ISSN: 2619-9793 • E-ISSN: 2148-094X

istanbul MEDICAL JOURNAL

İSTANBUL TIP DERGİSİ

VOLUME 24 • ISSUE 1 • February 2023

Original Articles

istanbulmedicaljournal.org

galenos yayınevi

İstanbul MEDICAL JOURNAL

İSTANBUL TIP DERGİSİ

Owned by on behalf of the University of Health Sciences Turkey, İstanbul Training and Research Hospital
Mehmet TOPTAŞ

Executive Editor

Feray AKBAŞ

Editor in Chief

Feray AKBAŞ
Department of Internal Medicine, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Associate Editors

Turgut KARABAĞ
Department of Cardiology, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Serkan SARI
Department of General Surgery, University of Health Sciences Turkey, Başakşehir Çam and Sakura Training and Research Hospital, İstanbul, Turkey

Özgür DİKME
Department of Emergency Medicine, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Ali ÇETİN
Department of Obstetrics and Gynecology, Division of Perinatology, University of Health Sciences Turkey, Haseki Training and Research Hospital, İstanbul, Turkey

Seda TURAL ÖNÜR
Department of Chest Diseases, University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey

Owner

Mehmet TOPTAŞ
Department of Anesthesiology and Reanimation, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Publishing Manager

Esra KARABAL ARDA
Specialist of Traditional and Complementary, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

galenos yayınevi

Galenos Publishing House
Owner and Publisher
Derya Mor
Erkan Mor
Publication Coordinator
Burak Sever
Web Coordinators
Turgay Akpınar
Ethem Candan
Fuat Hocalar
Graphics Department
Ayda Alaca
Ceyda Beyazlar
Çiğdem Birinci
Gülşah Özgül
Finance Coordinator
Sevinç Çakmak
Emre Kurtulmuş
Project Coordinators
Aybüke Ayvaz
Aysel Balta
Çilem Çağrı Çınar
Gamze Aksoy
Gülay Akın
Hatice Sever
Melike Eren
Özlem Çelik
Pınar Akpınar
Rabia Palazoğlu
Sümeyye Karadağ
Research&Development
Fırat Kahraman Aykara
Gözde Nur Beyaz
Digital Marketing Specialist
Ümit Topluoğlu

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, 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

Publication Date: February 2022
ISSN: 2619-9793 **E-ISSN:** 2148-094X
International periodical journal published three times in a year.

İSTANBUL MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

Emergency Medicine

Özgür DİKME

Department of Emergency Medicine, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Özlem DİKME

Department of Emergency Medicine, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Family Medicine

Zuhal AYDAN SAĞLAM

Department of Family Medicine, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Yalçın HACIOĞLU

Department of Family Medicine, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Anesthesiology and Reanimation

Mehmet TOPTAŞ

Department of Anesthesiology and Reanimation, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Kazım KARAASLAN

Department of Anesthesiology and Reanimation, Bezmialem Vakif University Faculty of Medicine, İstanbul, Turkey

Murat HALİLOĞLU

Department of Anesthesiology and Reanimation, Marmara University of Faculty of Medicine, İstanbul, Turkey

Ali Fuat ERDEM

Department of Anesthesiology and Reanimation, Sakarya University Faculty of Medicine, Sakarya, Turkey

Oktay DEMİRKIRAN

Department of Anesthesiology and Reanimation, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

Veysel ERDEN

Department of Anesthesiology and Reanimation, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Antonio M. ESQUİNAS

Intensive Care Unit and Non Invasive Ventilatory Unit, Hospital Morales Meseguer, Murcia, Spain

Fatma Yeşim Abut

Department of Anesthesiology and Reanimation, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Neurosurgery

Nuriye Güzin ÖZDEMİR

Department of Neurosurgery, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Okan TÜRK

Department of Neurosurgery, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Pediatrics

Özben CEYLAN

Department of Pediatrics, Pediatric Cardiology, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Murat ELEVLİ

Department of Pediatrics, University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital, İstanbul, Turkey

Öner ÖZDEMİR

Department of Pediatrics, Division of Pediatric Allergy and Immunology, Sakarya University Faculty of Medicine, Sakarya, Turkey

Kenan BARUT

Department of Pediatrics, Division of Pediatric Rheumatology, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

Hande KIZILOCAK

Department of Pediatrics, Children's Hospital Los Angeles Research Scientist, Los Angeles, United States of America

Pediatric Surgery

Ali İhsan DOKUCU

Department of Pediatric Surgery, Prof. Dr. Cemil Taşçıoğlu City Hospital, İstanbul, Turkey

istanbul
MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

Yunus SÖYLET

Department of Pediatric Surgery, Division of Urology, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

Pediatric Cardiovascular Surgery

Ali Can HATEMİ

Department of Pediatric Cardiovascular Surgery, University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, İstanbul, Turkey

Dermatology

Ayşe Esra KOKU AKSU

Department of Dermatology, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Mehmet Salih GÜREL

Department of Dermatology, İstanbul Medeniyet University Faculty of Medicine, İstanbul, Turkey

Infectious Diseases and Clinical Microbiology

Nagehan Didem SARI

Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Mustafa YILDIRIM

Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Naim MAHROUM

Department of Infectious Diseases and Clinical Microbiology, Tel Aviv University Faculty of Medicine, Tel Aviv, İsrail

Physical Medicine and Rehabilitation

Ebru AYTEKİN

Department of Physical Medicine and Rehabilitation, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Nalan ÇAPAN

Department of Physical Therapy and Rehabilitation, İstanbul University, İstanbul Faculty of Medicine, İstanbul, Turkey

General Surgery

Serkan SARI

Department of General Surgery, University of Health Sciences Turkey, Başakşehir Çam and Sakura Training and Research Hospital, İstanbul, Turkey

Mert Mahzuni SEVİNÇ

Department of General Medicine, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Ufuk Oğuz İDİZ

Department of General Medicine, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Hasan ÖKMEN

Department of General Medicine, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Gürhan ÇELİK

Department of General Medicine, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Chest Diseases

Erdoğan ÇETİNKAYA

Department of Chest Diseases, University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey

Seda TURAL ÖNÜR

Department of Chest Diseases, University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey

Sedat ALTIN

Department of Chest Diseases, University of Health Sciences Turkey, Yedikule Chest Diseases and Chest Surgery Training and Research Hospital, İstanbul, Turkey

Alexandru CORLATEANU

Department of Chest Diseases, State University of Medicine and Pharmacy, Moldova

İSTANBUL MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

Chest Surgery

Kemal KARAPINAR

Department of Chest Surgery, University of Health Sciences Turkey, İstanbul Yedikule Pulmonary Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey

Levent CANSEVER

Department of Chest Surgery, University of Health Sciences Turkey, Yedikule Chest Diseases and Chest Surgery Training and Research Hospital, İstanbul, Turkey

Eye Diseases

Özen AYRANCI

Department of Eye Diseases, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Yusuf YILDIRIM

Department of Ophthalmology, University of Health Sciences Turkey, İstanbul Beyoğlu Eye Training and Research Hospital, İstanbul, Turkey

Public Health

Elif ALTUNDAŞ HATMAN

Department of Public Health, University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey

Sibel SAKARYA

Department of Public Health, Koç University Faculty of Medicine, İstanbul, Turkey

Aleksandar VISNJIC

Department of Public Health, Division of Health Management, University of Nis Faculty of Medicine, Nis, Serbia

Internal Medicine

Feray AKBAŞ

Department of Internal Medicine, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Hanife USTA ATMACA

Department of Internal Medicine, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Mehmet Emin PİŞKİNPAŞA

Department of Internal Medicine, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Füsun ERDENEN

Department of Internal Medicine, Division of Immunology, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Savaş ÖZTÜRK

Department of Internal Medicine, Division of Nephrology, İstanbul University, İstanbul Faculty of Medicine, İstanbul, Turkey

Dragan MİCİC

Department of Internal Medicine, Division of Endocrinology, University of Belgrade, Belgrade, Serbia

Obstetrics and Gynaecology

Ali ÇETİN

Department of Obstetrics and Gynaecology, Division of Perinatology, University of Health Sciences Turkey, Haseki Training and Research Hospital, İstanbul, Turkey

Aşkın DOĞAN

Department of Gynecology, Gynecologic Oncology, Perinatal Medicine, Agaplesion Allgemeines Krankenhaus Hagen, Training and Research Hospital from Ruhr University Bochum, Germany

Emre Sinan GÜNGÖR

Department of Obstetrics and Gynaecology, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Gülşah İLHAN

Department of Obstetrics and Gynaecology, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Işık KABAN

Department of Obstetrics and Gynaecology, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Cardiovascular Surgery

Oruç Alper ONK

Department of Cardiovascular Surgery, Erzincan Binali Yildirim University Faculty of Medicine, Erzincan, Turkey

Cardiology

Turgut KARABAĞ

Department of Cardiology, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Mehmet Mustafa CAN

Department of Cardiology, University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital, İstanbul, Turkey

İSTANBUL MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

Matteo CAMELİ
Department of Medical Biotechnologies, Division of Cardiology, University of Siena, Siena, Italy

Otorhinolaryngology

Özgür YİĞİT
Department of Otorhinolaryngology, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Reşit Murat AÇIKALIN
Department of Otorhinolaryngology, University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital, İstanbul, Turkey

Neurology

Ufuk Emre TOPRAK
Department of Neurology, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Şenay AYDIN
Department of Neurology, University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey

Nuclear Medicine

Tevfik Fikret ÇERMİK
Department of Nuclear Medicine, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Orthopedics and Traumatology

Yusuf ÖZTÜRKMEN
Department of Orthopedics and Traumatology, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Yunus ATICI
Department of Orthopedics and Traumatology, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Mehmet Fatih KORKMAZ
Department of Orthopedics and Traumatology, Medeniyet University Faculty of Medicine, İstanbul, Turkey

Esra ÇİRCI ÖZYÜREK
Department of Orthopedics and Traumatology, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Plastic, Reconstructive and Aesthetic Surgery

Oğuz ÇETİNKALE
Department of Plastic, Reconstructive and Aesthetic Surgery, İstanbul University-Cerrahpaşa Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

Psychiatry

Mihriban DALKIRAN
Department of Psychiatry, Haydarpaşa Numune Training and Research Hospital, İstanbul, Turkey

Radiation Oncology

Özlem MERMUT
Department of Radiation Oncology, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Radiology

Abdullah Soydan MAHMUTOĞLU
Department of Radiology, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Özgür KILIÇKESMEZ
Department of Radiology, University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, İstanbul, Turkey

Medical Biochemistry

Berrin BELÇİK İNAL
Department of Medical Biochemistry, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Medical Pathology

Halide Nur ÜRER
Department of Medical Pathology, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey

Urology

Ali İhsan TAŞÇI
Department of Urology, Bakırköy Dr. Sadi Konuk Training and Research Hospital, İstanbul, Turkey

Mahmut Gökhan TOKTAŞ
Department of Urology, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

Hikmet KÖSEOĞLU
Department of Urology, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

istanbul
MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

AIMS AND SCOPE

İstanbul Medical Journal is the scientific, peer reviewed, open access publication of İstanbul Training and Research Hospital. The journal is published four times in a year; on February, May, August and November. The publication language of the journal is English.

The İstanbul Medical Journal is indexed in **Web of Science-Emerging Sources Citation Index, EBSCO, Gale, Index Copernicus, TUBITAK ULAKBIM TR Index, ProQuest, Türk Atif Dizini, Türk Medline, DOAJ, Ardi, Hinari, Goali, Oare, CAB International** (**CABI**) and **J-GATE.**

Processing and publication are free of charge with the journal. No fees are requested from the authors at any point throughout the evaluation and publication process.

All manuscripts must be submitted via the online submission system, which is available at www.istanbulmedicaljournal.org.

The journal guidelines, technical information, and the required forms are available on the journal's web page.

All expenses of the journal are covered by the İstanbul Training and Research Hospital. Potential advertisers should contact the Editorial Office.

The journal does not publish advertisement.

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

All published content is available online, free of charge at www.istanbulmedicaljournal.org.

İstanbul Training and Research Hospital holds the international copyright of all the content published in the journal.

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 the rules of the 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.

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND) International License.

CC BY-NC-ND: This license allows reusers to copy and distribute the material in any medium or format in unadapted form only, for noncommercial purposes only, and only so long as attribution is given to the creator.

CC BY-NC-ND includes the following elements:

BY – Credit must be given to the creator

NC – Only noncommercial uses of the work are permitted

ND – No derivatives or adaptations of the work are permitted

Editor in Chief: Feray Akbaş

Address: Clinic of Internal Diseases, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Türkiye

E-mail: atlibatur@yahoo.com

Publisher: Galenos Publishing House

Address: Molla Gürani Mahallesi Kaçamak Sokak No: 21/A 34093 Fındıkzade - İstanbul

Phone: +90 (212) 621 99 25

Fax: +90 (212) 621 99 27

E-mail: info@galenos.com.tr

OPEN ACCESS

İSTANBUL MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

INSTRUCTIONS TO AUTHORS

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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

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

An approval of research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 20, www.wma.net) is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement should be included that shows that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. In experimental animal studies, the authors should indicate that the procedures followed were in accordance with animal rights as per the Guide for the Care and Use of Laboratory Animals http://oacu.od.nih.gov/regs/guide/guide.pdf and they should obtain animal ethics committee approval. Information on patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Materials and Methods section of the manuscript. It is the authors' responsibility to carefully protect the patients' anonymity. For photographs that may reveal the identity of the patients, signed releases of the patient or of their legal representative should be enclosed.

All submissions are screened by a similarity detection software (iThenticate by CrossCheck).

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

Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE - www.icmje.org). The ICMJE recommends that authorship be based on the following 4 criteria:

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

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

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

İstanbul Medical Journal requires corresponding authors to submit a signed and scanned version of the authorship contribution form (available for download through www.istanbulmedicaljournal.org) during the initial submission process in order to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without further review. As part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all the responsibility for authorship during the submission and review stages of the manuscript.

İstanbul Medical Journal requires and encourages the authors and the individuals involved in the evaluation process of submitted manuscripts to disclose any existing or potential conflicts of interests, including financial, consultant, and institutional, that might lead to potential bias or a conflict of interest. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors. Cases of a potential conflict of interest of the editors, authors, or reviewers are resolved by the journal's Editorial Board within the scope of COPE and ICMJE guidelines.

The Editorial Board of the journal handles all appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in

İSTANBUL MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

INSTRUCTIONS TO AUTHORS

direct contact with the editorial office regarding their appeals and complaints. When needed, an ombudsperson may be assigned to resolve cases that cannot be resolved internally. The Editor in Chief is the final authority in the decision-making process for all appeals and complaints.

When submitting a manuscript to İstanbul Medical Journal, authors accept to assign the copyright of their manuscript to İstanbul Training and Research Hospital. If rejected for publication, the copyright of the manuscript will be assigned back to the authors. İstanbul Medical Journal requires each submission to be accompanied by a Copyright Transfer Form (available for download at www.istanbulmedicaljournal.org). When using previously published content, including figures, tables, or any other material in both print and electronic formats, authors must obtain permission from the copyright holder. Legal, financial and criminal liabilities in this regard belong to the author(s).

Statements or opinions expressed in the manuscripts published in İstanbul Medical Journal reflect the views of the author(s) and not the opinions of the editors, the editorial board, or the publisher; the editors, the editorial board, and the publisher disclaim any responsibility or liability for such materials. The final responsibility in regard to the published content rests with the authors.

MANUSCRIPT PREPARATION

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2016 - http://www.icmje.org/icmje-recommendations.pdf). Authors are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.istanbulmedicaljournal.org. Manuscripts submitted via any other medium will not be evaluated.

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

Authors are required to submit the following:

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

Preparation of the Manuscript

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

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

Abstract: An abstract should be submitted with all submissions except for Letters to the Editor in English.

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

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Methods, Results, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

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

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

Editorial Comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

Invited Review Articles: Reviews prepared by the invited authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on

istanbul MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

INSTRUCTIONS TO AUTHORS

the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	30	6	7 or tatal of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

Tables

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

Figures and Figure Legends

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

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

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

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

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

References

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

Journal Article: Rankovic A, Rancic N, Jovanovic M, Ivanović M, Gajović O, Lazić Z, et al. Impact of imaging diagnostics on the budget – Are we spending too much? Vojnosanit Pregl 2013; 70: 709-11.

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

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

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

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

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

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

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

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

istanbul
MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

INSTRUCTIONS TO AUTHORS

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

REVISIONS

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

Accepted manuscripts are copy-edited for grammar, punctuation, and format.

Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

Editor in Chief: Feray AKBAŞ
Address: Clinic of Internal Diseases, Health Science University, İstanbul Training and Research Hospital, İstanbul, Türkiye
E-mail: atlibatur@yahoo.com
Publisher: Galenos Publishing House
Address: Molla Gürani Mahallesi Kaçamak Sokak No: 21/A 34093 Fındıkzade - İstanbul
Phone: +90 (212) 621 99 25
Fax: +90 (212) 621 99 27
E-mail: info@galenos.com.tr

İSTANBUL MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

CONTENTS

Original Articles

istanbul
MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

CONTENTS

İstanbul Med J 2023; 24(1): 1-5
DOI: 10.4274/imj.galenos.2022.39018

Short-term Postoperative Outcomes of Platelet-rich Plasma after Inferior Turbinate Radiofrequency

Ozan Özdemir, Nihal Seden, Abdurrahman Çağlıyan, Özgür Yiğit

University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Otorhinolaryngology, Division of Head and Neck Surgery, İstanbul, Turkey

ABSTRACT

Introduction: To evaluate the effect of submucosal platelet-rich plasma (PRP) therapy on intraoperative bleeding and early postoperative pain and crusting in patients undergoing inferior turbinate radiofrequency.

Methods: A total of 70 adult patients with isolated inferior turbinate hypertrophy were included in this prospective study and randomized to the PRP or control groups. PRP was prepared for all patients. After applying submucosal radiofrequency to the inferior turbinates under local anesthesia, submucosal PRP was injected into the study group, and submucosal saline was injected into the control group. Patient controls were performed by another specialist. The patients and the specialist who performed the controls were blinded to which group they were in. All patients were evaluated endoscopically 1, 7, and 21 days after the operation.

Results: The mean age of the patients was 33.37±11.92 years (range: 18 to 54). The two groups had no significant differences in intraoperative bleeding and mucociliary clearance values ($p>0.05$). The amount of crusting and the visual analog scale pain values were significantly lower in the submucosal PRP -injected group ($p<0.05$).

Conclusion: Submucosal injection of PRP after radiofrequency of the inferior turbinate reduces nasal obstruction and pain due to crusting. With these features, it can be concluded that this procedure accelerates recovery and increases patient comfort in the early postoperative period.

Keywords: Platelet-rich plasma, turbinates, radiofrequency ablation, wound healing

Introduction

Wound healing begins with the activation and aggregation of circulating platelets after the endothelial wall is damaged. This process provides the formation of thrombin, a proteolytic enzyme and a potent platelet activator that catalyzes the conversion of fibrinogen to fibrin (1). Many mediators, including growth factors, cytokines, and extracellular matrix modulators, are released from the alpha granules of activated platelets (2-4).

Platelet-derived products have become increasingly popular since the 1990s. Different ways to prepare platelet-rich plasma (PRP) have emerged, and the methodology continues to evolve from a traditional blood centrifuge to commercial systems (5). Nowadays, PRP is being used for surgical operations, chronic wound recovery, ulcers, and burned care.

The inferior turbinates, whose submucosal layer consists of venous sinusoids, have essential functions such as heating, humidifying, filtering the inhaled air, directing the airflow to the olfactory zone, and secreting mucosal immunoglobulin A (IgA) (6). There are many techniques available to reduce the size of enlarged inferior turbinates. Recently, procedures have preserved nasal function by reducing turbinate volume rather than concha resection (7).

Inferior turbinate radiofrequency has recently become popular as it protects the nasal mucosa and improves nasal function with a low postoperative complication rate. This technique provides a sufficient reduction in turbinate volume, and submucosal tissues are replaced by sclerotic ligament-like tissue, while the nasal mucociliary function is apparently preserved (8).

Problems such as pain, crusting, bleeding, and synechia can be seen in the healing of wounds after ITR. To prevent these problems, we investigated the short-term effects of intraoperative submucosal PRP injection in patients undergoing ITR.

Methods

Ethical Approval

The study was reviewed and approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics

Address for Correspondence: Ozan Özdemir MD, University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Otorhinolaryngology, Division of Head and Neck Surgery, İstanbul, Turkey
Phone: +90 530 569 43 97 **E-mail:** opdrozanozdemir@gmail.com **ORCID ID:** orcid.org/0000-0001-6534-1672

Cite this article as: Özdemir O, Seden N, Çağlıyan A, Yiğit Ö. Short-term Postoperative Outcomes of Platelet-rich Plasma after Inferior Turbinate Radiofrequency. İstanbul Med J 2023; 24(1): 1-5.

Received: 26.09.2022
Accepted: 11.12.2022

©Copyright 2023 by the University of Health Sciences Turkey, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.

Committee (approval number: 2803, date: 16.04.2021). All procedures were performed in accordance with the ethical standards set forth by the World Medical Association Declaration of Helsinki (Scotland 2000). Informed consent forms were obtained from all the patients.

Patients and Study Design

Seventy patients with isolated inferior turbinate hypertrophy that did not respond to intranasal corticosteroids for 3 months were included in this prospective study and randomized to the PRP or control groups. All the patients were evaluated by endoscopic examination. Those with other causes of nasal obstruction such as septum deviation, nasal polyposis, allergic rhinitis, or comorbidities such as diabetes, hypertension, and coagulation disorder were excluded from the study. The PRP was prepared from all patients, and the procedures were performed by the same specialist. The patients were operated under local anesthesia with the same radiofrequency device. After providing local anesthesia with topical lidocaine spray, all patients received 15 watts and 300 joules of energy for 7-8 seconds from 3 different points on each inferior turbinate. After applying submucosal radiofrequency to the inferior turbinates under local anesthesia, submucosal PRP was injected into 35 patients in the study group, and submucosal saline was injected into 35 patients in the control group. The patients were discharged without prescribing medication.

All controls were performed by another specialist who was unaware of the group in which the patients were in. Pain, bleeding, crusting, and mucociliary clearance were compared between the two groups. Saccharin transit time (STT) was used for mucociliary clearance in the first week and stand-alone visual analog scale (VAS) was used for pain. The patients were evaluated for crusting on the first, 7th, and 21 days after surgery. All evaluations were performed under a 4 mm diameter 0-degree endoscope (Karl Storz, Germany).

Platelet-rich Plasma Preparation

PRP was prepared from patients' autologous blood samples and collected in anticoagulant-coated sterile vacuum tubes. An automated centrifugation machine (Centrifuge, CompactStar CS4, VWR International, England) was used for obtaining PRP with a speed of 1300 rpm for 10 min. After centrifugation, the platelet-poor upper layer and the lower layer consisting of erythrocytes were disposed of. Then "buffy coat" layer rich in platelets and growth factors was applied to the surgical site (9).

Inferior Turbinate Radiofrequency

All surgical procedures were performed by the same senior surgeon after local anesthesia was provided with topical lidocaine spray. By using a radiofrequency generator (CelonLabENT; Celon AG, Teltow, Germany), 15 watts and 300 joules of energy per shot were delivered submucosal to the anterior, middle, and posterior thirds of each inferior turbinate with the conchal probe.

Patient Evaluation

The intraoperative bleeding was calculated by the number of pads contaminated during the inferior turbinate radiofrequency. All patients were evaluated endoscopically 1, 7, and 21 days after the operation. A score between 1 and 4 was given according to the amount of crusting. 0-25% crusting was scored as 1, 25-50% crusting 2, 50-75% crusting 3, and above 75% crusting as 4. Patients were asked to complete a VAS questionnaire regarding pain during the first 7 days. Additionally, nasal mucociliary transport was evaluated with STT postoperatively in the first week.

Statistical Analysis

In the data obtained from the study of Sinem Gökçe Kutuk and Talih Özdaş using the G*Power 3.1.9.7 (Franz Faul, Germany) program, it was determined that there should be a total of at least 70 samples.

Statistical analysis was performed using the IBM SPSS Statistics 25.0 package program (SPSS Inc.; Chicago, IL, USA). The Kolmogorov-Smirnov test was used to determine whether the variables were normally distributed. While presenting descriptive analyses, mean ± standard deviation and median (minimum-maximum) values were used. The Mann-Whitney U test was used for unpaired group comparisons. Changes in measured values were examined by the Wilcoxon test within the group and with Repeated Measurements Analysis between the groups. A p-value less than 0.05 was considered statistically significant.

Results

The mean age of 48 male and 22 female patients was 33.37±11.92 years (range: 18 to 54). There was no significant difference between the two groups in the amount of bleeding according to the number of contaminated pads during the operation (p=0.056). Similarly, no significant difference was observed between the groups in the mucociliary transport times evaluated by a STT in the postoperative 1st week (p=0.077) (Table 1).

The amount of crusting on the 1st, 7th, and 21st days evaluated by endoscopic examination was significantly higher in the submucosal saline-injection group for all 3 days (p<0.05) (Table 2). Additionally, when both groups were evaluated separately, no significant difference was observed in the change in the amount of crusting (Figure 1). As a result, the amount of crusting on the PRP -injected group was lower from the first day.

Table 1. Changes in the amount of bleeding and mucociliary clearance between the two groups

	Saline-injected group		PRP-injected group		p
	Mean ± SD	Median	Mean ± SD	Median	
Amount of bleeding	1.66±0.73	2.00	1.29±0.75	1.00	0.056
Mucociliary clearance	1.31±0.93	1.00	0.91±0.82	1.00	0.077

Mann-Whitney U test (SD: Standard deviation). A value of p<0.05 was considered statistically significant

The daily scored facial pain scale values during the first week were compared between the groups and the values were found to be lower on the 3rd, 4th, 5th and 6th days in the PRP-injected group ($p<0.05$) (Table 3). When the changes in the facial pain scale were evaluated separately between the two groups, the pain decreased more rapidly in the PRP -injected group. (Figure 2). According to this result, we found that healing was faster in the PRP-injected group ($p<0.05$).

Discussion

For treating inferior turbinate hypertrophy, which causes nasal obstruction, radiofrequency has come to the fore with its local application, function preservation, and low complication rate (10). Karakurt et al. (11) demonstrated the effectiveness of this method objectively by providing a significant decrease in nasal resistance and a significant increase in nasal volume at the postoperative 6th month. Additionally, it has been observed in the literature that the mucociliary transport time is shorter in the early postoperative period in patients who underwent radiofrequency (12). In our clinic, we prefer this method because it can be applied locally, has a short duration, has low morbidity, long-term effectiveness, and is a mucosal preservation surgery.

In the study of Gunhan et al. (13), it was found that intranasal steroid therapy and radiofrequency ablation were similarly effective in improving the quality of life in patients with allergic rhinitis. We excluded patients with a diagnosis of allergic rhinitis in our study and selected our patients from patients who had symptoms of nasal obstruction due to isolated inferior turbinate hypertrophy and did not respond to 3-month intranasal corticosteroid therapy. All of these patients benefited significantly from the procedure according to the NOSE score at day 21.

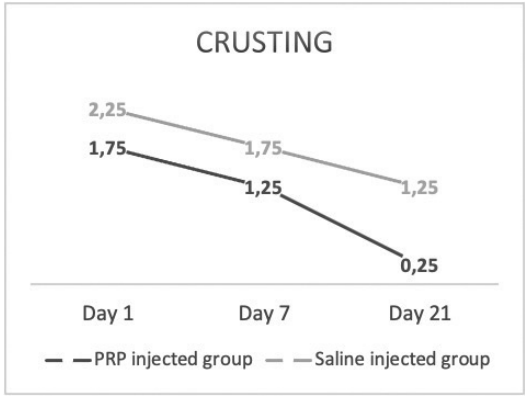


Figure 1. Changes in the amount of crusting between the two groups by day

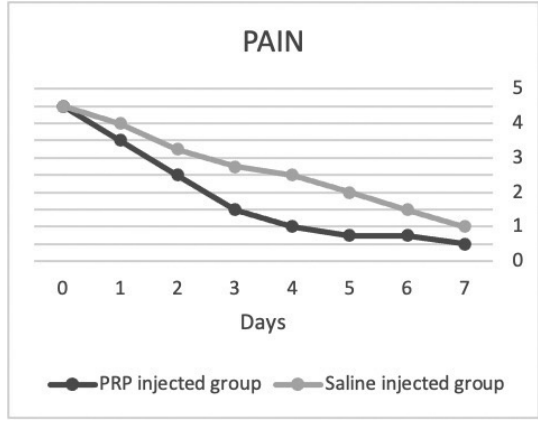


Figure 2. Changes in the amount of pain between the two groups by day

Table 2. The amount of crusting between the two groups by day

	Saline-injected group		PRP-injected group		p[1]	p[2]
	Mean ± SD	Median	Mean ± SD	Median		
Crusting, day 1	2.23±0.88	2.00	1.71±0.67	2.00	**0.011**	0.109
Crusting, day 7	1.69±0.63	2.00	1.26±0.66	1.00	**0.009**	
Crusting, day 21	1.09±0.56	1.00	0.34±0.48	0.00	**<0.001**	

[1]Mann-Whitney U test, [2]Repetitive measurements analysis (SD: Standard deviation). Bold values indicate significance ($p<0.05$)

Table 3. The amount of pain between the two groups by day

	Saline-injected group		PRP-injected group		p[1]	p[2]
	Mean ± SD	Median	Mean ± SD	Median		
Pain, day 0	4.60±2.43	5.00	4.49±2.52	4.00	0.789	0.030
Pain, day 1	3.94±2.42	4.00	3.57±2.37	4.00	0.469	
Pain, day 2	3.23±2.40	4.00	2.43±1.79	3.00	0.079	
Pain, day 3	2.71±2.08	3.00	1.63±1.44	2.00	**0.021**	
Pain, day 4	2.51±2.13	2.00	0.91±1.44	0.00	**0.001**	
Pain, day 5	2.03±2.12	2.00	0.66±1.53	0.00	**0.001**	
Pain, day 6	1.57±1.85	2.00	0.66±1.39	0.00	**0.007**	
Pain, day 7	0.94±1.64	0.00	0.43±1.14	0.00	0.067	

[1]Mann-Whitney U test, [2]Repetitive measurements analysis (SD: Standard deviation). Bold values indicate significance ($p<0.05$)

In the literature, there were only minimal adverse reactions reported, such as pain, crusting, adhesion, dryness, or nasal bleeding (14). We did not detect any dryness, adhesions, or postoperative bleeding in our patients. Bleeding was seen only during surgery, and there was no significant difference between the amount of bleeding in both groups during the procedure. Various amounts of crusting were detected in all our patients until the 21st day and the pain until the 8th day. To avoid these problems, PRP, known to accelerate wound healing, was injected submucosal following ITP. Crusting and pain were significantly less in the PRP-injected group.

There are only limited studies on postoperative wound healing of the nasal mucosa. Khalmuratova et al. (15) guided further studies on the healing stages. The positive effects of PRP on wound healing by secreting various growth factors and cytokines have been shown in various studies (16-18). Therefore, the hypothesis of this study was that PRP would reduce crusting in the nasal mucosa and have a positive effect on postoperative pain.

Pomerantz and Dutton (19) investigated the curative properties of PRP after endoscopic sinus surgery. The results revealed that PRP is beneficial in wound healing in nasal surgery; however, the patient population in the studies was severely limited (19). As in these studies, we found PRP to be effective in crusting and pain.

As an unexpected and unexplained result in the histopathological nasal mucosa study of Yildirim et al. (20), the number of ciliary cells in the PRP-injected group was found to be significantly lower than that in the saline-injected group. In our study, we found no difference between these two groups in terms of mucociliary transport time.

Study Limitations

The main limitation of this study is the need for further studies with larger case numbers. Additionally, adding patients diagnosed with allergic rhinitis to a group and performing long-term postoperative evaluations with rhinomanometric measurements may increase the value of the study.

Conclusion

This study is important because it is the first study on PRP injection into the inferior turbinates after inferior turbinate radiofrequency. Submucosal injection of PRP after inferior turbinate radiofrequency significantly reduced postoperative pain and crusting in the early postoperative period, but had no effect on intraoperative bleeding. With these features, it can be concluded that this procedure reduces nasal congestion and pain due to crusting, accelerates recovery, and increases patients' comfort in the early postoperative period.

Ethics Committee Approval: The study was reviewed and approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee (approval number: 2803, date: 16.04.2021).

Informed Consent: Informed consent forms were obtained from all the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - O.Ö., N.S., Ö.Y.; Concept - O.Ö., N.S., A.Ç.; Design - O.Ö., N.S., Ö.Y.; Data Collection or Processing - O.Ö., N.S., A.Ç.; Analysis or Interpretation - O.Ö., N.S., A.Ç.; Literature Search - O.Ö., N.S., Ö.Y.; Writing - O.Ö., N.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. Swieringa F, Spronk HMH, Heemskerk JWM, Heemskerk JWM, van der Meijden PEJ. Integrating platelet and coagulation activation in fibrin clot formation. Res Pract Thromb Haemost 2018; 2: 450-60.
2. Nurden AT. The biology of the platelet with special reference to inflammation, wound healing and immunity. Front Biosci (Landmark Ed) 2018; 23: 726-51.
3. Etulain J. Platelets in wound healing and regenerative medicine. Platelets 2018; 29: 556-68.
4. Alsousou J, Ali A, Willett K, Harrison P. The role of platelet-rich plasma in tissue regeneration. Platelets 2013; 24: 173-82.
5. Castillo TN, Pouliot MA, Kim HJ, Dragoo JL. Comparison of growth factor and platelet concentration from commercial platelet-rich plasma separation systems. Am J Sports Med 2011; 39: 266-71.
6. Li C, Farag AA, Leach J, Deshpande B, Jacobowitz A, Kim K, et al. Computational fluid dynamics and trigeminal sensory examinations of empty nose syndrome patients. Laryngoscope 2017; 127: E176-84.
7. Dogan R, Senturk E, Ozturan O, Yildirim YS, Tugrul S, Hafiz AM. Conchal contractility after inferior turbinate hypertrophy treatment:A prospective, randomized clinical trial. Am J Otolaryngol 2017; 38: 678-82.
8. Nease CJ, Krempl GA. Radiofrequency treatment of turbinate hypertrophy: a randomized, blinded, placebo-controlled clinical trial. Otolaryngol Head Neck Surg 2004; 130: 291-9.
9. Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). Trends Biotechnol 2009; 27: 158-67.
10. Garzaro M, Landolfo V, Pezzoli M, Defilippi S, Campisi P, Giordano C, et al. Radiofrequency volume turbinate reduction versus partial turbinectomy: clinical and histological features. Am J Rhinol Allergy 2012; 26: 321-5.
11. Karakurt SE, Çetin MA, Apaydın E, İkincioğulları A, Ensari S, Dere HH. Does inferior turbinate outfracture provide additional benefit when combined with inferior turbinate radiofrequency ablation?. Eur Arch Otorhinolaryngol 2021; 278: 2869-74.
12. Akagün F, İmamoğlu M, Çobanoğlu HB, Ural A. Comparison of radiofrequency thermal ablation and microdebrider-assisted turbinoplasty in ınferior turbinate hypertrophy: a prospective, randomized, and clinical study. Turk Arch Otorhinolaryngol 2016; 54: 118-23.
13. Gunhan K, Unlu H, Yuceturk AV, Songu M. Intranasal steroids or radiofrequency turbinoplasty in persistent allergic rhinitis: effects on quality of life and objective parameters. Eur Arch Otorhinolaryngol 2011; 268: 845-50.
14. Abdullah B, Singh S. Surgical ınterventions for ınferior turbinate hypertrophy: a comprehensive review of current techniques and technologies. Int J Environ Res Public Health 2021; 18: 3441.
15. Khalmuratova R, Kim DW, Jeon SY. Effect of dexamethasone on wound healing of the septal mucosa in the rat. Am J Rhinol Allergy 2011; 25: 112-6.

16. Fréchette JP, Martineau I, Gagnon G. Platelet-rich plasmas: growth factor content and roles in wound healing. J Dent Res 2005; 84: 434-9.

17. Nurden AT, Nurden P, Sanchez M, Andia I, Anitua E. Platelets and wound healing. Front Biosci 2008; 13: 3532-48.

18. Gökçe Kütük S, Özdaş T. The impact of platelet-rich plasma therapy on short-term postoperative outcomes of pediatric tonsillectomy patients. Eur Arch Otorhinolaryngol 2019; 276: 489-95.

19. Pomerantz J, Dutton JM. Platelet gel for endoscopic sinus surgery. Ann Otol Rhinol Laryngol 2005; 114: 699-704.

20. Yildirim U, Kemal O, Aksoy A, Karaca E, Terzi O, Atmaca S. Effects of submucosal PRP injection on wound healing in endonasal surgeries: an experimental study. Eur Arch Otorhinolaryngol. 2020; 277: 1681-9.

İstanbul Med J 2023; 24(1): 6-9
DOI: 10.4274/imj.galenos.2022.22309

Screening of Hyperaldosteronism on the Investigation of Secondary Hypertension: Single-centre Experience

Gülsüm Bingöl[1], Emre Özmen[2], Özge Özden[1], Leyla Bulut Arsoy[3], Yusuf Emre Uzun[1], Muharrem Nasifov[1], Esra Şüheda Hatipoğlu[4]

[1]Memorial Bahçelievler Hospital, Clinic of Cardiology, İstanbul, Turkey
[2]Siirt State Hospital, Clinic of Cardiology, Siirt, Turkey
[3]Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Clinic of Biochemistry, İstanbul, Turkey
[4]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Endocrinology, İstanbul, Turkey

ABSTRACT

Introduction: Primary hyperaldosteronism (PHA), is a clinical syndrome that is defined as inappropriately increased serum aldosterone secretion and low plasma renin levels. PHA has been reported as the most common cause of secondary hypertension. In this retrospective study, we planned to show the significance of screening for this disease in hypertensive patients admitted to our clinic.

Methods: Our study included 64 patients who were admitted to our cardiology outpatient clinic between April 2018 and August 2021 with high blood pressure and were selected to be checked for plasma renin activity (PRA), PAC, and PAC/PRA ratios to exclude secondary hypertension. Medical records, hypertension treatments, and medical histories of the patients were reviewed from our hospital database.

Results: Of the 64 patients, 25 (39.1%) were female and 39 (60.9%) were male. After the first evaluation of the patients, 13 patients were decided to be assessed with the saline infusion test. PHA was diagnosed in 7 of 13 patients evaluated. In the adrenal MRI performed in 3 of 7 patients diagnosed with PHA, one adrenal hyperplasia and one adrenal adenoma were diagnosed in 2 different patients.

Conclusion: Primary hyperaldosteronism is one of the most important causes of secondary hypertension. Although there are various methods such as screening tests, the most commonly used method is the aldosterone/renin ratio and it is very practical to screen. Considering the various cardiovascular diseases that PHA is associated with, and the simplicity of treatment of PHA, we strongly believe that the screening threshold for PHA should be kept as low as possible and should be independent of age.

Keywords: Hyperaldosteronism, secondary hypertension, renin

Introduction

Primary hyperaldosteronism (PHA); is a clinical syndrome that is defined as inappropriately increased serum aldosterone secretion and low plasma renin levels. PHA has been reported as the most common cause of secondary hypertension; its prevalence was reported as 20% in patients with resistant hypertension, 10% in patients with severe hypertension, and around 6% in patients with uncomplicated hypertension (1,2). While plasma aldosterone level (PAC), plasma renin activity (PRA), and PAC/PRA ratio are used as a screening test for PHA; fludrocortisone oral sodium loading test, saline infusion test (SIT), or captopril tests are used to confirm the diagnosis (3). Jerome W. Conn, who was the first to define PHA, stated that the absence or low level of PRA and increased aldosterone secretion may be the first finding for the diagnosis of PHA rather than hypokalemia (4). Considering this information, it must be considered that in the presence of hypokalemia in hypertensive patients, the diagnosis of PHA should be suspected immediately, and it must be kept in mind that PHA can be seen in many patients without hypokalemia. In addition, screening for PHA is not as complex as it seems.

In this retrospective study, we planned to show the significance of screening for this disease in hypertensive patients admitted to our clinic.

Methods

Our study included 64 patients who admitted to the cardiology outpatient clinic between April 2018 and August 2021 with high blood pressure and were selected to be checked for PRA, PAC, and PAC/PRA ratios to exclude secondary hypertension. The patient group with a high probability of secondary hypertension consisted of young individuals with high blood

Address for Correspondence: Gülsüm Bingöl MD, Memorial Bahçelievler Hospital, Clinic of Cardiology, İstanbul, Turkey
Phone: +90 505 803 13 58 **E-mail:** bulut_gulsum@hotmail.com **ORCID ID:** orcid.org/0000-0001-5879-7866

Cite this article as: Bingöl G, Özmen E, Özden Ö, Bulut Arsoy L, Uzun YE, Nasifov M, Hatipoğlu EŞ. Screening of Hyperaldosteronism on the Investigation of Secondary Hypertension: Single-centre Experience. İstanbul Med J 2023; 24(1): 6-9.

Received: 04.08.2022
Accepted: 20.12.2022

©Copyright 2023 by the University of Health Sciences Turkey, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.

pressure and individuals with resistant hypertension. Medical records, hypertension treatments, and medical histories of the patients were reviewed from our hospital database. Ethics committee approval was obtained from Memorial Bahçelievler Hospital Local Ethic Committee (approval number: 20, date: 13.09.2021). Written consent was obtained from all the patients. The blood pressure values and body mass index (BMI) of all patients were taken from the patient records.

The blood samples were taken from the patients for PAC and PRA between 08.00 and 09.00 a.m. in the morning with discontinuation of hypertension medication. The blood sample taken for PRA was taken into chilled tubes containing sodium ethylenediamine tetraacetate and centrifuged within the first 4 h after the sample was taken and stored in the freezer. PAC measurements were made with the aldosterone RIA kit (Beckman Coulter, Brea, CA). PRA measurements were made with an RIA kit (Beckman Coulter, Brea, CA) because of the production of angiotensin 1 *in vitro* in a pH 6.0 environment.

PHA screening test is considered positive in healthy and normotensive subjects; if PAC is over 75th percentile; PAC/PRC ratio is over 95th percentile, PAC >150 ng/dL, PRA <1 ng/mL/h, PAC/PRA ratio >30 (5-7). Patients with positive screening tests were evaluated by an endocrinologist. The SIT was performed to the patients who were considered suitable after the evaluation. After remaining in the supine position for at least 1 h before the start of the infusion, 2 L 0.9% saline was infused over a period of 4 h. Renin, aldosterone, and potassium levels were measured from the patients before and after the infusion. The diagnosis of PHA was confirmed in patients with a PAC value >10 ng/mL in the SIT after saline. Surrenal magnetic resonance imaging (MRI) was performed for the etiologic investigation of the patients whose diagnosis of PAH was confirmed by SIT.

Statistical Analysis

The data obtained because of the study were analyzed using the SPSS 24.0 program. Numerical values (age, systolic BP, diastolic BP, BMI, GFR, Na, K, Hb, and HbA1c, etc.) were given as minimum, maximum, mean, and standard deviation. Ordinal variables such as blood pressure, hospitalization complaint, smoking, and presence of hypertension were shown as percentages.

Results

Of the 64 patients included in the study, 25 (39.1%) were female and 39 (60.9%) were male. Demographic, clinical, and laboratory characteristics of the patients included in the study are shown in Table 1. The mean age of the patients was 40.9±13.8. Most of the patients (n=48, 75%) were admitted to the clinic with a complaint of high blood pressure. 8 (12.5%) patients were admitted to our clinic with complaints of headache, 3 (4.7%) patients with chest pain, and 5 (7.8%) patients with fatigue, dyspnea, facial flushing, drowsiness, and palpitations. There was no smoking history in 70.3% (n=45) of the patients. 37 patients (57.8%) had no history of additional disease, and 40 patients (62.5%) had no family history of hypertension.

Most patients participating in the study were not receiving any antihypertensive treatment. A small group of patients were multi-drug users and the drugs that may effect the result of the PAC, PRA, and PAC/PRA ratios were changed to those ones that had no effect on the abovementioned tests. Anti-hypertensive treatments used by the patients are given in Table 2.

Table 1. Clinical and labaratory features of patients

	n	Minimum	Maximum	Mean	SD
Age (y)	64	17.0	78.0	40.8	13.81
Systolic BP (mmHg)	64	110.0	220.0	147.5	18.01
Diastolic BP (mmHg)	64	60.0	120.0	91.8	9.86
BMI (kg/m^2)	64	20.2	38.1	27.5	3.90
GFR (mL/sec/1.7)	64	32.0	163.0	98.5	22.39
Na (mmol/L)	64	135.0	145.0	139.7	1.94
K (mmol/L)	64	3.4	5.2	4.3	0.35
Hb (g/dL)	57	9.4	18.6	14.2	1.77
HbA1c (%)	41	4.7	6.4	5.3	0.39

SD: Standard deviation, BP: Blood pressure, BMI: Body mass index, GFR: Glomerular filtration rate, Hb: Hemoglobin, HbA1c: Hemoglobin A1c

Table 2. Distribution of hypertensive drugs used by patients

Drug	n	%
ACEi	4	6.3
ARB	13	20.3
Beta blocker	13	20.3
Non-DHP CCB	2	3.1
DHP CCB	13	20.3
Diuretics	7	10.9

ACEi: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin 2 receptor blocker, non-DHP CCB: Non-dihydropyridine calcium channel blocker, DHP CCB: Dihydropyridine calcium channel blocker

Patients' PAC, PRA, and PAC/PRA ratios were evaluated by an endocrinologist. Because of this evaluation, it was decided to assess 13 patients with the SIT. PHA was diagnosed in 7 of 13 patients evaluated.

In the adrenal MRI performed in 3 of 7 patients diagnosed with PHA, one adrenal hyperplasia and one adrenal adenoma were diagnosed in 2 different patients, whereas no pathology was observed in the other patient.

Discussion

This study aimed to investigate the prevalence of PHA in outpatients with hypertension at our own institution and to determine the frequency of PHA diagnosis in patients without a classical PHA clinic.

PHA is a more common disease than previously thought, thanks to developing technology and research methods, although it was previously thought to be a rare cause of secondary hypertension. It has been shown that there is increased aldosterone secretion from one or both adrenal glands in the pathophysiology of PHA and that this release is independent of the primary regulators affecting aldosterone release. As a result, increased aldosterone binds to the epithelial sodium channel (ENaC) in the distal nephron, causing sodium retention and potassium excretion. Due to the sodium retained in the distal nephron, water retention increases and the classical findings in patients, such as hypertension, hypokalemia, and metabolic alkalosis, develop (8).

Different studies showed that PHA is closely associated with various cardiovascular diseases. Diseases such as coronary artery disease, atrial fibrillation, heart failure, and stroke are seen more frequently in patients with PHA patients (9-11). Therefore, it is critical to diagnose and treat PHA in terms of cardiovascular health.

Various studies have been conducted on the frequency of PHA in the community or among patients with hypertension and the prevalence varies according to the method used as a screening test. In a study by Monticone et al. (9), it has been demonstrated that because of a screening performed in 1700 hypertension patients, the screening test was positive in 14% of the patients. In addition, 6% of the patients were diagnosed with PHA when the confirmatory test was performed on these patients. In this study, serum aldosterone level >10 ng/dL and ARR >30 were determined as a screening test positivity criterion (9). In a study by Mosso et al. (12) in Chile, the prevalence of PHA was 6% in 609 hypertensive patients. In this study, ARR was accepted as >25 for screening test positivity.

Baudrand et al. (13), in a study of 241 mild-moderate hypertension patients, PRA <1 ng/mL/h; the prevalence of PHA was observed as 19% in patients with ARR >20 and aldosterone level >6 ng/mL. In our study, three different criteria positivity as PAC, PRA, and PAC/PRA (ARR) was accepted as "positive" as a screening test. and patients with ARR >30, PAC >150 ng/mL and PRA <1 ng/mL/h were evaluated further. Because of our study, the prevalence of PHA was observed to be 10.9%. The reason why our results differ from these studies; may be that our study did not adhere to a single criterion and the study population was small.

The most commonly known clinical features of PHA are hypertension, hypokalemia, and metabolic alkalosis, defined as the Conn triad. However, these three findings may not always be observed together in patients with PHA patients. In a multicenter study by Mulatero et al. (14), it was reported that hypokalemia was observed in 9-37% of patients diagnosed with PHA in the screening test for PHA in hypertensive patients. In another study by Käyser et al. (15), it was reported that all 343 hypertensive patients diagnosed with PHA in the screening were normokalemic.

In our study, all the patients diagnosed with PHA were normokalemic as well. PHA can also be observed in normotensive patients. In a study by Markou et al. (16), fludrocortisone-dexamethasone suppression test was performed in 100 normotensive patients independent of the baseline ARR rate, and the diagnosis of PHA was reached in 13% of these patients. In another study, Baudrand et al. (13) performed an oral sodium suppression test on 210 patients with normotensive but low renin activity (<1 ng/mL/h) and found the prevalence of PHA to be 14% (17). As shown in our study and other studies, the presence of classical clinical findings in patients should not be expected for PHA screening, and a screening test for PHA should be performed even in the absence of hypokalemia, particularly in patients with resistant hypertension. Although there is no specific age range for PHA screening in secondary hypertension in the established guideline, it is observed that clinicians mostly screen for PHA in young patients. Looking at the literature, there is no study investigating the presence of PHA in elderly (>65 y) hypertensive patients. However, considering that a patient diagnosed with PHA in our study was older than 75 years and two of them were older than 60 years; especially in patients with resistant hypertension, PHA screening regardless of age will be very meaningful in terms of regulating the treatment of patients and reducing the complications that may develop due to high blood pressure.

Study Limitations

The limitation of our study is the small number of study population because it is a single-center study.

Conclusion

In summary; primary hyperaldosteronism is one of the important causes of secondary hypertension and has a certain prevalence in hypertensive patients. Although there are various methods as screening tests, the most commonly used method is the aldosterone/renin ratio and it is a disease that is practical to screen. Considering the various cardiovascular diseases that PHA is associated with, and the simplicity of treatment of PHA, we strongly believe that the screening threshold for PHA should be kept as low as possible and should be independent of age.

Ethics Committee Approval: Ethics committee approval was obtained from Memorial Bahçelievler Hospital Local Ethic Committee (approval number: 20, date: 13.09.2021).

Informed Consent: Written consent was obtained from all the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - G.B., E.Ş.H., Y.E.U.; Concept - G.B., Y.E.U., E.Ş.H., L.B.A.; Design - G.B., L.B.A., E.Ş.H.; Data Collection or Processing - G.B., Ö.Ö.,; Analysis or Interpretation - L.B.A., Y.E.U., E.Ş.H., M.N.; Literature Search - G.B., Ö.Ö., E.Ö., L.B.A., M.N.; Writing - G.B., E.Ö., E.Ş.H.

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. Calhoun DA, Nishizaka MK, Zaman MA, Thakkar RB, Weissmann P. Hyperaldosteronism among black and white subjects with resistant hypertension. Hypertension 2002; 40: 892-6.
2. Strauch B, Zelinka T, Hampf M, Bernhardt R, Widimsky J Jr. Prevalence of primary hyperaldosteronism in moderate to severe hypertension in the Central Europe region. J Hum Hypertens 2003; 17: 349-52.
3. Li YM, Ren Y, Chen T, Tian HM. Update and Research Progress in the Diagnosis of Primary Aldosteronism. Sichuan Da Xue Xue Bao Yi Xue Ban 2020; 51: 267-77.
4. Loh KC, Koay ES, Khaw MC, Emmanuel SC, Young WF Jr. Prevalence of primary aldosteronism among Asian hypertensive patients in Singapore. J Clin Endocrinol Metab 2000; 85: 2854-9.
5. Concistrè A, Petramala L, Bisogni V, Mezzadri M, Olmati F, Saracino V, et al. Subclinical atherosclerosis due to increase of plasma aldosterone concentrations in essential hypertensive individuals. J Hypertens 2019; 37: 2232-9.
6. Montori VM, Young WF Jr. Use of plasma aldosterone concentration-to-plasma renin activity ratio as a screening test for primary aldosteronism. A systematic review of the literature. Endocrinol Metab Clin North Am 2002; 31: 619-32.
7. Pratt RE, Flynns JA, Hobartn PM, Paul M, Dzau J. Different secretory pathways of renin from mouse cells transfected with the human renin gene. J Biol Chem 1988; 263: 3137-41.
8. Hundemer GL, Vaidya A. Primary Aldosteronism Diagnosis and Management: A Clinical Approach. Endocrinol Metab Clin North Am 2019; 48: 681-700.
9. Monticone S, Burrello J, Tizzani D, Bertello C, Viola A, Buffolo F, et al. Prevalence and clinical manifestations of primary aldosteronism encountered in primary care practice. J Am Coll Cardiol 2017; 69: 1811-20.
10. Murata M, Kitamura T, Tamada D, Mukai K, Kurebayashi S, Yamamoto T, et al. Plasma aldosterone level within the normal range is less associated with cardiovascular and cerebrovascular risk in primary aldosteronism. J Hypertens 2017; 35: 1079-85.
11. Catena C, Colussi G, Nadalini E, Chiuch A, Baroselli S, Lapenna R, et al. Cardiovascular outcomes in patients with primary aldosteronism after treatment. Arch Intern Med 2008; 168: 80-5.
12. Mosso L, Carvajal C, González A, Barraza A, Avila F, Montero J, et al. Primary aldosteronism and hypertensive disease. Hypertension 2003; 42: 161-5.
13. Baudrand R, Guarda FJ, Torrey J, Williams G, Vaidya A. Dietary sodium restriction increases the risk of misinterpreting mild cases of primary aldosteronism. J Clin Endocrinol Metab 2016; 101: 3989-96.
14. Mulatero P, Stowasser M, Loh KC, Fardella CE, Gordon RD, Mosso L, et al. Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from five continents. J Clin Endocrinol Metab 2004; 89: 1045-50.
15. Käyser SC, Deinum J, de Grauw WJ, Schalk BW, Bor HJ, Lenders JW, et al. Prevalence of primary aldosteronism in primary care: a cross-sectional study. Br J Gen Pract 2018; 68: e114-22.
16. Markou A, Pappa T, Kaltsas G, Gouli A, Mitsakis K, Tsounas P, et al. Evidence of primary aldosteronism in a predominantly female cohort of normotensive individuals: a very high odds ratio for progression into arterial hypertension. J Clin Endocrinol Metab 2013; 98: 1409-16.
17. Baudrand R, Guarda FJ, Fardella C, Hundemer G, Brown J, Williams G, et al. Continuum of renin-independent aldosteronism in normotension. Hypertension 2017; 69: 950-6.

İstanbul Med J 2023; 24(1): 10–3
DOI: 10.4274/imj.galenos.2022.47786

Recommendation Versus Current Status: Retrospective Analysis of Age to Circumcise in a District Hospital

Muhammer Ergenç[1], Tevfik Kıvılcım Uprak[2]

[1]Istanbul Sultanbeyli State Hospital, Department of General Surgery, Istanbul, Turkey
[2]Marmara University Faculty of Medicine, Department of General Surgery, İstanbul, Turkey

ABSTRACT

Introduction: Circumcision is one of the oldest and most frequently performed surgeries worldwide. The age of circumcision varies according to the country and region. We aimed to analyze the age of circumcision in our hospital.

Methods: We evaluated the children who underwent circumcision at Istanbul Sultanbeyli State Hospital between February 2012 and February 2022. The following parameters were analyzed: age at operation, surgery date, and surgeon provider type. Children's age at operation were categorized as follows: neonatal period (<30 days), infancy (≥31 days and <1 year), early childhood (≥1 year and <5 years), late childhood (≥5 years and <13 years), and adolescence (≥13 years and ≤17 years).

Results: Seventeen thousand three hundred forty-five children were analyzed. Children's ages ranged from 0 to 209 months; the median age was 4.07 [interquartile range (IQR) 1.82-6.33] years. The percentage of the neonatal period, infancy, early childhood, late childhood, and adolescence were 1.1%, 13.6%, 46.3%, 38%, and 1%, respectively. Urology performed the most circumcisions in any age group (8374, 48.3%), followed by general surgery (4818, 27.8%) and pediatric surgery (4153, 23.9%). In all surgeon provider types, circumcision was performed primarily in early childhood.

Conclusion: Our study showed that most circumcision operations were performed in the inappropriate age range. A multidisciplinary effort is needed to implement healthcare professionals' recommendations from the neonatal period.

Keywords: Circumcision, male circumcision, age of circumcision, neonates, infant

Introduction

Male circumcision is the surgical excision of the skin covering the distal part of the penis to expose the glans penis. Circumcision, which is practiced for social, cultural, and medical reasons, is one of the oldest and most frequently performed surgeries worldwide. While almost all boys are circumcised in our country, the world health organization reports that 30% of men aged 15 and over are circumcised worldwide, predominantly Muslim men (1-4).

Studies reported that newborn circumcision heals quicker than in infancy, and fewer complications are observed when applied by an appropriate technique and specialist. There are many advantages to circumcising men at a younger age, including faster recovery, lower cost, and a lower risk of complications. While circumcision is widely practiced in the neonatal period in western societies, it is generally performed between the ages of three and six in our country. The age range of 3-6 is called the "phallic-oedipal period." Any intervention to the child's sexual organ during this period may be perceived as an attack and may adversely affect the child's spiritual development. It is recommended to avoid circumcision as much as possible during this period (1,2,4-10).

Although it is such a common procedure, the indications and timing of male circumcision are controversial (6). The American Academy of Pediatrics (AAP) states that the health benefits of newborn male circumcision, such as preventing urinary tract infections, penile cancer, and some sexually transmitted infections, outweigh its risks and that the benefits of the procedure justify access to the circumcision (2,6). Studies state that circumcision can be performed in infancy (7,8,11). Implementing these recommendations in countries like ours is even more challenging, where circumcision is practiced for religious reasons rather than medical indications (7,12).

In this article, the patients who were circumcised at our hospital were evaluated. We provided details regarding circumcisions, such as age and timing.

Methods

We performed a retrospective evaluation of the children who underwent circumcision at Istanbul Sultanbeyli State Hospital between February 2012 and February 2022. This study was approved by the Kartal Lütfi Kırdar City Hospital Clinical Research Ethics Committee (approval

Address for Correspondence: Muhammer Ergenç MD, Istanbul Sultanbeyli State Hospital, Department of General Surgery, Istanbul, Turkey
Phone: +90 216 564 24 00 **E-mail:** muhammerergenc@gmail.com **ORCID ID:** orcid.org/0000-0002-9233-0570

Cite this article as: Ergenç M, Uprak TK. Recommendation Versus Current Status: Retrospective Analysis of Age to Circumcise in a District Hospital. İstanbul Med J 2023; 24(1): 10-3.

Received: 09.09.2022
Accepted: 20.12.2022

©Copyright 2023 by the University of Health Sciences Turkey, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.

number: 2022/514/222/13, date: 30.03.2022). Written informed consent was not obtained from patients, as the data analysis was conducted retrospectively.

In 2022, the Istanbul Sultanbeyli State Hospital had 170 inpatient beds. The hospital's service area as a secondary care hospital covers a rural district in Istanbul, which has a population of approximately 350.000 (179.000 male, 170.000 female).

The hospital's electronic health record system was used for data acquisition. The following parameters of circumcised children were analyzed: age at operation, surgery date, and surgeon provider type.

Circumcisions performed with medical indications such as phimosis, paraphimosis, balanitis, and hypospadias; children who underwent circumcision concomitant with other surgical interventions, such as hydrocele, adenoidectomy, tonsillectomy, inguinal hernia, umbilical hernia, and patients with missing data were excluded from the analyses.

For further analysis, children's age at operation were categorized using the AAP age definitions as follows: neonatal period (<30 days), infancy (≥31 days and <1 year), early childhood (≥1 year and <5 years), late childhood (≥5 years and <13 years), and adolescence (≥13 years and ≤17 years) (6).

The primary outcome of this study was to determine the age of circumcision in our hospital and compare it with the literature.

Statistical Analysis

We performed statistical analysis using the Statistical Package for Social Sciences (version 25 for Mac, IBM Corporation). Descriptive data for continuous variables are expressed as median values and interquartile ranges (IQR). Frequency was used for categorical variables.

