to the autosomal dominant inheritance pattern, rarely seen biallelic individuals are expected to have severe clinical conditions. Since there was only one previous report of an individual harboring a homozygous *SMAD3* variant in the literature; this case was presented to further enhance our understanding of LDS.

Keywords: Loeys-Dietz syndrome, LDS, SMAD3, TGF-beta

***Content of this report has been presented before in "14. Ulusal Tıbbi Genetik Kongresi Uluslararası Katılımlı" in November 20-22, 2020, online.**

Introduction

Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disorder that is characterized by cardiovascular, skeletal, and craniofacial features as well as cutaneous findings. Significant clinical variability exists among the patients, even within the family members. *TGFBR1, TGFBR2, TGFB2, TGFB3, SMAD2, SMAD3* genes have been identified as the LDS-causing genes (1,2). Since there is no specific clinical diagnostic criteria, the diagnosis is confirmed by molecular testing. While type 1 and 2 LDS are the most common and aggressive types, *SMAD3* pathogenic variations are seen in 5 to 10% of patients, resulting in LDS type 3 (3). As an autosomal dominant disease, biallelic patients are uncommon and expected to have a severe phenotype. In this case, the goal was to improve our understanding of LDS by reporting a homozygous case and addressing potential differences in severity.

Case Report

A two-day-old male patient was referred to the Medical Genetics Department with club foot deformity, floppiness and congenital diaphragmatic hernia (October, 2019). He was born prematurely at 35 weeks of gestation. Physical examination showed; he had microretrognathia, low-set ears, medial deviation of the wrists, bilateral inguinal hernia, genu varum deformity and bilateral talipes equinovarus (Figure 1). In the echocardiography of the patient, a 3.2 mm atrial septal defect with left-to-right shunt, a 3 mm patent ductus arteriosus, dilatation of the ascending aorta (Z score: +4.7), tortuosity and marked elongation of the descending aorta after the isthmus were

Address for Correspondence: Betul Okur Altindas
Necmettin Erbakan University, Department of Medical Genetics, Konya, Turkey
Phone: +90 332 223 40 23 E-mail: betul.okurr@gmail.com ORCID: orcid.org/0000-0002-1754-4827
Received: 31.08.2021 **Accepted:** 01.12.2021

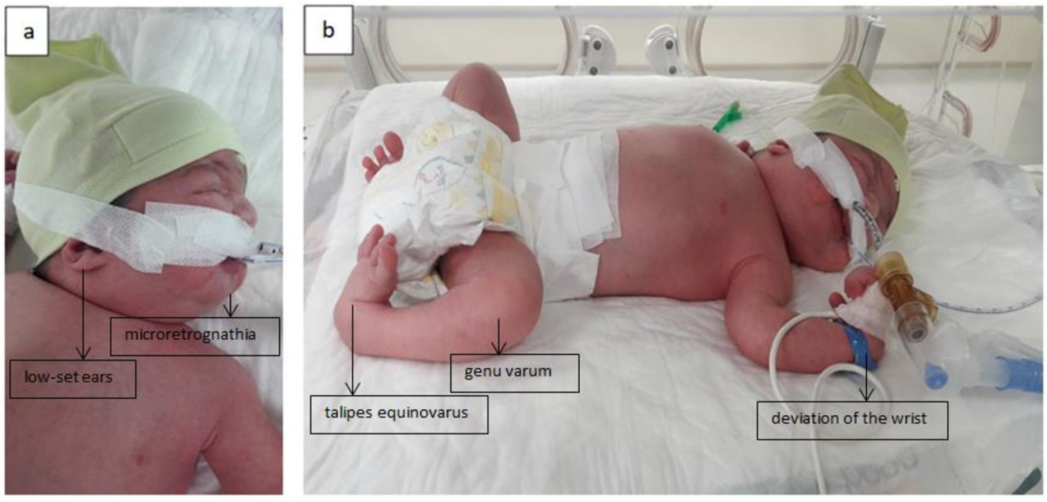


Figure 1. The proband's photographs show: a) microretrognathia, low-set ears; and b) skeletal findings, including a medial deviation of the left wrist, severe genu varum deformity, and bilateral talipes equinovarus.

