Southern Clinics of Istanbul Eurasia

Formerly Kartal Eğitim ve Araştırma Hastanesi Tıp Dergisi

Journal Abbreviation: South Clin Ist Euras

Volume 35 • Issue 3 • September 2024

KARE

ISSN 2587-0998

www.scie.online

Southern Clinics of Istanbul Eurasia

Formerly Kartal Eğitim ve Araştırma Hastanesi Tıp Dergisi

Publisher
Kare Publishing

Contact: Nihat Müjdat HÖKENEK

Kartal Dr. Lütfi Kırdar Şehir Hastanesi, Denizer Cad., No: 1, 34865 Cevizli, İstanbul
Phone: +90-216-441 39 00 (23311) Phone 2: +90-216-458 30 00 (23311)
e-mail: info@scie.online, editor@scie.online

Owned by on behalf of the Director of University of Medical Sciences Kartal Dr. Lütfi Kırdar Health Practice and Research Center, İstanbul: Recep DEMİRHAN | Executive Editor: Recep DEMİRHAN | Publication Type: Periodical | Printed: Yıldırım Matbaacılık +90 212 629 80 37 | Printing Date: September 2024 | Circulation: 50

ISSN 2587-0998

www.scie.online

Southern Clinics of Istanbul Eurasia

Formerly Kartal Eğitim ve Araştırma Hastanesi Tıp Dergisi

INTERNATIONAL ADVISORY BOARD

NATIONAL ADVISORY BOARD

Southern Clinics
of
Istanbul Eurasia
Formerly Kartal Eğitim ve Araştırma Hastanesi Tıp Dergisi

NATIONAL ADVISORY BOARD

Southern Clinics of Istanbul Eurasia

Formerly Kartal Eğitim ve Araştırma Hastanesi Tıp Dergisi

AIMS AND SCOPE

Southern Clinics of Istanbul Eurasia - SCIE (formerly Kartal Eğitim ve Araştırma Hastanesi Tıp Dergisi / Medical Journal of Kartal Training and Research Hospital) is the scientific open access publication of University of Health Sciences, Kartal Dr. Lütfi Kırdar City Hospital (the content may be accessed free of charge through the web site www.scie.online). Four issues are released every year in March, June, September, and December. The language of publication is English.

The aim of the journal is to publish high level clinical and experimental studies conducted in all medical branches, reviews comprising the latest research findings, reports on rare and educational cases, and letters to the editor.

The journal observes a double-blinded, peer-review process with external and independent reviewers in the evaluation and approval of manuscripts for publication.

The target population of the journal includes specialists in all medical branches, academicians, and relevant health care professionals.

Publication policy and editorial processes follow the guidelines of the International Committee of Medical Journal Editors, the World Association of Medical Editors, the Council of Science Editors, the European Association of Science Editors, and the Committee on Publication Ethics.

SCIE is indexed in the TUBITAK ULAKBIM TR Index, EBSCO, GALE, ProQuest, DOAJ, CABI, Scope Database, MIAR, Türk Medline, WorldCat and Türkiye Citation Index. The journal is financially supported by University of Health Sciences Kartal Dr. Lütfi Kırdar City Hospital.

Editor: Recep DEMİRHAN
Address: Kartal Dr. Lütfi Kırdar Şehir Hastanesi, Denizer Cad., No: 1, 34865 Cevizli, İstanbul
Phone: +90-216-441 39 00 (23311)
E-mail: editor@scie.online

Southern Clinics of Istanbul Eurasia

Formerly Kartal Eğitim ve Araştırma Hastanesi Tıp Dergisi

INSTRUCTIONS FOR AUTHORS

About the Journal

Southern Clinics of Istanbul Eurasia - SCIE (formerly Kartal Eğitim ve Araştırma Hastanesi Tıp Dergisi - The Medical Journal of Kartal Training and Research Hospital) is published four issue in English by the Kartal Dr. Lütfi Kırdar City Hospital, and is a peer reviewed general medical journal for all physicians, doctors, medical researchers, and health workers. The journal reports the advances and progress in current medical sciences and technology. The journal covers basic and clinical studies in medicine. Articles of clinical interest and implications will be given preference.

Contributions may be in the form of clinical and basic research articles, case reports, personal clinical and technical notes, and letters to the Editor. The Journal also publishes brief reports on original studies or evaluations, book reviews, and proceedings of scientific meetings. The Editor-in-Chief may request from the authors additional data, information, or complementary material concerning the manuscripts, and the authors must comply with such requests.

Manuscripts should be prepared in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals regularly updated by the International Committee of Medical Journal Editors, available at http:// www.icmje.org.

Ethics

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).

All manuscripts presenting data obtained from research involving human subjects must include a statement that the written informed consent of the participants was obtained and that the study was approved by an institutional review board or an equivalent body. This institutional approval should be submitted with the manuscript. Authors of case reports must submit the written informed consent of the subject(s) of the report or of the patient's legal representatives for the publication of the manuscript.

All studies should be carried out in accordance with the World Medical Association Declaration of Helsinki, covering the latest revision date. Patient confidentiality must be protected according to the universally accepted guidelines and rules. Manuscripts reporting the results of experimental studies on animals must include a statement that the study protocol was approved by the animal ethics committee of the institution and that the study was conducted in accordance with the internationally accepted guidelines, including the Universal Declaration of Animal Rights, European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, Principles of Laboratory Animal Science, and the Handbook for the Care and Utilization of Laboratory Animals. The authors are strongly requested to send the approval of the ethics committee together with the manuscript. In addition, manuscripts on human and animal studies should describe procedures indicating the steps taken to eliminate pain and suffering.

Submission and peer reviewing

The official language of the Journal is English. Following an initial evaluation and elimination for sufficient priority, manuscripts are subject to blind peer review by at least two reviewers. The Editor, who judges and analyzes the entire review process, reaches a final decision to accept or reject a manuscript, or to recommend a revision. The Editor has the right to reject a revised manuscript.

Copyright - Authors' approval - Conflict of interest

The authors should disclose all issues concerning financial relationship, conflict of interest, and competing interest that may potentially influence the results of the research or scientific judgement. All financial contributions or sponsorship, financial relations, and areas of conflict of interest should be clearly explained in a separate letter to the editor at the time of submission, with full assurance that any related document will be submitted to the Journal when requested.

Manuscripts should be sent with the Copyright-Authors' Approval-Conflict of Interest Letter signed by the author(s). A copy of this letter can be found at web site. Manuscripts will not be accepted for evaluation until the receipt of this document by the Journal.

The Editorial Office inspects all submitted manuscripts concerning plagiarism and duplication. If an ethical problem is detected, the editorial office will act according to the COPE guidelines.

Submitting a manuscript

SCIE accepts only on-line submission via the official web site (please click, http://www.scie.online/en/?s=online_submission) and refuses printed manuscript submissions by mail. All submissions are made by the on-line submission system called Journal Agent, by clicking the icon "Online manuscript submission" at the above mentioned web site homepage. The system includes directions at each step but for further information you may visit the web site.

Important notice

Before the corresponding author submits the manuscript, all authors must obtain ORCİD ID number and provide it to the corresponding author.

Manuscript preparation

The author(s) must declare that they were involved in at least 3 of the 5 stages of the study stated in the "acknowledgement of authorship and transfer of copyright agreement" as "designing the study", "collecting the data", "analyzing the data", "writing the manuscript" and "confirming the accuracy of the data and the analyses". Those who do not fulfill this prerequisite should not be stated as an author.

The number of authors should not exceed 6 for clinical, basic and experimental studies, 4 for case reports and technical notes, and 3 for letters to the editor and reviews. In multi-center or multi-discipline studies, each author's contribution regarding the 5 stages mentioned above should be stated clearly. For this kind of multi-center or multi-discipline studies with excessive number of authors, the editor has the right to request that the number of authors be reduced.

Southern Clinics of Istanbul Eurasia
Formerly Kartal Eğitim ve Araştırma Hastanesi Tıp Dergisi

Manuscripts should be designed in the following order: title page, abstract, main text, references, and tables, with each typeset on a separate page.

Title page: This page should only include the title of the manuscript, which should be carefully chosen to better reflect the contents of the study. Author names should not appear in the title and subsequent pages.

Abstract: It should not exceed 300 words. Abstracts should be structured in four paragraphs using the following subtitles: Objectives, Methods, Results, and Conclusion. Abstracts of case reports should be unstructured.

Main text: The body consists of Introduction, Patients/Materials and methods, Results, and Discussion. Use "Patients and methods" for clinical studies, and "Materials and methods" for animal and laboratory studies.

The Introduction section clearly states the purpose of the manuscript and includes a brief summary of the most relevant literature.

The Patients/Materials and Methods section describes the study population and the study design, with adequate information on the techniques, materials, and methods used. A clear description of the statistical methods should also be given.

The Results section should provide a detailed report on the findings of the study. Data should be concisely presented, preferably in tables or illustrations, which should not exceed the page layout of the Journal.

The Discussion section should mainly rely on the conclusions derived from the results of the study, with relevant citations from the most recent research.

Letter to the Editor: Letters to the editor should not exceed 350 words.

References: References should be numbered in the order in which they are mentioned in the text. Only published articles or articles in press can be used in references. Unpublished data or personal communications should not be used. The style should conform to the standards described in detail in "Citing Medicine-The NLM Style Guide for Authors, Editors, and Publishers" (http://www.nlm.nih.gov/citingmedicine), which is recommended in the most recent update of "Uniform Requirements for Manuscripts Submitted to Biomedical Journals". A brief presentation of these standards can also be found at http://www.nlm.nih.gov/bsd/uniform_requirements.html. Journal titles should be abbreviated according to the Index Medicus. The Journal's title is abbreviated as "South Clin Ist Euras".

The style and punctuation should follow the formats outlined below:

Standard journal article:

Napolitano LM, Corwin HL. Efficacy of red blood cell transfusion in the critically ill. Crit Care Clin 2004;20:255-68.

All authors if six or fewer should be listed; otherwise, the first six and "et al." should be written.

Epub ahead of print Articles:

Rupprecht H, Heppner HJ, Wohlfart K, Türkoglu A. The geriatric polytrauma: Risk profile and prognostic factors. Ulus Travma Acil Cerrahi Derg 2017 Jan 05. doi: 10.5505/tjtes.2016.77177. [Epub ahead of print].

Personal author(s):

Enzingerz FM, Weiss SW. Soft tissue tumors. St. Louis: Mosby; 1995. p. 27-50.

Editor(s), compiler(s) as author:

Günal İ, Barton NJ, Çallı İ, editors. Current management of scaphoid fractures. Twenty questions answered. London: The Royal Society of Medicine Press; 2002.

Chapter in a book:

Henick DK, Kennedy DW. Fungal sinusitis. In: Stankiewicz JA, editor. Advanced endoscopic sinus surgery. St Louis: Mosby; 1995. p. 69-80.

Conference paper:

Kouzelis A, Matzaroglou C, Kravvas A, Mylonas S, Megas P, Gliatis J. Anterior cruciate ligament reconstruction: patellar tendon autogaft versus four strand hamstring tendon. In: Proceedings of the 9th Turkish Sports Traumatology, Arthroscopy and Knee Surgery Congress; 2008 Oct 14-18; İstanbul, Türkiye. p. 223. Unpublished conference papers should not be used in the reference list.

Direct use of references is strongly recommended and the authors may be asked to provide the first and last pages of certain references. Publication of the manuscript will be suspended until this request is fulfilled by the author(s).

Figures and tables

All illustrations (photographs, graphics, and drawings) accompanying the manuscript should be referred to as "figure". All figures should be numbered consecutively and mentioned in the text. Figure legends should be added at the end of the text as a separate section. Each figure should be prepared as a separate digital file in "jpeg" format, with a minimum of 9×13 cm and at 300 dpi or better resolution.

All illustrations should be original. Illustrations published elsewhere should be submitted with the written permission of the original copyright holder.

For recognizable photographs of human subjects, written permission signed by the patient or his/her legal representative should be submitted; otherwise, patient names or eyes must be blocked out to prevent identification. Microscopic photographs should include information on staining and magnification.

Upon the author's request, color prints will be considered for publication; however, the authors are responsible for the extra cost of printing color illustrations. Each table should be prepared on a separate page, either at the end of the text file or as a separate supplementary file, with table heading on top of the table. Table heading should be added to the main text file on a separate page when a table is submitted as a supplementary file.

Checklist

Covering letter

- Signed by all contributors
- Previous publication / presentations mentioned

Southern Clinics of Istanbul Eurasia

Formerly Kartal Eğitim ve Araştırma Hastanesi Tıp Dergisi

Source of funding mentioned

Conflicts of interest disclosed

ORCİD ID number of all contributors

Authors

Last name and given name provided along with Middle name initials (where applicable)

Author for correspondence, with e-mail address provided

Number of contributors restricted as per the instructions

Identity not revealed in paper except title page (e.g. name of the institute in Methods, citing previous study as 'our study', names on figure labels, name of institute in photographs, etc.)

Presentation and format

Double spacing

Margins 2 cm from all four sides

Page numbers included at bottom

Title page contains all the desired information

Abstract page contains the full title of the manuscript

Abstract provided (structured abstract of 300 words for original articles, meta analysis (Backgroud, Methods, Results, Conclusions) and review articles (Objective, Data sources, Study selection, Results, Conclusions)

Key words provided (three or no more than 6 words) Introduction should be short and arresting. State the purpose of the article and summarize the rationale for the study or observation. Give only strictly pertinent references

The references cited in the text should be after punctuation marks

References according to the journal's instructions, punctuation marks checked

Language and grammar

Uniformly American English

Write the full term for each abbreviation at its first use in the title, abstract, keywords and text separately unless it is a standard unit of measure. Numerals from 1 to 10 spelt out

Numerals at the beginning of the sentence spelt out

Check the manuscript for spelling, grammar and punctuation errors

If a brand name is cited, supply the manufacturer's name and address (city and state/country).

Species names should be in italics

Tables and figures

No repetition of data in tables and graphs and in text

Actual numbers from which graphs drawn, provided

Figures necessary and of high quality (colour)

Table and figure numbers in Arabic letters (not Roman)

Labels pasted on back of the photographs (no names written)

Patients' privacy maintained (if not permission taken)

Credit note for borrowed figures/tables provided

Write the full term for each abbreviation used in the table as a footnote

Editor: Recep DEMİRHAN

Address: Kartal Dr. Lütfi Kırdar Şehir Hastanesi,
Denizer Cad., No: 1, 34865 Cevizli, İstanbul

Phone: +90-216-441 39 00 (23311)

E-mail: info@scie.online, editor@scie.online

Publisher: KARE Publishing - KARE Medya

Address: Göztepe Mah., Fahrettin Kerim Gökay Cad., No: 200,
Da: 2, Göztepe, Kadıköy, İstanbul

Phone: +90-216-550 61 11

Fax: +90-216-550 61 12

E-mail: kare@kareyayincilik.com

Southern Clinics of Istanbul Eurasia
Formerly Kartal Eğitim ve Araştırma Hastanesi Tıp Dergisi

CONTENTS

Volume 35 Issue 3 Year 2024

ORIGINAL ARTICLES

SCIE DOI: 10.14744/scie.2024.76743
South. Clin. Ist. Euras. 2024;35(3):197-201

Original Article

Evaluation of Risk Factors for Anastomotic Leakage and Mortality Following Esophageal Cancer Surgery

Cemal Hacıalioğlu,[1] Gizem Akcakoca,[1] Ahmet Anar,[1] Furkan Yağmur,[1] Sedef Poşul,[1] Aytaç Emre Kocaoğlu,[1] Beril Kara Esen,[2] Yasin Tosun,[1] Hasan Fehmi Küçük[1]

[1]Department of General Surgery, Kartal Dr Lutfi Kirdar City Hospital, İstanbul, Türkiye
[2]Department of Public Health, Istanbul University Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye

Submitted: 06.06.2024
Revised: 05.08.2024
Accepted: 13.08.2024

Correspondence: Yasin Tosun, Department of General Surgery, Kartal Dr Lutfi Kirdar City Hospital, Istanbul, Türkiye
E-mail: yasintosun@gmail.com

Keywords: Anastomotic leakage; esophageal cancer; McKeown esophagectomy.

ABSTRACT

Objective: Postoperative anastomotic leakage is one of the most severe complications of esophageal surgery, significantly increasing patient morbidity and mortality risk. This study aims to evaluate the impact of the anastomosis level on postoperative leakage and stricture rates in esophageal cancer surgery.

Methods: A total of 104 patients operated on for esophageal cancer at the General Surgery Department of Istanbul Dr. Lütfi Kırdar City Hospital between January 2010 and February 2023 were included.

Results: Mortality occurred in 47 patients during follow-up. Among the patients who developed mortality, the rates of McKeown operation, hand-sewn anastomosis, and lymphovascular invasion were significantly higher than in those who did not develop mortality.

Conclusion: Identifying risk factors and selecting the appropriate technique can reduce complication rates and improve postoperative outcomes.

INTRODUCTION

Esophageal cancer is a significant global health issue characterized by high mortality rates, with approximately 600,000 new cases diagnosed annually, most of which are detected at advanced stages.[1] Surgical treatment, particularly esophagectomy, is one of the most effective treatments for localized esophageal cancer. However, determining the anastomosis level post-surgery is critical for postoperative complications.

Postoperative anastomotic leakage (AL) is one of the most severe complications of esophageal surgery, significantly increasing patient morbidity and mortality risk. The literature reports anastomotic leakage rates ranging from 1.4% to 17%.[2] Anastomotic stricture is also a common complication that can negatively impact patients' quality of life. Cervical anastomoses are reported to have higher stricture rates compared to thoracic anastomoses.[1]

Recent years have seen intraoperative and postoperative interventions effectively reduce anastomotic leakage and stricture rates. The intraoperative frozen section method provides high accuracy in assessing surgical margins, potentially reducing the need for repeat surgeries and complication rates.[3] Additionally, advancements in perioperative management and early feeding protocols can accelerate recovery and reduce complication risks.[4,5]

This study aims to evaluate the risk factors affecting anastomotic leakage and mortality in esophageal cancer surgery. For this purpose, data from 104 patients operated on between 2010 and 2023 at our clinic were retrospectively analyzed and compared with existing literature.

MATERIALS AND METHODS

Study Design

This study was designed as a retrospective cohort study. 104 patients who were operated on for esophageal cancer at a tertiary reference hospital between January 2010 and February 2023 were included in the study. The study protocol was approved by the Kartal Dr. Lütfi Kırdar City Hospital (approval number 2024/010.99/2/34).

Inclusion and Exclusion Criteria

Patients aged >18 years who underwent surgery in the general surgery clinic were included. Patients whose data were inaccessible or who were operated on for reasons other than esophageal cancer were excluded.

Data Collection

Data were obtained from patient files, surgery reports, and pathology reports. Age, gender, type of surgery, postoperative pathology results, tumor characteristics, and

Table 1. Evaluation of patients who are alive and ex as a result of follow-up

	Total	Alive	Ex	p
Variable	n=104	n=57	n=47	
	n (%)	n (%)	n (%)	
Gender				
Female	58 (55.8)	36 (63.2)	22 (46.8)	0.095*
Male	46 (44.2)	21 (36.8)	25 (53.2)	
Age [median (IQR)]	57.5 (50.25-64.75)	57 (48-63)	58 (52-66)	0.209**
Preoperative Biopsy Result				
Squamous Cell Carsinoma	94 (90.4)	51 (89.5)	43 (91.5)	1.00f
Leiomyoma	1 (1.0)	1 (1.8)	0 (0)	
Adenocarcinoma	9 (8.7)	5 (8.8)	4 (8.5)	
Localization				
Distal esophagus	75 (72.1)	40 (70.2)	35 (74.5)	0.828f
Middle esophagus	27 (26.0)	16 (28.1)	11(23.4)	
Proximal esophagus	2 (1.9)	1 (1.8)	1 (2.1)	
Tumor Size	4 (3-5)	4 (2-5)	4 (3-5)	0.597**
Operation Type				
Transhiatal	24 (23.1)	16 (28.1)a	8 (17.0)a	0.018*
Mckeown	44 (42.3)	17 (29.8)a	27 (57.4)b	
Ivor Lewis	36 (34.6)	24 (42.1)a	12 (25.5)a	
Type of Anastomosis				
Hand Sewn	48 (46.2)	20 (35.1)a	28 (59.6)b	0.018f
Stapler	55 (52.9)	36 (63.2)a	19 (40.4)b	
Cervical	1 (1.0)a	1 (1.8)a	0 (0)a	
Site of Anastomosis				
Intrathoracic	37 (35.6)	24 (42.1)	13 (27.7)	0.126*
Cervical	67 (64.4)	33 (57.9)	34 (72.3)	
Surgical margin				
Negative	98 (94.2)	55 (96.5)	43 (91.5)	0.406f
Positive	6 (5.8)	2 (3.5)	4 (8.5)	
Pathology				
No residue tumor	39 (37.5)	24 (42.1)	15 (31.9)	0.544*
Squamous Cell Carsinoma	54 (51.9)	27 (47.4)	27 (57.4)	
Adenocarcinoma	11 (10.6)	6 (10.5)	5 (10.6)	
Total Lymph Nodes	12 (8.25-17)	11 (7-17)	14 (9-17)	0.218**
Pathological Lymph Nodes	0 (0-1)	0 (0-5)	0 (0-2)	0.052**
Lymphovascular Invasion	25 (24.0)	9 (15.7)	16 (34)	0.030*
Perineural Invasion	27 (26.0)	13 (22.8)	14 (29.8)	0.419*

*Chi square test, **Mann-whitney U test, fFisher's exact test. IQR: Interquartile range.

postoperative complications were recorded.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (version 24.0, IBM Corp., Armonk, NY, USA). Descriptive statistical methods (median, frequency, percent, minimum, and maximum) were used to present the data. The Pearson chi-square test was used to compare qualitative data, and Fisher's exact test was applied when the number of subgroups was low. The normal distribution of quantitative data was assessed by the Kolmogorov–Smirnov and Shapiro–Wilk tests. Quantitative data without normal distribution were compared using the Mann–Whitney U test. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 104 patients were operated on for esophageal cancer in our clinic between 2010 and 2023. The distribution of patients by year is shown in Figure 1.

Of the patients, 55.8% were female, with a mean age of 57.32±10.69 years. The characteristics of the patients are presented in Table 1. Mortality occurred in 47 patients during follow-up. Among the patients who developed mortality, the rates of McKeown operation, hand-sewn anastomosis, and lymphovascular invasion were significantly higher than in those who did not develop mortality.

The most common comorbidities in patients were hypertension, diabetes, and coronary artery disease, respectively. Intraoperative bleeding occurred in 2 patients (Table 2).

Among the patients who developed mortality, 16 died within the first month postoperatively, and 25 died within the first year postoperatively. Postoperative stricture occurred in 21.2% of patients, and postoperative leakage occurred in 7.7%, as shown in Table 3. There was no statistically significant difference between patients who developed and did not develop mortality in terms of postoperative stricture and leakage. Patients who developed postoperative leakage had longer operation and hospitalization times (p=0.030 and p<0.001, respectively). Among those who developed postoperative stricture, the proportion of males (63.9%) was significantly higher than those who did not develop stricture (39%) (p=0.039). There was no statistically significant difference between other factors and the development of postoperative stricture or leakage.

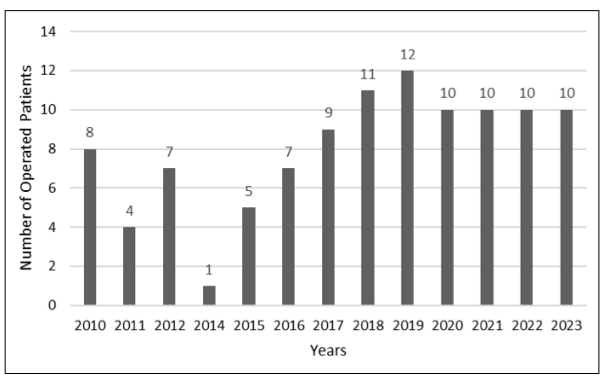

Figure 1. Distribution of the number of patients operated on due to esophageal cancer by years.

Table 2. Comorbidities of patients and preoperative complications

Variables	n	%
Comorbidities		
None	63	60.6
DM	17	16.3
HT	25	24.0
Coroner arter disease	11	10.6
Chronic kidney failure	2	1.9
Chronic heart failure	2	1.9
Chronic obstructive pulmonary disease	3	2.9
FMF	1	1.0
HCV	1	1.0
Complications (perop)		
Bleeding	2	1.9
Spleen Injury	1	1.0
Hepatic Vein Aberrant Branch Repair	1	1.0
Pleural Injury	1	1.0
Left Vocal Cord Sacrification/Tracheostomy	1	1.0

*DM: Diabetes mellitus; HT: Hypertension; CAD: Coroner arter disease; CKD: Chronic kidney failure; CHF: Chronic heart failure; COPD: Chronic obstructive pulmonary disease; FMF: Familial mediterrian fever; HCV: Hepatit C virus.

Table 3. Follow-up results of patients

	Mean±S.D.	Median (IQR)
Hospitalizition	19.04±21.35	12 (9-17)
	n	%
Complications		
Pneumonia	8	7.7
Pleural Injury	6	5.8
Pyloric Dysfunction	6	5.8
Relapse		
	1	1.0
Lymphatic Leakage	1	1.0
Evisceration	1	1.0
Number of patients hospitalized in ICU	90	86.5
Leakage	8	7.7
Stenosis	22	21.2
Results		
Ex in 1 Month	16	15.4
Ex in 1 Year	25	24.0
Ex in 2 Years	3	2.9
Ex in 3 Years	3	2.9

Table 4. Examining the factors affecting the development of mortality using multivariate analysis

	Adjusted O.R.	95% C.I.	p
Gender			116
Male	2.08	0.84-5.19	
Age	1.03	0.99-1.07	204
Type of Operation			17
Ivor Lewis	0.27	0.10-0.75	
Transhiatal	0.25	0.08-0.77	
Lymphovascular invasion	2.96	1.05-8.38	41
Leakage	4.03	0.62-26.10	144
Coronary artery disease	3.44	0.78-15.18	103

Nagelkerke R2: 0.271; Hosmer-Lemeshow Test: 0.325.

When the factors influencing the risk of developing mortality were examined using multivariate regression analysis, it was found that the type of operation and the presence of lymphovascular invasion were associated with mortality (Table 4). Compared to patients undergoing McKeown operation, those undergoing Ivor Lewis and transhiatal operations had a lower likelihood of developing mortality. The presence of lymphovascular invasion had an odds ratio of 2.96 for developing mortality.

DISCUSSION

The aim of this study was to identify risk factors for mortality following esophagectomy for esophageal cancer. Anastomotic leaks are the most common complications following esophageal resections. Postoperative surgical sepsis is responsible for the high rates of mortality and morbidity. The frequency of this complication is highly variable, with some studies reporting leakage rates over 30%.[6] The choice of surgical method is important in terms of postoperative morbidity and mortality. The potential advantages of transhiatal resection include being less invasive and faster. The literature indicates that transthoracic approaches lead to higher perioperative morbidity and mortality rates, but there is no significant difference in long-term survival between the two methods.[7] While some studies report higher leakage rates in cervical anastomoses, this is explained by the long intrathoracic segment through which the stomach tube passes and the reduced blood supply to the proximal stomach area.[8,9] In our study, the main findings increasing mortality risk were McKeown operation, hand-sewn anastomosis, and the presence of lymphovascular invasion. Therefore, when planning esophagectomy for esophageal cancer, attention should be paid to patients with these risk factors. Generally, cervical and intrathoracic anastomoses are performed either hand-sewn or with a stapler.[10] Although single-layer continuous suturing is the most commonly applied hand-sewn anastomosis technique, studies have shown lower leakage rates after double-layer anastomosis.[11] While some studies support the superiority of the stapler technique, a definitive comparison in leakage rates is not proven. Similar leakage rates have been observed with different stapler techniques.[12,13] In our study, we found higher leakage rates in cervical anastomoses, especially in hand-sewn anastomoses. We believe that surgical technique choice, experience, and patient comorbidities are important factors. The most common comorbidity in our study group was diabetes mellitus, and the literature supports that diabetes is a risk factor for anastomotic leakage.[14] Previous retrospective studies have shown a relationship between lymph node invasion and dissection status and anastomotic leakage in patients undergoing esophagectomy for esophageal cancer. A meta-analysis indicated that three-field lymph node dissection was significantly associated with higher leakage incidence compared to two-field lymph node dissection. Given the current and previous findings, the lymph node dissection status may have clinical implications in patients undergoing esophagectomy.[15,16] In our study, three-field lymph node dissection and lymphovascular invasion were associated with mortality. Another noteworthy finding in our study was that male gender was significantly more at risk for developing postoperative stricture. There are several limitations to this study. First, it was a retrospective, single-center study with a relatively small sample size. Second, many risk factors evaluated in previous studies, such as nutritional status, BMI, albumin level, and immunity, were not evaluated in this study. Additionally, the results of different surgeons and surgical approaches were analyzed. Given these limitations, the current findings need to be confirmed in other series with a larger number of patients.

Conclusion

Results from this study show that factors such as McKeown surgery and the presence of LVI are associated with increased mortality. As a result, these factors significantly increase mortality and morbidity. It seems that patients with these factors should be closely monitored and necessary precautions should be taken.

Ethics Committee Approval

The study was approved by the Kartal Dr. Lütfi Kırdar City

Hospital Ethics Committee (Date: 27.03.2024, Decision No: 2024/010.99/2/34).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: Y.T., H.F.K.; Design: Y.T.; Supervision: A.E.K., G.A.; Materials: C.H., S.P.; Data: F.Y., A.A; Literature search: Y.T., G.A.; Writing: C.H.; Critical revision: A.E.K.

Conflict of Interest

None declared.

REFERENCES

References:

1. Fabbi M, Hagens ERC, van Berge Henegouwen MI, Gisbertz SS. Anastomotic leakage after esophagectomy for esophageal cancer: definitions, diagnostics, and treatment. Dis Esophagus 2021;34:doaa039. [CrossRef]
2. Grigor EJM, Kaaki S, Fergusson DA, Maziak DE, Seely AJE. Interventions to prevent anastomotic leak after esophageal surgery: A systematic review and meta-analysis. BMC Surg 2021;21:42. [CrossRef]
3. Huang C, Yao H, Huang Q, Lu H, Xu M, Wu J. A novel nomogram to predict the risk of anastomotic leakage in patients after oesophagectomy. BMC Surg 2020;20:64. [CrossRef]
4. Scognamiglio P, Reeh M, Melling N, Kantowski M, Eichelmann AK, Chon SH, et al. Management of intra-thoracic anastomotic leakages after esophagectomy: Updated systematic review and meta-analysis of endoscopic vacuum therapy versus stenting. BMC Surg 2022;22:309. [CrossRef]
5. Gu HY, Luo J, Qiang Y. Postoperative complications analysis of circular stapled versus linear stapled anastomosis for patients undergoing esophagectomy: A systematic review and meta-analysis. J Cardiothorac Surg 2023;18:242. [CrossRef]
6. Aoyama T, Atsumi Y, Hara K, Tamagawa H, Tamagawa A, Komori K, et al. Risk factors for postoperative anastomosis leak after esophagectomy for esophageal cancer. In Vivo 2020;34:857–62. [CrossRef]
7. Blewett CJ, Miller JD, Young JE, Bennett WF, Urschel JD. Anastomotic leaks after esophagectomy for esophageal cancer: A comparison of thoracic and cervical anastomoses. Ann Thorac Cardiovasc Surg 2001;7:75–8.
8. Biere SS, Maas KW, Cuesta MA, van der Peet DL. Cervical or thoracic anastomosis after esophagectomy for cancer: A systematic review and meta-analysis. Dig Surg 2011;28:29–35. [CrossRef]
9. Chang AC, Ji H, Birkmeyer NJ, Orringer MB, Birkmeyer JD. Outcomes after transhiatal and transthoracic esophagectomy for cancer. Ann Thorac Surg 2008;85:424–9. [CrossRef]
10. Turkyilmaz A, Eroglu A, Aydin Y, Tekinbas C, Muharrem Erol M, Karaoglanoglu N. The management of esophagogastric anastomotic leak after esophagectomy for esophageal carcinoma. Dis Esophagus 2009;22:119–26. [CrossRef]
11. Nederlof N, Tilanus HW, Tran TC, Hop WC, Wijnhoven BP, de Jonge J. End-to-end versus end-to-side esophagogastrostomy after esophageal cancer resection: A prospective randomized study. Ann Surg 2011;254:226–33. [CrossRef]
12. Rostas JW, Graffree BD, Scoggins CR, McMasters KM, Martin RCG. Long-term outcomes after hand-sewn versus circular-stapled (25 and 29 mm) anastomotic technique after esophagogastrectomy for esophageal cancer. J Surg Oncol 2018;117:469–72. [CrossRef]
13. Honda M, Kuriyama A, Noma H, Nunobe S, Furukawa TA. Hand-sewn versus mechanical esophagogastric anastomosis after esophagectomy: A systematic review and meta-analysis. Ann Surg 2013;257:238–48.
14. Lin X, Li J, Chen W, Wei F, Ying M, Wei W, et al. Diabetes and risk of anastomotic leakage after gastrointestinal surgery. J Surg Res 2015;196:294–301. [CrossRef]
15. Igaki H, Tachimori Y, Kato H. Improved survival for patients with upper and/or middle mediastinal lymph node metastasis of squamous cell carcinoma of the lower thoracic esophagus treated with 3-field dissection. Ann Surg 2004;239:483–90. [CrossRef]
16. Blencowe NS, Strong S, McNair AG, Brookes ST, Crosby T, Griffin SM, et al. Reporting of short-term clinical outcomes after esophagectomy: A systematic review. Ann Surg 2012;255:658–66. [CrossRef]

Özofagus Kanseri Cerrahisi Sonrası Anastomoz Kaçağı ve Mortalite Risk Faktörlerinin Değerlendirilmesi

Amaç: Postoperatif anastomoz kaçağı, özofagus cerrahisinin en ciddi komplikasyonlarından biridir ve hasta morbidite ve mortalite riskini önemli ölçüde artırır. Bu çalışmanın amacı, özofagus kanseri cerrahisinde anastomoz seviyesinin postoperatif kaçak ve darlık oranlarına etkisini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Çalışmaya Ocak 2010 ile Şubat 2023 tarihleri arasında İstanbul Dr. Lütfi Kırdar Şehir Hastanesi Genel Cerrahi Bölümü'nde özofagus kanseri nedeniyle ameliyat edilen 104 hasta alındı.

Bulgular: Takip sırasında 47 hastada mortalite meydana geldi. Mortalite gelişen hastalarda McKeown operasyonu, elle yapılan anastomoz ve lenfovasküler invazyon oranları, mortalite gelişmeyenlere göre anlamlı derecede yüksekti.

Sonuç: Risk faktörlerinin belirlenmesi ve uygun tekniğin seçilmesi komplikasyon oranlarını azaltabilir ve ameliyat sonrası sonuçları iyileştirebilir.

Anahtar Sözcükler: Anastomoz kaçağı; McKeown özefajektomi; özefagus kanseri.

SCIE DOI: 10.14744/scie.2024.88609
South. Clin. Ist. Euras. 2024;35(3):202-208
Original Article

Effects of Increased Storage Period of Erythrocyte Suspensions on Patient Outcomes in Pediatric Patient Population Undergoing Craniosynostosis Surgery

Ayten Saraçoğlu,[1] Gamze Cabakli,[2] Gül Çakmak,[2] Can Kıvrak,[3] Canan Eren,[4] Tumay Umuroğlu[2]

[1]Department of Anesthesiology, Aisha Bint Hamad Al Attiyah Hospital HMC, ICU & Perioperative Medicine Doha, Qatar
[2]Department of Anesthesiology and Reanimation, Marmara University Pendik Training and Research Hospital, Istanbul, Türkiye
[3]Department of Neurosurgery, Marmara University Pendik Training and Research Hospital, Istanbul, Türkiye
[4]Marmara University Pendik Training and Research Hospital, Blood Center, Istanbul, Türkiye

Submitted: 15.08.2023
Revised: 05.06.2024
Accepted: 12.07.2024

Correspondence: Gamze Cabakli , Department of Anesthesiology and Reanimation, Marmara University Pendik Training and Research Hospital, Istanbul, Türkiye
E-mail: gamze_tanirgan@hotmail.com

Keywords: Craniosynostosis; blood transfusion; fresh frozen plasma; red blood cell.

ABSTRACT

Objective: Although the blood transfusion required due to bleeding caused by the large incision area during craniosynostosis surgery is necessary to maintain the oxygen-carrying capacity of the blood, it carries significant risks. Our aim in this study is to determine the effect of the storage period of erythrocyte suspensions (ESs) on patient outcomes in the postoperative period in a pediatric patient group who underwent craniosynostosis surgery.

Methods: Fifty-six patients aged 2-24 months who had undergone craniosynostosis surgery between 2018 and 2021 were included in our retrospective study. The patients were divided into two groups according to whether the storage time of the given ES and fresh frozen plasma (FFP) (time elapsed from the day it was received from the donor to the day it was transfused into the patients) was less or more than 10 days. Demographic data of the patients, mean arterial blood pressure, body temperature, hemoglobin (Hb), INR, platelet (plt) values, intraoperative bleeding, amount of transfusion, amount of crystalloid and colloid fluid administered, duration of operation, duration of anesthesia, complications, duration of stay in the postoperative intensive care unit (ICU), amount of transfusion given by drainage, and length of hospital stay were recorded.

Results: The mean age of the patients was 8.27±6.294 months. A positive correlation was found between the storage time of ESs used in the intraoperative period, ES and crystalloid amount, and postoperative drainage. A negative correlation was found between intraoperative FFP transfusion and the change in Hb values measured in the ICU, and between intraoperative ES transfusion and plt values on ICU discharge ($p<0.05$).

Conclusion: Our study concluded that the shortening of the storage time of ESs and FFPs may have a positive effect on postoperative drainage. However, since it was found to have no effect on hospital and ICU stay, it is thought that larger-scale studies are needed.

INTRODUCTION

Although blood transfusion is necessary to maintain the oxygen-carrying capacity of the blood, this benefit must be balanced with the risks of transfusion. Although this varies for each patient and type of surgery, even small amounts of blood loss result in hypotension in the pediatric patient group and adversely affect oxygen delivery, especially because the intravascular volume of patients in the pediatric age group is smaller than that of adults and the compensatory response to blood loss is insufficient.[1]

Craniosynostosis is a condition in which one or more fibrous sutures in the skull ossify prematurely, changing the shape of the skull. Since the skull cannot expand perpendicular to the fused suture, it grows more in parallel with

the closed sutures to compensate. Sometimes the resulting growth pattern can provide the necessary space for the growing brain, but it may result in an abnormal head shape and abnormal facial features, and large area resection and reshaping operations may be required. Massive transfusion is a common practice during craniosynostosis surgery due to the tissue damage that this large incision area causes.[2] Therefore, in this patient group, which is already susceptible to massive transfusion, correct blood transfusion management is of greater importance, considering the hemoglobin concentration in the blood and the presence of a serious systemic comorbidity in the patient. However, today, in addition to the optimal transfusion policy, the content of blood and blood products, which varies depending on the storage period, emerges as an important factor for the side effects and complications that may develop due to transfusion.

It has been revealed that a series of biochemical and cellular changes occur in erythrocytes during storage. Damage developing in stored erythrocytes, also called storage lesions, poses a risk for tissue perfusion and tissue oxygen delivery. Free hemoglobin released as a result of hemolysis in the bag binds nitric oxide and causes an increase in vascular tone. Free iron can also trigger the formation of reactive oxygen species, causing both kidney or liver damage and cardiac events.[3] It has been reported that transfusion of erythrocyte suspensions stored in both mice and dogs causes a systemic inflammatory response as a result of increased cytokine release in recipients.[4,5] In addition, it leads to the growth of ferrophilic bacteria.[6] During cold storage, oxidative stress and impaired adenosine triphosphate (ATP) metabolism lead to remodeling of the erythrocyte membrane and damage to the cytoplasmic composition.[7] In addition, loss of cellular antioxidant capacity, concentration changes of K+ and Na+, loss of membrane and skeletal proteins, loss of membrane lipids, formation of vesicles, and oxidation of skeletal proteins ocur.[8] Furthermore, the stored erythrocytes themselves develop procoagulant activity.[9] It is well established that stored erythrocyte concentrates are associated with pathological reactions such as immunomodulation and post-transfusion pro-inflammation. The developed microparticles act as pro-inflammatory mediators that induce inflammatory signals as paracrine messengers on the immune system.[10]

Although all these biochemical and structural changes have been demonstrated, the effect of changes secondary to cellular degeneration, which develops with an increase in the waiting time until the erythrocytes are taken from the donor and transfused, on the clinical outcomes of patients has not been proven in the literature, and clear evidence has not yet been obtained.

Our primary aim in this study is to determine the effect of the retention time of erythrocyte suspension on hospital and intensive care unit (ICU) stay in the pediatric patient group who underwent craniosynostosis surgery. Our secondary aim is to reveal its effect on the amount of bleeding that may develop in the postoperative period. Our hypothesis in this study is that erythrocyte suspensions with longer storage times may lead to an increase in morbidity.

MATERIALS AND METHODS

This study was planned retrospectively. Children aged 2-24 months with an ASA score of 1-2, who had undergone craniosynostosis surgery at our hospital between 2018 and 2021, were included in the study. Cases with congenital or traumatic extremity pathology, a history of allergy to sensor material, a history of cardiac or vascular disease such as heart failure or hypertension, a body weight of less than 5 kg, those who were admitted to emergency surgery, suffered from surgical complications during the operation, and whose operation lasted longer than 4 hours were excluded from the study.

The data were obtained by reviewing the hospital information system and anesthesia follow-up records of the patients. The storage time of the erythrocyte suspensions given to the patients was recorded by determining the day they were taken from the donor and the day they were transfused to the patients. The obtained data were grouped into two groups. A comparison was made between FFPs and erythrocyte suspensions with a storage period of less than and more than 10 days. Demographic data, including gender, age, and body weight of the patients, were recorded. Arterial blood gas samples were analyzed with the GEN-S hematology analyzer (Beckman-Coulter Inc., Brea, CA). Mean arterial blood pressure, peak heart rate, and body temperature were recorded at the beginning and end of the operation in both groups. Initial and postoperative lactate and pH values were recorded in perioperative arterial blood gas sampling. The amount of intraoperative bleeding; Hb, Htc, INR, and creatinine values at the beginning and end of the operation; the amount of perioperative transfusion of blood and blood products; the amount of crystalloid and colloid fluid administered; the duration of the operation; the duration of anesthesia; urine output; the need for vasopressors; and all the complications that developed in the perioperative period were recorded. The duration of postoperative ICU stay; the amount of transfusion given by drainage; the duration of invasive mechanical ventilation; the need for renal replacement therapy; the Hb, INR, fibrinogen, and creatinine values; the lactate and pH values in blood gas on ICU admission and discharge; reoperation, mortality, cardiac ischemia or infarction that developed during the postoperative period; thromboembolic events; acute respiratory failure; nosocomial infection; acute transfusion reaction; multiple organ failure; and the need for vasopressor or inotropic therapy were recorded.

Statistical Analysis

R version 2.15.3 (R Core Team, 2013) was used for statistical analysis. Descriptive statistical methods (minimum, maximum, median, first quartile, third quartile, mean, standard deviation, frequency, and percentage) were used when reporting the data. Whether the quantitative data

fit the normal distribution was evaluated with the Shapiro-Wilk test and graphical analysis. Independent samples t-test was used in the between-group evaluation of the normally distributed variables. The Mann-Whitney U test was used in the between-group evaluation of the non-normally distributed variables. Analysis of variance and Bonferroni-corrected binary evaluations were used for repeated measures in the within-group evaluations of the normally distributed variables with more than two iterations. Dependent samples t-test was used in the within-group evaluations of the normally distributed variables with two iterations. The Wilcoxon signed-rank test was used in the within-group evaluations of the non-normally distributed variables with two iterations. Pearson chi-square test and Fisher's exact test were used to compare the qualitative variables. Spearman correlation analysis (Spearman's rho) was used to determine the level of correlation between the quantitative variables. Linear regression analysis was used to determine the factors affecting the length of ICU and hospital stay and duration of use of vasopressor agents. Kaplan-Meier plot and log-rank test were used to compare survival between the groups. A P value of <0.05 was considered statistically significant.

RESULTS

Twenty-seven males (48.2%) and 29 females (51.8%) participated in our study. No patient was excluded from the study. When the diagnoses of the patients were examined, 13 patients were diagnosed with brachycephaly (23.2%), 3 patients (5.4%) with multiple suture synostosis, 1 (1.8%) with plagiocephaly and scaphocephaly, 1 with operated lambdoid suture synostosis and brachycephaly, 1 with Apert Syndrome, 1 with Crouzon Syndrome, 1 (1.8%) with calvarial remodeling, 8 (14.3%) with plagiocephaly, 1 with plagiocephaly and scaphocephaly, 12 (21.4%) with scaphocephaly, 1 (1.8%) with scaphocephaly and plagiocephaly, and 13 (23.2%) with trigonocephaly. The demographic data of the patients, the values of the blood and blood products used intraoperatively and the perioperative laboratory values, the duration of anesthesia and surgery, and the length of ICU stay are given in Table 1. No significant relationship was found between the age of the red blood cells (RBCs) and fresh frozen plasmas (FFPs) that were used and the intraoperative changes in pH and lactate levels. No relationship was found between the age of RBCs and FFPs used in the ICU and the changes in the Hb, pH, platelet, creatinine, and fibrinogen levels observed during the period between ICU admission and discharge. No relationship was found between the age of the RBCs and FFPs used and the length of ICU and hospital stay. No relationship was found between the age of the RBCs and FFPs used and the amounts of RBC and FFP transfusion performed in the ICU. No significant correlation was found between the age of the RBCs and FFPs used and the amount of colloid and crystalloid fluid administered in the intraoperative period and the amount of intraoperative bleeding. However, it was weakly associated with the amount of postoperative drainage ($r=0.29$, $p<0.05$). There was a very weak positive correlation between the age of RBC used and the amount of urine output ($r=0.30$, $p<0.05$) (Table 2).

The amount of intraoperative RBC and FFP, duration of anesthesia, duration of surgery, and amount of intraoperative colloid and crystalloid were compared with the duration of drainage, ICU, and hospital stay. A significant correlation was found between the amount of intraoperative RBC and crystalloid and the amount of postoperative drainage (Table 3).

There was a very weak significant positive correlation between the postoperative lactate values and the amount of FFP transfused intraoperatively ($r=0.31$, $p<0.05$) (Table 4).

Table 1. Demographic data of the patients, values of intraoperative blood and blood products used and perioperative laboratory values

	Mean	SD	Median	IQR25	IQR75
Month	8.27	6.294	7.00	6.00	9.00
Weight (kg)	8.99	2.309	8.50	7.85	10.00
Storage day of FFP (day)	13.30	8.922	9.00	6.00	22.00
Storage day of ES (day)	10.80	6.423	10.50	6.00	13.75
Intraop bleeding (ml)	227.26	149.356	200.00	145.00	285.00
Intraop ES (ml)	7.75	3.604	7.00	6.00	8.00
Intraop TDP	1.26	0.561	1.20	0.90	1.50
Intraop Hb baseline	9.94	1.039	9.75	9.20	10.67
Intraop Hb end	10.68	1.448	10.55	9.70	11.50
ICU stay (hour)	59.11	58.892	48.00	26.00	74.00
ICU ES tx (ml)	111.16	81.903	120.00	0	150.00
ICU TDP tx (ml)	35.98	69.592	0	0	37.50
Postop drainage (ml)	173.30	90.430	150.00	100.00	217.50
Hospital stay (day)	7.75	3.604	7.00	6.00	8.00

Table 2. The relationship between the age of the RBCs and FFPs used and the amount of colloid, crystalloid given in the intraoperative period, and the amount of intraoperative bleeding and drainage

	FFP (day)		RBC (day)	
	r	p	r	p
Intraoperative bleeding (ml)	0.255	0.140	0.054	0.703
Postoperative drainage (ml)	-0.075	0.659	0.287*	0.032*
Intraoperative bleeding (ml)	0.255	0.140	0.054	0.703
Intraoperative crystalloid (ml)	-0.105	0.536	-0.128	0.345
Intraoperative colloid (ml)	0.217	0.197	0.023	0.869
Anesthesia time (min)	-0.310	0.062	-0.111	0.416
Surgery time (min)	-0.262	0.118	-0.146	0.281

Table 3. The relationship between the amount of intraoperative RBC and FFP, duration of anesthesia, duration of surgery, amount of intraoperative colloid and crystalloid and drainage, ICU stay, and hospital stay

	Postoperative drainage (ml)		ICU stay (hour)		Hospital stay (day)	
	r	p	r	p	r	p
Intraoperative RBC (ml)	0.389**	0.003	0.253	0.062	0.124	0.364
Intraoperative FFP	0.140	0.304	0.045	0.746	0.134	0.326
Duration of anesthesia (min)	0.008	0.954	-0.082	0.553	0.102	0.455
Duration of surgery (min)	-0.009	0.950	-0.055	0.688	0.098	0.473
Intraoperative crystalloid (ml)	0.350**	0.008	0.260	0.055	0.260	0.053
Intraoperative colloid (ml)	0.211	0.119	-0.142	0.300	0.053	0.700

Table 4. Analysis of the relationship between intraoperatively measured lactate values, the amount of RBC and FFP transfused, the duration of anesthesia and surgery, and the amount of crystalloid and colloid fluid administered

	Intraoperative Lactate baseline		Intraoperative Lactate end of surgery		Intraoperative Lactate variance	
	r	p	r	p	r	p
Intraoperative RBC (mL)	0.097	0.475	0.103	0.448	-0.034	0.804
Intraoperative FFP (mL)	0.039	0.775	0.315*	0.018*	-0.235	0.081
Anesthesia time (min)	0.060	0.659	0.054	0.690	-0.013	0.923
Surgery time (min)	0.099	0.466	0.060	0.662	0.003	0.985
Intraoperative crystaloid (ml)	0.097	0.475	0.103	0.448	-0.034	0.804
Intraoperative colloid (ml)	0.053	0.698	-0.026	0.849	0.048	0.725

The difference between the Hb values on ICU admission and discharge and the amount of intraoperative FFP transfusion were very weakly, negatively, and significantly correlated ($r=-0.28$, $p<0.05$). There was a very weak significant positive correlation between the fibrinogen values on ICU admission and intraoperative FFP amounts ($r=0.34$, $p<0.05$). There was a very weak significant negative correlation between the platelet values on ICU admission and intraoperative FFP amounts ($r=-0.32$, $p<0.05$). There was a very weak significant negative correlation between the platelet values on ICU admission and intraoperative RBC amounts ($r=-0.50$, $p<0.001$). There was a very weak significant negative correlation between the platelet values on ICU discharge and intraoperative RBC amounts ($r=-0.35$, $p<0.001$). The data indicating the effect of FFP age, whether more or less than 10 days, on patient parameters are given in Table 5. The data indicating the effect of RBC age, whether more or less than 10 days, on patient parameters are given in Table 6.

DISCUSSION

Our study investigated the relationship between blood transfusion storage time in pediatric patients undergoing

Table 5. Changes in patient parameters when FFP age is below and above 10 days

FFP day	≤10		10<		
	Mean	SD	Mean	SD	p
ICU ES tx (ml)	107.37	91.414	125.28	88.359	0.549
ICU FFP tx (ml)	63.95	80.287	44.44	80.292	0.465
Postop drenage (ml)	186.84	119.131	165.83	73.008	0.525
ICU creatinin gap	0.0706	0.06682	0.0556	0.10623	0.615
ICU fibrinogen gap	-217.6316	133.71620	-126.8333	85.17197	0.020*
ICU trombosit gap	73.7368	73.55032	54.6111	150.38662	0.623
ICU pH gap	-0.1363	0.09570	-0.1567	0.19629	0.688
ICU lactat gap	1.6368	2.32862	1.5778	1.39603	0.927

Table 6. Changes in patient parameters when RBC age is below and above 10 days

FFP day	≤10		10<		
	Mean	SD	Mean	SD	p
Month	7.54	3.930	9.00	8.009	0.389
Weight (kg)	9.02	1.619	8.95	2.871	0.918
Intraop bleeding (ml)	220.00	170.571	235.40	124.381	0.712
Intraop ES (ML)	-0.1464	0.70579	-0.3214	0.68224	0.350
Intraop FFP (ML)	1.17	0.539	1.35	0.579	0.247
Intraop crystalloid (ml)	525.54	190.114	498.93	185.878	0.599
Intraop colloid (ml)	20.71	34.633	33.93	61.904	0.329
Urine output (ml)	50.18	33.374	81.07	53.253	0.012*
Anesthesia time (min)	264.50	36.943	260.89	39.676	0.726
Surgery time (min)	221.43	36.052	218.57	37.782	0.773
ICU stay (hour)	62.57	77.868	55.52	29.672	0.661
Postop drainage (ml)	162.68	72.194	183.93	105.886	0.384
Hospital stay (day)	7.64	4.262	7.86	2.877	0.826

craniosynostosis surgery and their laboratory parameters and incidence of complications. A positive correlation was found between RBC age and the amount of postoperative drainage. No significant correlation was found between the age of RBCs or FFPs and the length of stay in the hospital or ICU. A positive correlation was found between the amount of FFPs transfused intraoperatively and the postoperative lactate values. No significant correlation was found between whether the age of FFPs or RBCs was more or less than 10 days and the changes in patient parameters.