Results

In the decade between February 2012 and February 2022, circumcision was performed on 18,125 patients at Istanbul Sultanbeyli State Hospital. Seven hundred eighty patients were excluded from the analysis (Circumcisions performed with medical indications and circumcision concomitant with other surgical interventions: 702; over 18 years old: 78).

After the exclusion criteria were applied, 17,345 children were analyzed. Children's ages ranged from 0 to 209 months, and the median age was 49 (IQR: 22-76) months (Table 1).

Children were divided into age groups according to the AAP age definitions. The percentage of the neonatal period, infancy, early childhood, late childhood, and adolescence were 1.1%, 13.6%, 46.3%, 38%, and 1%, respectively (Table 2).

Although the number of surgeons operating in our hospital during the study duration changed, urology performed the most circumcisions in any age group (8374, 48.3%), followed by general surgery (4818, 27.8%) and pediatric surgery (4153, 23.9%) (Table 2). In all surgeon provider types, circumcision was performed primarily in early childhood (Figure 1).

The frequency of children circumcised by month was analyzed. We found that more circumcisions was performed in the summer, and the number of circumcisions due to Coronavirus disease-2019 (COVID-19) has decreased in the last two years (Figure 2). Although the number of

Table 1. Children's demographics of those who underwent circumcision surgery

Parameters		Children, (n=17345)
Age (years)	Median (interquartile range)	4.07 (1.82-6.33)
	Minimum-maximum	0-17
Age (months)	Median (interquartile range)	49 (22-76)
	Minimum-maximum	0-209

Table 2. Children's age classification according to surgical service

Parameters			Surgical service			Total
			Pediatric surgery	General surgery	Urology	
American Academy of Pediatrics age classification	Adolescence (≥13 and ≤17 years)	n	7	42	121	170
		% of total	0.0%	0.2%	0.7%	1.0%
	Early childhood (≥1 and <5 years)	n	2356	1923	3760	8039
		% of total	13.6%	11.1%	21.7%	46.3%
	Infants (≥30 days and <1 year)	n	71	1061	1226	2358
		% of total	0.4%	6.1%	7.1%	13.6%
	Late childhood (≥5 and <13 years)	n	1717	1701	3171	6589
		% of total	9.9%	9.8%	18.3%	38.0%
	Neonates (<30 days)	n	2	91	96	189
		% of total	0.0%	0.5%	0.6%	1.1%
Total		n	4153	4818	8374	17345
		% of total	23.9%	27.8%	48.3%	100%

circumcisions performed between February 2012 and February 2020 was 16357, the number of circumcisions conducted between March 2020 and February 2022 was 988.

Discussion

One of the oldest known surgical procedures is male circumcision. It is conventionally performed as a sign of cultural identity or religious significance or for sensed health benefits such as enhanced penile hygiene or decreased risk of infection. Worldwide, Muslims are the most significant religious group to practice circumcision, and an estimated 68% of circumcised men are Muslims. Circumcision will always be an issue to be researched in our country, where most of them are Muslims, and 99% of the male population is circumcised (4,13,14). Circumcision may be performed for medical indications or concomitant to other surgical procedures. The most common medical cause of circumcision is phimosis (4). These groups, who were circumcised except for religious reasons, constituted a small portion of 3.9 percent of our study population.

According to the data compiled by the *Republic of Turkey Ministry of Health,* General Directorate of Health Services, the number of circumcisions performed in health institutions has been increasing over the years. It was observed that 346,519 circumcision procedures were performed in 2013, 407,960 in 2015, and 418,283 circumcision procedures in 2017. According to the Turkish Statistical Institute data, there were 1,291,055 live births in Turkey in 2017. It is known that 51.3% of these births, in other words, 662,311 live births are male. It is hypothetically expected to have at least 650,000 circumcisions per year (15).

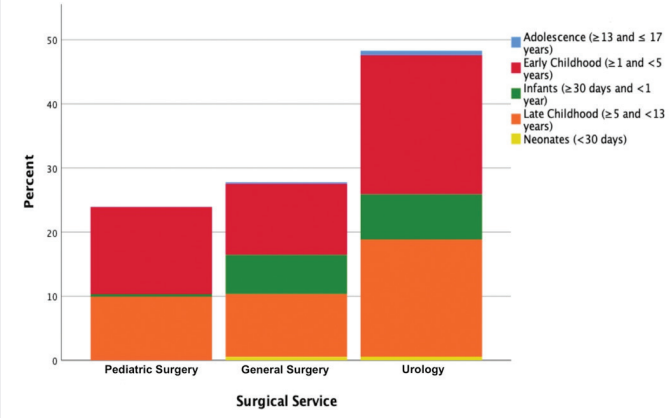


Figure 1. Percentage of circumcision age by surgical service

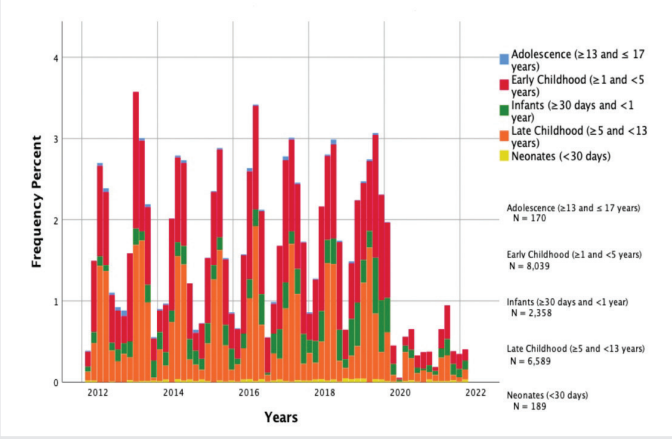


Figure 2. Frequency of circumcised children by months

In a study performed in Turkey in 2011, the mean age of circumcision was reported to be six years and over, in line with the results of previous studies (13,16-18). National studies published in the last decade showed variation in the age of circumcision. In a study in which 4059 circumcised boys were evaluated, the mean age was found to be 4.1 (±3.29), while in a study completed on 1669 boys, it was found to be 3.7±2.5 (19,20). In studies with the number of circumcised boys ranging between approximately 100 and 400, the mean age of circumcision was found to be 3.9±3.8 years, 7.2 (0-16) years, and 5.4±3.2 years, respectively (21-23).

The median age of 17,345 boys in our study was 4.07 (IQR: 1.82-6.33) years. Our large patient cohort result is consistent with the studies published in the last decade. However, it showed that many children are circumcised during the not recommended period.

Research from a country that does not support neonatal circumcision, such as Germany, revealed no increasing trend toward neonatal circumcision. In this study, circumcision in Germany was mainly associated with being descended from Turkish families and revealed that most of the circumcisions were performed between the ages of 1-4 (24). In the meta-analysis of 351 studies with 4,042,988 participants, the age of circumcision was defined as infants (under two years old) and children (2-18 years old), and complications were examined. This study showed that the overall risk of complications requiring treatment was 3.84%, and complications were higher in childhood than in infants (25).

Much of the discussion on the optimal age for male circumcision focuses on the following age groups: newborn and infancy, phallic stage (3-4 years), and school age (8). When we review the recommendations of the institutions in our country for the age of circumcision, The Pediatric Urology Bulletin of the Turkish Association of Urology recommends performing circumcision before the age of 2 or above the age of 6 or performing it under general anesthesia if circumcision cannot be avoided in the phallic period (9). Turkish Archives of Pediatrics, the official journal of the Turkish Pediatric Association: There is no definite age recommended for the age of circumcision. However, circumcision between 1.5 and 4 years of age is inconvenient for the child's psychological development. Neonatal circumcision, which has become widespread in our country recently, has some advantages (26). The turkish Pediatric Surgery Association with the Society for Pediatric Urology recommends following the American Academy of Pediatrics Male Circumcision report (2). In our study, the percentage of age groups did not differ between departments. During the study, all surgical specialties performed circumcision in early childhood. Our study results imply that a multidisciplinary effort is needed if efforts are made to bring circumcision age within the appropriate age range.

Our study showed that circumcision operations were mainly performed in the summer months, which is consistent with other studies (13). As with other surgical procedures, circumcisions were postponed entirely at the beginning of the COVID-19 pandemic (27,28). With the decrease in the effect of the pandemic, circumcision operations have been applied

again. However, a decrease of approximately 75 percent was observed in the number of circumcisions compared with the average of previous years.

Study Limitations

Our study had certain limitations. This is a retrospective, single-center study. The factors affecting the age of circumcision, such as parents' wishes and other medical conditions, were unavailable. We could not compare the complication rate and other perioperative parameters. Our hospital may not reflect national trends in circumcision as a secondary care center.

Circumcision operations are performed by many specialties in different levels of healthcare institutions. A national study to be conducted with more circumcised children from different levels of health institutions will more accurately reflect the age of circumcision in Turkey.

Conclusion

Our study showed that most circumcision operations are performed in the inappropriate age range. Although healthcare professionals' recommendations of the best age to circumcise are compatible with the literature, a multidisciplinary effort is needed to implement these recommendations during the neonatal period.

Acknowledgment: The first author would like to thank his darling wife, Dr. Merve Ergenç, and his lovely son, Umut, for their support.

Ethics Committee Approval: This study was approved by the Kartal Lütfi Kırdar City Hospital Clinical Research Ethics Committee (approval number: 2022/514/222/13, date: 30.03.2022).

Informed Consent: Written informed consent was not obtained from patients, as the data analysis was conducted retrospectively.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - M.E., T.K.U.; Concept - M.E., T.K.U.; Design - M.E., T.K.U.; Data Collection or Processing - M.E., T.K.U.; Analysis or Interpretation - M.E., T.K.U.; Literature Search - M.E., T.K.U.; Writing - M.E., T.K.U.

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. Akyüz O, Çoban S, Bodakçı MN, Özdemir MDAA. Every aspect of circumcision regarding contemporary literature. The New Journal of Urology 2018; 13: 70-6.
2. American Academy of Pediatrics Task Force on Circumcision. Male circumcision. Pediatrics 2012; 130: e756-85.
3. WHO-UNAIDS. Male circumcision: global trends and determinants of prevalence, safety and acceptability. Geneva; 2007.
4. WHO-UNAIDS. Neonatal and Child Male Circumcision: A Global Review; 2010.
5. Sahin F, Beyazova U, Aktürk A. Attitudes and practices regarding circumcision in Turkey. Child Care Health Dev 2003; 29: 275-80.
6. Many BT, Rizeq YK, Vacek J, Cheon EC, Johnson E, Hu YY, et al. A contemporary snapshot of circumcision in US children's hospitals. J Pediatr Surg 2020; 55: 1134-8.
7. Ben-Yami H. Circumcision: What should be done? J Med Ethics 2013; 39: 459-62.
8. Bicer S, Kuyrukluyildiz U, Akyol F, Sahin M, Binici O, Onk D. At what age range should children be circumcised? Iran Red Crescent Med J 2015; 17(3): e26258.
9. Sılay MS. Male circumcision during phallic period and psychological perspective. Turkiye Klinikleri J Urology-Special Topics 2018; 11: 45-8.
10. Yavuz M, Demir T, Doğangün B. The Effect of Circumcision on the Mental Health of Children: A Review. Türk Psikiyatri Dergisi 2012; 23: 63-70.
11. Morris BJ, Waskett JH, Banerjee J, Wamai RG, Tobian AA, Gray RH, et al. A 'snip' in time: what is the best age to circumcise? BMC Pediatr 2012; 12: 20.
12. Anwer AW, Samad L, Iftikhar S, Baig-Ansari N. Reported Male Circumcision Practices in a Muslim-Majority Setting. Biomed Res Int 2017; 2017: 4957348.
13. Türk E, Karaca F, Edirne Y. A Clinical and Epidemiological Study on the Age of Circumcision in Turkey. The Annals of Eurasian Medicine 2013; 1: 27-30.
14. Morris BJ, Wamai RG, Henebeng EB, Tobian AA, Klausner JD, Banerjee J, et al. Estimation of country-specific and global prevalence of male circumcision. Popul Health Metr 2016; 14: 4.
15. Republic of Turkey Ministry of Health General Directorate of Health Services, Health Technology Assessment (HTA) Study of the Disposable Medical Circumcision Instruments Ankara: Republic of Turkey Ministry of Health General Directorate of Health Services; 2018.
16. Benli E, Orhan K. Circumcision research in bingöl province. The New Journal of Urology 2011; 6: 24-7.
17. Senel FM, Demirelli M, Oztek S. Minimally invasive circumcision with a novel plastic clamp technique: a review of 7,500 cases. Pediatr Surg Int 2010; 26: 739-45.
18. Senel FM, Demirelli M, Pekcan H. Mass circumcision with a novel plastic clamp technique. Urology 2011; 78: 174-9.
19. Kaya M, Ozkan A, Kabaklioglu M. A Low Cost and Non-Complicated Circumcision; When, How, Where, Who Should Be Made by? Konuralp Medical Journal 2019; 11: 440-3.
20. Demir M, Eren H. Does the use of diapers have an effect on complications of circumcision? Çoc. Cer. Derg 2020; 34: 53-7.
21. Dörterler ME. Circumcision Complications: Our Eight-Year Experience. Journal of Harran University Medical Faculty 2020; 17: 256-60.
22. Aykac A, Yapici O, Baran O, Ural O, Cakan M. What is the ideal age of circumcision for wound healing time? The European Research Journal 2016; 2: 206-10.
23. Erdoğdu Ceylan E, Yıldız Çeltek N, Ünlü U, Demir O. Prevalence of Anemia in Boys Applying for Circumcision. Pediatr Pract Res 2021; 9:109-13.
24. Oetzmann von Sochaczewski C, Gödeke J, Muensterer OJ. Circumcision and its alternatives in Germany: an analysis of nationwide hospital routine data. BMC Urol 2021; 21: 34.
25. Shabanzadeh DM, Clausen S, Maigaard K, Fode M. Male Circumcision Complications - A Systematic Review, Meta-Analysis and Meta-Regression. Urology 2021; 152: 25-34.
26. Sözübir S. Circumcision information for pediatricians. Turkish Archives of Pediatrics 2010; 45(Suppl:2): 100-3.
27. Raheem AA, Banihani O, Abasher A, Alotay A, Alyami FA, Alsaad TA, et al. Pediatric urology surgical practice in the time of COVID-19: Results from tertiary Saudi Arabia hospitals. Urol Ann 2021; 13: 397-404.
28. Collaborative CO. Elective surgery cancellations due to the COVID-19 pandemic: global predictive modelling to inform surgical recovery plans. Br J Surg 2020; 107: 1440-9.

İstanbul Med J 2023; 24(1): 14-21
DOI: 10.4274/imj.galenos.2022.00194

Factors Influencing Diagnostic Success of Computed Tomography-guided Transthoracic Needle Biopsy in Intrathoracic Lesions: An Experience of a Reference Chest Disease Hospital

Hülya Abalı, Nurdan Şimşek Veske, Berat Uslu, Fatma Tokgöz Akyıl, Seda Tural Önür

University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Clinic of Chest Diseases, İstanbul, Turkey

ABSTRACT

Introduction: Transthoracic needle biopsy (TNB) is a common, safe and inexpensive procedure used in the diagnosis of intrathoracic lesions. Until today, there is still no study about the influence of standardized uptake value (SUV_{max}) in positron emission tomography/computed tomography (PET/CT) on the diagnostic success of TNB in intrathoracic lesions. We aimed to analyze the factors, one of which was the SUV_{max} value influencing the diagnosis success of CT-guided TNB in pulmonary, mediastinal and pleural lesions. Secondary aim was to investigate the predictive clinical factors of complications.

Methods: A retrospective study of 403 patients who underwent CT-guided TNB at a reference chest diseases hospital between February 2019 and February 2021 was conducted. A pulmonologist had performed the procedure with a 20-gauge fine-needle (Spinal) or a 14-gauge automated needle (tru-cut). Data of pathology, microbiology and clinical follow-up of the patients were collected. A chi-square and Student's t-test were used to evaluate the patient-related factors (gender and smoking), lesion-related factors (type, side, location, size, presence of necrosis observed by CT, SUV_{max} value in PET/CT), and procedure factor (type of needle) on the diagnostic success. Additionally, associations between clinical characteristics of patients and the complications were assessed.

Results: A total of 403 patients underwent CT-guided TNB were enrolled and overall success was 70% (284/403). Smoking history (75% vs 43%, p=0.02) was predictor for diagnostic success. Lesion size and SUV_{max} value were significantly high in diagnosed patients (for both p<0.001). Diagnostic success was high in peripheral and central lesions, more notably in central lesions (p=0.004, p=0.016, respectively). The 9.2 SUV_{max} cut-off value had sensitivity of 79%, specificity of %53, success of 79% (p<0.01). Cardiovascular diseases, anti-coagulants, vitamin K antagonists, and salicylate induced complications (p=0.031, p=0.022, p=0.011, p=0.04, respectively). Low-molecular-weight-heparin was associated with hemorrhage (p=0.016).

Conclusion: We observed that type, size and SUV_{max} value of lesion and smoking status were the predictive factors for a diagnostic biopsy.

Keywords: CT-guided, transthoracic biopsy, diagnostic success, SUV_{max}, complications

Introduction

Transthoracic needle biopsy (TNB) is used as an effective and safe diagnostic procedure in the intrathoracic lesions with diagnostic success rates ranging from 12% to 68% in benign (1), and from 76% to 97% in malignant lesions (2,3).

Computed tomography (CT) is an auxiliary radiological device with a perfect visualization capability used for TNB of the intrathoracic lesions. Real-time guidance of CT is a non-invasive marking and confirming method that allows high diagnostic success rates (4).

The most common complications of the procedure are pneumothorax (4-54%), followed by parenchymal hemorrhage at a rate of 2-42% (5,6). Chronic diseases and long-term medications of the patients have influence on the complications. Perilesional emphysema induces pneumothorax and hemorrhage (7). Antiplatelet and anti-coagulative long-term medications are risk factors for hemoptysis (8).

The main aim of this study was to contribute to the literature with the outcomes of the reference chest diseases hospital's experience in the factors influencing the diagnostic success rate of CT-guided TNB in intrathoracic lesions consisting of pulmonary, pleural, and mediastinal.

The present study was presented verbally at the Hybrid Turkish Thorax Congress in Antalya on 19.11.2021.

Address for Correspondence: Hülya Abalı MD, University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Clinic of Chest Diseases, İstanbul, Turkey
Phone: +90 505 758 42 97 **E-mail:** hulayab@gmail.com **ORCID ID:** orcid.org/0000-0003-4041-7479

Cite this article as: Abalı H, Şimşek Veske N, Uslu B, Tokgöz Akyıl F, Tural Önür S. Factors Influencing Diagnostic Success of Computed Tomography-guided Transthoracic Needle Biopsy in Intrathoracic Lesions: An Experience of a Reference Chest Disease Hospital. İstanbul Med J 2023; 24(1): 14-21.

Received: 23.05.2022
Accepted: 20.12.2022

©Copyright 2023 by the University of Health Sciences Turkey, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.

Among these factors, the influence of maximum standardized uptake (SUV_{max}) value in positron emission tomography/computerized tomography (PET/CT) on diagnostic success was also analyzed. Additionally, the predictive clinical factors for complications were investigated.

Methods

This single-center study was approved by the Local Ethics Committee of University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (approval number: 2021-107, date: 08.04.2021). Four hundred-three patients who underwent CT-guided TNB performed by five independent pulmonologists between February 2019 and February 2020 were analyzed retrospectively. Because of the retrospective design of the study, the patients were exempt from informed consent.

Data Collection and Measurements

Data of the study were obtained from the hospital registration system. Demographic characteristics of the patients (gender and smoking status) and the type of needle used were collected.

Lesion type was categorized as a solitary pulmonary nodule, multiple pulmonary nodules, central mass, peripheral mass, mediastinal mass, pleural mass, consolidation, abscess, and cavitary lesion in thoracic CT. The central mass was described as a mass in the 2/3 inner area of the pulmonary parenchyma, and peripheral mass was described as a mass in the 1/3 outer area of the pulmonary parenchyma.

Smoking status was grouped as ever-smoker and never-smoker. Ever-smokers included former and current smokers.

Size (cm), side (right/left/bilateral lung), location (right upper/middle/right lower lobe; left upper/lingula/left lower lobe), and necrosis content of a lesion in thoracic CT were recorded. The size of a lesion (cm) was classified as <1, 1-3, 3-5, >5.

The SUV is an activity concentration in the tissue, which is calculated by radionuclide dose administered/patient's weight. SUV_{max} values of the patients whose PET/CT reports could be accessed in the hospital registry system, were collected.

Procedural complications (pneumothorax, hemorrhage, air embolism, syncope) were collected from the interventional radiology registration system. Chronic diseases [chronic pulmonary diseases (CPD) (chronic obstructive pulmonary disease (COPD), emphysema, asthma), chronic cardiovascular diseases (CVD) (coronary artery disease, heart failure, hypertension)], and long-term medications such as anti-coagulant drugs [new oral anti-coagulants (NOAC), parenteral direct and indirect anti-coagulants], vitamin K antagonists, low-molecular-weight-heparin (LMWH), and antiplatelet drugs (salicylate and clopidogrel) were recorded from the pharmacy Medulla system.

Transthoracic Needle Biopsy Procedure

By the routine practice of the hospital and the Helsinki Declaration, consent was obtained from the patients for the procedure. All procedures were performed by five independent researcher pulmonologists with at least 10 years of professional experience.

A 16-slice CT scanner (Toshiba Alexion model 2013, Nasu, Japan) was used to guide the needle and locate the lesion. Anti-coagulant drugs were discontinued at least one week before the procedure. PET/CT and thoracic CT were pre-examined for biopsy site determination. A patient was positioned on the CT table according to the safest and shortest crossing for the biopsy and told to hold a breath. The location of a lesion was confirmed by a CT scanner. The needle -entry site of the skin was marked by an accompanying technician. After local antisepsis, the needle was inserted through the lesion. A 9 cm-long, 20-gauge fine needle (Spinal) was used for aspiration biopsy, and a 20 cm-long, 14-gauge automated needle (tru-cut) was used for core biopsy. The aspiration was performed once it was ascertained that the needle was exactly inside the lesion.

After aspiration of the adequate sample, the aspirated material was fixed in 96% alcohol solution. A core specimen was fixed in 10% formalin. Frozen section analysis was not performed at the time of the biopsy. The collected material was sent to the department of pathology for histopathological examination. The samples of patients with suspected pulmonary tuberculosis were sent to the department of microbiology for acid fast bacilli (AFB) staining and culture to identificate mycobacterial infection.

End-point of the Study

The pathological results were classified into three categories-malignant, benign, and non-diagnostic. The result of pathology as malignant or benign was deemed as a diagnostic success. AFB staining positivity and/or mycobacterium species proliferation in culture were also deemed as diagnostic success.

Statistical Analysis

All statistical analyses were carried out using a statistical software package (SPSS for Windows, version 16.0; SPSS Inc.; Chicago, IL, USA). Quantitative data were expressed as mean ± standard deviation and qualitative data were expressed as frequencies. A chi-square and Student's t-test were used to evaluate the data obtained from inter-group comparison. Receiver operating characteristic (ROC) analysis was used to determine the optimal SUV_{max} cut-off value in PET/CT. A p-value of <0.05 was considered significant.

Results

Four hundred-three patients underwent CT-guided TNB mainly with a prediagnosis of malignant diseases. The mean age of the patients, 81% (327) of whom were male, was 63±12 years. Eighty-nine percent of the patients (n=358) had a smoking history (Table 1).

The diagnostic success rate of TNB was 70% (284 of 403 patients). Two hundred-sixty-nine (95%) out of 284 patients were diagnosed with malignant disease, and 15 (5%) out of 284 patients were diagnosed with benign diseases by TNB. Of the benign lesions, only one was diagnosed with pulmonary tuberculosis based on microbiological examination [sample ARB (+)]. While the histopathological type was non-small-cell lung cancer in 220 patients and small cell lung cancer in 25 patients (Table 2).

Table 1. Demographic, clinical, and radiological characteristics of patients underwent transthoracic needle biopsy for intrathoracic lesion

	Number (n)	Percentages (%)
Gender		
Male	327	81
Female	76	19
Smoking status		
Ever-smoker	358	89
Never-smoker	45	11
Chronic diseases		
Cardiovascular diseases	117	29
Pulmonary diseases	98	24
Anti-coagulant drugs (one or more)	95	24
Vitamin K antagonists	17	4
Low-molecular-weight-heparin	14	4
Anti-platelet drugs	87	22
Clopidogrel	14	4
Salicylate	73	18
Lesion type		
Solitary pulmonary nodule	58	14
Multiple pulmonary nodules	16	4
Peripheral mass	236	59
Central mass	39	10
Mediastinal mass	7	1
Pleural mass	14	4
Consolidation	11	3
Cavitary lesion	15	4
Abscess	2	1
Lesion size (cm)		
<1	4	1
1-3	93	23
3-5	114	28
>5	192	48
Necrosis		
Yes	105	26
No	298	74
Lesion side (lung)		
Right	205	51
Left	196	48.6
Bilateral	2	0.4
Lesion location (lobe)		
Right upper	117	29
Middle	20	5
Right lower	73	18
Left upper	97	24
Lingula	11	3
Left lower	85	21

Among 119 patients undiagnosed by TNB, 18 patients were diagnosed via either bronchoscopy, endobronchial ultrasonography, video-assisted thoracoscopy, or open lung biopsy, and 4 patients were diagnosed clinically and radiologically by a pulmonologist (Table 2). No repeated TNB was applied. Out of 119 undiagnosed by TNB, 97 patients dropped out of our follow-up for unknown reasons.

The most common lesion type was the peripheral lesion (n=236, 59%), and the most common lesion location was the right upper lobe

Table 2. Diagnosis of patients

	Number (n)	Percentages (%)
Diagnosis by TNB		
Malign	269	95
SCLC	25	8.8
NSCLC	220	77.4
NSCLC with an undefined subtype	47	16.5
SqCLC	81	28.5
Adenocarcinoma	92	32.4
Mesothelioma	2	0.7
Mesenchymal tm	6	2.1
Neuroendocrine tm	3	1.1
Extrapulmonary cancer metastasis	13	4.6
Benign	15	5
Anthracosis	1	0.4
Sarcoidosis	3	1.1
Pulmonary tuberculosis	6	0.4
Organizing pneumonia	3	1.1
Aspergillus infection	1	0.4
Fungal infection	1	0.4
Diagnosis by a pulmonologist		
Infected bronchiectasis	1	25
Metastatic lung cancer	2	50
Primary lung cancer	1	25
Diagnosis by further invasive procedures		
Malignant solitary fibrous tm	1	5.6
Wilms tm	1	5.6
Anthracosis	1	5.6
B-cell Lymphoma	3	16.2
Hamartoma	1	5.6
Hyalinization	1	5.6
Mesothelioma	1	5.6
SCLC	1	5.6
Invasive mucinous carcinoma	1	5.6
SqCLC	2	11.1
Adenocarcinoma	1	5.6
Sarcomatous tm	1	5.6
Pulmonary tuberculosis	2	11.1
Lung metastasis from thyroid cancer	1	5.6

NSCLC: Non-small-cell lung cancer, SCLC: Small-cell lung cancer, SqCLC: Squamous-cell lung cancer, tm: Tumor, TNB: Transthoracic needle biopsy

Table 3. Associations between lesion type, location, and SUV_{max} value in PET/CT and diagnostic success of transthoracic needle biopsy in intrathoracic lesions

	Success	Failure	p
	n=284 (70%)	n=119 (30%)	
Lesion type			
Peripheral mass	184 (76)	58 (24)	-
Solitary pulmonary nodule	38 (65)	20 (35)	-
Multiple pulmonary nodules	11 (69)	5 (31)	-
Central mass	34 (87)	5 (13)	<0.001*
Mediastinal mass	1 (14)	6 (86)	-
Pleural mass	7 (50)	7 (50)	-
Consolidation	4 (36)	7 (64)	-
Cavitary lesion	5 (33)	10 (67)	-
Abscess	0 (0)	2 (100)	-
SUV_{max} value in PET/CT (µCu/g)	β15±7.5	β11±7.7	<0.001*
Lesion side (lung)			-
Right	142 (69)	63 (31)	-
Left	141 (72)	55 (28)	0.688*
Bilateral	1 (50)	1 (50)	-
Lesion location (lobe)	-	-	-
Right upper	88 (65)	29 (35)	0.145
Right middle	14 (70)	6 (30)	0.998
Right lower	44 (62)	27 (38)	0.087
Left upper	71 (74)	26 (26)	0.437
Lingula	8 (73)	3 (27)	0.998
Left lower	62 (73)	23 (27)	0.410

Percentage values given in parentheses, βmean value ± standard deviation, n: Number of patients, PET/CT: Positron emission tomography/computed tomography, SUV_{max}: Maximum value of standardized uptake, *p<0.05: Significant value

(n=210, 52%) (Table 1). While the diagnostic success rate of TNB was 76% in patients with peripheral lesions (p=0.004), it was 87% in central lesions (p=0.016). The diagnostic success rate was significantly lower in a mediastinal lesion (14% vs 86%, p=0.003). Five of 15 patients with cavitary lesions were diagnosed (33% vs 67%, p=0.003). Four of 11 patients with consolidations had definite diagnoses (36% vs 64%, p=0.018) (Table 3).

An ever-smoker patient had higher diagnostic success than a never-smoker patient (75% vs 43%, p=0.02) as shown in Table 4.

The mean lesion size of all patients was 5.5±2.9 cm. While the mean size of central lesions was 5.5±2.9 cm, the mean size of peripheral lesions was 5.9±2.2 cm. The procedural diagnostic rates of patients with the lesion size (cm) <1, 1-3, 3-5, >5 were 50%, 60%, 72%, and 79%, respectively. The mean SUV_{max} value of the lesions was 13.8±7.8 µCu/g. The lesion size and SUV_{max} value were statistically significantly higher in patients with a pathology diagnosis (for both, p<0.001) (Table 4).

The optimal SUV_{max} cut-off value for the diagnostic success of TNB was detected as 9.2 µCu/g (area under the curve: 0.669) by ROC analysis. TNB procedure was 21% diagnostic in patients with an SUV_{max} value below 9.2 µCu/g, and 79% in those with an SUV_{max} value above 9.2 µCu/g (p<0.001). The SUV_{max} value above 9.2 µCu/g had a sensitivity of 79% and specificity of 53% for the diagnostic success of CT-guided TNB (Figure 1).

The complications were observed in 9% (n=35) patients. The most common complication was pneumothorax at a percentage of 7% (n=29) patients, followed by hemorrhage in 2% (6) patients. None of the air embolism and syncope appeared among the complications.

CPD were recorded in 98 (24%) patients, and CVD were recorded in 117 (29%) patients (Table 1). Clinical characteristics such as anti-coagulant and antiplatelet drug use and chronic diseases of patients were compared with complications and hemorrhage rates. Statistically significant correlations were found between the development of complications and the history of CVD (p=0.031), the administration of anti-coagulant drugs (NOAC, parenteral direct and indirect anti-coagulants) (p=0.022), vitamin K antagonists (p=0.011), and salicylate (p=0.04). LMWH administration had a significant influence on hemorrhage (p=0.016). No significant associations were found between smoking and CPD and the occurrence of pneumothorax (p=0.998, p=0.415) (Table 5).

Discussion

The fast diagnosis of an intrathoracic lesion suspected for malignancy is important to avoiding mortality and morbidity of cancer by administering the optimal treatment as soon as possible.

TNB achieves a high technical success rate of 88-97% in different studies (9-11). The diagnostic success rate of this study was 70% (284 of 403 patients) compatible with the reported ranges.

Table 4. Influence of demographic and lesion characteristics of the patients and needle type on the diagnostic success of transthoracic needle biopsy in intrathoracic lesions

	Success	Failure	p
	n=284 (70%)	n=119 (30%)	
Gender			
Male	236 (72)	91 (28)	0.127
Female	48 (63)	28 (37)	-
Smoking history			
Ever-smoker	268 (75)	90 (25)	<0.001*
Never-smoker	19 (42)	26 (58)	-
Lesion size (cm)	β2.3±0.8	β2±0.9	<0.001*
<1 cm	2 (50)	2 (50)	-
1-3	52 (60)	41 (40)	<0.001*
3-5	82 (72)	32 (38)	-
>5	151 (79)	41 (31)	-
Necrosis in lesion			
Yes	72 (69)	33 (31)	0.621
No	212 (71)	86 (29)	-
Needle type			
FNB	268 (70)	115 (30)	0.454
CB	16 (80)	4 (20)	-

Percentage values given in parentheses, βmean value ± standard deviation, CB: Core biopsy, FNB: Fine-needle biopsy, n: Number of patients, *p<0.05: Significant value

Table 5. Associations between clinical characteristics of patients and complications of transthoracic needle biopsy in intrathoracic lesions

		Number (n)	Percentages (%)	p
Total complications	Anti-coagulants (n=95)	14	15	0.022*
	Vitamin K antagonists (n=17)	5	29	0.011*
	LMWH (n=14)	2	14	0.347
	Salicylate (n=73)	11	15	0.040*
	Clopidogrel (n=14)	1	7	1.000
	CPD (n=98)	6	6	0.410
	CVD (n=117)	16	14	0.031*
Pneumothorax	Ever-smoker (n=358)	18	5	0.998
	CPD (n=98)	29	29	0.415
Hemorrhage	Anti-coagulants (n=95)	3	3.2	0.146
	Vitamin K antagonists (n=17)	0	0	0.998
	LMWH (n=14)	2	14.3	0.016*
	Salicylate (n=73)	3	4.1	0.076
	Clopidogrel (n=14)	0	0	0.999

CPD: Chronic pulmonary diseases, CVD: Cardiovascular diseases, LMWH: Low-molecular-weight-heparin. *p<0.05: Significant value

The diagnostic success of TNB performed by a pulmonologist in a study including 224 patients was reported at 97% (12). The relatively low diagnostic success in this study may be explained by the lesions containing more necrotic tissues. Another fact is that diagnostic success seems to be higher in the case of TNB performed in the presence of a pathologist to evaluate sample adequacy (13). Unfortunately, no accompanying pathologist was present during the procedure in the interventional radiology department.

The procedure in 185 of 247 ever-smoker patients were diagnostic, and there was a significant association between smoking history and diagnostic success (p<0.001). This result was not surprising in this study with the malignant pathology results at a rate of 95%.

van Sonnenberg et al. (14) have determined the diagnostic success of 90% for lesions 3-4 cm, 89.3% for lesions 2-3 cm, 83.9% for lesions 1-2 cm, and 73.9% for lesions <1 cm (14). Tsukada et al. (15) have reported that diagnostic success decreased with decreasing lesion size (cm):

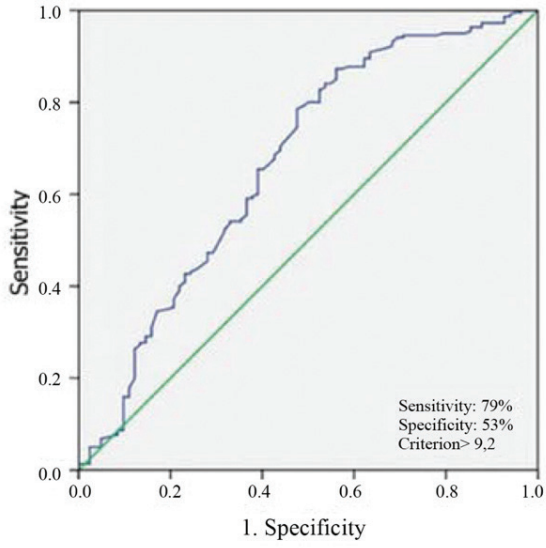


Figure 1. The ROC curves of the sensitivity and specificity of SUV_{max} above 9.2 µCu/g of cut-off value

ROC: Receiver operating characteristic

from 100% to 93%, 87%, 79%, and 67% for lesions >5, 3-5, 2-3, 1-2, <1, respectively. The diagnostic success related to the lesion size (cm) agreed with the previous studies: for <1, 1-3, 3-5, and >5 were 50%, 60%, 72%, and 79%, respectively. Lesions at a mean size of 2.3±0.8 cm had significant diagnostic success of TNB (p<0.001). Li et al. (9) have attributed the decrease in diagnostic success with the reduction in lesion size to sampling error. Because the technique of targeting small lesions is difficult, the needle can not be placed right inside the lesion or it can be placed in a necrosed area. Controversially, Priola et al. (13) have showed that diagnostic success was high in the lesions of which sizes were 1.5-5 cm (lesions <1.5 cm 68%, lesions 1.5-5.0 cm 87%, lesions >5 cm 78%). Another study has declared that CT-guided TNB of small pulmonary lesions <2 cm had higher diagnostic success (93.5%) (16). Luciderma et al. (17) have reported no significant difference in the success of 81% for ≤2 cm and 91% for lesions >2 cm. These conflicts may depend on the needle type and skill of the practitioner.

Peripheral and central lesions had significant influences on diagnostic success (p=0.004, p=0.016, respectively; conversely, mediastinal mass, cavitary lesion, and consolidation had significant influences on diagnostic failure (p=0.003, p=0.003, p=0.018, respectively) in this study. To date, there are few studies analyzing the influence of lesion type on the diagnostic value of this procedure. The diagnostic success rate of CT-guided TNB with a fine needle was 83.5% in central lesions, and diagnostic success increased gradually to the periphery of the lung to 95.6% in the study by De Filippo et al. (18). The lesion depth had no significant influence on the diagnostic success in another study (19). Unlikely these two studies, the diagnostic success rate of TNB was higher in central lesions in this study. Different outcomes of the three studies may be related to the differences in the mean lesion size and needle-pleural angle.

In some series of studies, the diagnostic success rates of TNB in cavitary lesions have been found at 100% and 94% (18,19). However, the diagnostic success rate was observed as 33% in this study. A study including 1,090 patients have declared that the diagnostic rate of TNB in consolidations is at 83% (20). On the contrast, the diagnostic success of TNB in consolidations was found to be 36%. The lower rates of diagnostic success in cavitary lesions and consolidations may be attributed to the lower percentages of these radiological appearances in this study.

The mean SUV_{max} value of the lesions was 13.8±7.8 µCu/g and was significantly high in diagnosed patients. In the current literature, there is no study on the cutoff value of SUV_{max}, which indicates the diagnostic success of TNB in intrathoracic lesions. A previous study (21) including the nodules in the size of 1-2 cm has investigated the SUV_{max} cut-off value for the diagnostic success of TNB. The 4.5 SUV_{max} cut-off value had a sensitivity of 80.2%, specificity of 54.4%, accuracy of 72.8% (p<0.001). Similarly, the 9.2 SUV_{max} cut-off value had sensitivity of 79%, specificity of 53%, and accuracy of 79% (p<0.001) in this study. The SUV_{max} value above 2.5 µCu/g predicted malignant lesions (22). While 58% of the lesions were malign in the previous study, 95% of the lesions were malign in this study. Compared with that study, the higher SUV_{max} cut-off value in this study had approximately the same specificity. This might be because our study included a higher proportion of malignant and infected lesions as F-18 fluorodeoxyglucose is not uptaken only by malign lesions but also by inflammatory lesions (23).

The most common complication was pneumothorax, followed by hemorrhage. The rates of these complications were within acceptable levels and even were less than that reported in the previous literature (5,6,24). Emphysema and smoking have been declared as risk factors for pneumothorax and hemorrhage in a study (25). Controversially, CPD and smoking had no influence on the occurrence of pneumothorax in this study. Another study has also found no association between smoking and pneumothorax (26). In a study, COPD has been reported as a risk factor for both pneumothorax and hemorrhage, and oral anti-coagulants and antiplatelet agents have been reported as risk factors for hemorrhage (27). Conversely, CPD had no association with total complications, and anti-coagulants and antiplatelet agents (salicylate, clopidogrel) had no associations with hemorrhage. LMWH was found to be the only risk factor for hemorrhage. However, anti-coagulants, salicylate, and vitamin K antagonists had associations with total complications (pneumothorax and hemorrhage). A previous study reported that hypertension was not a risk factor for complications of TNB, including pneumothorax, hemorrhage, hemoptysis, and hemothorax (28). In contrast, CVD was a significant factor in the occurrence of total complications in this study. Lesions of different sizes and depths, different patient populations may have led to the conflict between these studies.

Study Limitations

The main limitation of this study was the retrospective design. We consider that the most important reason for undiagnosed 97 patients to drop out of our follow-up is the coincident of the diagnostic interventions with the COVID-19 pandemic period.

Conclusion

This study demonstrated that lesion-related factors (type, size, SUV_{max} value in PET/CT) and patient-related factors (smoking history) were

predictors for the diagnostic success of TNB. The history of CVD, administration of anti-coagulants, vitamin K antagonists, and salicylate were observed to correlate with the higher complication rates. An association was observed between hemorrhage and only LMWH. Before ordering this procedure, a practitioner should consider these factors.

Acknowledgments

All authors thank the staff of the radiology department and Dilara Demir for her contribution in designing tables and figures.

Ethics Committee Approval: This single-center study was approved by the Local Ethics Committee of University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (approval number: 2021-107, date: 08.04.2021).

Informed consent: The patients were exempt from informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - H.A., N.Ş.V., B.U., F.T.A., S.T.Ö.; Concept - H.A.; Design - H.A., N.Ş.V., B.U.; Data Collection or Processing - H.A., N.Ş.V., B.U., F.T.A., S.T.Ö.; Analysis or Interpretation - H.A., N.Ş.V., B.U., F.T.A., S.T.Ö.; Literature Search - H.A.; Writing - H.A., F.T.A., S.T.Ö.

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

Financial Disclosure: The authors received no financial support for the research and/or authorship of this article.

References

1. Perlmutt LM, Johnston WW, Dunnick NR. Percutaneous transthoracic needle aspiration: a review. AJR Am J Roentgenol 1989; 152: 451-5.
2. Anderson JM, Murchison J, Patel D. CT-guided lung biopsy: factors influencing diagnostic yield and complication rate. Clin Radiol 2003; 58: 791-7.
3. Larscheid RC, Thorpe PE, Scott WJ. Percutaneous transthoracic needle aspiration biopsy: a comprehensive review of its current role in the diagnosis and treatment of lung tumors. Chest 1998; 114: 704-9.
4. Klein JS, Zarka MA. Transthoracic needle biopsy. Radiol Clin North Am 2000; 38: 235-6.
5. Klein JS, Salomon G, Stewart EA. Transthoracic needle biopsy with a coaxially placed 20-gauge automated cutting needle: results in 122 patients. Radiology 1996; 198: 715-20.
6. Laspas F, Roussakis A, Efthimiadou R, Papaioannou D, Papadopoulos S, Andreou J. Percutaneous CT-guided fine-needle aspiration of pulmonary lesions: results and complications in 409 patients. J Med Imaging Radiat Oncol 2008; 52: 458-62.
7. Lee DS, Bak SH, Jeon YH, Kwon SO, Kim WJ. Perilesional emphysema asa predictor of risk of complications from computed tomography-guided transthoracic lung biopsy. Jpn J Radiol 2019; 37: 808-16.
8. Hwang EJ, Park CM, Yoon SH, Lim HJ, Goo JM. Risk factors for haemoptysis after percutaneous transthoracic needle biopsies in 4,172 cases: Focusing on the effects of enlarged main pulmonary artery diameter. Eur Radiol 2018; 28: 1410-9.
9. Li H, Boiselle PM, Shepard JAO, Trotman-Dickenson B, McLoud TC. Diagnostic accuracy and safety of CT-guided percutaneous needle aspiration biopsy of the lung: comparison of small and large pulmonary nodules. AJR Am J Roentgenol 1996; 167: 105-10.
10. Chojniak R, Isbemer RK, Viana LM, Yu LS, Aita AA, Soares FA. Computed tomography guided needle biopsy: experience from 1,300 procedures. Sao Paulo Med J 2006; 124: 10-4.
11. Guimarães MD, Marchiori E, Hochhegger B, Chojniak R, Gross JL. CT-guided biopsy of lung lesions: defining the best needle option for a specific diagnosis. Clinics (Sao Paulo) 2014; 69: 335-40.
12. Ahn JH, Jang JG. Initial Experience in CT-Guided Percutaneous Transthoracic Needle Biopsy of Lung Lesions Performed by a Pulmonologist. J Clin Med 2019; 8: 821.
13. Priola AM, Priola SM, Cataldi A, Errico L, Di Franco M, Campisi P, et al. Accuracy of CT-guided transthoracic needle biopsy of lung lesions: factors affecting diagnostic yield. Radiol Med 2007; 112: 1142-59.
14. van Sonnenberg E, Casola G, Ho M, Neff CC, Varney RR, Wittich GR, et al. Difficult thoracic lesions: CT-guided biopsy experience in 150 cases. Radiology 1988; 167: 457-61.
15. Tsukada H, Satou T, Iwashima A, Souma T. Diagnostic accuracy of CTguided automated needle biopsy of lung nodules. AJR Am J Roentgenol 2000; 175: 239-43.
16. Li Y, Du Y, Yang HF, Yu JH, Xu XX. CT-guided percutaneous core needle biopsy for small (≤20 mm) pulmonary lesions. Clinic Radiol 2013; 68: e43-8.
17. Luciderma O, Howarth N, Finet JF, Grenier PA. Intrapulmonary lesions: percutaneous automated biopsy with a detachable, 18-gauge, coaxial cutting needle. Radiology 1998; 207: 759-65.
18. De Filippo M, Saba L, Concari G, Nizzoli R, Ferrari L, Tiseo M, et al. Predictive factors of diagnostic accuracy of CT-guided transthoracic fine-needle aspiration for solid noncalcified, subsolid and mixed pulmonary nodules. Radiol Med 2013; 118: 1071-81.
19. Arslan S, Yilmaz A, Bayramgürler B, Uzman O, Nver E, Akkaya E. CT-guided transthoracic fine needle aspiration of pulmonary lesions: Accuracy and complications in 294 patients. Med Sci Monit 2002; 8: 493-7.
20. Kiranantawat N, Petranović M, McDermott S, Gilman M, Digumarthy SR, Shepard JO, et al. Feasibility and accuracy of CT-guided percutaneous needle biopsy of cavitary pulmonary lesions. Diagn Interv Radiol 2019; 25: 435-41.
21. Yeow KM, Tsay PK, Cheung YC, Lui KW, Pan KT, Chou AS. Factors affecting diagnostic accuracy of CT-guided coaxial cutting needle lung biopsy: retrospective analysis of 631 procedures. J Vasc Interv Radiol 2003; 14: 581-8.
22. Kiranantawat N, McDermott S, Fintelmann FJ, Montesi SB, Price MC, Digumarthy SR, et al. Clinical role, safety and diagnostic accuracy of percutaneous transthoracic needle biopsy in the evaluation of pulmonary consolidation. Respir Res 2019; 20: 23.
23. Susam S, Çinkooğlu A, Ceylan KC, Gürsoy S, Kömürcüoğlu BE, Mertoğlu A, et al. Diagnostic success of Transthoracic needle biopsy and PET-CT for 1 to 2 cm solid indeterminate pulmonary nodules. Clin Respir J 2020; 14: 453-61.
24. Menda Y, Bushnell DL, Madsen MT, McLaughlin K, Kahn D, Kernstine KH. Evaluation of various corrections to the standardized uptake value (SUV) for diagnosis of pulmonary nodules. Nucl Med Commun 2001; 22: 1077-81.
25. Gould MK, Maclean CC, Kuschner WG, Rydzak CE, Owens DK. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. JAMA 2001; 285: 914-24.
26. Boskovic T, Stanic J, Pena-Karan S, Zarogoulidis P, Drevelegas K, Katsikogiannis N, et al. Pneumothorax after transthoracic needle biopsy of lung lesions under CT guidance. J Thorac Dis 2014; 6(1 Suppl): S99-S107.
27. César DN, Torres US, D'Ippolito G, Souza AS. CT-guided Transthoracic Core-Needle Biopsies of Mediastinal and Lung Lesions in 235 Consecutive Patients: Factors Affecting the Risks of Complications and Occurrence of a Final Diagnosis of Malignancy. Arch Bronconeumol 2018; 55: 297-305.

28. Taslakian B, Koneru V, Babb JS, Sridhar D. Transthoracic Needle Biopsy of Pulmonary Nodules: Meteorological Conditions and the Risk of Pneumothorax and Chest Tube Placement. J Clin Med 2019; 8: 727.

29. Vachani A, Zhou M, Ghosh S, Zhang S, Szapary P, Gaurav D, et al. Complications After Transthoracic Needle Biopsy of Pulmonary Nodules: A Population-Level Retrospective Cohort Analysis. J Am Coll Radiol 2022; 19: 1121-9.

30. Digumarthy SR, Kovacina B, Otrakji A, Lanuti M, Shepard JA, Sharma A. Percutaneous CT guided lung biopsy in patients with pulmonary hypertension: Assessment of complications. Eur J Radiol 2016; 85: 466-71.

İstanbul Med J 2023; 24(1): 22-5
DOI: 10.4274/imj.galenos.2022.21208

Evaluation of the Sterility of PRP Obtained with Multi-bag System (PRPBAG®)

Güven Çetin[1], Bilge Sümbül[2], Tuba Özkan[3], Seda Turgut[4], Nang Hseng Kyio[5], Kübra Şen[6], Damla Aslan Kirazoğlu[6]

[1]Bezmialem Vakıf University Hospital, Clinic of Internal Medicine, Division of Hematology, İstanbul, Turkey
[2]Bezmialem Vakıf University Hospital, Clinic of Medical Microbiology, İstanbul, Turkey
[3]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Internal Medicine, Division of Hematology, İstanbul, Turkey
[4]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Endocrinology and Metabolism, İstanbul, Turkey
[5]King Hamad University Hospital, Bahrain Oncology Center, Busaiteen, Bahrain
[6]Bezmialem Vakıf University Hospital, Clinic of Internal Medicine, İstanbul, Turkey

ABSTRACT

Introduction: The aim of this study is demonstrating the sterility of PRPBAG®, a multi-bag completely closed PRP preparation system different than PRP kits in the market and determining preservability of the sterility of PRP produced with PRPBAG® up to 5 days similar to other platelet products.

Methods: We recruited 60 participants for increased statistical significance. 150 mL of whole blood was collected in specially produced PRPBAG®. A double-spin preparation method was used for the samples with a refrigerated centrifuge specially manufactured for PRPBAG®. We started centrifugation within 1 h after collecting blood. In the 1st spin of the centrifugation, whole blood was centrifuged. Erythrocytes precipitated in the first bag because of blood component density, and the supernatant plasma was transferred into the second bag using a manual plasma extractor. The third bag was empty after the first spin. We used a hose-closing device to separate the first bag, which contained erythrocytes, from the other bags. In the second spin of centrifugation, the plasma was centrifuged.

Results: PRP product with high-quality was collected in the second bag. We have considered the European guidelines for the preparation, use, and quality assurance of blood components during the whole process. 1 cc of PRP was added into separate pediatric blood culture bottles on days 0, 1, 2, 3, 4, and 5. These samples were sent to the microbiology laboratory and incubated for 5 days. After this incubation period, the blood culture bottles that did not give positive signals were reported as sterile.

Conclusion: Currently, PRP is used immediately after preparation. Our study demonstrates that PRP prepared with a closed triple blood bag system PRPBAG® may be used for 5 days if agitated at room temperature. There was not any bacterial growth in any sample after 5 days.

Keywords: Platelet-rich plasma, PRPBAG, sterility

Introduction

Platelet-rich plasma (PRP) is an autologous blood fraction with increased concentration of platelets and plasma growth factors above a certain threshold (1-3). The most common PRP acquisition methods in the market are kits. However, they differ significantly in terms of platelet concentration because of unstandardized production processes, and these are open methods where the plasma gets in contact with air (4). Sterilization is the process of removing living and viable germs from objects (5). Sterilization, especially of blood products, is important for preventing secondary infections and transmission of diseases (6,7).

PRPBAG® is a patented multi-bag PRP preparation system that uses apheresis bag technology. Its oxygen-permeability prevents platelets from hypoxia, which results in a high-quality PRP product. PRPBAG® is a completely closed and sterile system. It can provide an increase of as high as eightfold in the concentration of platelets compared to plasma (8).

Thrombocytes are delicate blood cells that are typically stored at room temperature for 5 days with gentle agitation (9,10).

The aim of this study is demonstrating the sterility of PRPBAG®, a multi-bag completely closed PRP preparation system different than PRP kits

Address for Correspondence: Güven Çetin MD, Bezmialem Vakıf University Hospital, Clinic of Internal Medicine, Division of Hematology, İstanbul, Turkey
Phone: +90 532 551 47 98 **E-mail:** drgvn20@gmail.com **ORCID ID:** orcid.org/0000-0002-4265-8105

Cite this article as: Çetin G, Sümbül B, Özkan T, Turgut S, Kyio NH, Şen K, Aslan Kirazoğlu D. Evaluation of the Sterility of PRP Obtained with Multi-bag System (PRPBAG®). İstanbul Med J 2023; 24(1): 22-5.

Received: 13.07.2022
Accepted: 21.12.2022

©Copyright 2023 by the University of Health Sciences Turkey, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.

in the market and determining preservability of the sterility of PRP produced with PRPBAG® up to 5 days similar to other platelet products.

Methods

PRP was prepared using PRPBAG® and with the following the steps:150 mL of whole blood was drawn from the antecubital veins and collected in specially produced PRPBAG®. A double-spin preparation method was used for the samples with a refrigerated centrifuge specially manufactured for PRPBAG® (Large Capacity Refrigerated Centrifuge, Inovia Technology INO-FBC 5000). We started centrifugation within 1 h after collecting blood. In the 1st spin of the centrifugation, whole blood was centrifuged at 1600 (540 x g), 1800 (684 x g) and 2000 (845 x g) rpm for 10 min. Erythrocytes precipitated in the first bag because of blood component density, and the supernatant plasma was transferred into the second bag using a manual plasma extractor. The third bag was empty after the first spin. We used a hose-closing device to separate the first bag, which contained erythrocytes, from the other bags. The first bag was destroyed afterwards, and the process was continued with the remaining two bags. In the second spin of centrifugation, the remaining two bags were placed on the centrifuge. Plasma was centrifuged at 3500 rpm (2587 x g) for 15 min promptly. PRP product with high-quality was collected in the second bag. Supernatant plasma that is platelet-poor was transferred into the third bag using a manual plasma extractor, resulting in 10-18 mL of high-quality PRP in the second bag. We used hose-closing device to separate and destroy the third bag with platelet-poor plasma. We have considered the European guidelines for the preparation, use, and quality assurance of blood components during the whole process. The products used for acquiring PRP are medical devices authorized for clinical use and trade by the responsible institution (PRPBAG) (7).

1 cc of PRP was added into separate pediatric blood culture bottles (Becton-Dickinson, USA) on days 0, 1, 2, 3, 4, and 5. These samples were sent to the microbiology laboratory and incubated for 5 days. After this incubation period, the blood culture bottles that did not give positive signals were reported as sterile. The bottles that gave positive signals were planned to be gram-stained immediately and cultured. For culturing, the samples were to be inoculated into four quadrants of 5% sheep blood agar (BectonDickinson, ABD), Eosin-Methylene Blue agar (BectonDickinson, ABD), and chocolate agar (BectonDickinson, ABD) plates by the dilution method using sterile standard inoculating loop. The agar plates were planned to be incubated in CO_2 incubator aerobically at 35±2 °C for 24-48 hours. In the case of bacterial growth, colonies were projected to be processed for further identification. Bacterial strain typing was to be performed with a VITEK MS MALDI-TOF (bioMérieux, USA) system and VITEK® 2 Compact (bioMérieux, Marcy l'Etoile, Fransa) automatized in accordance with the recommendations of the producer.

Our study was approved by the Bezmialem Vakıf University Local Ethics Committee (approval number: 5/27, date: 06.03.2019), and we acquired individual informed consent from all participants.

Statistical Analysis

Statistical analyses were planned to be performed with SPSS version 20.0 for Windows (SPSS Inc. Chicago, IL, USA). The number of volunteers to be included in this study was calculated by the department of statistics as 40 with a 95% confidence level and 80% power. We determined the final number of participants was 60.

Results

The minimum number of volunteers to be included in this study required for 95% confidence level and 80% power was determined by the statistics department as 40. However, we recruited 60 participants for increased statistical significance. We took 6 samples of PRP from each patient making 360 samples and added them into pediatric blood culture bottles (Becton-Dickinson, USA). The samples were incubated in BACTEC FX (Becton-Dickinson, USA) for 5 days. There was not any bacterial proliferation in any of 360 samples. Therefore, the processes planned for further bacterial identification as explained in methods were not needed.

Discussion

As commonly known, most of the systems that produce PRP are open tubes, and the product has to be used immediately. In this study, we wanted to test the safety of closed triple bag systems in terms of bacterial contamination and safety for 5 days, which is the standard usage time of platelets. Therefore, we added 360 samples from 60 subjects into pediatric blood culture bottles (Becton-Dickinson, USA). There was not any bacterial proliferation in any sample. Therefore, there was no need to conduct a statistical analyzes. These results agree with the findings of blood banking and apheresis systems in terms of sterility and terms of use (Hoots, 2001) (6).

Currently, PRP is used immediately after preparation. Our study demonstrates that PRP prepared with a closed triple blood bag system may be used for 5 days if agitated at room temperature. There was not any bacterial growth in any sample after 5 days (Table 1).

PRP is a treatment option with few side effects and is considered almost harmless. However, it has certain complications as any intervention that include infection. Therefore, the sterility of PRP is important for preventing infections (11). Dincer et al. (12) report a case of a 27-year-old male soccer player who is treated with PRP injections for grade 2 rupture in the gastrocnemius muscle. He developed an ulcer on the leg after being treated with PRP. This article demonstrates the importance of using a method of obtaining PRP scientifically proven to be safe from bacterial contamination.

Conclusion

The use of a standardized closed system, the long-term use of the product, and the standardization of the amount of platelets in the sample have brought a new dimension to the use of PRP, which will be a scientific basis for further clinical studies.

Table 1. Bacterial proliferation on the corresponding day

Patient number	The patient name	Day 0*	Day 1*	Day 2*	Day 3*	Day 4*	Day 5*
1	Ö.B.	None	None	None	None	None	None
2	E.İ.	None	None	None	None	None	None
3	Ö.G.	None	None	None	None	None	None
4	A.T.	None	None	None	None	None	None
5	N.B.	None	None	None	None	None	None
6	S.K.	None	None	None	None	None	None
7	S.A.	None	None	None	None	None	None
8	S.F.P.	None	None	None	None	None	None
9	S.K.	None	None	None	None	None	None
10	O.Ş.	None	None	None	None	None	None
11	S.D.	None	None	None	None	None	None
12	İ.E.	None	None	None	None	None	None
13	O.K.	None	None	None	None	None	None
14	İ.S.	None	None	None	None	None	None
15	S.E.	None	None	None	None	None	None
16	Ö.P.	None	None	None	None	None	None
16	D.Ç.	None	None	None	None	None	None
18	Ç.Ü.	None	None	None	None	None	None
19	H.A.	None	None	None	None	None	None
20	Z.K.	None	None	None	None	None	None
21	N.Ö.	None	None	None	None	None	None
22	Ç.G.	None	None	None	None	None	None
23	B.K.	None	None	None	None	None	None
24	F.G.	None	None	None	None	None	None
25	F.K.	None	None	None	None	None	None
26	S.A.	None	None	None	None	None	None
27	K.D.	None	None	None	None	None	None
28	M.D.	None	None	None	None	None	None
29	M.A.	None	None	None	None	None	None
30	E.Ö.	None	None	None	None	None	None
31	Z.D.	None	None	None	None	None	None
32	N.B.	None	None	None	None	None	None
33	T.P.	None	None	None	None	None	None
34	E.A.	None	None	None	None	None	None
35	U.S.	None	None	None	None	None	None
36	N.T.	None	None	None	None	None	None
37	D.Ş.	None	None	None	None	None	None
38	S.K.	None	None	None	None	None	None
39	Ş.V.	None	None	None	None	None	None
40	S.K.	None	None	None	None	None	None
41	Ö.F.T.	None	None	None	None	None	None
42	A.Ö.	None	None	None	None	None	None
43	B.K.	None	None	None	None	None	None
44	E.Ö.	None	None	None	None	None	None
45	K.S.	None	None	None	None	None	None
46	A.K.	None	None	None	None	None	None
47	B.P.	None	None	None	None	None	None
48	Y.T.	None	None	None	None	None	None
49	A.E.	None	None	None	None	None	None
50	S.G.	None	None	None	None	None	None
51	M.S.	None	None	None	None	None	None
52	S.S.	None	None	None	None	None	None
53	A.V.	None	None	None	None	None	None
54	E.V.	None	None	None	None	None	None
55	S.P.	None	None	None	None	None	None
56	F.Ş.	None	None	None	None	None	None
57	A.K.	None	None	None	None	None	None
58	R.B.	None	None	None	None	None	None
59	Ç.Ö.	None	None	None	None	None	None
60	B.B.	None	None	None	None	None	None

*Bacterial proliferation on corresponding day

Acknowledgment

We are thankful to our Blood Bank technician Ömer Gül and microbiology laboratory technicians of Ufuk BAYRAM for their important contributions for this study.