observed. The interatrial septum was also aneurysmatic (Figure 2). The parents, who were 24 and 28 years old, had no complaints about their health and were consanguineous, being first-degree cousins. The first pregnancy in the family resulted in a missed abortus within the first trimester. The second child was born with severe anomalies, including club foot, complete atrioventricular canal defect and an absent pulmonary valve with pulmonary stenosis. She died on the fifth day of her life, without any genetic testing or sample collection. The third child only had mild joint laxity and intermittent eczema and the fourth one was our proband. The patient had undergone an operation for his diaphragmatic hernia, but he died due to cardiac complications on the eleventh day. A peripheral blood sample was taken and his karyotype analysis resulted (as) normal. Targeted next-generation sequence analysis using the NEXTflex Aortopathy panel kit (PerkinElmer Inc.) for *ACTA2, COL3A1, FBN1, SMAD3, TGFBR2, SLC2A10, TGFB2, MYH11, CBS, SMAD2, FBN2, TGFBR1* genes was performed on the Illumina MiniSeq platform. The analysis showed a homozygous c.859C>T missense variation (R287W [p.Arg287Trp]) in the *SMAD3* gene (RefSeq: NM_005902.4; Transcript ID: ENST00000327367.4). This variant was confirmed by Sanger sequencing analysis (Figure 3). The parents' molecular testing revealed that both of them harbor the same variation heterozygously. The father had typical manifestations of LDS; including turricephaly, hypertelorism, low-set ears, prognathism, bifid uvula, arachnodactyly, joint laxity, pectus carinatum, tall stature (198 cm of measured height) and dilatation

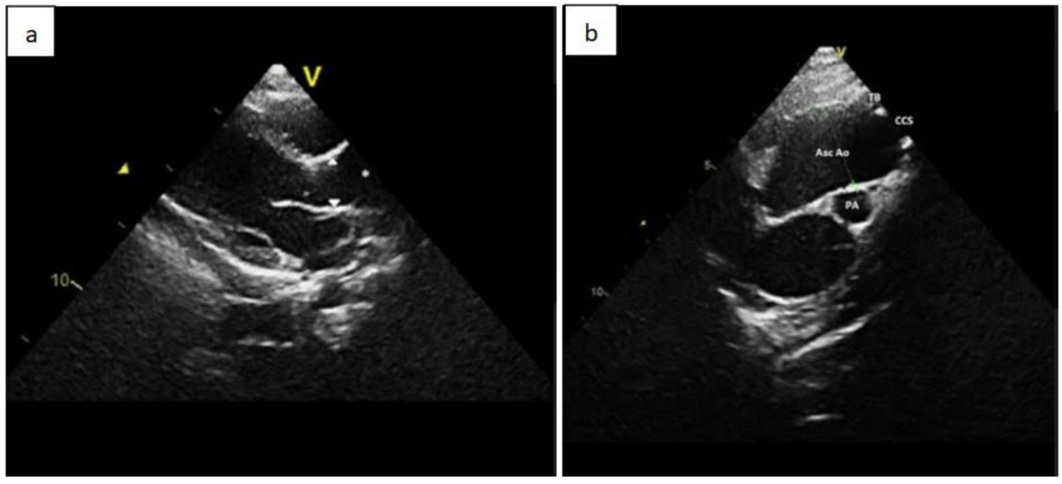


Figure 2. a) The proband's echocardiographic image of the parasternal long section shows the ascending aorta (*) is significantly wider than the aortic root (arrowheads). **b)** An echocardiographic image of the suprasternal section shows that the pulmonary artery is normal in width, but the ascending aorta (Asc Ao) is significantly dilated and wide.
TB: Truncus brachiocephalicus, CCS: Carotis communis sinistra