In the Informing Fresh versus Old Red Cell Management (INFORM) study conducted with a pediatric patient group, no significant difference was found between whether erythrocyte suspension was stored for less than 7 days, 8 to 35 days, or more than 35 days, and the patient outcomes.[11] In the Age of Red Blood Cells in Premature Infants (ARIPI) study by Fergusson et al.[12] erythrocyte suspensions stored in the neonatal ICU for less than 7 days and erythrocyte suspensions stored in the ordinary way were compared in 377 premature infants. While the mean duration was 5 days in the group with less storage time, it was 14.6 days in the group with longer storage time, and morbidity and infection-related results were found to be similar between the two groups.[12] The results of these studies also confirm our results.

In the study titled Tissue Oxygenation by Transfusion in Severe Anemia with Lactic Acidosis (TOTAL), which investigated the effect of transfusion of erythrocyte suspension with a longer or shorter storage period on blood lactate levels in 290 children (6-60 months) who suffered severe anemia due to malaria or sickle cell disease in Uganda between February 2013 and May 2015, it was found that longer storage time did not lead to higher lactate levels.[13] Similarly, no correlation was found between FFP age and lactate level in our study. However, the lactate level increased proportionally with the amount of transfused FFP. In light of all this data, it is not possible to reach a conclusion about the effect of the storage period of the blood product on the mortality and morbidity that may develop in patients. The most important feature of this study is that there is no study in the literature that could shed light

on the relationship between the storage time of erythrocyte suspensions used in craniosynostosis operations and patient outcomes in the postoperative period. One of the most important factors affecting patient survival is prolonged hospital or ICU stay. However, no increase was detected in either of them in our study. We believe that this is due to the small sample size.

On the other hand, in a prospective cohort study including 61 trauma patients, a significant correlation was found between elderly blood transfusion and the risk of postoperative infection.[14] It was argued that this might develop due to the immunomodulatory effects of pending blood transfusion. It was also suggested that the infection could be triggered due to the activation of the neutrophil nicotinamide adenine dinucleotide phosphate oxidase system.[15] In a study conducted with 128 pediatric patients who underwent palliation of congenital heart disease with cardiopulmonary bypass, longer erythrocyte storage time was associated with a 4-fold increase in postoperative nosocomial infections.[16] Older erythrocytes may cause a proinflammatory cytokine response, leading to the development of infection. For this reason, the use of leukocyte-reduced blood transfusions has become a current issue.[17] It was shown that reducing the leukocyte rate in dogs receiving transfusion of blood stored for 28 days does not significantly affect the rate of infection.[4] Being a controversial issue, leukoreduction was not applied before blood transfusion in our study, and no infectious complication was detected.

Recent publications indicate that acquired fibrinogen deficiency is a leading determinant in the development of perioperative dilutional coagulopathy.[18] In our study, a significant correlation was observed between the amount of intraoperative RBC and crystalloid and the amount of postoperative drainage. However, no difference was found between the fibrinogen levels, indicating that this may be due to the dilution of other factors. In this case, we believe that positive results will be obtained in clinics by shortening the storage period. In addition, the amount of drainage that would require reoperation was not observed in any of the patients.

Limitations

There are studies advocating that aged erythrocytes are rapidly destroyed after transfusion.[19] One of the limitations of our study is that the clinical changes and laboratory parameters of the intraoperative period and early postoperative period were investigated. The long-term effects resulting from erythrocyte destruction in the postoperative period were not investigated. Another limitation is that the study design was retrospective, and the sample size was small.

Conclusion

The results of our study concluded that shortening the storage time of blood and blood products may have a positive effect on postoperative drainage. However, larger-scale studies are needed as it was not proven whether this has an effect on hospital and ICU stay and laboratory parameters.

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: A.S.; Design: A.S.; Supervision: A.S., T.U.; Fundings: A.S., G.C., G.Ç.; Materials: G.C., G.Ç., C.K.; Data: A.S., G.C., G.Ç., C.K., C.E.; Analysis: A.S., G.C., T.U.; Literature search: A.S.; Writing: A.S.; Critical revision: A.S., G.C., G.Ç., C.K., C.E., T.U.

Conflict of Interest

None declared.

REFERENCES

1. Goobie SM, Haas T. Bleeding management for pediatric craniotomies and craniofacial surgery. Paediatr Anaesth 2014;24:678–89.
2. Slater BJ, Lenton KA, Kwan MD, Gupta DM, Wan DC, Longaker MT. Cranial sutures: A brief review. Plast Reconstr Surg 2008;121:170e–8e. [CrossRef]
3. Donadee C, Raat NJ, Kanias T, Tejero J, Lee JS, Kelley EE, et al. Nitric oxide scavenging by red blood cell microparticles and cell-free hemoglobin as a mechanism for the red cell storage lesion. Circulation 2011;124:465–76. [CrossRef]
4. Callan MB, Patel RT, Rux AH, Bandyopadhyay S, Sireci AN, O'Donnell PA, et al. Transfusion of 28-day-old leucoreduced or non-leucoreduced stored red blood cells induces an inflammatory response in healthy dogs. Vox Sang 2013;105:319–27. [CrossRef]
5. Hod EA, Zhang N, Sokol SA, Wojczyk BS, Francis RO, Ansaldi D, et al. Transfusion of red blood cells after prolonged storage produces harmful effects that are mediated by iron and inflammation. Blood 2010;115:4284–92. [CrossRef]
6. Hod EA, Spitalnik SL. Stored red blood cell transfusions: Iron, inflammation, immunity, and infection. Transfus Clin Biol 2012;19:84–9. [CrossRef]
7. Hess JR. Red cell storage. J Proteomics 2010;73:368–73. [CrossRef]
8. Orbach A, Zelig O, Yedgar S, Barshtein G. Biophysical and biochemical markers of red blood cell fragility. Transfus Med Hemother 2017;44:183–7. [CrossRef]
9. Hayek SS, Neuman R, Ashraf K, Sher S, Newman JL, Karatela S, et al. Effect of storage-aged red blood cell transfusions on endothelial function in healthy subjects. Transfusion 2015;55:2768–70.
10. Almizraq RJ, Seghatchian J, Acker JP. Extracellular vesicles in transfusion-related immunomodulation and the role of blood component manufacturing. Transfus Apher Sci 2016;55:281–91. [CrossRef]
11. Cook RJ, Heddle NM, Lee KA, Arnold DM, Crowther MA, Devereaux PJ, et al. Red blood cell storage and in-hospital mortality: A secondary analysis of the INFORM randomised controlled trial. Lancet Haematol 2017;4:e544–52. [CrossRef]
12. Fergusson DA, Hébert P, Hogan DL, LeBel L, Rouvinez-Bouali N, Smyth JA, et al. Effect of fresh red blood cell transfusions on clinical outcomes in premature, very low-birth-weight infants: The ARIPI randomized trial. JAMA 2012;308:1443–51. [CrossRef]
13. Dhabangi A, Ainomugisha B, Cserti-Gazdewich C, Ddungu H, Kyeyune D, Musisi E, et al. Effect of transfusion of red blood cells with longer vs shorter storage duration on elevated blood lactate lev-

els in children with severe anemia: The TOTAL randomized clinical trial. JAMA 2015;314:2514–23. [CrossRef]
14. Offner PJ, Moore EE, Biffl WL, Johnson JL, Silliman CC. Increased rate of infection associated with transfusion of old blood after severe injury. Arch Surg 2002;137:711–7. [CrossRef]
15. Almyroudis NG, Grimm MJ, Davidson BA, Röhm M, Urban CF, Segal BH. NETosis and NADPH oxidase: At the intersection of host defense, inflammation, and injury. Front Immunol 2013;4:45.
16. Cholette JM, Pietropaoli AP, Henrichs KF, Alfieris GM, Powers KS, Phipps R, et al. Longer RBC storage duration is associated with increased postoperative infections in pediatric cardiac surgery. Pediatr Crit Care Med 2015;16:227–35. [CrossRef]
17. Sharma RR, Marwaha N. Leukoreduced blood components: Advantages and strategies for its implementation in developing countries. Asian J Transfus Sci 2010;4:3–8. [CrossRef]
18. Bolliger D, Görlinger K, Tanaka KA. Pathophysiology and treatment of coagulopathy in massive hemorrhage and hemodilution. Anesthesiology 2010;113:1205–19. [CrossRef]
19. García-Roa M, Del Carmen Vicente-Ayuso M, Bobes AM, Pedraza AC, González-Fernández A, Martín MP, et al. Red blood cell storage time and transfusion: current practice, concerns and future perspectives. Blood Transfus 2017;15:222–31. [CrossRef]

Kraniyosinostoz Ameliyatı Geçiren Pediatrik Hasta Popülasyonunda Eritrosit Süspansiyonlarının Artan Depolama Süresinin Hasta Sonuçları Üzerindeki Etkileri

Amaç: Kraniyosinositoz cerrahisi sırasında geniş insizyon alanının yol açtığı kanama nedeniyle gereken kan transfüzyonu, kanın oksijen taşıma kapasitesinin devamlılığını sağlamak için gerekli olmakla beraber, önemli riskleri bulunmaktadır. Günümüzde kan ve kan ürünlerinin depolama süresiyle değişen içeriğine bağlı gelişen ciddi komplikasyonların postoperatif dönemde hasta sonuçlarını etkileyebileceği de düşünülmektedir. Bu çalışmadaki amacımız, kraniyosinositoz cerrahisi geçirmiş olan pediyatrik hasta grubunda eritrosit süspansiyonunun depolama süresinin postoperatif dönemde hasta sonuçları üzerine etkisini belirlemektir.

Gereç ve Yöntem: Retrospektif olarak planlanan çalışmamıza, hastane bilgi sistemi ve anestezi izlem kayıtlarından verileri alınarak 2018-2021 yılları arasında kraniyosinositoz cerrahisi geçirmiş olan 2-24 aylık 56 hasta alındı. Hastalar verilen eritrosit süspansiyonu (ES) ve taze donmuş plazmanın (TDP) depolama süresine göre (donörden alındığı gün ile hastalara transfüze edildiği gün arası süre) 10 günün altında olan ve 10 günün üzerinde olan şeklinde gruplara ayrıldı. Hastaların demografik verileri, ortalama arteryel kan basıncı, vücut sıcaklığı, hemoglobin (Hb), INR, trombosit (PLT) değerleri, intraoperatif kanama, transfüzyonu miktarı, verilen kristalloid ve kolloid sıvı miktarı, operasyon süresi, anestezi süresi, komplikasyonlar, postoperatif yoğun bakımda (YBÜ) kalış süresi, drenaj ile verilen transfüzyon miktarı ve hastanede kalış süresi kaydedildi.

Bulgular: Hastaların ortalama yaşı 8.27+6.294 ay idi. İntraoperatif dönemde kullanılan ES'lerin depolama süresi, ES ve kristalloid miktarı ile postoperatif drenaj arasında pozitif korelasyon saptanmıştır. İntraoperatif TDP transfüzyonu ile YBÜ'de ölçülen Hb değerlerinin değişimi ve intraoperatif ES transfüzyonu ile YBÜ çıkış PLT değerleri arasında negatif yönlü korelasyon saptandı ($p<0.05$).

Sonuç: Çalışmamızın sonuçlarına göre ES ve TDP'lerin depolama süresindeki kısalmanın postoperatif drenaj üzerine olumlu etkisi olabileceği kanısına varıldı. Ancak hastane ve YBÜ'de kalış üzerine bir etkisinin varlığı gösterilememesi daha büyük ölçekli çalışmalara ihtiyaç olduğunu düşündürmüştür.

Anahtar Sözcükler: Eritrosit süspansiyonu; kraniyosinostoz; taze donmuş plazma; kan transfüzyonu.

SCIE DOI: 10.14744/scie.2024.91129
South. Clin. Ist. Euras. 2024;35(3):209-212

Original Article

Large Language Model and Medical Education: Evaluation of Human and Artificial Intelligence Responses to Thoracic Surgery Questions

Mesut Buz, Recep Demirhan

Department of Thoracic Surgery, Health Sciences University, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Türkiye

Submitted: 05.08.2024
Revised: 05.08.2024
Accepted: 13.08.2024

Correspondence: Mesut Buz, Department of Thoracic Surgery, Health Sciences University, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Türkiye

E-mail: mesutbuzmd@gmail.com

Keywords: Artificial intelligence; ChatGPT-4; large language models; thoracic surgery.

ABSTRACT

Objective: This study aimed to evaluate the performance of ChatGPT-4, a large language model, in answering thoracic surgery questions compared to 5th-year medical students. The goal was to assess the potential of ChatGPT-4 as an educational tool in medical training.

Methods: A retrospective comparative analysis was conducted involving 10 fifth-year medical students and ChatGPT-4. Each participant answered 40 multiple-choice questions related to thoracic surgery. The students' scores were compared to the scores generated by ChatGPT-4. Statistical analysis was performed using an independent sample t-test to determine the significance of the differences in performance.

Results: The students' scores ranged from 80% to 97.5%, with an average score of 88.25% (SD=5.63). ChatGPT-4 scored 95% on the same set of questions. The t-test results indicated a statistically significant difference between the students' scores and ChatGPT-4's score (t=-3.98, p=0.00088).

Conclusion: The study demonstrated that ChatGPT-4 can provide accurate answers to thoracic surgery questions, surpassing the performance of 5th-year medical students. This indicates the potential of large language models as valuable educational tools in medical training. However, further research is needed to evaluate the model's performance across different medical disciplines and question types.

INTRODUCTION

Thoracic surgery is a medical specialty that involves the surgical treatment of organs within the thoracic cavity. This field deals with the surgical treatment of diseases and disorders affecting vital organs such as the lungs, esophagus, chest wall, and diaphragm. Thoracic surgery encompasses numerous serious health issues, including cancer, infections, trauma, and congenital anomalies. Therefore, accurate and timely interventions in the field of thoracic surgery play a critical role in enhancing patients' quality of life and improving survival rates.[1-5]

The significance of thoracic surgery is not limited to surgical techniques and applications alone. This field also requires working near complex anatomical structures and vital organs, demanding a high level of expertise and skill. Consequently, thoracic surgery training requires doctors to be well-equipped in both theoretical knowledge and practical skills.[6,7]

In recent years, the use of artificial intelligence (AI) and large language models (LLMs) in medical education and patient care has been increasing. LLMs have demonstrated significant potential in answering various medical questions, analyzing medical texts, and even providing diagnostic and treatment recommendations, thanks to their ability to learn from large datasets.[8,9] These models can be used as educational tools for medical students and doctors, aiding in the understanding of complex medical information.[10-12]

This study aimed to compare the responses of 5th-year medical students to thoracic surgery questions with those provided by an LLM, such as ChatGPT-4.

MATERIALS AND METHODS

This study was designed as a retrospective comparative analysis to compare the responses of 5th-year medical students from the the Health Sciences University Hamidiye International Faculty of Medicine thoracic surgery questions with those provided by a large language model like ChatGPT-4. The study includes 5th-year students enrolled in the Faculty of Medicine during the 2023-2024 academic year. A total of 10 students participated in the study. Ethics approval was obtained from the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee with the decision dated 26.07.2024 and numbered 2024/010.99/6/37.

To assess their knowledge in the field of thoracic surgery, participants were asked 40 multiple-choice questions. These questions were selected from those included in the medical school curriculum and prepared by the Division of Thoracic Surgery, covering theoretical knowledge and clinical applications. Each question was prepared in a five-choice multiple-choice format. The same questions were also posed to ChatGPT-4, and the model's responses were recorded. ChatGPT-4 provided answers by entering questions and options into the user interface. The model evaluated each of the selected options and determined the most appropriate answer.

ChatGPT-4 is a large language model developed by OpenAI and trained on millions of texts. The model is trained with deep learning algorithms to understand the structure and context of language using large datasets. ChatGPT-4 has the ability to generate text and answer questions on various topics using this pre-trained knowledge. The training of the model involves analyzing and processing a large amount of text data to develop the capacity to understand and produce human language.

Statistical Analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences software (Version 29, Chicago, IL, USA) for Windows. A significance level of $p<0.05$ was set for the analyses. An independent sample t-test was used to evaluate the differences in performance between the students and ChatGPT-4. The t-test was employed to assess whether the difference between the means of the two independent groups was due to chance. In this context, the difference in the number of correct answers given by the students and ChatGPT-4 was statistically analyzed.

RESULTS

In this study, the accuracy rates of responses to thoracic surgery questions given by 5th-year medical students and ChatGPT-4 were compared. When examining the scores of the 10 participating students (S1-S10) from 40 multiple-choice questions, it was observed that the students' performance ranged from 80% to 97.5% (Figure 1). The average exam performance of the students was calculated as 88.25% (SD=5.63). The accuracy rate of ChatGPT-4's responses to the same 40 questions was recorded as 95% (Figure 2). Although the individual scores of the students varied, ChatGPT-4's performance remained consistent and high. The results of the independent sample t-test indicated a statistically significant difference in performance between ChatGPT-4 and the students (t=-3.98, p=0.00088).

Examining the distribution of student scores reveals that while the scores were spread over a wide range, they were generally high. The performance comparison showing ChatGPT-4 outperforming the students highlights the potential of the language model. The comparison of correct

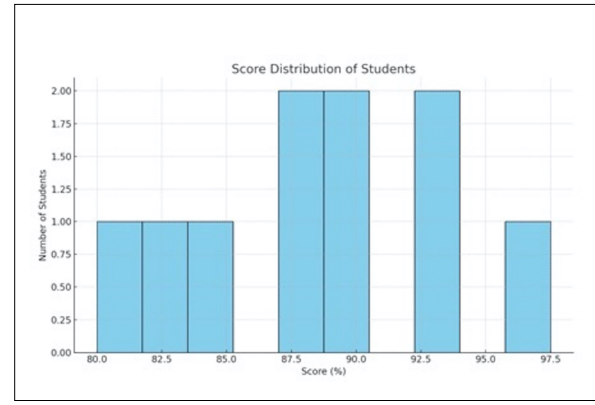

Figure 1. Score distribution of students.

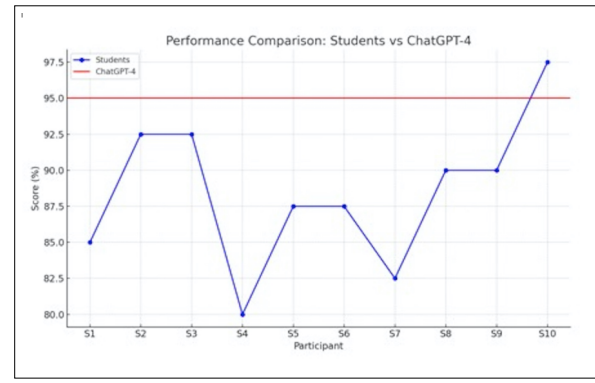

Figure 2. Performance comparison - Students vs ChatGPT-4.

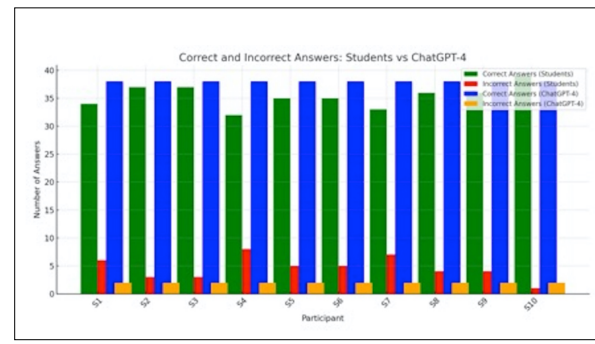

Figure 3. Correct and incorrect answers - Students vs ChatGPT-4.

and incorrect responses supports that ChatGPT-4 has a higher accuracy rate than the students by providing more correct answers (Figure 3).

DISCUSSION

This study concluded that ChatGPT-4 provided significantly higher accuracy in responding to thoracic surgery questions compared to 5th-year medical students. This result indicates that LLMs can be used as valuable tools in medical education and can be effective in enhancing the knowledge level of medical students.

LLMs are deep learning systems trained on large datasets. These models learn the meaning and context of language using text data and can generate human-like text outputs. Models like GPT-4, developed by OpenAI, are highly advanced systems with millions of parameters, offering strong capabilities in language generation and understanding.[13-15]

LLMs have revolutionized the field of natural language processing (NLP) and have been used in various applications. These models demonstrate high performance in tasks such as text generation, translation, question answering, text summarization, and many more. ChatGPT, developed by OpenAI, is a chatbot built on large language models like GPT-4. ChatGPT has the ability to engage in natural and meaningful dialogues with users.[16,17]

In a study conducted in the field of neurology, the performance of GPT-4 and other large language models (Bard and Claude 2) on epilepsy examinations was evaluated. The study found that GPT-4 achieved the highest performance with an accuracy rate of 72%, while the other models showed lower performance.[18] This study highlighted the ability of large language models to answer medical exam questions, emphasizing their potential use in medical education and exam preparation.

In another study conducted in the field of oncology, the performance of LLMs on medical oncology exam questions was evaluated. The study found that a proprietary LLM, Proprietary LLM 2, achieved the highest performance with an accuracy rate of 85%. However, a significant portion of the incorrect answers was found to have a moderate to high potential for harm in clinical practice.[19] These findings suggest that LLMs can be effective in answering questions based on medical knowledge, but caution should be exercised when using them in clinical practice.

Limitations

This study has several limitations. First, the number of students participating is limited, which may hinder the generalization of the results. Second, only questions from the field of thoracic surgery were used; therefore, the results cannot be generalized to other medical fields. Third, the performance of ChatGPT-4 was evaluated only with multiple-choice questions; its performance on open-ended questions was not assessed.

Conclusion

This study demonstrates that ChatGPT-4 has a superior accuracy rate compared to medical students' performance on thoracic surgery questions. Large language models can be valuable tools in medical education and exam preparation. However, they need to be carefully evaluated and validated before being used in clinical practice. Future research should assess the performance of large language models across different medical fields and various types of questions and strive to better understand their integration into medical education.

Ethics Committee Approval

The study was approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 26.07.2024, Decision No: 2024/010.99/6/37).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: M.B., R.D.; Design: M.B.; Supervision: R.D.; Fundings: M.B.; Materials: R.D. ; Data: M.B.; Analysis: M.B.; Literature search: M.B.; Writing: M.B., R.D.; Critical revision: M.B., R.D.

Conflict of Interest

None declared.

REFERENCES

1. Godoy LA, Hill E, Cooke DT. Social disparities in thoracic surgery education. Thorac Surg Clin 2022;32:91–102. [CrossRef]
2. Holmstrom AL, Meyerson SL. Obtaining meaningful assessment in thoracic surgery education. Thorac Surg Clin 2019;29:239–47. [CrossRef]
3. Shamji FM, Sekhon HJS, MacRae RM, Maziak DE. Guiding principles on the importance of thoracic surgical education on establishing integrated thoracic surgery program, interdisciplinary thoracic oncology conferences, and an interdisciplinary approach to management of thoracic malignancies. Thorac Surg Clin 2021;31:367–77. [CrossRef]
4. Faber LP, Liptay MJ, Seder CW. The history of the department of cardiovascular and thoracic surgery at rush. Semin Thorac Cardiovasc Surg 2016;28:687–99. [CrossRef]
5. Lou X. Thoracic surgery residents association ınaugural presidential address: Preserving the passion in cardiothoracic surgery training. J Thorac Cardiovasc Surg 2020;160:1002–3. [CrossRef]
6. Grossi S, Cattoni M, Rotolo N, Imperatori A. Video-assisted thoracoscopic surgery simulation and training: A comprehensive literature review. BMC Med Educ 2023;23:535. [CrossRef]
7. Van Schil PE. The present and future of thoracic surgery within the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2013;43:219–22. [CrossRef]
8. Thirunavukarasu AJ, Ting DSJ, Elangovan K, Gutierrez L, Tan TF, Ting DSW. Large language models in medicine. Nat Med 2023;29:1930–40. [CrossRef]
9. Lee H. The rise of ChatGPT: Exploring its potential in medical education. Anat Sci Educ 2024;17:926–31.

10. Jowsey T, Stokes-Parish J, Singleton R, Todorovic M. Medical education empowered by generative artificial intelligence large language models. Trends Mol Med 2023;29:971–3. [CrossRef]
11. Song H, Xia Y, Luo Z, Liu H, Song Y, Zeng X, et al. Evaluating the performance of different large language models on health consultation and patient education in urolithiasis. J Med Syst 2023;47:125. [CrossRef]
12. Ahn S. The impending impacts of large language models on medical education. Korean J Med Educ 2023;35:103–7. [CrossRef]
13. Bernstein IA, Zhang YV, Govil D, Majid I, Chang RT, Sun Y, et al. Comparison of ophthalmologist and large language model chatbot responses to online patient eye care questions. JAMA Netw Open 2023;6:e2330320. [CrossRef]
14. Nielsen JPS, von Buchwald C, Grønhøj C. Validity of the large language model ChatGPT (GPT4) as a patient information source in otolaryngology by a variety of doctors in a tertiary otorhinolaryngology department. Acta Otolaryngol 2023;143:779–82. [CrossRef]
15. Kane MJ, King C, Esserman D, Latham NK, Greene EJ, Ganz DA. A compressed large language model embedding dataset of ICD 10 CM descriptions. BMC Bioinformatics 2023;24:482. [CrossRef]
16. Dave T, Athaluri SA, Singh S. ChatGPT in medicine: An overview of its applications, advantages, limitations, future prospects, and ethical considerations. Front Artif Intell 2023;6:1169595. [CrossRef]
17. Liu J, Wang C, Liu S. Utility of ChatGPT in clinical practice. J Med Internet Res 2023;25:e48568.
18. Habib S, Butt H, Goldenholz SR, Chang CY, Goldenholz DM. Large language model performance on practice epilepsy board examinations. JAMA Neurol 2024;81:660–1. [CrossRef]
19. Longwell JB, Hirsch I, Binder F, Gonzalez Conchas GA, Mau D, Jang R, et al. Performance of large language models on medical oncology examination questions. JAMA Netw Open 2024;7:e2417641. [CrossRef]

Büyük Dil Modeli ve Tıp Eğitimi: Göğüs Cerrahisi Sorularında İnsan ve Yapay Zeka Yanıtlarının Değerlendirilmesi

Amaç: Bu çalışma, bir büyük dil modeli olan ChatGPT-4'ün, göğüs cerrahisi sorularına 5. sınıf tıp öğrencileri ile karşılaştırmalı olarak yanıt verme performansını değerlendirmeyi amaçlamaktadır. Çalışmanın hedefi, ChatGPT-4'ün tıp eğitiminde bir eğitim aracı olarak potansiyelini değerlendirmektir.

Gereç ve Yöntem: Çalışmada, 10 beşinci sınıf tıp öğrencisi ve ChatGPT-4'ün yer aldığı retrospektif karşılaştırmalı bir analiz yapıldı. Her katılımcı, göğüs cerrahisiyle ilgili 40 çoktan seçmeli soruyu yanıtladı. Öğrencilerin puanları, ChatGPT-4 tarafından üretilen puanlarla karşılaştırıldı. Performans farklarının anlamlılığını belirlemek için bağımsız örneklem t-testi kullanılarak istatistiksel analiz yapıldı.

Bulgular: Öğrencilerin puanları %80 ile %97.5 arasında değişmiş ve ortalama puan %88.25 (SD=5.63) olarak hesaplanmıştır. ChatGPT-4, aynı soru setinde %95 puan almıştır. T-testi sonuçları, öğrencilerin puanları ile ChatGPT-4'ün puanı arasında istatistiksel olarak anlamlı bir fark olduğunu göstermiştir (t=-3.98, p=0.00088).

Sonuç: Çalışma, ChatGPT-4'ün göğüs cerrahisi sorularına doğru yanıtlar verebildiğini ve 5. sınıf tıp öğrencilerinin performansını aştığını göstermiştir. Bu durum, büyük dil modellerinin tıp eğitiminde değerli eğitim araçları olarak potansiyelini ortaya koymaktadır. Ancak, modelin farklı tıbbi disiplinler ve soru türleri üzerindeki performansını değerlendirmek için daha fazla araştırmaya ihtiyaç vardır.

Anahtar Sözcükler: ChatGPT-4; büyük dil modelleri; göğüs cerrahisi; yapay zeka.

SCIE DOI: 10.14744/scie.2024.71354
South. Clin. Ist. Euras. 2024;35(3):213-218

Original Article

Evaluation of Balance and Gait in Idiopathic Scoliosis

Tuğba Özüdoğru Çelik, Saadet Selin Koç, Elif Yalçın, Hüma Bölük Şenlikci, Nilüfer Kutay Ordu Gökkaya

Department of Physical Medicine and Rehabilitation, University of Health Sciences, Ankara Bilkent City Hospital, Ankara, Türkiye

Submitted: 02.08.2024
Revised: 02.08.2024
Accepted: 23.08.2024

Correspondence: Tuğba Özüdoğru Çelik,
Department of Physical Medicine and Rehabilitation, University of Health Sciences, Ankara
E-mail: tugbaozudogru0626@gmail.com

Keywords: Balance; gait analysis; idiopathic scoliosis.

ABSTRACT

Objective: Idiopathic scoliosis (IS) is a three-dimensional deformity of the spine, defined radiographically as a lateral deviation of more than 10 degrees in the coronal plane, characterized by sagittal and transverse plane changes. Balance and walking are the most common activities of daily living. In our study, we aimed to analyze the effect of the curvature on balance and walking in IS individuals, who have a reduced risk of progression and whose curvatures are generally stable, by analyzing quantitative data.

Methods: The study included 34 patients with IS and 34 healthy individuals. All participants were questioned about their socio-demographic and physical characteristics. Balance parameters were recorded using a multi-axis, motorized platform system called Huber 360 with built-in force sensors and handles. The participants' gait analysis was performed using a Zebris FDM type 3 (Zebris Medical GmbH, Germany) walking platform.

Results: When gait parameters were examined, step time and walking cycle duration were significantly higher in the IS group compared to the control group (p=0.007 and p=0.008, respectively). On the contrary, right-foot loading response and walking speed of the control group were significantly higher than the scoliosis group (p=0.006 and p=0.0003, respectively). Stability speed with eyes closed was significantly higher in the IS group compared to controls (14.55±3.5 mm/s and 12.6±4.6 mm/s, respectively, p=0.012). No significant differences were observed between the groups in terms of other balance and gait characteristics.

Conclusion: This study revealed that balance and gait were affected in patients with IS, and individuals with scoliosis had poor balance and walking skills compared to healthy individuals. Therefore, in scoliosis rehabilitation, balance and walking problems that may be caused by spinal curvatures should definitely be taken into consideration.

INTRODUCTION

Idiopathic scoliosis (IS) is a three-dimensional deformity of the spine, defined radiographically as a lateral deviation of more than 10 degrees in the coronal plane, characterized by sagittal and transverse plane changes. The underlying factors in the etiology of IS and the cause of the deformity are not fully known. Since more than one factor is seen to be effective in the pathogenesis of IS, a multifactorial pathogenesis is considered. The most commonly blamed factors include maturation disorders of the central and peripheral nervous system, connective tissue disorders in elastic and collagen fibers, muscle and bone diseases, platelet disorders, melatonin, calmodulin, growth hormone imbalances, and leptin deficiency.[1] Scoliosis is divided into structural and non-structural scoliosis. One of the most common etiological causes of structural scoliosis is IS, and 75-80% of all scoliosis cases are in this group.[2]

Scoliosis is a three-dimensional torsional deformity that occurs with the rotation of one or more vertebrae in the spine. Chest deformity and pelvic asymmetry are often seen together with spinal deformity.[3] This deformity, which is usually painless, is asymptomatic and easily overlooked. In advanced and untreated cases, there is a high risk of developing significant health problems such as acute/chronic back and waist pain, cardiopulmonary dysfunction, functional limitation, depression, and deterioration in quality of life due to cosmetic deformity. IS classification is classically made based on the age at which the deformity is first diagnosed. The classical classification of idiopathic scoliosis according to age is: 1. Infantile (0-3 years) 2. Juvenile (3-10 years) 3. Adolescent (10-18 years) 4. Adult (18 years and older) IS. 80-90% of IS occurs during adolescence.[4] It is frequently seen during childhood and adolescence, when the growth plates develop, between the ages of 6 and 24 months, 5 and 8 years, and 11 and 14 years. These periods

are also the most obvious progression period in IS. After the completion of spinal growth in adolescence, the potential for progression of IS is much lower. In adulthood, it may progress as a result of spinal collapse and progressive osseous deformities.[5] After skeletal maturation, it may progress by one or two degrees per year, especially in cases with scoliosis exceeding 50°, and it is reported that curves with angles less than 35 degrees generally remain stable. [5] Knowing the risk of progression in IS is important for determining and continuing the treatment.

Postural balance is one of the most important factors that determine a person's ability to make and maintain movements. Adequate postural balance is an important proof of proper neuromuscular control and communication between the central nervous system and the muscles. Balance is related to the integration of data from the visual, somatosensory, and vestibular systems.[6] In scoliosis, poor posture causes imbalance in the spine, fatigue, and ultimately pain due to nociceptive stimuli. In order to correct the poor posture, the muscles are overstretched, and over time, spasm and pain occur in the muscles. As the apical region is approached on the convex side of the scoliotic curvature, spinal mobility decreases, the muscles on the convex side of the curvature are overstretched and strain the ligaments, and on the concave side, weakness and shortening occur in the muscles. As a result of scoliosis, the posture of the patients is deteriorated, the biomechanics of the spine are affected due to the poor posture, disuse atrophies develop, and this causes asymmetrical loads in the spine.

Carrying more body weight on one side also affects the load distribution of the lower extremity. This situation can cause postural control and body balance to deteriorate, and walking mechanics, including the kinematics of the lower extremity joints, can cause gait asymmetries and the development of a pathological gait. In addition, asymmetries in walking can affect the trunk-pelvis balance and cause the curve to progress.[7] Therefore, balance and walking training that affects the trunk-pelvis balance in the opposite direction according to the individual's curvature is of great importance in the exercise program planned for scoliosis treatment.

To our knowledge, there is no study that evaluates the effect of curvature on balance and walking, especially in adult IS, with quantitative analysis and data. The aim of this study is to examine the effect of curvature on balance and walking in adult IS individuals, in a period when the risk of progression has decreased, and the curvatures are generally stable.

MATERIALS AND METHODS

From February 2024 to May 2024, 34 IS patients and 34 healthy individuals were recruited for this study. In this observational case-control study, the patients were included if they were diagnosed with IS and healthy controls with a natural spine curve. Approval for this study was obtained from Bilkent City Hospital Ethics Committee (E2-24-6163), and the study was conducted in accordance with The Declaration of Helsinki.

The exclusion criteria of the study were determined as: other types of scoliosis, musculoskeletal system pathologies that may create asymmetry in the body and balance, primary pathologies of the ear, benign paroxysmal positional vertigo, Meniere's disease, previous head trauma, previous spinal surgery, presence of neurological disease, presence of metabolic disease, presence of rheumatological disease, and malignancies. All groups underwent demographic data collection and physical examination. Sociodemographic information (age, gender, height, weight, body mass index, employment status, education, smoking habitus, sports activity, family history of scoliosis, twin pair, foot size, hand dominance, pain assessment (rest and activity visual analog scale (VAS)), lower extremity length difference (shorter extremity side)) was recorded in IS and healthy individuals. All patients' measurements and evaluations in the study were performed and recorded by the same physician. The Cobb method is considered the gold standard for determining spinal curve severity in frontal plane radiography.[8] In this study, the Cobb angles of all individuals with scoliosis were measured and recorded in degrees.

Before the balance and gait analysis, all individuals in both groups were informed about how the tests would be performed. Balance parameters were recorded using a multi-axis, motorized platform system called Huber 360, which has built-in force sensors and handles. Participants' age, height, and weight information were recorded on the device before the test began. Participants were placed on the balance platform with their feet positioned according to the guidelines on the measurement plate while climbing onto the platform. During the measurement, participants were asked to stand as quietly as possible, without moving, and looking ahead, with their arms crossed in front of their chests, touching the opposite shoulder. Postural balance was evaluated in two different test conditions, lasting 30 seconds. Stability (eyes open (EO) and eyes closed (EC)) area, speed, single-leg (right and left separately) area, and walking step count data were recorded.

The participant was asked to step on the guidelines on the force platform and keep their arms together at the sides of the body. Before starting the test, the platform was calibrated according to the foot position by selecting "Reposition" on the application. With the test start command, the participant was asked to bend forward, backward, right, and left at the maximum level, each lasting 8 seconds, without lifting the sole and heel of the foot or taking a corrective step. In this way, the stability limits area of the person was tested and determined in four directions.

The Zebris FDM type 3 (Zebris Medical GmbH, Germany) walking platform was used to measure the spatio-temporal parameters of the participants during walking. The age, height, and weight information of the participants were recorded in the system. The participants were asked to take off their shoes and socks and walk barefoot at their own natural pace for 2 minutes from one end to the other.

In order to eliminate the acceleration and deceleration phases of walking during the turns, the participants started walking from a distance of 2.5 m on the 3+2 m platform and turned from a distance of 2.5 m. The participants walked from end to end on a total of a 10 m platform for 2 minutes, and the data were obtained from the 298 x 54.2 cm section containing the sensor and stored by computer and analyzed. The left and right forefoot, heel maximum load (% of body weight), walking cycle duration, cadence, and walking speed data of all patients were recorded using the Zebris Medical GmbH system.

Statistical Analysis

Statistical analyses of the study were performed using the IBM SPSS 26.0 package program (SPSS, Inc, Chicago, Illinois). In the comparison of demographic and clinical data, and balance and gait analysis data of the scoliosis and control groups, the chi-square test was used for categorical data, the independent sample t-test for normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data. The Shapiro-Wilk test was used to determine whether the data were normally distributed. The goodness of fit of the model was evaluated by the Hosmer-Lemeshow test. All statistical analyses were evaluated at a 95% confidence interval, and statistical significance was assessed at $p<0.05$.

RESULTS

The baseline demographic and clinical characteristics of the study participants are shown in Table 1. The median age of the IS group (23 female and 11 male) was 22 (18-

Table 1. Baseline demographic and clinical characteristics of study participants

Parameters	IS Patients (n=34) n (%) or Median (Min-Maks)	Controls (n=34) n (%) or Median (Min-Maks)	p-value
Age (years)	22 (18-45)	23 (22-47)	0.047*[2]
Gender			
Male	11 (32.4)	11 (32.4)	1[3]
Female	23 (67.6)	23 (67.6)	
Body mass index (kg/m2)	21.5 (17.3-33.8)	22.65 (18.3-36.3)	0.115[2]
Underweight	3 (8.8)	1 (2.9)	0.473[3]
Normal weight	23 (67.6)	22 (64.7)	
Overweight/Obese	8 (23.5)	11 (32.4)	
Employment status			
Unemployed	3 (8.8)	4 (11.8)	0.212[3]
Worker	16 (47.1)	9 (26.5)	
Student	15 (44.1)	21 (61.8)	
Sports activity			
No	25 (73.5)	28 (82.4)	0.38[3]
Yes	9 (26.5)	6 (17.6)	
Smoking			
No	29 (85.3)	27 (79.4)	0.525[3]
Yes	5 (14.7)	7 (20.6)	
Hand dominance			
Left	5 (14.7)	5 (14,7)	1[3]
Right	29 (85.3)	29 (85.3)	
Shoe number	39.5 (35-45)	39 (36-45)	0.666[2]
Family history of scoliosis			
No	27 (79.4)	31 (91.2)	0.171[3]
Yes	7 (20.6)	3 (8.8)	
Low back pain			
No	26 (76.5)	27 (79.4)	0.77[3]
Yes	8 (23.5)	7 (20.6)	
VAS Rest	0 (0-30)	0 (0-30)	0.62[2]
VAS Activity	0 (0-50)	0 (0-40)	0.648[2]
Lower extremity length difference			
No	30 (88.2)	32 (94.1)	0.673[3]
Yes	4 (11.8)	2 (5.9)	

[2]: Mann Whitney U test; [3]: , Chi-square test; *: $p<0.05$

Table 2. Balance parameters of IS and control groups

Parameters	IS Patients (n=34)			Controls (n=34)			p-value
	Median	Min-Maks	Mean±SD	Medyan	Min-Maks	Mean±SD	
Stability area with eyes opened (mm^2)	275.15	38.29-1330.12	371.15±361,7	163.51	35.12-2962,75	338.27±521.6	0.315[2]
Stability speed with eyes opened (mm/s)	10.815	5.76-18.23	11.49±3.7	9.365	6.3-22.88	10.35±3.4	0.139[2]
Stability acquisition time with eyes opened (sec)	30	30-30	30±0	30	30-30	30±0	1[2]
Stability area with eyes closed (mm^2)	442.46	52.43-2009.06	529.95±440.4	263.085	44.37-1288.56	354.61±294	0.108[2]
Stability speed with eyes closed (mm/s)	14.66	7.23-19.62	14.55±3.5	10.76	7.61-27.92	12.6±4.6	0.012*[2]
Stability acquisition time with eyes closed (sec)	30	30-30	30±0	30	30-30	30±0	1[2]
Left leg area (mm^2)	759.71	268.95-7981.76	1016.46±1305.8	669.495	340.98-2919.27	996.43±686.1	0.589[2]
Left leg acquisition time (sec)	30	30-30	30±0	30	30-30	30±0	1[2]
Right leg area (mm^2)	592.43	285.68-9162.19	953.5±1524.2	635.295	295.47-2696.7	913.37±609.1	0.404[2]
Right leg acquisition time (sec)	30	30-30	30±0	30	30-30	30±0	1[2]
Walking step count	70	52-100	70.94±10.5	77	45-112	76.35±14.3	0.085[2]
Walking gain time (sec)	50	50-50	50±0	50	50-50	50±0	1[2]
Stability limits area (mm^2)	68847.335	29056.79-104652.33	69119.32±17746.3	70780.505	35121.56-124693.69	75369.36±23720	0.223[1]

[1]: Independent samples t test; [2]: Mann Whitney U test; *: p<0.05.

Table 3. Comparison of spatio-temporal parameters of the participants

Parameters	IS Patients (n=34)			Controls (n=34)			p-value
	Median	Min-Maks	Mean±SD	Median	Min-Maks	Mean±SD	
Forefoot loading-left foot (%)	104	90-112	103.26±4.3	105	99-113	105.35±3.7	0.07[2]
Heel loading-left foot (%)	77.5	70-86	77.59±4.1	79	68-88	78.65±4.9	0.337[1]
Forefoot loading-right foot (%)	105	92-115	104.56±4	107.5	97-121	107.41±5	0.006**[2]
Heel loading-right foot (%)	78	60-85	77.94±4.9	79	68-96	78.56±5.9	0.868[2]
Step time-left (sec)	0.62	0.49-0,76	0.63±0.1	0.59	0.49-0.69	0.59±0.1	0.007**[1]
Step time-right (sec)	0.625	0.47-0,74	0.62±0.1	0.585	0.49-0.69	0.59±0.1	0.005**[1]
Walking cycle duration (sec)	1.25	0.96-1,49	1.25±0.1	1.17	0.98-1.36	1.17±0.1	0,008**[1]
Cadence (steps/min)	98.5	81-117	98.82±9.8	103	88-122	103.21±8.8	0.057[1]
Walking speed (m/s)	3.2	2-4.4	3.25±0.4	3.6	2.9-5.5	3.71±0.5	0.0003**[2]

[1]: Independent samples t test; [2]: Mann Whitney U test; *: p<0.05; **: p<0.01

45) years, and the mean age of the control group (23 female and 11 male) was 23 (22-47) 9 years (p=0.047). All groups had a female predominance. However, there was no statistically significant difference between the IS group and the control group in terms of gender, body mass index, employment status, sports activity, smoking habitus, dominant hand, family history of scoliosis, back pain, foot number, VAS score, and lower extremity length difference findings (p>0.05).

Table 2 lists the results of the balance analysis of the study population. When the balance parameters of the participants were examined under EO and EC conditions, it was revealed that stability speed with EC was significantly higher in the IS group compared to controls (14.55±3.5 mm/s and 12.6±4.6 mm/s, respectively, p=0.012). On the other hand, no statistically significant differences were

found between the scoliosis group and the control group in terms of other balance parameters.

Table 3 presents the comparisons of the right- and left-foot loading measurement values, cadence, walking speed, and step duration of the participants. In the forefoot loading measurements comparison, it was observed that the maximum right-foot loading value of the control group was significantly higher than the scoliosis group (107.41±5 vs. 104.56±4, p=0.006), whereas no significant difference was observed in the left foot. Similarly, a higher walking speed was recorded in the control group compared to the IS group (3.71±0.5 m/s and 3.25±0.4, respectively, p=0.0003). On the contrary, a higher step duration was found in the IS group compared to the control group in the right and left foot of the study subjects (0.62±0.1 sec and 0.59±0.1 sec, p=0.005 vs. 0.63±0.1 sec and 0.59±0.1 sec, respectively, p=0.007). Moreover, the evaluation of the walking cycle duration of the participants showed that the walking cycle duration was also significantly higher in patients with scoliosis compared to healthy subjects (1.25±0.1 sec and 1.17±0.1 sec, respectively, p=0.008). We also analyzed the cadence and observed that there were no significant differences for walking cadence (p>0.05).

DISCUSSION

To our knowledge, this study is the first to evaluate balance and walking parameters in adults with IS using current quantitative analysis. In the study, it was demonstrated that there were differences in the balance and walking analyses between the patients with IS and healthy controls. Balance and walking were affected in individuals with scoliosis, and patients with scoliosis had poorer balance and walking skills compared to healthy individuals.

The spine is extremely important in ensuring efficient human movement, primarily by providing the balance element that the body requires while it is moving. In this state, the spine function and the walking function are inseparable working mechanisms. Therefore, in recent years, walking and balance analysis studies have increasingly begun to be applied to spinal diseases. In our study, in the balance parameters obtained with the force platform, the stability speed with EC was significantly higher in the IS group compared to the control group, indicating that the balance of patients with IS is weaker than that of healthy individuals. In addition, although the stability area evaluated with EO and EC, and the stability speed evaluated with EO in the IS group were not statistically significant, they were numerically higher than those of healthy individuals, indicating that balance skills are also weaker in individuals with scoliosis.

Similarly, the fact that the IS group approached the stability limits less and that the stability limits area of the scoliosis group was numerically lower than that of healthy individuals, although not statistically significant, again shows the weak balance skills in individuals with scoliosis. Yamada et al.[9] found a positive correlation between scoliosis progression rate and balance disorder in individuals with AIS. Poor body segmental alignment as a result of IS has been associated with a lateral displacement of the body's center of mass, affecting the body's dynamic balance during walking. IS has also been shown to affect gait mechanics, including temporal distance parameters, ground reaction forces, and lower extremity joint kinematics.[10] Such kinematic changes are thought to be a compensatory mechanism to maintain whole-body balance during walking.[11]

Mahaudens et al.[12] reported that 6 months of corset use in the treatment of patients with idiopathic scoliosis reduced the curvature by 25% and that the patients' walking data improved with the correction of the curvature. In our study, in the gait analysis, it was observed that the cadence and walking speed decreased in the IS group and the walking cycle time was prolonged due to this decrease. Chen et al.[13] and Giakas et al.[14] also demonstrated the existence of a decrease in cadence and step length in their studies. In another study, Yang et al.[15] found no statistically significant difference in walking speed, step length, and cadence in scoliosis patients, contrary to expectations. Although the results differ, a meta-analysis study by Mahaudens et al.[16] reported that scoliosis shortens the duration of the stance phase in walking data, prolongs the double stance phase, and slows down walking speed. Considering that balance is also impaired in scoliosis cases, it has been suggested that changes in walking data should be evaluated from this perspective.

The present study has some limitations. One of the limitations of the study was that other external forces and kinematics, such as the loads at the cervico-thoracic and lumbosacral joints, were not assessed, which might have provided a better understanding of the role of balance and gait in IS. Another limitation of our study was the relatively small sample size. So, future large, prospective, and randomized clinical trials are required to confirm our results.

Conclusion

Adult IS is associated with poor balance and walking skills compared to healthy individuals. This demonstrates that patients with scoliosis should be evaluated in terms of static and dynamic balance and walking, and should be followed up regularly.

Ethics Committee Approval

The study was approved by the Bilkent City Hospital Ethics Committee (Date: 24.01.2024, Decision No: E2-24-6163).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: T.O.C., E.Y.; Design: T.O.C., E.Y.; Supervision: T.O.Y., E.Y., S.S.K., H.B.S.; Fundings: T.O.Y., E.Y., S.S.K.,

H.B.S., N.O.K.G.; Materials: T.O.C., S.S.K., N.O.K.G.; Data: T.O:C., S.S.K., H.B.S.; Analysis: T.O.C., E.Y., H.B.S.; Literature search: T.O.Y., E.Y., S.S.K., H.B.S.; Writing: T.O.Y., E.Y., S.S.K., H.B.S.; Critical revision: T.O.Y., E.Y., S.S.K., H.B.S., N.O.K.G.

Conflict of Interest

None declared.

REFERENCES

1. Weinstein SL, Dolan LA, Cheng JC, Danielsson A, Morcuende JA. Adolescent idiopathic scoliosis. Lancet 2008;371:1527–37. [CrossRef]
2. Atalay B, Yaltırık K. Adolesan idiopatik skolyoz epidemiyolojisi ve patogenezi. In: Akçalı Ö, ediyor. Adölesan İdiopatik Skolyoz. Ankara: Türk Omurga Derneği Yayınları; 2017. p.17–23.
3. Parent S, Newton PO, Wenger DR. Adolescent idiopathic scoliosis: Etiology, anatomy, natural history, and bracing. Instr Course Lect 2005;54:529–36.
4. Helenius I, Remes V, Lamberg T, Schlenzka D, Poussa M. Long-term health-related quality of life after surgery for adolescent idiopathic scoliosis and spondylolisthesis. J Bone Joint Surg Am 2008;90:1231–9. [CrossRef]
5. Tan KJ, Moe MM, Vaithinathan R, Wong HK. Curve progression in idiopathic scoliosis: Follow-up study to skeletal maturity. Spine (Phila Pa 1976) 2009;34:697–700. [CrossRef]
6. Shahidi B, Yoo A, Farnsworth C, Newton PO, Ward SR. Paraspinal muscle morphology and composition in adolescent idiopathic scoliosis: A histological analysis. JOR Spine 2021;4:e1169. [CrossRef]
7. Martínez-Llorens J, Ramírez M, Colomina MJ, Bagó J, Molina A, Cáceres E, et al. Muscle dysfunction and exercise limitation in adolescent idiopathic scoliosis. Eur Respir J 2010;36:393–400. [CrossRef]
8. Cobb JR. Outline for the study of scoliosis. In: Edwards JW, Arbor A, editors. AAOS, Instructional Course Lectures. Rosemont: American Academy of Orthopaedic Surgeons; 1948. p. 261–75.
9. Yamada K, Ikata T, Yamamoto H, Nakagawa Y, Tanaka H. Equilibrium function in scoliosis and active corrective plaster jacket for the treatment. Tokushima J Exp Med 1969;16:1–7.
10. Ohashi M, Watanabe K, Hirano T, Hasegawa K, Katsumi K, Shoji H, et al. Long-term impacts of brace treatment for adolescent idiopathic scoliosis on body composition, paraspinal muscle morphology, and bone mineral density. Spine (Phila Pa 1976) 2019;44:E1075–82. [CrossRef]
11. Smit TH. Adolescent idiopathic scoliosis: The mechanobiology of differential growth. JOR Spine 2020;3:e1115. [CrossRef]
12. Mahaudens P, Raison M, Banse X, Mousny M, Detrembleur C. Effect of long-term orthotic treatment on gait biomechanics in adolescent idiopathic scoliosis. Spine J 2014;14:1510–9. [CrossRef]
13. Chen PQ, Wang JL, Tsuang YH, Liao TL, Huang PI, Hang YS. The postural stability control and gait pattern of idiopathic scoliosis adolescents. Clin Biomech (Bristol, Avon) 1998;13:S52–8. [CrossRef]
14. Giakas G, Baltzopoulos V, Dangerfield PH, Dorgan JC, Dalmira S. Comparison of gait patterns between healthy and scoliotic patients using time and frequency domain analysis of ground reaction forces. Spine (Phila Pa 1976) 1996;21:2235–42. [CrossRef]
15. Yang JH, Suh SW, Sung PS, Park WH. Asymmetrical gait in adolescents with idiopathic scoliosis. Eur Spine J 2013;22:2407–13. [CrossRef]
16. Mahaudens P, Banse X, Mousny M, Detrembleur C. Gait in adolescent idiopathic scoliosis: kinematics and electromyographic analysis. Eur Spine J 2009;18:512–21. [CrossRef]

İdiyopatik Skolyozda Denge ve Yürümenin Değerlendirilmesi

Amaç: İdiyopatik skolyoz (İS), koronal düzlemde 10 dereceden fazla lateral sapma olarak radyografik olarak tanımlanan, sagital ve transvers düzlem değişiklikleriyle kendini gösteren, omurganın üç boyutlu bir deformitesidir. Denge ve yürüme günlük yaşamın en yaygın aktiviteleridir. Çalışmamızda, ilerleme riski azalmış ve eğrilikleri genellikle stabil olan İS bireylerinde eğriliğin denge ve yürüyüş üzerindeki etkisini analiz etmeyi amaçladık.