Ethics Committee Approval: Our study was approved by the Bezmialem Vakıf University Local Ethics Committee (approval number: 5/27, date: 06.03.2019).

Informed Consent: We acquired individual informed consent from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - B.S., N.H.K.; Concept - G.Ç., T.Ö.; Design - G.Ç., S.T.; Data Collection or Processing - G.Ç., B.S., S.T.; Analysis or Interpretation - G.Ç., K.Ş.; Literature Search - T.Ö., N.H.K., K.Ş., D.A.K.; Writing - G.Ç., D.A.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. Badran KW, Sand JP. Platelet-rich plasma for hair loss: review of methods and results. Facial Plast Surg Clin North Am 2018; 26: 469-85.
2. Everts P, Onishi K, Jayaram P, Lana JF, Mautner K. Platelet-Rich Plasma: New Performance Understandings and Therapeutic Considerations in 2020. Int J Mol Sci 2020; 21: 7794.
3. Marx RE. Platelet-rich plasma (PRP): what is PRP and what is not PRP? Implant Dent 2001; 10: 225-8.
4. Dhurat R, Sukesh M. Principles and Methods of Preparation of Platelet-Rich Plasma: A Review and Author's Perspective. J Cutan Aesthet Surg 2014; 7: 189-97.
5. Spicher G. Sterilization--the microbiology between claim and reality. Zentralbl Hyg Umweltmed 1993; 194: 223-35.
6. Hoots WK. History of plasma-product safety. Transfus Med Rev 2001; 15(2 Suppl 1): 3-10.
7. Sakudo A, Yagyu Y, Onodera T. Disinfection and Sterilization Using Plasma Technology: Fundamentals and Future Perspectives for Biological Applications. Int J Mol Sci 2019; 20: 5216.
8. Çetin G, Kyio NH, Turgut S, Özkan T. Optimisation of Centrifugal Speed for PRPBAG®: A Novel Multiple Bag System for Preparing Platelet-Rich Plasma. BezmialemScience; 2021; 9: 351-5.
9. Högman CF. Aspects of platelet storage. Transfus Sci 1994; 15: 351-5.
10. van der Meer PF, de Korte D. Platelet preservation: agitation and containers. Transfus Apher Sci 2011; 44: 297-304.
11. Martínez-Martínez A, Ruiz-Santiago F, García-Espinosa J. Platelet-rich plasma: myth or reality? Radiologia (Engl Ed) 2018; 60: 465-75.
12. Dincer D, Tanacan E, Cakir Akay GA, Atac GK, Evrin T. Localized infection and leg ulcer after platelet-rich plasma injection. Dermatol Ther 2020; 33: e13948.

İstanbul Med J 2023; 24(1): 26-31
DOI: 10.4274/imj.galenos.2022.58046

Second-trimester Uterine Artery Doppler Parameters but not Triple Test Analytes, May Predict Gestational Diabetes Mellitus

Filiz Yarşılıkal Güleroğlu[1], Murat Ekmez[2], Fırat Ekmez[3], Senem Karacabey[2], Ali Çetin[1]

[1]University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of Obstetrics and Gynecology, Division of Perinatology, İstanbul, Turkey
[2]University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey
[3]Private Clinic, Şırnak, Turkey

ABSTRACT

Introduction: Gestational diabetes mellitus (GDM) presents major health concerns due to its unfavorable impact on pregnancy outcomes and it has no established predictive test. The objective of this research is to determine out the value of triple test analytes and second-trimester uterine artery (UtA) Doppler analysis together in the estimation of GDM.

Methods: In this retrospective study, the clinical data of 87 women with GDM and 723 women with normal glucose tolerance (NGT) were compared. Maternal triple test analytes [human chorionic gonadotropin (hCG), estriol, and alpha-fetoprotein (AFP)] as multiples of the median values and second-trimester UtA Doppler examination for the presence or absence of notching, the left and right UtA pulsatility index (PI), and mean UtA PI was recorded for the NGT and GDM groups.

Results: In terms of maternal serum hCG, estriol, and AFP, the study groups were found as similar. The presence of UtA notching was considerably higher in the women who developed GDM. The mean UtA PI provided good diagnostic accuracy for predicting GDM with an optimal cut-off point of >1,195 with a sensitivity of 66.7% and a specificity of 77.3%. Multivariate logistic regression revealed that the presence of a history of GDM and bilateral UtA notching was found to be a predictor of the development of GDM.

Conclusion: Second-trimester UtA Doppler ultrasonography but not the triple test analytes has a place for predicting GDM in some pregnant populations, especially in women for whom GDM screening cannot be carried out because of the hesitancy of the oral glucose tolerance test.

Keywords: Doppler ultrasonography, gestational diabetes, predictive value of test, prenatal screening, uterine artery

Introduction

Diabetes mellitus (DM) detected after 24 weeks of pregnancy is referred to as gestational diabetes mellitus (GDM), assuming that overt diabetes was excluded before becoming pregnant or at the latter in the early stages of pregnancy (1). GDM affects around 7% of all pregnant women worldwide (2). GDM presents major health concerns due to its unfavorable short-term impact on pregnancy outcomes and its potential long-term implications for mother-baby dyads, including macrosomia, preeclampsia, and type 2 diabetes (3).

It is crucial to estimate the danger of GDM early in pregnancy to allow for initial measures to the prevent adverse outcomes of GDM. Therefore, the most effective means of GDM screening in early pregnancy is still being researched. Numerous models and algorithms have been created and evaluated to screen for disease processes that result in morbidity to develop novel modalities for prediction and screening (4-6). For this purpose, maternal clinical risk factors have historically been used. However, this method is constrained by the fact that these risk variables are often used in a binary manner that results in low sensitivity and specificity values (7). Using a representative model that combined maternal factors including ancestral background history of diabetes, history of GDM, parity, body mass index (BMI), ethnicity, mean arterial pressure, pregnancy-associated plasma protein A (PAPP-A), and uterine artery (UtA) pulsatility index (PI) in the first trimester, prediction of GDM provided a detection rate of 82.7% (8).

The analysis of the proteins human chorionic gonadotropin (hCG), alpha-fetoprotein (AFP), PAPP-A, inhibin-A, and estriol is used in the routine screening for maternal serum aneuploidy between 11 and 20 weeks of gestation (9). As placental function markers, these proteins have been linked to unfavorable pregnancy outcomes such as growth restriction, hypertension, miscarriage, premature delivery, and fetal demise (10).

There is still no consensus among the perinatal experts on the value of Doppler examination for the prediction and regulation of DM in pregnant

Address for Correspondence: Filiz Yarşılıkal Güleroğlu MD, University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of Obstetrics and Gynecology, Division of Perinatology, İstanbul, Turkey
Phone: +90 530 968 24 76 **E-mail:** filizyarsilikal@gmail.com **ORCID ID:** orcid.org/0000-0003-4577-3368

Cite this article as: Yarşılıkal Güleroğlu F, Ekmez M, Ekmez F, Karacabey S, Çetin A. Second-trimester Uterine Artery Doppler Parameters but not Triple Test Analytes, May Predict Gestational Diabetes Mellitus. İstanbul Med J 2023; 24(1): 26-31.

Received: 12.11.2022
Accepted: 29.12.2022

©Copyright 2023 by the University of Health Sciences Turkey, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.

women. Doppler examination, including the UtA, can provide valuable information about the status of fetal development and well-being. It may also help in the selection of the high-risk group of women with DM who need close follow-up and labor (11). In the current literature, there is no reliable data for the usage of UtA Doppler indices in the second-trimester for estimating GDM.

Considering that the assessment of results of the triple test and second-trimester UtA Doppler ultrasonography may be useful in the prediction of GDM, we analyzed their clinical values as well as other obstetric variables.

Methods

Study Population

This retrospective study was conducted after the affirmation of the Ethic Committee of University of Health Sciences Turkey, Haseki Training and Research Hospital (approval number: 116-2022, date: 08.06.2022) in accordance with the current Helsinki Declaration between June 2020 and December 2021 at the Perinatology Service of University of Health Sciences Turkey, Haseki Training and Research Hospital in İstanbul. This study was registered in the ClinicalTrials database (NCT05488197). Study participants were selected consecutively from pregnant women who had a detailed maternal-fetal ultrasound examination at 18-23 weeks of pregnancy, and all participants provided written informed consent. Inclusion criteria were having a maternal age of 18-42 years, a triple test at the 15-20 weeks of pregnancy, a Doppler ultrasound examination of uterine arteries at the 18-23 weeks of pregnancy, and a 75-g, 24-h oral glucose tolerance test (OGTT) at the 24-28 weeks of pregnancy. The exclusion criteria were hypertensive disorders of pregnancy, pregestational diabetes, placental and amniotic fluid abnormalities, family history of DM, fetal growth restriction, fetal congenital malformations, severe systemic disease, and multiple pregnancies.

GDM was identified during prenatal treatment when at least one of the three 75-g, 24-h OGTT threshold values met or exceeded in pregnant women who had performed the test: Fasting 92 mg/dL, 24-h 180 mg/dL, or 24-h 153 mg/dL at 24-28 weeks of gestation (12). Consequently, 810 pregnant women were evaluated as participants in the study and splitter with the following two groups in accordance with their diabetic statuses: pregnant women with normal glucose tolerance (NGT) as NGT group (n=723) and pregnant women with GDM as the GDM group (n=87).

Study Parameters

Maternal obstetric characteristics, ethnicity, pre-pregnancy BMI, gestational age at examination (week), the localization of the placenta on ultrasound (anterior, posterior, left side, right side), mode of delivery, gestational age at delivery (week), newborn birthweight, and fetal gender were reviewed retrospectively using electronic medical records.

Maternal serum glycated hemoglobin A1c (HbA1c) value and second-trimester triple test analytes (hCG, estriol, and AFP) as multiples of the median (MoM) values were also recorded. Additionally, from the records of detailed maternal-fetal ultrasound examination at the 18-23 weeks of pregnancy, Doppler ultrasound parameters of the uterine arteries were collected. All the ultrasound examinations had were performed using a high-definition ultrasonography machine with a 2.0-7.0 MHz convex probe by a professional perinatologist (FYG). Color Doppler was used to illustrate where the UtA crossed both external iliac arteries in the parauterine region of the lower uterine segment. Pulsed-wave Doppler was employed to obtain UtA waveforms at 30° insonation and 60 cm/s peak systolic velocity. Each side captured three identical waveforms consecutively. In addition to recording the presence or absence of notching, the left and right UtA PI values were obtained, and the mean UtA PI was calculated (13).

Statistical Analysis

The IBM SPSS v25 for Windows (IBM SPSS, Armonk, NY, USA) was used to conduct the descriptive and analytic evaluation of research parameters. The numerical variables as median with minimum and maximum, mean with standard deviation, or number with percentage were listed as accommodately. By analyzing the mundaneness of numerical variables using the Kolmogorov-Smirnov test, t and Mann-Whitney tests were used for their comparisons as appropriate. The chi-square test was performed to determine whether categorical data were significant. Initially, univariate logistic regression models were employed to determine the affiliation between the presence of GDM and each potential variable, including maternal age, gravidity, history of GDM, pre-pregnancy BMI, presence of male gender, birth weight, HBA1c, triple test analytes including hCG, estriol, and AFP, UtA notching (unilateral and bilateral), and UtA mean PI individually. A receiver-operating characteristic (ROC) curve was plotted with MedCalc version 15.0 for Windows (MedCalc Software, Ostend, Belgium) to evaluate the diagnostic performance of the mean UtA PI in GDM prediction. The determinants that were remarkable at the $p<0.10$ level in the univariate model were involved in the multivariate logistic regression model to identify factors independently associated with the existence of GDM. The regression coefficients and confidence intervals at 95% for the identified parameters substantially linked with GDM were calculated. If the p-value was lower than 0.05, the statistical results were significant.

Results

Table 1 presents the outline and clinical parameters for the NGT and GDM groups. In comparison to the NGT group, the GDM group's ratio of obstetric history was considerably higher ($p<0.05$). The median values of gestational age at delivery and neonatal birthweight were considerably higher in the NGT group compared with the GDM group [39 (28-41) vs 38 (31-41), respectively; $p<0.05$ and 3,230 (1,578-4,300) vs 2,980 (1,230-4,460), respectively; $p<0.05$]. Regarding the median values of gravidity, parity, maternal age, gestational age at examination, and pre-pregnancy BMI, no important distinction was found among the study groups. The rates of smoking status, ethnicity, types of conception and delivery, localization of the placenta on ultrasound, and male newborns were found to be similar among the study groups ($p>0.05$).

The maternal laboratory and ultrasonographic findings for the NGT and GDM groups are displayed in Table 2. In comparison to the NGT group, the HbA1c mean value was considerably greater in the GDM group ($p<0.05$). The mean values of hCG, estriol, and AFP did not significantly

Table 1. The selected baseline and clinical parameters of the NGT and GDM groups

	NGT (n=723)	GDM (n=87)	p-value
Maternal age (years)	29 (18-42)	30 (19-42)	0.055
Gravidity	2 (1-10)	2 (1-8)	0.312
Parity	1 (0-9)	1 (0-5)	0.511
Ethnicity, n (%)			
Native	706 (97.6%)	86 (98.9%)	0.516
Emigrant	17 (2.4%)	1 (1.1%)	
History of GDM, n (%)			
Yes	7 (1%)	8 (9.2%)	0.001
No	716 (99%)	79 (90.8%)	
Smoking, n (%)			
Yes	7 (1%)	2 (2.3%)	0.263
No	716 (99%)	85 (97.7%)	
Natural pregnancy, n (%)			
No	19 (2.6%)	0 (0%)	-
Yes	704 (97.4%)	87 (100%)	
Pre-pregnancy BMI (kg/m^2)	26.5 (17.6-41.4)	26.4 (20-35.8)	0.821
Gestational age at examination (weeks)	21 (18-23)	21 (18-23)	0.787
Placental localization			
Anterior	372 (51.5%)	48 (55.2%)	0.098
Posterior	334 (46.2%)	35 (40.2%)	
Left side	7 (1%)	0	
Right side	10 (1.4%)	4 (4.6%)	
Mode of delivery, n (%)			
No delivery	258 (35.6%)	32 (36.7%)	0.652
Vaginal	216 (29.9%)	22 (25.3%)	
Cesarean	249 (34.4%)	33 (37.9%)	
Gestational age at delivery (weeks)	39 (28-41)	38 (31-41)	0.002
Birthweight (g)	3,230 (1,578-4,300)	2,980 (1,230-4,460)	0.043
Fetal gender, n (%)			
Female	353 (48.8%)	43(49.4%)	0.706
Male	370 (51.2%)	44 (51.2%)	

NGT: Normal glucose tolerance, GDM: Gestational diabetes, BMI: Body mass index. A median with minimum and maximum values or counts with percentages were used to present the data

differ among the NGT and GDM groups ($p>0.05$). The ratios of the presence of unilateral and bilateral UtA notching were dramatically higher in the GDM group compared with the NGT group (35.6% vs 13.6%, respectively; $p<0.05$ and 27.6% vs 2.9%, respectively; $p<0.05$). The median value of mean UtA PI was significantly higher in the GDM group compared with the NGT group [1.3 (0.7-2.3) vs 1.0 (0.6-2.3), respectively; $p<0.05$]. The ROC curve analysis indicated that the mean UtA PI had good diagnostic accuracy for GDM (area under the curve=0.75, 95% confidence interval=0.721-0.782, $p<0.05$), with an optimal cut-off point of >1.195, resulting in a sensitivity of 66.7% and a specificity of 77.3% (Figure 1).

To further investigate potential GDM risk variables, univariate and multivariate logistic regression analyses were performed (Table 3). Univariate logistic regression analysis demonstrated that the selected parameters were related to GDM, including maternal age, history of GDM, HbA1c, UtA notching (unilateral and bilateral), and mean UtA PI ($p<0.05$). Furthermore, after regulating for all variables, multiple regression analyses of the examined parameters revealed a meaningful correlation, and among them, only a history of GDM and bilateral UtA notching provided meaningful associations with GDM. Consequently, the main study parameters, including mean UtA PI and triple test analytes, were not found among the independent predictors of GDM.

Discussion

In this study, the values of triple test analytes including hCG, estriol, and AFP, and second-trimester UtA Doppler ultrasonographic parameters including mean UtA PI and notching, were assessed to determine whether they could be used to predict the development of GDM. The baseline clinical determinants of the NGT and GDM groups were considerably similar, but the delivery of gestational age and neonatal

Table 2. Laboratory and ultrasonographic findings of the NGT and GDM groups

	NGT (n=723)	GDM (n=87)	p-value
HbA1c (%)	5.1±0.38	5.3±0.45	0.016
hCG (MoM)	1±0.5	0.9±0.5	0.482
Estriol (MoM)	0.9±0.4	0.9±0.4	0.889
AFP (MoM)	1.1±0.4	1.2±0.6	0.615
UtA notching			
No	604 (83.5%)	32 (36.8%)	0.001
Unilateral	98 (13.6%)	31 (35.6%)	
Bilateral	21 (2.9%)	24 (27.6%)	
Mean UtA PI	1.0 (0.6-2.3)	1.3 (0.7-2.3)	0.001

NGT: Normal glucose tolerance, GDM: Gestational diabetes mellitus, AFP: Alpha-fetoprotein, MoM: Multiples of the median, UtA: Uterine artery, PI: Pulsatility index. Data are shown as counts with percentages, median with minimum and maximum values, and mean with standard deviation

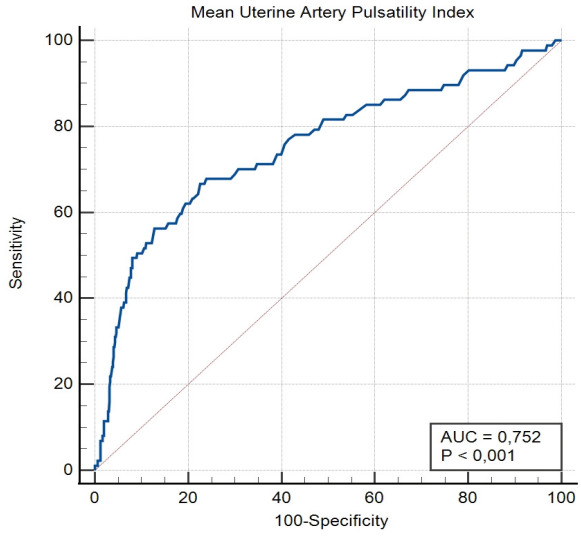


Figure 1. The ROC curve for the accuracy of the gestational diabetes mellitus (GDM) in participants. The overall predictive accuracy of the mean uterine artery pulsatility index for GDM was 0.75 (95% CI: 0.721-0.782, p<0.05), and the sensitivity and specificity were 66.7% and 77.3%, respectively

ROC: Receiver-operating characteristic, CI: Confidence interval

birthweight were higher in the NGT group. We thought that this might be regarding the close follow-up of pregnant women with GDM and their delivery before completing 39 weeks of gestation. The presence of UtA notching and serum HbA1c was considerably higher in the women who got GDM. In terms of maternal serum hCG, estriol, and AFP, the women who developed GDM have similarities with women who did not develop GDM. The mean UtA PI was higher in the women who developed GDM. Additionally, ROC curve analysis revealed that the mean UtA PI provided meaningful diagnostic accuracy for predicting GDM with an optimal cut-off point of >1,195 with a sensibility of 66.7% and a specificity of 77.3%. Univariate and multivariate logistic regression analyses showed that only clinical parameters including, the presence of a history of GDM and bilateral UtA notching, were found as a predictors of development of GDM but not our study parameters as a whole.

There have been concerns raised about screening for GDM after the 24th gestational week and diagnosing GDM in the last weeks of the second trimester due to the potential delay in achieving the favorable impact of pharmacological therapy, diet, and exercise on fetal development and maternal complications (14). Predicting gestational diabetes early allows for possible action to lower the risk of negative effects for the mother and fetus, since it may provide more time for measures that can reduce both GDM and its associated morbidities if patients at risk for GDM are identified early in the gestation among low-risk pregnancies. The diagnosis of GDM is frequently performed using OGTT techniques. However, these procedures may be more time-consuming, uncomfortable, and expensive in some populations. As a result, current investigations have focused on alternative predictive procedures.

In a recent study, Zhang et al. (15) performed a study on the estimation of GDM in the first-trimester. Maternal age, parity, BMI, serum lipid profile, blood pressure, and inflammatory parameters were evaluated as predictive factors. They found that women older than 35 and those with abnormal triglyceride values had 5.5% and 2.1 times, respectively, higher risk for GDM development. Zheng et al. (16) developed a model unifying maternal age, BMI, fasting blood glucose, and triglyceride levels between 8 and 20 weeks of pregnancy to foresee the risk of GDM. They concluded that their prediction model had a considerably good predictive value.

Several studies were performed in the first and early second trimesters to predict GDM by biomarkers such as fetuin-A, high-sensitivity C-reactive protein (17), adiponectin (18), sex hormone -binding globulin (19), placental protein 13, pentraxin 3, soluble fms-like tyrosine kinase-1, myostatin, and follistatin (20). All these studies concluded that developing prediction models to aid in the development of highly sensitive and specific testing should be the focus of future research in the first and early second trimesters.

To predict the likelihood of GDM in nulliparous women early in pregnancy, Snyder et al. (21) assessed the clinical efficacy of first and second-trimester prenatal screening biomarkers. GDM was related to lower first-trimester PAPP-A levels and higher second-trimester estriol and inhibin-A levels. The researchers concluded that PAPP-A, estriol, and inhibin-A had limited clinical usefulness for predicting the risk of GDM in nulliparous women. Sperling et al. (9) similarly used second-trimester maternal serum analytes to predict GDM. They found that rising levels of maternal AFP, hCG, and estriol in the second trimester were linked

Table 3. Logistic regression analysis of selected factors associated with the presence of GDM

	Univariate				Multivariate			
	p-value	OR	95% CI		p-value	OR	95% CI	
Maternal age (years)	0.048	1.04	1.00	1.09	0.885	1.01	0.94	1.08
Gravidity	0.244	1.09	0.94	1.26	-	-	-	-
History of GDM	<0.001	11.80	4.28	32.57	0.004	12.00	2.26	63.58
Pre-pregnancy BMI (kg/m^2)	0.742	0.98	0.87	1.11	-	-	-	-
Fetal gender, male	0.916	0.98	0.63	1.52	-	-	-	-
Birthweight (g)	0.129	1.00	1.00	1.00	-	-	-	-
HbA1c (%)	0.019	2.92	1.20	7.14	0.076	2.54	0.91	7.10
hCG (MoM)	0.474	0.56	0.12	2.71	-	-	-	-
Estriol (MoM)	0.886	0.87	0.14	5.50	-	-	-	-
AFP (MoM)	0.607	1.52	0.31	7.50	-	-	-	-
UtA notching	<0.001	-	-	-	0.004	-	-	-
Unilateral	<0.001	5.97	3.49	10.23	0.473	1.54	0.48	4.94
Bilateral	<0.001	21.57	10.87	42.80	0.011	5.70	1.48	21.98
Mean UtA PI	<0.001	20.29	9.70	42.48	0.077	4.67	0.84	25.86

GDM: Gestational diabetes mellitus, BMI: Body mass index, HbA1c: Glycated hemoglobin A1c, AFP: Alpha-fetoprotein, MoM: Multiples of the median, UtA: Uterine artery, PI: Pulsatility index, CI: Confidence interval, OR: Odds ratio

with a lower risk of GDM. However, they did not significantly improve the predictive model when combined with the clinical risk factors of age, BMI, and race. In contrast to these investigations, we were unable to detect a significant difference in the second-trimester serum analytes of women who would later develop GDM or not.

Overall, the results of the aforementioned studies focused on the clinical and laboratory parameters that were obtained during routine clinical care but that were not directly related to the development of GDM. Their predictive performance was found to be moderately adequate for routine clinical care. This subject seems to require studies examining the clinical parameters providing higher success rates for GDM prediction. Within this perspective, the current study examined for the first time the combination of parameters of second-trimester triple test analytes and second-trimester UtA PI.

Doppler ultrasonography, including UtA in the first (22) and second trimesters (23), is commonly used to predict unfavorable pregnancy outcomes such as premature birth, preeclampsia, and intrauterine growth restriction. Previously, researchers noted that in pregnant women with current or previous GDM, the findings of arterial stiffness and endothelial dysfunction were found to have increased (24,25). We thought that this condition may contribute to the clinical presentation of GDM earlier than its overt appearance in pregnant women who are candidates for developing GDM. In a study that involved the first trimester of pregnancy, Savvidou et al. (25) found that while there was no statistically significant difference in UtA PI MoM among women with and without GDM, there was an increased UtA PI in women with GDM who developed pre-eclampsia. Kim et al. (26) performed research to determine the relationship between maternal obesity and the UtA PI in the third trimester, as well as to predict the value of the UtA PI for the occurrence of adverse outcomes. They showed that obese women with increased UtA PI had an increased risk of GDM occurrence. The current study, however, was distinctive in that it examined the impact of mean UtA PI on the estimation of GDM in the second trimester. Our findings revealed that higher mean UtA PI values were linked to a higher risk of GDM.

Study Limitations

As a limitation of this study, no inclusion of placental laterality in the grouping of women with NGT and GDM can be considered a confounding factor that can reduce the value of the results of UtA PI measurements. Nevertheless, the fact that the comparison of the rate of placental localization type provided no difference between the women with or without GDM supports no meaningful influence of placental localization on the UtA PI values. UtA notching has a relationship with the development of pre-eclampsia, and this study had an exclusion criterium of hypertensive diseases of pregnancy. In further studies, with the inclusion of pregnant women with hypertensive diseases of pregnancy, the value of early second-trimester Doppler analysis for predicting development of GDM can be clarified.

Conclusion

In conclusion, our findings support the importance of second-trimester UtA Doppler ultrasonography but not the triple test analytes for predicting GDM. The UtA Doppler analysis may be an important contributor to the protocol of perinatal follow-up in women in whom GDM screening cannot be carried out because of the hesitancy of mothers about OGTT. addition, although there are first-trimester candidate parameters for predicting GDM, in some antenatal care settings, clinicians cannot have predictors obtained by early tests.

Ethics Committee Approval: This retrospective study was conducted after the affirmation of the Ethic Committee of University of Health Sciences Turkey, Haseki Training and Research Hospital (approval number: 116-2022, date: 08.06.2022).

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept - F.Y.G., F.E., A.Ç.; Design - F.Y.G., F.E., S.K., A.Ç.; Data Collection or Processing - F.Y.G., M.E., S.K., A.Ç.; Analysis or Interpretation - F.Y.G., M.E., S.K., A.Ç.; Literature Search - F.Y.G., M.E., F.E., S.K.; Writing - F.Y.G., A.Ç.

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. Minschart C, Beunen K, Benhalima K. An update on screening strategies for gestational diabetes mellitus: a narrative review. Diabetes Metab Syndr Obes 2021; 14: 3047-76.
2. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2011; 34(Suppl 1): S62-9.
3. Damm P, Houshmand-Oeregaard A, Kelstrup L, Lauenborg J, Mathiesen ER, Clausen TD. Gestational diabetes mellitus and long-term consequences for mother and offspring: a view from Denmark. Diabetologia 2016; 59: 1396-9.
4. Naser W, Adam I, Rayis DA, Ahmed MA, Hamdan HZ. Serum magnesium and high-sensitivity C-reactive protein as a predictor for gestational diabetes mellitus in Sudanese pregnant women. BMC Pregnancy Childbirth 2019; 19: 301.
5. Kang M, Zhang H, Zhang J, Huang K, Zhao J, Hu J, et al. A Novel Nomogram for Predicting Gestational Diabetes Mellitus During Early Pregnancy. Front Endocrinol (Lausanne) 2021; 12: 779210.
6. Wang J, Lv B, Chen X, Pan Y, Chen K, Zhang Y, et al. An early model to predict the risk of gestational diabetes mellitus in the absence of blood examination indexes: application in primary health care centres. BMC Pregnancy Childbirth 2021; 21: 814.
7. Naylor CD, Sermer M, Chen E, Farine D. Selective screening for gestational diabetes mellitus. Toronto Trihospital Gestational Diabetes Project Investigators. N Engl J Med 1997; 337: 1591-6.
8. Sweeting AN, Wong J, Appelblom H, Ross GP, Kouru H, Williams PF, et al. A first trimester prediction model for gestational diabetes utilizing aneuploidy and pre-eclampsia screening markers. J Matern Neonatal Med 2018; 31: 2122-30.
9. Sperling MM, Towner D, Davis J, Yamasato K. Second trimester prediction of gestational diabetes: maternal analytes as an additional screening tool. J Perinat Med 2022; 50: 63-7.
10. Yaron Y, Cherry M, Kramer RL, O'Brien JE, Hallak M, Johnson MP, et al. Second-trimester maternal serum marker screening: maternal serum alpha-fetoprotein, beta-human chorionic gonadotropin, estriol, and their various combinations as predictors of pregnancy outcome. Am J Obstet Gynecol 1999; 181: 968-74.
11. Pietryga M, Brazert J, Wender-Ozegowska E, Biczysko R, Dubiel M, Gudmundsson S. Abnormal uterine Doppler is related to vasculopathy in pregestational diabetes mellitus. Circulation 2005; 112: 2496-500.
12. Coustan DR, Lowe LP, Metzger BE, Dyer AR. International Association of Diabetes and Pregnancy Study Groups. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: paving the way for new diagnostic criteria for gestational diabetes mellitus. Am J Obstet Gynecol 2010; 202: 654.e1-6.
13. Sotiriadis A, Hernandez-Andrade E, da Silva Costa F, Ghi T, Glanc P, Khalil A, et al; ISUOG CSC Pre-eclampsia Task Force. ISUOG Practice Guidelines: role of ultrasound in screening for and follow-up of pre-eclampsia. Ultrasound Obstet Gynecol 2019; 53: 7-22.
14. Kumru P, Arisoy R, Erdogdu E, Demirci O, Kavrut M, Ardıc C, et al. Prediction of gestational diabetes mellitus at first trimester in low-risk pregnancies. Taiwan J Obstet Gynecol 2016; 55: 815-20.
15. Zhang X, Zhao X, Huo L, Yuan N, Sun J, Du J, et al. Risk prediction model of gestational diabetes mellitus based on nomogram in a Chinese population cohort study. Sci Rep 2020; 10: 21223.
16. Zheng T, Ye W, Wang X, Li X, Zhang J, Little J, et al. A simple model to predict risk of gestational diabetes mellitus from 8 to 20 weeks of gestation in Chinese women. BMC Pregnancy Childbirth 2019; 19: 252.
17. Kansu-Celik H, Ozgu-Erdinc AS, Kisa B, Findik RB, Yilmaz C, Tasci Y. Prediction of gestational diabetes mellitus in the first trimester: comparison of maternal fetuin-A, N-terminal proatrial natriuretic peptide, high-sensitivity C-reactive protein, and fasting glucose levels. Arch Endocrinol Metab 2019; 63: 121-7.
18. Kennelly MA, McAuliffe FM. Prediction and prevention of Gestational Diabetes: an update of recent literature. Eur J Obstet Gynecol Reprod Biol 2016; 202: 92-8.
19. Maged AM, Moety GA, Mostafa WA, Hamed DA. Comparative study between different biomarkers for early prediction of gestational diabetes mellitus. J Matern Neonatal Med 2014; 27: 1108-12.
20. Zhao B, Han X, Meng Q, Luo Q. Early second trimester maternal serum markers in the prediction of gestational diabetes mellitus. J Diabetes Investig 2018; 9: 967-74.
21. Snyder BM, Baer RJ, Oltman SP, Robinson JG, Breheny PJ, Saftlas AF, et al. Early pregnancy prediction of gestational diabetes mellitus risk using prenatal screening biomarkers in nulliparous women. Diabetes Res Clin Pract 2020; 163: 108139.
22. Poon LC, Shennan A, Hyett JA, Kapur A, Hadar E, Divakar H, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention. Int J Gynaecol Obstet 2019; 145(Suppl 1): 1-33.
23. Stoenescu M, Serbanescu MS, Dijmarescu AL, Manolea MM, Novac L, Tudor A, et al. Doppler Uterine Artery Ultrasound in the Second Trimester of Pregnancy to Predict Adverse Pregnancy Outcomes. Curr Heal Sci J 2021; 47: 101-6.
24. Anastasiou E, Lekakis JP, Alevizaki M, Papamichael CM, Megas J, Souvatzoglou A, et al. Impaired endothelium-dependent vasodilatation in women with previous gestational diabetes. Diabetes Care 1998; 21: 2111-5.
25. Savvidou MD, Syngelaki A, Balakitsas N, Panaiotova E, Nicolaides KH. First-trimester uterine artery Doppler examination in pregnancies complicated by gestational diabetes mellitus with or without pre-eclampsia. Ultrasound Obstet Gynecol 2013; 42: 525-9.
26. Kim YH, Lee HJ, Shin JE, Lee Y, Shin JC, Park TC, et al. The predictive value of the uterine artery pulsatility index during the early third trimester for the occurrence of adverse pregnancy outcomes depending on the maternal obesity. Obes Res Clin Pract 2015; 9: 374-81.

İstanbul Med J 2023; 24(1): 32-5
DOI: 10.4274/imj.galenos.2023.92972

Evaluation of Subclavian Central Venous Port Catheters Placed by Anesthesiologists: Single-Center Experience

Abdurrahman Tünay[1], Alican Açıkgöz[1], Mehmet Toptaş[1], Mensure Yılmaz Çakırgöz[2], Özlem Ateşal[1], Hasan Ökmen[3]

[1]University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey
[2]İzmir Katip Celebi University, Atatürk Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey
[3]University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of General Surgery, İstanbul, Turkey

ABSTRACT

Introduction: A Central Venous Port Catheter (CVPC) is a key part of the chemotherapy and palliative care of cancer patients. CVPC is placed by surgical clinics, oncologists, and anesthesia and reanimation specialists. In our study, we aimed to examine the complications related to subclavian CVPCs inserted by anesthesiology and reanimation specialists and to share the experiences obtained.

Methods: The study included 1,805 cancer patients who underwent CVPC in the anesthesiology and reanimation clinic of the University of Health Sciences Turkey, İstanbul Training and Research Hospital. The medical records of the patients were reviewed retrospectively. The data obtained were analyzed and the mean age, gender distribution, and distribution of patients according to diagnoses, count, and percentages of early and late complications were calculated.

Results: The records of 1,805 patients who underwent subclavian CVPC placement with the percutaneous method were reviewed retrospectively. Early complications occurred in 6 of our patients. Of these six, 3 patients had pneumothorax, (acute atrial fibrillation attack due to intervention in 1 patient, air embolism in 1, and cerebrovascular event complications in 1), whereas vessel perforation and hematoma were not seen in any patient. Considering the late complications, local port infection, port thrombosis, and skin necrosis were observed in 28, 50, and 26 patients, respectively. However, neither port dislocation or rupture, or catheter-related blood vessel infection, or pinch-off syndrome and nor reservoir access wounds were detected in the patients.

Conclusion: Our data analysis showed that the complication rate in our study was similar or better than many other studies compared with the data of other clinics in the literature.

Keywords: Subclavian central venous port catheter, oncology patients, anesthesiologists

Introduction

Central venous port catheters (CVPC) are used during the treatment of cancer patients, for taking samples for blood tests, surgical interventions, administering chemotherapeutic agents, and meeting other intravenous needs. CVPC are in high demand due to being the most comfortable method for long-term and intermittent chemotherapy for people receiving cancer treatment, being more comfortable for selfcare of the patient, not causing cosmetic and mental problems as it is not visible from the outside, the occurrence of less thrombosis and infection, no need for dressing, not disrupting the daily needs of the person, and the low maintenance requirements (1,2). Pneumothorax, hematoma, vessel perforation, acute atrial fibrillation attack, air embolism, and cerebrovascular event (CVE) can arise as early complications, while late complications include local port infection, port thrombosis, skin necrosis, port dislocation or rupture, catheter-related blood vessel infection, pinch- off syndrome, and reservoir access wound (3).

Although the right internal jugular vein is mostly preferred in the intravenous ports, the right subclavian vein, left subclavian, femoral vein, and axillary vein can also be used. As can be seen in the literature, CVPC are inserted by anesthesiologists, oncologists, radiologists, and surgeons (4,5). In this study, we aimed to retrospectively analyze the CVPC placed with the subclavian technique by experienced anesthesia and reanimation team and to share our five-year results.

Address for Correspondence: Abdurrahman Tünay MD, University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey
Phone: +90 212 459 63 39 **E-mail:** atunay.02@hotmail.com **ORCID ID:** orcid.org/0000-0001-7118-9312

Cite this article as: Tünay A, Açıkgöz A, Toptaş M, Yılmaz Çakırgöz M, Ateşal Ö, Ökmen H. Evaluation of Subclavian Central Venous Port Catheters Placed by Anesthesiologists: Single-Center Experience. İstanbul Med J 2023; 24(1): 32-5.

Received: 22.12.2022
Accepted: 05.01.2023

©Copyright 2023 by the University of Health Sciences Turkey, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.

Methods

After obtaining approval from the hospital ethics committee (approval number: 231, date: 22.07.2022), 1,805 cancer patients who underwent subclavian CVPC by University of Health Sciences Turkey, İstanbul Training and Research Hospital anesthesiology and reanimation specialists were included in the study. The medical records of the patients were analyzed retrospectively, and the data obtained were analyzed and the average age, gender distribution, the distribution of patients by age groups, the distribution of patients according to diagnoses, count, and percentages of early and late complications were calculated.

The patients were evaluated before the procedure using coagulation tests, PA chest radiography, and hemogram tests. Patients signed consent was obtained after informing the patients and/or their relatives about the procedure. All our port catheter interventions were performed in the operating room under local anesthesia, and with ultrasound (USG) monitoring of the patients. Antibiotics for prophylactic purposes were not routinely administered. All procedures were performed in the operating room by performing electrocardiography, peripheral oxygen saturation (SpO_2), and noninvasive blood pressure measurements. While the venous port catheter was being placed, the subclavian area was cleaned with povidone iodine and covered with sterile drapes. Local anesthesia was applied to the puncture site and reservoir pocket in all patients. After the subclavian vein puncture, a guide wire was sent through the needle. The port pocket was made - after an incision of approximately 2.5-3 cm subcutaneously in accordance with a reservoir by blunt dissection. It is tunneled from the puncture site in the subclavian area to the port pocket direction. The catheter was connected and irrigation was performed with heparinized fluid. After the port reservoir was identified, the skin was closed. Verification of the port catheter location and the presence of hemothorax or pneumothorax were checked by taking the PA chest X-ray in all patients. Age, gender, diagnosis of primary disease, early complications (hematoma, air embolism, pneumothorax, vessel perforation, acute atrial fibrillation, CVE) and late complications (local port infection, port thrombosis, skin necrosis, port dislocation or rupture, catheter-related blood vessel infection, port entrapment (pinch-off syndrome, and reservoir access wound) were recorded. Average age, gender distribution, the distribution of patients according to age groups, the distribution of patients according to cancer diagnosis, and number, and percentage of early and late complications were calculated.

Statistical Analysis

Mean, standard deviation, median lowest, highest, frequency, and ratio values were used in the descriptive statistics of the data. SPSS 28.0 program was used in the analysis.

Results

Out of the 1,805 patients who underwent subclavian CVPC by University of Health Sciences Turkey, İstanbul Training and Research Hospital anesthesiology and reanimation physicians, 51.5% were female and 48.5% were male. The mean age of the patients was 57.7. The highest number of patients, 590, was in the 55-64 age group. The youngest patient was 19 and the oldest patient was 95 years old (Table 1).

Among the early complications, pneumothorax, acute atrial fibrillation, air embolism and CVE were observed in 3, 1, 1, and 1 patient, respectively, whereas vascular perforation and hematoma were not observed. In our study, venous ports were most frequently inserted in colorectal cancers with a rate of 29%. Among the late complications, 28 patients had local port infection, 50 patients had port thrombosis, and 26 patients had skin necrosis while, port dislocation or rupture, catheter-related blood vessel infection, pinch-off syndrome, and reservoir access wound were not detected in the patients (Table 2).

Discussions

CVPCs, which have been in use since the first half of the 1980s, have been frequently used for chemotherapy, blood transfusion, nutritional purposes, antibiotic therapies and all kinds of intravenous treatments

Table 1. The demographic features and age distribution of the patients

		Min.-max.	Median		Average ± SD/(n,%)	
Gender	Women	-	-		929 (51.5%)	
	Man	-	-		876 (48.5%)	
Age	-	19.0-95.0	59.2		57.7±12.1	
Man-age	-	19.0-87.0	61.4		60.2±10.9	
Women age	-	21.0-95.0	56.0		55.1±12.7	
	Total		**Man**		**Women**	
	n	**%**	**n**	**%**	**n**	**%**
19-24 age	21	1.2%	7	0.8%	14	1.6%
25-34 age	58	3.2%	16	1.8%	42	4.8%
35-44 age	195	10.8%	57	6.5%	138	15.8%
45-54 age	401	22.2%	181	20.7%	220	25.1%
55-64 age	590	32.7%	336	38.4%	254	29.0%
65-74 age	448	24.8%	279	31.8%	169	19.3%
≥75 age	92	5.1%	53	6.1%	39	4.5%

Min.: Minimum, max.: Maximum, SD: Standard deviation

Table 2. The distribution of cancer types and early/late complications

	n	%
Early complications		
Not-observed	1799	99.7%
Observed	6	0.3%
Pneumothorax	3	0.16%
Acute atrial fibrillation	1	0.05%
Air embolism	1	0.05%
Cerebrovascular event	1	0.05%
Vascular perforation	0	0.0%
Hematoma	0	0.0%
Late complications		
Not-observed	1701	94.2%
Observed	104	5.8%
Local port infection	28	1.6%
Port thrombosis	50	2.8%
Skin necrosis	26	1.4%
Port dislocation/rupture	0	0.0%
Catheter related blood vessel infection	0	0.0%
Pinch-off syndrome	0	0.0%
Reservoir access wound	0	0.0%
Distribution of cancer types		
Breast cancer	411	22.8%
Colorectal cancer	523	29.0%
GIS (oral, nasopharynx, esophagus, stomach) cancer	325	18.0%
Liver, biliary tracts, pancreas cancer	194	10.7%
Liver cancer	172	9.5%
Urogenital cancer (uterus, cervix, prostate, bladder)	47	2.6%
Hematological cancer	32	1.8%
Other cancers	101	5.6%

GIS: Geographic Information System

and blood tests, and hence their complications have been a subject of research.

In Di Carlo et al.'s (6) study, while the cephalic vein was preferred in the open surgery method, it was seen that the subclavian vein was used more in the percutaneous method. The rate of early complications was found to be higher in those who were implanted by the percutaneous method compared with those implanted by the surgical method (4.5% in the surgical method, while 0.9% in the percutaneous method) (6). In our study, the subclavian vein was similarly used, and early complications were found at a lower rate of 0.3%.

While the frequency of pneumothorax was 0.5-6% in the literature (7,8), the frequency of pneumothorax was 0.16% in our study, less frequent than in the literature. We believe that this is due to the use of USG while implanting the CVPC.

The rate of acute AF caused by CVPC in the literature was between 0.1 and 0.9% (9), and similarly it was seen in 1 patient in our study, yielding a rate of 0.05, consistent with the literature.

Additionally, among other early complications, air embolism was detected in 1 patient and CVE was detected in 1 patient.

With regards to the late complications, local port pocket infection in our study was 1.6%, which is consistent with the literature (0.3-4.4%) (10).

Cancer patients have a higher risk of venous thrombosis, and catheterization further increases this risk. While the rate of catheter-related thrombosis was 12-64% (11,12) in the literature, this rate was much lower (2.8%) in our study than in the literature. The reason for the low rate of thrombosis in our clinic may be the catheter controls performed at regular intervals.

Skin necrosis may occur if there is a technical error while applying the port or if the appropriate port is not used in patients with low subcutaneous fat tissue. While skin necrosis was detected at a rate of approximately 0-1 (13) in the literature, this rate was found to be 1.4% in our study.

In our study, port dislocation/rupture, catheter-related blood vessel infection, Pinch-off syndrome, and reservoir access wounds were not observed. We believe that this is due the fact that all procedures are performed under sterile conditions in the operating room environment and regular checks were performed.

Study Limitations

The limitation of this study is to investigate the only subclavian venous port catheterization complications.

Conclusion

CVPC is a very comfortable and safe method preferred for long-term venous access due to their ease of use and cosmetically non-disturbance to the patients. CVPC, applied by surgical clinics, radiologists, and oncologists, is a method that is safely applied with a USG also by anesthesiologists with experience in interventional procedures.

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 231, date: 22.07.2022).

Informed Consent: Patients signed consent was obtained after informing the patients and/or their relatives about the procedure.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - A.T., A.A.; Concept - A.T., M.T., M.Y.Ç.; Design - A.T., A.A.; Data Collection or Processing - A.T., A.A., M.T., M.Y.Ç., Ö.A., H.Ö.; Analysis or Interpretation - A.T., M.T., M.Y.Ç., Ö.A., H.Ö.; Literature Search - A.T., A.A., M.T., M.Y.Ç., Ö.A., H.Ö.; Writing - A.T.

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. Biffi R, De Braud F, Orsi F, Pozzi S, Arnaldi P, Goldhirsch A, et al. A randomized, prospective trial of central venous ports connected to standard open-ended or Groshong catheters in adult oncology patients. Cancer 2001; 92: 1204-12.
2. Stanislav GV, Fitzgibbons RJ, Bailey RT, Mailliard JA, Johnson PS, Feole JB. Reliability of implantable central venous access devices in patients with cancer. Arch Surg 1987; 122: 1280-3.
3. Di Carlo I, Cordio S, La Greca G, Privitera G, Russello D, Puleo S, et al. Totally implantable venous access devices implanted surgically: a retrospective study on early and late complications. Arch Surg 2001; 136: 1050-3.
4. Sticca RP, Dewing BD, Harris JD. Outcomes of surgical and radiologic placed implantable central venous access ports. Am J Surg 2009; 198: 829-33.
5. Ozdemir NY, Abalı H, Oksüzoğlu B, Budakoğlu B, Akmangit I, Zengin N. It appears to be safe to start chemotherapy on the day of implantation through subcutaneous venous port catheters in inpatient setting. Support Care Cancer 2009; 17: 399-403.
6. Di Carlo I, Barbagallo F, Toro A, Sofia M, Lombardo R, Cordio S. External jugular vein cutdown approach, as a useful alternative, supports the choice of the cephalic vein for totally implantable access device placement. Ann Surg Oncol 2005; 12: 570-3.
7. Grannan KJ, Taylor PH. Early and late complications of totally implantable venous access devices. J Surg Oncol 1990; 44: 52-4.
8. Cil BE, Canyiğit M, Peynircioğlu B, Hazirolan T, Carkaci S, Cekirge S, et al. Subcutaneous venous port implantation in adult patients: a single center experience. Diagn Interv Radiol 2006; 12: 93-8.
9. Biffi R, de Braud F, Orsi F, Pozzi S, Mauri S, Goldhirsch A, et al. Totally implantable central venous access ports for long-term chemotherapy. A prospective study analyzing complications and costs of 333 devices with a minimum follow-up of 180 days. Ann Oncol 1998; 9: 767-73.
10. Schwarz RE, Groeger JS, Coit DG. Subcutaneously implanted central venous access devices in cancer patients: a prospective analysis. Cancer 1997; 79: 1635-40.
11. Champault G. Completely implantable catheters for anticancer chemotherapy. A French experience of 325 cases. J Chir (Paris) 1985; 122: 269-72.
12. Morris SL, Jaques PF, Mauro MA. Radiology-assisted placement of implantable subcutaneous infusion ports for long-term Venous access. Radiology 1992; 184: 149-51.
13. Dariushnia SR, Wallace MJ, Siddiqi NH, Towbin RB, Wojak JC, Kundu S, et al; Society of Interventional Radiology Standards of Practice Committee. Quality improvement guidelines for central venous access. J Vasc Interv Radiol 2010; 21: 976-81.

İstanbul Med J 2023; 24(1): 36-9
DOI: 10.4274/imj.galenos.2023.60251

Gait Analysis in Idiopathic Normal Pressure Hydrocephalus: A Single Centre Experience

Özgür Öztop-Çakmak[1,2], Kardelen Akar[2], Hussein Youssef[2], Atilla Deniz Kahraman[3], Esra Özkan[2], Mustafa Yavuz Samancı[4], Atay Vural[1,2]

[1]Koç University Faculty of Medicine, Department of Neurology, İstanbul, Turkey
[2]Koç University Research Center for Translational Medicine, İstanbul, Turkey
[3]Koç University Faculty of Medicine, İstanbul, Turkey
[4]Koç University Faculty of Medicine, Department of Neurosurgery, İstanbul, Turkey

ABSTRACT

Introduction: Gait impairment is the earliest symptom of idiopathic normal pressure hydrocephalus (iNPH). This study objectively investigates gait changes using Ambulatory Parkinson's Disease Monitoring inertial sensors after cerebrospinal fluid withdrawal in patients with iNPH.

Methods: Two-minute walkway tests were performed in eleven patients with iNPH before and after the spinal tap test (TT) or ventriculoperitoneal shunt surgery. Gait parameters were analyzed and compared for each patient individually before and after the intervention.

Results: Eleven patients with iNPH (six female, five male) with a median age of 76 (68-76) were included in the study. After the spinal TT or ventriculoperitoneal shunt surgery, patients exhibited increased cadence (steps per minute) and decreased step and stride time (p=0.008, for all).

Conclusion: APDM inertial sensors may provide a quantitative gait assessment in patients with iNPH.

Keywords: Normal pressure hydrocephalus, gait analysis, APDM

Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a syndrome characterized by a triad of progressive gait impairment, urinary incontinence, and cognitive decline with enlarged ventricles and normal cerebrospinal fluid (CSF) pressure (1). Gait impairment appears in the early stages leading to frequent falls and increased morbidity in the elderly (2). Installing a ventricle-peritoneal (VP) shunt to drain the CSF from the cerebral ventricles to the peritoneum is the most widely used treatment for NPH (3). After the initial improvement with VP shunt implants, symptoms may return despite evidence that the shunt is functioning (4). Patient selection for VPS treatment is critical, although clinical predictors for a favorable outcome are understudied and poorly recognized. The CSF tap test (TT) is a diagnostic test in which 30-50 mL CSF is removed by lumbar puncture, which may predict the iNPH patients' response to VP shunt (6). The assessment of the TT is based on clinical observation of the gait before and after the intervention. Instrumented gait analysis may objectively analyze gait and balance improvements and reveal features not commonly available through clinical observations or assessments (7). The Ambulatory Parkinson's Disease Monitoring (APDM) inertial sensor (Opals and Mobility Lab) is a wearable system that includes three-axis accelerometers, gyroscopes, and a magnetometer that can provide objective gait analysis (8,9). This study investigates the gait parameters of patients with iNPH using APDM inertial sensors before and after an intervention, such as a spinal TT or VP shunt.

Methods

Eleven patients who followed up with an iNPH diagnosis in the Neurology and Neurosurgery Departments at Koç University Hospital were included. After giving their informed consent, all patients were invited to the Motion Analysis Laboratory. They performed 2-Minute Walkway Test (2 MWT) with an APDM Mobility Lab System (APDM Inc., Portland, OR, USA). Participants wore three OPAL sensors on their feet and lumbar area to

Address for Correspondence: Özgür Öztop-Çakmak MD, Koç University Faculty of Medicine, Department of Neurology, İstanbul, Turkey
Phone: +90 535 868 36 73 **E-mail:** ooztop@ku.edu.tr **ORCID ID:** orcid.org/0000-0003-3413-0332

Cite this article as: Öztop-Çakmak Ö, Akar K, Youssef H, Kahraman AD, Özkan E, Samancı MY, Vural A. Gait Analysis in Idiopathic Normal Pressure Hydrocephalus: A Single Centre Experience. İstanbul Med J 2023; 24(1): 36-9.

Received: 20.12.2022
Accepted: 05.01.2023

©Copyright 2023 by the University of Health Sciences Turkey, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.

assess spatiotemporal parameters, trunk angles, turning angles, and velocity during the gait task. Patients performed 2 MWT on a 10-meter back-and-forth walkway at an average speed. Participants repeated the procedure 6 h after the spinal tap and one month after VP shunt surgery. Gait parameters were documented according to the PDM Motion Lab Guidelines, and pre and postinterventional data were compared.

Statistical Analysis

Continuous variables were presented as median (interquartile range), and categorical variables as numbers and percentages. Statical analyses were performed on gait parameters before and after the interventions using Graphpad Prism software 8.4.3 (GraphPad Software Inc., La Jolla, CA, USA). Normality assumptions were performed with Anderson-Darling and D'Agostino & Pearson tests. The paired t-test and Wilcoxon tests were used to determine the difference between the dependent gait data.

Results

Eleven patients with iNPH (six female, five male) with a median age of 76 (68-76) were included in the study. The demographic and clinical features of the patients are shown in Table 1. Three patients could not walk without support before the intervention, so the pre-intervention data from these patients were missing.

The number of steps per minute, counting steps made by both feet (cadence), was significantly increased after the intervention (p=0.008). The duration of the step is measured as the period from initial contact of one foot to the following initial contact of the opposite foot (step time) and the duration of a full gait cycle, measured from the left foot's initial contact to the next initial contact of the left foot (stride time) were significantly decreased after the intervention (for both, p=0.008), Figure 1. There was no difference in other gait parameters before and after the intervention. All analyzed gait parameters are summarized in Table 2.

Discussion

Wearable inertial sensors are small-sized mobile systems and are easy to use. Accumulating data demonstrate that portable systems are promising methods for gait analysis (13). Additionally, the quantitative measurement of gait parameters shows subtle changes in gait that may provide precious information in the assessment of TT response, which is being used as an indicator of surgery in patients with iNPH patients.

It has been demonstrated that gait and balance parameters are helpful for measuring changes after external lumbar drainage in patients with iNPH (10-12). Here, our results also support that instrumented gait analysis could detect subtle changes in gait after CSF removal interventions. We showed a significant increase in cadence, on the other hand, decrease in step and stride time parameters.

Improvement of gait velocity after the CSF removal test was determined by Stolze et al. (14), and the authors connected increased gait velocity with increased stride length rather than the cadence. However, He et al. (15) showed that stride length and cadence were increased after the external lumbar drainage. Similar to He et al. (15), our data confirmed a marked improvement in cadence. Further studies are required for verification.

Table 1. Demographic and clinical features of the patients

Parameters	Patients (n=11)
Age, years Median (IQR)	76 (68-76)
Female/male	6 (55%)/5 (45%)
Duration of symptoms, years median (IQR)	2 (1-4)
Intervention-surgery (n)	8 (73%)
Intervention-LP (n)	3 (27%)

IQR: Interquartile range, LP: Lumbar puncture, n: Number

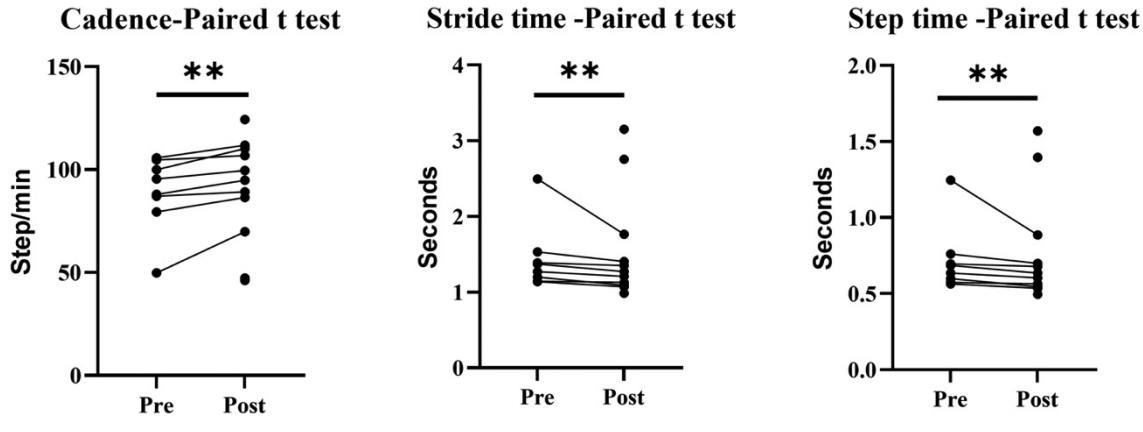


Figure 1. Differences in the cadence, stride time, and step time before and after intervention in the iNPH patients. The mean values of measurements done for each participant before and after the intervention are shown as dots. **Refers to p<0.01

iNPH: Idiopathic normal pressure hydrocephalus

In this study, we observed a significant decrease in stride time and step time that can be attributed to an increased gait velocity after an intervention such as a spinal TT or ventriculoperitoneal shunt consistent with previous studies (16-18). Spatial gait parameters such as stride length, were not observed in our cases, which may be due to the limited number of participants and the relatively early assessment of gait after the intervention.

Study Limitations

The main limitations of this study are the small sample size and the lack of a control group. Furthermore, we included patients who underwent two different interventions. However, studies have pointed out that gait improvement was noticeably better after shunt surgery than after CSF draining, which has both prognostic and functional relevance (19). Thus,

Table 2. Gait parameters before and after the intervention

	Pre	Post	p-value
Cadence, step/min Median (IQR)	91.72 (81.32-103.5)	97.24 (87.10-109.3)	**0.008**
Gait speed: m/s Mean ± SD	0.540±0.24	0.580±0.29	0.360
Stride length, m Mean ± SD	0.689± 0.25	0.697±0.29	0.860
Step time, s Median (IQR)	0.660 (0.581-0.743)	0.620 (0.550-0.695)	**0.008**
Stride time, m Median (IQR)	1.32 (1.15-1.49)	1.24 (1.10-1.39)	**0.008**
Stance phase, GCT (%) Median (IQR)	64.44 (63.60-68.14)	63.41 (62.94-67.86)	0.250
Swing phase, GCT (%) Median (IQR)	35.56 (31.86-36.40)	36.59 (32.14-37.06)	0.250
Double support phase, GCT (%) Median (IQR)	28.90 (27.31-36.36)	26.84 (25.96-35.95)	0.250
Terminal double support phase, GCT (%) Median (IQR)	14.35 (13.70-18.05)	13.36 (12.97-18.02)	0.190
Single-limb support, GCT (%) Median (IQR)	35.60 (31.76-36.28)	36.58 (31.91-36.97)	0.250
Elevation at the midswing, cm Median (IQR)	1.30 (0.496-2.09)	1.35 (0.748-2.19)	0.360
Lateral step variability, cm Mean ± SD	2.49±0.80	2.54±1.14	0.830
Circumduction, cm Median (IQR)	1.43 (0.817-3.20)	1.64 (0.942-3.22)	0.840
Foot strike angle, degree Median (IQR)	9.69 (4.68-17.79)	7.07 (2.85-19.04)	0.640
Toe-off angle, degree Mean ± SD	24.12±4.62	25.01±6.40	0.540
Toe out angle	16.71 (12.43-18.61)	13.53 (6.69-16.92)	0.070
Lumbar Coronal ROM, degree Mean ± SD	5.60±2.07	5.49±2.53	0.840
Lumbar Sagittal ROM, degree Mean ± SD	4.61±1.28	4.46±1.58	0.710
Lumbar Transverse ROM, degree Mean ± SD	7.37±1.66	7.24±1.94	0.800
Turn angleand degree Mean ± SD	135±48.58	147.4±35.63	0.340
Turn duration, s Mean ± SD	2.51±0.56	2.70±0.33	0.500
Turn velocity, degree/s Mean ± SD	103.5±34.37	112±28.62	0.120

Significant p-values are shown in bold.
IQR: Interquartile range, GCT: Ground contact time, ROM: Range of motion, SD: Standard deviation

further studies comparing the effects of a single intervention in larger patient populations may provide more objective parameters to use in managing patients in daily practice.