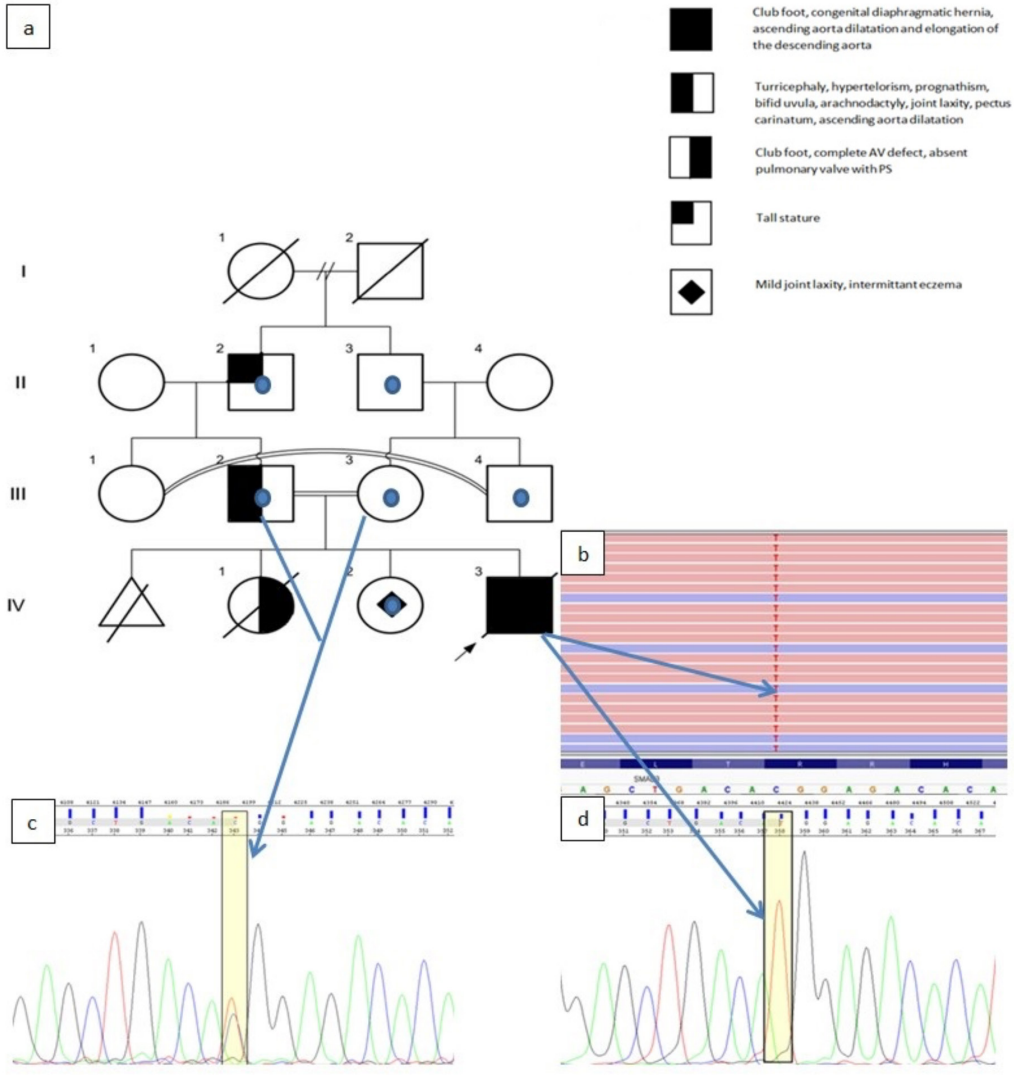


Figure 3. The pedigree of the family (individuals with a blue dot were shown to harbor the *SMAD3* variation.) and their DNA sequencing results.

a) The individual properties of the family members are as follows:

II-2: A 47-year-old male with a tall stature (measured height is 198 cm), who was found to have a heterozygous *SMAD3* R287W variation.

II-3, III-3, III-4: Individuals who were found to be heterozygous for the *SMAD3* R287W variant had no LDS-related symptoms or findings so far. Their echocardiography was normal.

III-2: A 31-year-old patient who had craniofacial and skeletal findings of Loeys-Dietz syndrome, including tall stature (measured height was 198 cm), turricephaly, hypertelorism, low-set ears, prognathism, bifid uvula, arachnodactyly, joint laxity, pectus carinatum, and ascending aorta dilatation.

IV-1: Newborn with club foot, complete atrioventricular defect, absent pulmonary valve with pulmonary stenosis; died in the first week of life without having a genetic test.

IV-2: A 5-year-old female with normal echocardiography, who had mild joint laxity and eczematoid dermatitis. A heterozygous *SMAD3* R287W variation was detected.