Gereç ve Yöntem: Çalışmaya 34 İS hastası ve 34 sağlıklı birey alındı. Tüm katılımcılara sosyo-demografik ve fiziksel özellikleri soruldu. Denge parametreleri, yerleşik kuvvet sensörleri ve tutacakları olan Huber 360 adlı çok eksenli, motorlu bir platform sistemi kullanılarak kaydedildi. Katılımcıların yürüme analizi, Zebris FDM tip 3 (Zebris Medical GmbH, Almanya) yürüme platformu kullanılarak gerçekleştirildi.

Bulgular: Yürüme parametreleri incelendiğinde, adım atma süresi ve yürüme döngüsü süresi İS grubunda kontrol grubuna göre anlamlı olarak yüksekti (sırasıyla, p=0.007 ve p=0.008). Buna karşın, kontrol grubunun sağ ayak yükleme yanıtı ve yürüme hızı skolyoz grubuna göre anlamlı olarak yüksekti (sırasıyla, p=0.006 ve p=0.0003). Gözler kapalıyken stabilite hızı İS grubunda kontrol grubuna göre anlamlı olarak yüksekti (sırasıyla, 14.55±3.5 mm/s ve 12.6±4.6 mm/s, p=0.012). Diğer denge ve yürüyüş özellikleri açısından gruplar arasında anlamlı bir fark gözlenmedi.

Sonuç: Bu çalışma, İS hastalarında denge ve yürüyüşün etkilendiğini ve skolyozlu bireylerin sağlıklı bireylere göre zayıf denge ve yürüme becerilerine sahip olduğunu ortaya koymuştur. Bu nedenle skolyoz rehabilitasyonunda omurga eğriliklerinden kaynaklanabilecek denge ve yürüyüş sorunlarının mutlaka dikkate alınması gerekmektedir.

Anahtar Sözcükler: Denge; idiyopatik skolyoz; yürüyüş analizi.

SCIE DOI: 10.14744/scie.2024.67878
South. Clin. Ist. Euras. 2024;35(3):219-223

Original Article

Perioperative and 90-day Clinical and Radiological Results of Endovascular Treatment of Symptomatic Basilar Artery Stenosis

Ayşenur Önalan, Erdem Gürkaş

Department of Neurology, University of Health Sciences, Kartal Dr Lütfi Kırdar City Hospital, İstanbul, Türkiye

Submitted: 13.08.2024
Revised: 14.08.2024
Accepted: 19.08.2024

Correspondence: Ayşenur Önalan, Department of Neurology, University of Health Sciences, Kartal Dr Lütfi Kırdar City Hospital, İstanbul, Türkiye

E-mail: draysenurkaymaz@gmail.com

Keywords: Angioplasty; atherosclerosis; basilar artery; ischemic stroke; stenting.

ABSTRACT

Objective: The aim of our study is to evaluate the safety and effectiveness of basilar artery stenosis cases in which we applied endovascular treatment due to recurrent stroke under optimal medical management.

Methods: Patients with severe basilar artery stenosis (70-99%) due to atherosclerosis, who had transient ischemic attack or ischemic stroke despite optimal medical management, and who underwent endovascular treatment were retrospectively examined. The primary outcomes were ischemic or hemorrhagic stroke within 90 days after stent deployment and death related to the endovascular procedure during hospitalization. Secondary outcomes were successful revascularization (residual stenosis <30%) and procedure-related complications.

Results: The median age of the 19 patients included in the study was 65 years (IQR, 53-68.5), and 74% were male. The most common area of stenosis was the proximal third of the basilar artery (63%), followed by the middle third (37%). According to the Mori classification, the most common lesion type was MORI A (53%), followed by MORI B (42%). While the stenosis rate before endovascular treatment was 85% (IQR, 80-90%), the median residual stenosis rate after successful stenting was 16% (IQR, 11-20). Treatment was successful in 18 of 19 patients (95%), and only 1 patient died due to basilar artery perforation during the procedure. The mortality rate was 5% (1/19). Asymptomatic stent restenosis was observed in one patient who underwent balloon angioplasty. During this period, no recurrent ischemic stroke was observed in any patient. The 3rd month mRS score was 1 (IQR, 0-1.5).

Conclusion: The endovascular treatment of basilar artery stenosis appears to be safe and effective in experienced centers, despite the potential risk of perioperative complications. Randomized controlled trials are necessary to validate the efficacy and safety outcomes of balloon angioplasty and stenting.

INTRODUCTION

Posterior circulation ischemia (PCI) constitutes around 20% of all cases of ischemic strokes and is often due to large vessel atherosclerosis.[1] Furthermore, the risk of recurrence of stroke or transient ischemic attack (TIA) within 90 days due to basilar artery or intracranial vertebral stenosis is significantly higher than in patients without stenosis.[2,3] Due to the high risk of early recurrence, this situation, where medical treatment is inadequate, has prompted the consideration of endovascular treatments. Comprehensive international studies have demonstrated the benefit of endarterectomy in symptomatic carotid stenosis and stent deployment in selected patients.[4,5] However, knowledge about the optimal management of basilar artery stenosis is insufficient.

The current treatment of basilar artery stenosis (BAS) consists of best medical therapy (BMT), which includes dual antiplatelet therapy and close control of risk factors, and endovascular percutaneous transluminal angioplasty and/or stenting (PTAS).[6]

SAMMPRIS (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke, n=451), VISSIT (Vitesse Intracranial Stent Study for Ischemic Stroke Therapy; n=112), and a single-center randomized controlled trial (RCT) in China (n=70) compared PTAS and BMT in patients with high (>70%) intracranial stenosis who had a stroke or TIA. In the 3 RCTs, 30-day stroke and death

rates were revealed to be higher in the PTAS group.[7-9] These studies mostly included patients with intracranial stenosis in the anterior system.

Nevertheless, the presence of severe symptomatic BAS and acute basilar artery occlusion (BAO) is associated with increased death rates, despite the implementation of BMT.[10]

MATERIALS AND METHODS

This study, collected prospectively and analyzed retrospectively, was conducted by Kartal Dr. Lütfi Kırdar City Hospital and approved by the Institutional Ethics Committee. Prior to the interventional procedure, written informed consent was obtained from all patients and/or their relatives.

Patients over 18 years of age who had a stroke or TIA that did not cause serious disability in the basilar artery vascular area within 90 days under BMT between February 2020 and January 2024 were retrospectively screened. According to the North American Symptomatic Carotid Endarterectomy Study (NASCET) standard, patients with severe stenosis of the basilar artery (stenosis ≥70%) on CTA or MRA whose stenosis was confirmed by DSA were included in the study.[11] Other inclusion criteria were pre-procedure modified Rankin Score (mRS) <3 and at least one atherosclerotic risk factor (hypertension, diabetes mellitus, hyperlipidemia, and smoking). Exclusion criteria included 1-Non-atherosclerotic stenosis, presence of thromboembolic or non-hemodynamic stroke symptoms (including perforator strokes), intracranial hemorrhage in the stenotic artery region within 3-6 weeks, 4-Simultaneous presence of an intracranial tumor, aneurysm, and cerebral arteriovenous malformation, 5-Concurrent ≥50% vertebral artery or extracranial carotid stenosis, 6-Documented contraindication to heparin, aspirin, clopidogrel, anesthetic, and contrast media, 7- Platelet count <100,000; international normalized ratio (INR) >1.5 (irreversible) and life expectancy <1 year due to uncorrectable bleeding diathesis and other medical conditions.

BMT was designed in accordance with the SAMPRISS study.[7] Pre-procedure, acetylsalicylic acid and clopidogrel resistance were requested for all patients.

The basilar artery was anatomically partitioned into three distinct segments: distal segment, middle segment, and proximal segment, utilizing the anterior inferior cerebellar artery and superior cerebellar artery.[12] In addition, based on the Mori classification, Mori A refers to a lesion that is small and concentric with a length of less than 5 mm. Mori B is a tubular or very eccentric lesion with a length ranging from 5 to 10 mm. The lesion Mori C, characterized by diffuseness and a length exceeding 10 mm, was classified.[13]

Successful stent deployment involves ensuring that the target lesion is fully covered, achieving less than 30% residual stenosis or reducing stenosis by more than 50%. However, since complete dilatation of the basilar artery to 100% is not recommended, a small residual stenosis is aimed for. Restenosis was described as ≥50% BAS detected at the latest available follow-up in individuals who underwent successful intervention.[10,14]

The endovascular therapy choices were balloon-mounted stenting, angioplasty alone, and angioplasty with a self-expanding stent inserted thereafter. The clinical and endovascular treatment processes were both carried out by two interventional neurologists. Clinical complications such as stroke, TIA, and mortality were documented after endovascular procedures. Following the treatment, a regimen of dual antiplatelet therapy was maintained for a minimum duration of 3 months. The National Institutes of Health Stroke Scale (NIHSS) and mRS were used for clinical assessment. Stenosis was identified by measuring distal normal vessel diameter as defined by the North American Symptomatic Carotid Endarterectomy Trial (NASCET). Self-expandable stenting Neuroform stent (Stryker, Kalamazoo, Michigan, USA) was utilized.

Primary outcomes were ischemic or hemorrhagic stroke after stent deployment within 30 days, TIA, and death from the endovascular procedure during hospitalization.[15] Secondary outcomes were successful revascularization (residual stenosis <30%) and peri-procedural complications such as vessel dissection and acute stent thrombosis after stenting.

Statistical Analysis

Continuous variables were presented as the median and interquartile range (IQR). Categorical variables were offered as frequency (n) and percentage (%). The statistical analyses were conducted using IBM SPSS Statistics Software 21 (SPSS Inc., Chicago, IL, USA).

RESULTS

Nineteen patients were included in the study. The median age of the participants was 65 years (IQR, 53–68.5), and 74% were male. The most typical comorbidities were arterial hypertension (74%), dyslipidemia (16%), diabetes mellitus (65%), and coronary artery disease (11%). The most common area of stenosis was the proximal third of the BA (63%), followed by the middle third (37%).

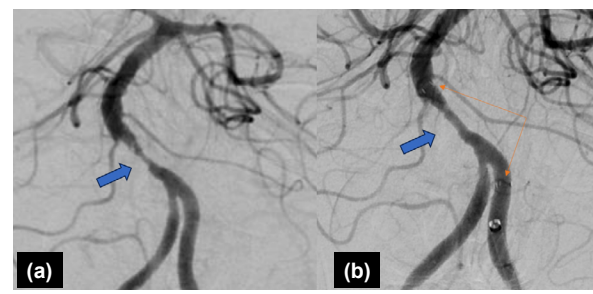

Figure 1. Angiographic imaging findings of a patient with basilar artery proximal stenosis before and after treatment. **(a)** Basilar artery angiography in frontal view before the procedure, high grade ostial stenosis in the proximal segment of basilar artery (blue arrow). **(b)** After primary stenting with a balloon-mounted stent, control angiography imaging confirms adequate restoration of the vessel lumen.

Table 1. Patients' clinical data and imaging features

No	Gender	Age	Location Class.	MORI (%)	Pre-stenosis methods	Interventional (%)	Post-stenosis	Complication	Re-stenozis
1	M	74	prx	2	80	PTA+Stenting	10	no	no
2	M	65	mid	2	90	PTA+Stenting	10	no	no
3	M	67	Prx	2	90	PTA+Stenting	10	no	no
4	M	76	prx	1	85	PTA+Stenting	15	no	no
5	F	68	mid	1	90	PTA+Stenting	20	no	no
6	M	54	Prx	2	90	PTA+Stenting	10	no	no
7	M	68	Prx	2	80	PTA+Stenting	20	no	no
8	M	69	Prx	1	80	PTA+Stenting	20	no	no
9	M	56	Prx	2	90	PTA+Stenting	20	no	no
10	M	36	Prx	1	80	PTA+Stenting	20	no	no
11	F	65	Prx	2	80	PTA	25	no	yes
12	M	52	mid	2	80	PTA+Stenting	15	dissection	no
13	M	46	mid	1	90	PTA+Stenting	20	no	no
14	M	63	mid	2	85	PTA+Stenting	10	no	no
15	F	50	Prx	1	75	PTA+Stenting	20	no	no
16	F	71	prx	1	85	PTA+Stenting	20	dissection	no
17	F	72	mid	2	90	X	n	perforation	X
18	M	46	prx	1	90	PTA+Stenting	10	no	no
19	F	64	mid	2	75	PTA+Stenting	20	no	no

M: Male; F: Female; Class: Classification; PTA: Percutaneous transluminal angioplasty; mid: Middle; Prx: Proximal; Dist: Distal.

Table 2. Three months post procedure clinical and imaging outcome

	Total n:19
mRS (n,%)	1 (IQR, 0-1.5)
0-2 16	
3-4 2	
5 locked-in syndrome	0
6 (death)	1
Imaging study at 3 months (n, %)	
Stent restenosis (>30%)	1
Stent occlusion	0

mRS: Modified Rankin Scale; IQR: Interquartile range.

Eighteen (95%) patients underwent balloon angioplasty, and 17 (89%) patients received stenting. According to the Mori classification, the most common lesion type was MORI A, with 53%, followed by MORI B, with a frequency of 42%. Patients' data, as well as clinical and technical results, are summarized in Table 1.

Before stenting, the rate of stenosis was 85% (IQR, 80–90%), while after successful stent deployment, residual stenosis of 16% (IQR, 11–20%) was observed. Out of the 19 patients who had the procedure, successful stent placement was performed on 18 of them (95%) (Figure 1a-1b). Dissection developed in two patients during the PTA procedure (Case 12, 16). In one of these patients (Case 12), an ischemic stroke attributed to perforator injury occurred within 24 hours after endovascular treatment. Another patient remained asymptomatic (Case 16). During the PTA procedure, the patient experienced vascular perforation due to microwire, resulting in diffuse ischemia and subsequent death during hospitalization (Case 17). The mortality rate was 5% (1/19).

The duration of observation for the surviving patients was measured as the median follow-up period of 12 months (IQR, 7–24). Stent restenosis was observed in one patient who only underwent the PTA procedure due to severe elongation of the vessel (Case 11). However, no intervention was carried out due to its asymptomatic status. The 3rd-month mRS score was 1 (IQR, 0–1.5) (Table 2).

DISCUSSION

The purpose of this study is to review our experiences on the safety and clinical outcomes of endovascular interventions in severe basilar artery stenosis. Our success rate in performing PTA or stenting on our patients was 95% (18/19). The rate of peri-procedural complications was 16% (3/19), with a symptomatic complication rate of 11% (2/19). Of these complications, two were dissections and one was vessel perforation. While one of the patients who developed dissection did not have any symptoms, the other patient developed ischemia as a result of perforator injury. The patient who developed perforation died during hospitalization. During follow-up, asymptomatic restenosis was observed in one patient. No patient had recurrent stroke.

Two large studies on the subject, the SAMMPRIS and VISSIT studies, distinctly showed the superiority of aggres-

sive medical treatment over PTAS in patients with stenosis of intracranial arteries.[7,9] In a subgroup analysis of patients with basilar artery stenosis from the SAMMPRIS trial, the endovascular treatment group had a higher primary endpoint of stroke or death than the aggressive medical treatment group (10%, n=51 vs. 25% in the PTAS group, n=49).[7,14] In the group of 97 patients with vertebrobasilar stenosis who underwent stenting by Liu et al.,[15] ischemic stroke occurred in 3.1% (3/97) and transient ischemic attack occurred in four patients (4.1%, 4/97). In the study by Bai et al.,[16] the perioperative ischemic stroke or death rate was 14.3% (13/92). When examining the primary outcome of our study, we observed dissection-related stroke in 5% (1/19) of patients and death during hospitalization in 5% (1/19) of patients.

Our study had a peri-procedural complication rate of 16% (3/19) and a symptomatic complication rate of 11% (2/19). In the study by Maier et al.,[14] nine (11.4%) peri-procedural events occurred in the endovascular treatment group. Six of these patients (7.5%) were diagnosed with ischemic stroke after the procedure, and the others had no clinically significant events.[14] It is thought that the selection of patients with good collateral circulation, strict implementation of perioperative management, performance of the procedure by experienced operators, and correct material choices contribute to the increase in treatment success.

In our study, while the stenosis rate before the procedure was 85% (IQR, 80–90%), the residual stenosis rate after successful stent placement was 16% (IQR, 11–20%). Looking at the literature, this rate varies depending on the type of stent used and the type of lesion.[13-17] In the meta-analysis conducted by Palmisciano et al.,[17] median BAS at baseline was 81% (range, 53–99%) (data available in 659 cases), while median BAS post-intervention was 13% (0–75%). The cause of this residual stenosis can be explained by the fact that the basilar artery is more tortuous in some patients, the perforators originate near the stenotic segment, and operators are forced to perform submaximal dilatation with small-caliber balloons.

Perforating strokes (PS) are frequent complications of intracranial endovascular management. Particularly, the basilar artery is one of the regions where perforator arteries are most frequently located. It has been discussed in the literature that this may result from migration of atherosclerotic debris or "snowplowing" on the perforator outlets during angioplasty or stent deployment. The SAMMPRIS trial reported a 16% occurrence rate of PS in the basilar artery.[7] In the study by Liu et al.,[15] which included 102 patients with vertebrobasilar artery stenosis, three dissection cases were observed, and all of them were patients with basilar stenosis. In our study, PS was observed in one (5%) of the patients who developed dissection, and it was observed to be low compared to the literature.

In BA pathologies, proximal and mid-segment occlusions are typically associated with atherosclerosis, while occlusion of the distal one-third is often caused by emboli.[10,18] In our patient group, stenosis was observed in the proximal BA (68%) and in the middle segment of the BA (32%), consistent with the literature. At the same time, the middle segment of the basilar artery (BA) is the segment that affects the clinic the most. This is mainly because the perforators are mostly located here.

During follow-up, stent restenosis was observed in one patient (5%), but no intervention was performed due to the patient being asymptomatic. When looking at the literature, Hatano et al.[19] reported a stent restenosis rate of 27% (4/15) and 7% (1/15) cases of stent thrombosis. In the study conducted by Machado et al.,[10] restenosis occurred in one out of 14 patients, while stent thrombosis developed in another patient. The reason why our results are more positive than the literature may be appropriate patient selection and the use of fit caliber balloon and stent.

In our study, no recurrent stroke occurred in the patients during the follow-up period. According to the literature, it has been reported that in patients with vertebrobasilar stenosis under intensive medical treatment, the annual rates of cerebrovascular events are around 10-15%.[10] Therefore, we believe that endovascular treatments will be prominent, especially in posterior system strokes, with the correct patient selection and intervention by experienced operators.

One of the limitations of our study is that it is retrospective, which may lead to potential selection bias since the enrolled patients were not randomized. Secondly, our small number of patients and relatively short follow-up period limit its value. The third limitation is the use of a single type of stent and the absence of comparison. Therefore, randomized, prospective, and large-sample studies are needed to provide stronger evidence about efficacy and safety results.

Conclusion

Endovascular treatment has the advantage of lowering the long-term risk of fatal and severely incapacitating stroke in patients with severe basilar artery stenosis, even though its superiority has not yet been proven in the literature. If perioperative complications can be minimized, we believe that basilar artery stenting may be beneficial for patients with severe basilar artery stenosis.

Ethics Committee Approval

The study was approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 26.07.2021, Decision No: 20211010.9916139).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: A.Ö.; Design: A.Ö., E.G.; Supervision: E.G.; Fundings: E.G.; Materials: A.Ö.; Data: A.Ö., E.G.; Analysis: A.Ö., E.G.; Literature search: A.Ö.; Writing: A.Ö.; Critical revision: E.G.

Conflict of Interest

None declared.

REFERENCES

1. Markus HS, van der Worp HB, Rothwell PM. Posterior circulation ischaemic stroke and transient ischaemic attack: Diagnosis, investigation, and secondary prevention. Lancet Neurol 2013;12:989–98. [CrossRef]
2. Marquardt L, Kuker W, Chandratheva A, Geraghty O, Rothwell PM. Incidence and prognosis of > or = 50% symptomatic vertebral or basilar artery stenosis: Prospective population-based study. Brain 2009;132:982–8. [CrossRef]
3. Stayman AN, Nogueira RG, Gupta R. A systematic review of stenting and angioplasty of symptomatic extracranial vertebral artery stenosis. Stroke 2011;42:2212–6. [CrossRef]
4. Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, et al; Carotid Endarterectomy Trialists' Collaboration. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet 2003;361:107–16. [CrossRef]
5. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, et al. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline from the American Heart Association/American Stroke Association. Stroke 2021;52:e364–467. [CrossRef]
6. Markus HS, Michel P. Treatment of posterior circulation stroke: Acute management and secondary prevention. Int J Stroke 2022;17:723–32. [CrossRef]
7. Derdeyn CP, Chimowitz MI, Lynn MJ, Fiorella D, Turan TN, Janis LS, et al; Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis Trial Investigators. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): The final results of a randomised trial. Lancet 2014;383:333–41. [CrossRef]
8. Miao Z, Jiang L, Wu H, Bao Y, Jiao L, Li S, et al. Randomized controlled trial of symptomatic middle cerebral artery stenosis: endovascular versus medical therapy in a Chinese population. Stroke 2012;43:3284–90. [CrossRef]
9. Zaidat OO, Fitzsimmons BF, Woodward BK, Wang Z, Killer-Oberpfalzer M, Wakhloo A, et al; VISSIT Trial Investigators. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: The VISSIT randomized clinical trial. JAMA 2015;313:1240–8. [CrossRef]
10. Machado M, Borges de Almeida G, Sequeira M, Pedro F, Fior A, Carvalho R, et al. Percutaneous transluminal angioplasty and stenting in acute stroke caused by basilar artery steno-occlusive disease: The experience of a single stroke centre. Interv Neuroradiol 2022;28:547–55. [CrossRef]
11. North American Symptomatic Carotid Endarterectomy Trial Collaborators; Barnett HJM, Taylor DW, Haynes RB, Sackett DL, Peerless SJ, Ferguson GG, et al. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991;325:445–53. [CrossRef]
12. Tang L, Wang L, Li C, Hu P, Jia Y, Wang G, et al. Treatment of basilar artery stenosis with an Apollo balloon-expandable stent: A single-centre experience with 61 consecutive cases. Acta Neurol Belg 2021;121:1423–7. [CrossRef]
13. Mori T, Mori K, Fukuoka M, Arisawa M, Honda S. Percutaneous transluminal cerebral angioplasty: Serial angiographic follow-up after successful dilatation. Neuroradiology 1997;39:111–6. [CrossRef]
14. Maier IL, Karch A, Lipke C, Behme D, Mpotsaris A, Kabbasch C, et al. Transluminal angioplasty and stenting versus conservative treatment in patients with symptomatic basilar artery stenosis: Perspective for future clinical trials. Clin Neuroradiol 2018;28:33–8. [CrossRef]
15. Liu L, Zhao X, Mo D, Ma N, Gao F, Miao Z. Stenting for symptomatic intracranial vertebrobasilar artery stenosis: 30-day results in a high-volume stroke center. Clin Neurol Neurosurg 2016;143:132–8. [CrossRef]
16. Bai WX, Gao BL, Li TX, Wang ZL, Cai DY, Zhu LF, et al. Wingspan stenting can effectively prevent long-term strokes for patients with severe symptomatic atherosclerotic basilar stenosis. Interv Neuroradiol 2016;22:318–24. [CrossRef]
17. Palmisciano P, Hoz SS, Algburi HA, Ventre G, Street S, Agyeman N, et al. Percutaneous transluminal angioplasty and/or stenting for the treatment of basilar artery stenosis: A systematic review and meta-analysis. Neuroradiology 2023;65:985–1000. [CrossRef]
18. Kim YW, Hong JM, Park DG, Choi JW, Kang DH, Kim YS, et al. Effect of intracranial atherosclerotic disease on endovascular treatment for patients with acute vertebrobasilar occlusion. AJNR Am J Neuroradiol 2016;37:2072–8. [CrossRef]
19. Hatano T, Tsukahara T, Ogino E, Aoyama T, Nakakuki T, Murakami M. Stenting for vertebrobasilar artery stenosis. Acta Neurochir Suppl 2005;94:137–41. [CrossRef]

Semptomatik Baziler Arter Stenozunun Endovasküler Tedavisinin Perioperatif ve 90 Günlük Klinik ve Radyolojik Sonuçları

Amaç: Çalışmamızın amacı, en iyi medikal tedavi altında tekrarlayan inme nedeni ile endovasküler tedavi uyguladığımız baziler arter stenozu olgularımızın tedavi güvenliği ve etkinliğini değerlendirmektir.

Gereç ve Yöntem: Ateroskleroza bağlı şiddetli baziler arter stenozu (%70-99) olan, en iyi medikal tedavi altında geçici iskemik atak veya iskemik inme geçiren ve endovasküler tedavi uygulanan hastalar geriye dönük incelendi. Birincil sonuçlar, stent yerleştirilmesinden sonra 90 gün içinde iskemik veya hemorajik inme ve hastanede yatış sırasında endovasküler prosedürden kaynaklanan ölümdü. İkincil sonuçlar başarılı revaskülarizasyon (rezidüel stenoz <%30) ve işleme bağlı komplikasyonlar olarak belirlendi.

Bulgular: Hastaların 19'unun yaş ortalaması 65 (IQR, 53-68.5) olup %74'ü erkekti. Stenozun en fazla görüldüğü alan BA'nın proksimal üçte birlik kısmı (%63) olurken, bunu orta üçte birlik kısım (%37) takip etti. Mori sınıflamasına göre lezyon tipi en sık %53 ile Mori A ve 42% Mori B ile idi. Stent öncesi darlık oranı ortalaması %85 (IQR, 80-90%), iken başarılı stent yerleştirme sonrası ortalama %16 (IQR, 11-20) rezidüel stenoz izlendi. Çalışmaya alınan 19 hastanın 18'sinde başarılı stent uygulandı (%95). İşlem sırasında 1 hastada damar perforasyonu ve 1 hastada diseksiyona bağlı iskemi gelişti. Mortalite oranı %5 (1/19) idi. PTA yapılan bir hastada asemptomatik stent restenozu izlendi. Bu süreçte hiçbir hastada tekrarlayan iskemik inme görülmedi. Üçüncü ay mRS skoru 1 (IQR, 0-1.5) idi.

Sonuç: Baziler arter stenozunun endovasküler tedavisi potansiyel perioperatif komplikasyon riskleri barındırmakla birlikte tecrübeli merkezlerde güvenli ve etkin tedaviler gibi görünmektedir. Balon anjiyoplasti ve stentlemenin etkinlik ve güvenlik sonuçlarını doğrulamak için randomize kontrollü çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Ateroskleroz; baziler arter; iskemik inme; perkutan anjiyoplasti ve stentleme.

SCIE DOI: 10.14744/scie.2024.82542
South. Clin. Ist. Euras. 2024;35(3):224-229

Original Article

A Study of The Spinal Muscular Atrophy Cohorts in The Eastern Anatolia Region of Türkiye

Oğuzhan Yaralı,[1] Ozge Beyza Gündoğdu Öğütlü,[1] Serdar Sarıtaş,[2] Mustafa Can Güler,[3] Filiz Keskin[2]

[1]Department of Medical Genetics, Erzurum Regional Training and Research Hospital, Erzurum, Türkiye
[2]Department of Pediatric Neurology, Erzurum Regional Training and Research Hospital, Erzurum, Türkiye
[3]Department of Physiology, Faculty of Medicine, Ataturk University, Erzurum, Türkiye

Submitted: 16.05.2024
Revised: 15.08.2024
Accepted: 16.08.2024

Correspondence: Oğuzhan Yaralı, Department of Medical Genetics, Erzurum Regional Training and Research Hospital, Erzurum, Türkiye
E-mail: medikant@gmail.com

Keywords: Alleles; carriers; exon 7; exon 8; genetic cohort; PCR-RFLP; SMA; SMN1; SMN2; Türkiye.

ABSTRACT

Objective: The purpose of this research is to carry out a genetic cohort study of SMA patients in the Eastern Anatolia region of Turkey, investigating the genetic causes of the illness, specifically the impact of the number of SMN1 and SMN2 gene alleles on the course of the disease.

Methods: The Erzurum Medical Faculty of Health Sciences at Erzurum City Hospital gave ethical approval for the study to be conducted. A total of 348 patients with an initial diagnosis of SMA underwent genetic testing. Using the PCR-RFLP approach, deletions of exons 7 and 8 in the SMN1 and SMN2 genes were examined.

Results: In examining the allele counts in the exon 7 and exon 8 regions of the SMN1 and SMN2 genes, 41 patients were found to have no copies of the SMN1 gene (0 alleles), while 112 people were identified as possible carriers. Analysis of the SMN2 gene's allele distribution revealed a substantial relationship between the number of alleles and the clinical severity of the disease.

Conclusion: The number of alleles in the SMN1 and SMN2 genes influences the course of the disease, as demonstrated by the genetic cohort analysis of SMA patients in the Eastern Anatolia region of Turkey presented in this paper. The findings indicate that sex does not influence the frequency of the disease or carrier status, offering significant new insights into the genetic diagnosis and treatment of SMA. The study also emphasizes the importance of establishing local genetic screening programs and counseling services to facilitate early diagnosis and treatment.

INTRODUCTION

Reduced motor neurons in the spinal cord and brainstem nuclei are the result of deletions or mutations in the SMN1 gene, which causes the uncommon autosomal recessive neuromuscular disease known as spinal muscular atrophy (SMA).[1] The currently used classification is shown in Table 1.[2]

The main symptoms of SMA include gastrointestinal issues, hypoventilation, and muscle weakness. However, as life expectancy has grown, more symptoms have been discovered, indicating that low SMN protein levels affect more organ systems. These symptoms include sensory dysfunction, cardiac arrhythmias, vascular issues like distal digital necrosis, decreased bone mineral content, and abnormal glucose metabolism.[3]

The genetic etiology of about 96% of SMA cases is SMN1 deficiency or conversion to SMN2, which usually results in homozygous deletion of exon 7 or both exons 7 and 8 of SMN1 (Figure 1).[4] In type II and type III SMA, there is frequently a gene conversion from SMN1 to SMN2, with an increase in the number of copies of SMN2. In type I SMA, most individuals have a genuine deletion of SMN1. Exon 7 of SMN2 and exon 8 of SMN1 can coexist in hybrid SMN1/SMN2 genes when this conversion isn't complete.[5,6] In 96% of type I, 94% of type II, and 86% of type III SMA patients, homozygous deletions are found through genetic screening. Subtle mutations are more common in those

Figure 1. The phenotype-genotype correlation and genetic basis of spinal muscular atrophy (SMA).

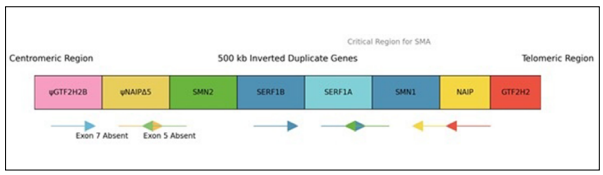

Figure 2. Organization of the 5q13 region on chromosome 5.

with milder manifestations of the disease than in those with more severe symptoms.[7,8]

About 4% of SMA patients have subtle abnormalities on chromosome 5 that result in the deletion of SMN1. Rarely, consanguineous marriages result in children with two mildly different SMN1 alleles. About 2% of SMA instances are de novo mutations, which are frequently the consequence of uneven recombination because of the high instability of the SMA locus at 5q13.[9,10] There are now 108 pathogenic SMN1 variants known to exist. A 4 bp deletion (c.399_402delAGAG) that causes a frameshift in Spaniards, p.Tyr272Cys in Germans, p.Thr274Ile in Poles, and a frameshift mutation p.Gly261fs*269 from an 11 bp duplication (c.770_780dup11) seen in Spanish, French, and US populations are examples of common subtle mutations.[11,12]

The technique of multiple ligation-dependent probe amplification (MLPA) for the SMN1 and SMN2 genes is the gold standard for the genetic diagnosis of SMA.[13] The copy number of SMN2, compound heterozygotes with a single copy of SMN1 and a potential modest SMN1 variant, and healthy heterozygous carriers can all be identified using this technique. Patients with homozygous SMN1 deletions cannot be identified. However, neither the detection of minor mutations in SMN1 (which account for 6% of cases) nor the distinction between persons with one copy of SMN1 on each chromosome 5 and those with two copies are possible with this method (Figure 2).[14] This means that an individual carrying two copies of SMN1 may still be carrying SMA, resulting in a false negative rate of approximately 5%.[15]

Two methods will be used in order to find subtle differences in SMN1: In order to detect SMN1 gene carriers, two methods can be used: (a) long-range PCR of the whole 28 kb SMN1 genomic area using SMN1-specific primers, followed by exon re-amplification and sequencing; or (b) amplification and cloning of SMN cDNA products, followed by PCR.[16] The latter technique additionally finds exonic and intronic variations that could impact splicing.

Generally speaking, an individual with SMA will have fewer severe symptoms the more copies of SMN2 they have. There is a substantial correlation between the severity of SMA symptoms and the number of SMN2 copies. For instance, although 78% of type II patients have three copies, 73% of type I SMA patients have two copies. Three copies are present in roughly 50% of type IIIa patients, 61% of type IIIb patients, and 75% of type IV patients, respectively. The predictive value varies; 20% of type I patients, 78% of type II patients, and 51% of type III patients have three copies of SMN2.[9,17] People with five or more copies of SMN2 may continue to be asymptomatic, whereas having no copies of SMN2 can be deadly.[17] Nevertheless, there is no clear correlation between phenotypic and SMN2 copy number. Variability within families is possible.[18] SMA classification today is based on clinical symptom severity and functional capacity.[19]

MATERIALS AND METHODS

The Ethics Committee of the Medical Faculty at Erzurum University of Health Sciences granted ethical permission for this study (decision number BAEK 2024/03-73). Between 2018 and 2023, we tested 348 patients for genetics at Erzurum City Hospital from pediatric neurology, neonatal clinics, and family practices. Genomic DNA was extracted from 10 milliliters of peripheral blood with informed consent.

Using the primers 5'-AGACTATCAACTTAATTTCT GATCA-3', 5'-CCTTCCTTCTTTGATTTTGTTT-3', 5'-GTAATAACCAAAATGCAATGTGAA-3', and 5'-CTACAACACCTTCTCACAG-3', deletions in SMN1 gene exons 7 and 8 were found by PCR-RFLP. After 35 cycles of PCR, the samples were digested overnight at 37°C using the enzymes DraI and DdeI. Ethidium bromide-stained 4% agarose gels were used for the analysis of the digestive products.

The PCR-RFLP method was used for the SMN2 gene exon 7 p.G287R (c.859G > C) variant. Primers 5'-AGACTATCAACTTAATTTCTGATCA-3' and 5'-ATTTAAGGAATGTGAGCACCTTA-3' were used for 40 cycles. The results were examined on 4% agarose gels following DdeI digestion.

Multiplex PCR was used to analyze NAIP gene deletions in exons 5 and 6 utilizing primers 5'-CATTTGGCATGTTCTTCCAAG-3', 5'-AAAGCCTCTGACGAGAGGATC-3', and 5'-TGCCACTGCCAGGCAATCTAA-3' for exons 5 and 6, respectively, and exon 13 co-amplified using

Table 1. Current SMA classification

SMA Type	Subclassification	Onset	Acquired Motor Milestones	Evolution/Natural History	Prevalent SMN2 Copies
I	Ia (also called type 0)	Prenatal	None	Death within weeks, Contractures, Cardiomyopathy	1
I	Ib	<3 months	Weak or no head control	Feeding and respiratory problems, Linear decline, Death after the second or third year	2
I	Ic	>3 months	Head control	Feeding and respiratory problems, Plateau within the first 2 years	3
II	IIa	>6 months	Sitters	Scoliosis, May lose sitting ability	3
II	IIb	Usually after 12 months	Sitters	Scoliosis, Can stand with support	3
III	IIIa	Between 18 and 36 months	Walks unassisted	Scoliosis, Earlier loss of walking ability	3
III	IIIb	>3 years	Walks unassisted	Later loss of walking ability	3-4
IV	None	Second/third decade	Walks unassisted	Can walk most of life	3-5
V	None	Minimal symptoms or asymptomatic with absence of SMN1	All major milestones	Full lifespan walking ability	3-5

primers 5'-CCAGCTCCTAGAGAAAGAAGGA-3' and 5'-ATGCTTGGATCTCTAGAATGG-3'. Three percent agarose gels were used for electrophoresis.

Finally, the SALSA P060-B1 SMA kit was used to perform the MLPA method in order to determine the copy number of the SMN1 and SMN2 genes. Following five minutes of denaturation at 98°C, an overnight hybridization at 60°C, fifteen minutes of ligation at 54°C, and PCR using FAM-labeled primers, the DNA samples were processed. PCR products were examined using Coffalyzer software on an ABI3130 Genetic Analyzer.

RESULTS

This study examined the number of alleles in the exon 7 and 8 regions of the SMN1 and SMN2 genes in a total of 348 patients. Forty-one patients were identified as having no copies (0 alleles) of exons 7 and 8 of SMN1, which are critical for diagnosing SMA. This is in line with the expected general prevalence of SMA, representing 11.8% of patients. Additionally, 112 individuals with single-copy loss (1 allele) of the SMN1 gene were identified as potential carriers, representing 32.2% of the population.

The distribution of SMN2 gene allele counts plays a significant role in influencing the course of the illness. There were two SMN2 alleles for exon 7 in 31 patients, three in four patients, and four in three patients among the 41 individuals who lacked copies of the SMN1 gene. Twenty-nine patients had two alleles for SMN2 exon 8, eight patients had three alleles, and one patient had four alleles. This distribution implies that the clinical severity of the condition is significantly influenced by the number of SMN2 copies. Milder symptoms might be indicated by higher SMN2 copy levels.

A total of 348 newborn infants with hypotonia and a family history of SMA were screened as part of this study. Of those who were screened, 166 were male and 182 were female. The distribution of the diagnosis of SMA and the carrier status according to sex was analyzed.

The prevalence of SMA was 9.0% (15/166) for men and 8.8% (16/182) for women. Regarding carrier status, 34.3% (57/166) of men and 30.2% (55/182) of women were identified as carriers. Although this gender difference in carrier rates may not be statistically significant, gender-specific carrier status is important for genetic counseling and family planning.

In summary, our research indicates that gender has no bearing on the frequency and carrier status of SMA and emphasizes the significance of screening for the condition in patients with hypotonia and a family history of it (Table 2-3).

Table 2. Frequency distribution of SMN1 and SMN2 exons

Allele Count	0	1	2	3	4
SMN1 Exon 7	41	112	185	8	1
SMN1 Exon 8	41	112	185	8	1
SMN2 Exon 7	11	91	220	22	3
SMN2 Exon 8	11	91	220	24	2

Table 3. Allele count of SMN2 exon 7 and exon 8 in patients with 0 copies of SMN1 Exon 7 and Exon 8

Exon/Allele Count	2 Alleles	3 Alleles	4 Alleles
SMN2 Exon 7	31	4	3
SMN2 Exon 8	29	8	1

DISCUSSION

The study focused on 348 spinal muscular atrophy (SMA) patients at Erzurum City Hospital, Eastern Anatolia, Turkey, analyzing the effect of SMN1 and SMN2 alleles on disease progression. The results indicate a significant relationship between allele variations and SMA severity, contributing to a broader understanding of the disease when compared to existing literature.

The identification of 41 patients (11.8% of the cohort) without any copies of SMN1 gene exons 7 and 8 underlines the diagnostic importance of the gene, in line with global prevalence rates. Notably, the study also identified 112 individuals (32.2% of participants) with a single-copy loss in the SMN1 gene. This suggests a significant carrier prevalence.

Current research shows that SMA type 1 patients typically suffer rapid and irreversible motor neuron loss starting perinatally. This leads to extensive motor unit loss within months.[20] Delays in diagnosis are common. For SMA types 1, 2, and 3, there are several months between symptom onset and diagnosis.[21]

In particular, the number of SMN2 alleles influences the clinical course of patients with missing SMN1 copies, with higher SMN2 levels correlating with milder symptoms. This highlights the potential therapeutic importance of SMN2.

The study found a minimal effect of sex on SMA prevalence and carrier status, consistent with the autosomal recessive nature of SMA. This suggests that sex should not be considered in genetic counseling or SMA risk assessment.

The 5q forms of SMA are primarily caused by homozygous deletions or, less frequently, other mutations in the SMN1 gene, notwithstanding the great clinical diversity of SMA (OMIM 600354).[22] The SMN2 gene (OMIM 601627), which functions as an alternate copy, primarily determines the severity of the disease; the phenotype tends to become milder as SMN2 copy numbers grow.[17] Furthermore, uncommon variations in SMN2 and other genetic variables such as plastin 3 (PLS3) or neurocalcin delta (NCALD) may have an impact on the severity of the condition.[23]

There is a significant variation of mutations found in SMA patients. Point mutations account for 4% of the total, while homozygous deletion of SMN1 accounts for 96%. Owing to the intricate genetic structure, gene conversions and de novo rearrangements occur often. Additional SMN2 variations or independent genes like PLS3 and NCALD can exacerbate the illness.[24,25] Research has shown that in people with two copies of SMN2, SMA-I develops in 79% of cases, whereas SMA-III occurs in 5% of cases; in people with three copies of SMN2, SMA-II occurs in 54% of cases, SMA-III in 31% of cases, and SMA-I in 16% of cases. Milder types of SMA are more common in patients with four copies of SMN2. Of those diagnosed, just 1% have SMA-II and 11% have SMA-I.[26]

By conducting this study in Eastern Anatolia, it is possible to examine regional genetic diversity and environmental influences on SMA prevalence and carrier rates. This highlights the importance of tailored regional screening and genetic counseling services.

Conclusion

In conclusion, by demonstrating the benefits of regional genetic screening and counseling in improving early diagnosis and disease management, this study at Erzurum City Hospital provides critical insights into the genetic basis and management of SMA. Such localized studies enhance national and international efforts in the screening and management of genetic disorders. They also aid in the development of strategies for genetic counseling and early diagnosis.

Ethics Committee Approval

The study was approved by the Erzurum Medical Faculty of Health Sciences Ethics Committee (Date: 14.03.2024,

Decision No: BAEK 2024/03-73).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: O.Y., Ö.B.G.Ö.; Design: O.Y., M.C.G.; Supervision: S.S.; Fundings: O.Y.; Materials: F.K.; Data: Ö.B.G.Ö., S.S.; Analysis: O.Y., F.K.; Literature search: O.Y., Ö.B.G.Ö.; Writing: O.Y.; Critical revision: S.S.

Conflict of Interest

None declared.

REFERENCES

1. Ross LF, Kwon JM. Spinal muscular atrophy: Past, present, and future. Neoreviews 2019;20:e437–51. [CrossRef]
2. Kolb SJ, Kissel JT. Spinal muscular atrophy. Neurol Clin 2015;33:831–46. [CrossRef]
3. Hamilton G, Gillingwater TH. Spinal muscular atrophy: going beyond the motor neuron. Trends Mol Med 2013;19:40–50. [CrossRef]
4. Chen TH. New and developing therapies in spinal muscular atrophy: From genotype to phenotype to treatment and where do we stand? Int J Mol Sci 2020;21:3297. [CrossRef]
5. Hahnen E, Schönling J, Rudnik-Schöneborn S, Zerres K, Wirth B. Hybrid survival motor neuron genes in patients with autosomal recessive spinal muscular atrophy: New insights into molecular mechanisms responsible for the disease. Am J Hum Genet 1996;59:1057–65.
6. Bussaglia E, Clermont O, Tizzano E, Lefebvre S, Bürglen L, Cruaud C, et al. A frame-shift deletion in the survival motor neuron gene in Spanish spinal muscular atrophy patients. Nat Genet 1995;11:335–7. [CrossRef]
7. Jędrzejowska M, Gos M, Zimowski JG, Kostera-Pruszczyk A, Ryniewicz B, Hausmanowa-Petrusewicz I. Novel point mutations in survival motor neuron 1 gene expand the spectrum of phenotypes observed in spinal muscular atrophy patients. Neuromuscul Disord 2014;24:617–23. [CrossRef]
8. Alías L, Bernal S, Fuentes-Prior P, Barceló MJ, Also E, Martínez-Hernández R, et al. Mutation update of spinal muscular atrophy in Spain: Molecular characterization of 745 unrelated patients and identification of four novel mutations in the SMN1 gene. Hum Genet 2009;125:29–39. [CrossRef]
9. Feldkötter M, Schwarzer V, Wirth R, Wienker TF, Wirth B. Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. Am J Hum Genet 2002;70:358–68. [CrossRef]
10. Wirth B, Schmidt T, Hahnen E, Rudnik-Schöneborn S, Krawczak M, Müller-Myhsok B, et al. De novo rearrangements found in 2% of index patients with spinal muscular atrophy: Mutational mechanisms, parental origin, mutation rate, and implications for genetic counseling. Am J Hum Genet 1997;61:1102–11. [CrossRef]
11. Clermont O, Burlet P, Benit P, Chanterau D, Saugier-Veber P, Munnich A, et al. Molecular analysis of SMA patients without homozygous SMN1 deletions using a new strategy for identification of SMN1 subtle mutations. Hum Mutat 2004;24:417–27. [CrossRef]
12. Parsons DW, McAndrew PE, Monani UR, Mendell JR, Burghes AH, Prior TW. An 11 base pair duplication in exon 6 of the SMN gene produces a type I spinal muscular atrophy (SMA) phenotype: Further evidence for SMN as the primary SMA-determining gene. Hum Mol Genet 1996;5:1727–32. [CrossRef]
13. Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, et al; SMA Care Group. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord 2018;28:103–15. [CrossRef]
14. Butchbach ME. Copy number variations in the survival motor neuron genes: Implications for spinal muscular atrophy and other neurodegenerative diseases. Front Mol Biosci 2016;3:7. [CrossRef]
15. Wirth B. An update of the mutation spectrum of the survival motor neuron gene (SMN1) in autosomal recessive spinal muscular atrophy (SMA). Hum Mutat 2000;15:228–37. [CrossRef]
16. Kubo Y, Nishio H, Saito K. A new method for SMN1 and hybrid SMN gene analysis in spinal muscular atrophy using long-range PCR followed by sequencing. J Hum Genet 2015;60:233–9. [CrossRef]
17. Wirth B, Brichta L, Schrank B, Lochmüller H, Blick S, Baasner A, et al. Mildly affected patients with spinal muscular atrophy are partially protected by an increased SMN2 copy number. Hum Genet 2006;119:422–8. [CrossRef]
18. Prior TW. Spinal muscular atrophy diagnostics. J Child Neurol 2007;22:952–6. [CrossRef]
19. Lunn MR, Wang CH. Spinal muscular atrophy. Lancet 2008;371:2120–33. [CrossRef]
20. Swoboda KJ, Prior TW, Scott CB, McNaught TP, Wride MC, Reyna SP, et al. Natural history of denervation in SMA: Relation to age, SMN2 copy number, and function. Ann Neurol 2005;57:704–12. [CrossRef]
21. Lin CW, Kalb SJ, Yeh WS. Delay in diagnosis of spinal muscular atrophy: A systematic literature review. Pediatr Neurol 2015;53:293–300. [CrossRef]
22. Lefebvre S, Burlet P, Liu Q, Bertrandy S, Clermont O, Munnich A, et al. Correlation between severity and SMN protein level in spinal muscular atrophy. Nat Genet 1997;16:265–9. [CrossRef]
23. Riessland M, Kaczmarek A, Schneider S, Swoboda KJ, Löhr H, Bradler C, et al. Neurocalcin delta suppression protects against spinal muscular atrophy in humans and across species by restoring ımpaired endocytosis. Am J Hum Genet 2017;100:297–315. [CrossRef]
24. Prior TW, Krainer AR, Hua Y, Swoboda KJ, Snyder PC, Bridgeman SJ, et al. A positive modifier of spinal muscular atrophy in the SMN2 gene. Am J Hum Genet 2009;85:408–13. [CrossRef]
25. Oprea GE, Kröber S, McWhorter ML, Rossoll W, Müller S, Krawczak M, et al. Plastin 3 is a protective modifier of autosomal recessive spinal muscular atrophy. Science 2008;320:524–7. [CrossRef]
26. Mercuri E, Pera MC, Scoto M, Finkel R, Muntoni F. Spinal muscular atrophy - Insights and challenges in the treatment era. Nat Rev Neurol 2020;16:706–15. [CrossRef]

Türkiye'nin Doğu Anadolu Bölgesi'ndeki Spinal Müsküler Atrofi Kohortları Üzerine Bir Çalışma

Amaç: Bu çalışmanın amacı, hastalığın genetik temelini ve özellikle SMN1 ve SMN2 genlerinin alel sayısının hastalığın ilerlemesi üzerindeki etkisini araştırmak için Türkiye'nin Doğu Anadolu bölgesindeki SMA hastalarında genetik bir kohort çalışması yapmaktır.

Gereç ve Yöntem: Çalışma, Erzurum Şehir Hastanesi'nde Erzurum Sağlık Bilimleri Üniversitesi Tıp Fakültesi'nin etik onayı ile yürütülmüştür. SMA ön tanısı olan toplam 348 hastaya genetik test uygulandı. SMN1 ve SMN2 genlerindeki ekzon 7 ve 8 delesyonları PCR-RFLP yöntemi ile analiz edildi.

Bulgular: SMN1 ve SMN2 genlerinin ekzon 7 ve ekzon 8 bölgelerindeki alel sayıları incelenerek SMN1 geninin hiç kopyası olmayan (0 alel) 41 hasta ve potansiyel taşıyıcı olarak değerlendirilen 112 birey belirlendi. SMN2 genindeki alel sayısının dağılımı analiz edilmiş ve hastalığın klinik şiddeti üzerinde önemli bir etkisi olduğu gösterilmiştir.

Sonuç: Bu çalışma, Türkiye'nin Doğu Anadolu bölgesindeki SMA hastalarının genetik kohort analizini sunmakta ve SMN1 ve SMN2 genlerindeki alel sayısının hastalığın ilerlemesi üzerindeki etkisini ortaya koymaktadır. Bulgular, cinsiyetin hastalık yaygınlığı ve taşıyıcılık durumu üzerinde sınırlı bir etkiye sahip olduğunu öne sürerek, SMA'nın genetik teşhisi ve yönetimi konusunda önemli bilgiler sağlamaktadır. Araştırma ayrıca bölgesel genetik tarama ve danışmanlık hizmetlerinin geliştirilmesinin kritik önemini vurgulamaktadır.

Anahtar Sözcükler: Genetik varyasyon; SMA; SMN1; SMN2.

SCIE DOI: 10.14744/scie.2024.52243
South. Clin. Ist. Euras. 2024;35(3):230-237

Original Article

Analysis of Pancreatitis Severity Scores and hospitalization length of Diabetic and Non-diabetic Patients with Nonbiliary Acute Pancreatitis

Meryem Dumlu,[1] Banu Boyuk,[1] Tunahan Refik Dumlu,[2] Hande Erman[1]

[1]Department of Internal Medicine, University of Health Science, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul Türkiye
[2]Department of Radiology, University of Health Science, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul Türkiye

Submitted: 15.05.2024
Revised: 03.08.2024
Accepted: 07.08.2024

Correspondence: Hande Erman, Department of Internal Medicine, University of Health Science, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul Türkiye
E-mail: handeerman@yahoo.com

Keywords: Acute pancreatitis severity scores; diabetes; length of hospital stay.

ABSTRACT

Objective: Many studies have compared scoring systems in the course of acute pancreatitis (AP), but comparative analyses of scoring systems in patients with diabetes are limited. In our study, we aimed to compare patients using more than one scoring system and also to investigate whether there was a scoring system that could be preferred in predicting the length of hospital stay (LOS) in individuals with diabetes.