Conclusion

Quantitative measurement of gait analysis in iNPH may improve the clinical assessment of TT response and follow-up after VP surgery. In particular, cadence, step, and stride time parameters should be interpreted for the clinical evaluation of patients with iNPH patients.

Ethics Committee Approval: The ethics committee approval was granted by the Ethics Committee of Koç University (approval number: 2020,418,IRB1,157).

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - M.Y.S., A.V.; Concept - Ö.Ö.Ç., K.A., H.Y., E.Ö., A.V.; Design - Ö.Ö.Ç., K.A., H.Y., E.Ö., A.V.; Data Collection or Processing - Ö.Ö.Ç., K.A., H.Y., A.D.K., E.Ö., M.Y.S., A.V.; Analysis or Interpretation - Ö.Ö.Ç., K.A., H.Y., A.D.K., E.Ö., M.Y.S., A.V.; Literature Search - Ö.Ö.Ç., K.A., H.Y., A.D.K., E.Ö., M.Y.S., A.V.; Writing - Ö.Ö.Ç., K.A., H.Y., A.D.K., E.Ö., M.Y.S., A.V.

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. Hakim S, Adams RD. The special clinical problem of symptomatic hydrocephalus with normal cerebrospinal fluid pressure. Observations on cerebrospinal fluid hydrodynamics. J Neurol Sci 1965; 2: 307-27.
2. Nikaido Y, Urakami H, Akisue T, Okada Y, Katsuta N, Kawami Y, et al. Associations among falls, gait variability, and balance function in idiopathic normal pressure hydrocephalus. Clin Neurol Neurosurg 2019; 183: 105385.
3. Toma AK, Papadopoulos MC, Stapleton S, Kitchen ND, Watkins LD. Systematic review of the outcome of shunt surgery in idiopathic normal-pressure hydrocephalus. Acta Neurochir (Wien) 2013; 155: 1977-80.
4. Benveniste RJ, Sur S. Delayed symptom progression after ventriculoperitoneal shunt placement for normal pressure hydrocephalus. J Neurol Sci 2018; 393: 105-9.
5. Halperin JJ, Kurlan R, Schwalb JM, Cusimano MD, Gronseth G, Gloss D. Practice guideline: Idiopathic normal pressure hydrocephalus: Response to shunting and predictors of response: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2015; 85: 2063-71.
6. Virhammar J, Cesarini KG, Laurell K. The CSF tap test in normal pressure hydrocephalus: evaluation time, reliability and the influence of pain. Eur J Neurol 2012; 19: 271-6.
7. Agostini V, Lanotte M, Carlone M, Campagnoli M, Azzolin I, Scarafia R, et al. Instrumented gait analysis for an objective pre-/postassessment of tap test in normal pressure hydrocephalus. Arch Phys Med Rehabil 2015; 96: 1235-41.
8. Mancini M, Horak FB. Potential of APDM mobility lab for the monitoring of the progression of Parkinson's disease. Expert Rev Med Devices 2016; 13: 455-62.
9. Fang X, Liu C, Jiang Z. Reference values of gait using APDM movement monitoring inertial sensor system. R Soc Open Sci 2018; 5: 170818.
10. Panciani PP, Migliorati K, Muratori A, Gelmini M, Padovani A, Fontanella M. Computerized gait analysis with inertial sensor in the management of idiopathic normal pressure hydrocephalus. Eur J Phys Rehabil Med 2018; 54: 724-9.
11. Lim YH, Ko PW, Park KS, Hwang SK, Kim SH, Han J, et al. Quantitative gait analysis and cerebrospinal fluid tap test for idiopathic normal-pressure hydrocephalus. Sci Rep 2019; 9: 16255.
12. Ferrari A, Milletti D, Giannini G, Cevoli S, Oppi F, Palandri G, et al. The effects of cerebrospinal fluid tap-test on idiopathic normal pressure hydrocephalus: an inertial sensors based assessment. J Neuroeng Rehabil 2020; 17: 7.
13. Muro-de-la-Herran A, Garcia-Zapirain B, Mendez-Zorrilla A. Gait analysis methods: an overview of wearable and non-wearable systems, highlighting clinical applications. Sensors 2014; 14: 3362-94.
14. Stolze H, Kuhtz-Buschbeck JP, Drücke H, Jöhnk K, Diercks C, Palmié S, et al. Gait analysis in idiopathic normal pressure hydrocephalus--which parameters respond to the CSF tap test? Clin Neurophysiol 2000; 111: 1678-86.
15. He M, Qi Z, Shao Y, Yao H, Zhang X, Zhang Y, et al. Quantitative Evaluation of Gait Changes Using APDM Inertial Sensors After the External Lumbar Drain in Patients With Idiopathic Normal Pressure Hydrocephalus. Front Neurol 2021; 12: 635044.
16. Marmarou A, Bergsneider M, Klinge P, Relkin N, Black PM. The value of supplemental prognostic tests for the preoperative assessment of idiopathic normal-pressure hydrocephalus. Neurosurgery 2005; 57(3 Suppl): S17-28.
17. McGirt MJ, Woodworth G, Coon AL, Thomas G, Williams MA, Rigamonti D. Diagnosis, treatment, and analysis of long-term outcomes in idiopathic normal-pressure hydrocephalus. Neurosurgery 2005; 57: 699-705.
18. Williams MA, Razumovsky AY, Hanley DF. Evaluation of shunt function in patients who are never better, or better than worse after shunt surgery for NPH. Acta Neurochir Suppl 1998; 71: 368-70.
19. Williams MA, Thomas G, de Lateur B, Imteyaz H, Rose JG, Shore WS, et al. Objective Assessment of Gait in Normal-Pressure Hydrocephalus. Am J Phys Med Rehabil 2008; 87: 39-45.

İstanbul Med J 2023; 24(1): 40-7
DOI: 10.4274/imj.galenos.2023.07348

Development of an Artificial Intelligence Method to Detect COVID-19 Pneumonia in Computed Tomography Images

Gülşah Yıldırım[1], Hakkı Muammer Karakaş[1], Yaşar Alper Özkaya[2], Emre Şener[2], Özge Fındık[1], Gülhan Naz Pulat[2]

[1]University of Health Sciences Turkey, Fatih Sultan Mehmet Training and Research Hospital, Clinic of Radiology, İstanbul, Turkey
[2]Ankara University Technology Development Zone, Simplex Information Technologies, Inc

ABSTRACT

Introduction: This study aimed to construct an artificial intelligence system to detect Coronavirus disease-2019 (COVID-19) pneumonia on computed tomography (CT) images and to test its diagnostic performance.

Methods: Data were acquired between March 18-April 17, 2020. CT data of 269 reverse tran-scriptase-polymerase chain reaction proven patients were extracted, and 173 studies (122 for training, 51 testing) were finally used. Most typical lesions of COVID-19 pneumonia were la-beled by two radiologists using a custom tool to generate multiplanar ground-truth masks. Us-ing a patch size of 128x128 pixels, 18,255 axial, 71,458 coronal, and 72,721 sagittal patches were generated to train the datasets with the U-Net network. Lesions were extracted in the or-thogonal planes and filtered by lung segmentation. Sagittal and coronal predicted masks were reconverted to the axial plane and were merged into the intersect-ed axial mask using a voting scheme.

Results: Based on the axial predicted masks, the sensitivity and specificity of the model were found as 91.4% and 99.9%, respectively. The total number of positive predictions has increased by 3.9% by the use of intersected predicted masks, whereas the total number of negative predic-tions has only slightly decreased by 0.01%. These changes have resulted in 91.5% sensitivity, 99.9% specificity, and 99.9% accuracy.

Conclusion: This study has shown the reliability of the U-Net architecture in diagnosing typical pulmonary lesions of COVID-19 in CT images. It also showed a slightly favorable effect of the intersection method to increase the model's performance. Based on the performance level pre-sented, the model may be used in the rapid and accurate detection and characterization of the typical COVID-19 pneumonia to assist radiologists.

Keywords: Computed tomography, computer aided diagnosis, convolutional neural networks, COVID-19, deep learning, machine learning, pneumonia, U-Net

Introduction

The outbreak of coronavirus disease (COVID) is caused by the severe acute respiratory syndrome-coronavirus-2 that is transmitted from person to person, mainly by respiratory droplets and surface contact (1). Patients may become a source of infection not only when they are symptomatic but also during the incubation or the recovery period (2). Therefore, accurate and quick diagnosis of the disease quickly became critical for the effective treatment and the control of the disease's spread. Currently, the COVID-19 pneumonia is diagnosed by a reverse transcriptase-polymerase chain reaction (RT-PCR) test. However, the high false -negative rate for the disease, up to 60%, and the unavailability of instant results create a real clinical problem where positive cases must be identified and isolated to prevent the disease spread to healthy (3).

Computed tomography (CT), in the above-described context, is a rapid and effective imaging tool for COVID-19 pneumonia. Concerning so-called "typical lung findings," it has very high sensitivity up to 98% (4-6). World Health Organization, therefore, acknowledged imaging as one element of the diagnostic workup of patients with suspected or probable COVID-19 disease where RT-PCR is not available, results are delayed or are initially negative in the presence of symptoms suggestive of that disease. CT has also been considered to complement clinical and laboratory evaluation in the management of patients already diagnosed with COVID-19 (7).

The disease typically presents on CT with bilateral, peripheral, patchy ground-glass opacities (GGOs) in more than 70% of RT-PCR proven COVID-19 cases (8). However, it is not uncommon to see many other findings. These typical findings include bilateral, peripheral, patchy

Address for Correspondence: Gülşah Yıldırım MD, University of Health Sciences Turkey, Fatih Sultan Mehmet Training and Research Hospital, Clinic of Radiology, İstanbul, Turkey
Phone: +90 538 321 35 65 **E-mail:** dr.gulsah.yildirim@gmail.com **ORCID ID:** orcid.org/0000-0002-5971-7079

Cite this article as: Yıldırım G, Karakaş HM, Özkaya YA, Şener E, Fındık Ö, Pulat GN. Development of an Arti-ficial Intelligence Method to Detect COVID-19 Pneumonia in Computed Tomography Images. İstanbul Med J 2023; 24(1): 40-7.

Received: 30.06.2022
Accepted: 09.01.2023

©Copyright 2023 by the University of Health Sciences Turkey, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.

GGOs with or without consolidation, which eventually develop into crazy-paving patterns, fibrotic band formation, and several others including but not limited to interstitial thickening, "reversed halo sign," "halo sign," and bronchovascular changes (9). These are seen in various combinations, locations, and disseminating patterns depending on the stage and severity of the disease (10). Full reading under routine clinical conditions requires searching and reporting all of these patterns. This task and the overwhelming number of patients scanned, exert extreme demand on radiologists, and exceed the effective capacity of radiological reporting processes in many institutions. These may, in turn, cause delay in the disease's diagnosis and in false negative and positive reads (11). Artificial intelligence (AI) technology may help overcome this problem by rapid and accurate detection and characterization of the CT findings of COVID-19. In that context, convolutional neural network (CNN) was recently used by several group of researchers (12-15).

In this study, we constructed an AI system to detect typical COVID-19 pneumonia on high-resolution CT images to assist radiologists and to test its diagnostic performance.

Methods

Research Ethics Standards Approval

The study was approved by the University of Health Sciences Turkey, İstanbul Fatih Sultan Mehmet Training and Research Hospital Institutional Review Boards (approval number: 17073117_050.06 on 11.12.2020, 2020/13). Informed consent was obtained for the study.

Institution

The study was conducted on a mid-size receiver hospital serving to a core population of circa 400,000. The facility has served as a pandemic center to where many patients from other hospitals and districts were referred.

Patients

For the study, data between March 18-April 17, 2020 were evaluated. This period encompassed 8th to 38th days after the first COVID-19 incidence in the country. In that time, the Fleischner Society Consensus Statement was not yet been published, and at our institution the CT imaging was mainly performed for the medical triage of patients with suspected COVID-19 who were presented with moderate-severe clinical features and a high pretest probability of disease (16). However, there were few cases where it was used for suspected COVID-19 and mild clinical features. During this period, 269 patients were tested RT-PCR positive and had chest CT. These patients were scanned immediately after being sampled with oropharyngeal and nasal swabs during their initial admission at the emergency clinic. Of them, only 173 patients could be scanned with a standard protocol, as detailed below, and had technically adequate CT images as assessed by annotating experts (Figure 1). These were 97 males (56.1%) and 76 females (43.9%). Their ages were between 18 and 93 (53.92±16.90) years.

Final Dataset

The final data set included axial chest CT scans of 173 patients, obtained at the time of their initial admission. These were acquired using the same scanner 128 slice scanner (Optima 660 SE, GE Healthcare) using a standart-dose scan below: tube voltage, 120 kV; tube current, auto mA to maximum 250 mA; slice thickness, 1.25 mm, reconstructed to 1.25 and 5.0 mm; slice interval, 1.25 mm; gantry rotation speed, helical full 0.5 s; matrix size, 512x512.

Annotation

All studies were read on DICOM -calibrated 3 MP diagnostic monitors (EMX 16, Eizo) at a fixed window level of -450 HU and window width at 1,600 HU using 5.0 mm and 1.2 mm axial reconstructions. Examinations were anonymized and shuffled by a randomization process. They were read by two radiologists (GY, OS) who were blinded to the identities of the patients. Consultants read all of these studies in the same week, starting from 25 days after the last case of the cohort was scanned. All studies were officially read by another team of radiologists. The findings on the context of this study were neither used for any official report or patient management.

Images were independently read and labeled using 5 mm axial slices for the most typical lesions of COVID-19 pneumonia (i.e. ground glass opacity and consolidation) (17). Of all the patients, 96 were already excluded from the study. A custom annotation application was developed by the authors (YAO) to draw the region of interest around lesions. Ground-truth masks (i.e., images that only contains labeled lesions) for each image were automatically generated with the same application after the annotation step.

Image Processing

Generation of coronal and sagittal slices from axial slices: Each study contains two series with different slice thickness (i.e., 5 mm and 1.25 mm). Images with 5 mm slice thickness were used for annotation (Figure 2A), as described above, and images with 1.25 mm slice thickness were used to generate coronal and sagittal series. Axial images with

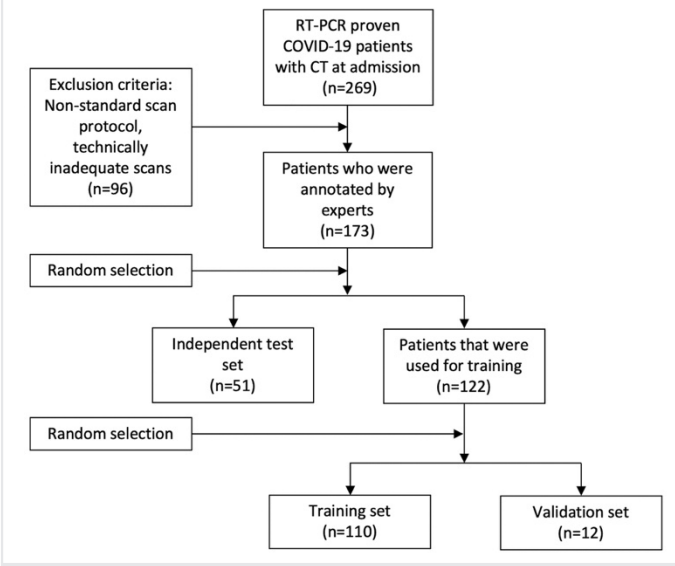


Figure 1. Patient selection process

RT-PCR: Reverse transcriptase-polymerase chain reaction, COVID-19: Coronavirus disease-2019, CT: Computed tomography

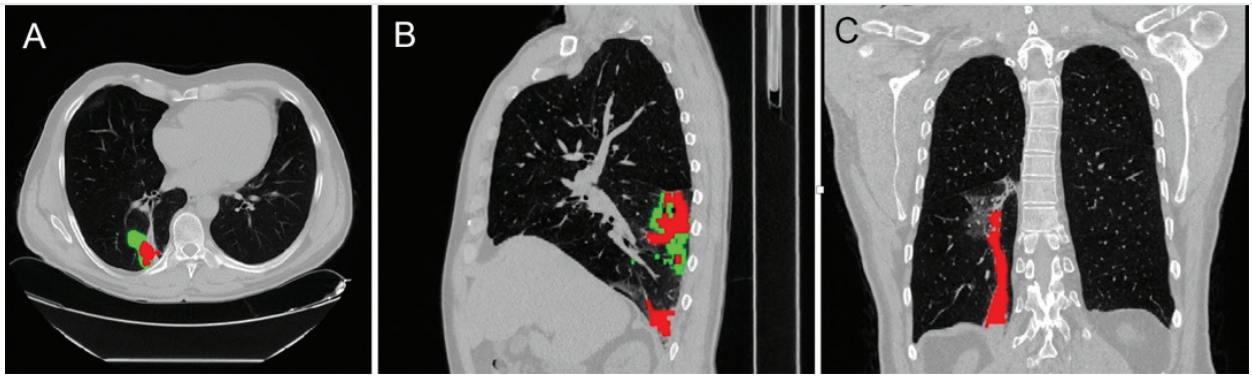


Figure 2. Annotated axial 5 mm (A), reconstructed sagittal (B), and coronal (C) 1.5 mm mask slices. Ground glass opacities were marked with green, and consolidations were marked with red

Table 1. Determination of the patch size with the highest normalized frequency

Patch size (pixel)	Frequency (n)	Normalization factor	Normalized frequency	Percentage	Cumulative percentage
8x8	394,058	1	394,058	9.18	9.18
16x16	46,284	4	185,136	4.31	13.49
32x32	29,980	16	479,680	11.17	24.66
64x64	15,047	64	963,008	22.43	47.08
128x128	6,468	256	1,655,808	38.56	85.64
256x256	602	1,024	616,448	14.36	100

1.25 mm slice thickness were resampled using nearest neighborhood interpolation to make their voxels isotropic (i.e., 0.8 x 0.8 x 0.8 mm). These resampled axial images were used to generate sagittal and coronal slices using multiplanar reconstruction. Axial mask images with 5 mm slice thickness were resampled using nearest neighborhood interpolation to make their voxels isotropic (i.e., 0.8 x 0.8 x 0.8 mm). These resampled axial mask images were used to generate sagittal (Figure 2B) and coronal (Figure 2C) mask slices using multiplanar reconstruction.

Determination of the patch size: In a mask image, the regions containing pixels that are connected to each other and have the same value form a region called "connected components" (a.k.a. blobs). In the context of the segmentation, blobs are separate regions of GGOs and consolidations. Before model training, blobs were extracted from the mask slices. The center points and bounding boxes of these blobs were calculated.

The ideal patch size was determined by finding a minimum patch size for the entire data set that any blob would optimally fit into. For that purpose, all blobs were individually evaluated to find the corresponding patch size that varies between 8x8 and 256x256 pixels. The frequency of each patch size was recorded. The frequencies were normalized to 8x8 patch size using a multiplication factor of 1 to 1024. The patch size that had the highest normalized frequency was 128x128, and was used in the model (Table 1).

Patches with 128x128 pixels in size were extracted by aligning the patch centers with the blob centers. By this principle, 18,255 axial, 71,458 coronal, and 72,721 sagittal patches were generated (Figure 3). These patches were used to train the datasets as described below.

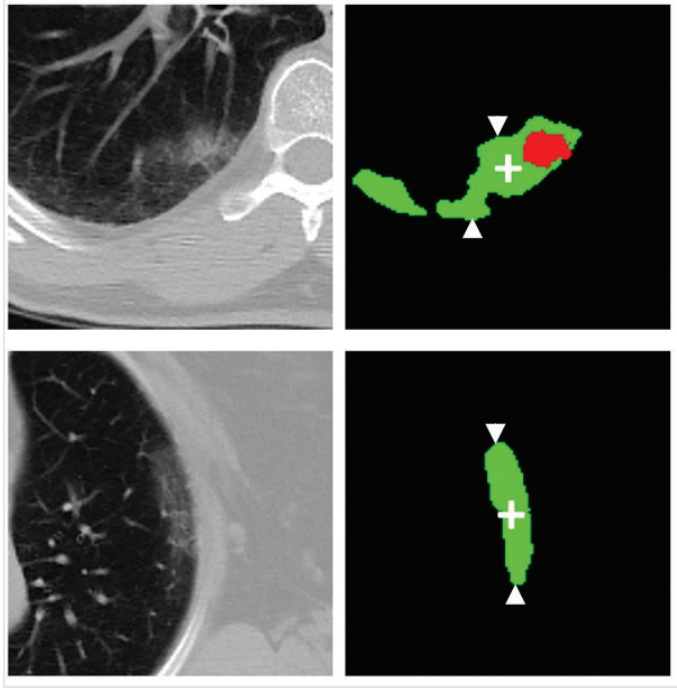


Figure 3. Representative patches that were extracted by aligning the patch centers with the blobs (between arrowheads) centers (+)

Splitting the data into groups: Patients were randomly assigned to the training set, validation set, and performance evaluation set. Of 173 studies, 110 (~63%) were used for training, 12 (~7%) were used for validation, and 51 (~30%) studies were used as independent test set for performance evaluation.

CNN model: The U-Net, a neural network model that was originally designed for medical image segmentation, was used (18). This model has certain advantages including: 1) Higher accuracy than other CNN models, 2) end-to-end fully-connected convolution layers, and 3) accepting images of any size as it does not contain any dense layer. The input of a U-Net is an image (i.e. 128x128 patches for this study), and the output is a semantic segmentation map in which every pixel is the classification of the corresponding pixel of the input image. The model consisted of three consecutive (i.e., the contraction, the bottleneck, and the expansion) sections (Figure 4). In the contraction section, 3x3 convolution layers and 2x2 max-pooling were applied to the input. In the bottleneck section, 3x3 convolution layers and 2x2 up-convolution layers were applied to the output of the contraction section. In the expansion section, 3x3 convolution layer and 2x2 up-sampling layer were applied to each output of the contraction section and output of the bottleneck section. Axial, sagittal, and coronal datasets were trained separately using the U-Net model.

Prediction: The model was applied consecutively to CT scans. Lesions were extracted in orthogonal (i.e., axial, coronal and sagittal) planes (Figure 5). An automated lung segmentation model was used to filter-out false-positive (FP) findings that was located external to the lung

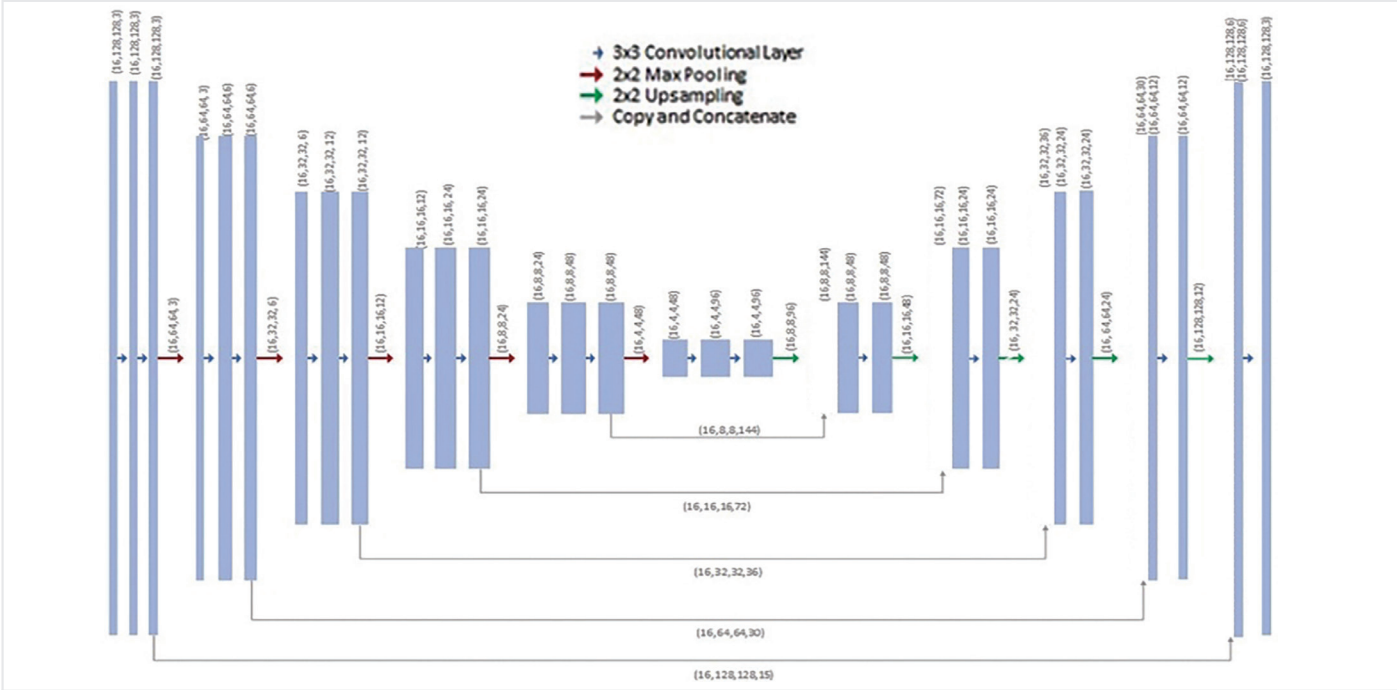


Figure 4. Schematic representation of the U-Net architecture. The contraction section is at the left, the bottleneck section is in the middle, and the expansion section is at the right. Straight arrows show the direction of flow and computation

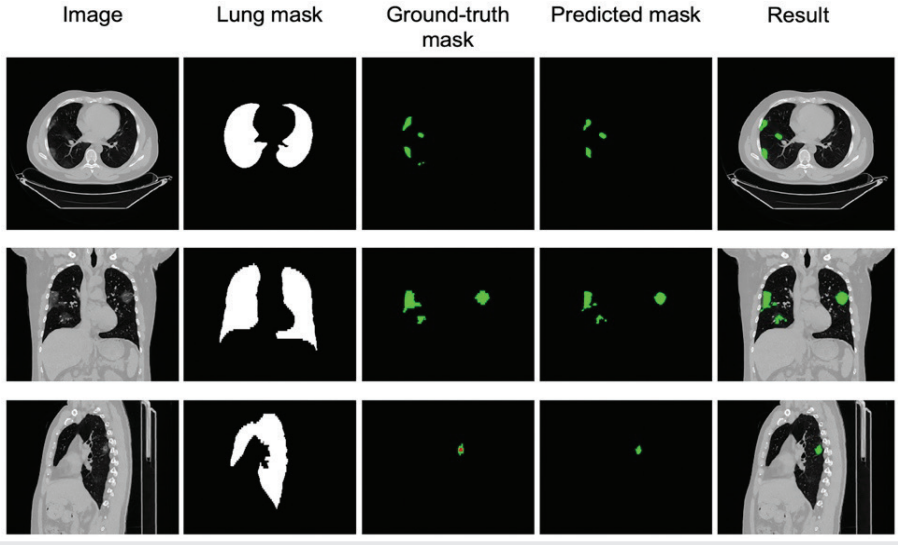


Figure 5. Steps in the extraction of COVID-19 lesions in the orthogonal planes
COVID-19: Coronavirus disease-2019

parenchyma (19). Intersections of the extracted lesions from orthogonal images were created to increase the specificity of the model. Sagittal and coronal predicted masks were reconverted to the axial plane. Axial reconverted coronal, and reconverted sagittal predicted masks were merged into the intersected axial mask using a two-step majority voting (Figure 6, 7). In the first step, the voxel in the final mask was set to "normal" if the corresponding voxels (i.e., axial, reconverted coronal, and sagittal were normal, otherwise a second step was applied. The second step was a majority vote between the "GGO" and "consolidation" in which corresponding voxels from each of the three planes were counted to make the final decision for the final mask value. Possible values were 0 (none), 1 (green) and 2 (red) for normal, GGO and consolidation, respectively.

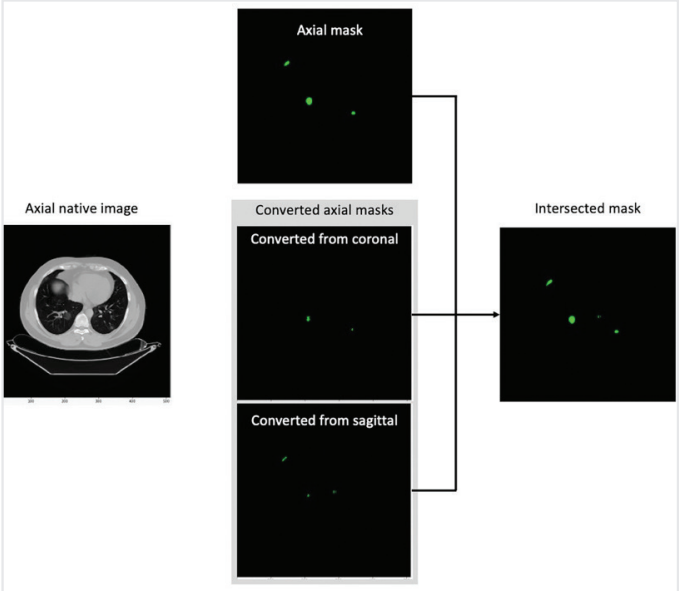


Figure 6. The sample section showing axial predicted, axial conversions of coronal and sagittal predicted, and intersected masks along with the native CT image of a COVID-19 patient

CT: Computed tomography, COVID-19: Coronavirus disease-2019

Statistical Measures of Performance

Sensitivity, specificity, and accuracy were used in the analytical validation of the model as the statistical measures of the performance. These measures were applied to each pixel of each independent image the performance evaluation set and were determined by an approach that used erosion and dilation of ground-truth masks and formulae (2-7). In that process, ground-truth masks were eroded and dilated separately using a 3x3 convolution kernel. The eroded and dilated versions of the axial ground-truth masks were compared with axial predicted, axial that was converted from coronal predicted and axial that was converted from sagittal predicted masks, and the intersected axial masks. The FP findings of the predicted mask were calculated with for each of its pixels as follows:

1) If the predicted mask's pixel value is greater than 0 and the dilated version of the ground-truth mask's pixel value equals to 0; this pixel is then considered FP, according to Formula 1:

1. $FP = count\left(dilation\, n_{x,y} = 0 \wedge predictedmas\, k_{x,y} > 0\right), x, y = coordinates$

2) If the predicted mask's pixel value equals to 0 and the eroded version of the ground-truth mask's pixel value is greater than 0; this pixel is then considered false-negative (FN), according to Formula 2:

2. $FN = count\left(erosio\, n_{x,y} > 0 \wedge predictedmas\, k_{x,y} = 0\right), x, y = coordinates$

3) The true-positive (TP) value was calculated by subtracting the number of FP counts for a predicted mask from the number of non-nonzero pixel counts for that mask according to Formula 3:

3. $TP = count(predictedmask > 0) - FP$

4. The true-negative (TN) value was calculated by subtracting the sum of FP, false-negative, and true-positive values from the total number of pixels in the corresponding image (N) according to Formula 4.

4. $TN = N - (FN + FP + TP), N = totalnumberofpixels$

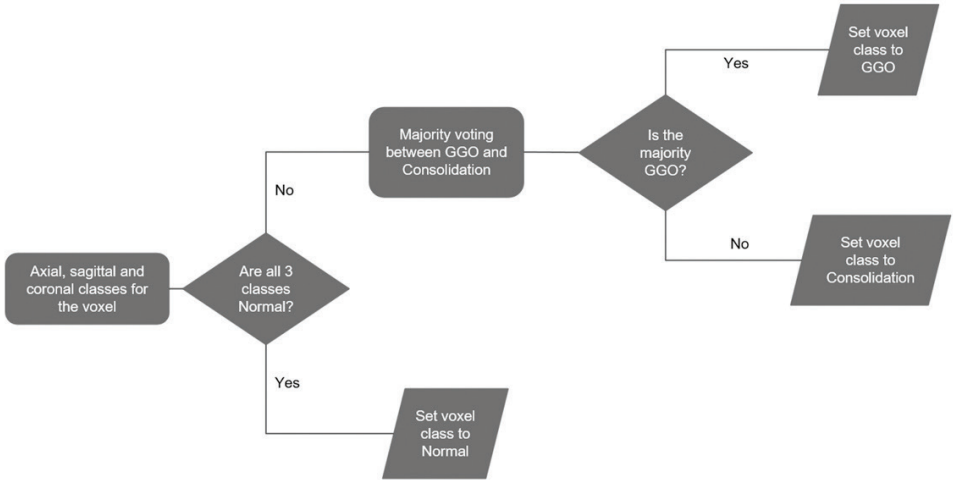


Figure 7. Schematic representation of the merging process to create an intersected predicted mask

GGO: Ground-glass opacities

5) Sensitivity and specificity were calculated using formulas:

5. $Sensitivity = \frac{TP}{TP + FN}$
6. $Specificity = \frac{TN}{TN + FP}$
7. $Accuracy = \frac{TP + TN}{TP + TN + FP + FN}$

This study has been presented as an oral presentation.

RESULTS

Test Data

Performance evaluation was conducted on an independent test set of 51 patients that were excluded from training and validation. In this dataset, there were 51 axial native series, 3340 axial sections, and 875,560,960 pixels. The model's performance was calculated for axial predicted and intersected predicted masks (Table 2).

K-Fold Cross Validation

The k-fold cross validation was used to assess the reliability of the model to ensure that the performance was affected minimally by the separation of the training sets. k was selected as 10 and the model was trained 10 times using different sets of 12 patients as the validation sets. The remaining 110 patients out of 122 were used for the training set. The sensitivity and specificity of each training were calculated against a testing set that contained 51 patients. The mean and the standard deviation of the sensitivity values were found as 91.8% and 1%, respectively. The mean and standard deviation of the specificity were obtained as 99.9% and 0.1%. The low standard deviation values indicate that the model performance was independent of how the training and validation sets were separated.

Confidence Interval

The confidence interval of the model was calculated using the 10 k-fold cross validation versions of the model to predict different sets of testing data sets. A total of 200 runs were performed for confidence analysis. In each run, a random version of the model was selected. The testing set for a run consists of a random number (from 20 to 40) of patients randomly chosen from the pool of 51 test patients. Over the 200 runs, the mean sensitivity was found as 91.6% with a 95% confidence interval of ±0.3% whereas the mean specificity was calculated as 99.9% with a 95% confidence interval of ±0.004%. The narrow confidence intervals show that the model could perform similarly on different test sets.

Performance

The lower performing of the two median models out of 10 models were selected for performance evaluation. Based on the axial predicted masks, the sensitivity and specificity of the model were found as 91.4% and 99.9%, respectively. The use of intersected predicted masks has caused an increase of 3.9% in the total number of positive predictions, whereas the total number of negative predictions has only slightly decreased by 0.01%. These changes have resulted in a sensitivity of 91.5% and a specificity of 99.88%. The accuracy, however, were the same (99.9%) for both.

The total number of false - positive predictions was 787,511 for axial predicted masks, and 867,437 for intersected predicted masks. Therefore, the number of false -positive predictions, was 10.1% higher for intersected predicted masks than for axial predicted masks.

Receiver Operating Characteristics

The model outputs three values p_{normal}, p_{GGO} and $p_{consolidation}$ for the normal, GGO and consolidation classes, and these values are in the interval (0,1). A likeliness value for each pixel was calculated so that it is equal to 1-p_{normal} when the pixel was marked as normal class. If the pixel was marked as GGO or consolidation (which are considered positive), then the likeliness value was set to max ($p_{GGO,}$ $p_{consolidation}$). In essence, the obtained value indicates the likeliness of a positive class as a real number between 0 and 1. A ROC curve is then formed by calculating the FP and true positive rates for different thresholds of the likeliness value. The ROC Curves for the two methods are shown in Figures 8, 9. The area under the curve values for the axial prediction and intersected prediction methods were calculated as 0.992 and 0.994 respectively.

Discussion

CT is a rapid and very sensitive imaging tool for COVID-19 pneumonia and is an acknowledged element of the diagnostic workup of patients with suspected or probable COVID-19 (4,7). For this reason, there was an excessive use of CT during the pandey. This practice has exerted extreme demand on radiologists and caused the effective and even design capacity of radiological reporting processes to be exceeded in many institutions. AI may help overcome this problem by extremely rapid and highly accurate detection and characterization of the CT findings of COVID-19.

Table 2. Summary table for statistical measures of performance

Mask	Value	Predicted			Performance		
		Positive	Negative	Total	Sensitivity (%)	Specificity (%)	Accuracy (%)
Actual	**Axial**						
	Positive	1,970,654	185,153	2,155,807	91.4	99.9	99.9
	Negative	787,511	872,617,642	873,405,153			
	Total	2,758,165	872,802,795	875,560,960			
	Intersected						
	Positive	1,999,518	184,657	2,184,175	91.5	99.9	99.9
	Negative	867,437	872,509,348	873,376,785			
	Total	2,866,955	872,694,005	875,560,960			

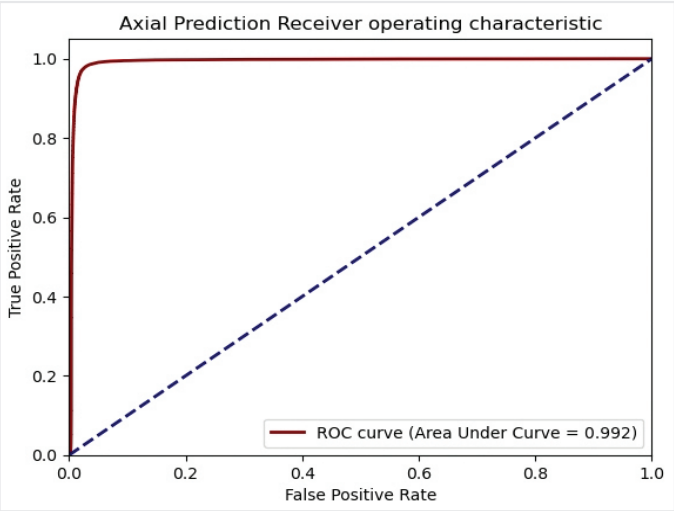


Figure 8. Receiver operating characteristic curve for the axial method
ROC: Receiver operating characteristic

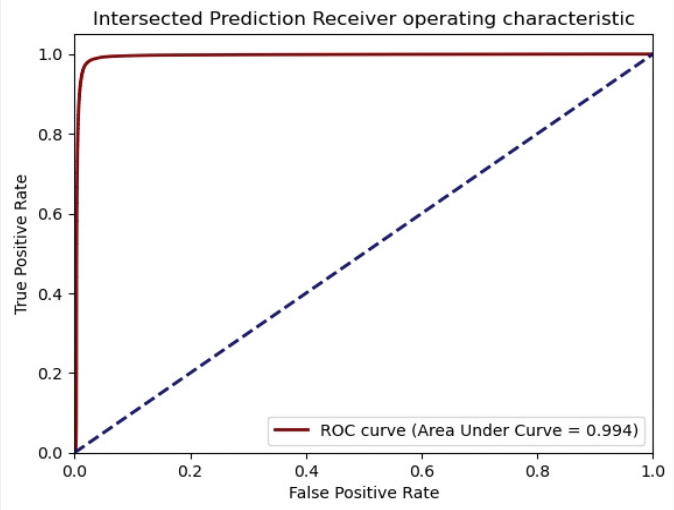


Figure 9. Receiver operating characteristic curve for the intersection method
ROC: Receiver operating characteristic

The detection of pulmonary pathologies is one of the earliest fields of interest for computer aided diagnosis to assist radiologists. Such systems are mainly based on the analysis of texture parameters, segmentation of anatomical structures, and the detection of lesions. They use radiological images obtained in routine diagnostic practice, but involves an ensemble of mathematical computations performed with the data contained within the images (20). Recently, research on that field has been concentrated on deep learning techniques (14). These techniques, such as CNN, are very efficient in identifying, classifying, and quantifying patterns in medical images, leading to enhanced performance in various medical applications (13). CNN, in particular, was designed to automatically and adaptively learn the spatial hierarchies of features through backpropagation by using multiple building blocks, such as convolution layers, pooling layers, and fully connected layers. In this study, a CNN -based deep learning model was developed to detect COVID-19 pneumonia on CT images to assist radiologists to diagnose infected cases rapidly and confidently during extreme conditions of the pandemic.

As stated before, there are certain studies on the use of deep learning to detect COVID-19 pneumonia using various algorithms. The largest of them, used Densnet-121 (15). In that study, the network was trained using a multinational cohort of 1,280 patients. It identified COVID-19 pneumonia with 84% sensitivity, 93% specificity, and 90.8% accuracy (15). Gozes et al. (14) and Chen et al. (13) have used Resnet-50 algorithms and could obtain more favorable results (98.2% sensitivity, 92.2% specificity and 95% accuracy for the former; 100% sensitivity, 81.8% specificity and 92.6% accuracy for the former;) in terms of sensitivity and accuracy. Ardakani et al. (12) have tested ten different CNN models in RT-PCR-proven COVID-19 patients and on non-COVID-19 controls. They achieved the best performance with the ResNet-101 and Exception networks. According to their findings, ResNet-101 could distinguish COVID-19 from non-COVID-19 cases with 100% sensitivity, 99.2% specificity and 99.51% accuracy. Exception, on the other hand, achieved 98.04% sensitivity, %100 specificity and 99.02% accuracy. In our study, we have adopted the U-Net. This model that was originally designed for medical image segmentation and has certain advantages, as stated above (18). With U-Net and intersected predicted masks, we have achieved 91.5% sensitivity, 99.9% specificity with 99.9% accuracy in detecting typical findings of COVID-19. Both the axial predicted masks and intersected predicted masks approximate the performance of this model to previous studies. The context, it had lower sensitivity but equally higher specificity than the studies summarized below. Nevertheless, its overall accuracy was higher than them (Table 3).

Study Limitations

This study has certain limitations. The use of a homogenous single-center data that might help us reach higher diagnostic performance, may also limit the applicability of the model to other populations, demographics, or geographies. Model training was limited to patients with positive RT-PCR testing and typical findings of pneumonia for COVID-19 on CT. However, patients with a positive RT-PCR tests may not always have chest CT findings or they may have indeterminate and atypical findings (9). Annotation was performed on axial slices for saving the expert's time; coronal, sagittal images were generated from axial slices. The sensitivity could be significantly increased if annotating could also be performed in other planes.

Conclusion

This study has showed the reliability of the U-Net architecture in diagnosing typical pulmonary lesions of COVID-19 in CT images. It also demonstrated the slightly favorable effect of the intersection method to increase the model's performance. Based on the performance level presented, the model may be used in the rapid and accurate detection and characterization of the typical COVID-19 pneumonia. The routine use of artificial machine learning models in COVID-19 and similar pneumonia outbreaks that may occur in the future could help relieve the excessive workload on frontline radiologists, reduce virus spread by early diagnosis and isolation, and improve patient prognosis by early treatment.

Table 3. Comparison of several CNN-based artificial intelligence studies on the detection of COVID-19 pneumonia in computed tomographic images

Author	Network	Cohort	Number of subjects (n)		Performance measure (%)[2]		
			Training set	Test set	Sensitivity	Specificity	Accuracy
Ardakani et al. (12)	ResNet-101	Single center (Iran)	172[1]	22[1]	100	99	100
Ardakani et al. (12)	Exception	Single center (Iran)	172[1]	22[1]	98	100	99
Chen et al. (13)	ResNet-50 +U-Net	Single center (China)	106	27	100	82	93
Gozes et al. (14)	Resnet-50	Multinational/multicenter	50	156	98	92	95
Harmon et al. (15)	Densnet-121	Multinational/multicenter	1,280	1,337	84	93	91
Present study	U-Net	Single center (Turkey)	122	51	91.5	99.9	99.9

CNN: Convolutional neural network, COVID-19: Coronavirus disease-2019

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İstanbul Fatih Sultan Mehmet Training and Research Hospital Institutional Review Boards (approval number: 17073117_050.06 on 11.12.2020, 2020/13).

Informed Consent: Informed consent was obtained for the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - G.Y., H.M.K., E.Ş., G.N.P.; Concept - G.Y., H.M.K., Y.A.Ö., E.Ş., Ö.F.; Design - G.Y., H.M.K., Y.A.Ö., E.Ş., Ö.F.; Data Collection or Processing - G.Y., H.M.K., Y.A.Ö., G.N.P.; Analysis or Interpretation - G.Y., H.M.K., Y.A.Ö., G.N.P.; Literature Search - G.Y., H.M.K.; Writing - G.Y., H.M.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. Chan JF, Yuan S, Kok KH, To KKW, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020; 395: 514-23.
2. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. N Engl J Med 2020; 382: 970-1.
3. Yang Y, Yang M, Shen C, Wang F, Yuan J, Li J, et al. Evaluating the accuracy of different respiratory specimens in the laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections. MedRxiv 2020.
4. Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang O, et al. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. Radiology 2020; 296: E115-7.
5. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of chest CT and RT-PCR testing for coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology 2020; 296: E32-40.
6. de Jaegere TMH, Krdzalic J, Fasen BACM, Kwee RM; COVID-19 CT Investigators South-East Netherlands (CISEN) study group. Radiological Society of North America Chest CT Classification System for Reporting COVID-19 Pneumonia: Interobserver Variability and Correlation with Reverse-Transcription Polymerase Chain Reaction. Radiol Cardiothorac Imaging 2020; 2: e200213.
7. WHO. Use of chest imaging in COVID-19: a rapid advice guide. Geneva: World Health Organization; 2020 (WHO/2019-nCoV/Clinical/Radiology_imaging/2020.1). Licence: CC BY-NC-SA 3.0 IGO.
8. Kwee TC, Kwee RM. Chest CT in COVID-19: What the Radiologist Needs to Know. Radiographics 2020; 40: 1848-65.
9. Karakaş HM, Yıldırım G, Çiçek ED. The reliability of low-dose chest CT for the initial imaging of COVID-19: comparison of structured findings, categorical diagnoses and dose levels. Diagn Interv Radiol 2021; 27: 607-14.
10. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis 2020; 20: 425-34.
11. Zhao Y, Xiang C, Wang S, Peng, C, Zou Q, Hu J. Radiology department strategies to protect radiologic technologists against COVID19: Experience from Wuhan. Eur J Radiol 2020; 127: 108996.
12. Ardakani AA, Kanafi AR, Acharya UR, Khadem N, Mohammadi A. Application of deep learning technique to manage COVID-19 in routine clinical practice using CT images: Results of 10 convolutional neural networks. Comput Biol Med 2020; 121, 103795.
13. Chen J, Wu L, Zhang J, Zhang L, Gong D, Zhao Y, et al. Deep learning-based model for detecting 2019 novel coronavirus pneumonia on high-resolution computed tomography. Sci Rep 2020; 10: 19196.
14. Gozes O, Frid-Adar M, Greenspan H, Browning PD, Zhang H, Ji W, et al. Rapid AI development cycle for the coronavirus (Covid-19) pandemic: initial results for automated detection & patient monitoring using deep learning CT image analysis. 2020, arXiv: 2003.05037.
15. Harmon SA, Sanford TH, Xu S, Turkbey EB, Roth H, Xu Z, et al. Artificial intelligence for the detection of COVID-19 pneumonia on chest CT using multinational datasets. Nat Commun 2020; 11: 4080.
16. Rubin GD, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, et al. The role of chest imaging in patient management during the COVID-19 pandemic: a multinational consensus statement from the Fleischner Society. Chest 2020; 158: 106-16.
17. Simpson S, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, et al. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA - Secondary Publication. J Thorac Imaging 2020, 35: 219-27.
18. Ronneberger O, Fischer P, Brox T: U-Net: Convolutional Networks for Biomedical Image Segmentation. In: Navab N, Hornegger J, Wells W, Frangi A (eds). Medical Image Computing and Computer-Assisted Intervention - MICCAI 2015. MICCAI 2015. Lecture Notes in Computer Science, vol 9351. Springer, Cham; 2015.
19. Hofmanninger J, Prayer F, Pan J, Röhrich S, Prosch H, Langs G. Automatic lung segmentation in routine imaging is primarily a data diversity problem, not a methodology problem. Eur Radiol Exp 2020; 4: 50.
20. Castellano G, Bonilha L, Li LM, Cendes F. Texture analysis of medical images. Clin Radiol 2004; 59: 1061-9.

İstanbul Med J 2023; 24(1): 48-52
DOI: 10.4274/imj.galenos.2023.92624

Assessment of Interest of Healthcare Employees in Distance Training in the Coronavirus Disease-2019 Pandemic Process

Arzu Kaplanoğlu[1], Gönül Şengöz[2], Filiz Pehlivanoğlu[2], Öznur Yıldırım[3], Yeşim Kanıpek[4]

[1]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Institute of Graduate Studies, Department of Management in Nursing, İstanbul, Turkey
[2]University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey
[3]University of Health Sciences Turkey, Haseki Training and Research Hospital, Department of Educational Nursing, İstanbul, Turkey
[4]University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of İnternal Medicine, İstanbul, Turkey

ABSTRACT

Introduction: In-service healthcare personnel training is an ongoing process. However, emerging unknowns require momentary planning. The Coronavirus disease-2019 (COVID-19) pandemic has made distance training (DT) compulsory for healthcare employees (HE). Thus, it is important to learn about their interest levels. This study investigates the interest of HE in DT during the pandemic process.

Methods: The research population consisted of 3,442 personnel registered to take the "HE COVID-19" training at research and training hospital in 2020. The population of the study consisted of all personnel employed at research and training hospital and registered for the training. The study was planned retrospectively for reaching all personnel whose training registrations were made between 17.03.2020 and 15.04.2020. This study was used the data of the personnel who completed the "HE COVID-19 Training" within the scope of the announcements that were made as DT as reported on the Hospital Training System.

Results: The total training completion rate of the participants was found to be 90%. When the interests of the HE in the DT in the process of the COVID-19 pandemic were compared, no statistically significant difference could be observed in the participation rates of the specialist doctors, resident doctors, and nurses ($p=0.094$). The rate of the resident doctors to complete the training until the second announcement was significantly lower compared to the specialist doctors and nurses (specialist doctor vs. resident doctor $p=0.044$; nurse vs. resident doctor $p<0.001$). The rates of completing the training after two announcements were significantly higher among the resident doctors than the specialist doctors and nurses and among the specialist doctors than the nurses (respectively $p=0.018$, $p<0.001$, $p=0.018$).

Conclusion: Continuous training must ensure that HE are adequately prepared to deal with public health emergencies such as the COVID-19 pandemic. DT should be prioritized in the Emergency Action Plan.

Keywords: COVID-19, distance training, healthcare employees, pandemic

Introduction

Developments in information and communication technologies have gained a new dimension with the concept of distance training (DT) that allows the individual to learn throughout their life by accessing information everywhere and any time (1,2). DT is a modern and effective form of learning where the educator and learner are at different places, and learning and instruction activities occur at a desired time (2,3). DT may be in the form of academic, organizational, or community education (4).

While the third decade of the twenty-first century was starting, humanity faced a threat of a pandemic. This disease related to this new virus high virulence defined for the first time on January 7, 2020, was named as Coronavirus disease-2019 (COVID-19) by the World Health Organization, and this epidemic experienced was announced as a pandemic on March 12, 2020. This threat on the global level has in a short time affected the healthcare systems of countries, social life, economy, and in a way, modern life. As much as the treatment of the disease, precautions toward preventing the spread and reducing the exposure of sensitive groups and protection of healthcare personnel have constituted the main topics of the fight. The way to reach these goals in the COVID-19 pandemic involves education and information. For this reason, DT has become the most frequently preferred channel by administrators and experts, especially in all countries that experience the viral distribution intensely. In this context, in the scope of the precautions by the Turkish

Address for Correspondence: Arzu Kaplanoğlu MD, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Institute of Graduate Studies, Department of Management in Nursing, İstanbul, Turkey
Phone: +90 505 401 59 09 **E-mail:** arzukaplanoglu@gmail.com **ORCID ID:** orcid.org/0000-0002-2476-0077

Cite this article as: Kaplanoğlu A, Sengöz G, Pehlivanoglu F, Yıldırım Ö, Kanipek Y. Assessment of Interest of Healthcare Employees in Distance Training in the Coronavirus Disease-2019 Pandemic Process. İstanbul Med J 2023; 24(1): 48-52.

Received: 08.11.2022
Accepted: 16.01.2023

©Copyright 2023 by the University of Health Sciences Turkey, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.

Ministry of Health in the fight against COVID-19, trainings to be given to healthcare personnel have been registered for all personals over the Hospital Training System (HTS) in the form of DT rather than face-to-face training on March 17, 2020. This study was planned to investigate the interest of healthcare employees (HE) in DT in the process of the COVID-19 pandemic.

Methods

The hospital where the research was conducted is one of the four pandemic hospitals declared in the province of İstanbul in Turkey due to epidemics experienced in the 2000s. It became prominent in epidemics that were experienced in previous years, and it has developed a hospital culture. During this pandemic, too, intense planning and work have been carried out for all necessary training and logistic support. The Turkish Ministry of Health canceled face-to-face training on 16.03.2020 in the scope of the precautions for the fight against COVID-19. With the organization of the İstanbul Provincial Directorate of Health, the "Healthcare Personnel COVID-19 Training" was prepared as a DT. With the organization of the Istanbul Provincial Directorate of Health, the "Healthcare Personnel COVID-19 Training" was prepared as DT. The DT contained general information about COVID-19 (epidemiology, form of contagiousness), case management, contact tracing, infection management precautions, personal protective equipment usage and isolation, patient room characteristics, entry-exit to and from the room, approach to the COVID-19 patient, cleaning of the patient room, patient transportation, and things to do after the death of a COVID-19-positive patient.

The "HE COVID-19 Training" DT registration was made for healthcare personnel on 17.03.2020, it was announced for all clinics, and it was stated to complete the training by the date of 20.03.2020. A second callout was made for the personnel who did not complete the treatment on 01.04.2020, and it was reminded that completing the training was a legal obligation according to the In-Service Training Directive of the Ministry of Health (Ministry of Health of Republic of Turkey 2009) (5).

The registration of the HE for access to the training system was made by the system administrator. It was added to hospital computers as a desktop shortcut, and information was provided that is was possible to access from home or via mobile phones. The entries to the system were checked in regular intervals. A short message service was sent again to those who did not enter the system. In addition, by having meetings with unit representatives, support was provided for entry to the training system. The completion status of the training program was examined by a report obtained from the administrator panel of the system.

The population of the study consisted of all personnel employed at research and training hospital and registered for the training. Sample selection was not made, and the study was planned retrospectively for reaching all personnel whose training registrations were made between 17.03.2020 and 15.04.2020.

This study uses the data of the personnel who completed the "HE COVID-19 Training" within the scope of the announcements that were made as DT as reported on HES. A DT report form was used as the data collection instrument. Institutional permission (date: April 20, 2020, and no: KAEK/2021.04.148) was acquired to collect data. All individuals gave informed consent. The ethical approval for this study was granted by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital (approval number: 148, date: 21.04.2021) and it was conducted in accordance with the principals of the Declaration of Helsinki.

Statistical Analysis

In the assessment of the results, the results are given as percentages. The ratios in the groups were compared by chi-squared test. The alpha significance level was accepted as $p<0.05$.

Results

The hospital where the study was conducted has a bed capacity of 700, whereas 170 these are beds for the intensive care units (ICU). Services at the hospital were provided by 3,142 personnel. The groups and distributions of these personnel were as follows: 672 physicians (21%), 850 nurses (27%), 428 medical technicians (13.6%), 440 patient admission personnel (14%), 422 cleaning and food personnel (13.4%), 150 security personnel (4.7%), and 180 administrative personnel (5.7%). Flexible working was practiced during the COVID-19 pandemic, and healthcare personnel who were specified in risk groups by Ministry of Health were considered on administrative leave. Pandemic-related training were initially provided as face-to-face training within the hospital starting at the end of January. When the face-to-face training was ended due to the contagious nature of the pandemic, the trainings were planned over HTS.

In this study with a retrospective design, which was planned to investigate the interests of HE in DT during the COVID-19 pandemic process, the total training completion rate of the participants was found to be 90% (Table 1). The rate of completion of the DT in the process of the COVID-19 pandemic among the HE was 93% for the physicians (specialist and resident doctors, general practitioner), 88% for the nurses, midwives and health technicians, 91% for the secretariat (medical secretary, patient admission, data entry personnel), 93% for the cleaning services, 80% for the support services (security staff, driver, clinical support unit, cook, technical services) and 93% for the administrative services. Analysing the participating groups, it was noticed that the participation rates in the groups that initially encountered the patient (emergency service, radiology unit, secretariat, resident doctors, pharmacy, drivers) were noticeably high.

After the observation of the first cases in Turkey (the first case confirmed by polymerase chain reaction was determined on March 11, 2020) and an increase in the number of cases, Ministry of Health canceled face-to-face training within the scope of precautions to fight COVID-19. Our hospital started hosting patients suspected for COVID-19 by March 10. The registration for the DT made for healthcare personnel was announced for all clinics, and the process was monitored after the first announcement. On the first day when the training was registered for the healthcare personnel, 323 individuals completed the training (10.3%).

Table 1. Distance training completion rates of healthcare employees

	Number	Those who completed training	%
Specialist doctor	341	311	91.2
Resident doctor	293	281	95.9
General practitioner	38	32	84.2
Midwifes, nurse, public health staff	850	733	86.2
EMT, first and emergency aid technician	9	9	100.0
Health technician, laboratory assistant, biologist	76	69	90.8
Health technician, radiology	67	67	100.0
Health technician, medical secretary	36	35	97.2
Health technician, anesthesia	63	58	92.1
Dialysis technician	10	10	100.0
Pathology technician	6	6	100.0
Orthosis - prosthesis technician	14	12	85.7
Physiotherapist, physiotherapy technician	16	14	87.5
Pharmacist, pharmacy technician	22	22	100.0
Audiologist, audiology technician	14	10	71.4
Other†	23	21	91.3
Social worker, psychologist, and dietician	22	19	86.4
Cleaning	362	335	92.5
Patient admission	169	151	89.3
Data entry (secretary)	226	224	99.1
Security	150	145	96.7
Administrative services	112	104	92.9
Driver	12	12	100.0
Clinical support	45	39	86.7
Cook, food service staff	60	8	13.3
Technical services	56	56	100.0
Genetics	50	48	96.0
Total	3142	2831	90.1

†Dental technician, forensic medicine, occupational therapist, child development, elderly care technician, drugstore, chemistry technician, and perfusionist. EMT:

At the date of 20.04.2020, given as the time of completing the training, 12% of the group was reached. However, due to the importance of the issue, a second announcement was made, the time of completing the training was extended, and the process was followed up (Figure 1).

Considering the interest of the physicians in the DT, it was seen that 7% of the specialist doctors, 9% of the resident doctors, and 11% of the general practitioners completed the training on the first day of registration.

When the interests of the healthcare personnel in the DT in the process of the COVID-19 pandemic were compared, no statistically significant difference could be observed in the participation rates of the specialist doctors, resident doctors, and nurses ($p=0.094$). The rate of the resident doctors to complete the training until the second announcement was significantly lower compared to the specialist doctors and nurses (specialist doctor vs. resident doctor $p=0.044$; nurse vs. resident $p<0.001$). The rates of completing the training after two announcements were significantly higher among the resident doctors than the specialist doctors and nurses and among the specialist doctors than the nurses (respectively $p=0.018$, $p<0.001$, $p=0.018$) (Table 2).

Discussion

As the rapidly increasing patient numbers in the pandemic process created a certain load on the healthcare system, exclusion of who are under risk from the system also increased the workload. Increased workload may lead to not only violations of protection precautions but also stress and carelessness in employees. To overcome this, in addition to regular training and raising awareness on the significance of this issue, it is needed to provide easy access to sufficient protective equipment and regulate the pace of working. The training during the pandemic could only be possible as DT as a compulsory necessity of transition to flexible working hours, increased workload, and isolation rules.