IV-3 (proband): newborn with club foot, congenital diaphragmatic hernia, ascending aorta dilatation (Z score: +4,7), and elongation of the descending aorta. A homozygous *SMAD3* R287W variation was observed.

b) The proband's raw IGV analysis data. All reads show a homozygous change from the reference allel (C) to the variant allel (T), which is visible in all reads (reads are depicted as lines, with red indicating the forward strand and blue indicating the reverse strand).

c) The father's Sanger sequencing plot for the chr15:67473779 region, with several base pairs surrounding it. Each peak represents a nucleotide read (red peak: T, blue peak: C, black peak: G, green peak: A). A highlighted region depicting the heterozygous change was observed.

d) Proband's Sanger sequencing plot for the same region In the highlighted region, a homozygous change was observed.

AV: atrioventricular, LDS: Loeys-Dietz syndrome, PS: Pulmonary stenosis, IGV: Integrative genomics viewer

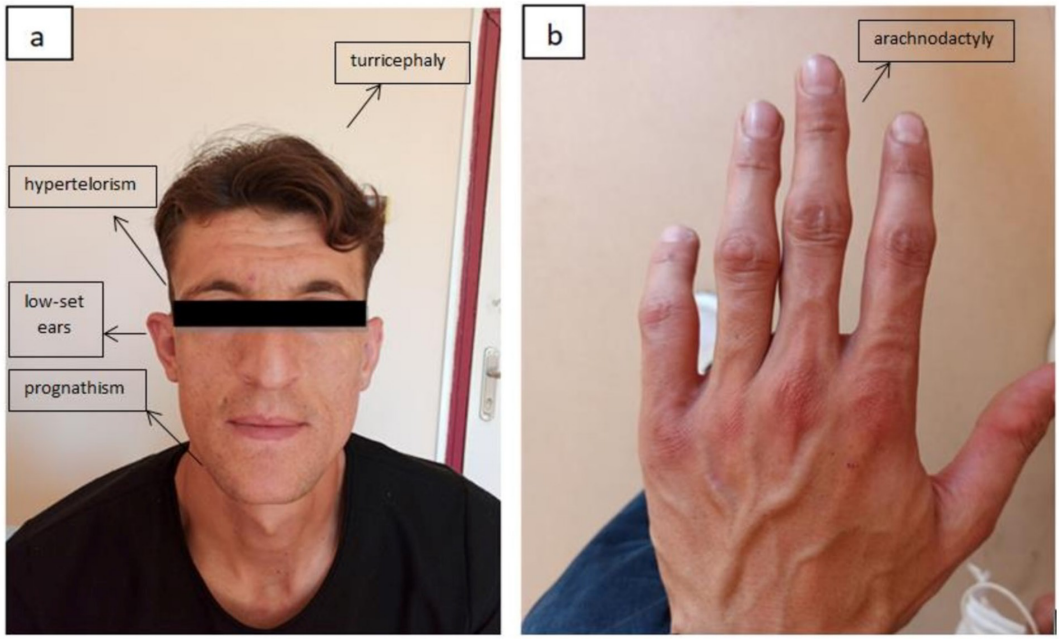


Figure 4. Photographs of the proband's father, **a)** showing turricephaly, hypertelorism, low-set ears, and a prominant chin; **b)** arachnodactyly of his left hand. (Informed consent regarding publication of the photos was taken from the patient)

of the ascending aorta up to 4.5 cm (Figure 4). Unlike the father, the mother, who had no symptoms or findings, was considered non-penetrant. The five-year-old sister of the proband who also had the heterozygous disease-causing variant had no known medical history. She had mild joint laxity and intermittent eczema on the anterior surface of her arms; her echocardiography was normal. Pedigree analysis demonstrated that the grandfathers of both sides of the patient were brothers. The brother of the proband's mother and the sister of the proband's father were also married. Since they were candidates for having this variant, Sanger sequencing analysis was performed on them all. It was confirmed that the grandfathers on both sides and the maternal uncle of the patient had the same variation. Clinical examination showed only the paternal grandfather, whose echocardiography was normal, had a tall stature (198 cm of measured height), but other family members had no complaints or findings. Further vascular testing and close cardiologic monitoring were advised. Appropriate informed consent for the publication of the patient's and their data was taken from the parents.