Methods: Mild and moderate-severe acute pancreatitis patients who were followed up with AP in the internal medicine clinic were evaluated retrospectively. The diagnosis of AP was confirmed in accordance with the revised Atlanta criteria. AP with mild and moderate severity was the inclusion criteria. Patients with severe pancreatitis were excluded. Patients with and without diabetes were analyzed according to demographic characteristics, laboratory and imaging findings in two groups. Ranson, Systemic Inflammatory Response Syndrome (SIRS), Bedside Index of Severity in Acute Pancreatitis (BISAP), Modified Glasgow II Scoring (IMRIE), Harmless Acute Pancreatitis Score (HAPS), Balthazar, and Computed Tomography Severity Index (CTSI) scores were calculated on admission.

Results: AP patients with diabetes had higher serum triglyceride, leukocyte, CRP, and procalcitonin levels ($p<0.05$). Serum amylase levels were slightly higher in non-diabetic patients ($p<0.05$). The presence of diabetes was positively correlated with Ranson on admission, SIRS, and Imrie scores ($p<0.05$; $r=0.437$; $r=0.274$; $r=0.317$). Among severity scores, only the CTSI score was significantly higher in patients with >7 days LOS ($p<0.004$). In addition, while there was no difference in LOS according to the presence of DM ($p=0.840$), mean HbA1c values were higher in patients with longer LOS ($p=0.037$). As a result of regression analysis, male gender and higher CTSI scores were related to increased LOS (OR=0.266, $p=0.037$ vs OR=1.579, $p=0.022$).

Conclusion: Among the scoring systems, IMRIE, SIRS, and Ranson scores were higher in mild-moderate AP patients with diabetes compared to non-diabetic patients. In addition, male gender and higher CTSI scores were associated with increased LOS in this specific patient group.

INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas, characterized by abdominal pain and elevated pancreatic enzyme levels in the blood. The most common causes of AP are alcohol, hypertriglyceridemia, hypercalcemia, drug-related, autoimmune disease, and genetic and anatomic anomalies.[1] According to the revised Atlanta criteria, acute pancreatitis is examined histopathologically in three groups as interstitial, edematous, and acute necrotizing types, and in three groups as mild, moderate, and severe acute pancreatitis according to the severity of the disease. Local or systemic complications and organ failure are not seen in mild acute pancreatitis. In moderate acute pancreatitis, there is transient organ failure that resolves within 48 hours and/or local-systemic complications that do not continue for more than 48 hours, whereas in severe acute pancreatitis, there is permanent failure involving one or more organs.[2] Many scoring systems have been developed, consisting of physical examination findings, laboratory, and imaging methods to evaluate the severity of acute pancreatitis and its complications. The Ranson

criteria,[3] Acute Physiology and Chronic Health Inquiry (APACHE II) scoring,[4] and Bedside Index of Severity in Acute Pancreatitis (BISAP) scoring, which also includes the Systemic Inflammatory Response Syndrome (SIRS) criteria, are the widely used AP scoring systems today.[5] In addition, Modified Glasgow II Scoring (IMRIE) is a one-time scoring at the 48th hour after the patient's admission to the hospital.[6]

Due to the complexity of the existing scoring systems, the Harmless Acute Pancreatitis Score (HAPS) has been developed, which evaluates both physical examination findings and hematocrit (HCT) and creatinine values at admission.[7] The Balthazar score was developed based on computed tomography (CT) imaging findings and is frequently used in the diagnosis and evaluation of complications of AP.[8] In addition, Computerized Tomography Severity Score (CTSI) scoring can be performed by adding the necrosis rate on CT to the Balthazar score, and it has been shown that it has high diagnostic accuracy in the evaluation of severe acute pancreatitis and can be used reliably in the early prediction of complications.[9] However, none of these scoring systems alone is sufficient to assess prognosis.

Diabetes mellitus (DM), a chronic metabolic disorder, is a rapidly growing global problem with major social, health, and economic consequences. DM causes the development of many complications, both acute and chronic, and is also known to be an important risk factor for many other diseases.[10] High glucose levels in patients with diabetes are suggested to induce oxidative stress in the pancreas as well as in various tissues of the body.[11] In addition, comorbid factors such as obesity and hypertriglyceridemia have also been associated with acute pancreatitis.[12,13] However, the number of studies comparing AP scoring systems in diabetics and non-diabetics is limited. In our study, we aimed to compare the pancreatic scoring systems in mild-moderate acute pancreatitis patients with and without T2DM and factors effective on the length of hospital stay (LOS) in this specific patient group.

MATERIALS AND METHODS

In our study, patients who were followed up with the diagnosis of AP in the internal medicine inpatient clinic between January 2018 and 2021 were evaluated retrospectively. The diagnosis of AP in these patients was confirmed by demonstrating the presence of two of the three basic criteria in accordance with the revised Atlanta criteria: typical abdominal pain in terms of pancreatitis, an increase in blood levels of amylase or lipase more than three times the upper limit, and significant imaging findings suggesting pancreatitis.

Patients with mild and moderate acute pancreatitis aged over 18 years who were not pregnant and were followed up for at least 48 hours in the internal medicine inpatient clinic were included in our study. Severe acute pancreatitis patients were excluded due to ICU follow-up. Patients diagnosed as having biliary pancreatitis in imaging methods, patients with a hospitalization period of under 2 days, patients without CT imaging during hospitalization, and patients diagnosed as having chronic pancreatitis were excluded. In addition, patients with severe acute pancreatitis were excluded from the study. Mild acute pancreatitis was defined for patients that had no concomitant organ failure and no local or systemic complications, and their Ranson, BISAP, and Imrie scores were <3. Moderate acute pancreatitis was characterized by transient organ failure (less than 48 hours) or the presence of local or systemic complications, and Ranson, BISAP, and Imrie scores ≥3. Severe acute pancreatitis was defined as persistent organ failure lasting longer than 48 hours.

Demographic characteristics, smoking status, alcohol use, comorbid diseases, and drug use of the patients were recorded. Laboratory parameters such as blood glucose, blood gases, hemoglobin, hematocrit, albumin, blood urea nitrogen (BUN), calcium, magnesium, amylase, lipase, thyroid-stimulating hormone (TSH), C-reactive protein (CRP), procalcitonin (PCT), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, glycated hemoglobin (HbA1c), and leukocyte counts were recorded. CT imaging findings and length of stay were analyzed. Ranson, SIRS, BISAP, Imrie, HAPS, Balthazar, and CTSI scores at admission were calculated according to the previously described formula.[11] All parameters were compared between patients with and without diabetes. The study was approved by Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (date/number: 14.04.2021, 2021/514/199/2).

Statistical Analyses

Statistical analysis was performed using the SPSS 25.0 (Statistical Package for the Social Sciences) program. Descriptive statistics (mean, standard deviation, median, minimum, maximum, percentage values) of the data were calculated. Student's t-test was used to compare parameters between groups of normally distributed quantitative data. Mann-Whitney U test was used for comparison of non-normally distributed parameters between groups. The Chi-square (χ^2) test was used for comparisons of qualitative data. Linear regression analysis was performed to analyze the relationship between the presence of diabetes and the scoring systems. The results were evaluated with a statistical significance of $p<0.05$ at the 95% confidence interval.

RESULTS

A total of 100 patients with acute pancreatitis were enrolled in the study. Among 100 patients, 51 had DM, and 49 patients did not have diabetes. Patients with diabetes were older and had higher BMI, systolic blood pressure, and comorbidities ($p<0.05$). Patients with and without diabetes were similar in terms of sex, alcohol use, and smoking history ($p>0.05$). As expected, patients with diabetes had higher fasting blood glucose (FBG) and HbA1c ($p<0.05$). Similarly, acute pancreatitis patients with dia-

betes had higher serum triglyceride, leukocyte, CRP, and procalcitonin levels (p<0.05). Serum amylase levels were slightly higher in non-diabetic patients (p<0.05) (Table 1).

We compared the scoring results of acute pancreatitis patients according to the presence of diabetes in Table 2. Ranson 0-hour scores, SIRS, BISAP, and Imrie scores were significantly higher in diabetes (p<0.05 for all). HAPS, Balthazar, and CTSI scores were similar in diabetics and non-diabetics (p>0.05 for all).

Among severity scores, only the CTSI score is significantly higher in patients with >7 days LOS (p<0.004). In addition, while there is no difference in LOS according to the presence of DM (p=0.840), mean HbA1c values were higher in patients with a longer duration of hospitalization (p=0.037). Male patients had a higher hospitalization duration (p=0.026). Serum triglyceride values are higher in patients with longer LOS (p=0.004) (Table 3).

We performed binary logistic regression analysis regarding the effective factors on LOS in patients with mild and moderate severity AP (Table 4). As a result of regression analysis, male sex and higher CTSI score are related to the increased LOS (OR=0.266, p=0.037 vs. OR=1.579, p=0.022).

Table 1. Demographic, laboratory, and clinical characteristics of patients according to the presence of T2DM

	Non-diabetics n=49	Diabetics n=51	p value
Age (years)	54±17.52	61±15.12	0.016
Male, n (%)	26 (53.06)	25 (49.01)	0.843
BMI (kg/m2)	28±4.59	31±5.33	0.002
Alcohol use, n (%)	8 (16.32)	5 (9.80)	0.371
Smoking history, n (%)	16 (32.65)	11 (21.56)	0.261
Clinical			
Fever (°C)	37±0.48	37±0.44	0.315
Pulse (rate/m)	84±11.42	82±14.96	0.293
Respiration Rate	17±2.65	18±3.18	0.059
Oxygen Saturation	97±2.65	96±2.62	0.149
SBP (mmHg)	125±15.12	132±18.00	0.011
DBP (mmHg)	77±11.07	75±9.86	0.449
LOS (days)	7±4.42	7±3.28	0.627
Co-morbidities (n/%)	15 (30.61)	33 (64.70)	0.001
Laboratory findings			
FBG (mg/dl)	130.33±50.10	246.88±137.72	0.001
HbA1C (%)	5.69±0.45	8.02±2.15	0.001
T.Cholesterol (mg/dL)	180.80±50.91	251.43±78.49	0.096
LDL- C (mg/dL)	116.19±42.31	115.52±44.53	0.952
HDL-C (mg/dL)	41.49±14.94	51.79±45.58	0.984
TG (mg/dL)	132.63±98.55	534.74±375.61	0.001
TSH (mIU/L)	1.44±1.19	1.49±1.42	0.673
Leukocytes (µl)	11309±4151,69	13592±5250,45	0.011
CRP (mg/l)	88.43±89.82	128.92±97,26	0.031
Pct (µg/l)	1.82±4.99	2.37±4.41	0.003
AST (IU/l)	115.84±182.92	131.94±199.58	0.87
LDH (U/l)	290.86±158.74	335.57±254.67	0.388
Albumin (g/dl)	3.79±0.53	3.98±0,45	0.061
BUN (mg/dl)	15.50±8.27	18.89±10.74	0,055
Calcium (mg/dl)	9.03±0.65	9.05±0.71	0.859
Magnesium (mg/ml)	1.86±0.12	1.83±0.19	0.172
Amylase (U/l)	1899.33±1202.20	1506.25±1228.52	0.048
Lipase (U/l)	1250.29±1133.16	996.05±382.38	0.711

Statistical significance: p<0.05. Abbreviations; DM: diabetes mellitus; BMI: Body mass index; SBP: systolic blood pressure; DPB: diastolic blood pressure; LOS: Length of hospital stay; FBG: Fasting blood glucose; T. Cholesterol: total cholesterol; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; TG: triglycerides; TSH: thyroid stimulating hormone; AST: Aspartate transaminase; BUN: Blood urea nitrogen; CRP: C-Reactive Protein; Hba1c: Hemoglobin A1c; LDH: Serum lactate dehydrogenase; Pct: Procalcitonin; TSH: Thyroid Stimulating hormone.

Table 2. Comparison of scoring systems according to the presence of T2DM

	Non-DM n=49	DM n=51	p-value
Ranson-0.hour	1.04±0.98	2.04±1.09	0.001
SIRS	0.53±0.76	0.98±0.84	0.004
BISAP	0.78±1.12	1.10±1.01	0.028
IMRIE	1.43±1.20	2.27±1.34	0.001
HAPS	0.78±0.67	0.78±0.73	0.936
Balthazar	1.57±1.30	2.04±1.33	0.087
CTSI	1.96±2.05	2.29±1.66	0.253

BISAP: Bedside Index for Severity in Acute Pancreatitis; CTSI: Computed Tomography Severity Index; HAPS: Harmless Acute Pancreatitis Score; SIRS: Systemic inflammatory response syndrome.

DISCUSSION

Acute pancreatitis (AP) is one of the common emergencies that can result in morbidity and mortality. There are various results on the etiology, severity, complications, and mortality rates of AP.[14] Although scoring systems have been developed to estimate the severity of the disease, no single scoring system gives the best results, and each has limitations in different aspects.[15] For this reason, different scoring systems based on comorbidities and AP severity have been preferred. Diabetes has special importance in the patient group with AP due to its increasing frequency. In our study, we evaluated the differences in scoring systems in showing the severity of AP in patients with and without diabetes, as well as the effective factors on LOS.

Patients with diabetes have an increased risk of acute

Table 3. Laboratory parameters and acute pancreatitis severity scores according to the length of hospital stay

	LOS > 7days n=41	LOS < 7days n=59	p value
Age (years)	58.20±17.89	56.74±15.97	0.255
Gender (male) n (%)	26 (63.41)	25 (42.37)	0.026
BMI (kg/m^2)	28.52±17.89	29.70±5.63	0.052
DM n (%)	20 (48.78)	31 (52.54)	0.840
FBG (mg/dl)	196.34±110.15	183.41±124.55	0.592
HbA1c %	7.05±2.30	6.71±1.74	0.037
BUN (mg/dl)	18.46±9.76	16.33±9.62	0.611
CRP (mg/l)	125.04±101.87	97.40±100.75	0.579
Procalcitonin (ng/ml)	2.08±5.61	2.11±5.65	0.982
Amylase (U/l)	1924.66±1243.49	1553.67±1200.28	0.317
Lipase (U/l)	1035.75±1046.63	1180.82±1197.66	0.443
Triglycerides (mg/dl)	309.54±519.44	215.61±301.77	0.004
RANSON	1.56±1.14	1.52±1.16	0.924
SIRS	0.78±0.72	0.74±0.89	0.051
BISAP	1.05±1.11	0.87±1.04	0.793
IMRIE	2.00±1.34	1.75±1.33	0.865
HAPS	0.83±0.66	0.75±0.72	0.233
CTSI	2.80±2.29	1.70±1.30	0.004
Baltazar	2.07±1.36	1.62±1.28	0.815

LOS: length of stay; BMI: body mass index; FBG: fasting blood glucose; BUN: Blood urea nitrogen; CRP: C-reactive protein; SIRS: Systemic Inflammatory Response Syndrome; BISAP: Bedside Index of Severity in Acute Pancreatitis; IMRIE: Modified Glasgow II Scoring; HAPS: Harmless Acute Pancreatitis Score; CTSI: Computerized Tomography Severity Score.

Table 4. Binary Logistic regression analysis for effective factor on LOS in mild-moderate AP patients

				95% C.I. for EXP (B)	
	B	p	O.R.	Lower	Upper
Gender (Male)	1.326	0.037	0.266	0.076	0.924
HbA1c %	-0.140	0.946	0.986	0.658	1.477
Triglycerides	0.001	0.610	1.000	0.999	1.002
CTSI	0.457	0.022	1.579	1.068	2.333

OR: odds ratio; CI: confidence interval; CTSI: computerized tomography severity score; AP: acute pancreatitis; LOS: length of stay. Statistical significance at p<0.05.

pancreatitis.[16] However, conflicting results have been reported on the hospital mortality risk of patients with diabetes with AP. A retrospective study in Taiwan showed that patients with AP and DM had a lower risk of hospital mortality.[17] In a study by Zhao et al.,[18] patients with AP with a previous history of DM or HbA1c levels higher than 6.5% had higher mortality than those without DM. In our study, patients with AP and DM had significantly higher blood glucose levels at admission than those without DM. In addition, the average HbA1c value of patients with diabetes was 8.02%. The mean LOS was 6.65±3.88 days in our study. In a study published by Ertaş et al.,[19] the hospitalization periods of individuals with edematous and necrotizing pancreatitis were 6.7±4.5 and 6.2±5.3 days, respectively, similar to our findings. On the other hand, our study revealed that patients with diabetes had higher scores in acute pancreatitis severity scores. However, there was no difference between the groups with and without diabetes in terms of LOS. Regression analysis showed that higher CTSI scores and male gender were related to the length of hospital stay longer than seven days. While BISAP and PANC3 scores have been suggested for early prediction of LOS,[20] there are limited data regarding the utility of prognostic severity scores for predicting LOS.

Hyperglycemia is a common early feature of AP and is used in prognostic scoring systems. In our current study, we found that the presence of diabetes in patients with AP was related to SIRS as well as being related to Ranson and Imrie scores. Although the extent to which pre-existing DM may increase the severity of AP has yet to be determined, there is an association between stress hyperglycemia and adverse outcomes. The association between hyperglycemia and poor functional outcomes in critically ill patients has been demonstrated. In the ICU, hyperglycemia is strongly associated with outcomes in patients without pre-existing DM, but it is not associated with outcomes in patients with pre-existing DM.[21]

In a study by Buter et al.[22] in 2002 with a group of 121 patients, both organ dysfunction and SIRS scoring were associated with increased mortality. It was observed that early organ dysfunction generally improved and had no significant effect on mortality by itself, whereas worsening organ dysfunction was associated with mortality in more than half of the patients.[22] In our study, we showed that patients with diabetes scored higher in SIRS scoring. This may be due to the mild and moderate AP profile of the patients included in the study and the higher leukocyte count in patients with diabetes.

We observed that the Ranson score at admission was higher in diabetic patients. This may be due to the presence of blood glucose levels in scoring. The inability to calculate 48th-hour Ranson scores due to data insufficiency affects the reliability of the findings. However, the meta-analysis by De Bernardis et al.[23] published in 1999 on 211 studies conducted since 1974 showed that the Ranson criteria had a weak power to predict findings. In BISAP scoring, patients with diabetes scored higher than those without diabetes, but despite this significant difference, both patient groups are in the scoring range with low expected mortality. The meta-analysis by Gao et al.[24] of 10 studies, which was conducted between 1980 and 2014 and published in 2015, focused on the predictive value of BISAP scores to evaluate the clinical outcomes of AP. It was shown that the cut-off value of ≥3 points had moderate sensitivity and high specificity to predict mortality and severe AP. At the cut-off value of ≥2 points, it was observed that although the sensitivity increased for both results, the specificity decreased. It was suggested that a BISAP score of ≥3 was successful in predicting the mortality and severity of AP.[24] However, in our study, when 3 points and above were considered as the cut-off value, no difference was observed in patients with diabetes. This may be a result of the low number of the study group.

Imrie scores were higher in patients with diabetes when 3 or more points were considered as the cut-off value in the scoring. The reason for this may be that leukocyte counts and glucose levels occur together in Imrie scoring. On the other hand, no difference was observed in the patient groups in terms of HAPS, Balthazar, and CTSI scores. In the study of Lankisch et al.,[25] which included 394 patients, it was shown that HAPS scoring was more correlated in the course of non-severe disease. In a study on 149 patients, it was shown that both CTSI and modified CTSI scores were associated with disease severity parameters, and there was a correlation between imaging severity and poor clinical outcomes.[26] In another study, the thresholds for the prediction of severe AP were Ranson ≥3, BISAP ≥2, APACHE-II ≥8, and CTSI ≥3.[27]

Aging and pancreatitis is an important issue due to the aging population worldwide. In our study, the mean age of patients with diabetes was higher than that of non-diabetics. Yadav et al.[28] reported that the risk of AP increased gradually with age, and chronic pancreatitis mainly affected middle-aged individuals. In another retrospective study, the mean age of the patients was similar to our study.[29]

In the pathophysiology, cytokines, adipokines, damage-related molecular models, and unsaturated fatty acid-mediated lipotoxicity have been considered. The role of obesity in exacerbating pancreatic necrosis has been discussed. It has been shown that there may be pancreatic fat necrosis associated with obesity and that peripancreatic fat necrosis can worsen organ dysfunction independent of pancreatic necrosis.[30] In our study, patients with diabetes had higher BMI values than non-diabetics. In the study published by Khatua et al.[30] in 2017, it was suggested that obesity led to type 2 DM (T2DM), which secondarily caused an increase in the incidence of gallstones and hypertriglyceridemia, and that incretin-based treatments used in the treatment of DM, surgery, and endoscopic interventions for the treatment of obesity, caused an increase in the incidence of AP in the obese group.

Previous animal studies suggested that sustained hypertension increases pancreatic oxidative stress that might lead to pancreatic damage in hypertensive rats.[31] Further-

more, studies regarding acute pancreatitis in metabolic syndrome patients revealed that hypertension is more frequently seen in patients with severe acute pancreatitis.[32,33] Considering the blood pressure values of the patients at the time of admission, systolic blood pressure was found to be higher in patients with diabetes in our study. This situation may be an indicator of concomitant hypertension in patients with diabetes in our study, and therefore, the inability to control hypertension in these patients.

In several studies, patients with T2DM had comorbidities (e.g., obesity, heart failure, kidney disease, liver disease) that might increase the risk of severe AP and were strong predictors of premature death from AP.[34,35] In our study, of the total patients, 48.04% had hypertension, 17.65% had hyperlipidemia, 23.53% had cardiac disease, 9.80% had hypothyroidism, 5.88% had respiratory disease, and 3.92% had chronic renal disease. We observed that the presence of comorbidities did not affect the length of stay and mortality. In the study published by Murata et al.[36] in 2015, severe comorbidity resulted in higher hospital mortality and longer stay when evaluated using the Charlson Comorbidity Index in 1,090 hospitalized older patients in Japan. This conflicting finding could be attributed to the fact that the patients had mild-to-moderate pancreatitis and that the number of patients was low.

In our study, it was observed that triglyceride levels were higher in those with diabetes. It was previously reported that poorly controlled diabetes and diabetic ketoacidosis can trigger hypertriglyceridemia-associated acute pancreatitis.[37] In a review published by Thambiah et al.[38] in 2021, it was emphasized that an impaired lipid profile could be seen in poorly controlled type 1 diabetes and type 2 diabetes, even though it was well controlled, and that this situation was associated with insulin resistance rather than impaired glycemic control. In patients with diabetes, there is a significant increase in acute phase reactants such as CRP, PCT, and leukocyte values compared with patients without diabetes. The early and serial CRP level in AP is used as an indicator of the severity and progression of inflammation. Diabetes exacerbates systemic inflammation during pancreatitis, may have a major impact on the progression of pancreatitis at the local level, and may also increase systemic inflammatory parameters such as interleukin (IL)-6 concentrations in plasma.[39]

It is already known that serum amylase is a useful biochemical tool to diagnose acute pancreatitis. We observed that the amylase levels of the patients at admission were lower in diabetic patients. In the meta-analysis of Ko et al.,[40] which was published in 2020 and included 20 studies comprising 20,916 participants, individuals with type 2 diabetes had serum amylase levels 3.1 times lower, serum lipase levels 2.9 times lower, and serum trypsin levels 2.5 times lower than the upper limits of normal. These findings support the low levels of amylase and lipase in our study. Low amylase levels in patients with diabetes may indicate impaired exocrine functions of the pancreas.

We made a comparison by calculating the scores related to AP in diabetic and non-diabetic groups, but the lack of APACHE-II scoring, which has proven its power in many studies to predict the severity of AP, constituted the most important limitation of our study. Similarly, the 48th-hour Ranson score could not be calculated. The main reason for this was that the study was conducted retrospectively, and therefore, some laboratory parameters, especially blood gas, were not studied. Finally, due to the retrospective design of the study, a causative relationship cannot be established.

Conclusion

Among the scoring systems, Imrie, SIRS, and Ranson scores are higher in patients with diabetes with mild-moderate AP in comparison to non-diabetic patients. In addition, male gender and higher CTSI scores are associated with increased LOS in this specific patient group.

Ethics Committee Approval

The study was approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 14.04.2021, Decision No: 2021/514/199/2).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: B.B.; Design: B.B.; Supervision: B.B.; Data: M.D.; Analysis: T.R.D.; Literature search: T.R.D.; Writing: M.D., H.E.; Critical revision: H.E.

Conflict of Interest

None declared.

REFERENCES

1. Roberts SE, Morrison-Rees S, John A, Williams JG, Brown TH, Samuel DG. The incidence and aetiology of acute pancreatitis across Europe. Pancreatology 2017;17:155–65. [CrossRef]
2. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102–11. [CrossRef]
3. Basit H, Ruan GJ, Mukherjee S. Ranson Criteria. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024.
4. Al-Hadeedi S, Fan ST, Leaper D. APACHE-II score for assessment and monitoring of acute pancreatitis. Lancet 1989;2:738. [CrossRef]
5. Hagjer S, Kumar N. Evaluation of the BISAP scoring system in prognostication of acute pancreatitis - A prospective observational study. Int J Surg 2018;54:76–81. [CrossRef]
6. Imrie CW. Prognostic indicators in acute pancreatitis. Can J Gastroenterol 2003;17:325–8. [CrossRef]
7. Ma X, Li L, Jin T, Xia Q. Harmless acute pancreatitis score on admission can accurately predict mild acute pancreatitis. Nan Fang Yi Ke Da Xue Xue Bao [Article in Chinese] 2020;40:190–5. Chinese.
8. Basterra G, Alvarez M, Marcaide A, Delgado E, Díaz de Otazu R, García Campos F. Acute pancreatitis: Evaluation of the prognostic criteria of the latest Balthazar tomographic classification. Rev Esp

Enferm Dig 1999;91:433–8.
9. Rehan A, Shabbir Z, Shaukat A, Riaz O. Diagnostic accuracy of modified CT severity index in assessing severity of acute pancreatitis. J Coll Physicians Surg Pak 2016;26:967–70.
10. Katsiki N, Tousoulis D. Diabetes mellitus and comorbidities: A bad romance. Hellenic J Cardiol 2020;61:23–5. [CrossRef]
11. Solanki NS, Barreto SG, Saccone GT. Acute pancreatitis due to diabetes: The role of hyperglycaemia and insulin resistance. Pancreatology 2012;12:234–9. [CrossRef]
12. Sempere L, Martinez J, de Madaria E, Lozano B, Sanchez-Paya J, Jover R, et al. Obesity and fat distribution imply a greater systemic inflammatory response and a worse prognosis in acute pancreatitis. Pancreatology 2008;8:257–64. [CrossRef]
13. Hernandez P, Passi N, Modarressi T, Kulkarni V, Soni M, Burke F, et al. Clinical management of hypertriglyceridemia in the prevention of cardiovascular disease and pancreatitis. Curr Atheroscler Rep 2021;23:72. [CrossRef]
14. Bálint ER, Fűr G, Kiss L, Németh DI, Soós A, Hegyi P, et al. Assessment of the course of acute pancreatitis in the light of aetiology: A systematic review and meta-analysis. Sci Rep 2020;10:17936. [CrossRef]
15. Balcı Z, Kılıç MÖ, Şenol K, Erdoğan A, Tez M. Prognostic scores in acute pancreatitis : A review. Acta Gastroenterol Belg 2016;79:337–47.
16. Gonzalez-Perez A, Schlienger RG, Rodríguez LA. Acute pancreatitis in association with type 2 diabetes and antidiabetic drugs: A population-based cohort study. Diabetes Care 2010;33:2580–5. [CrossRef]
17. Shen HN, Lu CL, Li CY. Effect of diabetes on severity and hospital mortality in patients with acute pancreatitis: A national population-based study. Diabetes Care 2012;35:1061–6. [CrossRef]
18. Zhao X, Chang Mei H, Chen L, Jiang L, He M, Chen J, et al. An increased level of haemoglobin A1C predicts a poorer clinical outcome in patients with acute pancreatitis. Clin Endocrinol (Oxf) 2012;77:241–5. [CrossRef]
19. Ertaş H, Duran C, Keskin M, Güney İ. Examining the clinical and laboratory characteristics of patients diagnosed with acute pancreatitis. Aegean J Med Sci [Article in Turkish] 2018;3:97–102. [CrossRef]
20. Gray R, Cagliani J, Amodu LI, Nauka P, Villacres B, Santos T, et al. Maximizing the use of scoring systems in the prediction of outcomes in acute pancreatitis. Digestion 2019;99:166–71. [CrossRef]
21. Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Hegarty C, et al. Blood glucose concentration and outcome of critical illness: the impact of diabetes. Crit Care Med 2008;36:2249–55. [CrossRef]
22. Buter A, Imrie CW, Carter CR, Evans S, McKay CJ. Dynamic nature of early organ dysfunction determines outcome in acute pancreatitis. Br J Surg 2002;89:298–302. [CrossRef]
23. De Bernardinis M, Violi V, Roncoroni L, Boselli AS, Giunta A, Peracchia A. Discriminant power and information content of Ranson's prognostic signs in acute pancreatitis: A meta-analytic study. Crit Care Med 1999;27:2272–83. [CrossRef]
24. Gao W, Yang HX, Ma CE. The value of BISAP score for predicting mortality and severity in acute pancreatitis: A systematic review and meta-analysis. PLoS One 2015;10:e0130412. [CrossRef]
25. Lankisch PG, Weber-Dany B, Hebel K, Maisonneuve P, Lowenfels AB. The harmless acute pancreatitis score: A clinical algorithm for rapid initial stratification of nonsevere disease. Clin Gastroenterol Hepatol 2009;7:702–607. [CrossRef]
26. Alberti P, Pando E, Mata R, Vidal L, Roson N, Mast R, et al. Evaluation of the modified computed tomography severity index (MCTSI) and computed tomography severity index (CTSI) in predicting severity and clinical outcomes in acute pancreatitis. J Dig Dis 2021;22:41–8. [CrossRef]
27. Cho JH, Kim TN, Chung HH, Kim KH. Comparison of scoring systems in predicting the severity of acute pancreatitis. World J Gastroenterol 2015;21:2387–94. [CrossRef]
28. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology 2013;144:1252–61. [CrossRef]
29. Polishchuk I, Halperin D, Algedafy A, Delgado JS, Zamir M, Zamir D. Epidemiology of acute pancreatitis in Southern Israel: A retrospective study. Isr Med Assoc J 2020;22:310–4.
30. Khatua B, El-Kurdi B, Singh VP. Obesity and pancreatitis. Curr Opin Gastroenterol 2017;33:374–82. [CrossRef]
31. Gao S, Park BM, Cha SA, Bae UJ, Park BH, Park WH, et al. Oxidative stress increases the risk of pancreatic β cell damage in chronic renal hypertensive rats. Physiol Rep 2016;4:e12900. [CrossRef]
32. Shen Z, Wang X, Zhen Z, Wang Y, Sun P. Metabolic syndrome components and acute pancreatitis: A case-control study in China. BMC Gastroenterol 2021;21:17. [CrossRef]
33. Szentesi A, Párniczky A, Vincze Á, Bajor J, Gódi S, Sarlós P, et al. Multiple hits in acute pancreatitis: Components of metabolic syndrome synergize each other's deteriorating effects. Front Physiol 2019;10:1202. [CrossRef]
34. Frey C, Zhou H, Harvey D, White RH. Co-morbidity is a strong predictor of early death and multi-organ system failure among patients with acute pancreatitis. J Gastrointest Surg 2007;11:733–42. [CrossRef]
35. Premkumar R, Phillips AR, Petrov MS, Windsor JA. The clinical relevance of obesity in acute pancreatitis: Targeted systematic reviews. Pancreatology 2015;15:25–33. [CrossRef]
36. Murata A, Ohtani M, Muramatsu K, Matsuda S. Influence of comorbidity on outcomes of older patients with acute pancreatitis based on a national administrative database. Hepatobiliary Pancreat Dis Int 2015;14:422–8. [CrossRef]
37. Fortson MR, Freedman SN, Webster PD 3rd. Clinical assessment of hyperlipidemic pancreatitis. Am J Gastroenterol 1995;90:2134–9.
38. C Thambiah S, Lai LC. Diabetic dyslipidaemia. Pract Lab Med 2021;26:e00248. [CrossRef]
39. Ołdakowska M, Ściskalska M, Kepinska M, Marek G, Milnerowicz H. Association of genetic variants in IL6 gene (rs1800795) with the concentration of ınflammatory markers (IL-6, hs-CRP) and superoxide dismutase in the blood of patients with acute pancreatitis-preliminary findings. Genes (Basel) 2022;13:290. [CrossRef]
40. Ko J, Cho J, Petrov MS. Low serum amylase, lipase, and trypsin as biomarkers of metabolic disorders: A systematic review and meta-analysis. Diabetes Res Clin Pract 2020;159:107974. [CrossRef]

Nonbiliyer Akut Pankreatit ile Takip Edilen Diyabetik ve Non-diyabetik Hastaların Pankreatit Şiddet Skorları ve Hastane Yatış Sürelerinin Değerlendirilmesi

Amaç: Akut pankreatit (AP) seyrinde skorlama sistemlerini karşılaştıran birçok çalışma vardır, ancak diyabetli hastalarda skorlama sistemlerinin karşılaştırmalı analizleri sınırlıdır. Çalışmamızda birden fazla skorlama sistemi kullanan hastaları karşılaştırmayı ve diyabetli bireylerde hastanede kalış süresini (HKS) tahmin etmede tercih edilebilecek bir skorlama sisteminin olup olmadığını araştırmayı amaçladık.

Gereç ve Yöntem: Dahiliye kliniğinde AP ile takip edilen hafif ve orta şiddetli akut pankreatit hastaları geriye dönük olarak değerlendirildi. Diyabetli ve diyabetsiz hastalar demografik özellikleri, laboratuvar ve görüntüleme bulgularına göre iki grupta incelendi. Ranson, Sistemik İnflamatuvar Yanıt Sendromu (SIRS), Akut Pankreatitte Yatak Başı Şiddet İndeksi (BISAP), Modifiye Glasgow II Skorlaması (IMRIE), Zararsız Akut Pankreatit Skoru (HAPS), Balthazar ve Bilgisayarlı Tomografi Şiddet İndeksi (CTSI) skorları hesaplandı.

Bulgular: Diyabetli AP hastalarında serum trigliserit, lökosit, CRP ve prokalsitonin düzeyleri daha yüksekti ($p<0.05$). Diyabetik olmayan hastalarda serum amilaz düzeyleri biraz daha yüksekti ($p<0.05$). Diyabet varlığı, başvuru anında Ranson, SIRS ve Imrie skorları ile pozitif korelasyon gösterdi ($p<0.05$; $r=0.437$; $r=0.274$; $r=0.317$). Ciddiyet skorlarından sadece CTSI skoru >7 günden fazla yaşam süresi olan hastalarda anlamlı olarak daha yüksektir ($p<0.004$). Ayrıca DM varlığına göre HKS'ta farklılık görülmezken ($p=0.840$), HKS'si yüksek olan hastalarda ortalama HbA1c değerleri daha yüksekti ($p=0.037$). Regresyon analizi sonucunda erkek cinsiyet ve daha yüksek CTSI puanı artan HKS ile ilişkilidir (OR=0.266, $p=0.037$ vs OR=1.579, $p=0.022$).

Sonuç: Skorlama sistemlerinden IMRIE, SIRS, Ranson skorları hafif-orta şiddette AP diyabetli hastalarda diyabetik olmayan hastalara göre daha yüksektir. Ayrıca bu spesifik hasta grubunda erkek cinsiyet ve daha yüksek CTSI skorları artan HKS ile ilişkilidir.

Anahtar Sözcükler: Akut pankreatit şiddet skorları; diyabet; hastanede kalış süresi.

SCIE DOI: 10.14744/scie.2024.02703
South. Clin. Ist. Euras. 2024;35(3):238-242

Original Article

Retrorectal Tumor Surgery: Single Center Study

Mehmet Karahan,[1] Cemal Hacıalioğlu,[1] Selçuk Kaya,[1] Osman Akdoğan,[2] Önder Altın,[1] Gökalp Okut,[3] Hasan Fehmi Küçük[1]

[1]Department of General Surgery, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye
[2]Department of General Surgery, Keşan State Hospital, Edirne, Türkiye
[3]Health Sciences University, Izmir City Hospital, Gastroenterological Surgery Clinic, Izmir, Türkiye

Submitted: 06.06.2024
Revised: 08.07.2024
Accepted: 02.08.2024

Correspondence: Mehmet Karahan , Department of General Surgery, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye
E-mail: mehmetkarahan1987@gmail.com

Keywords: Retrorectal; surgery; tumor.

ABSTRACT

Objective: Retrorectal or presacral tumors are rare, diagnostically challenging, and pathologically heterogeneous tumors. The exact incidence of these tumors is unknown, but it is estimated that tertiary care centers see 1-6 cases per year. The aim of this study is to evaluate the clinical and surgical outcomes of patients diagnosed with retrorectal tumors and treated surgically at our hospital.

Methods: A retrospective analysis was conducted on 23 patients diagnosed with retrorectal tumors and treated surgically at the General Surgery Clinic of our hospital between 2012 and 2022. Ethical approval was obtained for the study, and demographic data, presenting symptoms, radiological imaging methods, surgical details, and postoperative outcomes were recorded. All patients underwent preoperative radiological evaluation, and the surgical approach was determined based on the tumor's location.

Results: Between 2012 and 2022, 23 patients underwent RRT surgery. Of these patients, 20 (87.0%) were female, with a mean age of 45.2±12.2 (24-65) years. Twelve patients (52.2%) presented with coccygeal pain. On physical examination, a mass was palpated in the rectal examination of three patients (13.1%) and in the vaginal examination of three patients (13.1%). Preoperative radiological examination was performed on all patients; one patient underwent only CT, 12 patients underwent only MRI, and 10 patients underwent both CT and MRI. RRTs were reported as solid in nine patients (39.1%), cystic in ten patients (43.5%), and heterogeneous in four patients (17.4%). Fifteen patients underwent colonoscopy. Colonoscopy revealed external compression findings in two patients, and polyps were detected in three patients and histopathologically benign after polypectomy.

Conclusion: Retrorectal tumors are rare lesions requiring surgical treatment. Surgical interventions performed in experienced centers have shown successful outcomes and low recurrence rates. The management and surgical treatment of these tumors involve evaluating the tumor's imaging findings and location, leading to successful outcomes. This study provides a comprehensive approach to the surgical treatment of retrorectal tumors, emphasizing the importance of appropriate surgical strategies and complication management.

INTRODUCTION

Retrorectal tumors (RRT) are rare tumors that are difficult to diagnose and exhibit pathological heterogeneity. Although the actual prevalence in the general population is not well known, tertiary care centers report diagnosing approximately 1 to 6 cases annually, with an estimated incidence of 1 per 40,000 hospital admissions.[1] Benign RRTs are usually cystic, and malignant tumors are typically solid with necrotic areas and invasive potential. Although the majority of tumors are benign, 21-50% are malignant in natüre.[2]

Retrorectal tumors can originate from various embryological remnants, resulting in different histopathological types like congenital, neurogenic, osseous, inflammatory, or miscellaneous based on their origin. Histopathologically, they are further categorized as benign or malignant congenital and benign or malignant acquired.[3] Most retrorectal tumors are asymptomatic (26-50% of cases) and are often incidentally discovered during routine digital rectal examinations. Although patients exhibit a variety of symptoms, the most common symptom is chronic pain.[4] Also, symptoms like sacral pain, constipation, urinary incontinence, and pencil-thin stools may suggest that the tumor has invaded nearby structures. Patients might also suffer from lower back pain that intensifies when sitting

but gets better with walking or standing.[5] Retrorectal tumors should be considered in patients presenting with recurrent perianal fistulas and abscesses, prompting further imaging studies.[6] Digital rectal examination is crucial and can aid in diagnosing 90% of cases, but these soft and compressible lesions may be easily missed unless the clinician is vigilant.[5] Preoperative imaging is nearly universal in the diagnostic process, with computed tomography (CT) and magnetic resonance imaging (MRI) being particularly valuable for surgical planning (Figure 1).[7] CT is useful for determining the tumor's nature (cystic or solid) and its relationship with bone structures, while MRI excels in assessing soft tissue involvement and the extent of adjacent structure invasion (Figure 2).[8] Other imaging techniques, such as flexible sigmoidoscopy, transrectal ultrasonography (TRUS), and fistulograms, are also applicable.[9] While biopsy was once avoided because of potential complications and diagnostic inaccuracies, recent studies indicate that it can be safe and helpful for treatment planning.[10] Effective factors in the approach to RRTs include the location, size, and presence of malignancy of the tumor. Asymptomatic tumors with benign histopathology can be monitored with regular follow-ups; however, benign-appearing tumors can harbor malignant components or transform into malignancy.[10] Moreover, benign tumors can lead to infections in the urinary tract and meninges.[11] Surgery is the main treatment option for RRTs since they do not respond well to chemotherapy and radiation therapy, which are only used for palliative care.[12] Complications and recurrence can occur following surgeries not performed with free surgical margins and proper technique. For benign tumors, complete resection is advised, whereas malignant tumors require radical resection or en bloc resection of surrounding organs. Surgical methods include anterior (transabdominal), posterior (perineal), and combined approaches. Tumors located above the S3 level are typically treated with anterior or combined techniques, while those below the S3 level are treated with posterior techniques.[13] In this study, we provide an in-depth review of the diagnosis and surgical treatment of RRTs and share our clinical experiences.

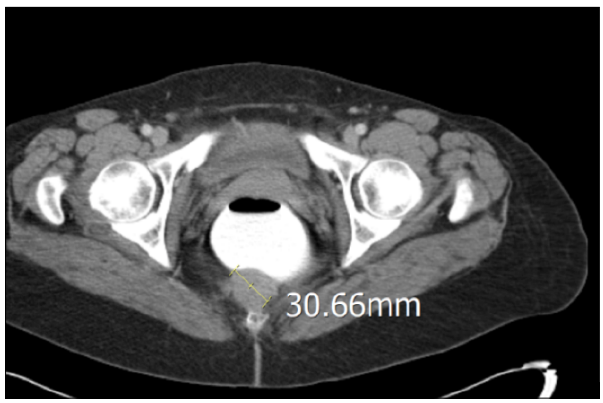

Figure 1. CT is useful for determining the tumor's nature (cystic or solid) and its relationship with bone structures.

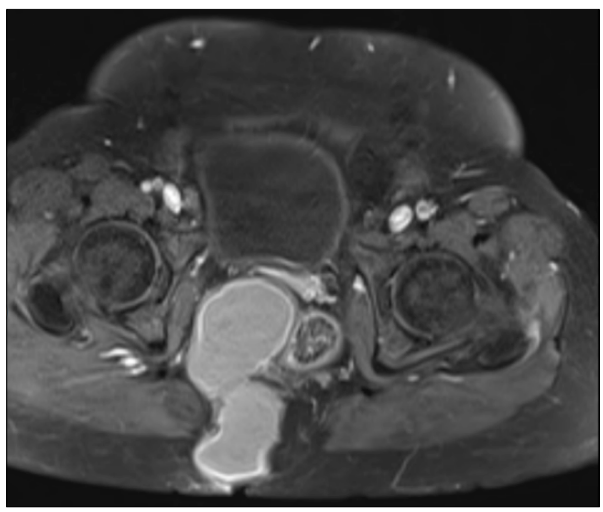

Figure 2. MRI excels in assessing soft tissue involvement and the extent of adjacent structure invasion.

MATERIALS AND METHODS

Between 2012 and 2022, patients treated surgically for RRT at Kartal Dr. Lütfi Kırdar State Hospital were retrospectively analyzed from a prospectively followed data pool. The study was approved by Kartal Dr. Lütfi Kırdar State Hospital ethics committee on 22.02.2022 with the number 2022/514/220/14. Medical data of the patients were obtained through the hospital information system, outpatient clinic visits, and consultations. Patients under 18 years of age, those with rectal cancer, gynecological malignancies, urological malignancies, or any retrorectal abscess diagnosis or history were excluded from the study. Demographic characteristics, American Society of Anesthesiologists (ASA) physical status classification, presenting symptoms, radiological imaging methods aiding diagnosis, whether histopathological sampling was performed, details related to the operation, intraoperative and postoperative complications (Clavien-Dindo classification),[12] postoperative hospital stay duration, 30-day postoperative mortality, mean follow-up duration, recurrence, and histopathological findings of the patients were recorded. As a clinical approach, preoperative biopsy was not planned to minimize the risk of tumor seeding and surgical site infection and to avoid other complications. All patients underwent preoperative radiological examination; imaging findings were reported by radiology specialists. Imaging report elements, including tumor size, localization, relationship with adjacent structures, and tumor morphology, were collected. Three main surgical approaches were used to remove RRTs depending on the tumor characteristics in the imaging. The anterior approach was generally preferred for tumors located above the S3 level, the posterior approach for tumors located below the S3 level, and the combined approach for large tumors or tumors located both above and below the S3 level. All patients received preoperative information and provided written consent for surgery. Bowel preparation was completed

Table 1. Characteristics of the patient group

Characteristics	n	%
Colonoscopy		
Polypectomy (Benign)	3	13.0
External compression on rectum	2	8.7
No colonoscopy	8	34.8
Normal colonoscopy	10	43.5
Symptoms		
Leg pain	1	4.3
Incidental	1	4.3
Constipation	3	13.0
Constipation and coccydynia	1	4.3
Abdominal pain	3	13.0
Abdominal pain and constipation	1	4.3
Abdominal pain and coccydynia	1	4.3
Coccydynia	12	52.2
ASA Score		
ASA1	4	17.4
ASA2	17	73.9
ASA3	2	8.6
Type of operation		
Kraske	17	73.9
Conversion from laparoscopy to laparotomy	1	4.3
Laparotomy	4	17.4
Conversion from laparotomy to Kraske	1	4.3
Preop Complication		
Rectum perforation - primary repair	2	8.6
Ureter injury - repair + double J catheter	1	4.3
None	20	87.0
Characteristics	**n**	**%**
Postop complication		
None	20	87.0
Yes (recurrence after 4 years)	3	13.0
Length of hospital stay		
1 day	1	4.3
2 days	6	26.1
3 days	7	30.4
4 days	5	21.7
5 days	4	17.4
Cyst perforated		
Yes	8	34.8
No	15	65.2
Preop biopsy		
Yes	1	4.3
No	22	95.7
Operation Duration (minutes)	35 (20-60)	
Follow up		
None	5	21.7
Yes	18	78.3
Follow-up Duration (months)	6 (2-12)	
S3 Involvement		
None	20	87.0
Yes	3	13.0

for all cases. Patients undergoing pelvic surgery received venous thromboembolism prophylaxis with low molecular weight heparin starting the night before surgery and continuing for up to 4 weeks after discharge. Antibiotic prophylaxis, consisting of 500 mg metronidazole and 1 g cefazolin, was administered 30 minutes before surgery. All procedures were conducted under general anesthesia, and ureteral stents were inserted in cases where ureteral invasion or suspicion was present. The data were analyzed using IBM SPSS Statistics Standard Concurrent User V 29 (IBM Corp., Armonk, New York, USA). Descriptive statistics included counts (n), percentages (%), mean±standard deviation, and median (minimum-maximum) values.

RESULTS

From 2012 to 2022, 23 patients underwent surgery for retrorectal tumors, with 20 (87.0%) being female and a mean age of 45.2±12.2 (24-65) years. Twelve patients (52.2%) presented with coccygeal pain. Other presenting symptoms are summarized in (Table 1). On physical examination, a mass was palpated in the rectal examination of three patients (13.1%) and in the vaginal examination of three patients (13.1%). Preoperative radiological examinations were performed on all patients; one patient underwent only CT, 12 underwent only MRI, and 10 underwent both CT and MRI. Retrorectal tumors were reported as solid in nine patients (39.1%), cystic in ten patients (43.5%), and heterogeneous in four patients (17.4%). Fifteen patients underwent colonoscopy, revealing external compression in two patients and benign polyps in three patients post-polypectomy. Resected RRTs' histopathologic findings are presented in (Table 2).

DISCUSSION

The literature indicates that retrorectal masses are generally seen in young to middle-aged adults, consistent with the demographic and clinical characteristics of our patients.[1] Postoperative pathology typically reveals benign findings, although malignant pathologies are also possible, emphasizing the importance of surgery. Wolpert et al.[2] indicated that the surgical treatment of retrorectal tumors usually yields successful results despite the risk of complications. Similarly, a study by Hopper et al.[3] emphasized that surgical excision is generally sufficient for benign retrorectal tumors and that radical surgical approaches are necessary for malignant tumors. Considering this, the importance and necessity of surgically resecting the tumor en bloc and achieving negative surgical margins are emphasized. In our study, we determined our surgical approach based on the location and characteristics of the tumor. Although intraoperatively rectal perforation and ureteral injury complications were encountered, these complications were managed with appropriate approaches. It has been shown that the rarity of retrorectal tumors and the potential complications and patient management in surgical treatment are quite successful in experienced centers.[13] In our study, surgical outcomes were generally satisfactory, with most patients not experiencing complications or recurrence. However, some patients experienced recurrence after surgery. The potential malignancy and recurrence rates of the cases were consistent with findings from other studies in the literature.[1,13]

Table 2. Histopathological findings

Pathology	n	%
Non-specific inflammation	2	8.7
Angiomyxoma	1	4.3
Epidermoid cyst	3	13.0
Keratinous cyst	4	17.4
Cystic hamartoma	1	4.3
Dystrophic calcification	1	4.3
Micropapillary ependymoma	3	13.0
Schwannoma	1	4.3
Benign cystic lesion	2	8.7
Tailgut cyst (benign cystic findings	4	17.4
No pathology sent (no cyst found)	1	4.3

Conclusion

The rarity of retrorectal tumors presents challenges in surgical treatment and patient management for physicians. However, it is observed that successful outcomes are achieved in experienced centers by evaluating the tumor imaging findings and localization and managing potential complications with appropriate surgical approaches.

Ethics Committee Approval

The study was approved by the Kartal Dr. Lütfi Kırdar State Hospital Ethics Committee (Date: 22.02.2022, Decision No: 2022/514/220/14).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: M.K., C.H.; Design: G.O.; Supervision: H.F.K.; Fundings: Ö.A., S.K.; Materials: O.A.; Data: C.H.; Analysis: M.K.; Literature search: C.H.; Writing: M.K., G.O.; Critical revision: H.F.K.

Conflict of Interest

None declared.

REFERENCES

1. Kwak HD, Ju JK. Laparoscopic resection of a huge retrorectal tumor. Ann Coloproctol 2020;36:54–7. [CrossRef]
2. Wolpert A, Beer-Gabel M, Lifschitz O, Zbar AP. The management of presacral masses in the adult. Tech Coloproctol 2002;6:43–9.
3. Balci B, Yildiz A, Leventoğlu S, Mentes B. Retrorectal tumors: A challenge for the surgeons. World J Gastrointest Surg 2021;13:1327–37.

4. Uçar AD, Yoldaş T, Oymaci E, Erkan N, Çalişkan C, Yildirim M, et al. Totally curative surgical resection of retrorectal tumors. Hepatogastroenterology 2015;62:606–11.
5. Hobson KG, Ghaemmaghami V, Roe JP, Goodnight JE, Khatri VP. Tumors of the retrorectal space. Dis Colon Rectum 2005;48:1964–74. [CrossRef]
6. Menteş BB, Kurukahvecioğlu O, Ege B, Karamercan A, Leventoğlu S, Yazicioğlu O, et al. Retrorectal tumors: A case series. Turk J Gastroenterol 2008;19:40–4.
7. Merchea A, Larson DW, Hubner M, Wenger DE, Rose PS, Dozois EJ. The value of preoperative biopsy in the management of solid presacral tumors. Dis Colon Rectum 2013;56:756–60. [CrossRef]
8. Toh JW, Morgan M. Management approach and surgical strategies for retrorectal tumours: A systematic review. Colorectal Dis 2016;18:337–50. [CrossRef]
9. Carpelan-Holmström M, Koskenvuo L, Haapamäki C, Renkonen-Sinisalo L, Lepistö A. Clinical management of 52 consecutive retro-rectal tumours treated at a tertiary referral centre. Colorectal Dis 2020;22:1279–85. [CrossRef]
10. Hopper L, Eglinton TW, Wakeman C, Dobbs BR, Dixon L, Frizelle FA. Progress in the management of retrorectal tumours. Colorectal Dis 2016;18:410–7. [CrossRef]
11. Mullaney TG, Lightner AL, Johnston M, Kelley SR, Larson DW, Dozois EJ. A systematic review of minimally invasive surgery for retrorectal tumors. Techn Coloproctol 2018;22:255–63. [CrossRef]
12. Bullard Dunn K. Retrorectal tumors. Surg Clin North Am 2010;90:163–71. [CrossRef]
13. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13.

Retrorektal Tümör Cerrahisi: Tek Merkez Çalışması

Amaç: Retrorektal veya presakral tümörler, teşhisi zor ve patolojik olarak heterojenite gösteren nadir tümörlerdir. Bu tümörlerin kesin insidansı bilinmemekle birlikte, üçüncü basamak sağlık merkezlerinde yıllık olarak 1-6 vaka görüldüğü tahmin edilmektedir. Bu çalışmanın amacı, 2012 ve 2022 yılları arasında hastanemiz genel cerrahi kliniğinde retrorektal tümör tanısı alarak cerrahi tedavi gören hastaların klinik ve cerrahi sonuçlarını değerlendirmektir.