Considering the sociodemographic characteristics of the sample, it is seen that most of the participants consisted of physicians (21%) and nurses (27%). The rate of completing the training among the healthcare personnel included in the study was found to be 90%. Participation in the training was high among groups that encountered the patients first such as the emergency services, tomography unit, secretariat, resident doctors, and cleaning staff. It was thought that, although

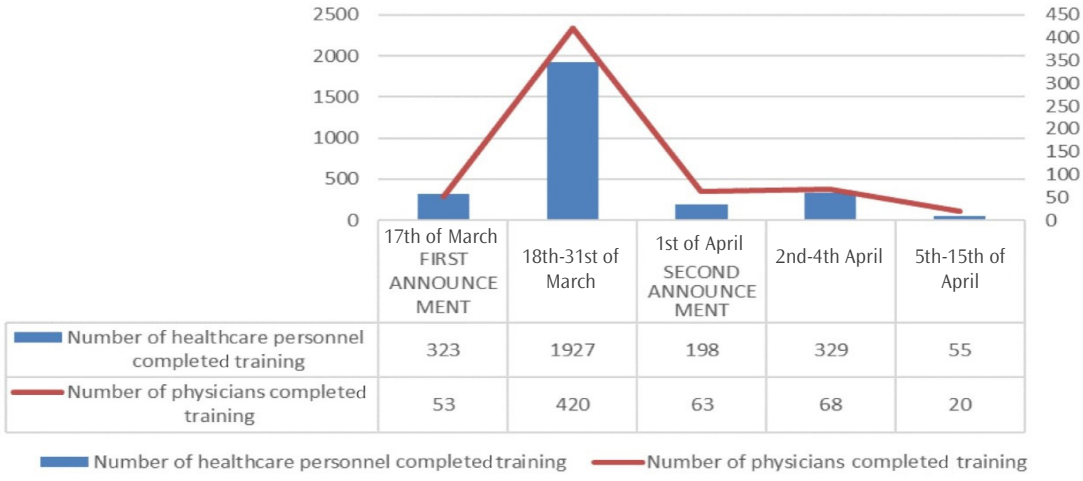


Figure 1. The interest of healthcare employees in distance training during the process of the Coronavirus disease-2019 pandemic. The study was designed as a retrospective study. Healthcare employees' interest in distant training was investigated. Participation in distant training was examined for the dates between the first announcement (March 17, 2020) and April 15, 2020. In the graph, bars represent the number of healthcare personnel that completed training and the line represents the number of physicians that completed them. Columns represent the training periods, and rows represent the personnel type attending the training. The column of numbers on the left-hand side between 0-2500 represents the number range of healthcare personnel, while the numbers on the right-hand side between 0-450 represent the number of physicians

Table 2. Comparison of interests of healthcare employees in training

	Specialist doctor		Resident doctor		Nurse		
	n	%	n	%	n	%	p
Rate of participation at the first announcement	24	7.0	25	8.5	93	10.9	0.094
Rate of completion until the second announcement	241	70.7	185	63.1	615	72.4	0.012*
Rate of completion after two announcements	311	91.2	281	95.9	733	86.2	<0.001**

*p<0.05, **p<0.01

the administrative units were not on the front lines, their interest in the training was high due to concerns of working at a hospital where COVID-19 patients were being monitored and willingness to learn.

Considering the interest of the physicians in the distant training, the higher interests of the resident doctors and general practitioner physicians than the specialist doctors may be explained that a large part of the healthcare personnel, especially at the emergency service and pandemic clinics consisting of resident doctors and general practitioners, they were the group encountering the patient first, and they needed sufficient experience and knowledge about approaching a COVID-19 patient.

In a study that was conducted to investigate the concerns of doctors in Pakistan during the COVID-19 pandemic, it was determined that 80% were concerned about infecting their family members, 63% were conserved about the rapid spread of the disease, and 60% were concerned that the disease would have late-stage complications, whereas 29% of doctors had fears of being a carrier of the disease, and 29% had concerns of not being able to make the diagnosis of the disease (6).

In a qualitative study in China that was conducted to reveal the experiences of providers of healthcare services during the COVID-19 pandemic, it was found that the participants experienced burnout due to working without toilet breaks, without using social environments due to the protection of social distancing measures, for long shifts with protective gear and due to critical patient care at ICUs, their workload significantly increased, and when their shift ended, they were to exhaust to even move (7). The lower interest of the nurses in our study in the training than the resident and specialist doctors suggested that the nurses could not spare time for the training.

It was seen that the employees were interested in the DT, although the COVID-19 pandemic has created a completely new working environment, it has significantly affected both working life and social life, and despite the additional difficulties experienced in this process. This situation shows that healthcare service employees can use technology to access information in all conditions, they are aware that they need knowledge to be able to adapt to newly emerging situations, and a sufficient awareness could be raised in society regarding the severity of the disease.

In the period of the pandemic that has affected the entire world, like all institutions that provide education, medical schools have also used distance education, and in this period, practical and bed-side training were stopped. However, while these training can be stopped for a short time, it cannot be in question to stop the training of the healthcare personnel in the field. The healthcare personnel in the field will not only provide care for their patients but also apply the ways of protection with

the training they receive. This is why the interest in the training involved a high participation rate (8).

Study Limitations

The most important limitation of our study was that it was retrospective. We did not question whether the participants participated in these training voluntarily or out of necessity. We did not compare the participation rate of COVID-19 training with the participation rates of in-service trainings on other topics.

Conclusion

Understanding of COVID-19 infection and risk factors for negative outcomes among HE is important not only for characterizing the contagion patterns of the virus and risk factors for infection but also for preventing future infections of HE and other patients, providing information, updating infection prevention and management precautions at healthcare facilities and on a national level, and reducing secondary COVID-19 contagions in healthcare settings (9).

When healthcare systems are not prepared to cope with an epidemic of a contagious disease, education, instruction, and improved communication are needed. Continuous education is needed to ensure that healthcare teams are sufficiently prepared to cope with public health emergencies.

The COVID-19 pandemic experienced by the world today has shown that distance education and training should be included in a prioritized manner in Emergency Action Plans after earthquakes, erosions, tsunamis, tornadoes, floods, or fires, as well as contagious diseases (pandemics) (10). COVID-19 should not be assessed as only a crisis. It also provides great opportunities to be tested from all aspects from education to social life.

Ethics Committee Approval: The ethical approval for this study was granted by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital (approval number: 148, date: 21.04.2021) and it was conducted in accordance with the principals of the Declaration of Helsinki.

Informed Consent: All individuals gave informed consent.

Peer-review: Internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - A.K., Ö.Y., Y.K.; Concept - A.K., G.Ş., F.P., Y.K.; Design - A.K., G.Ş., Ö.Y., Y.K.; Data Collection or Processing - A.K., G.Ş., F.P.; Analysis or Interpretation - A.K., F.P., Ö.Y.; Literature Search - A.K., G.Ş., F.P.; Writing - A.K., G.Ş., F.P., Ö.Y., Y.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. Senyuva E, Kaya H. Nurses' lifelong-learning tendencies and their attitudes toward distance education: A sample of Turkey. The New Educational Review 2014; 36: 17-29.
2. Fidan M. Distance education students' attitudes towards distance education and their epistemological beliefs. Hacettepe University J Education 2016; 3: 536-50.
3. Isman A. Distance education, 4th ed. Ankara: Pegem Akademi; 2011.
4. Welsh ET, Wanberg CR, Brown KG, Simmering MJ. E-learning: Emerging uses, empirical results and future directions. International Journal of Training and Development 2003; 1: 245-58.
5. Ministry of Health In-Service Training Regulations. Ministry of Health of Republic of Turkey 2009. B.10.0.SEG.0.72.00.03-010.03/15296. Available from: https://shgm.saglik.gov.tr/TR-9838/yönetmelik.html
6. Urooj U, Ansari A, Siraj A, Khan S., Tariq H. Expectations, fears and perceptions of doctors during COVID-19 pandemic. Pak J Med Sci 2020; 36: S37-42.
7. Liu Q, Luo D, Haase JE, Guo Q, Wang XQ, Liu S, et al. The experiences of health-care providers during the COVID-19 crisis in China: A qualitative study. Lancet Glob Health 2020; 6: 790-8.
8. Tokuç B, Varol G. Medical education in Turkey in time of COVID-19. Balkan Med J 2020; 37: 180-1.
9. World Health Organization. Protocol for assessment of potential risk factors for coronavirus disease 2019 (COVID-19) among health workers in a health care setting 2020. Available from: https://www.who.int/publications/i/item/protocol-for-assessment-of-potential-risk-factors-for-2019-novel-coronavirus-(2019-ncov)-infection-among-health-care-workers-in-a-health-care-setting
10. Telli S, Altun D. The coronavirus and the rising of online education. Journal of University Research 2020; 1: 25-34 (Turkish).

İstanbul Med J 2023; 24(1): 53-6
DOI: 10.4274/imj.galenos.2023.41882

Preoperative MELD-Na Score Predicts 30-day Post-operative Complications After Colorectal Resection for Malignancy

Adil Koyuncu[1], Ömer Akay[2], Hüsnü Şevik[2], Mert Güler[2], Sena Cağla Özden[1], Hogir Aslan[1], Fatih Göksel Seçkin[3], Cihad Tatar[3]

[1]University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of General Surgery, İstanbul, Turkey
[2]University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of General Surgery, İstanbul, Turkey
[3]Acıbadem Taksim Hospital, Clinic of General Surgery, İstanbul, Turkey

ABSTRACT

Introduction: Predicting possible complications in colon surgery is important in terms of reducing postoperative mortality and morbidity rates. Various scoring methods have been used to predict these complications. The MELD score was developed to predict mortality following Transjugular Intrahepatic Portosystemic Shunt (TIPS) placement in cirrhotic patients. This model was revised by adding Na data and used to predict complications in non-cirrhotic patients. We investigated the value of the MELD-Na score in predicting postoperative 30-day complications in patients undergoing colorectal resection for malignancy.

Methods: Patients who underwent colorectal resection for malignant diseases were included in the study. Demographics and clinical outcomes were recorded. The MELD-Na scores of the patients were calculated within 48 h before the surgery. Patients were divided into 2 groups according to the status of development of any complication.

Results: Age, gender, operative time, and length of stay was not statistically significant for developing complications. The MELD-Na score was significantly higher in patients with any complications. Also, MELD-NA score, stoma creation, and postoperative erythrocyte suspension replacement were found to be independent risk factors for developing complications in patients undergoing surgery for colon cancer.

Conclusion: The MELD-Na score may predict the complications that may develop in the first 30 days postoperatively in patients undergoing colorectal resection for malignant diseases.

Keywords: Colorectal cancer, complication, MELD-Na

Introduction

Following colon resection, perioperative morbidity and mortality are largely dependent on the elective or emergencies of the procedure (e.g. occlusive lesion, bowel perforation) and the patient's associated comorbidities (e.g. cardiopulmonary disease, multiple traumas, etc.). Colon cancer patients tend to have more comorbidities because of the higher mean age and as a result, postoperative morbidity and mortality are also higher (1).

The MELD score is a validated chronic liver disease severity scoring system to estimate three-month survival (2). The formula was updated in 2016 by adding serum sodium (3).

Various studies have reported that the addition of serum sodium concentration improves the predictive accuracy of the MELD score in hyponatremic patients who have low MELD scores and awaiting liver transplantation (4-11).

The primary use of the MELD and MELD-Na scores is to prioritize patients on the waiting list for cadaver donor liver transplantation based on liver disease severity and short-term risk of mortality. However, the MELD score also predicts mortality following placement of a Transjugular Intrahepatic Portosystemic Shunt (TIPS). It was shown to have a predictive value for outcomes in patients who have cirrhosis undergoing non-transplant surgical procedures (12).

In this study, the purpose was to investigate the value of the MELD-Na score in predicting early mortality and morbidity in the first postoperative 30 days in patients with colorectal cancer.

Methods

The patients who applied to Haseki Training and Research Hospital and Istanbul Training and Research Hospital between 01.07.2020 and 01.07.2022 and underwent colorectal resection were included in the study. Ethical approval for this study was obtained from a University of

Address for Correspondence: Adil Koyuncu MD, University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of General Surgery, İstanbul, Turkey
Phone: +90 533 659 98 89 **E-mail:** tatarcihad@gmail.com **ORCID ID:** orcid.org/0000-0002-5354-2036

Cite this article as: Koyuncu A, Akay Ö, Şevik H, Güler M, Özden SÇ, Aslan H, Seçkin FG, Tatar C. Preoperative MELD-Na Score Predicts 30-day Post-operative Complications After Colorectal Resection for Malignancy. İstanbul Med J 2023; 24(1): 53-6.

Received: 28.07.2022
Accepted: 16.01.2023

©Copyright 2023 by the University of Health Sciences Turkey, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.

Health Sciences Turkey, Haseki Training and Research Hospital Local Ethical Committee (approval number: 134-2022). Informed consent was received from the patients. Those who were diagnosed with cirrhosis, whose laboratory did not require the necessary parameters for MELD Na score measurement, and diagnosed with a different cancer were excluded. The MELD-Na scores of the patients were calculated by evaluating the blood results obtained within 48 h before the surgery. The patients were followed up for 30 days postoperatively for complications. The relationship between complications and MELD-Na score was investigated.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS®) version 17.0 software package for Windows, was used for statistical analysis. Comparisons of numerical variables in two independent groups were made with Student's t-test for normally distributed variable and Mann-Whitney U test for non-normally distributed variables. The ratios in the groups were analyzed using the chi-square test. Multivariate regression analysis was performed with the statistically significant data. The statistical alpha significance level was accepted as $p<0.05$

Results

A total of 206 patients were included in the study. Among these, 86 (41.7%) were female and 120 (58.3%) were male. Complications were observed in 66 (32%) patients. The mean age of patients who developed complications was 63.70±14.08 years, and those who did not develop complications were 66.47±10.82 years. Age was not statistically significant for developing complications (p=0.124). Although the mean surgery duration was 190.42±56.65 in the group with complications, the mean surgery duration was 205.88±67.45 in the group without complications. The mean Meld-Na score was found to be 11.65±4.71 in patients with complications, 9.72±2.41 in patients without complications, and the Meld-Na score was significantly higher in the group with complications (p<0.001). Although the mean hospital stay was 13.85±11.21 days in the group with complications, it was 5.78±1.87 days in the group without complications, and the difference was statistically significant (p<0.001). The mean number of erythrocyte suspension (ES) replacements was 2.16±2.44 in the group with complications and 0.67±1.20 in the group without complications and difference was statistically significant (p<0.001). The mean number of harvested lymph nodes was 21.40±13.63 in the group with complications and 16.70±5.77 in the group without complications, and more lymph nodes were removed in the group with complications at statistically significant levels (p<0.001). The mean number of metastatic lymph nodes was 1.14±2.03 in the group with complications, it was 2.46±3.80 in the group without complications (p<0.001). The general characteristics of the patients who developed complications are given in Table 1.

Among the patients who developed complications, 23 (34.8%) were female, 43 (65.2%) were male, and gender was not a risk factor for developing complications (p=0.168). The complication rate was higher in patients with comorbidity at a significant level (p=0.002). Complications were present in 34 of 72 patients with a stoma, and stoma creation was considered a risk factor for developing complications (p=0.001). Complications were observed in 27 of 54 patients who underwent emergency surgery, and it was observed that it increased the development of complications at a significant level (p=0.001). It was found that preoperative liver metastasis and the type of surgery were not significant in increasing the development of complications. However, 14 patients died and the MELD-Na scores of 11 of the patients who died were found to be above 10.75. The data on postoperative complication analysis are given in Table 2.

Table 1. Comparison of the features of the patients

	Complications (yes), (n=66)	Complications (no), (n=140)	p
MELD-Na	11.65±4.72	9.72±2.41	**<0.001**
Age	63.7±14.09	66.47±10.83	0.124
Operative time (minutes)	190.42	205.88	0.539
Postoperative ES	2.16±2.44	0.67±1.20	**<0.001**
Length of stay	13.85±11.21	5.79±1.87	**<0.001**
Metastatic lymph nodes	1.14	2.46	**<0.001**
Total harvested lymph nodes	21.40	16.70	**<0.001**

ES: Erythrocyte suspension

Table 2. Comparison of the features of the patients

		Complications (yes), (n=66)	Complications (no), (n=140)	p
Gender (female)		23 (26.7)	63 (73.3)	0.168
Comorbidity		26 (49.1)	27 (50.9)	**0.002**
Stoma creation		34 (47.2)	38 (52.8)	**0.001**
Liver metastasis		5 (27.8)	13 (72.2)	0.685
Surgical approach	Open	41 (29.9)	96 (70.1)	0.360
	Laparoscopic	25 (36.2)	44 (63.8)	
Emergency		27 (50.0)	27 (50.0)	**0.001**
Mortality		3 (21.4)	11 (78.6)	**0.001**

Complications were followed up in 2 groups of patients based on MELD-Na score ≤10.75 and >10.75. The rate of wound infection, anastomotic leakage, internal complications, and any complication development were found to be significantly higher in patients with a score of >10.75 than in patients with a score of ≤10.75. No positive correlations were detected between the intra-abdominal abscess, evisceration, and ileus and the Meld-NA scores of the patients. Complication analysis results according to the MELD-Na score are given in Table 3.

Because of the multivariate analysis, Meld-NA score, stoma creation, and postoperative ES replacement were found to be independent risk factors for developing complications in patients undergoing surgery for colon cancer. The results of the analysis are given in Table 4.

Discussion

In this study, patients who were operated on for colon cancer were examined, and a significant correlation was found between early postoperative complications and mortality and elevated MELD-Na score. We think that the elevated MELD-Na score to be checked preoperatively will contribute to the prediction of complications.

As is already known, the MELD score was first used to predict mortality following TIPS placement. The model was then validated in an independent cohort of patients with TIPS placement (13). Later, this model was revised by adding Na data. Although this scoring system was primarily used to identify patients who would undergo liver transplantation, it was later used to predict complications in patients who were scheduled for non-transplant surgery (14).

In Khachfe et al.'s (15) study, in which 1,096 cases of elective gastrectomy were examined, patients with a Meld-Na score of >11 and <11 were compared, and the rates of mortality, any complications, and major complications were found to be significantly higher in the group with elevated Meld-Na scores. In this study, it was concluded that the rates of wound infection, anastomotic leakage, internal complications, and any complication development increased significantly.

Al Abbas et al. (16) reported a positive correlation between an MELD score of >11 and mortality in patients who underwent Whipple. It was found that most patients with a mortal course had a MELD-Na score above 10.75.

Causey et al. (17) conducted a study in which 10,842 patients who were operated on for colon cancer were examined and reported that a MELD-Na score above 9 increased the risk of postoperative complications 1.3 times, and, the mortality risk increased 2.7 times in patients who had a score above 8. The increase in mortality and complications in this study is in parallel with this article.

Coakley et al. (18) conducted a study in which 44,540 elective colorectal cases were examined, MELD-Na score was found to be an independent risk factor for developing complications.

In a study that was conducted by Schlosser et al. (19) in which 48,955 patients who underwent elective hernia repair were examined, it was reported that the risk of postoperative complications, hospital stay, reoperation, and mortality increased in patients with a MELD-Na score above 10.

This study supports many studies on this subject. In this study, positive correlations were detected between the length of hospital stay, wound infection, anastomotic leakage, internal problems, and the development of any complications, and a high MELD-Na score.

Some studies report positive correlations between age and postoperative complications (20); however, the age factor was not found to be significant in terms of complication development in this study.

Table 3. Complication analysis according to the MELD-Na score

	MELDS-Na score		p
	<10.75 n, (%)	**>10.75 n, (%)**	
SSI	22 (84.6)	4 (15.4)	**0.036**
Intra-abdominal abscess	13 (81.3)	3 (18.7)	0.193
Evisceration	11 (68.8)	5 (31.2)	0.843
Ileus	18 (78.3)	5 (21.7)	0.205
Anastomotic leakage	21 (87.5)	3 (12.5)	**0.020**
Internal complications	15 (34.1)	29 (65.9)	**<0.001**
Any complications	37 (56.1)	29 (43.9)	**0.029**

SSI: Surgical site infection

Table 4. Multivariate analysis

	Complications (yes)	Complications (no)	p	OR
Comorbidity n, (%)	35 (63.6)	20 (36.4)	0.759	0.810
Elective surgery	58 (36.7)	100 (73.3)	0.147	0.461
Stoma creation	58 (38.9)	91 (61.1)	**<0.001**	9.784
Gender (female) n, (%)	65 (51.6)	61 (48.4)	0.186	0.488
Meld-Na score (mean ± SD)	11.65±4.72	9.72±2.41	**0.017**	0.843
Postoperative ES replacement	2.16±2.44	0.67±1.20	**<0.001**	0.532
Neoadjuvant therapy n, (%)	7 (15.2)	39 (84.8)	0.537	1.389

Study Limitations

The most important limitations of this article were the small number of patients and the retrospective nature of the study. Also, the fact that the surgery teams were different and their experience was not standardized was another limitation, and we think that this may affect the development of complications. Urgent colon resections were also added to the study data, increasing the risk of complications.

Conclusion

Our study concluded that the elevated MELD-Na scores calculated in the preoperative period of the patients who are scheduled for surgery for colorectal cancer can predict the complications that may develop in the first 30-days postoperatively.

Ethics Committee Approval: Ethical approval for this study was obtained from a University of Health Sciences Turkey, Haseki Training and Research Hospital Local Ethical Committee (approval number: 134-2022).

Informed Consent: Informed consent was received from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - A.K., Ö.A., H.Ş., M.G., S.C.Ö., H.A., F.G.S., C.T.; Concept - A.K., Ö.A., C.T.; Design - A.K., Ö.A., C.T.; Data Collection or Processing - A.K., Ö.A., H.Ş., M.G., S.C.Ö., H.A., F.G.S., C.T.; Analysis or Interpretation - A.K., Ö.A., H.Ş., M.G., S.C.Ö., C.T.; Literature Search - A.K., Ö.A., S.C.Ö., H.A., F.G.S.; Writing - A.K., Ö.A., C.T.

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. Neuman HB, Weiss JM, Leverson G, O'Connor ES, Greenblatt DY, Loconte NK, et al. Predictors of short-term postoperative survival after elective colectomy in colon cancer patients ≥ 80 years of age. Ann Surg Oncol 2013; 20: 1427-35.
2. Freeman RB Jr, Wiesner RH, Harper A, McDiarmid SV, Lake J, Edwards E, et al. UNOS/OPTN Liver Disease Severity Score, UNOS/OPTN Liver and Intestine, and UNOS/OPTN Pediatric Transplantation Committees. The new liver allocation system: moving toward evidence-based transplantation policy. Liver Transpl 2002; 8: 851-8.
3. (Accessed on June 19, 2018). https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/
4. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med 2008; 359: 1018-26.
5. Heuman DM, Abou-Assi SG, Habib A, Williams LM, Stravitz RT, Sanyal AJ, et al. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. Hepatology 2004; 40: 802-10.
6. Luca A, Angermayr B, Bertolini G, Koenig F, Vizzini G, Ploner M, et al. An integrated MELD model including serum sodium and age improves the prediction of early mortality in patients with cirrhosis. Liver Transpl 2007; 13: 1174-80.
7. Londoño MC, Cárdenas A, Guevara M, Quintó L, de Las Heras D, Navasa M, et al. MELD score and serum sodium in the prediction of survival of patients with cirrhosis awaiting liver transplantation. Gut 2007; 56: 1283-90.
8. Biggins SW, Kim WR, Terrault NA, Saab S, Balan V, Schiano T, et al. Evidence-based incorporation of serum sodium concentration into MELD. Gastroenterology 2006; 130: 1652-60.
9. Ruf AE, Kremers WK, Chavez LL, Descalzi VI, Podesta LG, Villamil FG. Addition of serum sodium into the MELD score predicts waiting list mortality better than MELD alone. Liver Transpl 2005; 11: 336-43.
10. Guy J, Somsouk M, Shiboski S, Kerlan R, Inadomi JM, Biggins SW. New model for end stage liver disease improves prognostic capability after transjugular intrahepatic portosystemic shunt. Clin Gastroenterol Hepatol 2009; 7: 1236-40.
11. Biselli M, Gitto S, Gramenzi A, Di Donato R, Brodosi L, Ravaioli M, et al. Six score systems to evaluate candidates with advanced cirrhosis for orthotopic liver transplant: Which is the winner? Liver Transpl 2010; 16: 964-73.
12. (Accessed on June 04, 2018). https://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/post-operative-mortality-risk-patients-cirrhosis
13. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000; 31: 864-71.
14. (Accessed on June 04, 2018). https://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/post-operative-mortality-risk-patients-cirrhosis
15. Khachfe HH, Araji TZ, Nassereldine H, El-Asmar R, Baydoun HA, Hallal AH, et al. Preoperative MELD score predicts adverse outcomes following gastrectomy: An ACS NSQIP analysis Am J Surg 2022; 224: 501-5.
16. Al Abbas AI, Borrebach JD, Bellon J, Zureikat AH. Does Preoperative MELD Score Predict Adverse Outcomes Following Pancreatic Resection: an ACS NSQIP Analysis. J Gastrointest Surg 2020; 24: 2259-68.
17. Causey MW, Nelson D, Johnson EK, Maykel J, Davis B, Rivadeneira DE, et al. The impact of Model for End-Stage Liver Disease-Na in predicting morbidity and mortality following elective colon cancer surgery irrespective of underlying liver disease. Am J Surg 2014; 207: 520-6.
18. Coakley KM, Sarasani S, Prasad T, Steele SR, Paquette I, Heniford BT, et al.: MELD-Na score as a predictor of anastomotic leak in elective colorectal surgery. J Surg Res 2018; 232: 43-8.
19. Schlosser KA, Kao AM, Zhang Y, Prasad T, Kasten KR, Davis BR, et al. MELD-Na score associated with postoperative complications in hernia repair in non-cirrhotic patients. Hernia 2019; 23: 51-9.
20. Zhang J, Linhua Jiang L, Zhu X. A Novel Nomogram for Prediction of Early Postoperative Complications of Total Gastrectomy for Gastric Cancer. Cancer Manag Res 2021; 13: 7579-91.

İstanbul Med J 2023; 24(1): 57-61
DOI: 10.4274/imj.galenos.2023.66502

Impact of Trigger Point Dry Needling on Neck Pain, Sleep, and Depression in Patients with Fibromyalgia

Esma Demirhan, Sevgi Atar, Rasim Akgün, Begüm Siret Özfırat, Ömer Kuru
University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Physical Medicine and Rehabilitation, İstanbul, Turkey

ABSTRACT

Introduction: The study aimed to assess the effectiveness of dry needling (DN) for neck pain in fibromyalgia caused by myofascial trigger points (MTrPs) in the trapezius muscle.

Methods: Fibromiyalgia patients who were treated with DN were retrieved from the hospital database. The study included people with trapezius MTrPs-related neck pain who were between the ages of 18 and 65 and had a two-month follow-up. DN treatment was applied to MTrPs in the trapezius muscle once a week for 4 sessions. Demographic data for the patients were recorded from their files. Before treatment and four weeks after the program was finished, all patients underwent evaluations. In each evaluation we assessed pain, neck disability, sleep quality, anxiety and depression and fibromyalgia severity with visual analogue scale (VAS), Neck Disability Index (NDI), Pittsburgh Sleep Quality Index (PSQI), Hospital Anxiety Depression scale (HADS) and Fibromiyalgia Impact scale (FIQ), respectively.

Results: In patients with FMS with neck discomfort, DN therapy administered to MTrPs in the trapezius muscle once per week for four sessions was beneficial in the short term. Additionally, with this treatment quality of sleep and life of the patients were improved; anxiety, depression levels, and pain severity were also significantly reduced. Statistically significant improvement was found in VAS, NDI, PSQI, HADS, and FIQ scores (for all parameters; $p<0.001$).

Conclusion: For better management of patients with FMS patients, MTrPs should not be ignored. DN treatment should also be among the treatment options as an effective treatment.

Keywords: Dry needling, fibromyalgia syndrome, myofascial trigger points, neck disability, neck pain

Introduction

Fibromyalgia syndrome (FMS) is characterized by multifocal pain, especially in the musculoskeletal system, accompanied by fatigue, depression, anxiety, cognitive dysfunction and sleep disorder (1). Although tender points are often mentioned in fibromyalgia, trigger points are frequently encountered in these patients, especially in the neck muscles (2,3) Muscle trigger points (MTrPs) are the hypersensitive points within muscle taut bands. They cause referred pain during compression and they can be latent or active (4) widespread musculoskeletal pain, low pain threshold, and hyperalgesia. Myofascial trigger points (MTrPs. Although MTrP is a hallmark of myofascial pain syndrome (MPS), it has been revealed that the random pain felt in FMS is generated by local and referred pain from active and common MTrPs (3,5). MTrPs that cause neck pain, are more common in trapezius muscle (6).

Although MPS and FMS are considered as two separate clinical entities, it is stated in the literature that these two conditions can coexist or overlap significantly (7,8). In fact, these two syndromes are so intertwined that central sensitization caused by MPS has begun to be blamed in the etiopathogenesis of FMS (2,7-9). Management of MTrPs reduces peripheral nociception thereby reducing central sensitization and leading to improvements in pain (10).

Dry needling (DN) is one of the treatment options for MTrP pain. It is applied directly to trigger points with an acupuncture needle or fine injector tip to relieve pain. It deactivates the trigger point without medication (1). It shows its effect through the mechanical effect and by stimulating nerve fibers and regulating neurotransmitters and hormones on the central nervous system (10).

This study aimed to evaluate the effectiveness of trapezius muscle DN treatment on patient's severity of pain, psychological state, sleep quality, and functionality in fibromyalgia patients with a predominant neck pain complaint.

Address for Correspondence: Esma Demirhan MD, University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Physical Medicine and Rehabilitation, İstanbul, Turkey
Phone: +90 212 314 55 55 **E-mail:** esmademirhan@gmail.com **ORCID ID:** orcid.org/0000-0001-7581-9406

Cite this article as: Demirhan E, Atar S, Akgün R, Özfırat BS, Kuru Ö. Impact of Trigger Point Dry Needling on Neck Pain, Sleep, and Depression in Patients with Fibromyalgia. İstanbul Med J 2023; 24(1): 57-61.

Received: 15.12.2022
Accepted: 19.01.2023

©Copyright 2023 by the University of Health Sciences Turkey, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.

Methods

Study Design and Participants

This was a retrospective study performed in a tertiary hospital in İstanbul, Turkey. The University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital Local Ethics Committee approved the study protocol (approval number: 2022/452). It was performed in accordance with the Declaration of Helsinki's principles, participants gave both written and verbal informed consent. Patients diagnosed with FMS, treated with 4 sessions of DN between February 2018 and June 2018, were retrieved from the hospital database. The study included people with trapezius MTrPs-related neck pain who were between the ages of 18 and 65 and had a two-month follow-up. Participants with cervical radiculopathy or myelopathy, rheumatological, psychiatric, neurologic, malign diseases, coagulopathy presence, and pregnancy presence were excluded. Patients who had received an injection or treatment with MTrPs during the previous three months and were on immunosuppressive or anti-coagulant medications were also excluded.

Demographic data of the patients such as weight, height, body mass index (BMI), gender, smoking history, and comorbidities were recorded from their files. Before starting treatment and four weeks after the program was finished, all patients underwent evaluations. In each evaluation we assessed pain, neck disability, sleep quality, anxiety and depression and fibromyalgia severity with visual analogue scale (VAS), Neck Disability Index (NDI), Pittsburgh Sleep Quality Index (PSQI), Hospital Anxiety Depression scale (HADS) and Fibromiyalgia Impact Scale (FIQ), respectively.

Dry Needling Technique

The sterile 0.25x25 mm (Hua Long) acupuncture needles were inserted deeply into the palpable trigger points while the patient was seated. Needles were left in situ for 20 min; at the 10th minute the needles were rotated clockwise. All participants received 4 sessions (once a week for four weeks). All recruited respondents were given patient education on DN therapy. Two physicians with more than 15 years of experience performed the DN.

Materials

Fibromyalgia impact questionneire: It consists of 10 subscales. The total score ranged from 0 to 100. Higher scores reflect a more negative impact.

Pittsburgh Sleep Quality Index: This was used to assess the sleep quality. It differentiates "poor" sleep from "good" sleep. It comprises 7 dimensions. A "poor" sleeper is one with a total score of 5 or higher (11).

Neck Disability Index: This was used to evaluate the severity of neck disability. It is composed of 10 questions including daily functional activities. Scores >25 reflect a severe disability (12).

The Hospital Anxiety Depression scale: This detects significant anxiety and depression. It contains 7 items in each of its two subscales. The scores ranged from 0-21 on each subscal; the cut-off score was 10 for HADS-A and 7 for HADS-D. Those who score above these values are considered at risk for anxiety and depression (13).

Visual analog scale: Patients score their pain on a scale with 0 representing "no pain" and 10 representing "most severe pain possible".

Statistical Analysis

The Statistical Package for the Social Sciences, version 25.0, for Windows, was used for statistical analyses (SPSS Inc; Chicago, IL, USA). For continuous variables, the data were shown as mean and standard deviation; for categorical variables, they were shown as number (n) and percentage (%); and for non-normalized variables, they were shown as median (min.-max.). Using the Shapiro-Wilk test or the Kolmogorov-Simirnov test, the degree of normalcy was determined. Where appropriate, the paired t-test or the Wilcoxon test was performed to compare continuous variables. The correlation between variables was also determined using the Pearson correlation. Results were assessed on a bilateral basis at a 95% confidence level, with a significance level of <0.05.

Results

The study included 34 female patients with a mean age of 44.2±8.3 (27-55) years and mean BMI of 25.3±3.2 kg/m^2. Table 1 presents the demographic and clinical characteristics of the patients. All the patients had poor slee; their PSQI scores were higher than five (PSQI: 12.32±2.8). All of them had higher VAS scores (VAS: 8.5±1.3) because of severe pain.

The comparison between baseline and one month after treatment is shown in Table 2 (Figure 1, 2). A statistically significant improvement was found in VAS, NDI, PSQI, HADS, and FIQ scores (for all parameters; $p<0.001$). Although there was an improvement in sleep scores ($p<0.001$), patients still had poor sleep one month after the treatment sessions (8.7±2.1). Also, their VAS scores were reduced but they still had moderate pain at the follow-up.

Total FIQ scores were correlated moderately with HADa scores ($r=0.443$, $p<0.01$), VAS scores ($r=0.460$, $p<0.01$), and PSQI scores ($r=0.423$, $p<0.01$). There were no correlations between FIQ scores and age, BMI, and HADd scores (Table 3).

Discussion

The main result of the current study is that MTrP DN treatment applied into the trapezius muscle in patients with FMS with severe neck pain is effective in one-month follow-up. Additionally, with this treatment, the patients' sleep and quality of life improve; anxiety, depression levels, and pain severity reduces.

It was argued that as a peripheral pain generator MTrPs, may cause FMS, increase disease activity or worsen symptoms (3,9). At least one active or latent trigger point was detected in most patients with FMS (14,15). It was reported that cervical MTrP accompanies 25% of patients with FMS (2,3). DN deactivates active MTrPs, reduces pain and improves mood, function, and level of disability (16-18).

There are an increasing number of researches in the literature about trapezius muscle MTrP DN. The beneficial effects of DN on neck disability, pain severity, quality of life, and range of motion were reported. Although the application of one session of DN was found effective in improving pain, in another study, it was reported that 2-4 sessions of DN were required to treat MTrP of trapezius muscle (6,18,19). Although lots

of the studies evaluated the immediate and short-term effect, there are studies with long-term effect (3-6 months) of DN therapy (6,18,20,21). Our patients had 4 sessions of DN therapy and they were evaluated one month after the therapy, this protocol was found to be effective for improvements in pain, sleep, anxiety, depression, and fibromyalgia impact scores.

Needling of different points was examined (active trigger point, latent trigger point, tender point and 2 cm close to the trigger point; it was

Table 1. Patient characteristics

		n (%)/median (min.-max.)/mean ± SD
Age		47 (27-55)/44.2±8.3
BMI		24.9 (20.2-33.6)/25.3±3.2
Smoking status	Smoker	21 (61.8%)
	Non-smoker	13 (38.2%)
Education	Primary	19 (55.9%)
	Secondary	8 (23.5%)
	University	7 (20.6%)
Occupational status	Has a job	12 (35.3%)
	Homemaker	22 (64.7%)
FIQ		67.3 (27-80)/64.8±14.8
PSQI		12 (7-16)/12.32±2.8
HAD[d]		8.5 (1-18)/8.1±3.8
HAD[a]		10.5 (5-18)/10.9±3.6
NDI		23.5 (14-47)/26.1±8.6
VAS		8 (6-10)/8.5±1.3

Mean ± standard deviation n, (%) median (minimum-maximum). min.-max.: Minimum-maximum, SD: Standard deviation BMI: Body mass index, FIQ: Fibromyalgia Inventory Questionaire, PSQI: The Pittsburgh Sleep Quality Index, HAD: Hospital Anxiety and Depression scale, [a]: Anxiety, [d]: Depression; NDI: Neck disability index, VAS: Visual analog scale

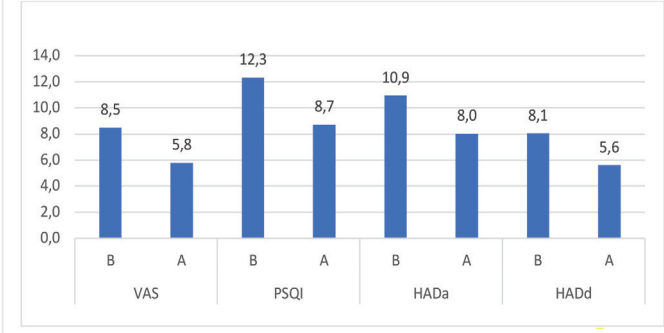


Figure 1. The comparison of parameters baseline and post-treatment*
*P<0.001 for all parameters, VAS: Visual analog scale, PSQI: The Pittsburgh Sleep Quality Index, HAD: Hospital Anxiety and Depression scale, a: Anxiety, d: Depression; B: Baseline, A: One month after treatment

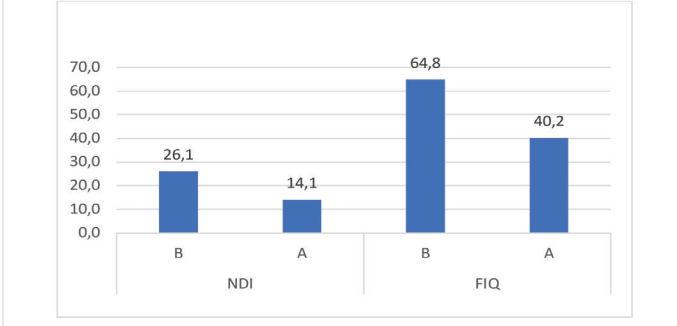


Figure 2. The comparison of parameters baseline and post-treatment
*P<0.001 for all parameters, FIQ: Fibromyalgia Inventory Questionaire, NDI: Neck Disability Index, B: Baseline, A: One month after treatment

Table 2. The comparison between baseline an one month after treatment

	Baseline	One month after post-treatment	p
FIQ	67.3 (27-80)/64.8±14.8	33.6 (7.2-76.6)/40.17±20.8	**<0.001[1]**
PSQI	12 (7-16)/12.3±2.8	8 (5-14)/8.7±2.1	**<0.001[1]**
HAD[d]	8.5 (1-18)/8.1±3.8	5 (0-14)/5.6±2.8	**<0.001[2]**
HAD[a]	10.5 (5-18)/10.9±3.6	7 (4-17)/8±3	**<0.001[1]**
NDI	23.5 (14-47)/26.1±8.6	12 (7-33)/14.1±6.1	**<0.001[1]**
VAS	8 (6-10)/8.5±1.3	3.5 (1-8)/3.6±1.7	**<0.001[1]**

Mean ± standard deviation, n, (%). [1]: Wilcoxon, [2]: Paired samples t-test, FIQ: Fibromyalgia Inventory Questionaire, PSQI: The Pittsburgh Sleep Quality Index, HAD: Hospital Anxiety and Depression scale, [a]: Anxiety, [d]: Depression; NDI: Neck disability index, VAS: Visual analog scale

Table 3. Relationship between the baseline parameters

		PSQI	NDI	FIQ
Age	r	0.24	0.06	-0.06
	p	0.17	0.72	0.72
BMI	r	0.05	0.06	-0.16
	p	0.80	0.72	0.36
PSQI	r	1.00	**0.467****	**0.423***
	p	0.00	0.01	0.01
HAD[a]	r	0.17	**0.394***	**0.443****
	p	0.34	0.02	0.01
HAD[d]	r	-0.05	0.11	0.15
	p	0.78	0.53	0.39
NDI	r	**0.467****	1.00	**0.506****
	p	0.01	0.00	0.00
FIQ	r	**0.423***	**0.506****	1.00
	p	0.01	0.00	0.00
VAS	r	0.33	**0.449****	**0.460****
	p	0.05	0.01	0.01

Pearson**: The correlation is significant at the 0.01 level (2-tailed), *: The correlation is significant at the 0.05 level (2-tailed). BMI: Body mass index, FIQ: Fibromyalgia Inventory Questionaire, PSQI: The Pittsburgh Sleep Quality Index, HAD: Hospital Anxiety and Depression scale, a: Anxiety, d: Depression, NDI: Neck Disability Index, VAS: Visual analog scale

emphasized that the needling point was unimportant. DN of the trapezius muscle improved local mechanical hyperalgesia, pain severity, and discomfort regardless of the point (6,22).

Different application technics such as superficial DN, deep DN, DN with 30 min retention, and peppering (moving the needle forward and backward 8-10 times at the same point) were proven to be useful in reducing pain and depression symptoms as well as enhancing daily activities (21,23). We used deep DN with 20 min retention technic, and after one month of MTrPs treatment for the trapezius muscle, we saw a considerable reduction in pain severity.

In a study with the first, third, and sixth month follow-up, stretching combined with four sessions of twice-weekly DN therapy for neck pain was found to be more beneficial than stretching alone for pain, neck disability, range of cervical motion, mechanical hyperalgesia, and quality of life (20,24).

In a study, four sessions of once-weekly MTrP DN therapy reduced neck region pain in patients with FMS in the short term. This protocol also improved depression, anxiety, sleep, quality of life and fatigue symptoms (9). In this study they needeled latent and active MTrPs in all the neck muscles with fast-in, fast-out technique (9). We needled only trapezius muscle with 20-minute retention technique. Altough our technique were different our results were the same as theirs. Tender-point DN treatment (six sessions,once-weekly) in FMS patients also produced positive effects in improving pain intensity, quality of life and depression (22).

Although there was a statistically significant improvement in sleep scores, and VAS scores, patients still had poor sleep and mild pain at the follow -up. Perhaps it was due to the higher baseline PSQI and VAS scores. Maybe we could have applied a treatment protocol with more sessions for better results.

Study Limitations

The current study has several limitations. First, this study didnot have long-term results, second only female patients were included in the study, the third current study could be conducted with a larger sample size. Another limitation we could have a control group to perform comparisons.

Conclusion

MrTP DN improves pain, neck disability, sleep quality, anxiety, depression, and quality of life in patients with FMS. For better management of patients with FMS patients, MTrPs should not be ignored. DN treatment should also be among the treatment options as an effective treatment.

Ethics Committee Approval: The University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital Local Ethics Committee approved the study protocol (approval number: 2022/452).

Informed Consent: Participants gave both written and verbal informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - E.D., S.A., R.A., B.S.Ö.; Concept - E.D., S.A., Ö.K.; Design - E.D., S.A., Ö.K.; Data Collection or Processing - E.D., R.A., B.S.Ö., Analysis or Interpretation - E.D., S.A., Ö.K.; Literature Search - E.D., R.A., B.S.Ö.; Writing - E.D., S.A., Ö.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. Valera-Calero JA, Fernández-de-Las-Peñas C, Navarro-Santana MJ, Plaza-Manzano, G. Efficacy of Dry Needling and Acupuncture in Patients with Fibromyalgia: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health 2022; 19: 9904.
2. Cakit BD, Taskin S, Nacir B, Unlu I, Genc H, Erdem HR. Comorbidity of fibromyalgia and cervical myofascial pain syndrome. Clin Rheumatol 2010; 29: 405-11.
3. Alonso-Blanco C, Fernández-de-las-Peñas C, Morales-Cabezas M, Zarco-Moreno P, Ge HY, et al. Multiple active myofascial trigger points reproduce the overall spontaneous pain pattern in women with fibromyalgia and are related to widespread mechanical hypersensitivity. Clin J Pain 2011; 27: 405-13.
4. Castro-Sánchez AM, Garcia-López H, Fernández-Sánchez M, Perez-Marmol JM, Leonard G, Gaudreault N, et al. Benefits of dry needling of myofascial trigger points on autonomic function and photoelectric plethysmography in patients with fibromyalgia syndrome. Acupunct Med 2020; 38: 140-9.
5. Fernández-de-Las-Peñas C, Nijs J. Trigger point dry needling for the treatment of myofascial pain syndrome: current perspectives within a pain neuroscience paradigm. J Pain Res 2019; 12: 1899-911.
6. Martín-Sacristán L, Calvo-Lobo C, Pecos-Martín D, Fernández-Carnero J, Alonso-Pérez JL. Dry needling in active or latent trigger point in patients with neck pain: a randomized clinical trial. Sci Rep 2022; 12: 3188.
7. Plaut S. Scoping review and interpretation of myofascial pain/fibromyalgia syndrome: An attempt to assemble a medical puzzle. PloS One 2022; 17: e0263087.
8. Giamberardino MA, Affaitati G, Fabrizio A, Costantini R. Effects of treatment of myofascial trigger points on the pain of fibromyalgia. Curr Pain Headache Rep 2011; 15: 393-9.
9. Castro Sánchez AM, García López H, Fernández Sánchez M, Pérez Mármol JM, Aguilar-Ferrándiz ME, Luque Suárez A. Improvement in clinical outcomes after dry needling versus myofascial release on pain pressure thresholds, quality of life, fatigue, pain intensity, quality of sleep, anxiety, and depression in patients with fibromyalgia syndrome. Disabil Rehabil 2019; 41: 2235-46.
10. Hernando-Garijo I, Jimenez-Del-Barrio S, Mingo-Gómez T, Medrano-de-la-Fuente R, Ceballos-Laita L. Effectiveness of non-pharmacological conservative therapies in adults with fibromyalgia: A systematic review of high-quality clinical trials. J Back Musculoskeletal Rehabil 2022; 35: 3-20.
11. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989; 28: 193-213.
12. Vernon H, Mior S. The Neck Disability Index: a study of reliability and validity. J Manipulative Physiol Ther 1991; 14: 409-15.
13. Aydemir, O. Validity and Reliability of Turkish Version of Hospital Anxiety and Depression Scale. Turkish Journal of Psychiatry 1997; 8: 280-7.
14. Saglam G, Karakullukcu S, Sahin HB, Aykut DS. Coexistence of Fibromyalgia, Myofascial Pain Syndrome and Depression Among Patients with Lumbar Disc Herniation. Med Bull Haseki 2022; 60: 358-65.
15. Fernández-de-Las-Peñas C, Arendt-Nielsen L. Myofascial pain and fibromyalgia: two different but overlapping disorders. Pain Manag 2016; 6: 401-8.
16. Manafnezhad J, Salahzadeh Z, Salimi M, Ghaderi F, Ghojazadeh M. The effects of shock wave and dry needling on active trigger points of upper trapezius muscle in patients with non-specific neck pain: A randomized clinical trial. J Back Musculoskelet Rehabil 2019; 32: 811-8.
17. Gerber LH, Shah J, Rosenberger W, Armstrong K, Turo D, Otto P. Dry Needling Alters Trigger Points in the Upper Trapezius Muscle and Reduces Pain in Subjects with Chronic Myofascial Pain. PM R 2015; 7: 711-8.
18. Abbaszadeh-Amirdehi M, Ansari NN, Naghdi S, Olyaei G, Nourbakhsh MR. Therapeutic effects of dry needling in patients with upper trapezius myofascial trigger points. Acupuncture Med 2017; 35: 85-92.
19. Hakim IK, Takamjani IE, Sarrafzadeh J, Ezzati K, Bagheri R. The effect of dry needling on the active trigger point of upper trapezius muscle: Eliciting local twitch response on long-term clinical outcomes. J Back Musculoskelet Rehabil 2019; 32: 717-24.
20. Cerezo-Téllez E, Torres-Lacomba M, Mayoral-Del-Moral O, Pacheco-da-Costa S, Prieto-Merino D, Sánchez-Sánchez B. Health related quality of life improvement in chronic non-specific neck pain: secondary analysis from a single blinded, randomized clinical trial. Health Qual Life Outcomes 2018; 16: 207.
21. Taşoğlu Ö, Şahin Onat Ş, Bölük H, Taşoğlu İ, Özgirgin N. Comparision of two different dry-needling techniques in the treatment of myofascial pain syndrome. Agri 2017; 29: 9-16.
22. Casanueva B, Rivas P, Rodero B, Quintial C, Llorca J, González-Gay MA. Short-term improvement following dry needle stimulation of tender points in fibromyalgia. Rheumatol Int 2014; 34: 861-6.
23. Khanittanuphong P, Saesim A. Comparison of the effectiveness between dry needling with and without needle retention in myofascial trigger points in upper trapezius muscle: A randomized comparative trial. J Back Musculoskelet Rehabil 2022; 35: 1247-55.
24. Cerezo-Téllez E, Lacomba MT, Fuentes-Gallardo I, Mayoral del Moral O, Rodrigo-Medina B, Gutiérrez Ortega C. Dry needling of the trapezius muscle in office workers with neck pain: a randomized clinical trial. J Man Manip Ther 2016; 24: 223-32.

İstanbul Med J 2023; 24(1): 62-4
DOI: 10.4274/imj.galenos.2023.21347

Characteristics of Patients in Follow-up After the Whipple Procedure in the Intensive Care Unit: Field-specific Intensive Care Experience

İlhan Ocak[1], Mustafa Çolak[1], Erdem Kınacı[2]

[1]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Transplant Intensive Care Unit, İstanbul, Turkey
[2]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Hepato-Pancreto-Biliary Surgery and Liver Transplantation, İstanbul, Turkey

ABSTRACT

Introduction: Pancreaticoduodenectomy (Whipple procedure) is an important surgical intervention in terms of adverse conditions that may occur after surgery. Our aim is to determine the change in the clinical course of the patients followed in the intensive care unit (ICU) after pancreaticoduodenectomy during the follow-up period.

Methods: We included 37 patients followed up after the Whipple procedure from August 2021 to August 2022 in a tertiary ICU specific for liver-pancreas-biliary tract and liver transplantation.

Results: The vital signs and laboratory values of the patients during the follow-up were examined. Statistically decreased arterial blood lactate levels and a significant increase in arterial blood partial oxygen pressures were seen upon admission to the ICU. The highest detected arterial lactate level was correlated with the percentage change in blood creatinine.

Conclusion: Patients should be followed closely after the Whipple procedure. Fluid volume treatment and respiratory support play a significant role in patient recovery.

Keywords: Pancreaticoduodenectomy, fluid volume, intensive care

Introduction

Pancreaticoduodenectomy, the so-called the Whipple operation, is the only potentially curative operation for neoplasms of the periampullary region of the duodenum. Allen Whipple defined this operation for periampullary carcinoma in 1935 (1). Specimens of the classical Whipple operation involves the duodenum, common bile duct, gallbladder, head of the pancreas, and antrum of the stomach.

There are some patients -dependent factors that have a negative effect on the postoperative course, such as age, comorbidities, jaundice, cholestasis, and need for biliary drainage. Additionally, intraoperative factors may also lead to negative outcomes, such as surgical technique, operation time, and amount of bleeding may also lead to negative outcomes (2). After major surgical operations, patients often require monitoring in the intensive care unit (ICU).

Our aim in this study: To determine out the change in the clinical course of the patients followed up in the tertiary ICU after pancreaticoduodenectomy during the follow-up period.

Methods

Patients hospitalized in the tertiary ICU specific to liver-pancreas-biliary tract and liver transplantation from August 2021 to August 2022 were retrospectively reviewed.

Patients followed-up after the Whipple procedure were included in the study.

Patient information and laboratory values were obtained from the hospital registry system (hospital information management system), whereas vital signs and treatments were obtained from patient observation notes.

Approval was obtained from the Ethics Committee of the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (approval number: 2022.12.390), where the study was conducted, for the use of data and conducting the research.

Statistical Analysis

SPSS Statistics 20 (IBM, Armonk, NY) was used for all statistical analyses. Kolmogorov-Smirnoff analysis was used to analyze the normality of

Address for Correspondence: İlhan Ocak MD, University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Transplant Intensive Care Unit, İstanbul, Turkey
Phone: +90 532 452 10 52 **E-mail:** ilhanocak.md@gmail.com **ORCID ID:** orcid.org/0000-0003-1770-0794

Cite this article as: Ocak İ, Çolak M, Kınacı E. Characteristics of Patients in Follow-up After the Whipple Procedure in the Intensive Care Unit: Field-specific Intensive Care Experience. İstanbul Med J 2023; 24(1): 62-4.

Received: 15.12.2022
Accepted: 24.01.2023

©Copyright 2023 by the University of Health Sciences Turkey, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.

the study data. A paired t-test was used when comparing before and after laboratory values. Pearson correlation test was used for the correlation between the blood lactate level, the amount of fluid volume administered, and the change in blood creatinine level.

Results

Thirty-seven patients were included in the study. Nineteen of the patients were female and 18 of them were male patients. The mean age was 61.08 (±14) years. Twenty patients had at least one comorbid disease in addition to pathology that needed surgery (Table 1). Two patients (0.5%) were transferred to the ICU as orotracheal intubated. The patients were then extubated and transferred to the service. High -flow nasal cannula oxygen therapy (YANKOT) was administered to 15 patients (40%). All three patients were taken over with inotropic therapy and stopped during their follow-up. Invasive arterial blood pressure follow-ups were performed during the follow-up of the patients in the ICU. Oxygen saturation (SpO_2) was monitored by non-invasive pulse oximetry, and partial oxygen pressure (pO_2) was monitored by arterial blood gas analysis. The mean of the highest detected systolic blood pressures was 152 (±13), and the mean of the lowest systolic blood pressure was 114 (±15). The mean of the detected high diastolic blood pressures was 76 (±4), and the mean of the lowest diastolic blood pressures was 61 (±49). The results of the hemogram and blood biochemistry tests taken when the patients were admitted to the ICU and at the 12th hour are shown in Table 2. The change between the blood creatinine values taken before the surgery and the blood creatinine values taken at the 12th h after the surgery was calculated as a percentage. A positive correlation was found between the lactate level of the patients at admission and the change in the fluid volume and blood creatinine in the ICU (Table 3).

Table 1. Patient demographic data

Age	61.08 (±14)
Gender (%)	
Male	18 (48%)
Female	19 (52%)
Comorbidities (%)	
DM	7 (19%)
CAD	10 (27%)
HT	11 (29%)
CVD	1 (2.7%)
Ulcerative colitis	1 (2.7%)
Ankylosing spondylitis	1 (2.7%)
MEN-1	1 (2.7%)
*Intensive care hospitalization day	1 (1-7)

*Median (range), DM: Diabetes mellitus, CAD: Coronary artery disease, HT: Hypertension, CVD: Cerebrovascular disease, MEN-1: Multiple Endocrine Neoplasia syndrome-1

Discussion

In our study, we examined patients followed in the ICU after the Whipple procedure. The Whipple procedure is perhaps the most associated with perioperative morbidity and mortality of all surgical procedures. The available data on the process and results in the ICU are insufficient (2). For this reason, we think that the contribution of the results of the field-specific ICU to the literature is important. In our study, the mean age of the patients was 61, which is consistent with the literature. Karim et al. (3). The mean age in the study was 55.9 years. In the study by Weinberg et al. (4), the mean age was found to be 67. Comorbidities accompanying the patients were also consistent with earlier studies (5). After the operation, high -flow nasal cannula oxygen therapy (YANKOT) support was provided to 14 patients. In studies, the need for respiratory support and reintubation rates decreased in the post-operative period with YANKOT treatment (6). We think that the use of YANKOT is a reason why we did not find low saturation in our study. Additionally, a

Table 2. Laboratory values in the intensive care unit follow-up

Laboratory values	0. hour	12. hour	p-values
Hemoglobin (g/dL)	11.4±1.8	11.19±1.7	0.158
Platelets (10^9/L)	258.4±76.2	247.3±81.4	0.315
AST (U/L)	171±213	132±134	0.115
ALT (U/L)	155.3±180.9	153.2±154.7	0.850
Creatinine (mg/dL)	0.87±0.2	0.83±0.2	0.403
Blood lactate *(mmol/L)	4.2±3.2	1.8±0.9	0.014
pO_2 (mmHg)	102.6±23.2	147.4±31.9	<0.01

*Lactate level in arterial blood gas, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, pO_2: Partial oxygen pressure

Table 3. Correlation of blood lactate level at admission to the intensive care unit, amount of fluid volume therapy, and blood creatinine

		Highest blood lactate level	Percentage of changes in blood creatinine
Percentage of changes in blood creatinine	Pearson's r	0.631	-
	p-value	0.021	-
Amount of Fluid volume delivered	Pearson's r	0.786	0.721
	p-value	< .001	0.012

significant increase was found when the arterial pO_2 level at the arrival of the patients to the ICU was compared with the level at the 12th h. Since the patients were in the ICU, respiratory supports were applied quickly and desaturation was not allowed. Thus, the patient was stabilized in terms of breathing during the hours when the sedation effect and pain control were just started. Considering the highest arterial blood lactate level saw at the time of admission to the ICU, a positive correlation was found between the amount of fluid volume administered and the arterial blood lactate level. The increase in the arterial blood lactate level reflects the development of anaerobic metabolism. This is the result of uncontrolled high production or reduced elimination (7).

The need for higher fluid volume in patients with higher arterial blood lactate levels can be explained by the need to increase the amount of intravascular fluid volume.

Study Limitations

The positive correlation between the increase in blood creatinine values and arterial blood lactate values is also particularly important in these patients. This result can be accepted as a sign that the kidney functions of patients with high arterial blood lactate levels may also be impaired. Our study was a single-center study. Patient data were also obtained by retrospective scanning. Additionally, the available data only covers the ICU follow-up. These are the limitations of our study.

Conclusion

Patients should be followed closely after the Whipple procedure, fluid volume therapy and respiratory support seem to play a significant role in the recovery of these patients. Conducting multicenter and randomized controlled studies on the subject may supply patient-specific fluid volume therapy and respiratory support determination.

Ethics Committee Approval: Approval was obtained from the Ethics Committee of the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (approval number: 2022.12.390), where the study was conducted, for the use of data and conducting the research.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - İ.O., M.Ç., E.K.; Concept - İ.O., M.Ç.; Design - İ.O., M.Ç.; Data Collection or Processing - İ.O., M.Ç., E.K.; Analysis or Interpretation - İ.O., E.K.; Literature Search - İ.O., M.Ç., E.K.; Writing - M.Ç., E.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. Changazi SH, Ahmed Q, Bhatti S, Siddique S, Abdul Raffay E, Farooka MW, et al. Whipple Procedure: A Five-Year Clinical Experience in Tertiary Care Center. Cureus 2020; 12: e11466.
2. Udhayachandhar R, Otokwala J, Korula PJ, Rymbai M, Chandy TT, Joseph P. Perioperative factors impacting intensive care outcomes following Whipple procedure: A retrospective study. Indian J Anaesth 2020; 64: 216-21.
3. Karim SAM, Abdulla KS, Abdulkarim QH, Rahim FH. The outcomes and complications of pancreaticoduodenectomy (Whipple procedure): Cross sectional study. Int J Surg 2018; 52: 383-7.
4. Weinberg L, Wong D, Karalapillai D, Pearce B, Tan CO, Tay S, et al. The impact of fluid intervention on complications and length of hospital stay after pancreaticoduodenectomy (Whipple's procedure). BMC Anesthesiol 2014; 14: 35.
5. Warrillow SJ, Weinberg L, Parker F, Calzavacca P, Licari E, Aly A, et al. Perioperative fluid prescription, complications and outcomes in major elective open gastrointestinal surgery. Anaesth Intensive Care 2010; 38: 259-65.
6. Lu Z, Chang W, Meng SS, Zhang X, Xie J, Xu JY, et al. Effect of high-flow nasal cannula oxygen therapy compared with conventional oxygen therapy in postoperative patients: a systematic review and meta-analysis. BMJ Open 2019; 9: e027523.
7. Vincent JL, Quintairos E Silva A, Couto L Jr, Taccone FS. The value of blood lactate kinetics in critically ill patients: a systematic review. Crit Care 2016; 20: 257.