Discussion

LDS is a rare connective tissue disorder characterized by vascular tortuosity and multisystemic involvement. All previously reported variants were found to be essential for the TGF-β signalling pathway. Our patient had a pathogenic variant in the *SMAD3* gene encoding a protein named exactly after its gene, *SMAD3*. It functions as an effector protein, transmitting chemical signals from the cell surface to the nucleus and acting as a direct mediator of TGF-β receptor mediated transcriptional activation (4). The variation in our patient resulted in a shift from arginine to triptophan in the primary structure of the relevant protein. Because the arginine residue is well-conserved across species and there is a moderate physicochemical difference between these two amino acids, *in silico* analysis predicted this variation would be damaging to the protein structure and/or function. This variant was not found in the population databases and was previously reported as "pathogenic" in the ClinVar database (5). As a consequence, it was interpreted as pathogenic.

Approximately 25% of the probands were shown to have an affected parent. Therefore, a clinical examination and molecular testing of the parents are needed. Our homozygous patient had both parents as carriers. By definition, an allele determining the phenotype of a heterozygote individual is dominant. Homozygotes for dominant phenotypes are not often seen in medical practice because matings that could produce homozygous offspring are very rare (6). In this family, both our patient and his sister, who had severe skeletal and cardiac conditions, could not survive the newborn period. They seem to represent a very severe form of the syndrome, indicating they probably had the same genotype. To our knowledge, there has only been one previous report of a proband with a biallelic *SMAD3* variant (7). That case reported by Baskin et al. (7) had notable musculoskeletal complications, including repetitive bone fractures, kyphoscoliosis, severe pectus excavatum,

and dysmorphic features concordant with the syndrome. The variant detected was intronic and predicted to affect splicing, while our case had a missense variant. In a study, Chesneau et al. (8) compared truncating and missense variations of the *SMAD3* gene and found they both cause aortic disease with no statistically significant difference. However, considering that the homozygote patient was in his teenage years and our case died in the second week of his life, homozygous cases could also have highly variable clinical courses, in terms of expression of the SMAD3 variants. In the literature, Camerota et al. (9) characterized LDS genotypic variants and showed more than half of the patients harboring *SMAD3* variations had hernia, pectus deformity, malar hypoplasia, mitral valve defects, and aortic root aneurysms, while none of them had strabismus or cervical malformation. Only the father, who had facial dysmorphism, skeletal findings, and aortic dilatation, and the grandfather, who was tall, had LDS-associated clinical presentation among our heterozygote cases. None of our patients, regardless of age, had osteoarthritis, indicating that the *SMAD3* gene has incomplete penetrance and variable expression (10).

LDS is a rare cause of aortic aneurysm; however, genetic testing is needed if the patient has accompanying skeletal and/or skin findings. Phenotypic variability in this disease has emerged as a fact, as more patients are identified. Because *SMAD3* gene mutations are rare causes of LDS and the majority of patients are heterozygous, reports of rare biallelic individuals are considered significant. It is clearly beneficial to keep homozygosity in mind, to facilitate early and accurate diagnosis of a newborn with a severe condition, especially in the case of consanguinity.

Ethics

Informed Consent: Informed consent regarding publication of the photos was taken from the family.

Authorship Contributions

Concept: B.O.A., A.G.Z., Design: M.B.O., B.O.A., Data Collection or Processing: M.G., B.O.A., Analysis or Interpretation: B.O.A., A.G.Z., Literature Research: M.S.Y., B.O.A., Writing: B.O.A.

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

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

References

1. Loeys BL, Chen J, Neptune ER, et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet 2005;37:275-81.
2. https://www.omim.org/phenotypicSeries/?phenotypicSeriesNumber=PS607086,PS609192.(accessed at 01.12.2021)
3. Loeys BL, Dietz HC. Loeys-Dietz Syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al. editors. GeneReviews®. Seattle (WA): University of Washington, Seattle; 2008.
4. Massagué J. TGFβ signalling in context. Nat Rev Mol Cell Biol 2012;13:616-30.
5. https://www.ncbi.nlm.nih.gov/clinvar/variation/30306/ (accessed at 01.12.2021)
6. Nussbaum RL, McInnes RR, Willard HF. Thompson & Thompson Genetics in Medicine. 8th ed. Philadelphia: Elsevier; 2016. p. 114.
7. Baskin SM, Morris SA, Vara A, Hecht JT, Farach LS. The first reported case of Loeys-Dietz syndrome in a patient with biallelic SMAD3 variants. Am J Med Genet A 2020;182:2755-60.
8. Chesneau B, Edouard T, Dulac Y, et al. Clinical and genetic data of 22 new patients with SMAD3 pathogenic variants and review of the literature. Mol Genet Genomic Med 2020;8:e1132.
9. Camerota L, Ritelli M, Wischmeijer A, et al. Genotypic Categorization of Loeys-Dietz Syndrome Based on 24 Novel Families and Literature Data. Genes (Basel) 2019;10:764.
10. van de Laar IM, Oldenburg RA, Pals G, et al. Mutations in SMAD3 cause a syndromic form of aortic aneurysms and dissections with early-onset osteoarthritis. Nat Genet 2011;43:121-6.