Gereç ve Yöntem: 2012 ve 2022 yılları arasında hastanemiz genel cerrahi kliniğinde retrorektal tümör tanısı alarak cerrahi tedavi gören 23 hasta üzerinde retrospektif bir analiz yapıldı. Çalışma için etik kurul onayı alınmış olup, hastaların demografik verileri, başvuru semptomları, radyolojik görüntüleme yöntemleri, cerrahi detaylar ve postoperatif sonuçlar kaydedilmiştir. Tüm hastalar ameliyat öncesi radyolojik olarak değerlendirilmiş ve cerrahi yaklaşım tümörün lokalizasyonuna göre belirlendi.

Bulgular: Retrorektal tümörler genellikle genç-orta yaş erişkin grubunda görülmekte olup, çalışmamızdaki hastaların demografik ve klinik özellikleri literatürdeki diğer çalışmalarla uyumludur. Çoğu vakada benign tümörler saptanırken, bazı malign vakalar da gözlenmiştir. Bu durum retrorektal tümörlerin cerrahi tedavisinin önemini vurgulamaktadır. Literatürde, retrorektal tümörlerin cerrahi tedavisinin genellikle başarılı sonuçlar verdiği, benign tümörlerde cerrahi eksizyonun yeterli olduğu, malign tümörlerde ise radikal cerrahi yaklaşımların gerektiği belirtilmektedir. Çalışmamızda cerrahi yaklaşım tümörün lokalizasyonuna ve özelliklerine göre belirlenmiş, komplikasyonlar uygun yöntemlerle yönetilmiştir.

Sonuç: Retrorektal tümörler nadir görülen ve cerrahi tedavi gerektiren lezyonlardır. Deneyimli merkezlerde yapılan cerrahi müdahaleler başarılı sonuçlar vermekte ve düşük nüks oranlarına sahiptir. Bu tümörlerin yönetimi ve cerrahi tedavisi, tümörün görüntüleme bulgularının ve lokalizasyonunun değerlendirilmesi ile başarılı bir şekilde gerçekleştirilmektedir. Bu çalışma, retrorektal tümörlerin cerrahi tedavisinde kapsamlı bir yaklaşım sunarak, uygun cerrahi stratejilerin belirlenmesi ve komplikasyonların yönetimi açısından önemli bir katkı sağlamaktadır.

Anahtar Sözcükler: Cerrahi; retrorektal; tümör.

SCIE DOI: 10.14744/scie.2024.46690
South. Clin. Ist. Euras. 2024;35(3):243-247

Original Article

Three-Dimensional Computed Tomography Measurements of Pedicle Diameters and Angles for the Safety of Posterior Cervical Spinal Instrumentation

Ali Börekci,[1] Tufan Hiçdönmez[2]

[1]Department of Neurosurgery, Istanbul Fatih Sultan Mehmet Training and Research Hospital, Republic of Türkiye University of Health Sciences
[2]Department of Neurosurgery, Liv Hospital Vadi Ulus İstinye University Faculty of Medicine İstanbul, Türkiye

Submitted: 19.03.2024
Revised: 28.05.2024
Accepted: 21.06.2024

Correspondence: Ali Börekci, Istanbul Fatih Sultan Mehmet Training and Research Hospital İstanbul, Türkiye
E-mail: aliborekci@hotmail.com

Keywords: Cervical pedicle morphometry; cervical pedicle screw; computed tomography.

ABSTRACT

Objective: The cervical pedicle screw fixation technique ensures rigid stabilization by offering superior correction capability for the restoration of the sagittal alignment of the cervical spine. Given the technical complexity of this procedure and its proximity to critical neurovascular structures, it is imperative for surgeons to thoroughly assess the patient's anatomy before undertaking pedicle instrumentation in the lower cervical spine. This comprehensive evaluation is crucial for minimizing risks and ensuring optimal surgical outcomes.

Methods: In the present study, the widths, heights, transverse angles, and maximum lengths of pedicle screws of the vertebral pedicles between C3 and C7 in posterior cervical spinal instrumentation were bilaterally evaluated in 50 adult patients using preoperative four-way direct radiographs, thin-section computed tomography (CT) scans, and 3-dimensional CT (3D-CT) images.

Results: The results revealed that pedicle height, pedicle width, and maximum screw length increased gradually as we descended caudally from the C3 vertebra to the C7 vertebra, whereas the transverse pedicle angle increased between C3 and C5 and decreased between C5 and C7. The mean maximum screw length varied between 29.7 mm and 33.1 mm.

Conclusion: The findings of this study emphasize the importance of the widths, heights, transverse angles, and maximum lengths of pedicle screws for their appropriate placement into the pedicle in surgical procedures.

INTRODUCTION

Abumi et al.[1] proposed lower cervical vertebrae stabilization with pedicle screws in 1994. Further research by Ito et al.[2] found that pedicle screws are more biomechanically stable than lateral mass screws for cervical fixation from C3 to C6. More specifically, pedicle screws were four times more resistant to rotational pressures and twice as robust against flexion and extension stresses than lateral mass screws. However, cervical vertebrae pedicle screw insertion is technically tough. Although morphological studies have established landmarks and angulation standards for placing cervical pedicle screws, these anatomical markers have proven to be unreliable when dealing with specific diseases such as rheumatic cervical spine disorders and degenerative cervical myelopathy. Due to the heterogeneity in architecture, researchers are now relying more on preoperative computed tomography (CT) scans and personalized guidelines to ensure precise screw placement that is suited to each patient's particular anatomy.[3]

In the present study, the widths, heights, and transverse angles of the vertebral pedicles between C3 and C7 and the maximum lengths of the pedicle screws that could be inserted in posterior cervical spinal instrumentation were bilaterally evaluated in 50 adult patients using preoperative four-way direct radiographs, thin-section CT scans, and 3-dimensional CT (3D-CT) images to produce a database. The findings of this study highlight the importance of these variables for the appropriate placement of pedicle screws into the pedicle in surgical procedures.

MATERIALS AND METHODS

Data from a cohort of 50 patients, comprising 25 female and 25 male individuals, aged between 25 and 65 years, who underwent 3D cervical computed tomography (CT) scans for various indications between 2000 and 2011 at the Department of Neurosurgery, were systematically analyzed utilizing the Novapacs system. Pedicle parameters were meticulously measured. Exclusion criteria included patients with infectious, neoplastic, traumatic, or congenital spinal anomalies. Axial and sagittal images of the C3-C7 cervical vertebral pedicles were selected for analysis, and the following parameters were measured:

1. Craniocaudal Height of the Pedicle: This parameter, also known as the rostrocaudal dimension, was obtained from sagittal images.

2. Pedicle Width: This refers to the mediolateral diameter of the pedicle isthmus.

3. Transverse Angle of the Pedicle: This is the angle between the pedicle axis and the midline of the vertebral corpus.

4. Maximum Screw Length: This measurement represents the distance from the posterior cortex of the lateral mass to the anterior wall of the vertebral corpus along the pedicle axis.

RESULTS

The C3 vertebral level had the lowest mean pedicle height, measuring 6.5 mm in males and 5.6 mm in females. Conversely, the C7 vertebral level had the highest pedicle height, measuring 7.6 mm in men and 6.7 mm in women (Table 1). The height of the pedicle exhibited a tendency to progressively rise towards the distal extremity.

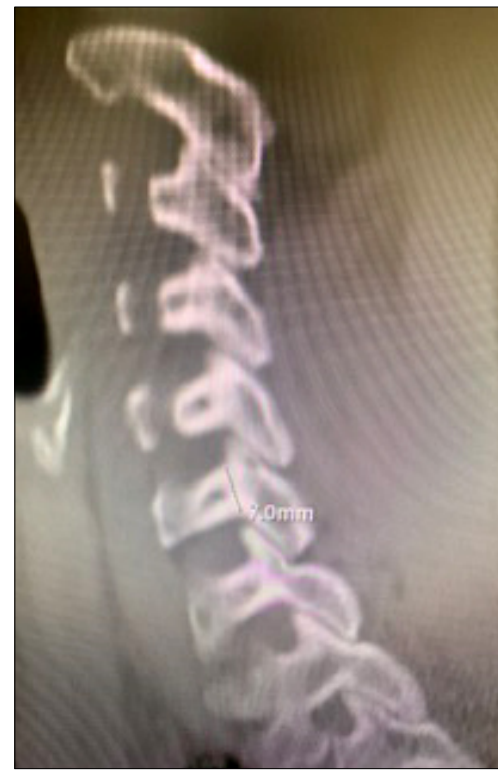

Figure 1. Pedicle height.

In both men and women, the smallest average pedicle width was found at the C3 vertebral level, measuring 5.0 mm for men and 4.0 mm for women. Conversely, the largest average pedicle width was seen at the C7 vertebral level, measuring 7.1 mm for males and 6.1 mm for females (Table 1). There was a tendency for the breadth of the pedicle to expand as one moved from the C3 to C7 vertebrae.

In both men and women, the smallest average transverse

Table 1. Mean values and standard deviations of measurements of cervical pedicle

		Pedicle Width (mm)	Pedicle Height (mm)	Transvers Pedicle Angle (degree)	Maximum Screw Length (mm)
C3	Mean	4.5+-1.0	6.2+-1.1	43.1+-4.8	29.7+-3.6
	Man	5.0+-1.1	6.5+-1.0	42.3+-4.9	30.0+-3.7
	Woman	4.0+-0.8	5.6+-1.0	44.2+-4.9	28.2+-3.3
C4	Mean	4.9+-1.1	6.3+-1.1	45.0+-4.6	29.9+-3.6
	Man	5.3+-1.0	6.7+-1.2	44.3+-4.8	31.2+-3.4
	Woman	4.3+-0.9	5.9+-1.1	45.1+-4.1	28.7+-3.5
C5	Mean	5.4+-1.1	6.5+-1.1	45.4+-4.5	31.1+-4.2
	Man	5.8+-1.1	6.8+-1.2	44.4+-4.1	32.3+-4.1
	Woman	4.9+-0.8	6.0+-1.1	45.8+-4.1	29.7+-3.6
C6	Mean	5.6+-1.0	6.8+-1.1	42.5+-4.8	32.0+-4.3
	Man	6.0+-1.1	7.1+-1.0	42.1+-4.8	32.9+-4.4
	Woman	5.1+-1.0	6.2+-1.1	42.9+-4.8	30.9+-4.0
C7	Mean	6.7+-1.2	7.2+-1.2	37.6+-4.9	33.1+-5.3
	Man	7.1+-1.0	7.6+-1.0	37.4+-4.9	34.4+-5.4
	Woman	6.1+-0.9	6.7+-1.1	38.3+-5.0	31.6+-4.8

Figure 2. Pedicle width (Medio-Lateral Width of the Pedicle Isthmus).

Figure 3. Transverse pedicle angle (Angle between the pedicle axis and the midline of the vertebral corpus).

pedicle angle was found at the C7 vertebral level, measuring 37.4 degrees for men and 38.3 degrees for women. On the other hand, the largest average transverse pedicle angle was observed at the C5 vertebral level, measuring 44.4 degrees for males and 45.8 degrees for females (Table 1).

The mean screw length varied between 29.7 mm and 33.1 mm. The smallest mean maximum screw length was obtained at the C3 vertebral level in men (30.0 mm) and women (28.2 mm), and the largest maximum screw length was obtained at the C7 vertebral level in both men (34.4 mm) and women (31.6 mm) (Table 1).

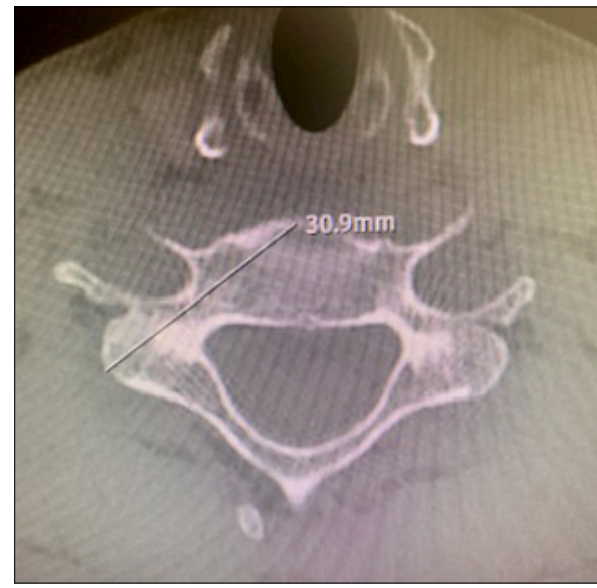

Figure 4. Maximum Screw Length (Distance from the Posterior Cortex of the Lateral Mass to the Anterior Wall of the Vertebral Corpus along the Pedicle Axis).

DISCUSSION

One significant peril associated with cervical pedicle screw insertion is the potential harm to the vertebral arteries. Injuries to the dominant side of the vertebral arteries can lead to significant and potentially severe effects. To reduce the chances of vertebral artery injury, it is important to have a better understanding of the morphological features. In a prior study conducted by Yang et al.,[4] it was discovered that the cervical pedicles on the same side as the dominant vertebral artery had a reduced size. Pedicle screws should not be used at the C3 and C4 vertebrae if the pedicle width is less than 4 mm and the total breadth and distance from the outer cortex to the vertebral artery is less than 5 mm. According to Liu et al.,[5] the third cervical vertebra pedicle was the smallest in the study. The pedicles covered the third to seventh cervical vertebrae.

Previous investigations found that cervical pedicles have a smaller transverse diameter than sagittal width.[6,7] According to Yusof et al.,[8] the pedicles of the lower cervical vertebrae have a greater width in the sagittal direction compared to their width in the transverse direction. A morphometric research study was conducted on the subaxial vertebrae of a Malaysian population using CT scans to determine the key factor affecting the feasibility of employing the pedicle screw procedure on these vertebrae, which is the transverse diameter of the pedicles. The findings from the study showed that the widest pedicle was found at the C7 vertebra for both male and female participants. On the other hand, the narrowest pedicle was seen at the C4 vertebra for male participants and at the C3 vertebra for female individuals. Additionally, they stated that a minimum pedicle width of 4.5 mm is necessary for the insertion of a 3.5-mm cervical pedicle screw.[8] According to

the existing literature, the findings from this study showed that the lowest diameter of the pedicle was found at the C3 vertebra, while the maximum diameter was seen at the C7 vertebra. Furthermore, the pedicle diameter tended to grow as it moved towards the distal end. The pedicle height values were similar to those reported in prior investigations and exceeded the pedicle width values in both males and females.

In a previous study performed using CT, Dong et al.[9] reported that the optimal medial angulation for cervical pedicle screw placement was 45-55 degrees at C3-6 and 30-45 degrees at C7 vertebrae. Liu et al.[5] reported that the pedicle transverse angle was the highest at C4 and lowest at C7. In the present study, the smallest medial angulation was at the C7 vertebra in both male and female patients, whereas the largest medial angulation was at the C5 vertebra.

Abumi posited that the optimal entry point for the insertion of a pedicle screw is located just inferior to the facet joint, approximately 1-2 mm lateral to the midpoint of the superior articular process.[1] The lateral margin of the cervical vertebrae's lateral mass features a notch that is approximately at the same level as the pedicle. Specifically, the pedicles are situated slightly inferior to this notch at the C2 vertebral level, at the level of the notch between C3 and C6, and at or superior to the notch at the C7 level.[10] Pan et al.[11] delineated this notch, which is considerably lateral to Abumi's prescribed entry point and proximate to the pedicle projection, as their designated entry point. Consequently, they positioned the screw at a significantly higher angle, closely aligning with the true pedicle transverse angle, which they postulated likely mitigated the risk of the proximal medial cortex deflecting the screw laterally.[11] In our clinical practice, we have adopted this notch as the entry point. Our measurements of the maximum feasible screw length from this reference point revealed that the average screw length ranged from 29.7 mm to 33.1 mm. Correspondingly, Mohi Eldin et al.[12] reported the minimum pedicle axis length as 29.5 mm.

Conclusion

Prior to performing pedicle instrumentation in the lower cervical spine, surgeons should thoroughly assess the patients' anatomy. Identifying the locations where the pedicle screws will be inserted, as well as the angles at which they will be placed, and their size prior to surgery might help minimize potential difficulties.

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: A.B., T.H.; Design: A.B., T.H.; Supervision: A.B., T.H.; Fundings: A.B., T.H.; Materials: A.B., T.H.; Data: A.B., T.H.; Analysis: A.B., T.H.; Literature search: A.B., T.H.; Writing: A.B., T.H.; Critical revision: A.B., T.H.

Conflict of Interest

None declared.

REFERENCES

1. Abumi K, Itoh H, Taneichi H, Kaneda K. Transpedicular screw fixation for traumatic lesions of the middle and lower cervical spine: description of the techniques and preliminary report. J Spinal Disord 1994;7:19–28. [CrossRef]
2. Ito Z, Higashino K, Kato S, Kim SS, Wong E, Yoshioka K, et al. Pedicle screws can be 4 times stronger than lateral mass screws for insertion in the midcervical spine: A biomechanical study on strength of fixation. J Spinal Disord Tech 2014;27:80–5. [CrossRef]
3. Upendra B, Raghavendra R. Techniques of cervical pedicle screw insertion in lower cervical spine - A review. J Clin Orthop Trauma 2020;11:794–801. [CrossRef]
4. Yang J, Li T, Wang Q, Wang G, Wang S, Xu S, et al. Morphological characteristics of subaxial cervical pedicles and surrounding critical structures in patients with vertebral artery dominance - An anatomical study based on computed tomographic imaging. BMC Musculoskelet Disord 2022;23:306. [CrossRef]
5. Liu J, Napolitano JT, Ebraheim NA. Systematic review of cervical pedicle dimensions and projections. Spine (Phila Pa 1976) 2010;35:E1373–80. [CrossRef]
6. Jones EL, Heller JG, Silcox DH, Hutton WC. Cervical pedicle screws versus lateral mass screws. Anatomic feasibility and biomechanical comparison. Spine (Phila Pa 1976) 1997;22:977–82. [CrossRef]
7. Panjabi MM, Duranceau J, Goel V, Oxland T, Takata K. Cervical human vertebrae. Quantitative three-dimensional anatomy of the middle and lower regions. Spine (Phila Pa 1976) 1991;16:861–9. [CrossRef]
8. Yusof MI, Ming LK, Abdullah MS, Yusof AH. Computerized tomographic measurement of the cervical pedicles diameter in a Malaysian population and the feasibility for transpedicular fixation. Spine (Phila Pa 1976) 2006;31:E221–4. [CrossRef]
9. Dong WX, Hu Y, Yuan ZS. Research into the anatomy of the subaxial cervical pedicle for ensuring screw insertion safety. Medicine (Baltimore) 2024;103:e34646. [CrossRef]
10. Abumi K. Cervical spondylotic myelopathy: posterior decompression and pedicle screw fixation. Eur Spine J 2015;24:186–96. [CrossRef]
11. Pan Z, Zhong J, Xie S, Yu L, Wu C, Ha Y, et al. Accuracy and safety of lateral vertebral notch-referred technique used in subaxial cervical pedicle screw placement. Oper Neurosurg (Hagerstown) 2019;17:52–60. [CrossRef]
12. Mohi Eldin MM. Cervical pedicle screw fixation: anatomic feasibility of pedicle morphology and radiologic evaluation of the anatomical measurements. Asian Spine J 2014;8(3):273–80. [CrossRef]

Posterior Servikal Spinal Enstrümantasyonda Uygulama Güvenliği İçin Pedikül Çapları ve Açılarının Üç Boyutlu Bilgisayarlı Tomografi İle Ölçümleri

Amaç: Servikal pedikül vida tekniği omurganın sagital diziliminin restorasyonu için yüksek korreksiyon kabiliyeti sağlayarak rijit fiksasyona olanak sağlar. Tekniğin zorluğu ve önemli nörovasküler yapılara komşuluğundan dolayı, cerrahlar alt servikal omurgada pedikül enstrümantasyonu yapmadan önce hastanın bireysel anatomisini ayrıntılı olarak değerlendirmelidir.

Gereç ve Yöntem: Bu çalışmada, posterior servikal spinal enstrümantasyonda C3-C7 arası vertebral pediküllerin genişlikleri, yükseklikleri, transvers açıları ve pedikül vidalarının maksimum uzunlukları, preoperatif dört yönlü direkt grafi, ince kesit bilgisayarlı tomografi (BT) ve 3 boyutlu bilgisayarlı tomografi (3B-BT) görüntüleri ile 50 erişkin hastada iki taraflı değerlendirilerek veritabanı elde edildi.

Bulgular: Elde edilen verilere göre C3 vertebrasından C7 vertebrasına doğru kaudale doğru inildikçe pedikül yüksekliğinin, pedikül genişliğinin ve yerleştirilebilecek maksimum vida boyunun giderek arttığı; transvers pedikül açısının ise C3-5 arası artıp, C5-7 arası azaldığı belirlendi. Ortalama maksimum vida uzunluğu 29.7 mm ile 33.1 mm arasında bulundu.

Sonuç: Bu değişkenlerin cerrahi uygulamalarda pedikül vidalarının pediküle uygun yerleştirilebilmesi için önemi vurgulandı.

Anahtar Sözcükler: Bilgisayarlı tomografi; servikal pedikül vidası; servikal pedikül morfometrisi.

SCIE DOI: 10.14744/scie.2024.59751
South. Clin. Ist. Euras. 2024;35(3):248-252

Original Article

What Is the Ideal Risk Scoring System for Acute Variceal Bleeding in Cirrhotic Patients?

Yavuz Çagir,[1] Muhammed Bahaddin Durak,[1] Cem Şimsek,[2] İlhami Yüksel[1]

[1]Department of Gastroenterology, Ankara City Hospital, Ankara, Türkiye
[2]Department of Gastroenterology, Health Sciences University, Mehmet Akif İnan Training and Research Hospital, Şanlıurfa, Türkiye

Submitted: 29.07.2023
Revised: 26.08.2024
Accepted: 27.08.2024

Correspondence: Muhammed Bahaddin Durak, Department of Gastroenterology, Ankara City Hospital, Ankara, Türkiye
E-mail: doctormbd@gmail.com

Keywords: AIMS65 score; Child-Turcotte-Pugh score; MELD score; mortality; rebleeding.

ABSTRACT

Objective: This study aimed to evaluate the predictive capacities of three risk scoring systems, Child-Turcotte-Pugh score (CTP), MELD score (Model for End-Stage Liver Disease), and AIMS65 score, in anticipating 3-month rebleeding and mortality in cirrhotic patients presenting with acute variceal bleeding (AVB).

Methods: At the time of initial presentation, we prospectively collected patients' medical histories, vital signs, laboratory results, endoscopic findings, and interventions. Clinical outcomes were defined as 3-month rebleeding and mortality.

Results: Among the three scoring systems, the CTP and MELD scores demonstrated comparable abilities to predict 3-month rebleeding, both statistically superior to the AIMS65 score (AUC: 0.676, 0.665, 0.558, respectively). The predictive capacities of the three scoring systems (CTP, MELD, AIMS65) for 3-month mortality were similar and demonstrated high accuracy (AUC: 0.861, 0.753, 0.769, respectively). In the high-risk patient group, the MELD scores showed significant sensitivity (87.5%).

Conclusion: The three scoring systems, which are easy to calculate, may be useful in predicting rebleeding and mortality, with the CTP score being particularly beneficial.

INTRODUCTION

Variceal hemorrhage, resulting from portal hypertension in patients with cirrhosis, is a significant cause of morbidity and mortality.[1] Cirrhosis is the most common cause of portal hypertension. Varices develop in order to decompress the hypertensive portal vein and return blood to the systemic circulation. They are seen when the pressure gradient between the portal and hepatic veins rises above 12 mmHg; patients with lower values do not form varices and do not bleed. The reduction of the hepatic vein pressure gradient to less than or equal to 12 mmHg was associated with a significant reduction in the risk of acute variceal bleeding (AVB) and mortality.[2]

Various clinical and physiological factors, including variceal location, size, and appearance, are employed to predict the risk of variceal hemorrhage in patients with cirrhosis. Several clinical scoring systems, namely the Child-Turcotte-Pugh score (CTP), MELD score (Model for End-Stage Liver Disease), and AIMS65 score, have been utilized to predict rebleeding and mortality in patients with acute variceal hemorrhage.[3]

The CTP score assesses the degree of liver dysfunction and is based on serum albumin concentration, bilirubin level, prothrombin time, and the presence of ascites and encephalopathy. The MELD score, developed to determine 3-month mortality, incorporates serum creatinine, bilirubin, sodium level, and international normalized ratio results. It is valuable in prioritizing patients for liver transplantation.[4,5] The AIMS65 score, developed by Saltzman and colleagues,[3] predicts mortality in patients presenting with upper gastrointestinal bleeding, including both variceal and nonvariceal etiologies. The AIMS65 score comprises albumin level <3.0 g/dL (A), international normalized ratio (INR) >1.5 (I), altered mental status (M), systolic blood pressure ≤90 mmHg (S), and age >65 years.[6] AIMS65 is a

simple, accurate risk score that predicts in-hospital mortality in patients with acute upper gastrointestinal bleeding.[6] All three scoring systems are straightforward to calculate without requiring endoscopic findings.

Each episode of active variceal hemorrhage carries a mortality risk of up to 20 percent.[7,8] Varices are present in 50% of cirrhotic patients, and their incidence increases at a rate of 5-15% per year.[8,9] Furthermore, survivors of variceal bleeding have a 70 percent chance of experiencing recurrent hemorrhage within one year.[10]

Despite the increasing utilization of CTP and MELD scores in predicting AVB, there is a lack of comparative studies investigating the long-term prediction of rebleeding and mortality among the three scoring systems. Therefore, the objective of this study was to evaluate the predictive capacity of these three risk scoring systems for 3-month rebleeding and mortality in cirrhotic patients presenting with AVB.

MATERIALS AND METHODS

Study Population

This investigation encompassed cirrhotic individuals aged 18 and above who had an endoscopic diagnosis of acute variceal bleeding (AVB), including esophageal, gastric, or both. Exclusion criteria incorporated patients incapable of undergoing endoscopy due to procedural refusal or adverse clinical progression, those unwilling to participate, noncirrhotic patients, patients with malignancy, and individuals with insufficient data. The study obtained approval from Ankara City Hospital Scientific Research and Ethics Committee, Approval No: E1/1051/2020, and date 02.09.2020.

Data Collection

Medical histories, vital signs, laboratory results, endoscopic findings, and interventions were compiled prospectively from February 2019 through September 2020. The CTP, MELD, and AIMS65 scores were calculated using a standardized app, following internationally accepted protocols. Data on 3-month rebleeding and mortality were recorded prospectively via the hospital's electronic medical records.

Patient Management

Patients with AVB were initially evaluated in the emergency department and were referred to a gastroenterologist for bleeding management. Vasopressors (somatostatin or terlipressin, as available) were administered to all patients diagnosed with AVB for 72–120 hours, followed by the calculation of the CTP, MELD, and AIMS65 scores by gastroenterologists. Patients were then transferred to the intensive care unit for further management. Pantoprazole 40 mg/day intravenously was administered to all patients during hospitalization to prevent esophageal ulceration.

The choice of endoscopic treatment was between endoscopic band ligation and cyanoacrylate sclerotherapy, contingent on the patient's hemodynamic status, decline in hemoglobin level despite blood transfusion, and presence of active bleeding. In the event of endoscopic therapy failure, a Sengstaken-Blakemore tube was inserted to temporarily control the bleeding. Rebleeding during hospitalization prompted a repetition of the endoscopic procedure. Patients showing clinical improvement after discharge were monitored for 90 days, with propranolol dose titration initiated in the absence of contraindications.

Study Outcomes

The primary outcomes were defined as 3-month rebleeding and mortality. Rebleeding was identified by a decrease in hemoglobin of more than 2 g/dL, coupled with signs of bleeding (hematemesis and/or melena). Subsequent endoscopy was performed to evaluate rebleeding in cases of a drop in hemoglobin. Mortality encompassed all-cause death, including in-hospital death and death within the three-month follow-up period. The accuracy of the three scoring systems was evaluated based on these outcomes. Patients were stratified into low- and high-risk groups using established scoring system cut-off values. Based on the reference studies of the scoring systems, those with CTP score ≤6, MELD score <11, and AIMS65 score =0 were considered low-risk, and those with CTP score >6, MELD score >19, and AIMS65 score >1 were considered high-risk patients.[4,5,11]

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA). The normality of numerical variables was assessed using the Kolmogorov-Smirnov test. Normally distributed variables were presented as mean±standard deviation (SD), while non-normally distributed variables were expressed as median (interquartile range [IQR]). Categorical variables were conveyed as frequency (percentage). The ability of risk scoring systems to predict outcomes (rebleeding within 8 weeks and 30-day mortality) was assessed using receiver operating characteristic (ROC) curves. Results were reported as the area under the curve (AUC), 95% confidence interval (CI), specificity, sensitivity, and p-value, with a p-value <0.05 denoting statistical significance.

RESULTS

Our study sample included 103 patients out of the 128 who presented with AVB at the emergency department. The excluded individuals comprised 14 patients with noncirrhotic AVB, 7 patients unable to undergo endoscopy, and 4 patients with incomplete data. The median age of the study cohort was 64 years (53–73), with a slight male predominance (55 men, 53.4%). Two-thirds of the patients had a history of previous variceal bleeding. The median serum hemoglobin, serum urea, INR, serum platelet, and serum albumin levels at presentation were 9.03 g/dL, 58 mg/dL, 1.38, 124x10^9/L, and 31 g/L, respectively.

Most patients were classified as CTP B or C, with the median CTP score being 8 (6-10). The distribution of patients

across CTP A, B, and C was 12%, 63%, and 25%, respectively. The median MELD score was 12 (9-32), and the median AIMS65 score was 1 (0-2). The application of somatostatin or terlipressin therapy was evenly split (46.6% versus 53.4%). The median duration of hospital stay was 8 days (4-11). Table 1 provides a comprehensive summary of patient characteristics, laboratory findings, treatment details, and outcomes.

Rebleeding

A total of 32 patients (31.1%) experienced rebleeding within 3 months. When the cutoff value was set at 6.5, CTP demonstrated a predictive accuracy for rebleeding with 78% sensitivity and 49% specificity (AUC: 0.676, 95% CI: 0.568-0.785, p=0.004). Using a cutoff value of 9.5, MELD predicted rebleeding with 90% sensitivity and 37% specificity (AUC: 0.665, 95% CI: 0.558-0.771, p=0.008). AIMS65, with a cutoff value of 1.5, predicted rebleeding with 53% sensitivity and 67% specificity (AUC: 0.558, 95% CI: 0.435-0.681, p=0.347). These findings are summarized in Table 2.

Table 1. Patients' characteristics, laboratory variables, treatment details, and outcomes*

	Study group (n=103)
Age, years	64 (53-73)
Gender, male, n (%)	55 (53.4)
Previous episode of variceal bleeding, n (%)	66 (64.1)
Pulse, >100 beats/min, n (%)	12 (11.7)
Systolic blood pressure, <90mmHg, n (%)	9 (8.7)
Hemoglobin level on admission (g/dL)	9.03±2.08
Urea level on admission (mg/dL)	58 (43-81)
INR on admission	1.38 (1.2-1.61)
Albumin level on admission (g/L)	31 (27-36)
Platelet level on admission (10^9/L)	124 (89-176)
Child-Pugh score	8 (6-9)
Child-Pugh class, n (%)	
A	12 (12)
B	65 (63)
C	26 (25)
MELD score	12 (9-16)
AIMS65 score	1 (0-2)
Medical therapy, n (%)	
Somatostatin	48 (46.6)
Terlipressin	55 (53.4)
Endoscopic intervention, n (%)	
None	4 (3.9)
Band ligation	81 (78.6)
Sclerotherapy	18 (17.5)
Length of stay, days	8 (4-11)
Rebleeding within 3 months, n (%)	32 (31.1)
Mortality within 3 months, n (%)	18 (17.5)

*Results are expressed as: mean ± standard deviation, median (interquartile range), or frequency (%). INR: International normalized ratio, MELD: Model for End-Stage Liver Disease.

Despite the demonstrated predictive abilities of these scoring systems, none were able to efficiently identify patients at low risk of 3-month rebleeding. In the low-risk patient group, the AUC value of all three scoring systems was low and statistically insignificant in predicting rebleeding (AUCs for CTP, MELD, and AIMS65 were 0.600, 0.695, and 0.500, respectively, p>0.05). In contrast, for high-risk patients, the MELD-Na scores showed significant sensitivity (87.5%, p=0.02) in predicting 3-month rebleeding.

Mortality

Of the study participants, 18 (17.5%) succumbed within 3 months. The CTP score predicted mortality with a sensitivity of 72% and specificity of 82% (AUC: 0.861, 95% CI: 0.774-0.948, p<0.001). The MELD score predicted mortality with 50% sensitivity and 92% specificity (AUC: 0.753, 95% CI: 0.621-0.885, p=0.001). The AIMS65 score predicted mortality with a sensitivity of 78% and specificity of 68% (AUC: 0.769, 95% CI: 0.634–0.904, p<0.001) (Table 2).

Among high-risk patients, the CTP score predicted 3-month mortality with 78% sensitivity and 33% specificity, outperforming the other two scoring systems (AUC: 0.725, 95% CI: 0.564-0.887, p=0.006). However, in the low-risk group, akin to the results for rebleeding, none of the scoring systems demonstrated predictive utility for mortality.

DISCUSSION

This study has highlighted the presence of acute variceal bleeding (AVB) in cirrhotic individuals as an indicator of disease progression and a leading cause of mortality. Identifying high-risk patients is crucial for devising effective strategies to reduce mortality and select suitable candidates for emergency interventions. While the Glasgow Blatchford Score is recommended for risk stratification in acute nonvariceal upper gastrointestinal bleeding (ANVUGIB), there is no universally accepted scoring system for patients with AVB. This condition is more dangerous than nonvariceal bleeding and, therefore, requires effective risk stratification.[12]

We analyzed three easily calculable scoring systems-CTP, MELD, and AIMS65-for risk stratification in patients with acute variceal bleeding (AVB). While none of these scoring systems proved optimal, the CTP score was superior in predicting 3-month rebleeding and mortality. The MELD and AIMS65 scores, however, were able to demonstrate comparable mortality prediction statistics to the CTP score.

When compared, the CTP and MELD scores showed a statistically significant and comparable ability to predict 3-month rebleeding, surpassing the AIMS65 score (AUC: 0.676, 0.665, 0.558, respectively). All three scoring systems

Table 2. The ability of risk scoring systems to predict rebleeding and mortality within 3 months

	AUC	95% CI	p	Cut-off	Sensitivity	Specificity
Rebleeding within 3-months						
Child-Pugh score	0.676	0.568-0.785	0.004	6.5	0.781	0.493
MELD score	0.665	0.558-0.771	0.008	9.5	0.906	0.366
AIMS65 score	0.558	0.435-0.681	0.347	1.5	0.531	0.662
Mortality within 3-months						
Child-Pugh score	0.861	0.774-0.948	<0.001	8.5	0.722	0.824
MELD score	0.753	0.621-0.885	0.001	19.5	0.500	0.918
AIMS65 score	0.769	0.634-0.904	<0.001	1.5	0.778	0.682

Significant P values are in bold. AUC: Area under curve, CI: Confidence interval; MELD: Model for End-Stage Liver Disease.

similarly exhibited high accuracy in predicting 3-month mortality (AUC: 0.861, 0.753, 0.769, respectively).

According to the determined low- and high-risk cut-off values of these scoring systems, none proved sufficient in identifying 3-month rebleeding and mortality in the low-risk patient group. In the high-risk patient group, the sensitivity of the MELD scores was significant (87.5%), while the CTP and AIMS65 scores had much lower sensitivity (66% and 35%, respectively) in predicting 3-month rebleeding. When compared to the MELD and AIMS65, the CTP score showed 78% sensitivity and 33% specificity in predicting mortality within 3 months in patients classified as high-risk based on the cutoff value.

Despite the limitations of these scoring systems, the CTP score showed superiority in predicting 3-month rebleeding and mortality. Other scoring systems, such as the Full Rockall Score and the GBS, were assessed in studies to predict rebleeding and mortality in AVB patients. However, their efficacy was found to be insufficient in AVB compared to the scoring systems in our study, even though they demonstrated efficacy in acute nonvariceal upper gastrointestinal bleeding (ANVUGIB).[3,13,14]

Previous studies have highlighted the high accuracy of the CTP and MELD scores in predicting rebleeding and mortality.[12-14] Our study corroborates these findings, particularly in terms of 3-month mortality prediction. Contrary to previous studies that focused on hospitalization or 4-6-week outcomes, our study investigated patients by risk stratification and evaluated mortality and rebleeding at a 3-month follow-up.

Aluizio and colleagues emphasized the importance of the CTP score in predicting 6-week mortality.[15] While the Child and MELD scores were shown to detect 6-week mortality with high accuracy (AUROC=0.72 and 0.74, respectively), they demonstrated poor accuracy in predicting rebleeding. In contrast, our study found that the CTP and MELD scores can accurately predict three-month rebleeding, and all three scoring systems (with CTP being the most accurate) are highly predictive of mortality. This discrepancy in three-month rebleeding predictions may be due to the fact that our study's patient population predominantly included high-risk patients.

The AIMS65 score, designed by Hyett et al. to assess the mortality risk of patients presenting with gastrointestinal bleeding, had high sensitivity in predicting death but was insufficient in predicting rebleeding, similar to our findings.[14] The AIMS65 score's advantage is its applicability in patients with both AVB and ANVUGIB.[11,16,17]

For patients presenting with ANVUGIB, they can be discharged if GBS is ≤1.[12] While GBS is effective in identifying low-risk patients among those with ANVUGIB, no scoring system has been found to reliably detect low-risk patients among those presenting with acute variceal bleeding (AVB).[18,19] In our evaluation of rebleeding and mortality in the low-risk patient group, all three scoring systems-CTP, MELD, and AIMS65-had low AUROC values and showed similar performance. The usability of these scoring systems for low-risk AVB patients appears to be limited. In the context of AVB, focusing on identifying high-risk patients may prove more beneficial than trying to pinpoint low-risk patients. This approach can enable timely and targeted interventions, potentially improving patient outcomes.

One limitation of this study was that the majority of the patient population consisted of high-risk patients, as our hospital is a tertiary general admission hospital and is usually where such patients are referred. This may have introduced bias in the evaluation of low-risk patients. Despite this limitation, our study had several strengths, including its prospective design, the inclusion of all patients presenting with AVB from cirrhotic patients, the application of vasopressor therapy to all patients as a standard treatment protocol, and endoscopic evaluation.

Conclusion

In conclusion, our findings suggest that the CTP and MELD scores can reliably predict 3-month rebleeding, and the CTP score is superior in predicting 3-month mortality. However, all three scoring systems are highly predictive. Therefore, calculating these simple scoring systems in patients with AVB may be beneficial in assessing prognosis.

Ethics Committee Approval

The study was approved by the The Ankara City Hospi-

tal Scientific Research and Ethics Committee (Date: 02.09.2020, Decision No: E1/1051/2020).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: M.B.D., Y.Ç., C.Ş., İ.Y.; Design: M.B.D., Y.Ç., C.Ş., İ.Y.; Supervision: M.B.D., C.Ş., İ.Y.; Materials: M.B.D., Y.Ç.; Data: M.B.D., Y.Ç.; Analysis: M.B.D., Y.Ç., C.Ş., İ.Y.; Literature search: M.B.D., Y.Ç., C.Ş., İ.Y.; Writing: M.B.D., Y.Ç., C.Ş., İ.Y.; Critical revision: C.Ş., İ.Y.

Conflict of Interest

None declared.

REFERENCES

1. Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. N Engl J Med 2010;362:823–32. [CrossRef]
2. D'Amico G, Garcia-Pagan JC, Luca A, Bosch J. Hepatic vein pressure gradient reduction and prevention of variceal bleeding in cirrhosis: A systematic review. Gastroenterology 2006;131:1611–24. [CrossRef]
3. Wang F, Cui S, Wang F, Li F, Tang F, Zhang X, et al. Different scoring systems to predict 6-week mortality in cirrhosis patients with acute variceal bleeding: A retrospective analysis of 202 patients. Scand J Gastroenterol 2018;53:885–90. [CrossRef]
4. Cholongitas E, Papatheodoridis GV, Vangeli M, Terreni N, Patch D, Burroughs AK. Systematic review: The model for end-stage liver disease - Should it replace Child-Pugh's classification for assessing prognosis in cirrhosis? Aliment Pharmacol Ther 2005;22:1079–89. [CrossRef]
5. Kamath PS, Kim WR; Advanced liver disease study group. The model for end-stage liver disease (MELD). Hepatology 2007;45:797–805. [CrossRef]
6. Saltzman JR, Tabak YP, Hyett BH, Sun X, Travis AC, Johannes RS. A simple risk score accurately predicts in-hospital mortality, length of stay, and cost in acute upper GI bleeding. Gastrointest Endosc 2011;74:1215–24. [CrossRef]
7. Ibrahim M, Mostafa I, Devière J. New developments in managing variceal bleeding. Gastroenterology 2018;154:1964–9. [CrossRef]
8. Reverter E, Tandon P, Augustin S, Turon F, Casu S, Bastiampillai R, et al. A MELD-based model to determine risk of mortality among patients with acute variceal bleeding. Gastroenterology 2014;146:412–19.e3. [CrossRef]
9. Grace ND. Prevention of initial variceal hemorrhage. Gastroenterol Clin North Am 1992;21:149–61. [CrossRef]
10. Graham DY, Smith JL. The course of patients after variceal hemorrhage. Gastroenterology 1981;80:800–9. [CrossRef]
11. Hyett BH, Abougergi MS, Charpentier JP, Kumar NL, Brozovic S, Claggett BL, et al. The AIMS65 score compared with the Glasgow-Blatchford score in predicting outcomes in upper GI bleeding. Gastrointest Endosc 2013;77:551–7. [CrossRef]
12. Gralnek IM, Stanley AJ, Morris AJ, Camus M, Lau J, Lanas A, et al. Endoscopic diagnosis and management of nonvariceal upper gastrointestinal hemorrhage (NVUGIH): European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2021. Endoscopy 2021;53:300–32. [CrossRef]
13. Yang L, Sun R, Wei N, Chen H. Systematic review and meta-analysis of risk scores in prediction for the clinical outcomes in patients with acute variceal bleeding. Ann Med 2021;53:1806–15. [CrossRef]
14. Rout G, Sharma S, Gunjan D, Kedia S, Nayak B, Shalimar. Comparison of various prognostic scores in variceal and non-variceal upper gastrointestinal bleeding: A prospective cohort study. Indian J Gastroenterol 2019;38:158–66. [CrossRef]
15. Aluizio CLS, Montes CG, Reis GFSR, Nagasako CK. Risk stratification in acute variceal bleeding: Far from an ideal score. Clinics (Sao Paulo) 2021;76:e2921. [CrossRef]
16. Lai YC, Hung MS, Chen YH, Chen YC. Comparing AIMS65 score with MEWS, qSOFA score, glasgow-blatchford score, and rockall score for predicting clinical outcomes in cirrhotic patients with upper gastrointestinal bleeding. J Acute Med 2018;8:154–67.
17. Motola-Kuba M, Escobedo-Arzate A, Tellez-Avila F, Altamirano J, Aguilar-Olivos N, González-Angulo A, et al. Validation of prognostic scores for clinical outcomes in cirrhotic patients with acute variceal bleeding. Ann Hepatol 2016;15:895–901.
18. Budimir I, Gradišer M, Nikolić M, Baršić N, Ljubičić N, Kralj D, et al. Glasgow Blatchford, pre-endoscopic Rockall and AIMS65 scores show no difference in predicting rebleeding rate and mortality in variceal bleeding. Scand J Gastroenterol 2016;51:1375–9. [CrossRef]
19. Thanapirom K, Ridtitid W, Rerknimitr R, Thungsuk R, Noophun P, Wongjitrat C, et al. Prospective comparison of three risk scoring systems in non-variceal and variceal upper gastrointestinal bleeding. J Gastroenterol Hepatol 2016;31:761–7. [CrossRef]

Sirotik Hastalarda Akut Varis Kanaması İçin İdeal Risk Puanlama Sistemi Nedir?

Amaç: Akut varis kanaması ile başvuran sirotik hastalarda 3 aylık yeniden kanama ve mortaliteyi tahmin etmede üç risk skorlama sisteminin (Child-Turcotte-Pugh skoru (CTP), MELD skoru ve AIMS65 skoru) prediktivitesini değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Başvuru sırasında, hastaların tıbbi öykülerini, vital bulgularını, laboratuvar sonuçlarını, endoskopik bulgularını ve müdahalelerini prospektif olarak topladık. Klinik sonuçlar 3 aylık tekrar kanama ve mortalite olarak tanımlandı.

Bulgular: Üç skorlama sistemi arasında, CTP ve MELD skorları, her ikisi de AIMS65 skorundan istatistiksel olarak daha üstün olan (sırasıyla, AUC: 0.676, 0.665, 0.558) 3 aylık yeniden kanamayı predikte etmede benzer doğrulukta idi. Üç puanlama sisteminin (CTP, MELD, AIMS65) 3 aylık mortaliteyi öngörme kapasiteleri benzerdi ve yüksek doğruluk gösterdi (sırasıyla, AUC: 0.861, 0.753, 0.769). Yüksek riskli hasta grubunda MELD skorunun duyarlılığı daha anlamlı idi (%87.5).

Sonuç: Hesaplanması kolay olan üç skorlama sistemi, özellikle CTP skoru olmak üzere, tekrar kanama ve mortaliteyi öngörmede faydalı olabilir.

Anahtar Sözcükler: Akut varis kanaması; AIMS65 skoru; Child-Turcotte-Pugh skoru; son dönem karaciğer hastalığı modeli.

SCIE DOI: 10.14744/scie.2024.29964
South. Clin. Ist. Euras. 2024;35(3):253-261

Original Article

Prognostic Nutritional Index and Systemic Immune Inflamatory Index: Can They Predict Mortality in Peritoneal Dialysis Patients?

Serap Yadigar,[1*] Pınar Özdemir,[1] Murat Tuğcu,[3] Erman Özdemir,[2]
Serkan Feyyaz Yalın,[1] Meral Meşe,[1] Ebru Asicioglu,[3] Ergün Parmaksız[1]

[1]Department of Nephrology, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye
[2]Division of Nephrology, Department of Internal Medicine, Pendik State Hospital, Istanbul, Türkiye
[3]Division of Nephrology, Department of Internal Medicine, Marmara University, Pendik Training and Research Hospital, Istanbul, Türkiye

Submitted: 06.03.2024
Revised: 22.05.2024
Accepted: 24.05.2024

Correspondence: Serap Yadigar, Department of Nephrology, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Türkiye
E-mail: serapsert2000@yahoo.com

Keywords: Peritoneal dialysis; prognostic nutritional index; systemic immune inflamatory index.

ABSTRACT

Objective: Nutritional evaluation in peritoneal dialysis patients, one of the replacement treatment methods in chronic renal failure, is becoming increasingly important in terms of mortality and morbidity. The Prognostic Nutritional Index (PNI) and Immune-Inflammation Index (SII) are new inflammatory indexes that have been shown to have prognostic value in many diseases. In our study, we investigated the relationship between high SII scores, low PNI scores, and mortality in PD patients.

Methods: PNI and SII scores were calculated in 84 patients undergoing peritoneal dialysis. Patients with low PNI scores and high SII scores were divided into groups. These indices were examined in terms of their prediction of mortality and morbidity in peritoneal dialysis patients.

Results: The mortality rate in the low PNI group was higher than in the high PNI score group (p=0.04). There was a difference between the groups in terms of mortality KT/v values in the low SII group (p=0.008). In the SII group, this value was higher in the high SII group, and there was a statistically significant difference in PTH values between the two groups (p=0.024).

Conclusion: In our study, overall mortality was found to be higher in the low PNI group. This supports the consideration of the PNI score in the evaluation of nutritional status in peritoneal dialysis patients. As expected, we did not find a relationship with increased mortality in patients with high SII scores, probably because our number of patients was small. However, these patients have lower dialysis adequacy rates and worse bone mineral metabolism control, and renal residual urine output was lower. These three parameters are known to contribute to mortality in PD patients.

INTRODUCTION

Peritoneal dialysis (PD) is one of the renal replacement therapy options for patients with end-stage renal disease (ESRD).[1] Cardiovascular diseases (CVD) are the most common cause of death in patients with chronic renal failure.[2] Early diagnosis and prevention of cardiovascular diseases are vital in order to reduce morbidity and mortality in ESRD patients.[3] Protein-energy malnutrition is a common condition in peritoneal dialysis patients and is associated with high mortality.[4,5] Studies have shown that morbidity and mortality decrease with the improvement of nutritional status in this group of patients.[6,7] Recently, the International Society for Peritoneal Dialysis (ISPD) recommended nutritional assessment in adult PD patients in order to reduce cardiovascular risk.[2] However, there is no single recommended method for the assessment of malnutrition in PD patients. Therefore, in terms of the assessment of malnutrition, a careful physical examination and questionnaire are evaluated with pooled data from various parameters, including weight loss, body mass index, and serum albümin.[8]

The prognostic nutritional index (PNI) is a formula formed by the serum albumin concentration in the peripheral blood and the total lymphocyte count.[9] Recently, the

prognostic value of PNI has been variously confirmed.[10-14] There are few articles investigating the prognostic role of a low PNI score in PD patients.[15,16] The first aim of our study was to investigate the prognostic value of a low PNI score in PD patients.

On the other hand, the immune-inflammation index (SII) is a new inflammatory index calculated based on peripheral blood neutrophils, platelets, and lymphocytes. Numerous studies have shown that SII can predict the prognosis of malignant tumors such as esophageal cancer and non-small cell lung cancer.[17-19] It has also been reported that there is a relationship between high SII and mortality in patients undergoing hemodialysis.[20] Qin et al.[21] also showed that patients with albuminuria had higher systemic immune-inflammatory index values. However, there are no reports on the relationship between SII and mortality in peritoneal dialysis patients. As a secondary aim, we investigated the relationship between high SII scores and morbidity-mortality in PD patients.

In addition to these goals, we examined whether the initial high SII and low PNI scores of PD patients may predict the risk of peritonitis, which is one of the factors that increase mortality in PD patients.

MATERIALS AND METHODS

Participants

Eighty-five peritoneal dialysis patients followed up between 2018-2022, from two centers were included in our study. Patients under the age of 18, followed up less than one year, switched from chronic hemodialysis, failed renal transplantation, pregnant, and presence of any active inflammatory situations were not included in the study. The study was conducted in compliance with the ethical principles of the Helsinki Declaration and approved by the Kartal Lütfi Kırdar State Hospital Ethics Committee (number: 2021/514/193/2).

Study Protocol

This was a retrospective observational study. Clinical, demographic, and laboratory data of the patients were recorded. PNI and SII scores of the patients during the onset of PD treatment were calculated. The patients were divided into the groups as low/high PNI and high/low SII. We investigated whether low PNI and high SII patients were associated with morbidity and mortality regarding our study group.

Age, gender, weight, blood pressure, primary etiology of ESRD, history of diabetes, hypertension, hyperlipidemia, heart failure, malignancy, CVD risk factors, history of cerebrovascular and peripheral vascular disease were recorded. Laboratory values: leukocytes, lymphocytes, hemoglobin, serum albumin at the onset of PD, serum creatinine, corrected serum calcium, phosphorus, parathormone levels, CRP, and serum uric acid values were also recorded. PNI score was calculated as 10× serum albumin value (g/dl) + 0.005× peripheral lymphocyte count (per mm^3). Systemic immune-inflammation index (SII) was calculated by (N×P)/L (N, P, and L represent neutrophil counts, platelet counts, and lymphocyte counts, respectively).

Total Kt/V (Kt/V is a formula that K=urea clearance by dialysis, t=dialysis time, V=urea distribution volume in proportion to body water. It is used to evaluate dialysis adequacy) was calculated using PD Adequest software 2.0 (Baxter Healthcare Ltd). All of the patients were followed up until either cessation of PD during the study period, death, or May 30, 2022.