İstanbul Med J 2023; 24(1): 65-70
DOI: 10.4274/imj.galenos.2023.44380

Investigation of the Prognostic Values of the Shock Index and Modified Shock Index in Predicting the Clinical Outcomes in Elderly Hospitalized Patients with Coronavirus Disease-2019

Serdar Yeşiltaş[1], Saadet Öztop[1], Mustafa Günay[1], İsmail Sümer[1], Sedat Akbaş[1], Sinan Yılmaz[1], Özge Pasin[2], Kazım Karaaslan[1]

[1]Bezmialem Vakıf University Faculty of Medicine, Department of Anesthesiology and Reanimation, İstanbul, Turkey
[2]Bezmialem Vakıf University Faculty of Medicine, Department of Biostatistics and Medical Informatics, İstanbul, Turkey

ABSTRACT

Introduction: Advanced age is an independent risk factor for increased mortality in coronavirus disease-2019 (COVID-19). However, the best method for estimating mortality in elderly patients with COVID-19 is still under debate. We performed this study to assess the shock index (SI) and the modified shock index (MSI) for the abovementioned problem.

Methods: A retrospective study was conducted including elderly cases (≥65 years) confirmed with COVID-19 who admitted to a tertiary university hospital between March-December 2020. The SI and MSI at the time of the emergency department visits were used to evaluate the intensive care unit admission, ventilator support, septic shock, and 30-day mortality in all patients. The receiver operating characteristic and area under the curve (AUC) were used to measure the overall ability of SI and MSI to predict clinical outcomes.

Results: We recruited 334 consecutive COVID-19 patients with a mean age of 75.2±7.3 and an almost equal gender distribution [170 males (50.9%)]. In deceased and surviving patients, the SI was 0.66±0.16 and 0.6±0.1 (p=0.014), while the MSI was 0.95±0.22 and 1.09±0.34 (p=0.003), respectively. In predicting mortality, the AUC of the SI and MSI were 0.590 [95% confidence interval (CI): 0.535 to 0.643] and 0.608 (95% CI: 0.553 to 0.660), respectively.

Conclusion: Increased SIs and MSIs are associated with 30-day mortality. SI and MSI can benefit the triage of elderly patients hospitalized for COVID-19. However, it was found that there is no single cut-off value of SI or MSI with optimum accuracy for predicting COVID-19-related clinical outcomes.

Keywords: COVID-19, modified shock index, mortality, shock index, septic shock

Introduction

Various risk factors for the clinical worsening of coronavirus disease-2019 (COVID-19) have been identified, including diabetes, hypertension, cardiovascular disease, and organ failure (1). Additionally, advanced age and male gender were defined as major non-modifiable risk factors associated with mortality (2-6). Older adults infected with COVID-19 have higher morbidity and mortality rates than younger ones. The mortality rate was higher in the elderly aged 64 years and over (6). Data from China and Italy show that the mortality rate for patients with COVID-19 is 2.3%, with more than 50% resulting in death in patients aged 50 years and older (7). In a study reported in Turkey, the overall mortality rate was 8.5%, while this rate was 14.5% in elderly patients (8).

The COVID-19 places a significant load on healthcare systems. Therefore, efforts are underway to develop simple, non-invasive, and reproducible early warning scores to predict the course of the disease to make appropriate triage at hospital admission, make different clinical decisions and encourage the correct use of medical equipment.

Shock index (SI) is a non-invasive, simple, and reproducible dynamic monitoring method. Allgöwer and Buri (9) introduced the SI in 1968 to measure the grade of hypovolemia in shocks due to hemorrhage and infections. The SI is a good predictor of mortality in different infectious conditions, exemplarily sepsis, and pneumonia (10-14). Additionally, the modified SI obtained by the ratio of the heart rate (HR) to the mean arterial pressure is a better indicator of prognosis than the SI in infectious diseases (15).

Address for Correspondence: Serdar Yeşiltaş MD, Bezmialem Vakıf University Faculty of Medicine, Department of Anesthesiology and Reanimation, İstanbul, Turkey
Phone: +90 542 363 26 30 **E-mail:** syesiltas@bezmialem.edu.tr **ORCID ID:** orcid.org/0000-0001-5811-0104

Cite this article as: Yeşiltaş S, Öztop S, Günay M, Sümer İ, Akbaş S, Yılmaz S, Pasin Ö, Karaaslan K. Investigation of the Prognostic Values of the Shock Index and Modified Shock Index in Predicting the Clinical Outcomes in Elderly Hospitalized Patients with Coronavirus Disease-2019. İstanbul Med J 2023; 24(1): 65-70.

Received: 18.12.2022
Accepted: 27.01.2023

©Copyright 2023 by the University of Health Sciences Turkey, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.

Several studies have described the association between SI and MSI and the severity and mortality of COVID-19 (16-21). However, these reviews exclude a sub-analysis of the elderly patients, and it is still unclear whether SI and MSI have prognostic value in elderly patients. Accordingly, we investigated the ability of SI and MSI, to the prediction of 30-day mortality in elderly patients (aged above 65 years) hospitalized due to COVID-19. Secondary aims were to expect intensive care unit (ICU) hospitalization, ventilator support, and septic shock (SS) development.

Methods

This study was conducted at Bezmialem Vakıf University, a 600-bed tertiary medical center located northwest of Turkey. We retrospectively analyzed elderly patients (age above 65 years) hospitalized due to COVID-19 between March 11, 2020, and December 31, 2020. According to the World Health Organization guidelines, between March 11, 2020 and December 31, 2020, all hospitalized patients aged 65 and over who were diagnosed with COVID-19 confirmed by positive reverse transcriptase-polymerase chain reaction and died or were discharged during their follow-up were included in our study. All patients were admitted to the emergency department with COVID-19-related symptoms and a positive reverse transcription polymerase chain reaction (RT-PCR) test. A consent form was not considered due to the retrospective design. Our study was approved by the Bezmialem Vakıf University Non-Interventional Research Ethics Committee (approval number: 14/308, date: 25.08.2020). Patients were excluded in the following conditions: under 65 years of age, negative RT-PCR results, end-stage liver and kidney failure, lung cancer, cystic fibrosis, pulmonary tuberculosis, immunosuppressive therapy, history of transplantation, hospitalization 72 h before symptom onset, and unavailable data. Additionally, all patients with a critical clinical presentation (ICU admission, coma, endotracheal intubation, or receiving vasoactive drug therapy) at the time of hospital admission were also excluded from the study.

We obtained the patient's demographics, diagnoses, medical history, and laboratory and test results from the hospital's electronic health records. In addition, we evaluated comorbidities, vital signs (HR, non-invasive blood pressure, basal body temperature), laboratory results, ICU admission, ventilator support, SS development, altered mental status, length of hospital stay, and 30-day mortality. The date of nasopharyngeal swab collection was defined as the onset of infection. Altered mental status was accepted as the threshold for all patients with worsening compared with baseline mental status. Altered mental status is a general term used to describe various disorders of cognitive functioning ranging from slight confusion to coma and assessed via the Glasgow Coma scale. ICU admissions were used to describe patients who needed intensive care during their follow-up. Ventilator support refers to patients requiring invasive and non-invasive mechanical ventilation modalities due to respiratory failure. SS was used to describe patients with a lactate value greater than two mmol/L in the absence of hypovolemia and given vasopressors to maintain mean arterial pressure above 65 mmHg (22). Patients hospitalized for less than 30 days were called to determine their survival if they were not seen in the outpatient clinic.

Initial blood pressure values measured in the emergency department were used to calculate SI and MSI. The SI was calculated as the HR to systolic blood pressure (SBP), while MSI was calculated as the ratio of HR to mean arterial pressure. Since no single cut-off point is specified for SI and MSI in COVID-19 patients in the literature, we used the optimal cut-off values calculated according to the Youden index.

Statistical Analysis

The descriptive statistics of the qualitative variables in the study are given as numbers and percentages, and the descriptive statistics of the numerical variables are presented as mean, median, standard deviation, minimum, and maximum. The pearson chi-square test was used to compare the qualitative variables in terms of the distribution of the groups. The conformity of numerical variables to normal distribution was examined by the Shapiro-Wilk test. The Mann-Whitney U test was used for the mean comparisons of the groups consisting of two categories. To evaluate the SI and MSI for ICU admission, ventilator support, SS development, and 30-day mortality receiver operating characteristic (ROC) analysis was performed to obtain the area under the curve (AUC), sensitivity, and specificity. Optimal cut-off points were obtained according to the Youden index. The statistical significance level was taken as 0.05. The SPSS Version 26.0 (Statistical Package for Social Sciences Statistics for Windows, Armonk, NY: IBM Corp) and the MedCalc statistical software package were used for statistical analysis.

Results

This study was conducted with 334 patients aged 65 and over that were diagnosed with COVID-19. We recruited 334 consecutive COVID-19 patients with a mean age of 75.2±7.3 and an almost equal gender distribution [170 males (50.9%)]. Of the 334 patients included in the study, 115 (34.4%) were admitted to the ICU, 97 (29%) required ventilator support, 38 (11.4%) patients developed SS, and 83 (24.9%) patients died within 30 days. Patients who died were significantly older than surviving patients and were more likely to be male. Of the deceased and surviving patients, the SI was 0.7±0.3 and 0.6±0.1 (p=0.044), while the MSI was 1.1±0.4 and 0.9±0.2 (p=0.022), respectively. The patients' demographics, clinical features, and severity scores were compared in Table 1 regarding deceased and surviving cases.

We evaluated SI and MSI to predict 30-day mortality, ICU admission, ventilator support, and SS development. Therefore, ROC curves were obtained, and AUC values were calculated. Regarding 30-day mortality, the optimal cut-off values for SI and MSI were found to be 0.84 and 1.16, respectively. Optimal cut-off values were obtained according to the Youden index. The sensitivity, specificity, positive predictive, and negative predictive values obtained based on the optimal cut-off points of SI and MSI for clinical outcomes are summarized in Table 2.

Of the predicting mortality, the AUC of the SI and MSI were 0.590 (95% CI: 0.535 to 0.643) and 0.608 (95% CI: 0.553 to 0.660), respectively. The AUC and corresponding ROC curves of SI and MSI for 30-day mortality, ICU admission, ventilator support, and SS development are shown in Figure 1, 2.

Table 1. The baseline characteristics data of surviving and deceased patients

	All patients, (n=334) Mean ± SD or n, (%)	Survival, (n=251) Mean ± SD or n, (%)	Non-survival, (n=83) Mean ± SD or n, (%)	p-value
Age	75.19±7.30	74.33±7.05	77.80±7.46	**<0.001**
Gender				**0.027**
Female	164 (49.1%)	132 (52.6%)	32 (38.6%)	-
Male	170 (50.9%)	119 (47.4%)	51 (61.4%)	-
Comorbidity				
HT	217 (65%)	158 (62.9%)	59 (71.1%)	0.178
DM	125 (37.4%)	92 (36.7%)	33 (39.8%)	0.612
CAD	101 (30.2%)	72 (28.7%)	29 (34.9%)	0.282
CHF	95 (28.4%)	66 (26.3%)	29 (34.9%)	0.130
COPD	84 (25.0%)	66 (26.3%)	18 (21.7%)	0.402
CVA	32 (9.6%)	20 (8.0%)	12 (14.5%)	0.082

HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, CHF: Congestive heart failure, COPD: Chronic obstructive pulmonary disease, CVA: Cerebrovascular accident, n: Number, SD: Standard deviation, p<0.05

Table 2. Comparison of surviving and deceased patients in terms of vital signs and clinical outcomes within 30 days of hospitalization

	All patients, (n=334) Mean ± SD or n, (%)	Survival, (n=251) Mean ± SD or n, (%)	Non-survival, (n=83) Mean ± SD or n, (%)	p-value
Vital signs				
BBT	36.59±0.88	36.56±0.86	36.69±0.94	0.154
HR	90.85±18.76	90.51±17.78	91.88±21.55	0.724
SBP	137.81±27.31	140.38±24.65	130.01±33.08	**0.004**
DBP	72.70±15.00	74.62±14.10	66.88±16.19	**<0.001**
MBP	94.40±17.32	96.54±15.67	87.92±20.33	**<0.001**
AMS	38 (11.4%)	18 (7.2%)	20 (24.1%)	**<0.001**
Septic shock	38 (11.4%)	9 (3.6%)	29 (34.9%)	**<0.001**
ICU admission	115 (34.4%)	37 (14.7%)	78 (94%)	**<0.001**
Ventilator support	97 (29%)	25 (10%)	72 (86.7%)	**<0.001**
LOS	9.99±9.52	9.84±10.03	10.42±7.82	**0.300**
SI	0.68±0.19	0.66±0.16	0.74±0.25	**0.014**
MSI	0.99±0.26	0.95±0.22	1.09±0.34	**0.003**

BBT: Basal body temperature, HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MBP: Mean blood pressure, AMS: Altered mental status, ICU: Intensive care unit, MV: Mechanical ventilation, LOS: Length of hospital stay, SI: Shock index, MSI: Modified shock index, n: Number, SD: Standard deviation, p<0.05

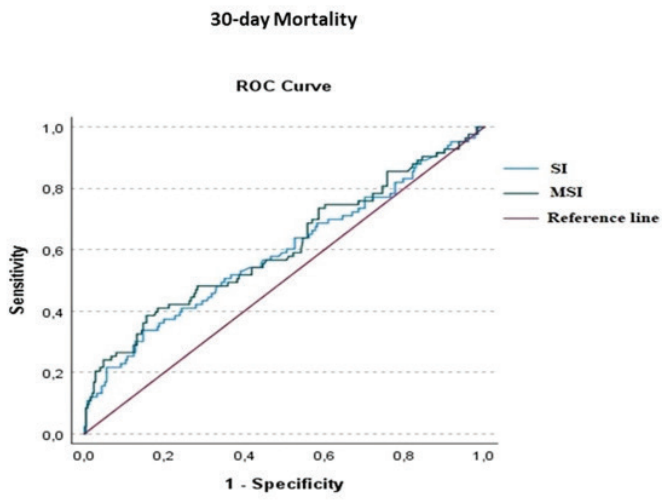
Discussion

This retrospective study evaluated the association between SI and MSI with critical clinical outcomes in elderly hospitalized patients with COVID-19. In our study, the SI and MSI were significantly higher in the group of deceased COVID-19 patients. Using SI and MSI, which are non-invasive, reproducible, and very simple to calculate, may be helpful in the triage of elderly COVID-19 patients. However, no single cut-off value of the SI and MSI with optimal accuracy for estimating critical clinical outcomes related to COVID-19 has been found.

COVID-19 has recently emerged as an essential cause of morbidity and mortality worldwide. As we mentioned, the clinical course is more severe in elderly patients. Early detection of patients who may be diagnosed with COVID-19 and need ICU is crucial. In this context, parameters that can help in clinical practice are still needed. Until today, only a few studies have analyzed the prognostic significance of SI and MSI in patients hospitalized due to COVID-19 (16-21). Studies on using SI and MSI as early warning scores in COVID-19 patients have not yielded consistent results.

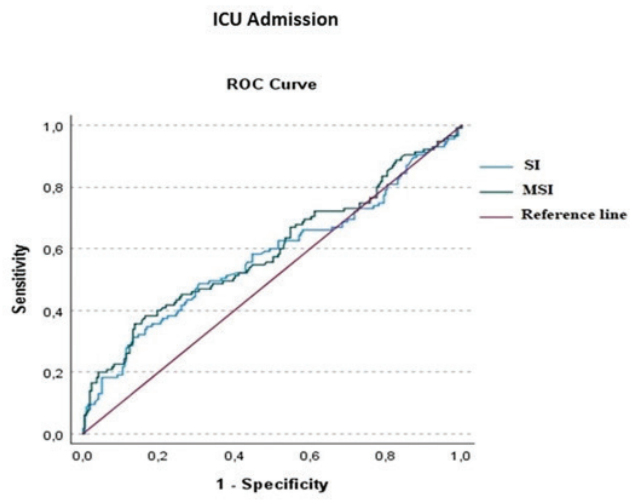
In the study with 364 COVID-19 patients, Ak and Doğanay (16) determined the AUC as 0.755, sensitivity as 63.64%, and specificity as 87.4%, based on the SI cut-off value of 0.9 to estimate the 30-day mortality. They concluded that SI could be a valuable tool for estimating mortality and ICU requirements in adult patients with COVID-19.

van Rensen et al. (17) stated that SI obtained from the emergency department is unhelpful in detecting clinical deterioration and ICU admission in COVID-19. In the study by Jouffroy et al. (18), it was determined that SI in the prehospital setting was not associated with ICU admission and 30-day mortality in COVID-19.



Severity scores	AUC	CI 95%
SI	0.590	0.535 to 0.643
MSI	0.608	0.553 to 0.660

*SI/MSI p=0.19

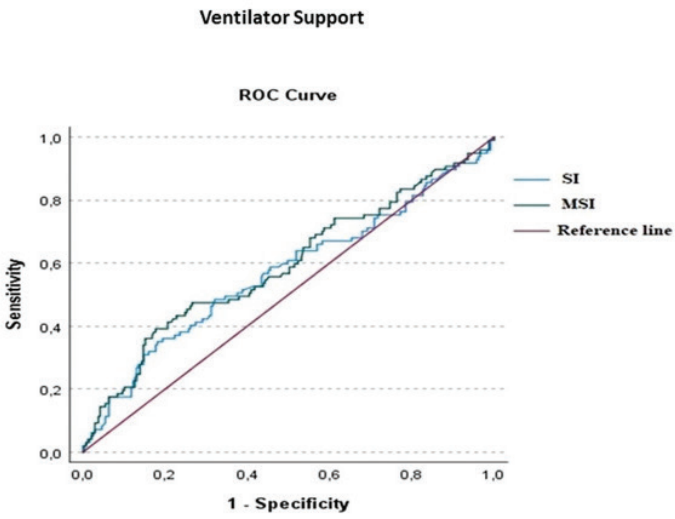


Severity scores	AUC	CI 95%
SI	0.573	0.518 to 0.627
MSI	0.593	0.538 to 0.646

*SI/MSI p=0.12

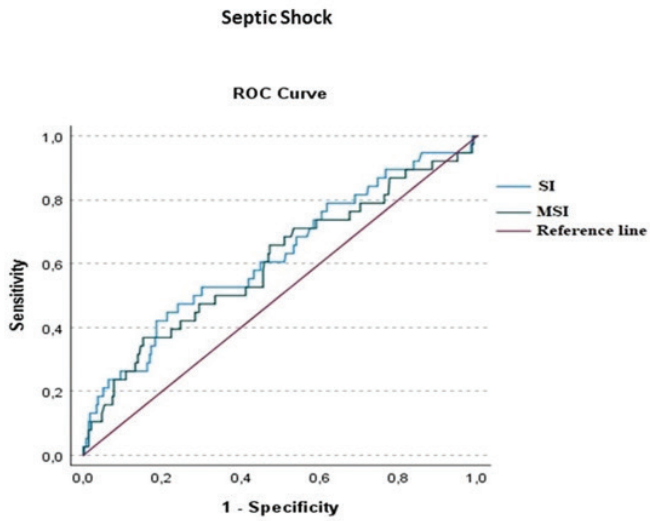
Figure 1. Receiver operating characteristic curve for sensitivity, specificity, and area under the curve for 30-day mortality and intensive care unit admission estimated by shock index and modified shock index

ROC: Receiver operating characteristic, AUC: Area under the curve, ICU: Intensive care unit, SI: Shock index, MSI: Modified shock index, CI: Confidence interval



Severity scores	AUC	CI 95%
SI	0.569	0.514 to 0.622
MSI	0.591	0,536 to 0,644

*SI/MSI p=0.10



Severity scores	AUC	CI 95%
SI	0.602	0.548 to 0.655
MSI	0.624	0.570 to 0.676

*SI/MSI p=0.25

Figure 2. Receiver operating characteristic curve for sensitivity, specificity, and area under the curve for ventilator support and septic shock estimated by shock index and modified shock index

ROC: Receiver operating characteristic, AUC: Area under the curve, ICU: Intensive care unit, SI: Shock index, MSI: Modified shock index, CI: Confidence interval

Aging is related to a high incidence of comorbidities and concomitant medication use. Blood pressure increases with age, and hypertension develops in almost 70% of the population over 70 (23,24). The use of antihypertensive drugs such as beta-blockers can decrease the HR rate and therefore mask the underlying shock (25). Some structural and functional changes in circulation occur with aging. So that even in the absence of these complicating factors, elderly patients may exhibit abnormal responses. Despite the high specificity, the low sensitivity of SI and MSI in our study may be explained by the deterioration of hemodynamic responses to physiological changes due to advanced age and high incidence of hypertension (65%).

HR and SBP are mainly vital signs that reflect the hemodynamic status and subsequent treatment effectiveness. However, HR and SBP can be within normal limits even in critical conditions. And it may cause delayed intervention and increased morbidity and mortality (26). Therefore, SI is a more sensitive indicator of hemodynamic decompensation. Moreover, bedside SI and vital sign evaluation may be beneficial in the clinical decision-making processes.

Study Limitations

As the main limitations, our study was retrospective, single-centered and had few participants. Since we used data from non-invasive blood pressure and HR measured at initial admission, we cannot guarantee that the measured values were obtained under optimal conditions. While the search for effective treatment regimens continued at the beginning of the coronavirus pandemic, patients were treated with different approaches as changes were made in the treatment algorithms. Our results may be biased, as this study needed to consider which treatment was effective and which was ineffective. However, new modifications are also needed to increase the sensitivity of SI and MSI in predicting COVID-19-related clinical deterioration. More extensive multicenter studies are required for this topic.

Conclusion

SI and MSI are valuable tools for predicting the disease behavior of hospitalized elderly coronavirus patients. Using SI and MSI, which are non-invasive, reproducible, and very simple to calculate, may be helpful in the triage of elderly COVID-19 patients.

Ethics Committee Approval: Our study was approved by the Bezmialem Vakıf University Non-Interventional Research Ethics Committee (approval number: 14/308, date: 25.08.2020).

Informed Consent: A consent form was not considered due to the retrospective design.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - S.Y., İ.S., S.A.; Concept - S.Y., İ.S., S.A., K.K.; Design - S.Y., İ.S., S.A., S.Y., Ö.P., K.K.; Data Collection or Processing - S.Y., S.Ö., M.G., İ.S., S.Y., Ö.P.; Analysis or Interpretation - S.Y., S.Ö., M.G., S.A., S.Y., Ö.P., K.K.; Literature Search - S.Y., S.Ö., M.G., S.Y.; Writing - S.Y., Ö.P.

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. Gallo Marin B, Aghagoli G, Lavine K, Yang L, Siff EJ, Chiang SS, et al. Predictors of COVID-19 severity: A literature review. Rev Med Virol 2021; 31: 1-10.
2. Cecconi M, Piovani D, Brunetta E, Aghemo A, Greco M, Ciccarelli M, et al. Early Predictors of Clinical Deterioration in a Cohort of 239 Patients Hospitalized for Covid-19 Infection in Lombardy, Italy. J Clin Med 2020; 9: 1548.
3. Imam Z, Odish F, Gill I, O'Connor D, Armstrong J, Vanood A, et al. Older age and comorbidity are independent mortality predictors in a large cohort of 1305 COVID-19 patients in Michigan, United States. J Intern Med 2020; 288: 469-76.
4. Ciceri F, Castagna A, Rovere-Querini P, De Cobelli F, Ruggeri A, Galli L, et al. Early predictors of clinical outcomes of COVID-19 outbreak in Milan, Italy. Clin Immunol 2020; 217: 108509.
5. Liang W, Liang H, Ou L, Chen B, Chen A, Li C, et al; China Medical Treatment Expert Group for COVID-19. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. JAMA Intern Med 2020; 180: 1081-9.
6. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al; COVID-19 Lombardy ICU Network. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA 2020; 323: 1574-81.
7. Porcheddu R, Serra C, Kelvin D, Kelvin N, Rubino S. Similarity in Case Fatality Rates (CFR) of COVID-19/SARS-COV-2 in Italy and China. J Infect Dev Ctries 2020; 14: 125-8.
8. Altunok ES, Alkan M, Kamat S, Demirok B, Satici C, Demirkol MA, et al. Clinical characteristics of adult patients hospitalized with laboratory-confirmed COVID-19 pneumonia. J Infect Chemother 2021; 27: 306-11.
9. Allgöwer M, Burri C. Shock-index. Ger Med Mon 1968; 13: 14-9.
10. Sankaran P, Kamath AV, Tariq SM, Ruffell H, Smith AC, Prentice P, et al. Are shock index and adjusted shock inde useful in predicting mortality and length of stay in community- acquired pneumonia? Eur J Intern Med 2011; 22: 282-5.
11. Cannon CM, Braxton CC, Kling-Smith M, Mahnken JD, Carlton E, Moncure M. Utility of the shock index in predicting mortality in traumatically injured patients. J Trauma 2009; 67: 1426-30.
12. Jaimes F, Farbiarz J, Alvarez D, Martínez C. Comparison between logistic regression and neural networks to predict death in patients with suspected sepsis in the emergency room. Crit Care 2005; 9: R150-6.
13. Otero R, Trujillo-Santos J, Cayuela A, Rodríguez C, Barron M, Martin JJ, et al; Registro Informatizado de la Enfermedad Tromboembólica (RIETE) Investigators. Haemodynamically unstable pulmonary embolism in the RIETE Registry: systolic blood pressure or shock index? Eur Respir J 2007; 30: 1111-6.
14. Rousseaux J, Grandbastien B, Dorkenoo A, Lampin ME, Leteurtre S, Leclerc F. Prognostic value of shock index in children with septic shock. Pediatr Emerg Care 2013; 29: 1055-9.
15. Jayaprakash N, Gajic O, Frank RD, Smischney N. Elevated modified shock index in early sepsis is associated with myocardial dysfunction and mortality. J Crit Care 2018; 43: 30-5.
16. Ak R, Doğanay F. Comparison of 4 different threshold values of shock index in predicting mortality of COVID-19 patients. Disaster Med Public Health Prep 2021; 1-15.

17. van Rensen IHT, Hensgens KRC, Lekx AW, van Osch FHM, Knarren LHH, van Kampen-van den Boogaart VEM, et al. Early detection of hospitalized patients with COVID-19 at high risk of clinical deterioration: Utility of emergency department shock index. Am J Emerg Med 2021; 49: 76-9.

18. Jouffroy R, Brami E, Scannavino M, Daniel Y, Bertho K, Abriat A, et al. Association between prehospital shock index and mortality among patients with COVID-19 disease. Am J Emerg Med 2022; 56: 133-6.

19. Doğanay F, Elkonca F, Seyhan AU, Yılmaz E, Batırel A, Ak R. Shock index as a predictor of mortality among the Covid-19 patients. Am J Emerg Med 2021; 40: 106-9.

20. Kurt E, Bahadirli S. The Usefulness of Shock Index and Modified Shock Index in Predicting the Outcome of COVID-19 Patients. Disaster Med Public Health Prep 2022; 16: 1558-63.

21. Avci M, Doganay F. Prognostic Performance of Shock Index, Diastolic Shock Index, Age Shock Index, and Modified Shock Index in COVID-19 Pneumonia. Disaster Med Public Health Prep 2022; 17: e189.

22. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315: 801-10.

23. Pedelty L, Gorelick PB. Management of hypertension and cerebrovascular disease in the elderly. Am J Med 2008; 121(8 Suppl): 23-31.

24. Wills AK, Lawlor DA, Matthews FE, Sayer AA, Bakra E, Ben-Shlomo Y, et al. Life course trajectories of systolic blood pressure using longitudinal data from eight UK cohorts. PLoS Med 2011; 8: e1000440.

25. Koch E, Lovett S, Nghiem T, Riggs RA, Rech MA. Shock index in the emergency department: utility and limitations. Open Access Emerg Med 2019; 11: 179-99.

26. Shoemaker WC. Relation of oxygen transport patterns to the pathophysiology and therapy of shock states. Intensive Care Med 1987; 13: 230-43.

İstanbul Med J 2023; 24(1): 71-5
DOI: 10.4274/imj.galenos.2023.23682

Idiopathic Thrombocytopenic Purpura and Cardiovascular Disease: Is Elevated Triglycerides to High-density Lipoprotein Cholesterol Ratio a Marker?

Arzu Cennet Işık[1], Esra Turan Erkek[2], Müjgan Kaya Tuna[3]

[1]University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Internal Medicine İstanbul, Turkey
[2]University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Hemotology, İstanbul, Turkey,
[3]University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Family Medicine, İstanbul, Turkey

ABSTRACT

Introduction: Triglycerides to high-density lipoprotein cholesterol (TG/HDL-C) ratio is used as a cardiovascular risk marker. We aimed to investigate the relationship between TG/HDL ratio and eltrombopag use, current platelet values and whether or not splenectomy was performed in patients with chronic idiopathic thrombocytopenic purpura (ITP), and to emphasize its prognostic importance in terms of cardiovascular markers.

Methods: One hundred and thirty-nine chronic ITP patients followed in the hematology outpatient clinic were evaluated retrospectively. We investigated the negative effect of splenectomy, eltrombopag use and current platelet values on cardiovascular diseases. Patients were stratified into two groups according to their baseline TG/HDL-C ratio, using a TG/HDL-C ratio cut-off value of 2.5.

Results: A total number of 139 chronic ITP patients aged between 18-76 years, followed-up in the hematology outpatient clinic, were included in the study; and 102 of the patients were female (75%). The mean platelet value was 2913.24±103353.64/mm^3, and the mean TG/HDL-C ratio was 2.91±2.09. There were 46 (33.8%) patients who had splenectomy. When patients were evaluated in terms of treatment modalities; 127 patients (93.4%), 60 patients (44.1%), and 19 (13.9%) patients were using methyl prednisolone, intravenous immunoglobulin, and eltrombopag, respectively. It was observed that the parameters were similar in patients using and not using eltrombopag ($p>0.05$). There was a weak and statistically significant correlation between TG/HDL-C values and age ($r=0.275$; $p=0.001$). There was a significant correlation between the presence of DM and hyperlipidemia and the TG/HDL-C ratio ($p<0.05$). In risk assessment, the TG/HDL-C ratio of individuals without coronary artery disease was 2.29 (1.47 3.38) and it was found to be statistically significantly low ($p=0.025$).

Conclusion: TG/HDL-C ratio can be used as an independent risk marker that can be diagnostic in predicting cardiovascular disease risk in ITP patients with advanced age and additional comorbid diseases (DM and hyperlipidemia).

Keywords: Triglycerides to high-density lipoprotein cholesterol ratio (TG/HDL-C), ITP, cardiovascular disease, splenectomy

Introduction

Worldwide, cardiovascular disease (CVD) is a major factor in both death and morbidity. Hypertriglyceridemia is clinically useful for estimating CVD risk independently. Low levels of high-density lipoprotein cholesterol (HDL) are significantly linked to the development and death from CVD (1). Additionally, the biomarker Triglycerides (TG)/HDL-C, which measures the relationship between high plasma TG and good cholesterol, was studied to help people with high cardiometabolic risk (2). High TG levels and rapidly catabolized HDL particles result in lower HDL concentrations and smaller, and dense TG-enriched HDL particlesreduce the cardio-protective, antioxidant and anti-inflammatory effects. As a result, the risk of atherosclerotic disease is increased by higher TG levels and lower HDL-C concentrations (3).

In patients who are unresponsive to first-line treatments, including corticosteroids, intravenous immunoglobulin (IVIG), and RhoGA, thrombopoietin receptor analogs used recently are among the treatment options in addition to splenectomy, rituximab, and immunosuppressive treatments. Rompilostim and eltrombopag are agents with proven efficacy in this group. In our country, only eltrombopag is used among this group of drugs.

An autoimmune condition called idiopathic thrombocytopenic purpura (ITP) is characterized by a low platelet count and a higher risk of

Address for Correspondence: Arzu Cennet Işık MD, University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Internal Medicine İstanbul, Turkey
Phone: +90 505 817 45 19 **E-mail:** arzukaracelik@gmail.com **ORCID ID:** orcid.org/0000-0001-9844-8599

Cite this article as: Işık AC, Turan Erkek E, Kaya Tuna M. Idiopathic Thrombocytopenic Purpura and Cardiovascular Disease: Is Elevated Triglycerides to High-density Lipoprotein Cholesterol Ratio a Marker?. İstanbul Med J 2023; 24(1): 71-5.

Received: 21.06.2022
Accepted: 27.01.2023

©Copyright 2023 by the University of Health Sciences Turkey, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.

bleeding. Patients receiving continuous steroid therapy with hemostatic agents are at risk of atherosclerosis and thrombosis at the same time (4). Our main objective was to investigate the association between chronic patients with ITP' risk status and coronary artery disease (CAD); however, but we also wanted to determine how splenectomy, eltrombopag use, and current platelet values affected CAD.

Methods

One hundred and thirty-nine chronic patients with ITP followed in the University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital Hematology Outpatient Clinic were included in the study. The patients who were included were split into two groups: those who had splenectomy surgery and those who did not. The use of methylprednisolone, IVIG, rituximab, and eltrombopag was evaluated in terms of treatment. Newly diagnosed solid organs or untreated malignancies, advanced neuropsychiatric disease, pregnancy, emergencies, and acute or chronic infections were excluded. Age, gender, splenectomy surgery, presence of CAD, and additional disease [hypertension (HT), diabetes mellitus (DM), hypothyroidism, hyperlipidemia], use of eltrombopag, TG and HDL levels, and platelet counts were recorded. Previous myocardial infarction and cardiac surgery, presence of a cardiac pace-maker and arrhythmia, and heart failure with stent were accepted for the diagnosis of CAD. Patients diagnosed with DM, HT, hypercholesterolemia, and hypothyroidism under medical treatment were included.

After 8 h of fasting, venous blood was drawn in a lab setting to examine the basic blood sample. Low levels of HDL (mmol/L) and TG (mmol/L) were tested and recorded. By dividing the TG level (mmol/L) by the HDL-C level (mmol/L) for each patient, the baseline TG/HDL-C ratio was calculated. Two groups of patients were categorized based on a cut point of 2.5.

Ethics committee approval was obtained from University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital for the study (approval number: 2022/514/228/26, date: 30.06.2022). Informed consent papers were collected after inviting patients to participate in the study.

Statistical Analysis

The Shapiro-Wilk test was used to determine whether numerical variables were normal. Student's t-test was used to compare differences between two groups whose data were regularly distributed, whereas the Mann-Whitney U test was used to compare differences between groups whose data were not normally distributed. To determine the linear association between the TG/HDL and PLT variables, Spearman's rank correlation coefficient was used. For numerical variables, the descriptive statistics were mean ± SD, median (25%, 75%), and numbers and percentages (%) for categorical variables. P-values less than 0.05 were statistically significant when doing statistical analyses using the SPSS Windows version 21.0 program (SSPSS Inc, Chicago, IL, USA).

Results

A total number of139 chronic patients with ITP aged between 18 and 76 years, followed up in the hematology outpatient clinic, were included in the study; and 102 of the patients were female (75%) and 34 were male (25%). The average age was 46.24±14.14 years and the median age was 44. The average platelet count was 92913.24±103353.64/mm^3, and the median platelet count was 66,500/mm^3; maximum platelet count was determined as 588,000/mm^3. Average TG level was 128.12±74.73 mg/dL and median TG level was 114 mg/dL. The average HDL level was 50.02±22.86 mg/dL, and the median HDL level was 48 mg/dL. The average TG/HDL-Cratio was 2.91±2.09 and median TG/HDL-C ratio was 2.45. There were 46 (33.8%) patients who had splenectomy and comparison of age, platelet count, HDL, TG, TG/HDL-C parameters were found to be similar with those without splenectomy (p>0.05) (Table 1).

When patients were evaluated in terms of treatment modalities: 127 patients (93.4%), 60 patients (44.1%), and 19 (13.9%) patients were

Table 1. Descriptive statistics of demographic characteristics

	Median	Mean ± SD	Min.-max.
Age	44	46.24±14.14	18-76
Female, n (%)	102 (75)	-	-
Male, n (%)	34 (25)	-	-
Methylprednisolone, n (%)	127 (93.4)	-	-
IVIG, n (%)	60 (44.1)	-	-
Hypothyroidism, n (%)	22 (16.2)	-	-
Splenectomy, n (%)	46 (33.8)	-	-
Coronary artery disease, n (%)	12 (8.8)	-	-
Hyperlipidemia, n (%)	7 (5.1)	-	-
Diabetes mellitus, n (%)	24 (17.6)	-	-
Hypertension, n (%)	27 (19.9)	-	-
Platelet	66,500	92913.24±103353.64	0-588000
HDL	48	50.02±22.86	0-188
Triglyceride	114	128.12±74.73	0-581
TG/HDL	2.45	2.91±2.09	0.48-15.70

SD: Standard deviation, IVIG: Intravenous immunoglobulin, Min.: Minimum, max.: Maximum, TG/HDL: Triglycerides to high-density lipoprotein cholesterol

using methyl prednisolone, IVIG, and eltrombopag, respectively. We observed that the parameters were similar in patients using and not using eltrombopag (p>0.05). The distribution of additional diseases is as follows: CAD in 12 patients (8.8%), hyperlipidemia in 7 patients (5.1%), DM in 24 patients (17.6%), HT in 27 patients (19.9%), and hypothyroidism in 22 patients (16.2%) (Table 1).

When the relationship between the demographic data, comorbidities, demographic characteristics of the patients, and an analysis of the TG/HDL-C ratio revealed a strong correlation between the levels of DM and hyperlipidemia and the ratio. In the presence of DM and hyperlipidemia, the TG/HDL-C value was determined to be statistically significant (p<0.05) (Table 2).

The relationship between the presence of CAD and demographic and biochemical parameters in the patients is shown in Table 3. It was determined that the age values of individuals with CAD, 59.5 (50 61.5), were found to be significantly higher the age values of individuals without CAD, 43 (34.5 57.5) (p=0.003). It was determined that the TG/HDL-C values of individuals with CAD, 3.50 (2.67 4.11), were found to be significantly lower than the TG/HDL-C values of individuals without CAD, 2,29 (1.47 3.38) (p=0.025) (Figure 1).

Discussion

We found that the TG/HDL-C ratios of the patients differed significantly among those without CAD, and the ratio suggests that it can be used as an independent predictor and biomarker. The coexistence of ITP and cardiovascular disease requires serious management by evaluating the thrombosis and hemorrhagic risk. In a meta-analysis of 207,515 participants, the TG/HDL-C ratio was independently associated with a higher risk of cardiovascular events (10). In the cohort study conducted between 2010 and 2020, 9,704 participants were followed for 6 years, and it was concluded that TG/HDL-C may be an important unique biomarker to predict CVD outcomes and progression when evaluating cardiovascular diseases (11).

"Early diagnosis, early treatment" has become critical to the prevention of coronary heart disease as the incidence of the condition has increased

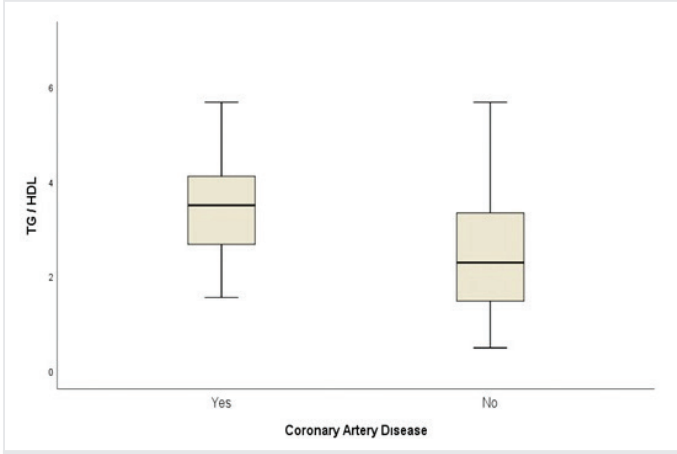


Figure 1. Coronary artery disease and healthy triglycerides to high-density lipoprotein cholesterol (box-plot)
TG/HDL: Triglycerides to high-density lipoprotein cholesterol

Table 2. The relation of triglyceride/HDL ratio of general features of the cases

		TG/HDL	p
Gender	Male Female	2.58 (1.76 3.53) 2.32 (1.47 3.40)	0.426
Methylprednisolone	Yes No	2.46 (1.55 3.39) 1.59 (1.19 7.97)	0.905
Diabetes mellitus	Yes No	2.92 (2.30 3.93) 2.28 (1.47 3.39)	**0.012**
Hypertension	Yes No	2.75 (2.20 4.25) 2.28 (1.47 3.34)	0.097
Hypothyroidism	Yes No	2.33 (1.48 4.54) 2.47 (1.57 3.38)	0.557
Hyperlipidemia	Yes No	4.54 (2.32 8.58) 2.31 (1.48 3.39)	**0.026**

P-value Mann-Whitney U or Student's t- obtained from the test. M: Median, Q1: Quarter 1 (p25), Q3: Quarter 3 (p75), HDL: High-density lipoprotein cholesterol

Table 3. Relationship between cardiovascular disease and biochemical parameters

	Yes (n=12) M (Q1-Q3)	No (n=124) M (Q1-Q3)	p
Age	59.5 (50-61.5)	43 (34.5-57.5)	**0.003**
Platelet	74,500 (15,000-141,500)	66,500 (23,000-112,000)	0.830
HDL	42 (38.5-47)	48.5 (39.5-55.5)	0.148
Triglyceride	138 (125-162)	111 (82-138.5)	0.055
TG/HDL	3.50 (2.67-4.11)	2.29 (1.47-3.38)	**0.025**

P-value Mann-Whitney U obtained from the test. M: Median, Q1: Quarter 1 (p25), Q3: Quarter3 (p75), TG/HDL: Triglycerides to high-density lipoprotein cholesterol

(7). Advanced age, male gender, diabetes, aberrant lipid metabolism, HT, smoking, impaired renal function, and inflammation are risk factors for vascular calcification (8-10). Although there has been improvement in the management of coronary heart disease, mortality rates are rising and the illness's prevalence and morbidity remain significant. In the study, which analyzed 106,653 patients with ITP and 79,636,090 members of the control group between 2002 and 2011, it was discovered that patients with ITP had a considerably greater incidence of non-ST segment elevation myocardial infarction than people without ITP (13).

While 17% of the patients in our study were diagnosed with DM and under treatment; 5% were under treatment for hyperlipidemia and had no additional cardiovascular outcome. The examination of the TG/HDL-C levels revealed a statistically significant connection (p=0.05). When other diseases are present in patients with ITP patients, cardiovascular risk evaluations are useful for making an early diagnosis. In a study that involved 3,131 patients and compared the rates of cataract, diabetes, renal failure, vascular events, lymphoma, and leukemia in those with and without chronic ITP, it was discovered that patients have a higher risk of developing many comorbidities, including hematological malignancies (15).

In a retrospective cohort research that included 6,591 patients with ITP and 24,275 control individuals, the CVD risk was assessed, and during a 6-year observation period, a diagnosis of CVD was reported in 392 (5.9%) patients with ITP and 1,114 (4.5%) control patients. It has been determined that people with ITP are more likely to acquire CVD, and that people with ITP who have splenectomy are considerably more likely to do so (12). In our study, we found no difference in the risk between patients who underwent splenectomy and those who did not.

A relative risk of 1.82 (95% CI: 0.78-4.24) was revealed by the meta-analysis in 2022. Our results show that patients with ITP who receive TPO-RA (eltrombopag) treatments have a non-significantly increased risk of thrombosis than patients with ITP who do not receive TPO-RA treatments (14). In our investigation, it was not discovered that using TPO-RA increased the frequency of cardiovascular events.

Study Limitations

Our study was designed as a retrospective-observational study. The fact that the cholesterol values of the patients were not checked before the treatment, the history of previous acute cardiac events is not known, the short follow-up period, the insufficiency of the number of patients, and the fact that it is a single-center study can be counted among the limitations of the study, and for this reason, this study may not reflect the general population. The strength of our study is that it consisted of hematology outpatients of a tertiary hospital with regular follow-up.

Conclusion

Limited use of steroid therapy in the future, and less frequent splenectomy with the widespread use of new generation therapies, may change the development of cardiovascular events in chronic patients with ITP. While the advanced age of the patients and additional comorbid diseases (DM, hyperlipidemia) pose a risk, the TG/HDL-C ratio can be used as an independent risk marker in this sense with diagnostic efficacy in predicting cardiovascular disease.

Ethics Committee Approval: Ethics committee approval was obtained from University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital for the study (approval number: 2022/514/228/26, date: 30.06.2022).

Informed Consent: Informed consent papers were collected after inviting patients to participate in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - A.C.I., E.T.E.; Concept - E.T.E.; Design - A.C.I., M.K.T.; Data Collection or Processing - E.T.E., M.K.T.; Analysis or Interpretation - A.C.I., E.T.E.; Literature Search - A.C.I., E.T.E.; Writing - A.C.I., M.K.T.

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. Silbernagel G, Schöttker B, Appelbaum S, Scharnagl H, Kleber ME, Grammer TB et al. High-density lipoprotein cholesterol, coronary artery disease, and cardiovascular mortality. Eur Heart J 2013; 34: 3563-71.
2. Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. Relation of high TG-low HDL cholesterol and LDL cholesterol to the incidence of ischemic heart disease. An 8-year follow-up in the Copenhagen Male Study. Arterioscler Thromb Vasc Biol 1997; 17: 1114-20.
3. Welty FK. How do elevated triglycerides and low HDL-cholesterol affect inflammation and atherothrombosis? Curr Cardiol Rep 2013; 15: 400.
4. Cines DB, Bussel JB, Liebman HA, Luning Prak ET. The ITP syndrome: pathogenic and clinical diversity. Blood 2009; 113: 6511-21.
5. Cooper N. State of the art- how I manage immune thrombocytopenia. Br J Haematol 2017; 177: 39-54.
6. González-López TJ, Fernández-Fuertes F, Hernández-Rivas JA, Sánchez-González B, Martínez-Robles V, Alvarez-Román MT, et. al. Efficacy and safety of eltrombopag in persistent and newly diagnosed ITP in clinical practice. Int J Hematol 2017; 106: 508-16.
7. Li X, Zhang G, Zhang H. Comparison of position, morphology and calcification of Coronary Plaque with 320-row dynamic volume CT (DVCT) and coronary angiography (CAG). Pak J Med Sci 2014; 30: 824-9.
8. Madhavan MV, Tarigopula M, Mintz GS, Maehara A, Stone GW, Généreux P. Coronary artery calcification: pathogenesis and prognostic implications. J Am Coll Cardiol 2014; 63: 1703-14.
9. Abd Alamir M, Goyfman M, Chaus A, Dabbous F, Tamura L, Sandfort V, et al. The Correlation of Dyslipidemia with the Extent of Coronary Artery Disease in the Multiethnic Study of Atherosclerosis. J Lipids 2018; 2018: 5607349.
10. Chen Y, Chang Z, Liu Y, Zhao Y, Fu J, Zhang Y, et al. Triglyceride to high-density lipoprotein cholesterol ratio and cardiovascular events in the general population: A systematic review and meta-analysis of cohort studies. Nutr Metab Cardiovasc Dis 2022; 32: 318-29.
11. Mirshafiei H, Darroudi S, Ghayour-Mobarhan M, Esmaeili H, AkbariRad M, Mouhebati M, et al. Altered triglyceride glucose index and fasted serum triglyceride high-density lipoprotein cholesterol ratio predict incidence of cardiovascular disease in the Mashhad cohort study. Biofactors 2022; 48: 643-50.

12. Chandan JS, Thomas T, Lee S, Marshall T, Willis B, Nirantharakumar K, Gill P. The association between idiopathic thrombocytopenic purpura and cardiovascular disease: a retrospective cohort study. J Thromb Haemost 2018; 16: 474-80.

13. Davis M, Movahed MR, Hashemzadeh M, Hashemzadeh M. The presence of idiopathic thrombocytopenic purpura and incidence of acute non-ST elevation myocardial infarction. Ann Hematol 2022; 101: 21-6.

14. Tjepkema M, Amini S, Schipperus M. Risk of thrombosis with thrombopoietin receptor agonists for ITP patients: A systematic review and meta-analysis. Crit Rev Oncol Hematol 2022; 171: 103581.

15. Enger C, Bennett D, Forssen U, Fogarty PF, McAfee AT. Comorbidities in patients with persistent or chronic immune thrombocytopenia. Int J Hematol 2010; 92: 289-95.

İstanbul Med J 2023; 24(1): 76-82
DOI: 10.4274/imj.galenos.2023.77503

Association Between Atherogenic Index of Plasma and Atherogenic Coefficient and in-Stent Restenosis After Drug-eluting Stent Implantation for Stable Coronary Artery Disease

Yasin Yüksel[1], Cennet Yıldız[2], Burak Ayça[3], Fahrettin Katkat[4], Süleyman Çağan Efe[5], Dilay Karabulut[2], Fatma Nihan Turhan Çağlar[2]

[1]Private Reyap Hospital, Clinic of Cardiology, İstanbul, Turkey
[2]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey
[3]University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey
[4]Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey
[5]University of Health Sciences Turkey, İstanbul Kartal Koşuyolu Yüksek İhtisas Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey

ABSTRACT

Introduction: Despite improvements in stent science, in-stent restenosis (ISR) remains a major problem. This study was designed to evaluate the atherogenic index of plasma (AIP) and atherogenic coefficient (AC) levels and their predictive values in patients who developed ISR after drug-eluting stent implantation for stable coronary artery disease.

Methods: One hundred ninety-nine patients with ISR and 377 without ISR were included in the study. The biochemical and hematological parameters of the patients were measured. The AIP and AC values were calculated.

Results: Patients with ISR had significantly longer stent length, lower stent diameter, lower ejection fraction, and higher SYNTAX score. They also had significantly higher levels of low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), total cholesterol, AIP, and AC compared to that of patients who did not develop ISR. AIP had a sensitivity of 61.3% and specificity of 72.1% for predicting ISR a cut-off value of 0.58. AC had sensitivity and specificity of 69.8% and 58.8%, respectively, for the presence of ISR a cut-off value of 3.44. LDL-C level of 111.5 mg/dL had sensitivity and specificity of 65.3% and 54% for developing ISR, respectively. Paired comparisons of area difference under the receiver operating characteristic curve showed that AIP and AC had significantly greater area compared with that of LDL-C. Stent diameter, stent length, SYNTAX score, ejection fraction, AIP, and AC were the predictors of ISR.

Conclusion: AIP and AC had higher specificities compared with that of LDL-C in predicting ISR. The calculation of AIP and AC is simple and could be used easily in clinical practice.

Keywords: Atherogenic index of plasma, atherogenic coefficient, in-stent restenosis

Introduction

The treatment of coronary artery disease (CAD) with stent implantation has become a standard procedure in clinical practice. Although the stent implantation success rate is high, stent thrombosis and in-stent restenosis (ISR) continue to be problematic. ISR, which is defined as more than a 50% reduction in stent luminal diameter, occurs within one year after stent implantation in approximately 30% and 10% of patients who undergo bare metal stent (BMS) and drug-eluting stent (DES) implantation, respectively (1). Neointimal hyperplasia with infiltration of inflammatory cells into the stent area and development of neoatherosclerosis have been proposed as major contributory mechanisms in the development of ISR (2). Stent related factors, including stent length, diameter, and position; patient-related factors, including diabetes mellitus (DM), hypertension (HT), higher hs-C-reactive protein, low-density lipoprotein-cholesterol (LDL-C), and homocysteine levels; and lesion-related factors, including bifurcation lesions, have been found as independent predictors of ISR (3,4).

The atherogenic index of plasma (AIP) and atherogenic coefficient (AC), two biomarkers that are calculated from blood lipid parameters, could provide more robust information compared to single lipid parameter measurement. AC, which is calculated by dividing non-high-density lipoprotein-cholesterol (non-HDL-C) to HDL-C levels, more closely reflects apolipoprotein B levels, which is a superior measure of atherogenic risk than LDL-C levels (5). Similarly, AIP, which is derived from the logarithmic transformation of the triglyceride (TG) to HDL-C ratio, has been suggested to provide information about the equilibrium between atherogenic and

Address for Correspondence: Cennet Yıldız MD, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey
Phone: +90 533 746 99 96 **E-mail:** cennet_yildiz@live.com **ORCID ID:** orcid.org/0000-0003-2456-3206

Cite this article as: Yüksel Y, Yıldız C, Ayça B, Katkat F, Efe SÇ, Karabulut D, Turhan Çağlar FN. Association Between Atherogenic Index of Plasma and Atherogenic Coefficient and in-Stent Restenosis After Drug-eluting Stent Implantation for Stable Coronary Artery Disease. İstanbul Med J 2023; 24(1): 76-82.

Received: 11.12.2022
Accepted: 29.01.2023

©Copyright 2023 by the University of Health Sciences Turkey, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.

antiatherogenic factors (6). Several studies have shown that AIP and AC associated with the existence of DM, metabolic syndrome, CAD, and obesity are strongly correlated with oxidative stress (5,7-11). In this study, the AIP and AC values of patients with ISR after receiving a DES were evaluated and compared with those of the controls. We investigated whether AIP and AC had any value in predicting ISR development after DES implantation.

Methods

We retrospectively screened coronary angiography files of 6,358 patients who underwent coronary angiography between August 2016 and February 2022 in a cardiology clinic of a tertiary hospital center. The clinical and demographic characteristics of the patients were picked from the data system. Patients who were older than eighteen years of age and who had stents implanted for stable CAD were included in the study. Patients with inflammatory, hematological, infectious diseases, thyroid function abnormalities, hepatic and/or renal failure, acute coronary syndrome, and BMS implantation, had stents implanted at bypass graft lesions were excluded. Patients who underwent DES implantation and developed ISR was enrolled in the study. For this purpose, angiographic examinations of the patients who underwent DES implantation for stable CAD were reevaluated. The mean follow-up period between percutaneous intervention and coronary angiography was 6 to 24 months with a median of 11 months. The indications of coronary angiography were stable angina pectoris or the presence of myocardial ischemia on exercise stress test or myocardial perfusion imaging. During the study period, 717 patients underwent repeat coronary angiography after percutaneous intervention. Of these patients, 108 of them underwent coronary angiography with the diagnosis of acute coronary syndrome, 13 of them had stent implantation in venous bypass grafts, 28 of them had bare-metal stent implantation, and 13 patients had severe renal, hepatic, inflammatory, or oncologic diseases and were excluded from the study. The remaining 536 patients constituted our study population. A total of 199 patients who developed ISR and 337 patients who did not develop ISR were included as study and control groups, respectively. During the study period, ten operators performed percutaneous coronary interventions. The approval of the study was obtained from a University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethical Committee (approval number: 238, date: 22.07.2022) and it was conducted in concordance with the declaration of Helsinki. Informed consent of all patients was also obtained before study inclusion.

Patients were required to be in an overnight fasting state before blood sample collection. All blood samples were taken from the forearm vein in a sitting position. The biochemical and hematological parameters of the patients were measured. AIP was determined from the logarithmic transformation of the TG to HDL-C ratio. AC was computed from the division of non-HDL-C to HDL-C. A patient was considered a diabetic if she/he had blood glucose levels of greater than 125 mg/dL or was taking anti-diabetic drugs. HT was interpreted as systolic and/or diastolic blood pressures greater than 140 and 90 mmHg or taking anti-hypertensive drugs. Dyslipidemia was interpreted as blood levels of total cholesterol (TC) and LDL-C levels of greater than 200 mg/dL and 100 mg/dL, respectively.

The Siemens Axiom Artis Zee Cath Lab system was used for the coronary angiographic evaluations of the patients. Coronary angiography was performed from common femoral arterial access and 6F catheter was inserted into the arterial system with the Judkins technique. Images of coronary arteries from different imaging planes were obtained. The indication for coronary angiography was the presence of patients' symptoms, ischemia on an exercise stress test, or myocardial perfusion scanning findings. ISR was defined as more than 50% reduction in the luminal diameter within the stent or within 5 mm distal or proximal to the stented region. The SYNTAX score for each patient was calculated using an online calculator.

Statistical Analysis

Distribution of the data was assessed by evaluating skewness, kurtosis of the data, and by use of Kolmogorow-Smirnow test. Comparisons of the patients who had ISR and did not have ISR were performed by using the Mann-Whitney U test or Independent samples-t test for the non-normally and normally distributed data, respectively. Receiver operating characteristic (ROC) curve analysis was used to check out the values of AIP and AC for prediction of ISR. Univariate logistic analysis was conducted to determine the predictors for the presence of ISR. Parameters that were found to be meaningful in univariate analysis were put into multivariate logistic regression analysis. A two-tailed p value of less than 0.05 was considered significant.

Results

The mean ages of the study and control groups were 63.20±10.96 years and 63.07±10.53 years, respectively. We did not find any differences between the two groups with respect to age, gender, body mass index, smoking habits, the presence of DM, HT, hyperlipidemia, creatinine, albumin, hemoglobin levels, and neutrophil, lymphocyte, monocyte, and platelet counts. The ISR patients had significantly longer stent lengths, lower stent diameters, lower ejection fractions, and higher SYNTAX scores. They also had significantly higher levels of LDL-C, TG, non-HDL-C, TC, AIP, and AC compared with those of patients without ISR. Statin use was lower the study group compared in the control group. the clinical and biochemical variables of the two groups are presented in Table 1.

According to the ROC curve analysis, AIP had a sensitivity of 61.3% and a specificity of 72.1% for predicting ISR, with a cut-off value of 0.58. It was found that AC had sensitivity and specificity of 69.8% and 58.8%, respectively, for the presence of ISR with a cut-off value of 3.44. LDL-C level of 111.5 mg/dL had sensitivity and specificity of 65.3% and 54% for developing ISR, respectively. Table 2 and Figure 1 show the ROC curve results of for AIP and AC. Paired comparisons of area difference under the ROC curve showed that AIP and AC had significantly greater area compared with that of LDL-C (Table 3).

Univariate logistic regression analysis demonstrated that stent diameter, stent length, SYNTAX score, ejection fraction, TC, HDL-C, TG, LDL-C, AIP, and AC were independent predictors of the presence of ISR.