Case Report

DOI: 10.4274/haseki.galenos.2021.7985
Med Bull Haseki 2022;60:89-91

Acute Segmental Testicular Infarction caused by COVID-19 Disease: A Case Report and Current Literature Review

Murat Demir*, Ilyas Dundar**

*Van Yuzuncu Yil University Faculty of Medicine, Department of Urology, Van, Turkey

**Van Yuzuncu Yil University Faculty of Medicine, Department of Radiology, Van, Turkey

Abstract

Coronavirus disease-2019 (COVID-19) is known to cause sepsis-associated hypercoagulopathy. Thromboembolic complications affecting many systems associated with COVID-19 disease have been described in the literature. The direct effect of this virus on male urogenital organs and possible testicular damage is still being evaluated. Follow-up studies in recovering male patients are necessary to investigate the possibility of testicular damage. In this article, we aimed to present a 30-year-old patient who presented with acute testicular pain and was diagnosed with testicular infarction due to COVID-19 with ultrasonography and contrast-enhanced magnetic resonance imaging findings.

Keywords: COVID-19, coronavirus disease, testicolar infarction, ultrasonography, magnetic resonance inaging

Introduction

Although the most frequently affected system is the respiratory system in Coronavirus disease-2019 (COVID-19), this infection leads to symptoms in other systems as well. Moreover, it affects other systems mostly due to hypercoagulation, and although most thrombotic events related to COVID-19 are associated with deep vein thrombosis, complications related to arterial structures have also been reported (1). On the other hand, although COVID-19 has been shown to act through angiotensin converting enzyme (ACE) receptors and disrupt spermatogenesis in the testicles, to our knowledge, there has been no report of testicular infarction associated with COVID-19 in the literature (2). In this report, we present a case of segmental testicular infarction caused by COVID-19.

Case Report

A consent form was obtained from the patient for this case report. The 30-year-old male patient presented to our urology clinic with a two-week history of pain in the left testicle. The patient had no history of orchitis, vasculitis, polycythemia, or other comorbidities, and no history of trauma. The patient's complaint started as an acute, severe pain on the 4th day of COVID-19 treatment, and he recovered from COVID-19 two weeks earlier, which had been confirmed by polymerase chain reaction. It was also revealed that the patient discontinued his favipiravir therapy that was initiated for COVID-19 treatment and used no anticoagulant drug throughout the infection. Physical examination was unremarkable except for left testicular tenderness. Complete blood and biochemistry tests were normal, and complete urinalysis, brucella, acid-resistant bacilli in urine, tuberculosis, and culture tests were negative. Scrotal doppler ultrasonography (US) that was performed due to the presence of varicocele four weeks earlier was also unremarkable, whereas it showed a hypoechoic area with geographic borders without vascular flow in the subcapsular region at the inferior pole of the left testicle, which was approximately 7x6 mm in size and was suggestive of an infarction (Figure 1). Contrast-enhanced magnetic resonance imaging (MRI) showed increased signal intensity on T2-weighted images (T2-WI) and showed no contrast enhancement

Address for Correspondence: Murat Demir
Van Yuzuncu Yil University Faculty of Medicine, Department of Urology, Van, Turkey
Phone: +90 432 215 04 70 E-mail: urologmurat72@gmail.com ORCID: orcid.org/0000-0001-5029-8800
Received: 26.11.2021 **Accepted:** 25.12.2021