Statistical Analysis

Descriptive data were expressed as mean ± standard deviation (SD) and median with interquartile range (IQR) for the continuous variables and frequency and percentages (%) for the categorical variables. The Shapiro-Wilk test was used for evaluating the conformity of continuous variables to normal distribution. Peritoneal dialysis patients were divided into two groups according to their Systemic Immune-Inflammation (SII) and Prognostic Nutritional Index (PNI) levels. PNI levels were defined as low PNI (PNI≤36.6) and high PNI (PNI>36.6), and SII levels were defined as low SII (SII≤390) and high SII (SII>390). PNI groups and SII groups were compared using an independent samples t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Categorical variables were compared by using the Chi-Square or Fisher's Exact test for proportions. The survival of the PD patients was assessed using the Kaplan–Meier method, and comparisons of survival probability between PNI groups or SII groups were analyzed using the log-rank test. The univariate Cox model was applied to investigate the association between independent factors and all-cause mortality. An age-adjusted Cox model for mortality was applied. All statistical analyses were performed by SPSS software version 21 (Chicago, IL) and R (v. 4.0.2). All significance tests were two-tailed, and values of $p<0.05$ were considered statistically significant.

RESULTS

A total of 84 (35 men/49 women) PD patients were recruited in this study (Table 1). Our mean follow-up time was 44.5 months. The overall mortality rate is 20.2%. All of our patients were evaluated for cardiovascular risk factors (Table 1). SII and PNI groups are similar in terms of cardiovascular risks. Five patients were on automated PD. Conventional PD solutions, Y-sets, and twin-bag systems were utilized in continuous ambulatory PD patients. The primary cause of ESRD was diabetic nephropathy (n=69, 82.1%). Glomerulonephritis was present in 17 patients, vesicoureteral reflux in 9 patients, amyloidosis in 4 patients, polycystic renal disease in 3 patients, and renal stone disease in 3 patients. The median PNI level at baseline was 36.82 (range: 33.28-39.22) for all patients. The median SII level at baseline was 672.57 (range: 69.13-

Table 1. Demographic and characteristics of patients

	Patients (n=84)
Age	56.16±13.67
Sex, n (%)	
Men	35 (41.7)
Women	49 (58.3)
Weight	72.98±10.55
Mortality, n (%)	
Yes	17 (20.2)
No	67 (79.8)
Smoking, n (%)	
Yes	73 (86.9)
No	11 (13.1)
HT, (%)	
No	29 (34.5)
Yes	55 (65.5)
DM, n (%)	
No	69 (82.1)
Yes	15 (17.9)
Hyperlipidemia (LDL)	122 (98-157.5)
Family history of cardiovascular disease, n (%)	
No	74 (88.1)
Yes	10 (11.9)
Heart failure, n (%)	
No	75 (89.3)
Yes	9 (10.7)
Serebrovascularinfarct, n (%)	
No	80 (95.2)
Yes	4 (4.8)
Peripheral arterial disease, n (%)	
No	80 (95.2)
Yes	4 (4.8)
PD time (months)	44.5 (22.25-97.25)
Kt/V	2.26 (1.95-2.80)
PNI score	36.82 (33.28-39.22)
PNI, n (%)	
Low	43 (51.2)
High	41 (48.8)
SII score	655.83 (33.28-39.22)
SII, n (%)	
Low	20 (23.8)
High	64 (76.2)
Late onset peritotinitis frequency, n (%)	
No	48 (57.1)
Yes	36 (42.9)

HT: hypertension, DM: Diabetes Mellitus, PD time: Periton diyalysis time, PNI score: prognostic nutritional index score.

1796.67) for all patients. The patients with a high SII score had a lower rate of dialysis adequacy, worse bone mineral metabolism control, and lower renal residual urine output. The overall mortality rate was 20.2% (17/67).

The patients were divided into groups as low/high PNI and high/low SII. The comparison of demographic and laboratory values of the SII groups and PNI groups are shown in Tables 2 and 3.

The median Kt/V value was found to be 2.2 (1.92–2.75) in the high SII group and 2.71 (2.1–3.43) in the low SII group, with a statistically significant difference between the groups in terms of Kt/V values (p=0.008). The median PTH value was found to be 463 (223.25–641.25) in the high SII group. This value was higher in the high SII group, and there was a statistically significant difference between the two groups in terms of PTH values (p=0.024). There was a statistically significant difference between the two groups in terms of median residual urine values (p=0.027). The mortality rate was 21.9% in the high SII group, while it was 15% in the low SII group. There was no statistically significant difference (p=0.75) (Table 2).

On the other hand, the low PNI score group had lower serum calcium levels and higher serum CRP levels. There was a statistically significant difference between the two groups in terms of calcium levels (p=0.004) and CRP levels (p=0.007) (Table 2). Additionally, hypertension was more common in the low-score PNI group (p=0.007). The mortality rate was 12% in the low PNI group, while it was 5% in the high PNI group. There was no statistically significant difference (p=0.10) (Table 3).

The survival probabilities for the PNI groups are shown in Figure 1. The number of deaths in all patients was 17 (20.2%). The number of patients who died in the low PNI group was 12 (27.9%), whereas the number of mortalities in the high PNI group was 5 (12.2%). The mortality rate in the low PNI group was statistically significantly higher compared to the group with a higher PNI score (p=0.04).

The survival probabilities for the SII groups are shown in Figure 2. The number of patients who died in the low SII group was 3 (15%), while the number of mortalities in the high SII group was 14 (21.9%). In terms of the mortality rate, there was no statistically significant difference in the

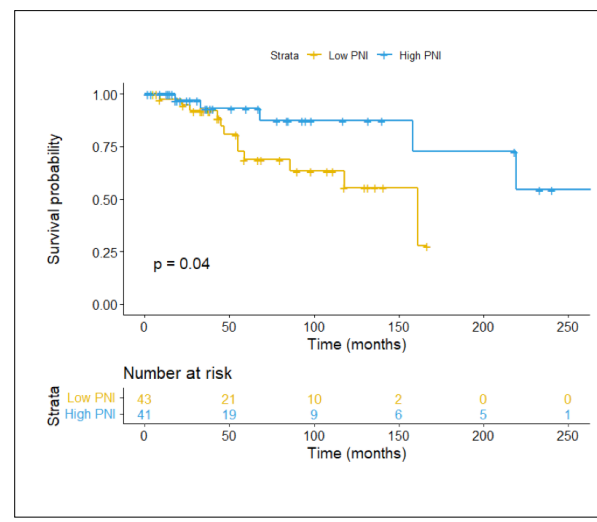

Figure 1. Survival probilities of PNI groups.

Table 2. Comparison of demographic and laboratory values of the SII groups

	Low SII (n=20)	High SII (n=64)	p
Age	54.05±16.39	56.81±12.78	0.434
Sex, n (%)			
Men	6 (30)	29 (45.3)	0.225
Women	14 (20)	35 (54.7)	
Weight	70.2±10.3	73.84±10.56	0.179
Mortality, n (%)			
No	17 (85)	50 (21.9)	0.751
Yes	3 (15)	14 (21.9)	
Smoking, n (%)			
Yes	18 (90)	55 (85.9)	0.928
No	2 (10)	9 (14.1)	
HT, n(%)			
No	7 (35)	22 (34.4)	0.959
Yes	13 (65)	42 (65.6)	
DM, n(%)			
No	15 (75)	54 (84.4)	0.535
Yes	5 (25)	10 (15.6)	
Hyperlipidemia (LDL)	117.5 (80.45–156)	123.5 (102–157.5)	0.323
Family history of cardiovascular disease (%)			
No	19 (95)	55 (85.9)	0.439
Yes	1 (5)	9 (14.1)	
Heart failure, n (%)			
No	20 (100)	55 (85.9)	0.106
Yes	0 (0)	9 (14.1)	
Serebrovascularinfarct, n (%)			
No	19 (95)	61 (95.3)	1.000
Yes	1 (5)	3 (4.7)	
Peripheral arterial disease, n (%)			
No	20 (100)	60 (93.8)	0.568
Yes	0 (0)	4 (6.2)	
PD time	37.5 (16–76.75)	49 (27.5–107.75)	0.126
Kt/V	2.75 (2.1–3.43)	2.2 (1.92–2.57)	0.008
PNI score	36.12 (32.31–38.36)	37.11 (33.91–40.09)	0.167
PNI, n (%)			
Low	12 (60)	31 (48.4)	0.367
High	8 (40)	33 (51.6)	
Albumin(gr/dl)	3.6 (3.2–3.8)	3.7 (3.39–4)	0.165
Hemoglobin	10.65 (9.73–11.5)	10.6 (9.6–11.38)	0.462
PTH	223 (133–539.5)	463.5 (223.25–641.25)	0.024
Ca	8.75 (8.2–9.5)	8.9 (8.23–9.5)	0.535
P	5.35 (4.78–5.8)	4.7 (4.23–5.9)	0.233
CRP	3.11 (3–7.77)	6 (3.11–13)	0.066
Residual urine output (ml)	1050 (214.75–1950)	375 (0–1287.5)	0.027
Late onset peritonitis frequency, n (%)			
No	13 (65)	35 (54.7)	0.416
Yes	7 (35)	29 (45.3)	

HT: hypertension; DM: Diabetes Mellitus; PD time: Periton diyalysis time; PNI score: prognostic nutritional index score; PTH: parathormone; Ca: calchıum; P: phosporus; CRP:C reaktive protein.

Table 3. Comparison of demographic and laboratory values of the PNI groups

	Low PNI (n=43)	HighPNI (n=41)	p
Age	58.61±15.09	53.59±11.64	0.091
Sex, n (%)			
Men	17 (39.5)	18 (43.9)	0.685
Women	26 (60.5)	23 (56.1)	
Weight	72 (62-83)	73 (67-78)	0.925
Mortality, n (%)			
No	31 (72.1)	36 (87.8)	0.104
Yes	12 (27.9)	5 (12.2)	
Smoking, n (%)			
Yes	39 (90.7)	34 (82.9)	0.345
No	4 (9.3)	7 (17.1)	
HT, n (%)			
No	9 (20.9)	20 (48.8)	0.007
Yes	34 (79.1)	21 (51.2)	
DM, n (%)			
No	33 (76.7)	36 (87.8)	0.186
Yes	10 (23.3)	5 (12.2)	
Hyperlipidemia (LDL)	122 (98-158)	123 (97.5-157)	0.651
Family history of cardiovascular disease, n (%)			
No	35 (81.4)	39 (95.1)	0.089
Yes	8 (18.6)	2 (4.9)	
Heart failure, n (%)			
No	38 (88.4)	37 (90.2)	1.000
Yes	5 (11.6)	4 (9.8)	
Serebrovascular infarct, n (%)			
No	40 (93)	40 (97.6)	0.616
Yes	3 (7)	1 (2.4)	
PD time (months)	47 (2-98)	39 (18-96.5)	0.788
Kt/V	2.33 (1.96-2.94)	2.11 (1.94-2.78)	0.256
SII 688.29±403.41	650.36±295.7	0.626	
SII, n (%)			
Low	12 (27.9)	8 (19.5)	0.367
High	31 (72.1)	33 (80.5)	
Ca 8.6 (8.1–9.1)	9.1 (8.55–9.95)	0.004	
CRP	8 (3.11-15)	4 (3-8)	0.007
Residual urine output (ml)	700 (0-1250)	400 (0-1700)	0.862
Late onset peritonitis frequency, n (%)			
No	26 (60.5)	22 (53.7)	0.529
Yes	17 (39.5)	19 (46.3)	

HT: Hypertension; DM: Diabetes Mellitus; PD time: Periton diyalysis time; SII score: Systemic immun inflamatory index score; PTH: Parathormone; Ca: Calchium; CRP: C reactive protein.

low SII group compared to the high SII group (p=0.98).

Univariate Cox model results are given in Table 4. According to the univariate Cox model results, there was a statistically significant increase in the risk of death in diabetic patients (HR=4.083 [95% CI 1.295–12.87], p=0.016). Age was a statistically effective factor on the risk of death; with a one-year increase in age, the risk of death increased by HR=1.041 (95% CI 1.003–1.081) (p=0.034). The increase in phosphorus value increased the risk of death statistically significantly (HR=1.446 [95% CI 1.045–2], p=0.026). High PNI, high SII, hypertension, smoking, gender, Kt/V, calcium, PTH, late peritonitis, and changes in residual urinary values were not found to be effective factors for mortality (p>0.05). According to the age-adjusted Cox model analysis, we found that only serum phosphorus levels were effective on mortality. Details are shown in Table 5.

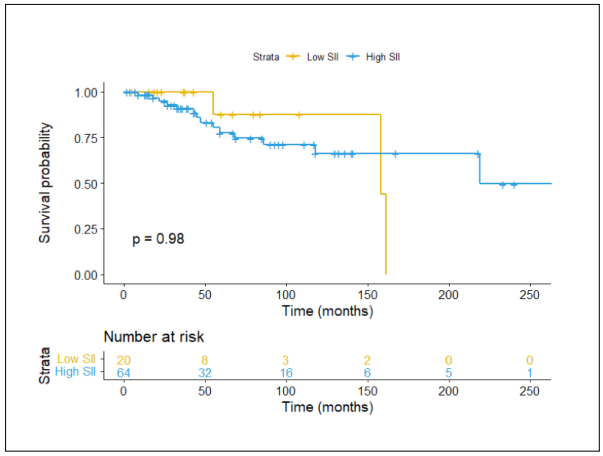

Figure 2. Survival probilities of SII groups.

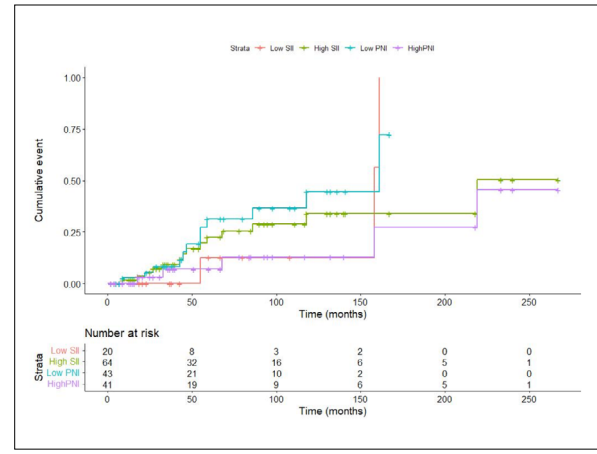

Figure 3. Cumulative comparison of mortality of patients with low PNI,high PNI, low SII and high PNI scores in peritoneal dialysis patients.

Table 4. Univariate Cox analysis results showing the consequences of low PNI score on mortality in peritoneal dialysis patients

	HR (95% CI)	SE	p
PNI, Low PNI	0.316 (0.099-1.001)	0.588	0.050
SII, HighSII	0.984 (0.279-3.47)	0.643	0.981
DM	4.083 (1.295-12.87)	0.586	0.016
HT	3.127 (0.708-13.81)	0.758	0.133
Smoking	0.292 (0.037-2.292)	1.051	0.242
Age	1.041 (1.003-1.081)	0.019	0.034
Sex female/male	1.122 (0.406-3.1)	0.518	0.824
Kt/v	1.446 (0.735-2.845)	0.345	0.285
Calcium	1.015 (0.634-1.531)	0.225	0.946
Phosphorus	1.446 (1.045-2)	0.165	0.026
Parathormone	1.001 (0.999-1.002)	0.0006	0.209
Peritonitis history	1.119 (0.423-2.959)	0.496	0.820
Residue urine output	1.0001 (0.996-1.001)	0.003	0.558

Table 5. Age adjusted cox analysis results showing the consequences of low PNI score on mortality in peritoneal dialysis patients

	HR (95% CI)	Adjusted HR (95% CI)	SE	p
PNI, low PNI	0.316 (0.099-1.001)	0.371 (0.115-1.195)	0.597	0.097
SII, HighSII	0.984 (0.279-3.47)	0.968 (0.274-3.142)	0.643	0.968
DM, yes	4.083 (1.295-12.87)	2.697 (0.729-9.972)	0.567	0.137
HT	3.127 (0.708-13.81)	2.947 (0.651-13.334)	0.770	0.160
Cigarette	0.292 (0.037-2.292)	0.352 (0.045-2.769)	1.053	0.321
Sex female	1.122 (0.406-3.1)	1.580 (0.543-4.608)	0.546	0.402
Kt/v	1.446 (0.735-2.845)	0.359 (0.753-2.725)	0.328	0.273
Calcium	1.015 (0.634-1.531)	1.050 (0.667-1.654)	0.232	0.833
Phosphorus	1.446 (1.045-2)	1.625 (1.158-2.280)	0.173	0.005
PTH	1.001 (0.999-1.002)	1.001 (1-1.003)	0.001	0.101
Late onset peritonitis	1.119 (0.423-2.959)	0.921 (0.346-2.447)	0.499	0.868
Residual urine	1 (0.996-1.001)	1 (0.999-1.001)	0.001	0.911

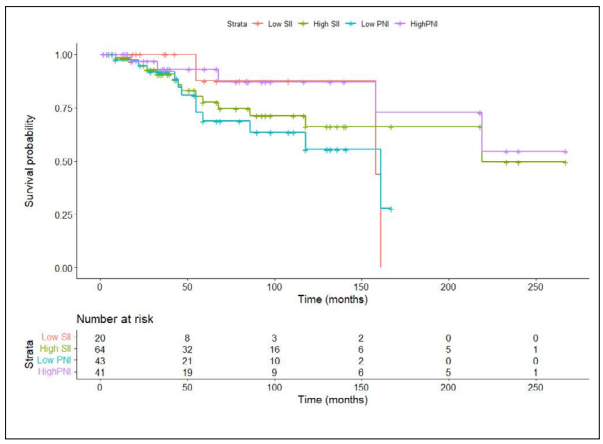

Figure 4. Cumulative comparison of survival of patients with low PNI,high PNI, low SII and high PNI scores in peritoneal dialysis patients.

When we evaluated our patients with both low PNI scores and high SII scores, we found that the difference in mortality was dependent on the PNI score. Our data are shown in Figures 3 and 4.

DISCUSSION

There are various indicators that reveal nutritional status but lack an ideal standard and simple marker. PNI, calculated by serum albumin and lymphocyte count, has been shown to be a prognostic factor in various malignancies. [12] A low PNI level is associated with a decrease in albumin and lymphocyte counts. Serum albumin is one of the markers of nutritional status and inflammation.[22] Hypoalbuminemia is associated with reduced quality of life in dialysis patients.[23] According to the results of the Canada-USA Peritoneal Dialysis Working Group, an increase of 1 g/L of serum albumin is associated with a 6% reduction in mortality.[4] In various studies, higher serum albumin levels have been shown to be associated with the stabilization of circulating levels of inflammatory cytokines and increases in oxidative stress.[24] Therefore, low albumin may be considered to be associated with impaired immunity. Absolute lymphocyte count, another aspect of PNI, is a marker of malnutrition. It has been found to be associated with all-cause mortality in non-dialysis-dependent chronic kidney patients with a lower lymphocyte percentage.[25] Evidence suggests that PNI can be used in nutritional assessment. According to numerous studies, CVD is the most common cause of death in PD patients.[2,3] One of the risk factors, malnutrition, is an important determinant of mortality in these patients, as demonstrated in various studies. Peng et al.[15] found that low PNI increased the risk of CVD and all-cause mortality in their study. In another Korean study, it was reported that low PNI was associated with increased mortality in PD patients.[16] PNI needs to be widely validated in different populations in the future. In our study, mortality was found to be higher in the low PNI group. Also, we researched mortality using the Kaplan-Meier method. In the assessment between groups, mortality rates were higher in the low PNI groups.

Accumulating evidence suggests that chronic inflammation is a major contributor to the pathogenesis and progression of chronic kidney disease (CKD) and is associated with the prognosis of dialysis patients.[26] In a study of 86 Parkinson's patients followed for 36 months, chronic inflammation was found to be associated with all-cause and cardiovascular mortality and arterial stiffness.[27] In a large sample study of 1,652 Parkinson's disease patients, chronic inflammation was again associated with an increased risk of CVD events and CVD mortality in both multivariate Cox regression models and competitive risk models.[28] Similar results were found in another study from China.[29] Chen et al.[30] in a multicenter retrospective study involving 1,753 participants, showed that chronic inflammation was independently correlated with CVD mortality. We also evaluated the relationship between high SII scores and mortality in our study, but we could not find statistical significance. The contradictory results of our study with the literature may be associated with the presence of a history of malignancy in 14 of our patients. In addition, due to the insufficient number of events/cases, we could not perform a cause-related mortality analysis. Although their malignancies were not active, we thought that this might affect the results. In addition, there were more patients with a history of systemic vasculitis as a primary nephrological disease in the low SII group. We thought that this may also be effective.

Although we did not find a relationship between mortality and patients with high SII scores, they had a lower rate of dialysis sufficiency, worse bone mineral metabolism control, and lower renal residual urine output. These three parameters may contribute to long-term mortality in PD patients. The median Kt/V value was found to be lower in the high SII group. These results may suggest that dialysis efficiency and bone mineral control will be more difficult in the future in patients with a high initial SII score. Therefore, patients with high initial SII scores may need to be followed more closely in terms of dialysis efficiency and bone mineral disorder control. In addition, since residual urine output is lower in patients with high SII scores, we think that more sensitive follow-up regarding volume control and residual urine preservation may be required in such patients.

We evaluated survival analysis between low and high PNI groups using the log-rank test. We also evaluated survival analysis between low and high SII groups using the log-rank test. In both evaluations, the low PNI score had lower survival than high PNI, and the high SII score had lower survival than low SII.

The effect of high serum phosphorus on mortality and morbidity in peritoneal dialysis patients is well known. Two of the current studies in the literature are the study conducted by Huang et al.[31] in 2021 and the study conducted by Gong et al.[32] in 2020. In both studies, it was shown that high serum phosphorus levels increase mortality and

morbidity. In our study, we also found the relationship between high serum phosphorus levels and mortality in the univariate Cox model and the age-adjusted model. In the cumulative evaluation, the effect of this situation on mortality was not observed, even if the patients with low PNI scores had high SII scores (Figures 3-4). This may suggest that initial PNI evaluation may be predictive of mortality in peritoneal dialysis patients.

Another issue we investigated in our study was whether initial SII and PNI scores could predict the risk of late-onset peritonitis in PD patients. According to the univariate Cox model statistical analysis, we could not find statistical significance in the association of low PNI and high SII scores with late-onset peritonitis. We thought that the high number of our patients with a history of cancer and vasculitis could cause the result. The retrospective design of our study and the small number of patients can be considered limitations. Longer follow-up time may be valuable. A recent study revealed that elevated systemic immune inflammation level on admission was an independent risk factor for all-cause, cardiovascular, and cancer mortality among CKD patients.[20] Because of the insufficient number of events/cases, we think that we could not show the association of those with high SII scores with overall mortality.

Conclusion

We found a correlation between low PNI score and general mortality. This supports us in also considering the PNI score in the evaluation of nutritional status in peritoneal dialysis patients.

Ethics Committee Approval

The study was approved by the Kartal Lütfi Kırdar State Hospital Ethics Committee (Date: 13.01.2021, Decision No: 2021/514/193/2).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: S.Y., M.T.; Design: M.T., P.Ö.; Supervision: S.Y., P.Ö.; Fundings: M.M., S.F.Y., S.Y. Materials: P.Ö., E.P.; Data: M.T., S.Y.; Analysis: S.Y., E.Ö.; Literature search: E.Ö., S.F.Y. Writer: S.Y., P.Ö. Critical review: E.A., E.P., M.M.

Conflict of Interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Yu X, Yang X. Peritoneal dialysis in China: Meeting the challenge of chronic kidney failure. Am J Kidney Dis 2015;65:147–51.
2. Wang AY, Brimble KS, Brunier G, Holt SG, Jha V, Johnson DW, et al. ISPD Cardiovascular and metabolic guidelines in adult peritoneal dialysis patients part II - Management of various cardiovascular complications. Perit Dial Int 2015;35:388–96. [CrossRef]
3. Peev V, Nayer A, Contreras G. Dyslipidemia, malnutrition, inflammation, cardiovascular disease and mortality in chronic kidney disease. Curr Opin Lipidol 2014;25:54–60. [CrossRef]
4. Canada-USA (CANUSA) Peritoneal Dialysis Study Group. Adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcomes. J Am Soc Nephrol 1996;7:198–207.
5. Dong J, Li Y, Xu Y, Xu R. Daily protein intake and survival in patients on peritoneal dialysis. Nephrol Dial Transplant 2011;26:3715–21.
6. Han SH, Han DS. Nutrition in patients on peritoneal dialysis. Nat Rev Nephrol 2012;8:163–75. [CrossRef]
7. Yang Y, Zhou H, Zhang P, Chao W, Zou Y, Yang M. Evaluation of objective nutritional indexes as predictors of worse outcomes in peritoneal dialysis patients. Nutrition. 2020;79–80:110963. [CrossRef]
8. Jager KJ, Merkus MP, Boeschoten EW, Dekker FW, Stevens P, Krediet RT. Dialysis in The Netherlands: The clinical condition of new patients put into a European perspective. NECOSAD Study Group. Netherlands Cooperative Study on the Adequacy of Dialysis phase 1. Nephrol Dial Transplant 1999;14:2438–44. [CrossRef]
9. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. Nihon Geka Gakkai Zasshi [Article in Japanese] 1984;85:1001–5.
10. Sakurai K, Tamura T, Toyokawa T, Amano R, Kubo N, Tanaka H, et al. Low preoperative prognostic nutritional index predicts poor survival post-gastrectomy in elderly patients with gastric cancer. Ann Surg Oncol 2016;23:3669–76. [CrossRef]
11. Mohri T, Mohri Y, Shigemori T, Takeuchi K, Itoh Y, Kato T. Impact of prognostic nutritional index on long-term outcomes in patients with breast cancer. World J Surg Oncol 2016;14:170. [CrossRef]
12. Yang L, Xia L, Wang Y, Hong S, Chen H, Liang S, et al. Low Prognostic Nutritional Index (PNI) predicts unfavorable distant metastasis-free survival in nasopharyngeal carcinoma: A propensity score-matched analysis. PLoS One 2016;11:e0158853. [CrossRef]
13. Chan AW, Chan SL, Wong GL, Wong VW, Chong CC, Lai PB, et al. Prognostic Nutritional Index (PNI) Predicts tumor recurrence of very early/early stage hepatocellular carcinoma after surgical resection. Ann Surg Oncol 2015;22:4138–48. [CrossRef]
14. Hong S, Zhou T, Fang W, Xue C, Hu Z, Qin T, et al. The prognostic nutritional index (PNI) predicts overall survival of small-cell lung cancer patients. Tumour Biol 2015;36:3389–97. [CrossRef]
15. Peng F, Chen W, Zhou W, Li P, Niu H, Chen Y, et al. Low prognostic nutritional index associated with cardiovascular disease mortality in incident peritoneal dialysis patients. Int Urol Nephrol 2017;49:1095–101. [CrossRef]
16. Kang SH, Cho KH, Park JW, Yoon KW, Do JY. Onodera's prognostic nutritional index as a risk factor for mortality in peritoneal dialysis patients. J Korean Med Sci 2012;27:1354–8. [CrossRef]
17. Feng JF, Chen S, Yang X. Systemic immune-inflammation index (SII) is a useful prognostic indicator for patients with squamous cell carcinoma of the esophagus. Medicine (Baltimore) 2017;96:e5886.
18. Diao P, Wu Y, Li J, Zhang W, Huang R, Zhou C, et al. Preoperative systemic immune-inflammation index predicts prognosis of patients with oral squamous cell carcinoma after curative resection. J Transl Med 2018;16:365. [CrossRef]
19. Guo W, Cai S, Zhang F, Shao F, Zhang G, Zhou Y, et al. Systemic immune-inflammation index (SII) is useful to predict survival outcomes in patients with surgically resected non-small cell lung cancer. Thorac Cancer 2019;10:761–8. [CrossRef]
20. Lai W, Xie Y, Zhao X, Xu X, Yu S, Lu H, et al. Elevated systemic immune inflammation level increases the risk of total and cause-specific mortality among patients with chronic kidney disease: A large multicenter longitudinal study. Inflamm Res 2023;72:149–58.
21. Qin Z, Li H, Wang L, Geng J, Yang Q, Su B, et al. Systemic Immune-

Inflammation Index is associated with increased urinary albumin excretion: A population-based study. Front Immunol 2022;13:863640.
22. Spiegel DM, Breyer JA. Serum albumin: A predictor of long-term outcome in peritoneal dialysis patients. Am J Kidney Dis 1994;23:283–5. [CrossRef]
23. Kaysen GA. Biological basis of hypoalbuminemia in ESRD. J Am Soc Nephrol 1998;9:2368–76. [CrossRef]
24. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: A systematic review of the epidemiological literature. Nutr J 2010;9:69. [CrossRef]
25. Kovesdy CP, George SM, Anderson JE, Kalantar-Zadeh K. Outcome predictability of biomarkers of protein-energy wasting and inflammation in moderate and advanced chronic kidney disease. Am J Clin Nutr 2009;90:407–14. [CrossRef]
26. Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD. Malnutrition-inflammation complex syndrome in dialysis patients: Causes and consequences. Am J Kidney Dis 2003;42:864–81.
27. Lu X, Wang S, Zhang G, Xiong R, Li H. High neutrophil-to-lymphocyte ratio is a significant predictor of cardiovascular and all-cause mortality in patients undergoing peritoneal dialysis. Kidney Blood Press Res 2018;43:490–9. [CrossRef]
28. Basu N, Karabayas M, Pusey C. Prognosis and future developments in vasculitis. Best Pract Res Clin Rheumatol 2018;32:148–65.
29. Halpern SE, Moris D, Shaw BI, Krischak MK, Olaso DG, Kesseli SJ, et al. The Systemic Immune-Inflammation Index predicts clinical outcomes in kidney transplant recipients. In Vivo 2020;34:3349–60.
30. Chen MQ, Wang HY, Shi WR, Sun YX. Estimate of prevalent hyperuricemia by systemic inflammation response index: Results from a rural Chinese population. Postgrad Med 2021;133:242–9.
31. Huang N, Li H, Fan L, Zhou Q, Fu D, Guo L, et al. Serum phosphorus and albumin in patients undergoing peritoneal dialysis: interaction and association with mortality. Front Med (Lausanne) 2021;8:760394. [CrossRef]
32. Gong N, Xiao Z, Zhang F, Zhong X, He Y, Yi Z, et al. Duration of serum phosphorus control associated with overall mortality in patients undergoing peritoneal dialysis. Kidney Dis (Basel) 2020;6:434–43. [CrossRef]

Prognostik Nutrisyonel İndeks ve Sistemik İmmün İnflamatuar İndeks: Periton Diyaliz Hastalarında Mortaliteyi Öngörebilirler mi?

Amaç: Kronik böbrek yetersizliğinde replasman tedavi yöntemlerinden biri olan periton diyalizi hastalarında nutrisyonel değerlendirme, mortalite ve morbidite açısından giderek önemli hale gelmektedir. Prognostik nutrisyonel indeksi (PNI) ve immün-inflamasyon indeksi (SII) ise birçok hastalıkta prognostik değeri gösterilmiş yeni bir inflamatuvar indekstir. Çalışmamızda PD hastalarında yüksek SII skorları ile düşük PNI skorları mortalite arasındaki ilişkiyi araştırdık.

Gereç ve Yöntem: Periton diyalizi yapılan 84 hastada PNI VE SII skorları hesaplandı. Düşük PNI skoru ile yüksek SII skorları olan hastalar gruplara ayrıldı. Periton diyaliz hastalarında mortalite ve morbiditeyi öngöstermeleri açısından incelendi.

Bulgular: Düşük PNI grubunda mortalite oranı, yüksek skorlu PNI grubuna göre yüksekti (p=0.04). Düşük SII grubunda mortalite KT/v değerleri açısından gruplar arasında fark vardı (p=0.008). SII grubunda bu değer yüksek SII grubunda daha yüksekti ve iki grup arasında PTH değerleri açısından istatistiksel olarak anlamlı fark vardı (p=0.024).

Sonuç: Çalışmamızda genel mortalite, düşük PNI grubunda daha yüksek bulunmuştur. Bu durum periton diyalizi hastalarında beslenme durumunun değerlendirilmesinde PNI skorunun da dikkate alınmasını desteklemektedir. Beklediğimiz gibi yüksek SII skoru olan hastalarda muhtemelen hasta sayımız az olduğu için, artmış mortalite ile bir ilişki bulamadık ancak bu hastaların diyaliz yeterlilik oranları daha düşük, kemik mineral metabolizması kontrolü daha kötü ve renal rezidüel idrar çıkışı daha düşüktü. Bu üç paramatrenin PD hastalarında mortaliteye katkıları bilinmektedir.

Anahtar Sözcükler: Periton diyalizi; prognostik nutrisyonel indeks; sistemik immun inflamatuvar indeks.

SCIE DOI: 10.14744/scie.2024.82584
South. Clin. Ist. Euras. 2024;35(3):262-268

Original Article

Bibliometric Analysis of Chronic Lateral Ankle Instability Research: Mapping the Landscape of Influential Publications

Lercan Aslan,[1,2*] Cemil Cihad Gedik,[2] Batuhan Yürük,[2]
Bedri Karaismailoğlu[3,4]

[1]Department of Orthopaedic Surgery, Foot & Ankle Research and Innovation Laboratory, Massachusetts General Hospital, Harvard Medical School, Boston, USA
[2]Department of Orthopaedics and Traumatology, Koç University School of Medicine, Istanbul, Türkiye
[3]Department of Orthopaedics and Traumatology, İstanbul University Cerrahpaşa Faculty of Medicine, Istanbul, Türkiye
[4]Cerrahpasa Research Simulation and Design Laboratory, Istanbul University, Istanbul, Türkiye

Submitted: 30.05.2024
Revised: 03.07.2024
Accepted: 15.07.2024

Correspondence: Lercan Aslan, Department of Orthopaedic Surgery, Foot & Ankle Research and Innovation Laboratory, Massachusetts General Hospital, Harvard Medical School, Boston, USA
E-mail: laslan@mgh.harvard.edu.tr

Keywords: Bibliometric study; chronic lateral ankle instability; citation count; citation density.

ABSTRACT

Objective: We aimed to conduct a comprehensive bibliometric analysis of the top 100 most-cited publications in the field of Chronic Lateral Ankle Instability (CLAI). We sought to identify key research themes, trends, and the collaborative network among scholars, institutions, and countries within the CLAI domain, and to offer insights into the evolution of CLAI research and its impact on clinical practice and patient care in the context of evidence-based medicine.

Methods: We conducted a bibliometric analysis of the 100 most-cited articles on CLAI using the Web of Science database up to the end of 2023. The mean citation count and citation density were calculated. Additionally, we classified studies by evidence level, design, and subject matter, and investigated correlations with citation metrics, including evidence level, publication decade, and journal title. Additional analyses examined the influence of author specialty, inter-institutional collaborations, and quantitative aspects such as the number of authors, institutions, page count, and references on citation numbers.

Results: The analysis of the top 100 cited articles on CLAI revealed a maximum citation count of 1,074 and an average of 166.15±127.05 across articles, with citation density ranging from 2.50 to 60.60. The research was predominantly from the United States (52 studies), involved an average of 4.42±4.32 authors per article, and spanned 2 to 18 pages with 10 to 260 references. The University of North Carolina emerged as a leading institution with eight articles, and Hertel was noted as a key contributor with contributions to 15 papers.

Conclusion: This bibliometric analysis on CLAI underscores the evolving interest in recent studies, particularly from 2011-2020, and highlights the importance of multicenter research and the need for higher-level evidence. It reveals the United States, Sweden, and the United Kingdom as key contributors, suggesting a potential for global collaboration.

INTRODUCTION

Chronic lateral ankle instability (CLAI) is a commonly encountered condition that has garnered significant attention from orthopaedic surgeons, especially in the field of foot and ankle surgery, over the years. It encompasses a spectrum of anatomical and functional abnormalities resulting from recurrent ankle sprains or traumatic injuries, leading to persistent pain, instability, and impaired function.[1] The management of CLAI has evolved substantially, driven by advancements in our understanding of its pathophysiology, diagnosis, and treatment options.[2,3]

In this era of evidence-based medicine, the identification and analysis of seminal publications play a pivotal role in shaping the direction of research, clinical practice, and patient care. Bibliometric studies, which involve the quantitative analysis of scientific literature, have become invaluable tools for assessing the impact, trends, and knowledge

dissemination within specific fields of medicine.[4,5] Such analyses provide an objective means to evaluate the influence and evolution of research topics, as well as to recognize key contributors and institutions that have shaped the field.

The objective of this manuscript is to present a comprehensive bibliometric analysis of the top 100 publications in the domain of CLAI research that have received the highest citations. Through systematic review and data extraction, we aim to unravel the pivotal research themes, emerging trends, and the global network of collaboration among researchers, institutions, and countries. By delving into these influential publications, we intend to provide insights into the trajectory of CLAI research.

MATERIALS AND METHODS

Literature from the Web of Science database was reviewed. Utilizing the search term "Chronic lateral ankle instability," the top 100 most-cited articles up to the end of 2023 were identified. A total of 1,325 articles were documented. Each article was individually examined to gather necessary information and confirm its relevance to chronic lateral ankle instability. After excluding the articles that were not relevant, the top 100 articles were taken into consideration for analysis.

Information such as the year of publication, names of the authors, the institution and country of the lead author, and the names of the journals was documented. The mean citation count and citation density (mean citations per annum) were computed. The studies were classified by their evidence level (following the criteria set by The Journal of Bone and Joint Surgery–American Volume [J Bone Joint Surg Am]), the design of the study (for example, case series, case-control study, randomized controlled trial), and the primary subject matter of the article. The association between the average number of citations with evidence level, decade of publication, and journal title was sought. Additionally, the impact of the first author's specialty and the effect of inter-institutional collaborations on average citation numbers were examined. Correlation analyses were also performed to assess the relationship between average citation numbers and the number of authors, institutions involved, page count, and reference count.

Statistical Analysis

Statistical evaluations were conducted using the IBM SPSS 28.0 software suite (IBM Corp., Armonk, New York). Quantitative data were presented as means and standard deviations. The distribution of the data was assessed using the Levene test. For comparing mean values, the Student's t-test was utilized for normally distributed data, while the Mann-Whitney U test was employed for data not following a normal distribution. In situations where the comparison involved more than two groups, the analysis of variance (ANOVA) test was applied if the data were normally distributed; otherwise, the Kruskal-Wallis test was used. To identify significant differences among multiple group means, the Bonferroni post hoc test was performed. Furthermore, the Spearman rank correlation test was used to explore potential correlations between variables. A p-value of less than .05 was considered statistically significant. The software VOSviewer, version 1.6.16, was utilized to generate a map displaying the co-occurrence of keywords in articles. Charts were produced using Python scripts.

RESULTS

The investigation yielded 1,325 articles, with the top 100 most-referenced articles analyzed in depth as detailed in Supplemental Table 1. The maximum citation count for a single article reached 1,074, whereas the mean number of citations per article was 166.15±127.05, with citation counts spanning from 78 to 1,074. The average citation density was 10.59±9.45, and values ranged from 2.50 to 60.60. On average, articles were authored by 4.42 individuals ± 4.32, with the number of authors per article varying from 1 to 38. Moreover, out of the total 100 articles, 7 were the result of collaborative efforts among multiple institutions, while 93 originated from individual institutions. The length of the articles averaged 7.59±3.50 pages, extending from 2 to 18 pages, and they contained an average of 53.61±43.63 references, with a reference count ranging from 10 to 260.

The analysis covered four types of articles, which were 63 clinical studies, one basic science study, 32 review articles, and four consensus studies. The distribution of first authors by country highlighted the United States at the forefront with 52 articles, followed by Sweden with seven articles, and the United Kingdom contributing five articles, as shown in Figure 1A. Moreover, the United States had the most citations as well, as shown in Figure 1B. At the institutional level, the University of North Carolina (NC, USA) led with contributions to eight articles. It was closely followed by the University of Kentucky (KY, USA) and East Hospital Göteborg (Sweden), each with five articles, as summarized in Figure 1C. Pennsylvania State University had the most citations, and the top institutions by citation count are shown in Figure 2A. In terms of individual contributions, Hertel was the most prolific author, participating in 15 articles. Wikström was involved in ten articles, and both McKeon and Karlsson contributed to seven articles each. The study types included 40 case series, 13 case-control studies, 25 reviews, four systematic reviews, three meta-analysis studies, and four consensus studies.

Hertel's review, titled "Functional Anatomy, Pathomechanics, and Pathophysiology of Lateral Ankle Instability," published in the Journal of Athletic Training, emerged as the top-cited work, amassing 1,074 citations. This 2002 publication thoroughly examines lateral ankle instability and boasts a citation density of 48.82. Another highly influential piece by Hertel and Corbett, "An Updated Model of

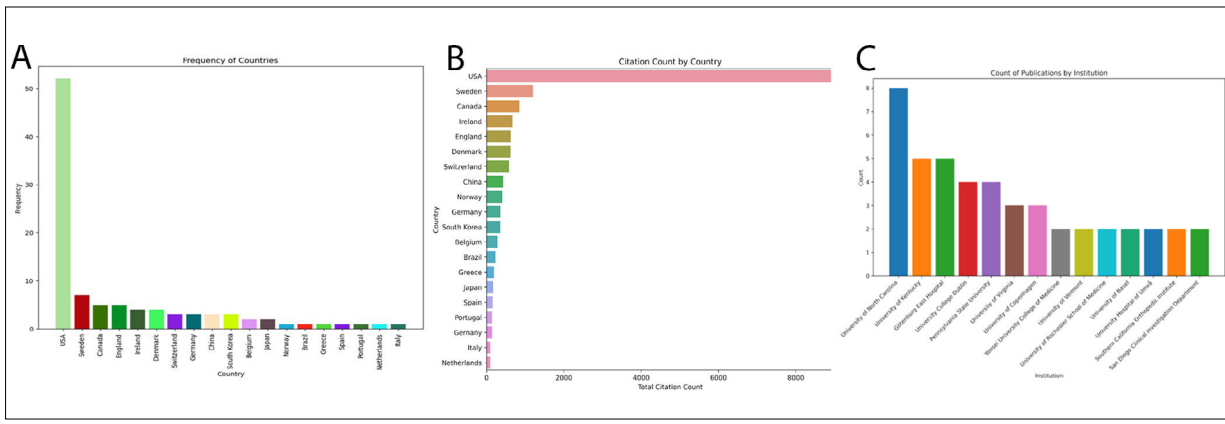

Figure 1. (a) Frequencies of countries. **(b)** Total citation count by country. **(c)** Bar chart for count of publications.

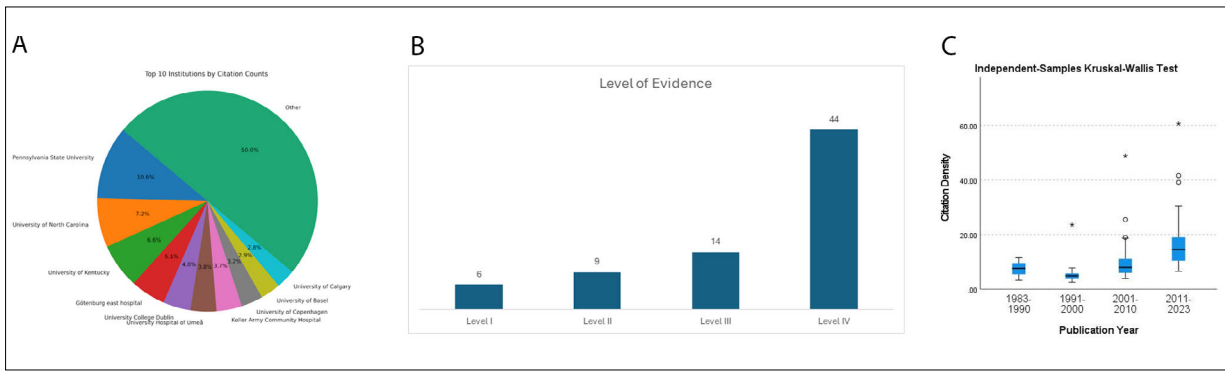

Figure 2. (a) Pie chart showing the top 10 institutions by citation counts. **(b)** Distribution of Level of Evidence. **(c)** Citation density by publication year.

Chronic Ankle Instability," holds the record for the highest citation density at 60.60. This review was featured in the Journal of Athletic Training in 2019.

The articles' evidence levels were categorized as follows: 44 articles at level IV, 14 at level III, nine at level II, and six at level I (Figure 2B). Statistical analysis revealed no significant differences in average citation and citation density across these evidence level groups, with p-values of 0.951 and 0.237. The bulk of the articles were published between 2001 and 2010, with the year 2002 alone seeing the publication of 9 articles. There was no notable difference in the mean number of citations across decades (p=0.515). However, a significant difference was observed in average citation density across the groups (p<0.001), with articles from 2001-2010 showing significantly higher citation densities compared to those from 1991-2000 (p=0.001). Additionally, the average citation density of articles published between 2011-2020 was higher than those from the previous decades, 1991-2000 (p<0.001) and 2001-2010 (p=0.001), as shown in Figure 2C.

The American Journal of Sports Medicine (AJSM) led in the number of published articles on the topic with 22 studies, followed by Foot & Ankle International (Foot Ankle Int) with 18 studies, and the Journal of Athletic Training featuring 13 articles. Statistical analysis showed no significant differences in the average number of citations or citation density among these journals, with p-values of 0.416 and 0.116, respectively. Average citation counts are shown in Figure 3.

The analysis revealed "sprains" as the most frequently appearing keyword in 24 articles, followed by "joint" in 20, "functional instability" in 18, "instability" and "reconstruction" each in 17, and "chronic ankle instability" in 16 instances. The map for keyword co-occurrence is shown in Figure 4. The majority of first authors specialized in orthopedic surgery, contributing to 64 articles, while the remaining 36 articles featured first authors from non-orthopedic disciplines, including 13 from physical therapy backgrounds, as shown in Figure 5. Out of the total, 93 articles were the work of single institutions, and 7 were from inter-institutional collaboration. However, multicenter papers had significantly higher average citation density compared to single-institution papers (p<0.001), although no significant difference was found for average citation counts (p=0.627). The specialty of the first author was not related to average citation count (p=0.150); however, a significant difference was found for citation density (p=0.016). Further analysis showed a higher citation density for physical therapy-affiliated first authors compared to orthopaedic surgery-affiliated authors (p=0.021). The mean citation density for the physical therapy group was 16.64±10.69 and 9.39±9.51 for the orthopaedic surgery group.

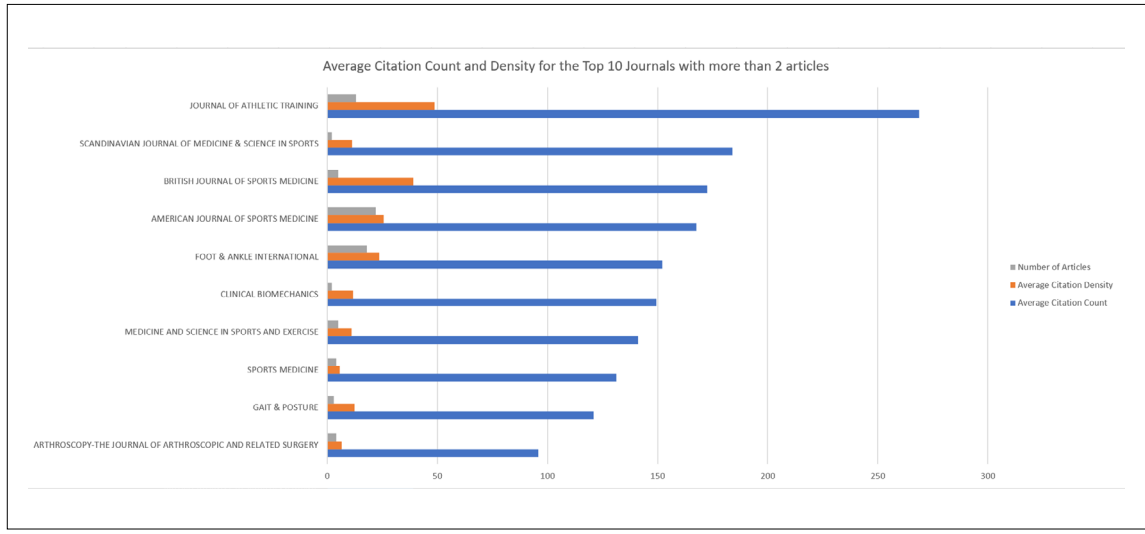

Figure 3. Average citation count by journal.

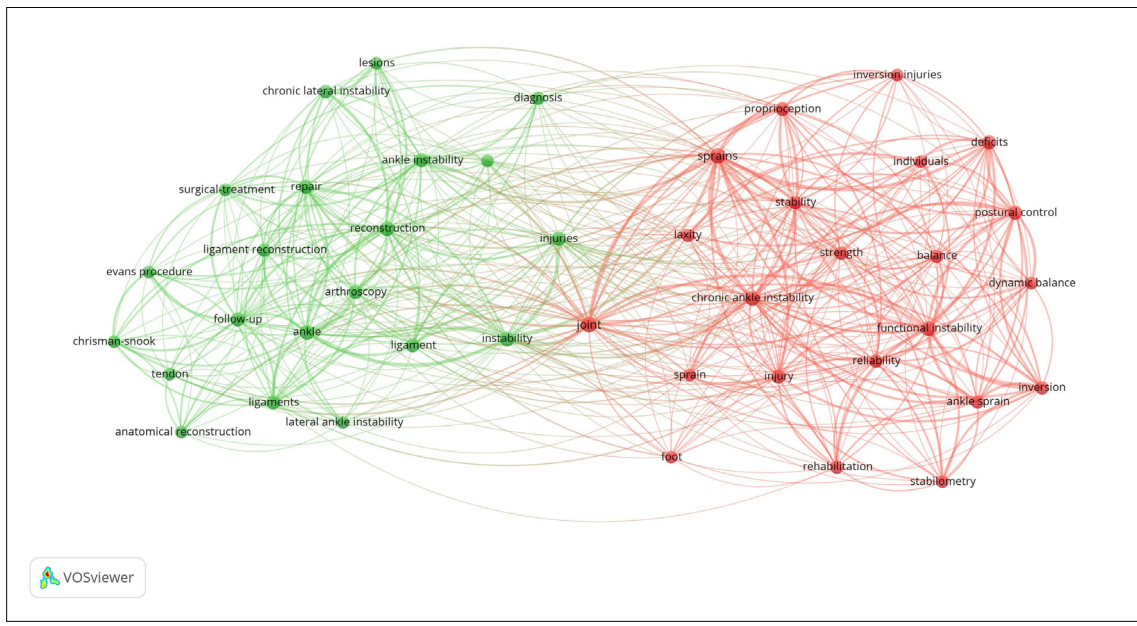

Figure 4. Map for keyword co-occurrence.

Further analysis showed a positive correlation between citation density and the year of publication (Spearman's rho 0.660, p<0.001) (Figure 6A), as well as between citation density and the number of references cited (Spearman's rho 0.273, p=0.006) (Figure 6B). There was also a significant correlation between the number of authors and the year of publication (Spearman's rho 0.294, p=0.003). Moreover, citation density and the number of authors were also correlated (Spearman's rho=0.244, p=0.015).

DISCUSSION

In this bibliometric analysis, we aimed to offer a comprehensive overview of the literature on CLAI, encompassing a review of 100 of the most frequently cited papers. The citation metrics revealed a significant range in the impact of research on CLAI, with the highest-cited article receiving 1,074 citations and an average citation count of 166.15. This wide difference likely underscores the pivotal role of certain studies in advancing our understanding of ankle instability. Notably, the higher mean citation density for newer articles, especially in the 2011-2020 period, suggests that newer articles, particularly those published in the last decade, are garnering attention at an accelerated rate, likely reflecting the growing importance and recognition of recent scientific advances in this field. A similar trend was seen in the articles on flatfoot as well.[6] Additionally, previous studies suggested a higher impact for review papers.[4,7] In our research, we identified 23 studies that were classified as review papers. This outcome aligns

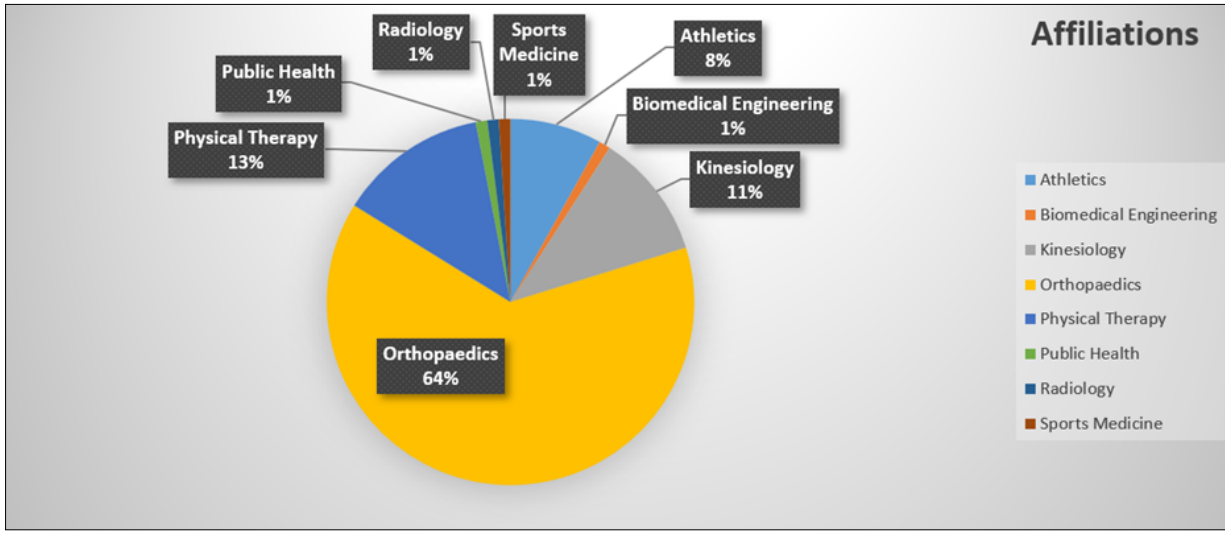

Figure 5. Affiliations of the first authors.