Table 1. Clinical and biochemical variables of the two groups

	Control group restenosis (-) (n=337)	Study group restenosis (+) (n=199)	p
Age (years)	63.07±10.53	63.20±10.96	0.896
Gender (n, %)			0.343
Male	252 (74.8)	156 (78.4)	-
Female	85 (25.2)	43 (21.6)	-
Smoking (n, %)			0.867
No smoking	156 (46.3)	89 (16.6)	-
Current smoking	126 (37.4)	79 (39.7)	-
Ex smoker	55 (16.3)	31 (5.7)	-
Diabetes mellitus (n, %)	119 (35.3)	76 (38.2)	0.503
Hypertension (n, %)	307 (91.1)	185 (93.0)	0.447
Hyperlipidemia (n, %)	314 (93.2)	176 (88.4)	0.059
Stent diameter (mm)	3.0 (2.75-3.25)	2.75 (2.75-3.0)	**<0.001**
Stent length (mm)	20 (20-24)	24 (20-28)	**<0.001**
BMI (kg/m^2)	27.68 (25.30-30.10)	27.60 (25.30-29.39)	0.551
Syntax score	8 (5-13.75)	12 (7-18)	**<0.001**
Ejection fraction (%)	56.11±7.72	52.92±9.85	**<0.001**
Creatinine (mg/dL)	0.88 (0.71-1.06)	0.86 (0.72-1.06)	0.750
GFR (mL/min/1.73 m^2)	88 (70-101)	89 (69-103)	0.896
TC (mg/dL)	180 (147.7-218.8)	198.8 (156-237)	**0.003**
LDL-C (mg/dL)	109 (88.5-136.5)	125 (87-155)	**0.005**
Triglycerides (mg/dL)	126 (96.5-169.59	166 (124-217)	**<0.001**
HDL-C (mg/dL)	42 (36-48.5)	39 (34-44)	**<0.001**
Non-HDL-C	135.2 (107.2-173.2)	160 (118-196.8)	**<0.001**
Atherogenic index of plasma	0.46 (0.33-0.61)	0.64 (0.47-0.77)	**<0.001**
Atherogenic coefficient	3.22 (2.5-4.12)	4.15 (3.18-4.97)	**<0.001**
Albumin (g/L)	4.1 (3.8-4.31)	4.12 (3.82-4.4)	**0.030**
Hemoglobin (g/dL)	13.2 (11.5-14.4)	13.3 (11.8-14.5)	0.288
Neutrophil (10^9/L)	5.51 (4.18-7.12)	5.12 (4.11-6.73)	0.314
Platelets (10^9/L) (10^9/L)	243 (197-287)	237 (195-291)	0.837
Lymphocytes (10^9/L)	2.09 (1.66-2.59)	2.18 (1.51-2.74)	0.639
Monocytes (10^9/L)	0.69 (0.51-0.81)	0.69 (0.54-0.85)	0.319
ACEI/ARB (n, %)	260 (77.2)	157 (78.9)	0.639
B-blocker (n, %)	292 (86.6)	177 (88.9)	0.437
Ca-channel blocker (n, %)	110 (32.8)	59 (29.6)	0.471
Diuretic (n, %)	122 (36.2)	76 (38.2)	0.645
Statin (n, %)	262 (77.7)	133 (66.8)	**0.006**
ASA (n, %)	296 (87.8)	163 (81.9)	0.059
Clopidogrel (n, %)	174 (51.6)	124 (62.3)	**0.018**
Oral anticoagulant (n, %)	44 (13.1)	30 (15.1)	0.513
Anti-diabetic (n, %)			0.338
Oral antidiabetic	91 (27)	52 (26.1)	-
Insulin	29 (8.6)	25 (12.6)	-
COPD	51 (15.1)	30 (15.1)	0.986

BMI: Body mass index, GFR: Glomerular filtration rate, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker, ASA: Acetylsalicylic acid, COPD: Chronic obstructive pulmonary disease

Table 2. ROC curve results of AIP and AC for prediction of ISR

	AUC	p	95% CI	Cut-off	Sensitivity	Specificity
LDL-C	0.573	0.005	0.522-0.625	111.5	65.3	54.0
AIP	0.672	<0.001	0.623-0.720	0.58	61.3	72.1
AC	0.670	<0.001	0.622-0.718	3.44	69.8	58.8

ROC: Receiver operating characteristic, AIP: Atherogenic index of plasma, AC: Atherogenic coefficient, AUC: Area under the curve, CI: Confidence interval, LDL-C: Low-density lipoprotein cholesterol

Table 3. Paired comparisons of area difference under the ROC curve

	z	p	AUC difference	95% CI
LDL-C/AIP	-2.809	0.005	-0.098	-0.167- -0.030
LDL-C/AC	-4.768	<0.001	-0.097	-0.137- -0.057
AIP/AC	0.069	0.945	0.002	-0.043-0.046

ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval, LDL-C: Low-density lipoprotein cholesterol, AIP: Atherogenic index of plasma, AC: Atherogenic coefficient

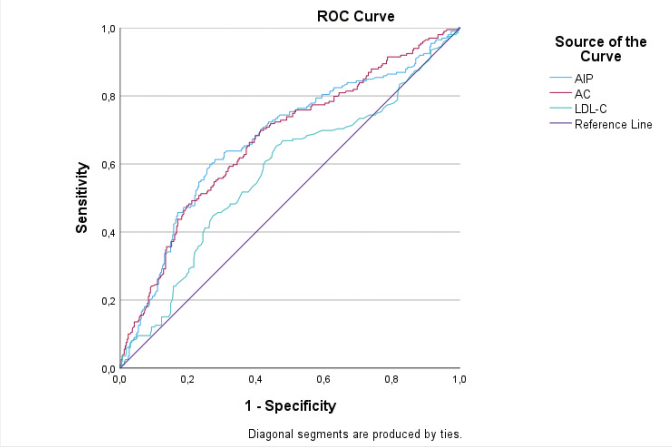


Figure 1. ROC curves of AIP, AC, and LDL-C for prediction of ISR

ROC: Receiver operating characteristic, AIP: Atherogenic index of plasma, AC: Atherogenic coefficient, LDL-C: Low-density lipoprotein cholesterol, ISR: In-stent restenosis

Variables that were found to have meaningful results were put into multivariate logistic regression analysis. We conducted two models of multivariate logistic regression analysis. In the first model, AIP and AC were included in the analysis. According to the results of multivariate analysis, stent diameter, stent length, SYNTAX score, ejection fraction, AIP, and AC were the predictors of ISR. In the second model, TG, HDL-C, and LDL-C were included in the analysis. The results of the second model demonstrated that stent diameter, stent length, SYNTAX score, ejection fraction, LDL-C, TG, and HDL-C were the predictors of ISR. AIP had the greatest odds ratio with a value of 3.979. Table 4, 5 show the results of the univariate and multivariate logistic regression analyses results, respectively.

Discussion

Our study revealed that in addition to the risk factors of stent length, stent diameter, SYNTAX score, ejection fraction, and lipid parameters, including LDL-C, HDL-C, and TG, both AIP and AC had a statistically significant value for predicting ISR. A comparison of the ROC curves demonstrated that AIP and AC each had a significantly higher area under the curve compared to LDL-C. Additionally, among the lipid parameters, AIP had the highest odds ratio for predicting ISR.

Although the incidence of ISR with DES is lower than that associated with BMS, ISR remains a therapeutic challenge (12). Several studies have investigated the risk factors for ISR, with most of finding that cytokines and biomarkers, such as C-reactive protein, homocysteine, and tumor necrosis factor-α, are associated with the presence of ISR (13-15). Additionally, patient-related and lesion-related risk factors have been assessed in various studies, which have found that stent length, diameter, bifurcation lesions, and the presence of DM and HT are risk factors for ISR (3).

Hyperlipidemia is a major factor related to the development of atherosclerosis. Increased levels of LDL-C stimulate inflammation, and cause endothelial damage and cholesterol collection in the vessel wall (16). However, the role of hyperlipidemia in the occurrence of ISR remains less clear, and studies investigating the relationship between hyperlipidemia and ISR have yielded weaker associations. In Kim et al.'s (17) study, patients with a small LDL-C particle size had higher rates of ISR, even after controlling for other CAD risk factors. Fang et al. (18) assessed the LDL-C to HDL-C ratio in acute coronary syndrome patients treated with percutaneous intervention and found that the ratio had a good predictive performance for the presence of ISR. Investigated the risk factors for ISR in patients treated for chronic coronary syndromes. Although TC, HDL-C, and TG levels did not differ between patients with or without ISR, LDL-C levels were significantly elevated in ISR patients (4). Özkalaycı et al. (19) showed that the TG glucose index, a surrogate marker of insulin resistance, had a better value compared the TG/HDL-C ratio and glucose levels in predicting all-cause mortality in ST-elevation myocardial infarction patients. The value of the TG glucose index in risk stratification and prediction of adverse events in patients with ST-elevation myocardial infarction has also been shown in other studies (20). However, Xu et al. (21) did not find any association between lipid parameters and the development of ISR. Similarly, Li et al. (2) found no differences in the lipid profile of patients with or without ISR. Our results were align with the previous studies that found abnormalities in lipid parameters to be a risk factor for ISR.

Table 4. Univariate logistic regression for the presence of in-stent restenosis

	p	OR	95% CI
Age	0.896	1.001	0.985-1.018
Stent diameter	<0.001	0.059	0.026-0.131
Stent length	<0.001	1.325	1.248-1.408
BMI	0.164	0.969	0.927-1.013
Smoking	0.899	1.016	0.798-1.292
Syntax score	<0.001	1.058	1.033-1.083
Ejection fraction	<0.001	0.959	0.940-0.979
Creatinine	0.449	1.098	0.862-1.399
GFR	0.876	0.999	0.993-1.006
TC	0.002	1.005	1.002-1.009
LDL-C	0.006	1.006	1.002-1.010
Triglyceride	<0.001	1.005	1.003-1.008
HDL-C	<0.001	0.995	0.935-0.976
Atherogenic index of plasma	<0.001	11.253	5.004-25.305
Atherogenic coefficient	<0.001	1.613	1.393-1.869
Albumin	0.052	1.529	0.997-2.344
Hemoglobin	0.198	1.060	0.970-1.158
Neutrophil	0.456	0.969	0.892-1.053
Platelet	0.803	1.000	0.998-1.002
Lymphocyte	0.359	1.100	0.897-1.348
Monocyte	0.542	1.252	0608-2.570
Diabetes mellitus	0.503	1.132	0.787-1.627
Hypertension	0.448	1.291	0.667-2.499

OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, GFR: Glomerular filtration rate, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol

Table 5. Multivariate logistic regression for the presence of in-stent restenosis

Model A

	p	OR	95% CI
Stent diameter	<0.001	0.053	0.020-0.141
Stent length	<0.001	1.348	1.258-1.446
Syntax score	0.002	1.047	1.017-1.078
Ejection fraction	<0.001	0.953	0.929-0.978
Atherogenic index of plasma	0.022	3.979	1.218-12.997
Atherogenic coefficient	0.036	1.270	1.016-1.586

OR: Odds ratio, CI: Confidence interval

Model B

	p	OR	95% CI
Stent diameter	<0.001	0.050	0.019-0.132
Stent length	<0.001	1.345	1.255-1.442
Syntax score	0.002	1.048	1.018-1.079
Ejection fraction	<0.001	0.954	0.930-0.978
LDL-C	0.043	1.006	1.000-1.011
Triglyceride	0.003	1.004	1.001-1.007
HDL-C	0.039	0.971	0.945-0.999

OR: Odds ratio, CI: Confidence interval, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol

The pathogenesis of ISR has not been fully elucidated and involves complex pathological processes. Vascular wall injury and endothelial denudation caused by balloon dilatation and stent implantation result in an inflammatory response characterized by vascular smooth muscle cell migration, proliferation, extracellular matrix synthesis, and neointimal proliferation (22). Incomplete regeneration of the endothelium leads to excessive uptake of lipids from circulation and foam cell formation, which contributes to the occurrence of neoatherogenesis (23). Neoatherosclerosis, which is characterized by impaired endothelial healing with lipoprotein migration into the subendothelium, results in late stent failure, including ISR and thrombosis (24,25). As such, inflammation and atherosclerotic progression are probably the two main mechanisms for the occurrence of ISR. Consistent with these findings, we found that increased levels of TC, LDL-C, and TG and decreased levels of HDL-C predicted ISR. According to the ROC curve analysis, both AIP and AC had higher specificities compared to LDL-C in predicting ISR. Moreover, among the lipid parameters, AIP had the highest odds ratio in predicting ISR.

Study Limitations

This was a single -center study and had a retrospective design. We did not use intravascular ultrasound or optical coherence tomography for evaluating ISR. Our study could fail to show all confounding risk factors for ISR and fails to evaluate the effect of consecutive changes in AIP during follow-up on ISR incidence. Finally, operator experience might have affected the outcomes.

Conclusion

Development of ISR necessitates repeat interventions that hamper the quality of life of the patients and are associated with increased mortality. As such, secondary prophylaxis with the aim of prevention of ISR is critical after percutaneous interventions. Both AIP and AC had higher specificities compared with that of LDL-C in predicting ISR. The calculation of these parameters is simple and could be used easily in clinical practice. To confirm our findings, multicenter, randomized, and prospective studies are necessary.

Ethics Committee Approval: The approval of the study was obtained from a University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethical Committee (approval number: 238, date: 22.07.2022) and it was conducted in concordance with the declaration of Helsinki.

Informed Consent: Informed consent of all patients was also obtained before study inclusion.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Design - Y.Y., C.Y., B.A., F.K., S.Ç.E., D.K.; Data Collection or Processing - Y.Y., B.A., F.K., S.Ç.E., F.N.T.Ç.; Analysis or Interpretation - Y.Y., C.Y., B.A., F.K., S.Ç.E., D.K., F.N.T.Ç.; Literature Search - Y.Y., C.Y., B.A., S.Ç.E., D.K., F.N.T.Ç.; Writing - C.Y., S.Ç.E., D.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. Sclofmitz E, Iantorno M, Waksman R. Restenosis of Drug-Eluting Stents: A New Classification System Based on Disease Mechanism to Guide Treatment and State-of-the-Art Review. Circ Cardiovasc Interv 2019; 12: e007023.
2. Li M, Hou J, Gu X, Weng R, Zhong Z, Liu S. Incidence and risk factors of in-stent restenosis after percutaneous coronary intervention in patients from southern China. Eur J Med Res 2022; 27: 12.
3. Cheng G, Chang F, Wang Y, You PH, Chen H, Han W, et al. Factors Influencing Stent Restenosis After Percutaneous Coronary Intervention in Patients with Coronary Heart Disease: A Clinical Trial Based on 1-Year Follow-Up. Med Sci Monit 2019; 25: 240-7.
4. Wang P, Qiao H, Wang R, Hou R, Guo J. The characteristics and risk factors of in-stent restenosis in patients with percutaneous coronary intervention: what can we do BMC Cardiovasc Disord 2020; 20: 510.
5. Çelik E, Cora AR, Karadem KB. The Effect of Untraditional Lipid Parameters in the Development of Coronary Artery Disease: Atherogenic Index of Plasma, Atherogenic Coefficient and Lipoprotein Combined Index. J Saudi Heart Assoc 2021; 33: 244-50.
6. Bo MS, Cheah WL, Lwin S, New TM, Win TT, Aung M. Understanding the Relationship between Atherogenic Index of Plasma and Cardiovascular Disease Risk Factors among Staff of an University in Malaysia. J Nutr Metab 2018; 2018: 7027624.
7. Pourfarzam M, Zadhoush F, Sadeghi M. The difference in correlation between insulin resistance index and chronic inflammation in type 2 diabetes with and without metabolic syndrome. Adv Biomed Res 2016; 5: 153.
8. Zhu XW, Deng FY, Lei SF. Meta-analysis of atherogenic index of plasma and other lipid parameters in relation to risk of type 2 diabetes mellitus. Prim Care Diabetes 2015; 9: 60-7.
9. Zhu X, Yu L, Zhou H, Ma Q, Zhou X, Lei T, et al. Atherogenic index of plasma is a novel and better biomarker associated with obesity: a population-based cross-sectional study in China. Lipids Health Dis 2018; 17: 37.
10. Akıncı S, Coner A, Akbay E, Adar A, Mudersioglu H. Association of the Atherogenic Index of Plasma with C-Reactive Protein and Urinary Albumin Excretion in a Normotensive Nondiabetic Population. Metab Syndr Relat Disord 2022; 20: 421-7.
11. Drwila D, Rostoff P, Nessler J, Konduracka E. Prognostic significance of atherogenic index of plasma, atherogenic coefficient and lipoprotein combined index among elderly patients with non-ST-segment elevation myocardial infarction in 1-year follow-up Bratisl Lek Listy 2022; 123: 872-7.
12. Bønaa KH, Mannsverk J, Wiseth R, Aaberge L, Myreng Y, Nygård O, et al; NORSTENT Investigators. Drug-Eluting or Bare-Metal Stents for Coronary Artery Disease. N Engl J Med 2016; 375: 1242-52.
13. Li JJ, Ren Y, Chen KJ, Yeung AC, Xu B, Ruan XM, et al. Impact of C-reactive Protein on in-stent restenosis. Tex Heart Inst J 2010; 37: 49-57.
14. Guo J, Gao Y, Ahmed M, Dong P, Gao Y, Gong Z, et al. Serum Homocysteine Level Predictive Capability for Severity of Restenosis Post Percutaneous Coronary Intervention. Front Pharmacol 2022; 13: 816059.
15. Guildford AL, Stewart HJ, Morris C, Santin M. Substrate-induced Phenotypic Switches of Human Smooth Muscle Cells: an In Vitro Study of In-Stent Restenosis Activation Pathways. J R Soc Interf 2011; 8: 641-9.
16. Shiiba M, Zhang B, Miura SI, Ike A, Nose D, Kuwano T, et al. Association between discordance of LDL-C and non-HDL-C and clinical outcomes in patients with stent implantation: from the FU-Registry. Heart Vessels 2018; 33: 102-12.
17. Kim JS, Kim MH, Lee BK, Rim SJ, Min PK, Yoon SJ, et al. Effects of increasing particle size of low-density lipoprotein on restenosis after coronary stent implantation. Circ J 2008; 72: 1059-64.

18. Fang Y, Lin M, Chen L, Yang C, Liu A. Association between LDL/HDL ratio and in-stent restenosis in patients with acute coronary syndrome after stent implantation. Biomark Med 2022; 16: 673-80.

19. Özkalaycı F, Karagöz A, Karabay CY, Tanboga IH, Türkyılmaz E, Saygı M, et al. Prognostic value of triglyceride/glucose index in patients with ST-segment elevation myocardial infarction. Biomark Med 2022; 16: 613-22.

20. Zhao X, Wang Y, Chen R, Li J, Zhou J, Liu C, et al. Triglyceride glucose index combined with plaque characteristics as a novel biomarker for cardiovascular outcomes after percutaneous coronary intervention in ST-elevated myocardial infarction patients: an intravascular optical coherence tomography study. Cardiovasc Diabetol 2021; 20: 131.

21. Xu HY, Qiao SB, Zhang JF, Dong QT, Li JJ. Different impacts of C-reactive protein and lipid profile on coronary lesions following a percutaneous coronary intervention. Coron Artery Dis 2012; 23: 181-7.

22. Jakubiak GK, Pawlas N, Cieślar G, Stanek A. Pathogenesis and Clinical Significance of In-Stent Restenosis in Patients with Diabetes. Int J Environ Res Public Health 2021; 18: 11970.

23. Tsigkas GG, Karantalis V, Hahalis G, Alexopoulos D. Stent restenosis, pathophysiology and treatment options: a 2010 update. Hellenic J Cardiol 2011; 52: 149-57.

24. Hirota Y, Nomura T, Ono K, Sakaue Y, Ueno D, Hori Y, et al. Vulnerable neoatherosclerosis in coronary artery with whole circumference showing intravascular echo attenuation. Clin Case Rep 2019; 7: 1094-7.

25. Siontis GCM, Stefanini GG, Mavridis D, Siontis KC, Alfonso F, Pérez-Vizcayno MJ, et al. Percutaneous coronary interventional strategies for treatment of in-stent restenosis: a network meta-analysis Lancet 2015; 386: 655-64.

İstanbul Med J 2023; 24(1): 83-7
DOI: 10.4274/imj.galenos.2023.37531

A Randomized, Prospective Evaluation the Effect of Oral Pregabalin in Forearm Surgery with Infraclavicular Nerve Block

Özlem Deligöz

University of Health Sciences Turkey, Haydarpaşa Numune Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey

ABSTRACT

Introduction: The infraclavicular block method has been increasingly used in hand, wrist, and forearm surgery in anesthesia practice. Although the infraclavicular block method provides appropriate postoperative analgesic effect, patients still suffer from postoperative pain at high rates. Opioids are widely used for postoperative analgesia. There are many studies showings that taking oral pregabalin before the operation reduces postoperative pain and opioid use. In this study, we investigated the effect of preoperative use of 150 mg oral pregabalin on infraclavicular sensory block duration and opioid use.

Methods: Ethics committee approval and patient consents were obtained for the study. The study included 60 patients between the ages of 18 and 65 who would undergo an American Society of Anesthesiologists I-II hand, wrist or forearm surgery. The control group (group K) did not take medication before the operation. The pregabalin group (group P) took 150 mg of oral pregabalin an hour before the operation. Ultrasound-guided infraclavicular block was applied to both groups. Patients were observed for 24 hours per operatively and postoperatively in terms of analgesic medication needs and complications.

Results: Postoperative analgesic use was observed to be higher in group K ($p<0.05$). There was no significant difference in sensory block and motor block initial durations in group K and group P ($p>0.05$). However, the sensory block completion time was statistically significantly longer in group P than in group K ($p<0.05$). There was no statistically significant difference between the motor block ending times of both study groups in terms of side effects ($p>0.05$).

Conclusion: In this study, we concluded that a single dose of 150 mg oral pregabalin treatment applied before the operation prolongs the infraclavicular sensory block duration and reduces the need for analgesic drugs in the first 24 hours postoperatively.

Keywords: Infraclavicular block, pregalabalin, postoperative analgesia

Introduction

Recently, peripheral nerve blocks have been frequently used in anesthesia practice. Infraclavicular block practice is actually a type of brachial plexus block that is used safely and effectively in both anesthesia and postoperative analgesia management in hand, wrist, and forearm surgeries (1). The World Health Organization classifies the relief of pain as a human right (2). Successful pain management ensures early patient ambulation and shortens the duration of hospital stay. It is also a quality indicator (1).

Despite significant advances in analgesia techniques, surgical procedures still cause moderate to severe postoperative pain in 50-70% of patients (3). Postoperative pain includes both inflammatory and neuropathic components (3). Pregabalin is an anticonvulsant agent that is widely used as an analgesic with membrane-stabilizing and antinociceptive effects for neuropathic pain. It is rapidly absorbed through the intestine and reaches its highest plasma concentration with 90% bioavailability after about an hour (4). Pregabalin is an anti-epileptic, analgesic, and anxiolytic agent. It binds to the α-2-δ subunit of voltage-gated calcium channels. Reduces the release of various excitatory neurotransmitters such as glutamate and prevents the development of hyperalgia (5). In doing so, it inhibits central sensitization and progression of pain (6). In this way, it can be used for perioperative and postoperative analgesia. Opioids are also frequently used in postoperative pain management despite numerous side effects (7). Use of Pregabalin has been found to reduce postoperative opioid consumption and opioid side effects in many surgical operations (3). The increase in opioid consumption led to increasing side effects and complications resulting from opioids.

We investigated the effect of preoperative use of 150 mg oral pregabalin on infraclavicular sensory block duration and opioid use (8). The hypothesis of this randomized controlled trial is that a single dose of 150 mg oral pregabalin will prolong the duration of infraclavicular sensory

Address for Correspondence: Özlem Deligöz MD, University of Health Sciences Turkey, Haydarpaşa Numune Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey
Phone: +90 531 781 04 00 **E-mail:** ozlem.deligoz@gmail.com **ORCID ID:** orcid.org/0000-0002-5651-9827

Cite this article as: Deligöz Ö. A Randomized, Prospective Evaluation the Effect of Oral Pregabalin in Forearm Surgery with Infraclavicular Nerve Block. İstanbul Med J 2023; 24(1): 83-7.

Received: 26.12.2022
Accepted: 30.01.2023

©Copyright 2023 by the University of Health Sciences Turkey, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.

blockade, reduce the need for peroperative and postoperative opioids, and mitigate the side effects that may develop due to opioid use.

Methods

The Recep Tayyip Erdoğan Training and Research Hospital Ethics Committee approval was obtained for this study (approval number: 137, date: 07.08.2019). All patients were evaluated and then were explained the procedure preoperatively. Oral and written consent were obtained from the patients. Sixty patients between the ages of 18 and 65 who were planned to undergo the hand, wrist, elbow, and forearm bone surgeries within the scope of American Society of Anesthesiologists (ASA) I and II were included in the study. Patients with hypersensitivity to the drugs to be used in the study or the substances in their composition, patients with severe cardiac, hepatic, renal disorders, patients who did not want to participate, and who did not allow infraclavicular blocking were excluded from the study. Patients were randomized in a computer environment and divided into two groups. The group that was not administered any medication before the operation was named the control group (group K), and the group that was orally administered 150 mg pregabalin 1 h before the operation was named the pregabalin group (group P). The study was planned as a prospective and double-blind study. Preoperative randomization was done by a computer. Postoperative follow-ups were performed by different physicians. Age, gender, body mass index (BMI), type of surgery, and duration of surgery were recorded in all patients. In the first 24 postoperative h, motor block and sensory block return times and analgesic needs of the patients were recorded. Again, possible side effectsand complications within 24 h peroperatively and postoperatively were noted.

An hour before the operation, the patients were taken to the preoperative room of the operating theater. Group P was administered 150 mg of oral pregabalin with a small amount of water. Patients underwent standard monitoring with electrocardiogram, peripheral oxygen saturation, and noninvasive arterial pressure. The vascular route was opened with 18/20 G cannula and 500 mL 0.9% isotonic solution was inserted. The necessary space cleaning was performed using 10% povidone-iodine in the supine position. Then, the axillary artery and brachial plexus cords were imaged in both groups under ultrasound guidance using a linear probe (Philips-Sparq device, high-speed 5.2 mHz). Following up, ultrasonography (USG)-guided peripheral block needle (Stimuplex ultra360, 22G*80mm) was used to perform infraclavicular blocking. 30 mL of local anesthetics, which consisted of 15 mL 0.5% bupivacaine and 15 mL 2% Lidocaine, were administered in a way to spread in a U-shaped manner to the posterior, lateral, and medial cords of the brachial plexus observed around the axillary artery. Modified Bromage Motor Scale (4. normal muscle strength, 3. muscle strength decreased but overcomes resistance, 2. muscle strength unable to overcome resistance but gravity, 1. tremor style muscle strength, 0. no muscle strength) was used for motor block. The initial motor block duration was determined as the duration between the time of local anesthetic administration and the time of scale 1. A pin - Prick test (0-no sensory block, 1-tactile sensation without pain, 2-no tactile sensation and pain) was used for sensory block. The onset duration of sensory block was determined between the time of local anesthetic administration and the time of Pin - Prick test 1. Motor and sensory block onset time was recorded.

In the peroperative period, it was planned to administer fentanyl (50 µgr + 50 µgr) IV in case the patient felt pain. The time of fentanyl administration and the total amount administered were recorded. Patients who still felt pain after 100 h of fentanyl administration were treated with deep sedo-analgesia and were excluded from the study.

Postoperatively, patients were followed up in the orthopedics and traumatology service for the first 24 h. The full return of muscle strength was the return of the motor block. The onset of pain was also considered to be the time of sensory block recovery. Both time were recorded. Numerical rating scale (NRS) number 11 (0=no pain, 10=very severe unbearable pain) was used as a pain scale. It was planned to administer paracetamol 500 mg orally up to NRS 3 in case the patient-required analgesics. Administration of tramadol HCL 1-2 mg/kg i.v. was planned in case of insufficient paracetamol or NRS above 4.

Statistical Analysis

Statistical analyses were performed using the NCSS 2007 Statistical Software (Utah, USA) package software. In addition to descriptive statistical methods (mean, standard deviation) in the evaluation of the data, the distribution of the variables was examined using the Shapiro-Wilk normality test, an independent t-test was used in the comparison of the binary groups of the variables with normal distribution, chi-square and Fisher reality test were used in the comparisons of qualitative data. $P<0.05$ was considered significant.

Results

Seventy-eight patients were enrolled in the study. Sixty eligible patients were analyzed. All details about the inclusion of patients in the study are presented in the CONSORT flowchart (Figure 1).

There was no statistically significant difference between the two groups in the demographic data of the patients such as age, gender, BMI, ASA, duration of surgery, and type of surgery (Table 1).

There were no statistical differences in the time and dose of fentanyl use during the operation in both study groups. Likewise, the time of the first postoperative analgesic use and the dose of paracetamol and tramadol were not found to be significant (Table 2). However, postoperative analgesic use was higher in the control group ($p=0.01$) (Table 2, Figure 2).

In the control group and pregabalin group, the onset durations of sensory block ($p=0.641$) and motor block ($p=0.570$) were not significant (Table 3). Sensory block ending the duration of the pregabalin group ($p=0.0001$) (1098±470.87 min) was statistically significantly shorter than in the control group (606.67±399.19 min) (Table 3, Figure 3). There were no statistical differences between the motor block -ending durations of both study groups ($p=0.231$) (Table 3, Figure 3).

There were no statistical differences between the two groups in terms of complications and side effects during the process of performing block procedures in the peroperative and postoperative periods (Table 4).

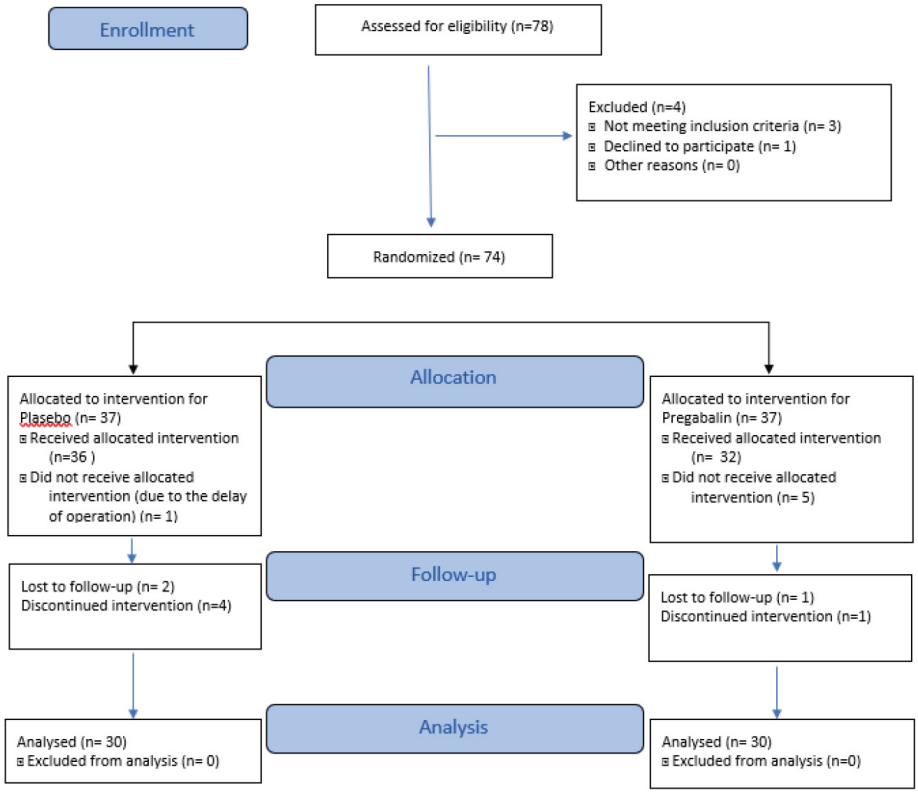


Figure 1. CONSORT 2010 flow diagram

Table 1. Demographic and clinical characteristics in the study groups

		Control group		Pregabalin group		p
Age (years)		43.93±16.62		49.83±15.89		0.165*
Gender	Male	20	(66.67%)	19	(63.33%)	0.787+
	Female	10	(33.33%)	11	(36.67%)	
BMI		23.3±2.63		24.65±3.74		0.110*
ASA Class	Class I	8	(26.67%)	3	(10.00%)	0.095+
	Class II	22	(73.33%)	27	(90.00%)	
Surgery duration (min)		94.53±36.7		109.67±33.81		0.102*
Type of surgery	Wrist	2	(6.67%)	0	(0.00%)	0.117+
	Hand	2	(6.67%)	0	(0.00%)	
	Forearm	26	(86.67%)	30	(100.00%)	

*Independent t-test, +chi-square test, BMI: Body mass index, ASA: American Society of Anesthesiologists

Table 2. Per operative and postoperative analgesic use in the study groups

	Control group		Pregabalin group		p
First fentanyl time (min)	71±29.24		71±31.9		1*
Second fentanyl time (min)	40±		85±63.64		0.667*
Per operative fentanyl dose (µg)	60±22.36		70±27.39		0.545*
Presence of analgesic use	19	(63.33%)	9	(30.00%)	**0.01**+
The first analgesic use time (min)	585±254.42		553.89±256.22		0.765*
Total dose of paracetamol (mg)	791.67±334.8		583.33±204.12		0.184*
Total dose of contramal (mg)	68.75±37.2		75±28.87		0.776*

*Independent t-test, +chi-square test

Discussions

Peripheral nerve blocks are widely used in anesthesia applications. Especially with the introduction of ultrasonography, the success of blockade has increased, and complications have decreased significantly (9). Pain is a complex structure formed because of transmissions to the central and peripheral nervous systems (1). Local anesthetics infiltrate around the nerves and block pain transmission to the brain for several hours. For this reason, peripheral nerve block duration may be insufficient for the postoperative period and postoperative pain management remains an important problem (1).

We aimed to determine the effect of premedication of pregabalin on the sensory and motor block time of infraclavicular block and on analgesic needs. In the results of our study, oral pregabalin prolonged sensory block duration and did not affect motor block duration. There was no difference in the peroperative and postoperative opioid requirements in the pregabalin and non-pregabalin groups. However, more analgesics were used in the control group in the postoperative 24-h period.

In previous studies, oral pregabalin had been administered in the dose range of 75-600 mg, sometimes as a single dose and sometimes with added doses 1-2 h before surgery. Postoperative 12th and 24th h were compared with the placebo group. A 150 mg dose of pregabalin was observed to provide adequate postoperative analgesia and opioid-protective effect (8-10). In addition, high doses of pregabalin have more side effects (3). We used 150 mg oral pregabalin, as recommended in the literature (8-10). We also administered pregabalin to patients preoperatively, 1 h before surgery, to reach the maximum plasma concentration (30 min - 2 h) during surgical stimulation (10).

A objective of preoperative pregabalin use is to increase the duration of sensory block. They reported that preoperative 150 mg oral pregabalin contributed to postoperative sensory and motor block (11). Cegin et al. (9) reported that 150 mg and 300 mg oral pregabalin increased the motor block onset duration and sensory block ending duration before administering infraclavicular block and that there was no difference between these two doses (9). Omara et al. (11) reported that

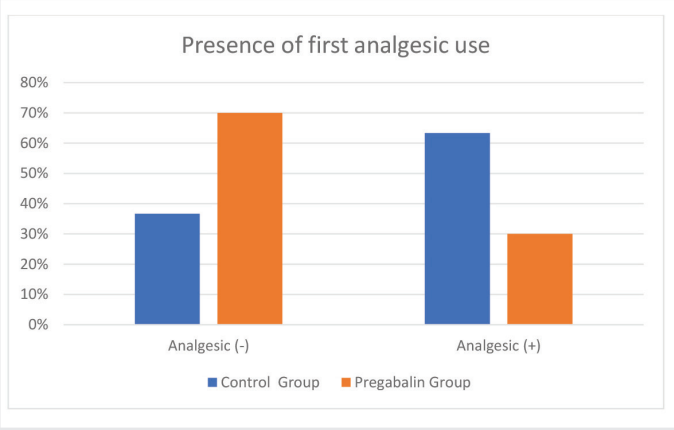


Figure 2. Presence of postoperatif analgesic use

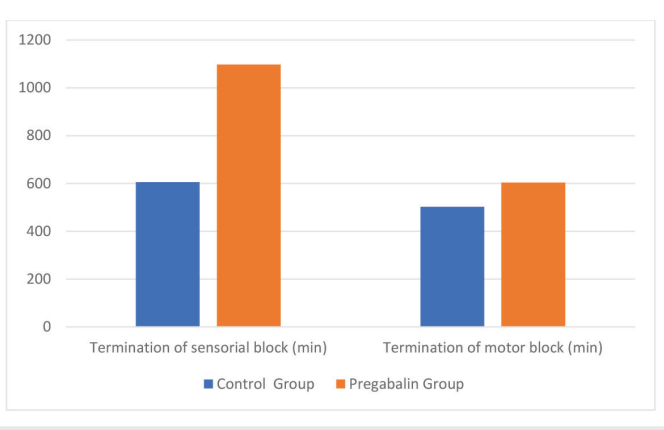


Figure 3. Termination of sensorial and motor blocks in the study groups

Table 3. Comprasion of sensorial and motor block initiation and termination durations in the study groups

	Control group	Pregabalin group	p
Initiation of the sensorial block (min)	3.1±3.21	2.77±2.21	0.641*
Initiation of motor block (min)	13.9±9.67	15.33±9.76	0.570*
Termination of the sensorial block (min)	606.67±399.19	1098±470.87	**0.0001***
Termination of motor block (min)	502±256.28	604.5±386.24	0.231*

*Independent t-test

Table 4. Side effects recorded in the study groups

		Control group		Pregabalin group		p
Block complications		3	10.00%	2	6.67%	0.640+
Peroperative complications		0	0.00%	0	0.00%	-
Postoperative complications	Nausea	7	23.33%	3	10.00%	0.166+
	Vomiting	5	16.67%	5	16.67%	1+
	Pruritus	5	16.67%	1	3.33%	0.085+
	Dizziness	5	16.67%	3	10.00%	0.448+
	Others	1	3.33%	1	3.33%	1

*Independent t-test, +chi-square test

administration of 150 mg oral pregabalin 1 h before spinal anesthesia in patients undergoing orthopedic surgery prolonged the durations of sensory and motor blocks. They reported that this contributed to sleep quality on the first postoperative night (11). Panse et al. (10) found that there was no difference in the onset durations of motor and sensory blocks in patients who underwent spinal anesthesia, as in our study, but the duration of sensory motor block was prolonged. Unlike our study, they also reported that the duration of motor block was prolonged (10). In our study, we found that the duration of sensory block was prolonged, and motor block was not added to this prolongation. Kushwaha et al. (12) also found that in brachial plexus block with oral pregabalin, the duration of sensorial block prolonged and the duration of motor block was not affected, as we did. We believe that a prolonged duration of postoperative sensory block and a non-prolonged duration of motor block will increase the postoperative satisfaction of patients.

The side effects of pregabalin are dose-dependent and usually transient (13). Similar to other studies, nausea, vomiting, pruritus and dizziness were the most frequently observed effects in our study (13,14). However, there is no difference in side effects between the groups (13-15). There was no difference between the peroperative and postoperative complications and side effects of both groups. The onset durations of motor and sensory block were similar in both groups.

Study Limitations

Our study is subject to certain limitations. First, although 150 mg oral pregabalin was shown to be sufficient preoperatively in previous studies, using only 1 dose (150 mg) of pregabalin and not comparing it with other doses was a limitation. Second, the preoperative anxiety scores and pain level of the patients were not analyzed. Pregabalin may affect the preoperative pain and anxiety scores.

Conclusion

In this study, we found that a preoperative single dose of 150 mg oral pregabalin prolonged the duration of sensory block without affecting the duration of motor block and reduced the need for analgesic use in the first 24 h postoperatively in patients undergoing the hand, wrist, elbow, and forearm bone surgeries with infraclavicular block. We believe that further studies and experience are needed to support these results.

Ethics Committee Approval: The Recep Tayyip Erdoğan Training and Research Hospital Ethics Committee approval was obtained for this study (approval number: 137, date: 07.08.2019).

Informed Consent: Oral and written consent were obtained from the patients.

Peer-review: Externally and internally peer-reviewed.

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

References

1. Mandloi D, Ningawal B, Arora K, Vaskle P. To Evaluate and Compare the Effect of Magnesium Sulfate and Dexmedetomidine as an Adjuvant to 0.5% Ropivacaine in Infraclavicular Brachial Plexus Block. International Journal of Pharmaceutical and Clinical Research 2022; 14: 248-55.
2. White PF, Kehlet H. Improving pain management: are we jumping from the frying pan into the fire? Anesth Analg 2007; 105: 10-2.
3. Farladansky E, Hazan S, Maman E, Reuveni AM, Cattan A, Matot I, et al. Perioperative Oral Pregabalin Results in Postoperative Pain Scores Equivalent to Those of Interscalene Brachial Plexus Block After Arthroscopic Rotator Cuff Repair: A Randomized Clinical Trial. Arthroscopy 2022; 38: 31-7.
4. Łuszczki JJ. Third-generation antiepileptic drugs: mechanisms of action, pharmacokinetics and interactions. Pharmacol Rep 2009; 61: 197-216.
5. Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. Epilepsia 2004; 45: 13-8.
6. Chizh BA, Göhring M, Tröster A, Quartey GK, Schmelz M, Koppert W, et al. Effects of oral pregabalin and aprepitant on pain and central sensitization in the electrical hyperalgesia model in human volunteers. Br J Anaesth 2007; 98: 246-54.
7. Benyamin R, Trescot AM, Datta S, Buenaventura RM, Adlaka R, Sehgal N, et al. Opioid complications and side effects. Pain Physician 2008; 11: 105-20.
8. Chen Z, Chen J, Luo R, Jiang J, Xiang Z. The preemptive effects of oral pregabalin on perioperative pain management in lower limb orthopedic surgery: a systematic review and meta-analysis. J Orthop Surg Res 2022; 17: 237.
9. Cegin MB, Soyoral L, Yuzkat N, Baydi V, Goktas U. Pregabalin administered as an anxiolytic agent in ultrasound-guided infraclavicular block: a controlled, double-blind, dose-ranging trial. Eur Rev Med Pharmacol Sci 2016; 20: 568-74.
10. Panse NA, Adate KU, Panchal SH. Comparative Evaluation of Two Different Doses of Pre-Emptive Oral Pregabalin on Duration of Spinal Anesthesia and Postoperative Pain. Archives of Anesthesiology and Critical Care 2021; 7: 75-81.
11. Omara AF, Ahmed SA, Abusabaa MM. The effect of the use of pre-emptive oral pregabalin on the postoperative spinal analgesia in patients presented for orthopedic surgeries: randomized controlled trial. J Pain Res 2019; 12: 2807-14.
12. Kushwaha BB, Singh S, Srivastava VK, Prakash R, Verma R, Verma S. A Randomized, Double-Blind, Prospective Study to Evaluate the Effect of Oral Pregabalin in Upper Limb Surgeries Under Brachial Plexus Block. Cureus 2022; 14: e29117.
13. Çiçekci F, Sargın M, Yıldırım A, Körez MK, Günaydın G, İnci K. The Efficacy of Preemptive Pregabalin Administration on Pre-and Postoperative Anxiety and Postoperative Analgesia in Arthroscopic Shoulder Surgery: A Prospective, Randomized, Double-Blind, Placebo-Controlled Clinical Study. Genel Tıp Dergisi 2022; 32; 12-8.
14. Ezema EC, Ezema OO, Nebuwa E, Oranusi IO, Geofrey OC, Okoro C, et al. Effects of Preoperative Pregabalin on Outcome of Spinal Anaesthesia for Patients Undergoing Open Myomectomy. Eur J Biomed 2020; 7: 202-8.
15. Park M, Lee H, Jeon Y. Preoperative pregabalin prolongs duration of spinal anesthesia and reduces early postoperative pain: A double-blind, randomized clinical CONSORT study. Medicine (Baltimore) 2016; 95: e4828.

İstanbul Med J 2023; 24(1): 88-93
DOI: 10.4274/imj.galenos.2023.75418

Evaluation of Anesthesia-related Knowledge and Concerns of Patients According to Their Education Levels: A Survey Study

Ayşe Gül Ferlengez[1], Duygu Demiröz[2]

[1]University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey
[2]Malatya İnönü University Faculty of Medicine, Department of Anesthesiology and Reanimation, Malatya, Turkey

ABSTRACT

Introduction: The adequate level of anesthesia practices in the community and the role of aids in the hospital could not be reached. In this study, the purpose was to evaluate the relationship between the education level of patients receiving anesthesia, their knowledge, and fears about anesthesia.

Methods: The educational status of the patients was evaluated by questioning their age, educational status, and concerns about anesthesia.

Results: It was concluded that the level of knowledge about anesthesia increased as the level of education of patients increased, but the fears of patients related to anesthesia were similar.

Conclusion: As the education level of the patients increases, their level of knowledge about anesthesia increases. We think that communication with anesthesiologists in the preoperative period will reduce patients' fears about anesthesia.

Keywords: Anesthesiology, education level, questionnaire

Introduction

Although society has an interest in medical issues today, many people still do not have a sufficient level of knowledge about anesthesia practices and the role of an anesthesiologist in a hospital (1,2). Even many people do not know that the anesthesiologist is a medical doctor (3). Previous studies conducted revealed that the patients mostly do not know the anesthesiologists and do not have information about their educational status and are not aware of their duties in the operating room (1-3).

Books and brochures prepared to increase the level of knowledge of patients for anesthesia applications have been effective (4). Information about anesthesia applications reduces the anxiety and stress of the patient (5). Additionally, patient information before anesthesia reduces morbidity and increases patient satisfaction (6).

There is a fear of death during surgery and the inability to wake up from anesthesia in our country. For this reason, patients may experience intense distress when will to have surgery. Increasing the level of knowledge of patients will help reduce these fears (7,8).

In this study, the purpose was to evaluate the relationship between the education level of the patients scheduled to receive anesthesia in the preoperative period and their knowledge and fears about anesthesia.

Methods

The study was initiated after ethics committee approval. The survey questions to be applied were deconstructed by scanning electronic databases and selected from studies similar to our purpose (9,10). Using the G*Power 3.1 program to calculate the sample size, the effect power was taken as 0.5 and the sample number was found to be 100. However, since the number of patients admitted to the outpatient clinic of our hospital was high, a higher rate of patient participation was planned in our study. After receiving the approval of the ethics committee of the University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 1729, date: 01.03.2019), the survey study was briefly described verbally to the patients who applied to the anesthesiology and reanimation polyclinic of our hospital for preoperative evaluation within 3 months' period. A total of 290 patients between the ages of 18-75 who wanted to participate voluntarily were included in the study after receiving the written informed consent of the patients who agreed to participate in the study.

A 17-question survey was administered to the patients, which could be answered in an average of five minutes, questioning their gender, age, educational status, previous anesthesia experiences, and anesthesia-related concerns. The questions asked the patients are presented in Table 1. The questionnaire for illiterate patients was completed by reading by a doctor of anesthesiology and reanimation. A total of 40 patients who

Address for Correspondence: Ayşe Gül Ferlengez MD, University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey
Phone: +90 532 783 41 23 **E-mail:** aysegulsoylemez@yahoo.com **ORCID ID:** orcid.org/0000-0002-0440-2467

Cite this article as: Ferlengez AG, Demiröz D. Evaluation of Anesthesia-related Knowledge and Concerns of Patients According to Their Education Levels: A Survey Study. İstanbul Med J 2023; 24(1): 88-93.

Received: 14.05.2022
Accepted: 31.01.2023

©Copyright 2023 by the University of Health Sciences Turkey, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.

could not answer all the questions for various reasons were excluded from the study, and 250 patients who answered the questions completely were included in the study and their research answers were evaluated.

Statistical Analysis

The data were analyzed in a 95% confidence interval in the IBM SPSS Statistics Version 22 package program in a computer environment. Since the ages of the cases were not normally distributed (Kolmogorov-Smirnov, $p<0.05$), Mann-Whitney U was used to compare the ages of men and women, Pearson chi-square, Fisher's exact test and chi-square trend statistical analyses were used to compare the categorical variables between the groups. In the study, a p-value of <0.05 was considered statistically significant. In the data analysis and statistical analysis in multiple-choice questions, the percentages were assessed by the researchers using the mean and standard deviation.

Results

Of the 290 patients who applied to anesthesiology and reanimation outpatient clinic for preoperative evaluation, 40 patients were excluded from the study because they did not answer all the questions, and 250 of the cases were included in the study. Of the patients, 124 were female (49.6%) and 126 were male (50.4%), with an average age of 46.2 years. When the educational status of the patients was evaluated, 30% were in primary school, 12.8% were in secondary school, 20.8% were in high school, 10.4% were university graduates, and 26% of the patients were illiterate (Table 1).

In the questions where the anesthesia information was evaluated according to the educational status of the patients, the patients were asked "Do you know what surgery you will have?". When 128 patients answered "Yes" to this question were examined, it was seen that primary school graduates ranked first with 77.3% and university graduates followed them with 73.1%. Of the 122 patients who answered "No," the highest proportion was found to be in illiterate people (61.5%).

To the question, "What does an anesthesiologist do?", 54% of the patients gave the correct answer, and the highest number of university graduates of the patients had an idea about this issue compared to 80.7%.

To the question, "Do you know why you came to the anesthesia clinic?", 69.6% answered "Yes" and 30.4% answered "No." When examining the cases that answered "Yes," it was observed that this was the highest rate among university graduates with 100%, while 76.9% of those who answered "No" were made up of a non-literate group.

Table 1. Demographic data for the patients

		n (%)	%
Gender	Female	124	49.6
	Male	126	50.4
Educational status	Primary	75	30
	Secondary	32	12.8
	High school	52	20.8
	University	26	10.4
	Illiterate	65	26

To the question, "Who decides if the patient is fit or not to be able to have surgery?", whereas 60.4% of the patients answered "anesthesiologist," it was observed that the largest proportion of these patients were university graduates 84.6%, and the lowest proportion belonged to illiterate ones.

To the question, "Who applies anesthesia during surgery?", whereas 60.4% of the total number of patients gave the correct answer to the question, it was found that the highest proportion of this group were university graduates (84%) and 32.4% of the patients responded to the doctor who would perform the surgery.

To the question, "Who monitors the patient's vital functions such as heart rate and blood pressure during surgery?", whereas 67.2% of anesthesiologists answered the question, the highest proportion of university graduates was 88.4%, and the lowest proportion of illiterate people was 24.6%.

To the question, "Who ensures that the patient wakes up comfortably after surgery?", 48.4% of the patients answered anesthesiologist, while the surgeon's answer was the least given with 12%. When those who gave the correct answer to this question were investigated, the highest proportion was found with 53.8% in university graduates (Table 2).

In the questions where the anesthesia fears of patients were evaluated according to their educational status, 66.8% of patients answered the question "Do you want to be informed in detail by the anesthesia doctor before surgery?" as they want to receive detailed information, while 10.4% of patients stated that they did not want to receive detailed information for fear of worrying.

The patients who had anxiety fear were highest among primary school graduates, while this rate was the lowest among university graduates, and 6.4% of the patients answered "No" to this question with the least proportion.

To the question, "Are you afraid of anesthesia?", 39.6% of patients answered "Yes," while this rate was the highest among the illiterate 58.4%, followed by university graduates 38.4%, and the lowest was primary school graduates at 28%.

To the question, "What are your fears about the anesthesia process?", while 50.4% of the patients had the highest fear that they would experience pain, 30.4% of the patients stated that they had no fear and 20.8% of the patients felt that they could not wake up from anesthesia, while 10% of the patients stated that they had a fear of death. The fear of pain was the highest among the illiterate at 66.1%, while the second place was occupied by university graduates at 57.6%. The fear of death was found to be the highest among university graduates. While 30.4% of the patients stated that they did not have any fear, the highest proportion of those who were illiterate 30.7% gave this answer (Table 3).

To the question, "What do you think about the pain after surgery?", 52.4% of the patients answered "a normal condition and is tolerable." The highest proportion of these patients was university graduates (69.2%). In this study, 20% of the patients answered that the pain would be unbearable and the highest proportion of these patients was illiterate 36.9% (Table 3).

Table 2. Distribution of anesthesia information according to the educational status of patients

		Primary, (%)	Secondary, (%)	High, (%)	University, (%)	Illiterate, (%)	Total, (%)	p
Do you know what surgery you will have?	Yes	58 (77.3)	13 (40.6)	25 (48.1)	19 (73.1)	25 (21.7)	128 (51.2)	<0.001
	No	17 (22.6)	19 (59.3)	27 (51.9)	7 (26.9)	40 (61.5)	122 (48.8)	<0.001
Have you ever heard of such a word as "anesthesia"?	Yes	69 (92)	26 (81.2)	49 (94.2)	26 (100)	56 (86.1)	226 (90.4)	0.081
	No	6 (8)	6 (18.7)	3 (5.7)	0 (0)	9 (13.8)	24 (9.6)	0.081
What does an anesthesiologist do?	Puts the patient to sleep who will have surgery	24 (32)	8 (25)	5 (7.9)	2 (7.7)	24 (6.9)	63 (25.2)	<0.001
	He puts the patient who will have surgery to sleep, follows and wakes him up during the operation	41 (54.6)	16 (50)	42 (31.1)	42 (80.7)	13 (20)	135 (54)	<0.001
	Does the surgery	2 (2.6)	0 (0)	0 (0)	0 (0)	2 (3.1)	4 (1.6)	<0.001
	Not know	8 (16.6)	8 (25)	5 (10.4)	5 (9.6)	26 (40)	48 (19.2)	<0.001
Do you know why you came to the anesthesia clinic?	Yes	59 (78.6)	23 (71.8)	51 (98.1)	26 (100)	15 (23.1)	174 (69.6)	<0.001
	No	16 (21.3)	9 (28.1)	1 (1.9)	0 (0)	50 (76.9)	76 (30.4)	<0.001
Who decides whether the patient is fit to undergo surgery or not?	The doctor who will perform the operation	6 (8)	12 (37.5)	11 (21.1)	4 (15.3)	48 (73.8)	81 (32.4)	<0.001
	Anesthesiologist	61 (81.3)	20 (62.5)	38 (73.1)	22 (84.6)	10 (15.3)	151 (60.4)	<0.001
	Nurse	1 (1.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.4)	<0.001
	Not Know	7 (9.3)	0 (0)	3 (5.7)	0 (0)	7 (10.7)	17 (6.8)	<0.001
Who performs anesthesia during surgery?	The doctor who will perform the operation	6 (8)	12 (37.5)	11 (21.1)	4 (15.3)	48 (73.8)	81 (32.4)	<0.001
	Anesthesiologist	61 (81.3)	20 (62.5)	38 (73.1)	22 (84.6)	10 (15.3)	151 (60.4)	<0.001
	Nurse	1 (1.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.4)	<0.001
	Do not know	7 (9.3)	0 (0)	3 (5.7)	0 (0)	7 (10.7)	17 (6.8)	<0.001
Who monitors the patient's vital functions such as heart rateand blood pressure during surgery?	The doctor who will perform the operation	7 (9.3)	4 (12.5)	2 (3.8)	0 (0)	12 (73.8)	25 (10)	<0.001
	Anesthesiologist	59 (78.6)	22 (68.7)	48 (92.3)	23 (88.4)	16 (24.6)	168 (67.2)	<0.001
	Nurse	1 (1.3)	1 (3.1)	0 (0)	2	20 (7.6)	24 (9.6)	<0.001
	Technician	1 (1.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.4)	<0.001
	Do not know	7 (9.3)	5 (15.6)	2 (3.8)	1 (3.8)	17 (26.1)	32 (12.8)	<0.001
Who ensures a comfortable awakening of the patient after surgery?	The doctor who will perform the operation	8 (110.6)	5 (15.6)	2 (3.8)	1 (3.8)	14 (21.5)	30 (12)	<0.001
	Anesthesiologist	40 (53.3)	13 (40.6)	35 (67.3)	22 (84.6)	11 (16.9)	121 (48.4)	<0.001
	Nurse	10 (13.3)	4 (12.5)	4 (7.6)	1 (3.8)	24 (36.9)	43 (17.2)	<0.001
	Do not know	10 (13.3)	10 (31.2	11 (21.1)	2 (7.6)	16 (24.6)	56 (22.4)	<0.001
Who ensure that the patient wakes up painlessly after surgery?	The doctor who will perform the operation	18 (24)	3 (9.3)	6 (11.5)	1 (3.8)	13 (20)	41 (16.4)	0.061
	Anesthesiologist	26 (34.6)	14 (43.7)	15 (28.8)	14 (53.8)	14 (21.5)	83 (33.2)	0.061
	Nurse	9 (12)	4 (12.5)	12 (23.1)	5 (19.2)	16 (24.6)	46 (18..4)	0.061
	Do not know	22 (29.3)	11 (34.3)	19 (36.5)	6 (23.1)	22 (33.8)	80 (32)	0.061

Discussion

In this study, it was concluded that the level of knowledge about anesthesia increases as the level of education of patients increases, but the fears of patients related to anesthesia are similar.

Recently, many studies have been conducted to investigate the knowledge of patients with anesthesia applications and anesthesiologists (11,12). In developing countries, the perception of anesthesia and the role of the anesthesiologist are still lagging behind the developed world (13). Anesthesiology gradually progressed after the first application of anesthesia in 1846 and has reached an important point in the field of medicine (14). Unfortunately, it is not known to many individuals that anesthesiology is a branch that requires special expertise or even that an anesthesiologist is a doctor. In the studies conducted, the knowledge

Table 3. Patients' fears according to their educational status

		Primary, n (%)	Secondary, n (%)	High, n (%)	University, n (%)	Illiterate, n (%)	Total, n (%)	p
Do you want to be informed in detail by the anesthesiologist before the operation?	Yes, I would like detailed information	54 (72)	25 (78.1)	37 (71.1)	24 (92.3)	32 (49.2)	172 (68.8)	<0.001
	Yes, but I would not like to have too detailed information for the fear that I will worry	10 (13.3)	3 (9.3)	4 (7.7)	1 (3.8)	8 (12.3)	26 (10.4)	<0.001
	No, I would not	4 (5.3)	1 (3.1)	10 (19.2)	0 (0)	1 (1.5)	16 (6.4)	<0.001
	I do not know	7 (9.3)	3 (9.3)	1 (1.9)	1 (3.8)	24 (36.9)	36 (100)	<0.001
Are you afraid of anesthesia?	Yes	21 (28)	11 (34.3)	19 (36.5)	10 (38.4)	38 (58.4)	99 (39.6)	0.006
	No	54 (72)	21 (65.6)	33 (63.5)	16 (61.6)	27 (41.5)	151 (60.4)	0.006
What are your fears about the anesthesia process? (you can mark more than one)	I'll feel pain	40 (53.3)	15 (46.8)	13 (25)	15 (57.6	43 (66.1)	126 (50.4)	<0.001
	I will have nausea and vomiting	9 (12)	4 (12.5)	6 (11.5)	4 (15.3)	6 (9.2)	29 (11.6)	0.944
	I can not wake up from anesthesia	21 (28)	9 (28.1)	9 (17.3)	7 (26.9)	6 (9.2)	52 (20.8)	0.047
	I wonot recognize the surroundings	3 (4)	2 (6.2)	8 (15.3)	1 (3.8)	1 (1.5)	15 (6)	0.025
	My throat will hurt	3 (4)	0	6 (11.5)	3 (11.5)	1 (1.5)	13 (5.2)	0.039
	I wonot be able to fully wake up from surgery	4 (5.3)	3 (9.3)	7 (13.4)	6 (23.1)	1 (1.5)	21 (8.4)	0.007
	I'll lose my blinker and do things I don't want to	8 (10.6)	5 (15.6)	19 (36.5)	9 (34.6)	6 (9.2)	47 (18.8)	<0.001
	I will die	6 (8)	5 (15.6)	2 (3.8)	5 (19.2)	7 (10.7)	25 (10)	0.188
	I do not have any fears	17 (22.6)	11 (34.3)	22 (42.3)	6 (23.0)	20 (30.7)	76 (30.4)	0.164
What do you think about postoperative pain?	A normal condition, tolerable	42 (56)	18 (56.2)	30 (57.6)	18 (69.2)	23 (35.3)	131 (52.4)	<0.001
	This is an indicator of recovery	5 (6.6)	5 (15.6)	6 (11.5)	4 (15.3)	17 (26.1)	37 (14.8)	
	Pain medication should be used	10 (13.3)	5 (15.6)	13 (2)	3 (11.5)	1 (1.5)	32 (12.8)	
	It is an unbearable condition	18 (24)	4 (12.5)	3 (5.7)	1 (3.8)	24 (36.9)	50 (20)	

acquisition rate with anesthesia was 5.8% in the study by Şahinkaya et al. (9) in Denizli, 17.7% emphasized that the patient did not hear the word anesthesia (15,16). In their survey study, showed that there is a significant relationship between educational status and the level of knowledge about anesthesiology (DEC1). In our study, similarly, it was observed that as the level of education increased, the level of knowledge of the patients also increased. It was concluded in our study that 9.6% of patients did not hear the word anesthesia. We consider that the high number of illiterate patients participating in our study is associated with this result. The highest proportion was in secondary school graduates and the lowest was in university graduates.

Despite the innovations in anesthesia and the important role of anesthesiologists, Kong et al. (17) emphasized that patients know very little about anesthesiologists and their tasks, whereas Marulasiddappa and Nethra (18) documented that patients have insufficient knowledge about anesthesia and the role of anesthesiologists in developing and developed countries. In their study, reported that 48% of the patients stated that anesthesia should be performed by an anesthesiologist. Gençay and Aydın (19) emphasized that this ratio was 90% (11). In our study, this rate was found to be 60.4%. Similarly, the level of knowledge about anesthesia applications was also questioned with the question "Who decides if the patient is suitable to be operated on?" and we received the answer "anesthesia physician" at a rate of 60.4%. When our results were examined, it was found that illiterate people had the lowest rate of knowledge in both questions.

According to Bataineh et al. (20), the patients were asked questions about the intraoperative roles of the anesthesiologist and it was emphasized that the most obvious answers to the cases were to put the patients to sleep with 75%, to monitor them throughout the operation with 73%, to wake the patients with 72%. In their studies, Yoldaş et al. (11) reported that 54.6% of their patients knew that vital sign monitoring was performed by an anesthesiologist. In our study, it was also seen that 67.2% of the patients had information about the intraoperative tasks of the anesthesiologist, and the highest proportion of university graduates dominated the subject. We think that the high level of this information in patients is related to advanced technology.