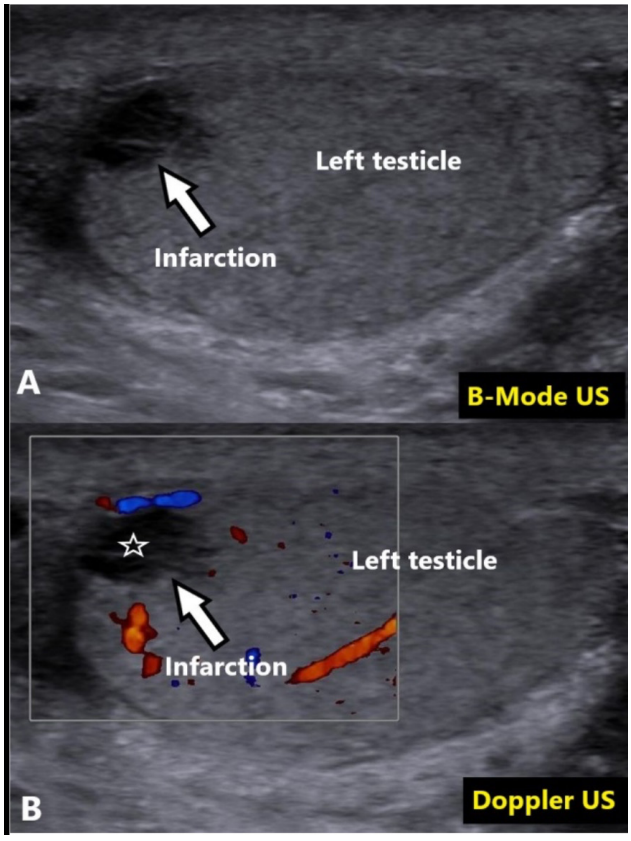


Figure 1. Scrotal US showing a wedge-shaped hypoechoic area with geographic borders, approximately 7x6 mm in size, in the subcapsular region at the inferior pole of the left testicle in B-mode images. (A, arrow). There was no vascularity (star) in this area on doppler US (B, arrow)
US: Ultrasonography

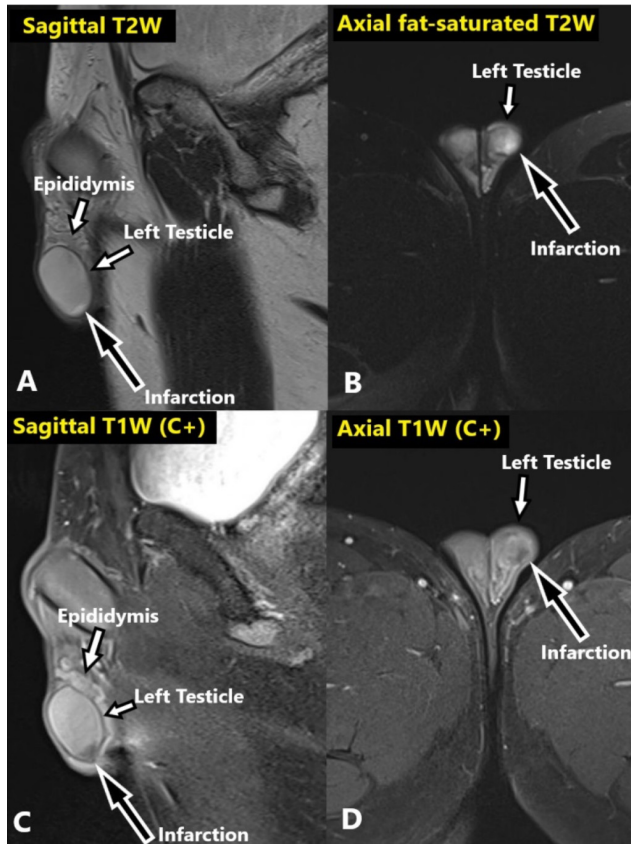


Figure 2. Non-fat-saturated sagittal (A) and fat-saturated axial (B) T2-weighted MRI showing an increased wedge-shaped signal intensity in the subcapsular region at the inferior pole of the left testicle (arrows). Contrast-enhanced sagittal (C) and axial (D) T1-weighted MRI showing no contrast enhancement in that area
MRI: Magnetic resonance imaging

on T1-weighted images (T1-WI) in the region detected by the US (Figure 2). These radiological findings were consistent with a segmental testicular infarction. An anticoagulant was given to the patient as treatment. The patient did not continue to follow-up.