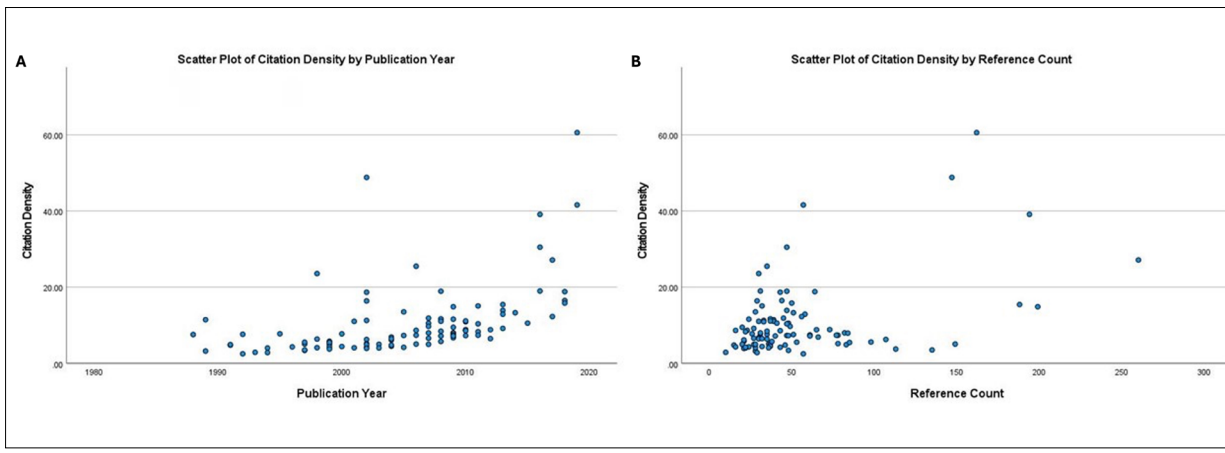

Figure 6. (a) Citation density by publication year. Spearman's rho 0.660, p<0.001 (b) Citation density by reference count. Spearman's rho 0.273, p=0.006.

closely with figures documented in existing literature, where the number of review studies stood at 17 for ankle arthroscopy and 19 for plantar fasciitis.[8,9]

Our analysis revealed that a predominant number of studies originated from a single institution; however, multi-institutional papers had higher citation density. Similarly, Frazer et al.[7] have posited that multicentered studies could wield a more significant impact. This suggestion underscores the potential benefits of conducting more multicenter research specifically on CLAI, highlighting the importance of diverse institutional collaboration to enhance the robustness and applicability of research findings in this area. This may reflect the necessity to produce more multicenter research on CLAI.

The distribution of evidence levels among the papers, with a predominance of Level IV studies (44%), aligns with the broader challenge in orthopedic research of generating high-level evidence.[6] Previous studies also reported a prevalence of Level IV studies, as high as 74% in articles for the top 50 most-cited total ankle arthroplasty[4] and even higher, 86%, for olecranon fracture studies.[10] Karslı et al.[8] also reported that Level IV studies represent 58% of the top 100 most-cited ankle arthroscopy studies. This finding underscores the ongoing need for more randomized controlled trials and systematic reviews that can offer stronger evidence to guide clinical decision-making in the management of ankle instability.

The findings highlight a significant concentration of research output from the United States, followed by Sweden and the United Kingdom. Previously, multiple other studies for the top 100 foot and ankle surgery articles, as well as for the most influential flatfoot articles and others, have reported similar findings regarding the country distribution, with the United States leading the list.[6,8,11-14] Moreover, Luo et al.[15] reported that North America led the list in four highly cited journals from 2009 to 2014. This geographical distribution not only illustrates the leading role of these countries in ankle instability research but

also indicates potential areas for global collaboration to enrich the diversity of research perspectives.

The distribution of articles across journals, with the American Journal of Sports Medicine, Foot & Ankle International, and the Journal of Athletic Training leading in terms of publication volume, reflects the interdisciplinary nature of research on ankle instability, spanning orthopedics, sports medicine, and athletic training.

We found that the mean citation density for studies led by physical therapy and rehabilitation was 16.64, which was markedly higher than the 9.39 observed for orthopaedic surgery-led research (p=0.021). One explanation for this finding might lie in the fact that despite the longstanding history of surgical treatments for CLAI, there is a continuous evolution in techniques. This evolution is propelled by industrial advancements, which facilitated the development of more durable implants, leading to better outcomes.[16] Another explanation could be that surgical intervention is not the primary treatment option for CLAI.[17]

The prevalence of keywords related to sprains, joint instability, and functional instability indicates a focused interest in the underlying mechanisms, clinical manifestations, and therapeutic approaches to managing chronic ankle instability. The emphasis on surgical and rehabilitation strategies highlights the clinical relevance of this research to improving patient outcomes.

The positive correlation between citation density and publication year, along with the number of references, suggests an increasing recognition of recent studies and the importance of comprehensive literature referencing for enhancing a study's visibility and impact. This was in parallel with the findings of our previous bibliometric study on flatfoot articles.[6]

While our analysis provides valuable insights, it is limited to the most cited articles, potentially overlooking emerging research that has yet to achieve high citation counts. Popular bibliometric analysis designs include global analysis of a specific time period, investigation of specific journals, and analysis of the most influential studies.[7,11,18] In this study, we analyzed the most cited articles, as all designs have different shortcomings.[6] Future bibliometric studies could include a broader range of articles to capture the full spectrum of research on CLAI. Additionally, the evolving nature of research topics and methodologies underscores the importance of continuous review and analysis to identify shifting trends and gaps in the literature.

Conclusion

In conclusion, our bibliometric analysis highlights the dynamic and evolving field of research on CLAI, emphasizing the need for high-quality, collaborative research efforts to advance our understanding and management of this condition. By identifying key trends, contributions, and gaps in the current literature, this study sets the stage for future investigations aimed at addressing the remaining questions in this important area of orthopedic research.

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: L.A., B.K..; Design: L.A., B.K., C.C.G., B.Y.; Supervision: S L.A., B.K..; Design: L.A., B.K., C.C.G., B.Y.; Fundings: L.A., B.K..; Design: L.A., B.K., C.C.G., B.Y.; Materials: L.A., B.K..; Design: L.A., B.K., C.C.G., B.Y.; Analysis: L.A., B.K., C.C.G., B.Y.; Literature search: L.A., B.K., C.C.G., B.Y.; Writing: L.A., C.C.G., B.Y.; Critical revision: L.A., B.K.

Conflict of Interest

None declared.

REFERENCES

1. Peters JW, Trevino SG, Renstrom PA. Chronic lateral ankle instability. Foot Ankle 1991;12:182–91. [CrossRef]
2. Hertel J, Corbett RO. An updated model of chronic ankle ınstability. J Athl Train 2019;54:572–88. [CrossRef]
3. Strauss JE, Forsberg JA, Lippert FG 3rd. Chronic lateral ankle instability and associated conditions: A rationale for treatment. Foot Ankle Int 2007;28:1041–4. [CrossRef]
4. Malik AT, Noordin S. The Top 50 most-cited articles on total ankle arthroplasty: A bibliometric analysis. Orthop Rev (Pavia) 2018;10:7498. [CrossRef]
5. Konar NM, Karaismailoglu S, Karaismailoglu E. Status and trends of personalized medicine research from 2000 to 2020: A bibliometric analysis. Curr Med Res Opin 2022;38:837–46. [CrossRef]
6. Karaismailoglu B, Tutuncu MN, Sahin E, Aslan L. Characteristics and research trends of the 100 most-cited flatfoot articles. J Am Podiatr Med Assoc 2023;113:21–77. [CrossRef]
7. Frazer PM, Pastore G, McGarry AK, Walsh TP, Platt SR. A bibliometric analysis of 4 major foot and ankle surgery journals. J Foot Ankle Surg 2021;60:692–6. [CrossRef]
8. Karslı B, Tekin SB. The top 100 most-cited articles on ankle arthroscopy: Bibliometric analysis. J Foot Ankle Surg 2021;60:477–81. [CrossRef]
9. Feeney KM. The top 100 cited articles on plantar fasciitis: A bibliometric analysis. J Foot Ankle Surg 2022;61:1246–50. [CrossRef]
10. Marder RS, Koehler SM, Aibinder WR. The top 50 most cited articles on olecranon fractures: A bibliometric analysis. Eur J Orthop Surg Traumatol 2022;3 2:99–106. [CrossRef]
11. Bayley M, Brooks F, Tong A, Hariharan K. The 100 most cited papers in foot and ankle surgery. Foot (Edinb) 2014;24:11–6. [CrossRef]
12. DeHeer PA, Adams W, Grebenyuk FR, Meshulam E, Miskin K, Koch TT, et al. Top 100 cited foot and ankle-related articles. J Am Podiatr Med Assoc 2016;106:387–97. [CrossRef]
13. Gürbüz Y, Süğün TS, Özaksar K. A bibliometric analysis of orthopedic publications originating from Turkey. Acta Orthop Traumatol Turc 2015;49:57–66. [CrossRef]
14. Dokur M, Uysal E. Top 100 cited articles in traumatology: A bibliometric analysis. Ulus Travma Acil Cerrahi Derg 2018;24:294–302. [CrossRef]
15. Luo X, Liang Z, Gong F, Bao H, Huang L, Jia Z. Worldwide productivity in the field of foot and ankle research from 2009-2013: a bibliometric analysis of highly cited journals. J Foot Ankle Res 2015;8:12. [CrossRef]

16. Song Y, Li H, Sun C, Zhang J, Gui J, Guo Q, et al. Clinical Guidelines for the surgical management of chronic lateral ankle instability: A consensus reached by systematic review of the available data. Orthop J Sports Med 2019;7:2325967119873852. [CrossRef]
17. McCriskin BJ, Cameron KL, Orr JD, Waterman BR. Management and prevention of acute and chronic lateral ankle instability in athletic patient populations. World J Orthop 2015;6:161–71. [CrossRef]
18. Ferreira GF, Stéfani KC. A global bibliometric analysis of Hallux Valgus research (1999-2019). J Foot Ankle Surg 2021;60:501–6. [CrossRef]

Kronik Lateral Ayak Bileği İnstabilitesi Araştırmalarının Bibliyometrik Analizi: Etkili Yayınların Haritalandırılması

Amaç: Bilimsel literatürü niceliksel olarak değerlendiren bibliyometrik analiz yöntemiyle, Kronik Lateral Ayak Bileği İnstabilitesi (KLAI) alanındaki en çok alıntı yapılan ilk 100 yayını kapsamlı bir şekilde analiz etmeyi amaçladık. KLAI alanı içindeki ana araştırma temalarını, eğilimleri ve araştırmacılar, kurumlar ve ülkeler arasındaki işbirliği ağını tanımlamayı ve KLAI araştırmasının değişimine ve klinik uygulama ile hasta bakımına olan etkisine, kanıta dayalı tıp bağlamında içgörüler sunmayı hedefledik.

Gereç ve Yöntem: Web of Science veritabanı kullanılarak 2023 yılı sonuna kadar KLAI üzerine en çok alıntı yapılan 100 makale üzerinde bir bibliyometrik analiz gerçekleştirildi. Ortalama alıntı sayısı ve alıntı yoğunluğu hesaplandı. Yayın yılı, yazarlık, kurumsal ve coğrafi kökenler ve dergi isimleri gibi ilgili veriler kayıt altına alındı. Ayrıca, çalışmalar kanıt düzeyi, tasarım ve konu başlığına göre sınıflandırıldı ve alıntı metrikleriyle kanıt düzeyi, yayın on yılı ve dergi başlığı arasında olan korelasyonlar incelendi. Yazar uzmanlığının, kurumlararası işbirliklerinin ve yazar sayısı, kurum sayısı, sayfa sayısı ve referanslar gibi niceliksel yönlerin alıntı sayıları üzerindeki etkisi ek analizlerle incelendi.

Bulgular: KLAI konusunda en çok atıf almış ilk 100 makale üzerine yapılan analiz, atıf sayısı maksimum 1,074 ve makale başına ortalama 166.15±127.05 atıf ile atıf yoğunluğunun 2.50 ile 60.60 arasında değiştiğini ortaya koydu. Araştırmalar ağırlıkla Amerika Birleşik Devletleri'ndendi (52 çalışma), makale başına ortalama 4.42±4.32 yazarlıydı, 2 ila 18 sayfa arasındaydı ve 10 ila 260 arası referans içermekteydi. Kuzey Karolina Üniversitesi, sekiz makale ile öne çıkan bir kurum olarak belirlendi ve Hertel, 15 makaleye katkıda bulunmasıyla önemli bir yazar olarak tespit edildi.

Sonuç: KLAI üzerine yapılan bu bibliyometrik analiz, özellikle 2011-2020 yılları arasında yapılan son çalışmalara olan artan ilgiyi vurgulamakta ve çok merkezli araştırmaların önemini ve daha yüksek düzeyde kanıta olan ihtiyacı ortaya koymaktadır. Amerika Birleşik Devletleri, İsveç ve Birleşik Krallık'ın ana katkıda bulunanlar olarak belirlenmesi, küresel işbirliği potansiyelini göstermektedir.

Anahtar Sözcükler: Atıf sayısı; atıf yoğunluğu; bibliyometrik çalışma; kronik lateral ayak bileği instabilitesi.

Supplementary Table 1

Rank	Top 100 Most Cited Chronic Lateral Ankle Instability Articles	Times Cited
	Title	WoS Core
1	Functional anatomy, pathomechanics, and pathophysiology of lateral ankle instability	871
2	Persistent disability associated with ankle sprains: a prospective examination of an athletic population	554
3	Ligamentous posttraumatic ankle osteoarthritis	409
4	Chronic lateral instability of the ankle - roentgen stereophotogrammetry of talar position	382
5	Efficacy of the star excursion balance tests in detecting reach deficits in subjects with chronic ankle instability	327
6	Arthroscopic findings in patients with chronic ankle instability	321
7	Evidence review for the 2016 international ankle consortium consensus statement on the prevalence, impact and long-term consequences of lateral ankle sprains	279
8	An updated model of chronic ankle instability	273
9	Reconstruction of the lateral ligaments of the ankle for chronic lateral instability	266
10	Systematic review of postural control and lateral ankle instability, part i: can deficits be detected with instrumented testing?	241
11	A multi-station proprioceptive exercise program in patients with ankle instability	218
12	Recovery from a first-time lateral ankle sprain and the predictors of chronic ankle instability: a prospective cohort analysis	216
13	Seven years follow-up after ankle inversion trauma	215
14	The effect of external ankle support in chronic lateral ankle joint instability - an electromyographic study	212
15	Reliability and sensitivity of the foot and ankle disability index in subjects with chronic ankle instability	201
16	Prolonged reaction-time in patients with chronic lateral instability of the ankle	194
17	Arthroscopic-assisted brostrom-gould for chronic ankle instability a long-term follow-up	182
18	Understanding acute ankle ligamentous sprain injury in sports	180
19	Associated injuries found in chronic lateral ankle instability	180
20	Epidemiology of ankle sprains and chronic ankle instability	175
21	Treatment and prevention of acute and recurrent ankle sprain: an overview of systematic reviews with meta-analysis	168
22	Contributing factors to chronic ankle instability	158
23	The clinimetric qualities of patient-assessed instruments for measuring chronic ankle instability: a systematic review	152
24	Chronic lateral instability: arthroscopic findings and long-term results	152
25	Arthroscopic treatment of anterolateral impingement of the ankle	152
26	Individuals with mechanical ankle instability exhibit different motion patterns than those with functional ankle instability and ankle sprain copers	151
27	Chronic lateral ankle instability	151
28	National athletic trainers' association position statement: conservative management and prevention of ankle sprains in athletes	148
29	Twenty-six-year results after brostrom procedure for chronic lateral ankle instability	147
30	Systematic review of postural control and lateral ankle instability, part ii: is balance training clinically effective?	146
31	A comparison of star excursion balance test reach distances between acl deficient patients and asymptomatic controls	140
32	2016 consensus statement of the international ankle consortium: prevalence, impact and long-term consequences of lateral ankle sprains	137
33	Ankle sensorimotor control and eversion strength after acute ankle inversion injuries	136
34	Arthroscopic findings associated with the unstable ankle	135
35	Isolated anterior talofibular ligament brostrom repair for chronic lateral ankle instability 9-year follow-up	134

36	Postural control differs between those with and without chronic ankle instability	133
37	Comprehensive reconstruction of the lateral ankle for chronic instability using a free gracilis graft	133
38	Arthroscopic repair of chronic lateral ankle instability	131
39	Comparison of two anatomic reconstructions for chronic lateral instability of the ankle joint	130
40	Treatment of acute lateral ankle ligament rupture in the athlete -: conservative versus surgical treatment	129
41	Treatment of acute ankle ligament injuries: a systematic review	123
42	Chronic ankle instability alters central organization of movement	123
43	Chronic lateral ankle instability the effect of intra-articular lesions on clinical outcome	123
44	Invertor vs. evertor peak torque and power deficiencies associated with lateral ankle ligament injury	123
45	Is stress radiography necessary in the diagnosis of acute or chronic ankle instability?	121
46	Minimum reporting standards for copers in chronic ankle instability research	117
47	Chronic ankle instability - evaluation with mr arthrography, mr-imaging, and stress radiography	116
48	Outcomes of the chrisman-snook and modified-brostrom procedures for chronic lateral ankle instability - a prospective, randomized comparison	115
49	Medial ankle instability - an exploratory, prospective study of fifty-two cases	113
50	Joint mobilization improves spatiotemporal postural control and range of motion in those with chronic ankle instability	111
51	Chronic tibiofibular syndesmosis injury: the diagnostic efficiency of magnetic resonance imaging and comparative analysis of operative treatment	109
52	Lateral ankle sprains: a comprehensive review - part 1: etiology, pathoanatomy, histopathogenesis, and diagnosis	109
53	Surgical-treatment of chronic lateral instability of the ankle joint - a new procedure	109
54	Balance capabilities after lateral ankle trauma and intervention: a meta-analysis	106
55	Management of acute and chronic ankle instability	106
56	Combination of modified brostrom procedure with ankle arthroscopy for chronic ankle instability accompanied by intra-articular symptoms	105
57	Peroneus brevis tendon tears: pathophysiology, surgical reconstruction, and clinical results	105
58	Arthrogenic muscle inhibition in the leg muscles of subjects exhibiting functional ankle instability	104
59	Clinical assessment of acute lateral ankle sprain injuries (roast): 2019 consensus statement and recommendations of the international ankle consortium	103
60	Evaluation of ankle instability using the biodex stability system	101
61	Factors contributing to chronic ankle instability: a strength perspective	100
62	Outcome of the modified brostrom procedure for chronic lateral ankle instability using suture anchors	100
63	Long-term results after modified brostrom procedure without calcaneofibular ligament reconstruction	97
64	The all inside arthroscopic brostrom procedure: a prospective study of 40 consecutive patients	95
65	Bilateral balance impairments after lateral ankle trauma: a systematic review and meta-analysis	95
66	Treatment of common deficits associated with chronic ankle instability	95
67	Correlations among multiple measures of functional and mechanical instability in subjects with chronic ankle instability	95
68	Anatomical reconstruction for chronic lateral ankle instability in the high-demand athlete functional outcomes after the modified brostrom repair using suture anchors	93
69	Quantitative assessment of mechanical laxity in the functionally unstable ankle	93
70	Peroneus longus ligamentoplasty for chronic instability of the distal tibiofibular syndesmosis	93
71	A new paradigm for rehabilitation of patients with chronic ankle instability	91

72	Dynamic postural control but not mechanical stability differs among those with and without chronic ankle instability 91	
73	Is there a link between chronic ankle instability and postural instability?	91
74	Sensorimotor function as a predictor of chronic ankle instability	89
75	The management of concomitant tears of the peroneus longus and brevis tendons	89
76	Chronic pain following ankle sprains in athletes: the role of arthroscopic surgery	89
77	Searching for consensus in the approach to patients with chronic lateral ankle instability: ask the expert	88
78	Current concepts: lateral ankle instability	87
79	Anatomical reconstruction and evans tenodesis of the lateral ligaments of the ankle - clinical and radiological findings after follow-up for 15 to 30 years	87
80	Long-term outcome of anatomical reconstruction versus tenodesis for the treatment of chronic anterolateral instability of the ankle joint: a multicenter study	87
81	Arthroscopic treatment of synovial impingement of the ankle	87
82	In vivo cartilage contact strains in patients with lateral ankle instability	86
83	Peroneal activation deficits in persons with functional ankle instability	86
84	Factors contributing to chronic ankle instability: kinesthesia and joint position sense	86
85	Acute and chronic lateral ankle instability in the athlete	85
86	Mechanical contributions to chronic lateral ankle instability	84
87	Comparison of lateral ankle ligamentous reconstruction procedures	84
88	Open and arthroscopic lateral ligament repair for treatment of chronic ankle instability: a systematic review	83
89	Arthroscopy and endoscopy of the foot and ankle: indications for new techniques	83
90	Acute ankle injury and chronic lateral instability in the athlete	82
91	Osteochondral lesions of the talar dome associated with trauma	82
92	Ct analysis of hindfoot alignment in chronic lateral ankle instability	81
93	Biomechanics of the unstable ankle joint and clinical implications	79
94	Lateral instability of the ankle joint	78
95	Arthroscopic findings in chronic lateral ankle instability - do focal chondral lesions influence the results of ligament reconstruction?	77
96	Effects of chronic ankle instability on kinetics, kinematics and muscle activity during walking and running: a systematic review	75
97	Strength-training protocols to improve deficits in participants with chronic ankle instability: a randomized controlled trial	75
98	Ankle ligament injuries	75
99	Anatomic suture anchor versus the brostrom technique for anterior talofibular ligament repair a biomechanical comparison	74
100	Biomechanics of ankle instability. part 1: reaction time to simulated ankle sprain	74

SCIE DOI: 10.14744/scie.2024.06936
South. Clin. Ist. Euras. 2024;35(3):269-275

Original Article

Association Between Endometrial Pathologies and Triglyceride Glucose Index & Body Shape Index: Retrospective Cohort Study

Serap Topkara Sucu,[1] Tuğba Kolomuç Gayretli,[1] Selver Özge Şefik,[1]
Eyüp Gökhan Turmuş,[2] Candost Hanedan,[2] Çaganay Soysal[1]

[1]Department of Gynecology and Obstetrics, Ankara Etlik City Hospital, Ankara, Türkiye
[2]Department of Gynecologic Oncology Surgery, Ankara Etlik City Hospital, Ankara, Türkiye

Submitted: 22.05.2024
Revised: 13.06.2024
Accepted: 12.07.2024

Correspondence: Serap Topkara Sucu, Department of Gynecology and Obstetrics, Ankara Etlik City Hospital, Ankara, Türkiye
E-mail: academicserapts@gmail.com

Keywords: Carcinoma, endometrioid, insulin resistance, obesity.

ABSTRACT

Objective: We aimed to investigate the association between the triglyceride glucose index and body shape index in predicting premalignant-malignant endometrial pathologies.

Methods: The results of patients who presented to the Department of Gynecology and Obstetrics at our hospital due to abnormal uterine bleeding and underwent endometrial biopsy were reviewed. We formed two groups: benign pathologies and premalignant-malignant pathologies. Multiple logistic regression analysis was performed to evaluate the relationship between the triglyceride glucose index, body shape index, and premalignant-malignant endometrial pathology. The study is a retrospective cohort study.

Results: There were 579 patients whose fasting blood glucose and fasting triglycerides were measured before endometrial biopsy. After applying exclusion criteria, 330 patients (age: 43-56 years) were included in the study. Significant differences were observed between the groups in terms of age, weight, waist circumference, BMI, and body shape index Z scores ($p<0.05$). Triglyceride glucose index, anthropometric measurements, and waist circumference had the highest AUC. Regression analysis showed that a one-unit increase in the triglyceride glucose index value increased the probability of the patient having premalignant-malignant pathology by 164 times.

Conclusion: Consequently, obesity increases the likelihood of endometrial pathology. Therefore, it is recommended to assess the triglyceride glucose index and body shape index Z scores in patients with abnormal uterine bleeding. Both of these methods are simple and cost-effective to calculate. It is important to inform patients about the risks identified in these calculations and to provide preventive advice.

INTRODUCTION

Endometrial carcinoma (EC) is a common gynecologic malignancy, and its incidence is increasing.[1] Endometrial intraepithelial neoplasia often precedes it. Frequently identified risk factors include increased age, obesity (especially abdominal obesity), increased body mass index (BMI), insulin resistance, diabetes, dyslipidemia, and hormonal imbalance.[2,3]

The development of cancer is a complex process that can be traced back to serious disturbances in the regulation of cell growth and proliferation. Recent evidence has shown that insulin resistance, which is regulated in part by fasting and lifestyle, is closely associated with the morbidity and mortality of several cancers, including breast, colorectal, and cervical cancers.[4,5] This may be because insulin resistance increases cell proliferation, inhibits apoptosis, activates IGF-1 receptors, and triggers inflammation and oxidative stress, which promote cancer growth.[6,7]

Obesity is a risk factor for EC.[8] The underlying process is thought to be related to insulin resistance and the release of adipokines. Insulin resistance causes higher insulin levels that stimulate endometrial cell mitogenesis, and adipokines such as adiponectin and leptin also contribute to the development of EC.[9] In addition, hyperinsulinemia leads to excessive proliferation of granulosa cells and the production of large amounts of androgens, which are converted to estrogens by the enzyme aromatase. Insulin

resistance thus becomes a risk factor for endometrial hyperplasia and early-stage endometrial cancer.[10-12]

It is well known that insulin resistance can be measured by the Homeostatic Model Assessment and the hyperinsulinemic-euglycemic clamp test.[13] In addition, several studies have shown that the triglyceride glucose (TyG) index may be a more appropriate and reliable predictor of insulin resistance compared with these two measurement tools. Therefore, because of its availability and cost-effectiveness, the TyG index may be a promising indicator of insulin resistance in large-scale epidemiological studies.[14]

Our aim was to investigate the relationship between insulin resistance and endometrial pathologies using the TyG index, taking into account existing risk factors for EC. In addition, we investigated the relationship between endometrial pathologies and anthropometric measurements such as BMI and a body shape index (ABSI).

MATERIALS AND METHODS

Study Design

This study is a retrospective cohort study. The results of patients who presented to the Department of Gynecology and Obstetrics at our hospital with abnormal uterine bleeding and underwent endometrial biopsy between October 2022 and June 2023 were reviewed. Over the past year, 579 patients were found whose fasting blood sugar and fasting triglyceride levels were measured before biopsy. According to the study's purpose, two groups of patients were formed: benign (endometrial polyp, endometrial hyperplasia without atypia, atrophic endometrium) and premalignant (endometrial intraepithelial neoplasia)-malignant (endometrial cancer). Patients were contacted, informed about the study, and invited to the outpatient clinic. All patients were informed that their medical data and records could be used in the studies without revealing the patient's identity. Informed consent was obtained from the patients. We prepared a form including risk factors for EC. The form was completed in a face-to-face interview with the patients, and height, weight, and waist circumference were measured. All patients had a confirmed histopathological diagnosis. Patients with fasting glucose and fasting triglyceride values checked within the past year were included in the study. Patients currently taking medications due to diabetes, hyperlipidemia, and a history of cancer were excluded from the study.

The triglyceride-glucose index of the patients was calculated according to the equation TyG=ln [fasting triglyceride (mg/dl) x fasting glucose (mg/dl)] /2.[15] To determine the risk of early death due to the patients' body shape, ABSI scores were calculated by adding waist circumference, height, and BMI to sex and age, and ABSI Z-scores were calculated to compare the results with similar age groups. ABSI values were calculated using the formula ABSI=Waist circumference/(height1^11/2_22×BMI2^22/3_33), ABSI Z-score: ABSI-ABSIMean/ABSISD.[16]

RESULTS

In the past year, 579 patients whose fasting blood sugar and fasting triglyceride levels were measured before biopsy were identified. After applying the exclusion criteria, 134 patients (22%) were excluded from the study because they were taking antidiabetic drugs, 70 patients (12%) were taking antilipidemic drugs, 20 patients (3%) had a history of cancer, and 25 patients (4%) declined to participate in the study, leaving 330 patients eligible for the study. The groups formed based on the number of patients and the pathology results are shown in Figure 1.

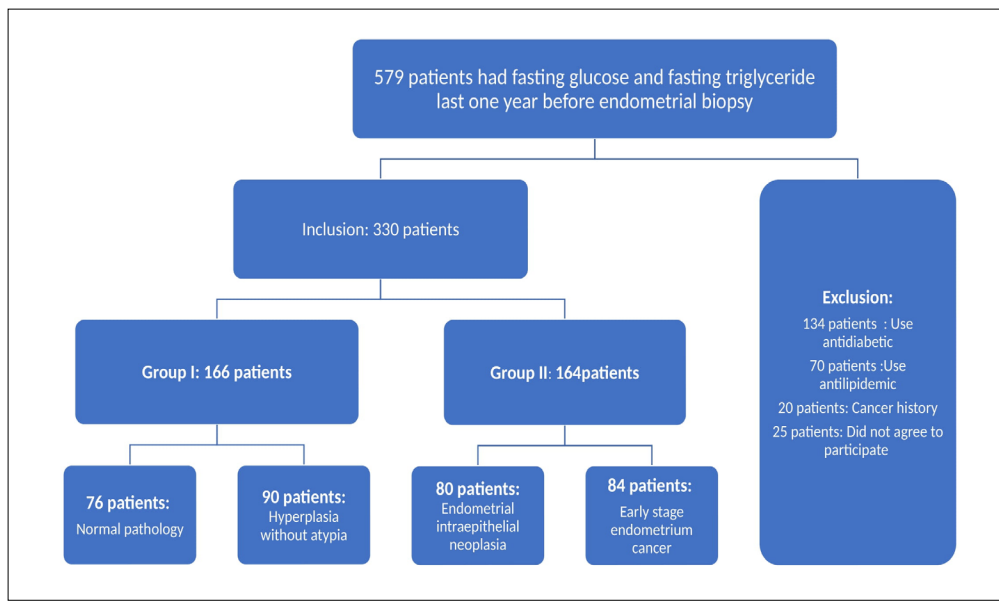

Figure 1. Flowchart.

Primary Outcome

There was a significant difference in age, weight, BMI, waist circumference, and ABSI Z-score between the two groups. Group II had a higher number of menopausal patients (p<0.05). Smoking and plasma albumin levels were statistically higher in Group I than in Group II. In Group II, plasma fasting triglyceride level, fasting blood glucose, TyG index, leukocyte count, and neutrophil count were higher than in Group I (p<0.05) (Table 1).

In evaluating the laboratory and anthropometric measurements with statistically significant differences between groups with ROC analysis, weight, waist circumference, BMI, ABSI Z-score, plasma triglyceride, fasting blood glucose, and the TyG index were found to be statistically significant (p<0.05). The TyG had the highest AUC (AUC:0.813, CI%:0.744-0.869, p<0.001, sensitivity:67.1, specificity:88, cut-off value: >4.79). Among the anthropometric measurements, waist circumference had the highest AUC value (AUC:0.779, CI%:0.708-0.840, p<0.001, sensitivity: 68.3, specificity: 45.8, cut-off value: >73 cm). The values of AUC, CI%, p-value, cut-off value, sensitivity, specificity, negative likelihood ratio, and positive likelihood ratio of each parameter are shown in Table 2. In the ROC

Table 1. Demographic and clinical characteristics of the study population

Variables	Benign (n=166)	Malign- premalignant (n=164)	Total (n=330)	p
Age	41.75 (45.5-50)	53 (47-63.5)	48 (43-56)	<0.001
Gravida	2.5 (2-3.75)	3 (2-4)	3 (2-4)	0.219
Parity	2 (2-3)	3 (2-4)	2 (2-3)	0.233
Abort	0 (0-0)	0 (0-0.75)	0 (0-0)	0.481
Menarcheal				
Age (years)	13 (12-14)	13 (12-14)	13 (12-14)	0.151
Weight (kg)	75 (66-85)	83.5 (74-97.25)	78 (71.5-90)	<0.001
BMI (kg/m^2)	29.3 (25.8-32.8)	32.1 (29.2-38.6)	35.2 (30.5-27.5)	<0.001
Waist circumference (cm)	95 (86-103)	110 (98-125.25)	102 (91-116)	<0.001
ABSI	0.0791	0.0846	0.0820	
	(0.0749-0.0840)	(0.0798-0.0886)	(0.0861-0.0770)	<0.001
ABSI Z score	0.0494	0.8403	0.4990	
	(-0.7508-1.0514)	(0.0488-1.4491)	(-0.4525-1.3128)	0.003
Fasting triglyceride level (mg/dL)	113 (78-145)	174 (117-256)	133 (97-184.5)	<0.001
Fasting glucose level (mg/dL)	88 (80-95)	100.5 (88-121)	91 (84.5-105)	<0.001
TyG index	4.58±0.242	4.90±0.267	4.74±0.300	<0.001
Hemoglobin (g/dL)	12.5 (11-13.1)	12.4 (11.5-13.4)	12.4 (11.1-13.3)	0.444
Smoking status				
No	120 (72.3)	144 (87.8)	264 (80)	0.022
Yes	46 (27.7)	20 (12.2)	66 (20)	
Previous endometrial hyperplasia diagnosis				
No	156 (94)	160 (97.6)	316 (95.8)	0.443
Yes	20 (6)	8 (2.4)	28 (4.2)	
Family history of colorectal cancer or endometrial cancer				
No	146 (88)	158 (96.3)	304 (92.1)	0.087
Yes	20 (12)	6 (3.7)	26 (7.9)	
Menopause status				
No	142 (85.5)	78 (47.6)	220 (66.7)	<0.001
Yes	24(14.5)	86 (52.4)	110 (33.3)	
Previous infertility diagnosis				
No	154 (92.8)	160 (97.6)	314 (95.2)	0.277
Yes	12 (7.2)	4 (2.4)	16 (4.8)	

kg: kilogram; BMI: body mass index; kg/m2: kilogram per square meter; cm, centimeter; ABS: A Body Shape Index; mg/dL: milligrams per decilitre; TyG: Triglyceride glucose index; g/L: gram per liter; µL: microlitre; g/dL: grams per decilitre; WBC: white blood cell. Data are expressed as the mean±SD, median (Q1-Q3), or number (percentage) where appropriate. A p value of <0.05 indicates a significant difference. Statistically significant p values are in bold.

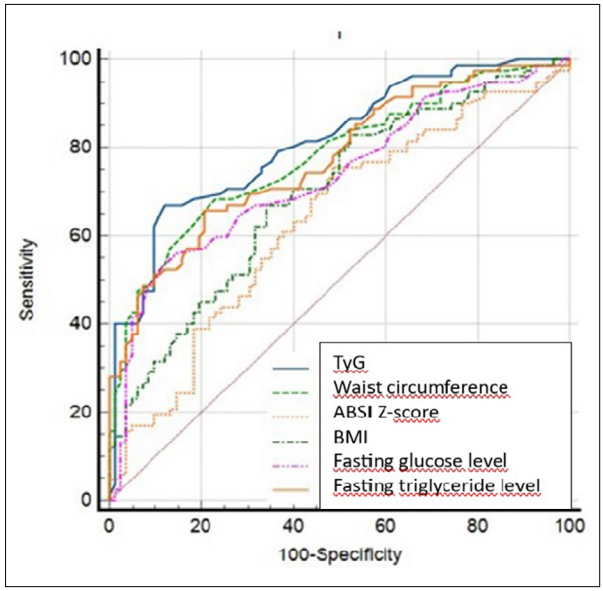

Figure 2. Comparison of the ROC graphs of various parameters.

analysis performed to determine the superiority of AUC values of all statistically significant parameters over each other, waist circumference was found to be superior to all other anthropometric measurements (waist circumference vs. BMI p:0.004; vs. ABSI p:0.023; vs. ABSI Z-score p<0.001) (Figure 2). The TyG index has better sensitivity and specificity values than other laboratory parameters and has a statistically significantly higher AUC value (TyG vs. Plasma triglyceride level p:0.015; vs. fasting glucose level p:0.045). The p-values expressing the superiority and difference of all parameters in terms of AUC values are shown in Table 3.

Secondary Outcomes

In the regression analysis performed to determine the risk factors for premalignant-malignant pathologies and the rates of risk increase among the categorical variables, not smoking (OR:2.871, p: 0.047) is considered a risk factor, while premenopause appears to be a protective factor with a 6.41-fold reduction in risk (OR:0.156, p<0.001). However, each year, the patient's age increases, resulting in a 1.089-fold increase in the risk of premalignant-malignant pathology (p<0.001). Of the anthropometric measurements, only waist circumference (OR:1.056, p: 0.001) showed a statistically significant risk increase, while of the laboratory measurements, plasma triglyceride level (OR:1.02, p<0.001), fasting blood glucose (OR:1.025, p: 0.024), and TyG index (OR:164.67, p<0.001) showed significantly increased risk. A one-unit increase in the patient's TyG index value increases the likelihood of the patient having premalignant-malignant pathology 164-fold. Weight, ABSI Z-score, white blood cell count, neutrophil count, and albumin levels alone were not sufficient to determine the risk increase (p>0.05) (Table 4).

DISCUSSION

Endometrial cancer is increasing daily due to rising obesity worldwide. Obesity, metabolic disorders, and insulin resistance pose serious risks, especially for estrogen-related EC.[17] In our study, we wanted to draw attention to the relationship between endometrial pathologies and obesity by calculating waist circumference, weight, BMI, ABSI, and

Table 2. The results of ROC curve analysis for various parameters that can be used to predict the outcome of a premalignant-malignant biopsy

Variables	AUC	CI 95%	p	Cut-off value	Sensitivity (%)	Specificity (%)	LR+	LR-
Weight	0.670	0.592-0.741	<0.001	>73	80.5	45.8	1.48	0.43
Waist circumference	0.779 0.840	0.708-<0.001	103	68.3	77.1	2.98	0.41	
BMI	0.693	0.617-0.763	<0.001	>30.45	67.1	65.1	1.92	0.51
ABSI Z-score	0.636	0.557-0.709	0.001	>0.0667	75.6	51.2	1.55	0.48
Fasting triglyceride level	0.755	0.703-0.836	<0.001	>150	65.9	79.5	3.22	0.43
Fasting glucose level	0.728	0.653-0.794	<0.001	>97	56.1	84.3	3.58	0.52
TyG	0.813	0.744-0.869	<0.001	>4.79	67.1	88	5.57	0.37

ROC: receiver operating characteristic; AUC: the area under the curve; C: confidence interval; LR+: positive likelihood ratio; LR: negative likelihood ratio; BMI: body mass index; ABSI: A Body Shape Index; TyG: Triglyceride glucose index; p-value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

Table 3. The p-values obtained when the parameters for which ROC calculations were performed are compared using the AUC values

Variables	Height	Weight	Waist circumference	BMI	ABSI	ABSI z score	TyG	Fasting glucose level
Height		0.215	<0.001$^{\Phi}$	0.040$^{\Phi}$	0.091	0.489	<0.001$^{\Phi}$	0.024$^{\Phi}$
Weight	0.215		0.002$^{\Phi}$	0.209	0.755	0.572	0.002$^{\Phi}$	0.285
Waist circumference	<0.001$^{\Phi}$	0.002$^{\Phi}$		0.004$^{\Phi}$	0.023$^{\Phi}$	<0.001$^{\Phi}$	0.456	0.378
BMI	0.040$^{\Phi}$	0.209	0.004$^{\Phi}$		0.938	0.330	0.010$^{\Phi}$	0.489
ABSI	0.091	0.755	0.023$^{\Phi}$	0.938		<0.001$^{\Phi}$	0.027$^{\Phi}$	0.458
ABSI z score	0.489	0.572	<0.001$^{\Phi}$	0.330	<0.001$^{\Phi}$		0.001$^{\Phi}$	0.097
TyG	<0.001$^{\Phi}$	0.002$^{\Phi}$	0.456	0.010$^{\Phi}$	0.027$^{\Phi}$	0.001$^{\Phi}$		0.045$^{\Phi}$
Plasma Triglyceride level	0.001$^{\Phi}$	0.034	0.910	0.108	0.161	0.020$^{\Phi}$	0.015$^{\Phi}$	0.372

ROC: receiver operating characteristic; BMI: body-mass index; ABSI: A Body Shape Index; TyG: Triglyceride glucose index; p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold. $^{\Phi}$For comparisons where the p value is significant, the parameter with the higher AUC value in Table 2 is superior in predicting the outcome of a premalignant-malignant biopsy.

Table 4. Results of regression analysis showing the risk of a premalignant-malignant pathological outcome for statistically significant variables

Variables	OR	95% CI	p
Age$^{¥}$	1.089	1.044-1.135	<0.001
Premenopause$^{¥}$	0.156	0.062-0.389	<0.001
Smoking status (no)$^{¥}$	2.871	1.012-8.147	0.047
Weight$^{£}$	1.019	0.991-1.047	0.192
BMI$^{£}$	1.044	0.975-1.118	0.219
Waist circumference$^{£}$	1.056	1.024-1.088	0.001
ABSI Z-score$^{£}$	1.285	0.995-1.661	0.055
Fasting triglyceride level$^{\Omega}$	1.020	1.011-1.029	<0.001
Fasting glucose level$^{\Omega}$	1.025	1.003-1.048	0.024
TyG$^{\Omega}$	164.67	21.635-1253.415	<0.001
WBC$^{\Omega}$	1.000	0.999-1.000	0.143
Albumin$^{\Omega}$	0.895	0.791-1.013	0.078

OR: odds ratio; CI: confidence interval; BMI: body mass index; ABSI: A Body Shape Index; TyG: triglyceride glucose index; WBC: white blood count. A p-value of <0.05 indicates a significant difference. Statistically significant p-values are in bold. $^{¥}$In modeling involving only demographic data, all demographic data were adjusted with statistically significant parameters. $^{£}$Each anthropometric measurement was adjusted for statistically significant demographic data and the laboratory parameter (TyG) with the highest AUC in the ROC analysis. $^{\Omega}$Each laboratory measurement and index were adjusted with statistically significant demographic data and anthropometric measurement (waist circumference) with the highest AUC in the ROC analysis.

ABSI Z-score of the patients participating in the study.

Metabolic syndrome is a combination of various metabolic abnormalities such as obesity, insulin resistance, hypertension, and dyslipidemia.[18] Studies suggest that metabolic abnormalities and obesity may be important risk factors for the development of EC.[19]

Obesity is associated with gynecological cancers in women. Alsansan et al.[20] showed that EC is common in women with obesity. Nicholson et al.[21] found that there is a linear relationship between increasing BMI scores and early-stage endometrial intraepithelial neoplasia in premenopausal patients. Laslov et al.[22] concluded that patients with a higher BMI increase during follow-up had higher recurrence rates of EC.

In our study, we observed a significant association between increased BMI and endometrial pathologies, consistent with previous findings. It is important to note that BMI has limitations. It cannot distinguish between fat and lean mass or central and peripheral obesity. To overcome these limitations, a new anthropometric index called the body shape index (ABSI) has been proposed as an alternative. ABSI values are associated with all-cause mortality, metabolic syndrome, diabetes, and hypertension, making it useful in estimating the risk of diseases that BMI cannot detect easily.[23,24]

Our study focused on waist circumference as one of the diagnostic criteria for metabolic syndrome. We calculated ABSI scores to predict the risk of early mortality. Our results showed that increased waist circumference, especially due to abdominal adipose tissue, was more closely

associated with premalignant endometrial pathologies. In addition, the ABSI Z-scores of patients in the premalignant-malignant group were higher. Although there have been studies on the association between metabolic disorders and endometrial pathology, none have considered ABSI and endometrial pathology outcomes. Our study suggests that ABSI should be considered an important parameter for determining the risk of premalignant and malignant endometrial pathology.

It is well known that smoking increases the risk of many chronic diseases and cancers. However, it has been shown to have an estrogen-inhibiting effect due to the changes it causes in the estrogen mechanism. Smoking can reduce estrogen-induced cell proliferation in the endometrial glands. This effect may contribute to protection against the development of endometrial cancer. In our study, we found that smoking was more frequent in the benign group, which is consistent with the results reported in the literature.[25]

Dyslipidemia is an independent risk factor for EC.[26] Sethre et al.[27] found a positive correlation between serum lipid/lipoprotein levels (e.g., triglycerides) and EC risk in a cohort of 31,473 women.[27] Abnormal lipid metabolism increases the risk of endometrial cancer through several mechanisms. High triglyceride levels resulting from abnormal lipid metabolism increase free estrogen levels by decreasing the binding of the sex hormone to proteins (e.g., globulin).[9,28] The TyG index results evaluated in our study show that dyslipidemia and insulin resistance increase the risk of EC, which is consistent with the literature. It is noteworthy that the TyG index is particularly high in the endometrial intraepithelial neoplasia group. This may suggest that the association between endometrial cancer and diabetes in the population may be due to previously untreated insulin resistance. Most of the literature has examined the relationship between the TyG index and cardiovascular disease. In the article that examined the association between the TyG index and obesity-related cancers, no association was found between ovarian and endometrial cancer and the TyG index.[20] There was only one study that examined the association between endometrial cancer and the triglyceride glucose index, and it found that the index was high in premalignant-malignant endometrial pathologies, which was consistent with our study.[29]

The strength of our study is that, using indices calculated with a simple method, we can predict people's risk of endometrial pathologies and provide opportunities for preventive medicine. It is important to point out that this study has certain limitations. First, the patients were selected from only one institution, and the sample size is relatively small. Therefore, our results may not be fully representative of the wider population. However, if multicenter studies with larger patient cohorts are conducted in the future, we may obtain more precise and accurate results that reflect the general population.

Conclusion

The triglyceride glucose index provides information about insulin resistance. It is determined using a simple method and helps to assess a patient's risk of endometrial cancer. In this way, we can explain the current risk to the patient and make recommendations to reduce the risk through lifestyle changes and an appropriate dietary program. These parameters, which we have examined in diagnosed patients, can be used as a screening program in primary care to calculate individual risk by examining all women over the age of 35.

Ethics Committee Approval

The study was approved by the Ankara Etlik City Hospital Ethics Committee (Date: 19.07.2023, Decision No: AESH-EK1-2023/332).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: S.T.S., T.K.G.; Design: S.T.S., S.Ö.Ş.; Supervision: S.T.S., C.H., Ç.S.; Fundings: S.T.S.; Materials: T.K.G., E.G.T.; Data: T.K.G., C.H.; Analysis: S.Ö.Ç., E.G.T., Ç.S.; Literature search: S.T.S., C.H., E.G.T.; Writing: S.T.S., S.Ö.Ş.; Critical revision: S.T.S., Ç.S.

Conflict of Interest

None declared.

REFERENCES

1. Rodriguez AC, Blanchard Z, Maurer KA, Gertz J. Estrogen signaling in endometrial cancer: A key oncogenic pathway with several open questions. Horm Cancer 2019;10:51–63.
2. Dossus L, Lukanova A, Rinaldi S, Allen N, Cust AE, Becker S, et al. Hormonal, metabolic, and inflammatory profiles and endometrial cancer risk within the EPIC cohort - A factor analysis. Am J Epidemiol 2013;177:787–99.
3. Köse C, Korpe B, Kurdoglu Z, Korkmaz H, Engin Ustüm Y, Korkmaz V. Predictive utility of Systemic Immune Inflammation Index (SII) in identifying endometrial carcinoma in premalignant endometrial lesions. Van Med J 2023;30:418–25.
4. Wang H, Yan F, Cui Y, Chen F, Wang G, Cui W. Association between triglyceride glucose index and risk of cancer: A meta-analysis. Front Endocrinol (Lausanne) 2023;13:1098492.
5. Roberts CK, Hevener AL, Barnard RJ. Metabolic syndrome and insulin resistance: Underlying causes and modification by exercise training. Compr Physiol 2013;3:1–58.
6. Fürstenberger G, Senn HJ. Insulin-like growth factors and cancer. Lancet Oncol 2002;3:298–302.
7. Li J, Yang H, Zhang L, Zhang S, Dai Y. Metabolic reprogramming and interventions in endometrial carcinoma. Biomed Pharmacother 2023;161:114526.
8. Cheung M, O'Brien O, Byrne D, Geoghegan T, LeRoux C, Brennan D. 262 Obesity-related neutrophilia in endometrial cancer. Int J Gynecol Cancer 2019;29:A1–197.
9. Tzenios N, Chahine M, Tazanios M. Obesity and endometrial cancer: the role insulin resistance and adipokines. Spec J Med Acad 2023;1.
10. Meireles CG, Pereira SA, Valadares LP, Rêgo DF, Simeoni LA, Guerra ENS, et al. Effects of metformin on endometrial cancer: Sys-

tematic review and meta-analysis. Gynecol Oncol 2017;147:167–80.
11. Kose C, Korpe B, Korkmaz V, Engin-Ustun Y. Is hemoglobin A1c valuable for predicting concurrent endometrial cancer in diabetic women with endometrial intraepithelial neoplasia? Gynecol Endocrinol 2022;38:1003–7.
12. Çakır AT, Sucu S. Evaluation of the relationship between obesity and obesity type and endometrial thickness-endometrial pathologies. Turk J Diabetes Obes [Article in Turkish] 2020;4:253–9.
13. Son DH, Lee HS, Lee YJ, Lee JH, Han JH. Comparison of triglyceride-glucose index and HOMA-IR for predicting prevalence and incidence of metabolic syndrome. Nutr Metab Cardiovasc Dis 2022;32:596–604.
14. Duan S, Zhou M, Lu F, Chen C, Chen S, Geng L, et al. Triglyceride-glucose index is associated with the risk of chronic kidney disease progression in type 2 diabetes. Endocrine 2023;81:77–89.
15. Ramdas Nayak VK, Satheesh P, Shenoy MT, Kalra S. Triglyceride Glucose (TyG) Index: A surrogate biomarker of insulin resistance. J Pak Med Assoc 2022;72:986–8.
16. Krakauer NY, Krakauer JC. A new body shape index predicts mortality hazard independently of body mass index. PLoS One 2012;7:e39504.
17. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of ıncidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–49.
18. O'Neill S, O'Driscoll L. Metabolic syndrome: A closer look at the growing epidemic and its associated pathologies. Obes Rev 2015;16:1–12.
19. World Cancer Research Fund, & American Institute for Cancer Research. Diet, nutrition, physical activity, and the prevention of cancer: A global perspective. Available at: https://www.wcrf.org/wp-content/uploads/2021/02/Summary-of-Third-Expert-Report-2018.pdf. Accessed Aug 28, 2024.
20. Alsannan B, Upadhyay A, Raman VV, Singh JB, Raj A, Haridas K. Obesity and its associated cancer-related risk with gynaecology. J Coast Life Med 2023;11:689–95.
21. Nicholson K, Macharia A, Furuya R, Manning C, Hacker MR, Harris DA, et al. Association of body mass index with early age at diagnosis of endometrial intraepithelial neoplasia. Gynecol Oncol 2023;175:15–9.
22. Laskov I, Zilberman A, Maltz-Yacobi L, Peleg Hasson S, Cohen A, Safra T, et al. Effect of BMI change on recurrence risk in patients with endometrial cancer. Int J Gynecol Cancer 2023;33:713–8.
23. Ji M, Zhang S, An R. Effectiveness of A Body Shape Index (ABSI) in predicting chronic diseases and mortality: A systematic review and meta-analysis. Obes Rev 2018;19:737–59.
24. Rico-Martín S, Calderón-García JF, Sánchez-Rey P, Franco-Antonio C, Martínez Alvarez M, Sánchez Muñoz-Torrero JF. Effectiveness of body roundness index in predicting metabolic syndrome: A systematic review and meta-analysis. Obes Rev 2020;21:e13023.
25. Dimou N, Omiyale W, Biessy C, Viallon V, Kaaks R, O'Mara TA, et al. cigarette smoking and endometrial cancer risk: Observational and mendelian randomization analyses. Cancer Epidemiol Biomarkers Prev 2022;31:1839–48.
26. Zhang H, Kong W, Han C, Liu T, Li J, Song D. Correlation of metabolic factors with endometrial atypical hyperplasia and endometrial cancer: Development and assessment of a new predictive nomogram. Cancer Manag Res 2021;13:7937–49.
27. Seth D, Garmo H, Wigertz A, Holmberg L, Hammar N, Jungner I, et al. Lipid profiles and the risk of endometrial cancer in the Swedish AMORIS study. Int J Mol Epidemiol Genet 2012;3:122–33.
28. Madak-Erdogan Z, Band S, Zhao YC, Smith BP, Kulkoyluoglu-Cotul E, Zuo Q, et al. Free fatty acids rewire cancer metabolism in obesity-associated breast cancer via estrogen receptor and mTOR signaling. Cancer Res 2019;79:2494–510.
29. Shi H, Guo F, Zheng K, Li R, Zhou H. Triglyceride-glucose index (TyG index) and endometrial carcinoma risk: A retrospective cohort study. Int J Gynaecol Obstet 2024;164:298–304.