The fact that the anesthesiologist introduces himself at the preanesthetic visit, informs them about anesthesia, and informs the patients about possible complications reduces the anxiety levels of the patients (21). Informing the patient will suppress the patient's fears and increase

their confidence in the health system (22). While 68.8% of our patients requested to be informed, 10.4% stated that they did not want detailed information in order not to worry. Most patients who wanted to inform were university graduates.

According to Ruhaiyem et al. (23), it was emphasized that 88% of the patients experienced fear before surgery and most of their fears were fear of postoperative pain at 77.3%, followed by the fear of intraoperative awareness at 73.7%. According to Çelik and Edipoglu (24), it was found that the greatest fear of patients was pain in 49.2% of cases, followed by the fear of death in 26.7%. Lim et al. (25) stated that the fear of not being able to wake up from anesthesia was the highest in elderly patients. Gençay and Aydın (19) reported that the fear of not being able to wake up in 53% of patients, the fear of pain in 17.5% of patients, and the fear of death in 10% of patients were emphasized. In our study, it was found that 39.6% of patients had fears about anesthesia, while in our study, we found that 58.4% of illiterates were the highest in this group, while the university graduates ranked second with 38.4%. In our study, it was found that 50.4% of patients felt pain in the first place, 20.8% felt inability to wake up from anesthesia, and 10% felt a fear of death, similar to other studies. Also, there was no relationship between education level and anesthesia-related fears. Since our study aimed to evaluate the relationship between education level and fears about anesthesia, the relationship between age-related fears was not evaluated. When we questioned thoughts about pain, we concluded that 52.4% of patients considered it a normal condition and university graduates think about it at a higher rate.

Study Limitations

Since this study was based on volunteerism, randomization could not be performed. Our study aim was explained in detail to each patient who came to the anesthesia clinic of our hospital for a preoperative visit, but those who wanted to participate could be included in our study. For this reason, the distribution of literacy levels in our sample did not come out at close values to each other. In our study, there are at least n=26 university graduate patients. To investigate the knowledge and concerns of patients about anesthesia, new prospective, randomized, new studies are needed whose literacy levels do not differ from each other. In our study, we think that the previous experience may be effective in addition to the education level of the findings, there is a need for more comprehensive studies on this subject.

Conclusion

In our study, it was seen that as the level of education of the patients increased, the level of knowledge about the anesthesiologist and anesthesia increased. However, it was concluded that the fears associated with anesthesia were similar, regardless of the level of education. We believe that introducing anesthesia physicians to themselves and informing patients about the anesthesia methods to be applied in the preoperative evaluation will increase the patient's level of knowledge about anesthesia and physicians and reduce their fears related to anesthesia.

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 1729, date: 01.03.2019).

Informed Consent: The written informed consent was obtained of the patients who agreed to participate in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - A.G.F.; Concept - A.G.F., D.D.; Design - A.G.F., D.D.; Data Collection or Processing - A.G.F., D.D.; Analysis or Interpretation - A.G.F., D.D.; Literature Search - A.G.F.; Writing - D.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. Gottschalk A, Seelen S, Tivey S, Gottschalk A, Rich G. What do patients know about anesthesiologists? Results of a comparative survey in an U.S., Australian, and German university hospital. J Clin Anesth 2013; 25: 85-91.
2. Ribeiro CS, de Mourão JI. Anesthesiologist: the patient's perception. Braz J Anesthesiol 2015; 65: 497-503.
3. Aras D, Çil C, Akçaoğlu AC, Erbay RH, Zencir M. People's Knowledge, Attitude and Anesthesia Experience on Anesthesiology Practice in Denizli Yenişehir Primary Health Care Center Area. Pam Med J 2009; 2: 76-82.
4. Baaj J, Takrouri MS, Hussein BM, Al Ayyaf H. Saudi patients' knowledge and attitude toward anesthesia and anesthesiologists--A prospective cross-sectional interview questionnaire. Middle East J Anaesthesiol 2006; 18: 679-91.
5. Fitzgerald BM, Elder J. Will a 1-page informational handout decrease patients' most common fears of anesthesia and surgery? J Surg Educ 2008; 65: 359-63.
6. Demirhan İ, Pınar G. Enhanced Recovery After Surgery and Nursing Practices Enhanced Recovery and Nursing. Yıldırım Beyazıt Üniversitesi Hemşirelik E Dergisi 2014; 2: 43-53.
7. Waisel DB, Truog RD. The benefits of the explanation of the risks of anesthesia in the day surgery patient. J Clin Anesth 1995; 7: 200-4.
8. Gaskey NJ. Evaluation of the effect of a pre-operative anesthesia videotape. AANA J 1987; 55: 341-5.
9. Şahinkaya HH, Akpınar V, Parlak M, Damar N, Yılmaz Duran F, Yıldırım H. Evaluation the awareness of anesthesia and effectiveness of preoperative consultation among the patients in our hospital. Tepecik Eğit Hast Derg 2018; 28: 75-82.
10. Uyar Türkyılmaz E, Camgöz Eryılmaz N, Aydın Güzey N, Gedikli A. Determining patients' knowledge and fear of anaesthesia. J Contemp Med 2018; 8: 350-5.
11. Yoldaş TK, Yoldaş M, Güngör H, Karagöz S, Güven AÇ, Çelik Y, et al. A Questionnaire Study Related to Patient's Knowledge, Experience and Anxiety on Anesthesiology Practice During Preanesthetic Evaluation. Ege Tıp Dergisi 2016; 55: 109-16.
12. Sagün A, Birbiçer H, Yapici G, Patients', who applied to the anesthesia clinic, perceptions and knowledge about anesthesia in Türkiye. Saudi J Anaesth 2013; 7: 170-4.
13. Mooruth V. Knowledge and perceptions of patients regarding anaesthetists and anaesthesia. Johannesburg: University of the Witwatersrand, 2015. (Accessed 2 May 2020). Available from: https://pdfs.semanticscholar.org/734a/ab4119dc3b1e2ff38d6103b8256974754de6.pdf

14. Üçpunar B. (Çev). Osmanlı Tıbbı: Tedavi ve Tıbbi Kurumlar. (Ed) Shefer-Mossensohn M. 1500-1700. İstanbul: Kitap Yayınevi; 2014.

15. Aras D, Çil C, Akçaoğlu AC, Erbay RH, Zencir M. People's Knowledge, Attitude And Anesthesia Experience on Anesthesiology Practice in Denizli Yenişehir Primary Health Care Center Area. Pamukkale Tıp Dergisi 2009; 2: 76-82.

16. Şahinkaya H, Akpınar V, Parlak M, Damar N, Yılmaz Duran F. Yıldırım H. Evaluation of the awareness of anesthesia and effectiveness of preoperative interviews among patients consulted to our hospital. Tepecik Eğit. ve Araşt. Hast. Dergisi 2018; 28: 75-82.

17. Kong KL, Budd J, Allen M, Foo I, Leng C, Adam Low PS. Chapter 13 Guidelines for the Provision of Anaesthesia Services (GPAS). 2017. Available from: https://www.nice.org.uk/about/what-we-do/accreditation

18. Marulasiddappa V, Nethra HN. Assessment of surgical patients' knowledge about anaesthesia and anaesthesiologist in a tertiary care teaching institute-a survey. Int J Res Med Sci 2018; 6: 486-92.

19. Gençay I, Aydın G. Assessment of Anesthesia Awareness in Patients Scheluded for Surgery. KÜ Tıp Fak Derg 2020; 22: 225-32.

20. Bataineh AM, Qudaisat IY, El-Radaideh K, Alzoubi RA, Abu-Shehab MI. Patients' perception of the practice of anaesthesia in a teaching hospital in Northern Jordan: a survey. BMC Anesthesiol 2020; 20: 276.

21. Taşdemir A, Arzum Erakgün A, Deniz MN, Agah Çertuğ A. Comparison of Preoperative and Postoperative Anxiety Levels with State-Trait Anxiety Inventory Test in Preoperatively Informed Patients. Turk J Anaesth Reanim 2013; 41: 44-9.

22. Nakahira J, Sawai T, Ishio J, Nakano S, Minami T. Factors Associated with Poor Satisfaction with Anesthesia in Patients Who Had Previous Surgery: A Retrospective Study Anesth Pain Med 2019; 9: 90915.

23. Ruhaiyem ME, Alshehri AA, Saade M, Shoabi TA, Zahoor H, Tawfeeq NA. Fear of going under general anesthesia: A cross-sectional study. Saudi J Anaesth 2016; 10: 317-21.

24. Çelik F, Edipoglu IS. Evaluation of preoperative anxiety and fear of anesthesia using APAIS score. Eur J Med Res 2018; 23: 41.

25. Lim S, Oh Y, Cho K, Kim MH, Moon S, Ki S. The question of preoperative anxiety and depression in older patients and family protectors. Anesth Pain Med 2020; 15: 217-25.

İstanbul Med J 2023; 24(1): 94-9
DOI: 10.4274/imj.galenos.2023.70846

The Relationship Between the Frontal QRS-T Angle and High Blood Pressure Response to Exercise

Ferit Böyük[1], Serhat Çalışkan[2], Aykut Demirkıran[3]

[1]University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey
[2]Bahçelievler Public Hospital, Clinic of Cardiology, İstanbul, Turkey
[3]Tekirdağ Namık Kemal University, Clinic of Cardiology, Tekirdağ, Turkey

ABSTRACT

Introduction: In this study, we compared frontal QRS-T angles between normotensive subjects with high blood pressure (BP) respons to exercise test and the control group.

Methods: Patients who were scheduled for an exercise test between January 2017 and January 2022 were included in the study. The patient group consisted of people who responded to the exercise test with elevated BP, and the control group included people who responded to the exercise test with normal BP. The data in the electrocardiography device's report section was used to calculate the QRS and T-axis. The frontal QRS-T angle was identified as the absolute difference between these two axes.

Results: Frontal QRS-T angles were found to be significantly higher in the patient group compared with the control group (36.09±14.51 and 20.46±8.12; p<0.001). In multivariate analysis, frontal QRS-T angles were found to be an independent predictor of higher BP response to exercise test [odds ratio: 1,189, 95% confidence interval (CI); 1,083-1,305; p<0.001]. Receiver operating characteristic curve analysis showed that the frontal QRS-T angle value predicting an excessive BP response to exercise test was 27.5º with a sensitivity of 71% and a specificity of 75% (area under the curve: 0.832; 95% CI: 0.75-0.91; p<0.001).

Conclusion: The frontal QRS-T angles were found to be significantly higher in the group that gave higher BP response to the exercise test compared to the control group. Patients with a high BP response to exercise test can be detected using the frontal QRS-T angle before the test.

Keywords: Hypertension, exercise test, excessive blood pressure response, F (QRS-T)

Introduction

Hypertension (HT) is one of the most common preventable cardiovascular risk factors (1-3). An increase in the prevalence of HT is observed with the aging population, and it is predicted that it will affect approximately 1.5 billion people worldwide by 2025. HT is a global public health problem that causes end-organ damage, leading to complications such as myocardial infarction, cerebrovascular disease, and renal failure because of delays in early diagnosis and treatment (4). The exercise test is a non-invasive, inexpensive, and easy diagnostic method used by clinicians for many years to assess the effectiveness and functional capacity of the therapy applied in the diagnosis of cardiovascular diseases (5). During the exercise test, blood pressure (BP) and electrocardiography (ECG) recordings were taken at the initial stage and all stages of the test. During exercise, BP increases because of the rise in cardiac output that occurs to fulfill the increased metabolic requirements of the body. In some individuals, BP rises excessively during exercise, and systolic BP increases to 210 mmHg or more in males and 190 mmHg or more in women. This group is considered to be patients with an excessive hypertensive response to exertion (6). The response to high BP that occurs when exercising is multifactorial and its mechanism is unclear. The higher BP response to exercise has been associated with endothelial dysfunction, increased vascular resistance, and morphological abnormalities of peripheral arteries (7,8). Patients who are normotensive before the exercise test and who experience an excessive BP response during the test are at risk of developing HT during subsequent follow-up, according to research (9). Patients in the Framingham Heart Study who had an elevated BP response after an exercise test developed HT during their 8-year follow-up (10).

The surface ECG measurements QT dispersion (QTd) and Tp-e interval demonstrate the heterogeneity of ventricular repolarization. The literature has demonstrated that individuals with HT have longer QTd and Tp-e intervals, which demonstrate cardiac repolarization heterogeneity (11-

Address for Correspondence: Ferit Böyük MD, University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey
Phone: +90 212 409 02 00 **E-mail:** doctorferit.fbyk@gmail.com **ORCID ID:** orcid.org/0000-0003-2313-1495

Cite this article as: Böyük F, Çalışkan S, Demirkıran A. The Relationship Between the Frontal QRS-T Angle and High Blood Pressure Response to Exercise. İstanbul Med J 2023; 24(1): 94-9.

Received: 04.12.2022
Accepted: 01.02.2023

©Copyright 2023 by the University of Health Sciences Turkey, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.

13). Recently, a novel ECG measure called frontal QRS-T angles has been employed to demonstrate ventricular repolarization heterogeneity. It is easily calculable using data from ECG and known as the angle between the QRS and T-axis. The association between various diseases and QRS-T angle has been demonstrated in earlier investigations (14-17).

Previous studies have examined how QRS-T angle and HT are related. We compared the frontal QRS-T angle, which depicts ventricular repolarization heterogeneity, between participants who responded to the exercise test with elevated BP and a control group.

Methods

Patient population: The study included patients who visited the cardiology clinic between January 2017 and January 2022 and underwent a treadmill exercise test. Excessive hypertensive response to exertion was defined as systolic BP increase of 210 mmHg or more in men and 190 mmHg or more in women (6). The patient group consisted of people who responded to the exercise test with elevated BP, and the control group included people who responded to the exercise test with normal BP. Retrospective reviews of patient data, laboratory results, and electrocardiographic parameters were performed using hospital information system data. The following patients were excluded from the current study: Those with a history of HT or taking antihypertensive medication, those with a history of diabetes, those with severe valve pathology, left ventricular hypertrophy, those taking oral contraceptives, hormone replacement therapy, or steroids, those with known coronary artery disease, cancer, thyroid dysfunction, or those who were pregnant at the time of diagnosis. The University of Health Sciences Turkey, İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital Local Ethics Committee approved the study protocol (approval number: 2022-10-07, date: 23.05.2022).

Echocardiography: The same cardiologist who evaluated the patients for our study used the EPIQ 7C, S5-1, and X5-1 transducer from Philips Healthcare (Andover, Massachusetts). Before the surgery, the patients were placed in the left lateral decubitus position. By the standards of the American Society of Echocardiography recommendations, imaging was carried out through the parasternal long and apical windows (18). This research excluded patients with significant valve pathology, left ventricular hypertrophy, and heart failure.

Frontal QRS-T angle: All patients underwent 12-lead ECG using the (Mortara Instrument ELI 250) equipment in the supine position at a speed of 25 mm/s and voltage of 10 mm/mv before the exercise test, after resting for at least 15 min. With the use of a magnifying lens, the same cardiologist computed each measurement. The data in the ECG device's report section were used to calculate the QRS and T-wave axis. The frontal QRS-T angle was identified as a difference between the QRS and T-axis. Figure 1 shows the frontal QRS-T angle calculation method.

Exercise stress test: Exercise stress testing was performed on research participants using the Bruce protocol (Schiller, Cardiovit Cs-200). Throughout the test, the patient's BP and ECG were checked and recorded every three minutes. BP readings below 210 mmHg for males and 190 mmHg for women were deemed excessive BP responses to exertion (12). The exercise test was stopped if the heart rate was exceeded by more than 85% of the target heart rate, if the ECG recordings revealed ischemia abnormalities, if the systolic BP dropped by more than 10 mmHg, or if the patient requested that the test be stopped because of a complaint.

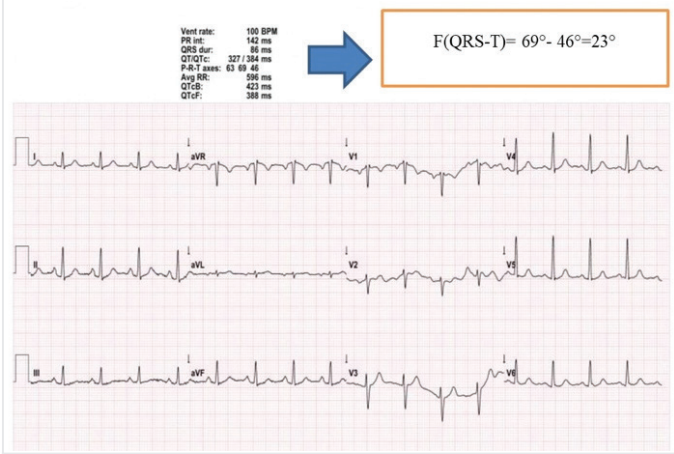


Figure 1. Frontal QRS-T angle measurement using a 12-lead surface ECG
ECG: Electrocardiography

Biochemical parameters: Biochemical parameters of the patients were measured using the AU5800 Clinical Chemistry System (Beckman Coulter, INC, California, USA) device, and hematological parameters with the XT-400Oi Hematology Analyzer (Sysmex, Kobe, Japan). A BP Holter device was used to measure 24-h ambulatory BP in all trial participants (Suntech, Bravo 24-HR ABP), and white-coat HT was eliminated.

Statistical Analysis

All statistical analysis was performed using the NCSS 2007 (Kaysville, Utah, USA). The Independent sample t-test and the Mann-Whitney U test were used to analyze the study data. The Independent sample t-test was used to compare normally distributed parameters, and the Mann-Whitney U test was used to compare non-normally distributed parameters between the patient and control groups. Comparing qualitative data was performed using the pearson chi-square test. To ascertain the impacts on risk categories, a multivariate analysis was conducted. The cut-off value was determined using receiver operating characteristic analysis. Statistical significance was assessed at the $p<0.01$ and $p<0.05$ levels.

Results

Basic demographic and laboratory findings: Table 1 presents the demographic details of the research participants. A total of 101 participants were included, of whom 53 were the control group and 48 showed high BP response to the exercise test (patient group). The mean age was 47.23±9.28 in the patient group and 45.07±7.76 years in the control group ($p=0.663$). Body mass index (BMI) was different between the two groups (27.34±2.32 and 23.2±1.95; $p=0.021$). In Table 2, laboratory data comparisons are shown. The white blood cell count was substantially greater in the patient group when the hematological parameters were analyzed (7.51±1.48 and 7.38±2.01; $p<0.001$). Serum HDL levels were substantially lower in the patient group compared with the control group (43±8.01 and 54.83±12.28; $p<0.001$).

ECG findings: Table 3 shows the comparison of the heart rates, PR duration, QRS duration, and frontal QRS-T angle between the patient and control groups using ECG measurements. The frontal QRS-T angle in the patient group was found to be substantially wider than in the control group (36.09±14.51 and 20.46±8.12; p<0.001). Other ECG parameters across the two groups did not significantly differ from one another. BMI [odds ratio (OR): 2.63; 95% confidence interval (CI): 1,517-4,559; p<0.001] and QRS-T angle (OR: 1,189; 95% CI: 1,083-1,305; p<0.001) independently predicted patients with high BP in the multivariate logistic regression analysis (Table 4). As a result, individuals with high BP who responded to exercise were predicted to have a frontal QRS-T angle ≥27.5º with 71% sensitivity and 75% specificity (area under the curve: 0.831; 95% CI: 0.75-0.91; p<0.001) (Figure 2, Table 5).

Discussion

The frontal QRS-T angle is simple to measure using a surface ECG. The frontal QRS-T angle was considerably higher in patients who responded to the exercise test with higher BP in comparison to the control group, which was the major finding. To the best of our knowledge, this study is the first to demonstrate a relationship between the frontal QRS-T angle and elevated BP response to exercise.

Table 1. Comparison of the basic demographic and clinical characteristics between the groups

Variables	Patient group (n=48)	Control group (n=53)	p-values
Gender, male, n (%)	21 (43.8)	26 (49.1)	0.593
Age, years	47.23±9.28	45.07±7.76	0.663
Body mass index	27.34±2.32	23.2±1.95	**0.001**
Smoking, n (%)	11 (22.9)	10 (18.8)	0.236
Rest BP, mmHg			
Systolic	125±12	122±16	0.142
Diastolic	78±8	76±10	0.211
Maximum BP during exercise, mmHg			
Systolic	212±24	187±28	**0.001**
Diastolic	94±10	88±12	**0.041**
Proportion achieving target heart rate	34 (70)	48 (90)	**0.022**
Exercise capacity and metabolic equivalents	7.4±2.1	10.3±3.2	**0.043**

BP: Blood pressure

Table 2. Comparison of laboratory parameters between the groups

Variables	Control group, (n=53)	Patient group, (n=48)	p-values
Glucose, (mg/dL)	94.15±14.26 (93)	95.2±9 (92.5)	0.529
Creatinine, (mg/dL)	0.85±0.13 (0.87)	0.69±0.1 (0.68)	0.200
AST, (IU/L)	22.47±12.95 (22)	17.07±4.02 (17)	0.466
ALT, (IU/L)	23.7±15.03 (21)	15.68±5.82 (15)	0.500
Total cholesterol, (mg/dL)	193.38±36.54 (192)	200.28±38.49 (205)	0.511
Triglycerides, (mg/dL)	172.62±97.15 (148)	139.11±82.41 (108.5)	0.960
LDL, (mg/dL)	119.51±44.4 (111)	117.26±33.67 (121)	0.836
HDL, (mg/dL)	54.83±12.28 (54.5)	43±8.01 (42)	**0.001**
White blood cells (10^3/µL)	7.38±2.01 (7.18)	7.51±1.48 (7.15)	**0.001**
Hemoglobin, (g/L)	15.25±1.14 (15.2)	13.1±1.22 (13.2)	0.701
Thrombocyte, (10^3/µL)	242.15±66.51 (235)	273.67±63.73 (270)	0.450

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

Table 3. Comparison of the electrocardiographic parameters between the groups

Variables	Control group, (n=53)	Patient group, (n=48)	p-values
Heart rate	77.13±11.97	79.45±12.98	0.353
QRS time (ms)	90.48±9.26	90.74±11.62	0.903
PR interval (ms)	152.65±21.27	147.68±17.86	0.205
P wave (ms)	96.65±5.62	97±5.49	0.750
Frontal QRS-T angle (º)	20.46±8.12	36.09±14.51	**0.001**

Table 4. Multivariate analysis of independent predictors of excessive BP response to the exercise test

	Odd's ratio	95% Confidence interval		p-values
		Lower	Upper	
Body mass index	2,630	1,517	4,559	**0.001**
HDL	1,012	0.950	1,078	0.710
Frontal QRS-T angle	1,189	1,083	1,305	**0.001**
White blood cell	22,213	1,887	261,496	**0.014**
Neutrophil	0.015	0.001	0.677	**0.031**
Neutrophil/lymphocyte	213,273	4,870	9239.389	**0.005**

BP: Blood pressure, HDL: High-density lipoprotein

Table 5. ROC analysis of the frontal QRS-T angle

					95% confidence interval	
	Cut-off value	AUC	Sensitivity	Specificity	Lower	Upper
Frontal QRS-T angle (º)	≥27.50	0.831	0.717	0.750	0.754	0.910

ROC: Receiver operating characteristic, AUC: Area under the curve

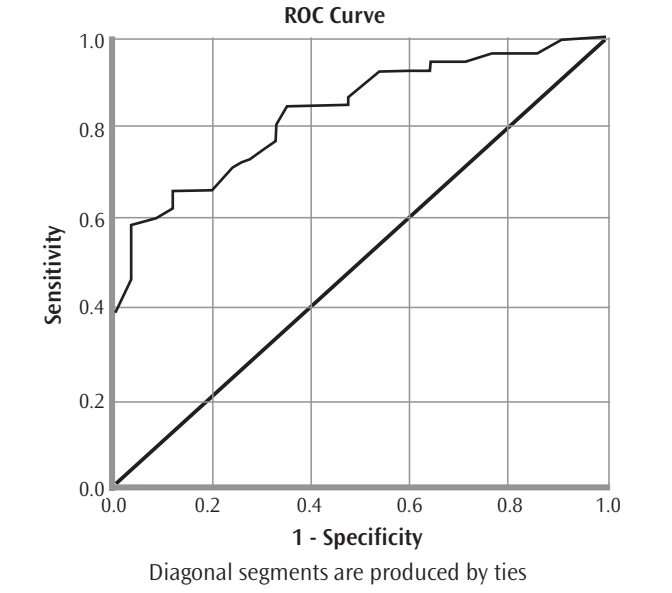


Figure 2. ROC curve analysis of the frontal QRS-T angle in predicting the excessive BP response to the exercise test

ROC: Receiver operating characteristic, BP: Blood pressure

Studies on normotensive groups without a history of HT but with an excessive BP response during an exercise test have also been conducted (18). In healthy subjects performing the test, there is a progressive increase in BP brought on by an enhanced cardiac output. However, during the exercise test, some individuals with confirmed normotension experience an abnormal rise in BP. According to studies in the literature, the group with an excessive BP response during the exercise test is more likely to develop HT during their follow-up (19). The high BP response to the exercise test group in the CARDIA trial, which comprised 3,741 young adults with normotension, was linked to the onset of HT over a 5-year follow-up (20). Similar to this, participants in the 8-year-long Framingham Heart Study who had an elevated BP response to exercise were linked to the emergence of HT (10). It is well known that with an increase in the BMI, the prevalence of HT also increases. The mean BMI was found to be 26.8 kg/cm^2 in the PATENT research, which was carried out to determine the prevalence of HT in our country (21). BMI and non-dipper HT were shown to be correlated in a study of 269 people with newly diagnosed HT (22). BMI is a reliable predictor of the higher QRS-T angle (23). Similar to previous studies, the BMI was a predictor of QRS-T angle in our study.

The angle difference between the QRS and T waves, which is used to determine QRS-T angle, is a novel measure of the heterogeneity of cardiac repolarization (14). Two approaches may be used to compute it. Calculating the QRS-T angle is challenging and needs specialized software however, the surface ECG report section may be used to quickly compute QRS-T angle (24). It has been demonstrated that a QRS-T angle is associated with increased left ventricular mass and poor prognosis (14,25). There are studies in the literature that demonstrate a correlation between the frontal and spatial QRS-T angles. Previous investigations have demonstrated a correlation between the frontal QRS-T angle and coronary artery disease severity. In a study including 1,299 patients who underwent coronary angiography, those with a QRS-T angle greater than 90º had a higher frequency of two or three-vessel disease. A high QRS-T angle was detected in postoperative atrial fibrillation (26). Tanriverdi et al. (27) demonstrated that in individuals without left ventricular hypertrophy, QRS-T angle was higher in the non-dipper hypertensive group than in the dipper group. Bağcı and Aksoy (28) revealed that in pre-hypertensive patients, QRS-T angles were higher than in normotensive individuals. Collagen deposition in myocytes has been shown in pre-HT. Fibrosis leads to disruption of the homogenous structure of the ventricle (29). Echocardiographic imaging can not exclude pathological myocardial fibrosis.

Study Limitations

The relationship between patients with high BP reaction to an exercise test and frontal QRS-T angle requires more research with larger patient populations and longer-term follow-up. However, there was no study conducted on the relationship between excessive BP response and QRS-T angle.

Conclusion

ECG measurements may be crucial in identifying individuals who are at risk of developing HT in the future. Cardiovascular events may be avoided by early identification of individuals who are predisposed to developing HT and early initiation of antihypertensive medication. To support these results, larger and more randomized controlled investigations are required.

Ethics Committee Approval: The University of Health Sciences Turkey, İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital Local Ethics Committee approved the study protocol (approval number: 2022-10-07, date: 23.05.2022).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Concept - F.B., S.Ç., A.D.; Design - F.B., S.Ç., A.D.; Data Collection or Processing - F.B., S.Ç., A.D.; Analysis or Interpretation - F.B., S.Ç., A.D.; Literature Search - A.D.; Writing - F.B., S.Ç., A.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. Rosendorff C, Black HR, Cannon CP, Gersh BJ, Gore J, Izzo JL Jr, et al; American Heart Association Council for High Blood Pressure Research; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Epidemiology and Prevention. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. Circulation 2007; 115: 2761-88.
2. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018; 39: 3021-104.
3. de Simone G, Devereux RB, Roman MJ, Ganau A, Saba PS, Alderman MH, et al. Assessment of left ventricular function by the midwall fractional shortening/end-systolic stress relation in human hypertension. J Am Coll Cardiol 1994; 23: 1444-51.
4. Belaid L, Bayat-Makoei S, Laguerre B, Vigneau C. Monitoring of hypertension in patients orally treated by angiogenesis inhibitor in daily practice. Nephrol Ther 2017; 14: 99-104.
5. Detrano R, Gianrossi R, Froelicher V. The diagnostic accuracy of the exercise electrocardiogram: a meta-analysis of 22 years of research. Prog Cardiovasc Dis 1989; 32: 173-206.
6. Allison TG, Cordeiro MA, Miller TD, Daida H, Squires RW, Gau GT. Prognostic significance of exercise-induced systemic hypertension in healthy subjects. Am J Cardiol 1999; 83: 371-5.
7. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006; 27: 2588-605.
8. Fagard RH, Pardaens K, Staessen JA, Thijs L. Prognostic value of invasive hemodynamic measurements at rest and during exercise in hypertensive men. Hypertension 1996; 28: 31-6.
9. Nakashima M, Miura K, Kido T, Saeki K, Tamura N, Matsui S, et al. Exercise blood pressure in young adults as a predictor of future blood pressure: a 12-year follow-up of medical school graduates. J Hum Hypertens 2004; 18: 815-21.
10. Singh JP, Larson MG, Manolio TA, O'Donnell CJ, Lauer M, Evans JC, et al. Blood pressure response during treadmill testing as a risk factor for new-onset hypertension. The Framingham heart study. Circulation 1999; 99: 1831-6.
11. Kohno I, Takusagawa M, Yin D, Okutani M, Mochizuki Y, Sano S, et al. QT dispersion in dipper- and nondipper-type hypertension. Am J Hypertens 1998; 11: 280-5.
12. Kim EJ, Jeong MH, Kim JH, Ahn TH, Seung KB, Oh DJ, et al; KAMIR-NIH registry investigators. Clinical impact of admission hyperglycemia on in-hospital mortality in acute myocardial infarction patients. Int J Cardiol 2017; 236: 9-15.
13. Zhao Z, Yuan Z, Ji Y, Wu Y, Qi Y. Left ventricular hypertrophy amplifies the QT, and Tp-e intervals and the Tp-e/ QT ratio of left chest ECG. J Biomed Res 2010; 24: 69-72.
14. Oehler A, Feldman T, Henrikson CA, Tereshchenko LG. QRS-T angle: a review. Ann Noninvasive Electrocardiol 2014; 19: 534-42.
15. Lown MT, Munyombwe T, Harrison W, West RM, Hall CA, Morrell C, et al; Evaluation of Methods and Management of Acute Coronary Events (EMMACE) Investigators. Association of frontal QRS-T angle--age risk score on admission electrocardiogram with mortality in patients admitted with an acute coronary syndrome. Am J Cardiol 2012; 109: 307-13.
16. Jogu HR, O'Neal WT, Broughton ST, Shah AJ, Zhang ZM, Soliman EZ. Frontal QRS-T Angle and the Risk of Atrial Fibrillation in the Elderly. Ann Noninvasive Electrocardiol 2017; 22: e12388.
17. Erdogan G, Yontar OC, Yenercag M, Gul S, Arslan U. Frontal QRS-T angle predicts syntax score in patients with non-ST elevation myocardial infarction. J Electrocardiol 2020; 61: 86-91.
18. Schultz MG, La Gerche A, Sharman JE. Blood Pressure Response to Exercise and Cardiovascular Disease. Curr Hypertens Rep 2017; 19: 89.
19. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-13.
20. Manolio TA, Burke GL, Savage PJ, Sidney S, Gardin JM, Oberman A. Exercise Blood Pressure response and 5-year risk of elevated blood pressure in a cohort of young adults: the CARDIA study. Am J Hypertens 1994; 7: 234-41.
21. Altun B, Arici M, Nergizoglu G, Derici Ü, Karatan O, Turgan Ç, et al; Turkish Society of Hypertension and Renal Diseases. Prevalence, awareness, treatment and control of hypertension in Turkey (the PatenT study) in 2003. J Hypertens 2005; 23: 1817-23.
22. Kanbay M, Turgut F, Işık A, Köroğlu M, Akçay A. Relation Between Circadian Rhythm of Blood Pressure and Serum Uric Acid and Body Mass Index. Turk Neph Dial Transpl 2011; 20: 32-7.
23. Kurisu S, Nitta K, Sumimoto Y, Ikenaga H, Ishibashi K, Fukuda Y, et al. Frontal QRS-T angle and World Health Organization classification for body mass index. Int J Cardiol 2018; 272: 185-8.
24. Zhang ZM, Prineas RJ, Case D, Soliman EZ, Rautaharju PM; ARIC Research Group. Comparison of the prognostic significance of the electrocardiographic QRS/T angles in predicting incident coronary heart disease and total mortality (from the atherosclerosis risk in communities study). Am J Cardiol 2007; 100: 844-9.
25. Okin PM. Electrocardiography in women: taking the initiative. Circulation 2006; 113: 464-6.

26. Kuyumcu MS, Uysal D, Özbay MB, Aydın O, İbrişim E. Frontal plane QRS-T angle may be a predictor for post-coronary artery bypass graft surgery atrial fibrillation. Rev Assoc Med Bras 2020; 66: 1673-8.

27. Tanriverdi Z, Unal B, Eyuboglu M, Bingol Tanriverdi T, Nurdag A, Demirbag R. The importance of frontal QRS-T angle for predicting non-dipper status in hypertensive patients without left ventricular hypertrophy. Clin Exp Hypertens 2018; 40: 318-23.

28. Bağcı A, Aksoy F. The frontal plane QRS-T angle may affect our perspective on prehypertension: A prospective study. Clin Exp Hypertens 2021; 43: 402-7.

29. Berk BC, Fujiwara K, Lehoux S. ECM remodeling in hypertensive heart disease. J Clin Invest 2007; 117: 568-75.

İstanbul Med J 2023; 24(1): 100–5
DOI: 10.4274/imj.galenos.2023.64928

Investigation of Internet Addiction, Cyberbullying, and Cyber Victimization in Adolescents During the COVID-19 Pandemic and Their Relationship with Anxiety and Depression

Uğur Tekin

University of Health Sciences Turkey, İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Child and Adolescent Psychiatry, İstanbul, Turkey

ABSTRACT

Introduction: The present study examined the problems of internet addiction (IA) and cyberbullying in the use of digital technology, which has become the most important part of adolescents' lives during the pandemic period. These cyber problems are discussed in the context of their relationship with anxiety/depression.

Methods: Adolescents (n=111, female 67%, male 33%) aged 11-18 years (mean: 13.7±2.05) were included in the study. Internet Addiction scale (IAS), Cyberbullying scale (CBS), Cyberbullying Sensibility scale (CBSS), Cyber Victimization scale (CVS), and Revised child anxiety/depression scale-child version (RCADS-CV) scales were used. The scales were filled out online twice according to the participants' situations before and during the pandemic.

Results: The IAS, CBS, and CBSS scores were significantly higher during the pandemic period (respectively: z=-7,227, p<0.001, z=-2,623, p=0.009, z=-2,382, p=0.017). There was no significant difference in the CVS scores (p=0.326). The IAS, CVS, and CBSS scores were associated with RCADS-CV scores. The CBS scores showed a correlation with panic and social anxiety scores.

Conclusion: The findings indicate that the pandemic has negatively affected the behaviors of adolescents in cyberspace in terms of IAS and CBS. Moreover, anxiety and depression symptoms were associated with risky cyber behaviors such as addiction and bullying in cyberspace. Considering that adolescents are among the most important actors in the cyber world, they should be supervised and psychosocially supported in terms of increased cyber risks and anxiety and depression in a global stress period such as a pandemic.

Keywords: Internet addiction, cyberbullying, anxiety, depression, adolescent, COVID-19

Introduction

The Coronavirus disease-2019 (COVID-19) pandemic caused significant changes in the lives of people of all age groups. Social isolation measures have reduced face-to-face interactions and increased the time spent online (1). Some measures implemented during the pandemic were as follows: Education was suspended, online education was started, schools, gyms, places of worship, restaurants, shopping centers, entertainment venues, and restaurants were closed, and long and comprehensive quarantine and curfew were applied. These changes brought some risks. However, due to the maturation and transition period, adolescents are more vulnerable to the changes and effects of this period (2). A high rate of increase has been observed in the use of digital technologies among adolescents during the pandemic (3). In addition to the positive effects of the internet, there are some negative consequences of heavy internet use. With the increasing use of digital technology, adolescents' spending most of their time on the internet has exposed them to various potential cyber problems. Especially, internet addiction (IA) and cyberbullying (CB) have an important place among these cyber problems.

IA is described as intense use of the internet despite the negative effects on the person's life, loss of control in internet use, an irresistible desire to use, the development of tolerance, unsuccessful attempts to reduce/quit using the internet, and feeling irritable, depressed, and nervous due to internet overuse (4). Children's increased online time because of the interruption of daily life-increased feelings of loneliness, and the school closures have increased the risk of IA. Among the studies reporting an increase in addictive behaviors associated with internet use during the pandemic, most of them are in the adult population (1). Merely, some studies have reported that IA in children and adolescents increased during the pandemic. For example, Dong et al. (5) reported that IA and problematic internet use increased among Chinese children and adolescents during the pandemic. The rate of IA in adolescents is higher than that in adults. The underdeveloped frontal cortex, which is

Address for Correspondence: Uğur Tekin MD, University of Health Sciences Turkey, İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Child and Adolescent Psychiatry, İstanbul, Turkey
Phone: +90 543 450 52 30 **E-mail:** drutekin@gmail.com **ORCID ID:** orcid.org/0000-0001-6720-4292

Cite this article as: Tekin U. Investigation of Internet Addiction, Cyberbullying, and Cyber Victimization in Adolescents During the COVID-19 Pandemic and Their Relationship with Anxiety and Depression. İstanbul Med J 2023; 24(1): 100-5.

Received: 05.12.2022
Accepted: 01.02.2023

©Copyright 2023 by the University of Health Sciences Turkey, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.

responsible for executive control and emotional regulation, immature cognitive control, low problem-solving and coping skills, and finding a sense of belonging, autonomy, and power on the internet play a role in adolescents being riskier (6). It has been reported that there has been an increase of 8-38% in the use of digital technologies by adolescents worldwide from 2019 to 2021 (7). This increase may have positive effects on mental health and coping with negative emotions during the pandemic. It is argued that using digital technologies can reduce loneliness, feelings of insecurity and stress, and increase social connections and self-esteem (3). Although there are useful sides to using the internet, in the literature, more attention has been paid to the negative effects rather than the positive effects. However, a better understanding of the relationship between the pandemic and adolescent' IA is still needed.

Apart from IA, the online world contains risks that can affect human life and functionality just like the real world. In particular, CB and cyber victimization (CV) are some examples of them. Today, a new environment has emerged where adolescents can bully each other, and as a result, cyberbullies and CB victims have emerged. Looking at the effects of CB on young people, it has been shown that it is associated with an increased risk of suicide and depressive symptoms, and it can also have negative effects on confidence, self-esteem, and peer relationships (8). CB is described as offensive, intentional, and recurrent action by a person or a group using digital technologies against a victim who has difficulty defending himself (9). In line with this, CV is defined as being a victim of harassment, receiving offensive and/or threatening messages or emails, slandering, and sending embarrassing pictures through digital technologies (10). Studies have shown that CB is associated with more negative outcomes compared to traditional bullying due to its unique features such as anonymity and being targeted in front of a larger community (11,12). Studies have reported that the prevalence of CV ranged from 10% to 40% (13), and CV has been an increasingly serious handicap for young people (14,15). Researchers point out that the consequences of the pandemic may cause increased risks related to CB in children (16-18).

IA and CB have been shown to be associated with lower mental well-being (19). In adolescents, IA has been associated with anxiety and depression (20,21). Similarly, victims of CB experience more psychological, emotional, and social problems than their peers (22,23). The excessive use of digital technologies, which is reported to be a method of coping with the stress brought by the pandemic, may increase the symptoms of anxiety and depression by increasing the risk of adolescents in terms of IA and CB (24). The anxiety and depressive symptoms associated with CB and IA can cause significant functional disruption that may negatively affect daily life, adversely affect friend-family relationships, or lead to psychiatric problems that require treatment in the future (25). There is limited knowledge in the literature about risky cyber behaviors of adolescents and its relationship with psychiatric symptoms during the pandemic.

In our study, we assumed that the pandemic process increased risky cyber behaviors such as IA, CB, and CV in adolescents. We showed their changes during the pandemic by comparing them with the pre-pandemic period and to find the relationship between these behaviors and symptoms of anxiety and depression.

Methods

Ethical approval of the study was obtained from the University of Health Sciences Turkey, İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval number: 2021-07-09, date: 05.04.2021). All participants and their parents provided written informed consent. This cross-sectional study was conducted as an online survey in April-May 2021. Middle and high school students aged between 11 and 18 were included in the study. After the participants were given detailed information about the research, the sociodemographic data form and scales were applied to the volunteers via Google e-forms. The participants were asked to fill out the applied scales twice: First, according to the pre-pandemic period, and second, according to the pandemic period.

With the sociodemographic data form prepared by the researchers, information about the participant's age, gender, school/education, economic status (classified according to the country's official poverty line), and family/parent characteristics were collected. The sociodemographic data form was filled in by the parents, and all other scales were filled in by the young people who participated.

Internet Addiction Scale

Internet Addiction scale (IAS) is a valid and reliable IAS developed by Young (Cronbach's alpha: 0.91) (26). Consisting of 20 items, this scale is a six-point Likert-type scale. Participants answer each item as "never," "rarely," "sometimes," "often," "very often" and "always" and the items are scored 0, 1, 2, 3, 4, and 5 points. Higher scores mean more risk for IA.

Cyberbullying Scale

The Cyberbullying scale (CBS) is a valid and reliable scale that evaluates CB behavior of adolescents (Cronbach's alpha: 0.86) (27). The CBS had 24 items. Participants answer each item as "always," "mostly," "sometimes" and "never, and the items are scored 4, 3, 2, and 1 point, respectively. Higher scores indicate greater levels of CB.

Cyberbullying Sensibility Scale

The Cyberbullying sensibility scale (CBSS) is developed to detect adolescents' sensibility for CB (Cronbach's alpha: 0.87) (28). The CBSS had 14 items. Participants answer each item as "yes," "sometimes" and "no", and the items are scored 3, 2, and 1 point, respectively. Higher scores indicate greater levels of CB sensibility.

Cyber Victimization Scale

The scale is designed to assess the CV level (Cronbach's alpha: 0.86) (29). The Cyber Victimization scale (CVS) had 24 items on the scale. Each item has binary options (no/yes), with "no" receiving 1 point and "yes" receiving 2. Higher scores indicate higher levels of CV.

Revised Child Anxiety/Depression Scale-child Version

The scale is a 47-item, 4-point Likert-type questionnaire designed to evaluate anxiety, obsessive-compulsive, and depressive symptoms in children and adolescents. The scale grants a total anxiety score and a total anxiety/depression score. The Cronbach's alpha values for the total scale were 0.95 (30).

Statistical Analysis

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences Statistics 22 statistical software package program. The statistical data were expressed using the mean and standard deviation. Comparisons between the pre-pandemic and the pandemic periods were compared using the Wilcoxon signed-rank test. Correlations of scale scores with revised child anxiety/depression scale-child version (RCADS-CV) scores in the pandemic were analyzed using Spearman's rank correlation coefficient for non-parametric variables. A value of $p<0.05$ and $p<0.01$ were considered statistically significant levels.

Table 1. Sociodemographic characteristics of the sample

	n (%)
Female gender	74 (67%)
Age (mean, year ± SD)	13.7±2.05 Min.: 11 Max.: 18
Education	
Middle school	70 (63%)
High school	41 (37%)
SES	
Low	52 (47%)
High	59 (53%)
Mother	
Age (mean ± SD)	41.7 ± 5.25
University education*	46 (41%)
Father	
Age (mean ± SD) (y)	45.2 ± 6.7
University education*	59 (53%)
Divorced Parents	4 (3.6%)

SES: Socioeconomic status, SD: Standard deviation, y: Years, Min.: Minimum, Max.: Maximum, *: Number of parents with university or higher education

Results

The sample of the study consisted of 111 young people, 74 girls, and 37 boys. The sociodemographic characteristics of the sample are summarized in Table 1.

Scale scores of the pandemic and the pre-pandemic period were compared using the Wilcoxon signed-rank test since the data were not normally distributed. We observed that the IAS, CBS, and CBSS scores were significantly higher in the pandemic period compared with the pre-pandemic period. However, there was no significant difference in the CVS scores between the two periods. The mean values of the various scale scores are shown in Table 2.

The Spearman rho correlation coefficient was performed to evaluate the relationship between cyber scale and RCADS-CV scores during the pandemic period. The IAS scores showed moderate and strong positive correlations with all RCADS-CV sub-scores. While the CVS and CBSS scores showed low and moderate positive correlations with all RCADS-CV sub-scores (except the CVS and separation anxiety), CBS scores showed low positive correlations with some RCADS-CV sub-scores, including panic, social anxiety, total anxiety, and total anxiety and depression. The mean values of the RCADS-CV scores and their correlations with the various cyber scale scores are presented in Table 3.

Table 2. Comparison of cyber scales' scores of the pandemic period with the pre-pandemic period

	Pre-pandemic period	Pandemic period		
	Mean ± SD	Mean ± SD	z	p*
IAS scores	20±16.3	27.08±18.5	-7.227	<0.001
CBS scores	24.41±1.63	24.55±1.75	-2.623	0.009
CBSS scores	35.26±6.43	35.61±6.38	-2.382	0.017
CVS scores	24.78±2.65	24.88±2.69	-0.983	0.326

IAS: Internet Addiction scale, CBS: Cyberbullying scale, CBSS: Cyberbullying Sensibility scale, CVS: Cyber Victimization scale, SD: Standard deviation

Table 3. Correlations of cyber scales' scores with RCADS-CV scores in pandemic

		IAS scores	CBS scores	CBSS scores	CVS scores
	Mean ± SD	r	r	r	r
Separation anxiety	50.75±10.92	0.460**	0.123	0.246**	0.112
Generalized anxiety	47.95±13.38	0.408**	0.149	0.400**	0.318**
Panic	48.86±11.6	0.513**	0.289**	0.262**	0.353**
Social anxiety	44.36±13.32	0.573**	0.261**	0.254**	0.227*
OCD	48.09±11.65	0.540**	0.094	0.335**	0.207*
Depression	51.58±15.43	0.648**	0.182	0.292**	0.363**
Total anxiety	46.98±13.17	0.596**	0.252**	0.350**	0.313**
Total anxiety and depression	48.03±14.41	0.632**	0.243*	0.341**	0.342**

RCADS-CV: Revised Child Anxiety and Depression Scale-Child Version, IAS: Internet Addiction scale, CBS: Cyberbullying scale, CBSS: Cyberbullying Sensibility scale, CVS: Cyber Victimization scale, **: The correlation is significant at the 0.01 level (2-tailed), *: The correlation is significant at the 0.05 level (2-tailed)

Discussion

The psychological and behavioral effects of the COVID-19 pandemic on children have just begun to be understood. In the current study, we examined risky behaviors of adolescents related to the cyber environment such as IA and CB during the pandemic period. The widespread use of the internet as a strategy for coping with stress in such a stressful period is an expected outcome. In adolescence, the risks of the cyber environment are likely to increase as the time spent online increases. Moreover, it can be expected that depression and anxiety levels may be associated with these risky cyber behaviors. Our study has demonstrated relevant results on these issues. A significant increase was observed in the IA, CB, and CBS scores of adolescents compared with the pre-pandemic period. However, no significant change was found in the CV score. Additionally, it was shown in the current study that during the pandemic, IA was strongly associated with an increase in all kinds of anxiety and depressive symptoms. Moreover, it was found that, while CB was associated with only panic and social anxiety symptoms, CBS and CV were associated with all kinds of anxiety and depressive symptoms (excluding separation anxiety).

In recent decades, with the development of technology, communication and the use of media has evolved and become widespread through internet-based devices. These developments have made positive contributions to coping with the isolation caused by the measures taken during the pandemic (3). However, overuse can have some risks and negative consequences. In one study, adolescents spend 4-6 h a day in front of the screen for recreational activities and more than 6 h a day for educational purposes during the pandemic (31). In another study, it was shown that the total daily screen time increased from 87.1 to 334.3 min in children (32). In this way, while getting away from the negative experiences created by the pandemic, being more online in the cyber world caused children and adolescents to have internet-based addictive behaviors (1). The findings of our study support the reports in the literature that adolescents' IA has increased during the pandemic. However, our study found that all types of anxiety and depressive symptoms were strongly associated with increased IA during the pandemic. It has been argued that problematic internet use may be operating as a new type of emotion regulation method (33). Emotion regulation is a critical skill that develops during childhood and adolescence for coping with difficult life events and intense emotions (34). In this respect, it can be speculated that addictive internet use has been used as a method of the regulation (or dysregulation) of negative emotions by adolescents in the pandemic (35).

As a vicious circle, while real-life problems push the individual into the virtual world, the increase in the time spent in the virtual world and the decrease in the time spent offline cause more and more problems (36). CB and CV are other important aspects of this vicious circle. The increase in the rate of being online and having devices such as smartphones during the pandemic process has been considered a factor that increases interactions and bullying in the cyber world (18,37). However, there are studies have reporting different results in this regard. For example, a study from the US reported that school-age CB decreased in the pandemic compared with the pre-pandemic period (38). The authors attributed this finding to the reduction of in-person bullying with school closures and argued that consistent with previous evidence referring that CB rarely occurs independently of personal bullying. However, in another study involving 240 youth aged 17 and over, no significant increases were found in CB during the pandemic (39). This study was interpreted as a decrease in face-to-face interaction with peers during periods of social isolation, making CB less attractive. Contrary to these studies, we found in our study that adolescents' CB and CBS increased, whereas CV did not change. These different results may be related to the fact that these two studies were conducted in older age groups compared with our study. In line with our results, another study reported that the frequency of CV did not increase among adolescents during quarantine due to the pandemic (40). Although there is no study in the literature on the CBS of adolescents during the pandemic, we interpreted the finding of increased CBS as consistent and supportive with the finding of increased CB and may contribute to the understanding of the reason for this increase. There may be different explanations for the increase in CB and the absence of a change in CV. Those who have experienced CV may have given up reporting it and seeking support because of the embarrassment they experienced (40). Our finding that can be interpreted in parallel and in support of this interpretation was that CB was not associated with most anxiety symptoms, whereas CV was associated with almost all anxiety and depression complaints.

Some of the key strengths of our work are as follows. First, the study focused on the adolescent age group. It is important to investigate the impact of the pandemic on adolescents since they are important actors in the cyber world and are in a vulnerable life period. The second point, the risky cyber behaviors evaluated in the study was attempted to be examined by taking the pre-pandemic period as the baseline. Finally, risky cyber behaviors have been extensively researched by examining CB, CBS, and CV as well as IA.

Study Limitations

Our study had some limitations. First, our study has a modest sample size. Compared to online surveys in the literature, the sample size of our study was relatively small. Second, not dealing with data such as the purpose and duration of screen use is one of the important limitations of our study. Since online surveys often carry biases, another limitation of the study is that the data were collected online. Additionally, the results of the study are based on correlational analysis, and a causal relationship cannot be established based on the data of this cross-sectional study. In future studies, there is a need to conduct follow-up studies in a large sample, to examine the effect of the pandemic on cyber behaviors, and to examine the course of these risky cyber behaviors after the pandemic.

Conclusion

The results of this study indicate that the COVID-19 pandemic and associated events have a negative impact on the risky cyber behaviors of adolescents. During the pandemic, an increase was observed in adolescents' IA and cyberbullying behaviors, as well as their sensitivity to cyberbullying levels compared to the pre-pandemic period. Risky cyber behaviors of adolescents during the pandemic period were associated with anxiety and depression symptoms. Consequently, our findings

point to the importance of supervising adolescents in cyberspace and providing them with psychosocial support during stressful global events such as pandemics.

Ethics Committee Approval: Ethical approval of the study was obtained from the University of Health Sciences Turkey, İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval number: 2021-07-09, date: 05.04.2021).

Informed Consent: All participants and their parents provided written informed consent.

Peer-review: Externally peer-reviewed.

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

References

1. Masaeli N, Farhadi H. Prevalence of Internet-based addictive behaviors during COVID-19 pandemic: A systematic review. J Addict Dis 2021; 39: 468-88.
2. Singh S, Roy D, Sinha K, Parveen S, Sharma G, Joshi G. Impact of COVID-19 and lockdown on mental health of children and adolescents: A narrative review with recommendations. Psychiatry Research 2020; 293: 113429.
3. Marciano L, Ostroumova M, Schulz PJ, Camerini AL. Digital media use and adolescents' mental health during the Covid-19 pandemic: A systematic review and meta-analysis. Front Public Health 2022; 9: 793868.
4. Young KS. Internet addiction: A new clinical phenomenon and its consequences. Am Behav Sci 2004; 48: 402-15.
5. Dong H, Yang F, Lu X, Hao W. Internet addiction and related psychological factors among children and adolescents in China during the coronavirus disease 2019 (COVID-19) epidemic. Front Psychiatry 2020; 11: 00751.
6. Kwon JH. Toward the prevention of adolescent internet addiction. Internet addiction: A handbook and guide to evaluation and treatment. 2017: 223-43.
7. Dixon S. Social media platforms growth of MAU worldwide 2019-2021 Aug 1, 2022 Available from: https://www.statista.com/statistics/1219318/social-media-platforms-growth-of-mau-worldwide/
8. Price M, Dalgleish J. Cyberbullying: Experiences, impacts and coping strategies as described by Australian young people. Youth Studies Australia 2010; 29: 51-9.
9. Kowalski RM, Limber SP, Agatston PW. Cyberbullying: Bullying in the digital age: John Wiley & Sons; 2012.
10. Dempsey AG, Sulkowski ML, Nichols R, Storch EA. Differences between peer victimization in cyber and physical settings and associated psychosocial adjustment in early adolescence. Psychology Schools 2009; 46: 962-72.
11. Wang J, Nansel TR, Iannotti RJ. Cyber and traditional bullying: Differential association with depression. J Adolesc Health 2011; 48: 415-7.
12. van Geel M, Vedder P, Tanilon J. Relationship between peer victimization, cyberbullying, and suicide in children and adolescents: a meta-analysis. JAMA Pediatr 2014; 168: 435-42.
13. Garaigordobil M. Cyberbullying in adolescents and youth in the Basque Country: prevalence of cybervictims, cyberaggressors, and cyberobservers. J Youth Studies 2015; 18: 569-82.
14. Lenhart A, Purcell K, Smith A, Zickuhr K. Social Media & Mobile Internet Use among Teens and Young Adults. Millennials. Pew internet & American Life Project; 2010.
15. Slonje R, Smith PK, Frisén A. The nature of cyberbullying, and strategies for prevention. Computers Human Behavior 2013; 29: 26-32.
16. Yang F. Coping strategies, cyberbullying behaviors, and depression among Chinese netizens during the COVID-19 pandemic: a web-based nationwide survey. J Affect Disord 2021; 281: 138-44.
17. Babvey P, Capela F, Cappa C, Lipizzi C, Petrowski N, Ramirez-Marquez J. Using social media data for assessing children's exposure to violence during the COVID-19 pandemic. Child Abuse Negl 2021; 116: 104747.
18. Shin SY, Choi YJ. Comparison of Cyberbullying before and after the COVID-19 Pandemic in Korea. Int J Environ Res Public Health 2021; 18: 10085.
19. Bailin A, Milanaik R, Adesman A. Health implications of new age technologies for adolescents: a review of the research. Curr Opin Pediatr 2014; 26: 605-19.
20. Lam LT, Peng Z, Mai J, Jing J. The association between internet addiction and self-injurious behaviour among adolescents. Inj Prev 2009; 15: 403-8.
21. Yen JY, Ko CH, Yen CF, Wu HY, Yang MJ. The comorbid psychiatric symptoms of Internet addiction: attention deficit and hyperactivity disorder (ADHD), depression, social phobia, and hostility. J Adolesc Health 2007; 41: 93-8.
22. Juvonen J, Gross EF. Extending the school grounds?--Bullying experiences in cyberspace. J Sch Health 2008; 78: 496-505.
23. McLoughlin C, Meyricke R, Burgess J. Bullies in cyberspace: How rural and regional Australian youth perceive the problem of cyberbullying and its impact. Improving Equity Rural Education 2009; 178.
24. Chen IH, Chen CY, Pakpour AH, Griffiths MD, Lin CY. Internet-related behaviors and psychological distress among schoolchildren during COVID-19 school suspension. J Am Acad Child Adolesc Psychiatry 2020; 59: 1099-102.
25. Fazeli S, Zeidi IM, Lin CY, Namdar P, Griffiths MD, Ahorsu DK, et al. Depression, anxiety, and stress mediate the associations between internet gaming disorder, insomnia, and quality of life during the COVID-19 outbreak. Addict Behav Rep 2020; 12: 100307.
26. Kutlu M, Savcı M, Demir Y, Aysan F. Turkish adaptation of Young's Internet Addiction Test-Short Form: a reliability and validity study on university students and adolescents. Anadolu Psikiyatri Dergisi 2016; 17: 69-77.
27. Arıcak O, Kınay H, Tanrıkulu T. Siber Zorbalık Ölçeği'nin İlk Psikometrik Bulguları. HAYEF Journal Education 2012; 9: 101-14.
28. Tanrıkulu T, Kınay H, Arıcak OT. Cyberbullying Sensibility Scale: Validity and Reliability Study. Trakya University Journal of Education 2013; 3: 38-47.
29. Arıcak OT, Tanrıkulu T, Kınay H. Initial Psychometric Findings of Cyber Victimization Scale. Mediterranean Journal of Educational Research 2012; 11: 1-6.
30. Gormez V, Kılınçaslan A, Orengul AC, Ebesutani C, Kaya I, Ceri V, et al. Psychometric properties of the Turkish version of the Revised Child Anxiety and Depression Scale-Child Version in a clinical sample. Psychiatry and Clinical Psychopharmacology 2017; 27: 84-92.
31. Salzano G, Passanisi S, Pira F, Sorrenti L, La Monica G, Pajno GB, et al. Quarantine due to the COVID-19 pandemic from the perspective of adolescents: the crucial role of technology. Italian J Pediatr 2021; 47: 40.
32. Xiang M, Zhang Z, Kuwahara K. Impact of COVID-19 pandemic on children and adolescents' lifestyle behavior larger than expected. Prog Cardiovasc Dis 2020; 63: 531-2.
33. Spada MM, Langston B, Nikčević AV, Moneta GB. The role of metacognitions in problematic Internet use. Computers in Human Behavior 2008; 24: 2325-35.
34. Mennin DS, Heimberg RG, Turk CL, Fresco DM. Preliminary evidence for an emotion dysregulation model of generalized anxiety disorder. Behaviour Research and Therapy 2005; 43: 1281-310.
35. Hoge E, Bickham D, Cantor J. Digital media, anxiety, and depression in children. Pediatrics 2017; 140: S76-80.

36. Strittmatter E, Parzer P, Brunner R, Fischer G, Durkee T, Carli V, et al. A 2-year longitudinal study of prospective predictors of pathological Internet use in adolescents. Eur Child Adolesc Psychiatry 2016; 25: 725-34.

37. Barlett CP, Simmers MM, Roth B, Gentile D. Comparing cyberbullying prevalence and process before and during the COVID-19 pandemic. J Soc Psychol 2021; 161: 408-18.

38. Bacher-Hicks A, Goodman J, Green JG, Holt MK. The COVID-19 pandemic disrupted both school bullying and cyberbullying. American Economic Review: Insights 2022; 4: 353-70.

39. Englander E. Bullying, cyberbullying, anxiety, and depression in a sample of youth during the coronavirus pandemic. Pediatr Rep 2021; 13: 546-51.

40. Schunk F, Zeh F, Trommsdorff G. Cybervictimization and well-being among adolescents during the COVID-19 pandemic: The mediating roles of emotional self-efficacy and emotion regulation. Comput Human Behav 2022; 126: 107035.