Discussion

Segmental testicular infarction is a type of ischemia caused by arterial occlusion of a focal area in the testicle, mostly presenting with acute pain (3). It is highly difficult to distinguish this entity from other acute testicular pathologies. Common etiologies include trauma, orchitis, polycythemia, vasculitis, and diseases that cause hypercoagulation. In most cases, the underlying cause cannot be determined, while infectious events are the most commonly blamed. Color doppler US is the primary imaging method, with the most common findings including rounded or wedge-shaped intra-testicular hypoechoic lesions with decreased or completely disappearing vascularity (4).

In patients that cannot be diagnosed definitively on doppler US, the diagnosis can be supported by MRI since it can easily visualize the borders of segmental testicular infarction not only on T2-WI but also on contrast-enhanced images. In segmental testicular infarction, the signal intensity of T1-T2-WI varies depending on the age of the infarction (5). Although T2-WI shows well-defined borders and mostly shows lower signal intensity (66%), they may also show a high (17%) or intermediate signal (17%) intensity (3). In our case, T2-WI showed high signal intensity in the infarction area. In our case, we think that this high signal intensity is related to the infarction age in the chronic period. The infarction area shows no contrast enhancement on contrast-enhanced T1-WI (3,6). In our case, there was no contrast enhancement consistent with the literature.

COVID-19 has been shown to have several effects on testicles, such as necrosis and apoptosis in spermatogenic cells via inflammatory infiltration. Autopsies performed after COVID-19 showed that ACE receptor expression and spermatogenesis were

impaired in the testis (7). In addition to these effects, the present study detected another effect of COVID-19 on testicles, i.e. infarction associated with testicular arterial embolism, which, to our knowledge, has never been reported in the literature.

Infections in the body trigger inflammation, thereby leading to an increase in inflammatory elements, ultimately activating the coagulation system. This cascade system is known as thromboinflammation, which is a complement system involving microorganism-derived products, polyphosphate, free DNA fragments, and mast cells. In turn, these triggering events cause increased D-dimer and interleukin-6 levels, thereby leading to an increased risk of hypercoagulative complications (8,9). Although hypercoagulative complications associated with COVID-19 mostly occur in deep veins, complications associated with arterial structures have also been reported in the literature, some of which include cardiac embolism and retinal artery occlusion due to COVID-19 (10).

In conclusion, utmost care should be taken for the development of testicular arterial embolism in COVID-19 patients presenting with testicular pain.

Ethics

Informed Consent: A consent form was obtained from the patient for this case report.

Authorship Contributions

Concept: M.D., I.D., Design: M.D., Data Collection or Processing: M.D., I.D., Analysis or Interpretation: M.D., I.D., Literature Research: M.D., I.D., Writing: M.D., I.D.

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

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

References

1- Yilmaz A, Zerde HC, Alay B, Ergul Z. Effect of COVID-19 Pandemic on the Working of Blood Transfusion Center: A Cross-Sectional Study. Med Bull Haseki 2021;59(Suppl 1):15-20.

2- Younis JS, Abassi Z, Skorecki K. Is there an impact of the COVID-19 pandemic on male fertility? The ACE2 connection. Am J Physiol Endocrinol Metab 2020;318:878-80.

3- Fernández-Pérez GC, Tardáguila FM, Velasco M, et al. Radiologic findings of segmental testicular infarction. Am J Roentgenol 2005;184:1587-93.

4- Madaan S, Joniau S, Klockaerts K, et al. Segmental testicular infarction: conservative management is feasible and safe. Eur Urol 2008;53:441-5.

5- Sweet DE, Feldman MK, Remer EM. Imaging of the acute scrotum: keys to a rapid diagnosis of acute scrotal disorders. Abdom Radiol (NY) 2020;45:2063-81.

6- Smets T, Reichman G, Michielsen DPJ. Segmental testicular infarction: a case report. J Med Case Rep 2017;11:140.

7- Achua JK, Chu KY, Ibrahim E, et al. Histopathology and ultrastructural findings of fatal COVID-19 infections on testis. World J Mens Health 2021;39:65-78.

8- Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020;135:2033-40.

9- Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J Thromb Haemost 2020;18:1747-51.

10- Shantha JG, Auld SC, Anthony C, et al. Retinopathy and Systemic Disease Morbidity in Severe COVID-19. Ocul Immunol Inflamm 2021;29:743-50.