Endometriyal Patolojiler ile Trigliserit Glikoz İndeksi ve Vücut Şekli İndeksi Arasındaki İlişki: Retrospektif Kohort Çalışması

Amaç: Bu çalışmada, premalign-malign endometrial patolojileri öngörmede trigliserid glukoz indeksi ve vücut şekil indeksi arasındaki ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntem: Hastanemiz Kadın Hastalıkları ve Doğum Kliniğine anormal uterin kanama nedeniyle başvuran ve endometrial biyopsi yapılan hastaların sonuçları tarandı. Benign patolojiler ve premalign-malign patolojiler olmak üzere iki grup oluşturuldu. Trigliserid glukoz indeksi, vücut şekil indeksi ve premalign-malign endometriyal patoloji arasındaki ilişkiyi değerlendirmek için çoklu lojistik regresyon analizi yapıldı. Çalışma retrospektif bir kohort çalışmasıdır.

Bulgular: Endometriyal biyopsi öncesinde açlık kan şekeri ve açlık trigliseritleri ölçülen 579 hasta vardı. Dışlama kriterleri uygulandıktan sonra 330 hasta (yaş: 43-56) çalışmaya dahil edildi. Gruplar arasında yaş, kilo, bel çevresi, VKİ ve vücut şekil indeksi Z skorları açısından anlamlı farklılıklar gözlendi ($p<0.05$). Trigliserid glukoz indeksi, antropometrik ölçümler ve bel çevresi en yüksek AUC'ye sahipti. Regresyon analizi, trigliserit glukoz indeksi değerindeki bir birimlik artışın hastanın premalign-malign patolojiye sahip olma olasılığını 164 kat artırdığını göstermiştir.

Sonuç: Obezite endometriyal patoloji olasılığını artırmaktadır. Bu nedenle, anormal uterin kanaması olan hastalarda trigliserit glukoz indeksi ile vücut şekil indeksi Z skorları arasındaki ilişkiye bakılması önerilmektedir. Bu yöntemlerin her ikisinin de hesaplanması basit ve uygun maliyetlidir. Hastaları bu hesaplamalarda belirlenen riskler hakkında bilgilendirmek ve önleyici tavsiyelerde bulunmak önemlidir.

Anahtar Sözcükler: Endometrioid; insülin direnci; karsinom; obezite.

SCIE DOI: 10.14744/scie.2024.04764
South. Clin. Ist. Euras. 2024;35(3):276-280

Original Article

Iron Levels and Dysfunctional Adipose Index in Women

Osman Erinç,[1] Almila Şenat,[2] Türker Demirtakan,[3] Soner Yeşilyurt[1]

[1]Department of Internal Medicine, Taksim Education and Research Hospital, Istanbul, Türkiye
[2]Department of Biochemistry, Taksim Education and Research Hospital, Istanbul, Türkiye
[3]Department of Emergency, Taksim Education and Research Hospital, Istanbul, Türkiye

Submitted: 17.07.2024
Revised: 28.07.2024
Accepted: 30.07.2024

Correspondence: Osman Erinç, Deparment of Internal Medicine, Taksim Education and Research Hospital, Istanbul, Türkiye
E-mail: doctorerinc@gmail.com

Keywords: Anemia; Dysfunctional Adipose Index; ferritin iron; iron deficiency; waist circumference.

ABSTRACT

Objective: The intricate connection between serum iron levels, adipose tissue, and metabolic parameters has been the subject of many clinical studies. In this direction, the aim of this study was to evaluate the relationship between the Dysfunctional Adiposity Index (DAI) and serum iron status.

Methods: This single-center retrospective study included 32 women with iron deficiency (ID) as a patient group and 45 women without ID as a control group. The individuals' demographic data, laboratory tests, height, weight, and waist circumference (WC) measurements were obtained from our hospital's records. DAI was calculated by the following formula: [WC/[24.02 + [2.37 * Body Mass Index (BMI)]] * [triglyceride (mmol/L) / 1.32] * [1.43 / high-density lipoprotein (mmol/L)]].

Results: We found statistically significant differences between the two groups in terms of hemoglobin values and iron parameters, such as ferritin, total iron-binding capacity, and transferrin saturation ($p<0.001$). While there was a statistically significant difference in waist circumference between the groups ($p<0.001$), the other DAI components did not differ. We also detected a negative correlation among DAI and serum iron, ferritin levels, and transferrin saturation ($r=-0.321$, $p=0.004$; $r=-0.416$, $p<0.001$; $r=0.359$, $p=0.001$, respectively).

Conclusion: This study tries to add information to the current literature on the interaction between serum iron parameters and DAI as a metabolic risk marker. The results of our study emphasize the close relationship between iron deficiency and increased waist circumference, which are very common and constitute global health problems, and underline the importance of the interaction of these two entities in clinical evaluation. However, the contradictory results of the existing literature highlight the complexity of this relationship, pointing to the need for larger, well-designed prospective studies to provide a more detailed understanding of the role of serum iron parameters, especially among individuals with high waist circumference and DAI levels.

INTRODUCTION

According to the World Health Organization report[1] published in 2024, 16% of the adult population is obese (over 890 million), while those with overweight increased up to 43% (2.5 billion). The most often used tool for determining excess body weight is the body mass index (BMI). Nonetheless, a number of researchers have cast doubt on the reliability of BMI and suggested that assessing the morpho-functional features of adipose tissue (AT) may be a more effective way to determine the risk of developing metabolic disorders.[2-4] Given that metabolic abnormalities are detected in one-fifth of individuals with normal body weight and approximately one-fourth of overweight or obese subjects are metabolically healthy, several clinical markers, such as the visceral adiposity index and the body adiposity index, have been proposed to identify metabolic abnormalities that may reflect AT functionality.[5-7]

The process of adipose tissue dysfunction involves several steps. Initially, hypertrophic adipocytes are produced when subcutaneous AT is unable to preserve energy appropriately. This leads to inflammation and visceral AT fat deposition. Subcutaneous and visceral AT dysfunction eventually results in impaired systemic metabolism.[8,9]

Iron deficiency (ID) and iron deficiency anemia (IDA) are global health problems. IDA accounts for 66.2% of all anemias and affects approximately 825 million women. It is approximately twice as common in the female sex as in men. In developing societies, the most common cause is inadequate intake, whereas in developed societies, there are different causes depending on age, gender, and region.[10]

Iron plays a crucial role in many biological processes in the body and is also essential for maintaining the homeostasis

of adipose tissue. For adipocyte differentiation, especially brown fat tissue production, endocrine function, energy supply, and other physiological processes, iron is vital.[11] On the other hand, fat tissue accumulation and obesity also affect many steps of iron metabolism.[12] Numerous chronic metabolic diseases, including obesity, type 2 diabetes mellitus, and non-alcoholic fatty liver disease, are influenced by iron homeostasis. ID is linked to obesity in adipose tissue, primarily as a result of systemic inflammation.[13-15]

This intricate connection between iron and fat tissue is the subject of many clinical studies. In the present study, we aimed to evaluate the association between ID and the dysfunctional adiposity index (DAI), which is a clinical measurement linked to the morpho-functional traits of AT (leptin, adiponectin, and adipocyte area) and is simply measured by using BMI, waist circumference, triglycerides, and high-density lipoprotein cholesterol.

MATERIALS AND METHODS

Study Design and Measurements

This retrospective study included 32 women with ID and 45 women as a control group who were applied to the internal medicine outpatient clinic of our hospital. This study excluded those who were pregnant and had autoimmune, oncological, or chronic diseases. The determination of all participants was summarized in Figure 1 as a flow chart.

Participants' demographic data, height, weight, and waist circumference (WC) measurements, and laboratory test results were obtained from our hospital's electronic records. The following formula was used to calculate the DAI: [WC / [24.02 + [2.37 * Body mass index (BMI)]] * [triglyceride (mmol/L) / 1.32] * [1.43 / high-density lipoprotein (mmol/L)]].[9] WC was measured via non-extensible tape at the midpoint between the upper iliac crest and the inferior costal edge. The subjects were measured when they were standing with their feet together, their arms swinging loosely at their sides, and breathing regularly. BMI is derived from height and weight measurements as kg/m².

Statistical Analysis

Due to the retrospective nature of the study, a formal power analysis could not be performed at the study design phase. The statistical software SPSS 26.0 was used for all of the analyses (Chicago, IL, IBM Corp.). The Kolmogorov-

Table 1. Demografic and clinical features and laboratory findings of groups

	Group 1 n=32	Group 2 n=45	p
Age, years	33 (23-41)	40 (29-45)	0.06
Body weight, kg	66.8 (55.2-68.2)	65 (54-75)	0.681
Blood pressure, mmHg			
-Systolic	112 (110-120)	110 (106-124)	0.247
-Diastolic	75 (70-80)	70 (68-82)	0.473
Smoking status, %			
-No-smoker/current	71.9/28.1	84.4/15.6	0.231
Iron, mg/dL	20 (9.5-29.7)	102 (70-108)	<0.001
Ferritin, ug/L	7 (5.2-9.1)	36 (24-61)	<0.001
TIBC, mg/dL	377 (333-427)	310 (297-349)	<0.001
Transferrin saturation, %	5.25 (2.82-7.32)	30 (20.4-39.1)	<0.001
Hemoglobin, g/dL	10.9 (9.9-11.3)	12.8 (12.25-13.4)	<0.001
Leukocyte, 10^3/uL	6.86 (5.84-7.8)	6.71 (5.7-7.48)	0.266
Platelet, 10^3/uL	273 (240-299)	258 (233-286)	0.153
CRP, mg/L	0.86 (0.6-1.86)	1.54 (0.6-2.62)	0.129
Blood glucose, mg/dL	90 (88-94)	89 (86-97)	0.567
Creatinine, mg/dL	0.65 (0.57-0.7)	0.64 (0.61-0.7)	0.727
eGFR, ml/min/1.73m^2	120 (109-125)	111 (103-119)	0.012
ALT, U/L	13 (9-17)	11 (9-21)	0.379
LDL, mg/dL	101 (83-120)	106 (85-123)	0.322
Uric acid, mg/dL	3.6 (3.1-4.1)	3.9 (3.4-4.6)	0.184
Vitamin B12, µg/L	315 (275-438)	289 (247-394)	0.434
Folic acid, µg/L	7.63 (6.47-9.95)	7.2 (6.06- 8.88)	0.632
TSH, mIU/L	1.62 (1.2-2.19)	1.7 (1.15-2.35)	0.868

TIBC: total iron binding capacity, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, ALT: alanin aminotransferase, LDL: low density lipoprotein, TSH: thyroid stimulating hormone.

Table 2. Demografic and clinical features and laboratory findings of groups

	Group 1 n=32	Group 2 n=45	p
Waist circumference (cm)	81 (75-91)	75 (69-81)	0.001
Body mass index (kg/m²)	24.4 (20.3-27.8)	25.9 (20.1-30. 1)	0.795
HDL (mg/dL)	64 (54-72)	67 (54-74)	0.445
Tryglyceride (mg/dL)	85 (95-104)	72 (52-90)	0.068
DAI	1.4 (1.19-1.8)	1.01 (0.74- 1.53)	0.07

BMI: body mass index; HDL: high density lipoprotein; DAI: dysfunctional adipose index.

Smirnov test determined the distributions of variables. The variables that were not normally distributed were expressed as the median. Categorical parameters were indicated as percentages. The Kruskal-Wallis test was used to assess significance among study groups. Additionally, the correlations between serum iron, ferritin, and hemoglobin levels and DAI were determined with the Spearman correlation test. The statistical significance cut-off value was deemed to be $p<0.05$.

RESULTS

As shown in Table 1, no differences were observed between the groups in terms of demographic data and clinical features. There were statistically significant differences between the values of hemoglobin, ferritin, total iron-binding capacity, and serum iron in the biochemical data.

Table 2 unveils statistical disparities in DAI and its components across the delineated groups. The difference between the groups in terms of waist circumference reached the $p<0.001$ significance level. Other DAI components, including BMI, HDL, and triglycerides, showed no differences.

Concurrently, correlation analysis, as outlined in Table 3, unearthed a robust negative correlation between serum ferritin levels, transferrin saturation, and DAI ($r=-0.416$, $p<0.001$; $r=0.359$, $p=0.001$, respectively). There was also a significant negative correlation between serum iron level and DAI ($r=-0.321$, $p=0.004$).

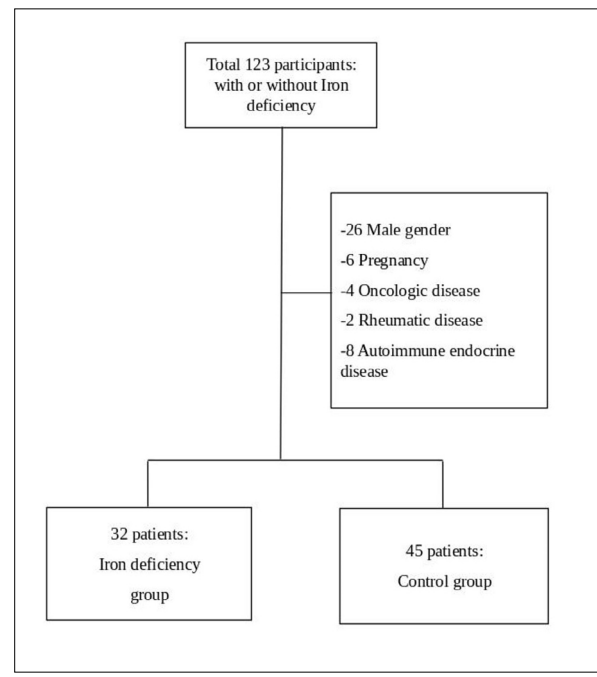

Figure 1. The determination of all participants.

DISCUSSION

In the present retrospective study, we assessed the relationships between serum iron parameters and DAI. We found statistically significant differences between the values of hemoglobin and iron parameters such as ferritin and TIBC. While there was a statistically significant difference in waist circumference between the groups, the other DAI components did not differ. We also detected negative correlations among serum iron, ferritin, transferrin saturation levels, and DAI.

Several studies have shown close relationships between

Table 3. Correlation analysis between DAI and anemia parameters.

	Serum iron	Serum ferritin	TS	Hb
DAI				
r	-0.321	-0.416	-0.359	-0.197
p	0.004	<0.001	0.001	0.86

DAI: Dysfunctional adipose index; TS: Transferrin saturation; Hb: Hemoglobin.

iron status, body weight status, and adipose tissue. Chambers et al.[16] found a negative correlation between serum iron and BMI, WC, and fat mass. In another study conducted by Laudisio et al.,[17] a significant but weak inverse correlation was found between serum iron levels and BMI and WC. Our study revealed that while there was no significant difference in BMI between the groups with and without ID, similar to the mentioned studies, WC and DAI were found to be significantly higher in the ID group. Considering the critical role iron ion plays in adipose tissue homeostasis, these results may also indicate that the use of BMI alone is not sufficient to evaluate the morpho-functional properties of adipose tissue and thus the risk of metabolic diseases.

In the present study, as indicated in the studies by Stoffel et al.[18] and Olefsky et al.,[19] transferrin saturation, ferritin, and serum iron levels were found to be lower in women with increased waist circumference. In the mentioned studies, it was stated that one of the possible pathways of this effect may be systemic low-level inflammation caused by central obesity.

It is known that the iron ion plays a role in many metabolic biological processes and is in a complex interaction with lipid, glucose metabolism, insulin resistance, and obesity.[14] In the present study, no difference was observed between the two groups in terms of lipid parameters, including HDL, LDL, and triglyceride levels, as in a study conducted by Wolide et al.[20] Nonetheless, HDL levels in the ID group were considerably higher than those in the normal group in the research published by Sawada et al.[21] and Ellidag et al.[22] Ferritin levels were positively correlated with TG and LDL levels, according to Ellidag et al.[22] study.

Due to its retrospective design, the inability to evaluate HOMA-IR-like insulin resistance parameters, body composition by bioimpedance analysis, and the relatively small number of patients can be considered among the limitations of the study.

Conclusion

We think that this study contributes valuable information to the current understanding of the interaction between serum iron parameters and DAI, a metabolic risk marker. The results of our study emphasize the close relationship between iron deficiency and increased waist circumference, which are very common and constitute global health problems, and underline the importance of the interaction of these two entities in clinical evaluation. However, the contradictory nature of the literature highlights the complexity of this relationship, highlighting the need for larger, well-designed prospective studies to provide a more detailed understanding of the role of serum iron parameters, especially among individuals with high waist circumference and DAI.

Ethical Approval

This study was conducted in accordance with the ethical principles outlined in Declaration of Helsinki and approved by Gaziosmanpaşa Education and Research Hospital Ethics Committee with the date 25.10.2023 and number 100.

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: O.E:, A.S., S.Y.; Design: O.E:, A.S..; Supervision: OE; Fundings: O.E.; Materials: O.E.; Data: O.E., S.Y., A.S.; Analysis: O.E., S.Y.; Literature search: O.E., S.Y., A.S.; Writing: O.E.; Critical revision: O.E., A.S.

Conflict of Interest

None declared.

REFERENCES

1. World Health Organization. Obesity and overweight. Available at: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed Aug 23, 2024.
2. Banack HR, Wactawski-Wende J, Hovey KM, Stokes A. Is BMI a valid measure of obesity in postmenopausal women? Menopause 2018;25:307–13.
3. Donini LM, Pinto A, Giusti AM, Lenzi A, Poggiogalle E. Obesity or BMI paradox? Beneath the tip of the iceberg. Front Nutr 2020;7:53.
4. Caputo T, Tran VDT, Bararpour N, Winkler C, Aguileta G, Trang KB, et al. Anti-adipogenic signals at the onset of obesity-related inflammation in white adipose tissue. Cell Mol Life Sci 2021;78:227–47.
5. Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). Arch Intern Med 2008;168:1617–24.
6. Amato MC, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, et al; AlkaMeSy Study Group. Visceral adiposity index: A reliable indicator of visceral fat function associated with cardiometabolic risk. Diabetes Care 2010;33:920–2.
7. Reyes-Barrera J, Antonio-Villa NE, Posadas-Sánchez R, Vargas-Alarcón G, Medina-Urrutia AX. The dysfunctional adiposity index is a clinical surrogate of pericardial fat in adults without premature CVD: A sub-analysis of the GEA Mexican study control group. Nutr Metab Cardiovasc Dis 2024;34:2002–11.
8. Goossens GH. The metabolic phenotype in obesity: Fat mass, body fat distribution, and adipose tissue function. Obes Facts 2017;10:207–15.
9. Reyes-Barrera J, Sainz-Escárrega VH, Medina-Urritia AX, Jorge-Galarza E, Osorio-Alonso H, Torres-Tamayo M, et al. Dysfunctional adiposity index as a marker of adipose tissue morpho-functional abnormalities and metabolic disorders in apparently healthy subjects. Adipocyte 2021;10:142–52.
10. GBD 2021 Anaemia Collaborators. Prevalence, years lived with disability, and trends in anaemia burden by severity and cause, 1990-2021: Findings from the Global Burden of Disease Study 2021. Lancet Haematol 2023;10:e713–34.
11. Moreno-Navarrete JM, Fernández-Real JM. Iron: The silent culprit in your adipose tissue. Obes Rev 2024;25:e13647.
12. González-Domínguez Á, Visiedo-García FM, Domínguez-Riscart J, González-Domínguez R, Mateos RM, Lechuga-Sancho AM. Iron metabolism in obesity and metabolic syndrome. Int J Mol Sci

2020;21:5529.
13. Ma W , Jia L , Xiong Q , Feng Y , Du H . The role of iron homeostasis in adipocyte metabolism. Food Funct 2021;12:4246–53.
14. Hilton C, Sabaratnam R, Drakesmith H, Karpe F. Iron, glucose and fat metabolism and obesity: An intertwined relationship. Int J Obes (Lond) 2023;47:554–63.
15. Qiu F, Wu L, Yang G, Zhang C, Liu X, Sun X, et al. The role of iron metabolism in chronic diseases related to obesity. Mol Med 2022;28:130.
16. Chambers EC, Heshka S, Gallagher D, Wang J, Pi-Sunyer FX, Pierson RN Jr. Serum iron and body fat distribution in a multiethnic cohort of adults living in New York City. J Am Diet Assoc 2006;106:680–4.
17. Laudisio D, de Alteriis G, Vetrani C, Aprano S, Pugliese G, Zumbolo F, et al. Iron levels and markers of inflammation in a population of adults with severe obesity, a cross-sectional study. Nutrients 2023;15:4702.
18. Stoffel NU, El-Mallah C, Herter-Aeberli I, Bissani N, Wehbe N, Obeid O, et al. The effect of central obesity on inflammation, hepcidin, and iron metabolism in young women. Int J Obes (Lond) 2020;44:1291–300.
19. Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. Annu Rev Physiol 2010;72:219–46.
20. Wolide AD, Zawdie B, Alemayehu T, Tadesse S. Association of trace metal elements with lipid profiles in type 2 diabetes mellitus patients: A cross sectional study. BMC Endocr Disord 2017;17:64.
21. Sawada T, Konomi A, Yokoi K. Serum lipid profiles of young Japanese women with iron deficiency without anemia. J Trace Elem Med Biol 2020;57:126408.
22. Ellidag HY, Eren E, Akdag M, Giray O, Kiraz K, Yilmaz N. The relationship between serum ferritin levels and serum lipids and HDL function with respect to age and gender. Ukr Biochem J 2016;88:76–86.

Kadınlarda Demir Düzeyi ile Disfonksiyonel Adipoz İndeks Arasındaki İlişki

Amaç: Serum demir düzeyleri ile yağ dokusu ve metabolik parametreler arasındaki karmaşık bağlantı birçok klinik çalışmanın konusudur. Bu doğrultuda çalışmamızda serum demir durumu ile disfonksiyonel adipoz indeks (DAİ) arasındaki ilişkiyi değerlendirmeyi amaçladık.

Gereç ve Yöntem: Tek merkezli retrospektif çalışmamıza hasta grubu olarak demir eksikliği olan 32 kadın, kontrol grubu olarak ise demir eksikliği olmayan 45 kadın dahil edildi. Bireylerin demografik verileri, laboratuvar testleri, boy, kilo ve bel çevresi (BÇ) ölçümleri hastanemiz kayıtlarından elde edildi. DAİ şu formülle hesaplandı: [BÇ/[24.02+[2.37* vücut kitle indeksi]]*[trigliserid (mmol/L)/1,32]*[1.43/yüksek yoğunluklu lipoprotein (mmol/L)].

Bulgular: Hemoglobin değerleri ve ferritin, total demir bağlama kapasitesi, transferrin satürasyonu gibi demir parametreleri açısından iki grup arasında istatistiksel olarak anlamlı fark bulduk ($p<0.001$). Gruplar arasında bel çevresi açısından istatistiksel olarak anlamlı fark bulunurken ($p<0.001$), diğer DAİ bileşenleri açısından farklılık yoktu. Ayrıca DAİ ile serum demiri, ferritin düzeyleri ve transferrin satürasyonu arasında da güçlü bir negatif korelasyon tespit ettik (sırasıyla, $r=-0.321$, $p=0.004$; $r=-0.416$, $p<0.001$; $r=0.359$, $p=0.001$).

Sonuç: Bu çalışma, serum demir parametreleri ile bir metabolik risk belirteci olarak DAI arasındaki etkileşime ilişkin mevcut literatüre katkı sağlamayı amaçlamaktadır. Çalışmamızın sonuçları, toplumda yaygın olarak görülen ve küresel sağlık sorunu oluşturan demir eksikliği ile özellikle bel çevresi artışı arasındaki yakın ilişkiye dikkati çekip klinik değerlendirmede bu iki antitenin etkileşimlerinin önemini vurgulamaktadır. Bununla birlikte, mevcut literatürün çelişkili sonuçları bu ilişkinin karmaşıklığını vurgulamakta ve özellikle yüksek bel çevresi ve DAI seviyelerine sahip bireyler arasında serum demir parametrelerinin rolünün daha ayrıntılı bir şekilde anlaşılmasını sağlamak için daha büyük, iyi tasarlanmış prospektif çalışmalara ihtiyaç duyulduğuna işaret etmektedir.

Anahtar Sözcükler: Anemi; bel çevresi; demir; demir eksikliği; disfonksiyonel adipoz indeks; ferritin.

SCIE DOI: 10.14744/scie.2024.26234
South. Clin. Ist. Euras. 2024;35(3):281-287

Original Article

Comparison of Fully Threaded Cannulated Screw, Half Threaded Cannulated Screw, and Tension-Band Wiring in the Fixation of Herscovici Type C Medial Malleolus Fractures: A Retrospective Clinical Study

Suat Batar,[1] Muhammed Enes Karataş,[3] Furkan Başak,[2] Mehmet Mete Oruç,[4] Bahattin Kemah,[2] Serdar Kamil Çepni[2]

[1]Department of Orthopaedics and Traumatology, Nev Anadolu Hospital, Bursa, Türkiye
[2]Department of Orthopaedics and Traumatology, Umraniye Training and Research Hospital, Istanbul, Türkiye
[3]Department of Orthopaedics and Traumatology, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye
[4]Department of Orthopaedics and Traumatology, Şırnak İdil State Hospital, Şırnak, Türkiye

Submitted: 08.06.2024
Revised: 25.06.2024
Accepted: 20.07.2024

Correspondence: Muhammed Enes Karataş,
Department of Orthopaedics and Traumatology, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye

E-mail: menskrts@hotmail.com

Keywords: Cannulated screw fixation; medial malleolus fracture; tension-band wiring method.

ABSTRACT

Objective: Surgical treatment is often preferred for medial malleolus fractures to achieve anatomic reduction and enable early mobilization. This study aims to evaluate the clinical and radiological outcomes of fixing Herscovici Type C medial malleolus fractures using tension-band wiring (TBW) and half and fully threaded cannulated screws.

Methods: This retrospective study included patients aged 18 to 65 who underwent surgery for isolated medial malleolus fractures between January 2012 and December 2022. Exclusion criteria were a follow-up period of less than one year, fractures other than Herscovici Type C, open fractures, use of other implants, or loss to follow-up. Radiological evaluations were conducted using preoperative anterior-posterior, lateral, and mortise radiographs, along with computed tomography scans. The talocrural angle, corner angle, and alignment between the talus and tibial plafond were assessed. Clinical outcomes were measured using the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale. Statistical analysis was performed using SPSS software.

Results: A total of 178 patients were included: 55 (30.9%) underwent TBW fixation, 60 (33.7%) had half-threaded cannulated screw fixation, and 63 (35.4%) received fully threaded cannulated screw fixation. The mean follow-up period was 76 months, and the mean age was 32.2 years. The TBW group had a significantly longer follow-up period than the other groups (p=0.000), with no difference between the half and fully threaded screw groups. There were no differences among the groups regarding fracture side, trauma mechanism, or need for implant removal. Postoperative talocrural angles were similar across groups (p=0.530). The postoperative corner angle was significantly lower in the TBW group (mean: 63.4) compared to the half-threaded (mean: 65.8) and fully threaded (mean: 65.2) screw groups (p=0.049). AOFAS scores were significantly higher in the half-threaded screw group (mean: 89.1) compared to the TBW (mean: 84.2) and fully threaded screw groups (mean: 85.9) (p=0.02). No significant difference was found between the half-threaded and fully threaded screw groups regarding the alignment between the superior facet of the talus and the anterior tibial plafond. The TBW group had a significantly higher number of patients with misaligned joints compared to the other groups (p=0.000).

Conclusion: Radiological outcomes were better in the half and fully threaded cannulated screw fixation groups compared to the TBW fixation group. The AOFAS scores were highest in the half-threaded screw fixation group. No significant differences were found among the groups regarding complications. The study concludes that cannulated screw fixation is a safer and more effective method for treating isolated medial malleolus fractures than the TBW fixation method.

INTRODUCTION

Medial malleolus fractures are common among ankle and talocrural region fractures, with an annual isolated medial malleolus fracture incidence of 10-12/100,000. In addition, it is rare among other talocrural region injuries.[1] Clinical and biomechanical studies suggest that the medial malleolus has primary significance in ankle stability.[2] Isolated medial malleolus fractures make up only 10% of all ankle fractures.[3-5] The surgical treatment of these fractures is still controversial. While conservative follow-up is suggested in displaced and non-displaced cases, there are also surgeons in favor of surgical treatment. Surgical treatment stands out when it comes to early mobilization of the patients and essential joint range of motion (ROM).[6] The alignment of the ankle mortise is vital for the functioning of the tibiotalar joint. Even one millimeter of talar displacement can decrease tibiotalar joint contact by 40%, accelerating the development of osteoarthritis (OA), which results in poor functional outcomes. Thus, surgical treatment is preferred in medial malleolus fractures to provide anatomic reduction and early joint ROM.[5-7] The aim of this study is to evaluate the clinical and radiological outcomes of the fixation of Herscovici Type C medial malleolus fractures by using the tension-band wiring (TBW) (Zuggurtung) technique and half and fully threaded cannulated screws.

MATERIALS AND METHODS

The study is approved by Ümraniye Training and Research Hospital Ethics Committee for Clinical Trials (registration no: 240623882). This single-centered retrospective study examined a total of 243 patients between 18-65 years of age who were operated on due to isolated medial malleolus fractures between January 2012 and December 2022. Patients with a follow-up period of less than one year, with fractures other than Herscovici Type C, with open fractures, and patients having another implant, and those lost to follow-up were excluded from the study. After the exclusion of the aforementioned patients, a total of 178 patients who attended their last follow-up visit were included in the study. The patients in Group 1 (55 patients, 30.9%) were treated using the TBW technique with Kirschner wire and transosseous cerclage wire. The fractures of Group 2 (60 patients, 33.7%) and Group 3 (63 patients, 35.4%) were fixated using half-threaded cannulated screws and fully threaded cannulated screws, respectively. The fixation method depended on the preference of the surgeon. The fractures were postoperatively classified according to the fracture classification system described by Herscovici et al.[8] Only the patients with Herscovici Type C were included in the study.

Preoperative views of anterior-posterior, lateral, and mortise radiographs, and computed tomography (CT) scans were considered in the radiological evaluation. The unseen fracture pattern and/or the bone callus tissue that forms the fracture pattern were accepted as a sign of radiological bone union in the radiographs. The alignment of the talocrural angle, corner angle, talus, and tibia plafonds were evaluated from the radiographs taken in the latest follow-up visits. An experienced orthopedic specialist (MD), who did not participate in the surgical process, carried out the radiological measurements and all clinical evaluations. The American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale (AHFS) score was used for the evaluation of the clinical outcomes.[9]

All patients were followed up according to the standard postoperative follow-up protocol of our clinic. Thus, all patients were immobilized with short leg braces in the first four weeks. After the removal of the braces, active and passive ankle joint ROM exercises were started. Weight bearing was allowed only after the patients showed recovery not only in clinical examination results but also in radiological findings. All patients were postoperatively prescribed aspirin 100 mg/day for 4 weeks as standard venous thromboprophylaxis treatment.

Surgical Technique

The patients were positioned in the supine position and received intravenous prophylactic cefazolin. After the placement of the thigh tourniquets, the operations were begun. Through the incisions made over the medial malleolus, the fractures were anatomically reduced and fixated. In the TBW technique, the incisions were slightly extended proximally, and a bone tunnel was made 4-5 cm proximal to the malleolus, and the cerclage wire was passed through this tunnel (Figure 1). Fixations were achieved with two parallel screws in the half and fully threaded cannulated screw fixation methods (Figure 2-3).

Statistical Analysis

The data was analyzed using the Statistical Package for the Social Sciences (SPSS) software (ver. 22.0; IBM Corp., Armonk, NY, USA). The normal distribution of the data was evaluated with the Shapiro-Wilk test and Levene test. Non-parametric variables were analyzed using the Mann-Whitney U test, and parametric variables were analyzed using the Student t-test and ANOVA test. Categorical variables were compared using Pearson's chi-squared test, Monte Carlo simulations, and Fisher's exact test. Quantitative variables were described as mean±standard deviation or interquartile range (IQR), and median. Qualitative variables were described as frequencies or rates. A p-value less than 0.05 was considered statistically significant.

RESULTS

A total of 178 patients were included in the study. Of these patients, 55 (30.9%), 60 (33.7%), and 63 (35.4%) were in Group 1 (TBW fixation group), Group 2 (half-threaded cannulated screw fixation group), and Group 3 (fully threaded cannulated screw fixation group), respectively. The mean follow-up period was 76 (13-127) months, and the mean age was 32.2 (18-65) years. The mean follow-up period was significantly longer in Group 1 compared to the other two groups (p=0.000), but there

Figure 1. Post-union radiograph of the patient fixed with tension band wiring.

Figure 2. Fixation with fully threaded cannulated screw early post operative radiograph.

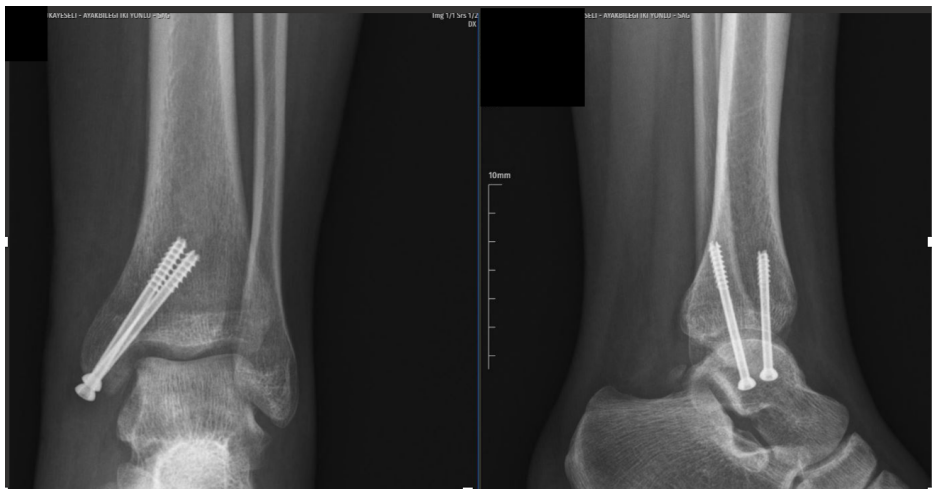

Figure 3. Fixation with half threaded cannulated screw.

was no significant difference between Group 2 and Group 3. There was no difference among the groups regarding age, fracture side, trauma mechanism, and the need for implant removal (p=0.307, p=0.949, p=0.112, p=0.105, respectively) (Table 1). There was no significant difference among the groups in terms of postoperative talocrural angles (p=0.530). Postoperative corner angle was found to be significantly lower (mean:63.4) in Group 1 than in the

Table 1. Demographic characteristics of the patients

	Group 1 (n=55)		Group 2 (n=60)		Group 3 (n=63)		Total	p
Age	**Mean**	**±SD**	**Mean**	**±SD**	**Mean**	**±SD**		
	27.3	12.4	38	15.4	30.5	13.6		0.307
	n	**%**	**n**	**%**	**n**	**%**		
Gender								
Female	16	35.6	20	44.4	9	20	**45 100%**	**0.038**
Male	39	29.3	40	30.1	54	40.6	133 100%	
Fracture Side								
Right	23	31.1	24	32.4	27	36.5	74 100%	
Left	32	30.8	36	34.6	36	34.6	104 100%	0.949
Trauma mechanism								
Distortion	16	43.2	9	24.3	12	32.4	37 100%	
Traffic accident	22	32.4	20	29.4	26	38.2	68 100%	
Falling	14	26.4	19	35.8	20	37.7	53 100%	0.112
Crush injury	3	15	12	60	5	25	20 100%	

Group 1: Tension-band wiring Fixation. Group 2: Half threaded cannulated screw Fixation. Group: Fully threaded cannulated screw Fixation.

Table 2. Comparison of post operative radiologic and clinical values of the patients

Group 1			
Mean	12.2	63.4	84.2
Max	19	75	100
Min	5	53	73
±SD	2.95	5.13	7.15
Group 2			
Mean	12.8	65.8	89.1
Max	18	78	100
Min	7	55	68
±SD	2.76	4.95	7.73
Group 3			
Mean	12.7	65.2	85.9
Max	20	80	100
Min	4	50	75
±SD	3.28	6.09	7.39
p	0.530	0.049	0.02

Group 1: Tension-band wiring Fixation. Group 2: Half threaded cannulated screw Fixation. Group: Fully threaded cannulated screw Fixation AOFAS: American Orthopaedic Foot and Ankle Society.

other two groups, but there was no difference between half- (mean:65.8) and fully (mean:65.2) threaded cannulated screw fixation groups (p=0.049). AOFAS scores obtained at the last follow-up visit were significantly higher in Group 2 (mean: 89.1) compared to the other two groups, but there was no significant difference between Group 1 (mean:84.2) and Group 3 (mean:85.9) (p=0.02). There was no significant difference between Group 2 and Group 3 regarding the alignment of the superior facet of the talus and anterior tibial plafond. The number of patients with misaligned joints was found to be significantly higher in Group 2 than in the other two groups (p=0.000) (Table 2).

DISCUSSION

The surgical treatment of ankle medial malleolus fractures constitutes an anatomical joint surface and ensures early mobilization exercises and early weight-bearing to accelerate patients' return to normal life. Studies suggest that prognosis depends on anatomic reduction and the maintenance of this reduction, which is crucial for the union of ankle fractures.[10] The medial malleolus is also supposed to be aligned in the ankle mortise for normal tibiotalar joint alignment.[9] The medial malleolus and anterior talofibular ligaments prevent the medial translation of the talus.[9] Due to the anatomical importance of medial malleolus fractures, surgical treatment is preferred to minimize joint misalignments, instability, and arthritis formation due to trauma.[11,12]

There are many methods for fracture fixation in the literature. In this study, we compared three of the most com-

mon methods of fixation. Lee YK et al.[13] carried out a study on 12 fresh cadavers and found that after Herscovici Type C fractures, the mean contact area decreased by 9%, and a 2 mm displacement increased mean contact pressure by 8%. After Herscovici Type C fractures, a 2 mm displacement showed significant changes in contact area and contact pressure when compared to a normal tibiotalar joint.[13] Except for the treatment method, the degree of the fracture displacement was also an independent risk factor for a lower functional result.[5]

Many methods have been described in the surgical fixation of the medial malleolus.[7,14-18] The most common ones are the TBW technique that involves Kirschner wire and cerclage wire, and fixation with cancellous lag screws.[7,19-21] There is no clear evidence on which method is superior to the others.[7] Studies indicated that the TBW technique was more effective in medial malleolus avulsion fractures, comminuted fractures, and osteoporotic fractures.[7] TBW converts tensile force on the fracture pattern into compression force. Wire and cerclage tension can be adjusted according to the type of fracture. It can also be used for cracked or rebroken fractures during the fixation process with screws.[22-23] In one study, functional scores were found to be better in fixation with TBW when compared to fixation with screws. TBW fixation was also found to cause less fixation failure and delayed union.[22]

Ebraheim et al.[24] carried out a study evaluating implants according to medial malleolus fracture types and found that fixation with TBW had fewer complications and lower revision rates when compared to screw fixation in Herscovici Type C fractures. However, screw fixation demonstrated better outcomes compared to TBW fixation in Herscovici Type D fractures. TBW was superior in small broken bone pieces, poor bone quality, and transverse fractures, while screws were superior in young patients and oblique fractures. They concluded that when the suitable fixation method was chosen according to the size and type of the fracture and the patient's general condition, excellent clinical and radiological results could be achieved without any complications.[23,24] However, in our study, no functional superiority was observed in patients who underwent the TBW procedure, and the outcomes were similar for both TBW fixation and fully threaded cannulated screw fixation. We also found TBW fixation to have poorer outcomes compared to half-threaded cannulated screw fixation. The TBW fixation group was also observed to have poorer joint alignment and a smaller ankle corner angle. Contrary to the literature, TBW fixation was observed to have poorer clinical and radiological outcomes. We concluded that the poor clinical outcomes of TBW fixation corresponded to the radiological evaluations. Although we found no significant difference among fixation methods regarding complications, TBW was found to have other disadvantages when compared to screw fixation. These disadvantages were the proximal extension of the incision to the fracture pattern and the necessity of a secondary surgery.[22,23] We believe that one of the reasons for the TBW group having the lowest AOFAS score was patient dissatisfaction due to implant irritation.

In a biomechanical and clinical study by Ricci et al.,[25] fully threaded cannulated screws were used in 46 patients, and half-threaded cannulated screws were used in another 46 patients. Fully threaded cannulated screws had better biomechanical, radiographical, and clinical outcomes when compared to half-threaded cannulated screws. Screw loosening was found to be significantly higher (11 times) in fully threaded cannulated screw fixation when compared to half-threaded cannulated screw fixation. In transverse fractures, the strongest fixation was observed in the fully threaded screw fixation group after the tension and compression forces.[19,25] In a study by Yammine et al.,[26] they emphasized less screw loosening and less necessity for implant removal in fully threaded cannulated screw fixation when compared to half-threaded cannulated screw fixation.

They also stated that fixation with screws might not achieve rigid fixation in this region due to the spongiform nature of the distal tibial metaphysis, especially in the presence of osteoporosis. They supported that fully threaded cannulated screws provided better compression in the distal tibial metaphysis region and showed better outcomes by increasing tensile force.[27] When compared with TBW fixation, fully and half-threaded cannulated screw fixations were found to have shorter operation times, less need for implant removal due to less implant irritation, and the incisions could be made smaller during operations.[28] However, in our study, we did not find any significant difference between half-threaded and fully threaded cannulated screw fixation groups, but we obtained better results regarding AOFAS scores in the half-threaded cannulated screw fixation group.

In a biomechanical study by Parker et al.,[29] 4 mm fully threaded cancellous screws were found to apply a significantly higher amount of compression into the fracture region when compared to partially threaded isometric cancellous screws.

Our study had limitations. Headless compression screws were not included in the study as we did not use them due to their high cost. Bone density (DEXA) scans were not carried out to evaluate the bone quality of the patients, and time to union for the fractures was not assessed. We also believe that potential bias might have occurred due to the retrospective design of the study, the relatively low number of patients, the lack of a biomechanical comparison with other fixation methods, and the lack of an independent orthopedist's evaluation. The strength of our study was the assessment of similar isolated medial malleolus fractures.

Conclusion

Our study demonstrated satisfying results in all three fixation methods used for medial malleolus fractures. Moreover, the incidence of pain/sensitivity and palpation of the

medial malleolus associated with implant irritation was lower in the fully threaded cannulated screw group when compared to the other two groups. Radiological measures were found to be better in the TBW group than in the other two groups, and the AOFAS score was found to be higher in the half-threaded cannulated screw group. No significant difference was found among the three groups regarding complications. We concluded that fixation with cannulated screws was a safer and more effective method when compared to the TBW method in the treatment of the medial malleolus. There is a shortage of studies comparing these three methods in the literature. We believe our study will make a valuable contribution to the literature. Prospective, double-blind, randomized controlled studies are needed to reach more accurate results.

Ethics Committee Approval

The study was approved by the Ümraniye Training and Research Hospital Ethics Committee (Date: 28.03.2024, Decision No: 240623882).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: S.B.; Design: M.E.K.; Supervision: S.K.Ç.; Fundings: B.K.; Materials: M.M.O.; Data: F.B.; Analysis: M.E.K.; Literature search: S.B.; Writing: S.B.; Critical revision: M.E.K.

Conflict of Interest

None declared.

REFERENCES

1. Court-Brown CM, Caesar B. Epidemiology of adult fractures: A review. Injury 2006;37:691–7.
2. Yablon IG, Heller FG, Shouse L. The key role of the lateral malleolus in displaced fractures of the ankle. J Bone Joint Surg Am 1977;59:169–73.
3. Earll M, Wayne J, Brodrick C, Vokshoor A, Adelaar R. Contribution of the deltoid ligament to ankle joint contact characteristics: A cadaver study. Foot Ankle Int 1996;17:317–24.
4. Pakarinen HJ, Flinkkil TE, Ohtonen PP, Ristiniemi JY. Stability criteria for nonoperative ankle fracture management. Foot Ankle Int 2011;32:141–7.
5. Hanhisuanto S, Kortekangas T, Pakarinen H, Flinkkilä T, Leskelä HV. The functional outcome and quality of life after treatment of isolated medial malleolar fractures. Foot Ankle Surg 2017;23:225–9.
6. Jaffe D, Christian MW, Weber A, Henn RF 3rd. Incarceration of the posterior tibial tendon in an isolated comminuted medial malleolus fracture. J Foot Ankle Surg 2017;56:1312–5.
7. Bulut T, Gursoy M. Isolated medial malleolus fractures: conventional techniques versus headless compression screw fixation. J Foot Ankle Surg 2018;57:552–6.
8. Herscovici D Jr, Scaduto JM, Infante A. Conservative treatment of isolated fractures of the medial malleolus. J Bone Joint Surg Br 2007;89:89–93.
9. Lareau CR, Bariteau JT, Paller DJ, Koruprolu SC, DiGiovanni CW. Contribution of the medial malleolus to tibiotalar joint contact characteristics. Foot Ankle Spec 2015;8:23–8.
10. Burwell HN, Charnley AD. The treatment of displaced fractures at the ankle by rigid internal fixation and early joint movement. J Bone Joint Surg Br 1965;47:634–60.
11. Barnes H, Cannada LK, Watson JT. A clinical evaluation of alternative fixation techniques for medial malleolus fractures. Injury 2014;45:1365–7.
12. Maniar H, Kempegowda H, Tawari AA, Rutter MR, Borade A, Cush G, et al. Medial malleoli fractures: Clinical comparison between newly designed sled device and conventional screws. Foot Ankle Spec 2017;10:296–301.
13. Lee YK, Oh YS, Lee DK, Lee MJ, Song YN, Lee HS, et al. Evaluation of contact area and pressure after malreduction in ısolated medial malleolar fractures with 2 mm of displacement: A cadaveric study. J Foot Ankle Surg 2023;62:774–8.
14. Rovinsky D, Haskell A, Liu Q, Paiement GD, Robinovitch S. Evaluation of a new method of small fragment fixation in a medial malleolus fracture model. J Orthop Trauma 2000;14:420–5.
15. Pollard JD, Deyhim A, Rigby RB, Dau N, King C, Fallat LM, et al. Comparison of pullout strength between 3.5-mm fully threaded, bicortical screws and 4.0-mm partially threaded, cancellous screws in the fixation of medial malleolar fractures. J Foot Ankle Surg 2010;49:248–52.
16. Jennings MM, Schuberth JM. Fixation of the medial malleolar fracture: A simplified technique. J Foot Ankle Surg 2008;47:368–71.
17. Koslowsky TC, Mader K, Kirchner S, Gausepohl T, Pennig D. Treatment of medial malleolar fractures using fine-threaded K-wires: A new operative technique. J Trauma 2007;62:258–61.
18. Kupcha P, Pappas S. Medial malleolar fixation with a bicortical screw: technique tip. Foot Ankle Int 2008;29:1151–3.
19. Fowler TT, Pugh KJ, Litsky AS, Taylor BC, French BG. Medial malleolar fractures: A biomechanical study of fixation techniques. Orthopedics 2011;34:e349–55.
20. Wegner AM, Wolinsky PR, Robbins MA, Garcia TC, Maitra S, Amanatullah DF. Antiglide plating of vertical medial malleolus fractures provides stiffer initial fixation than bicortical or unicortical screw fixation. Clin Biomech (Bristol, Avon) 2016;31:29–32.
21. Wegner AM, Wolinsky PR, Cheng RZ, Robbins MA, Garcia TC, Amanatullah DF. Sled fixation for horizontal medial malleolus fractures. Clin Biomech (Bristol, Avon) 2017;42:92–6.
22. Kim CH, Ma DS, Yoon YC. Tension band wiring versus screw fixation for the treatment of medial malleolar fractures: A systematic review and meta-analysis. Orthop Traumatol Surg Res 2023;109:103447.
23. Johnson BA, Fallat LM. Comparison of tension band wire and cancellous bone screw fixation for medial malleolar fractures. J Foot Ankle Surg 1997;36:284–9.
24. Ebraheim NA, Ludwig T, Weston JT, Carroll T, Liu J. Comparison of surgical techniques of 111 medial malleolar fractures classified by fracture geometry. Foot Ankle Int 2014;35:471–7.
25. Ricci WM, Tornetta P, Borrelli J Jr. Lag screw fixation of medial malleolar fractures: A biomechanical, radiographic, and clinical comparison of unicortical partially threaded lag screws and bicortical fully threaded lag screws. J Orthop Trauma 2012;26:602–6.
26. Yammine K, Karam K, Assi C. Cortical versus cancellous screws in treating medial malleolar fractures: A systematic review of comparative clinical and biomechanical studies. Foot (Edinb) 2019;40:81–6.
27. Sayyed-Hosseinian SH, Bagheri F, Ebrahimzadeh MH, Moradi A, Golshan S. Comparison of partially threaded and fully threaded 4mm cancellous screws in fixation of medial malleolar fractures. Arch Bone Jt Surg 2020;8:710–5.
28. Park YH, Cho HW, Choi JW, Kim HJ. Comparison between head-

less compression screws and tension band wires for the fixation of medial malleolar fractures: A prospective randomized trial. Arch Orthop Trauma Surg 2022;142:2627–33.

29. Parker L, Garlick N, McCarthy I, Grechenig S, Grechenig W, Smitham P. Screw fixation of medial malleolar fractures: a cadaveric biomechanical study challenging the current AO philosophy. Bone Joint J 2013;95-B:1662–6.

Herscovici Tip C Medial Malleol Kırıklarında Tam Yivli Kanüle Vida, Yarım Yivli Kanüle Vida ve Gergi Bandı ile Tespitin Karşılaştırılması: Retrospektif Bir Klinik Çalışma

Amaç: Medial malleol kırıklarında anatomik redüksiyon sağlamak ve erken mobilizasyonu mümkün kılmak için genellikle cerrahi tedavi tercih edilir. Bu çalışma, Herscovici Tip C medial malleol kırıklarının tension-band wiring (TBW) ve yarım ve tam yivli kanüle vidalar kullanılarak tespit edilmesinin klinik ve radyolojik sonuçlarını değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Bu retrospektif çalışma, Ocak 2012 ile Aralık 2022 arasında izole medial malleol kırığı nedeniyle ameliyat edilen 18-65 yaş arası hastaları içermektedir. Bir yıldan az takip süresi olanlar, Herscovici Tip C dışındaki kırıkları olanlar, açık kırıkları olanlar, başka implant kullananlar veya takibi kaybedilenler çalışma dışı bırakıldı. Radyolojik değerlendirmeler, preoperatif anteroposterior, lateral ve mortis radyografileri ile bilgisayarlı tomografi taramaları kullanılarak yapıldı. Talokrural açı, köşe açısı ve talus ile tibia tavanı arasındaki hizalanma değerlendirildi. Klinik sonuçlar, Amerikan Ortopedik Ayak ve Ayak Bileği Derneği (AOFAS) Ayak Bileği-Arka Ayak Skalası kullanılarak ölçüldü. İstatistiksel analiz SPSS yazılımı kullanılarak yapıldı.

Bulgular: Toplam 178 hasta çalışmaya dahil edildi: 55'i (%30.9) TBW tespiti, 60'ı (%33.7) yarım yivli kanüle vida tespiti ve 63'ü (%35.4) tam yivli kanüle vida tespiti uygulandı. Ortalama takip süresi 76 ay ve ortalama yaş 32.2 yıldı. TBW grubunun takip süresi diğer gruplara göre anlamlı derecede daha uzundu (p=0.000), yarım ve tam yivli vida grupları arasında fark yoktu. Kırık tarafı, travma mekanizması veya implant çıkarma ihtiyacı açısından gruplar arasında fark yoktu. Postoperatif talokrural açı gruplar arasında benzerdi (p=0.530). Postoperatif köşe açısı, TBW grubunda (ortalama: 63.4), yarım yivli (ortalama: 65.8) ve tam yivli (ortalama: 65,2) vida gruplarına göre anlamlı derecede daha düşüktü (p=0.049). AOFAS skorları, yarım yivli vida grubunda (ortalama: 89,1), TBW (ortalama: 84.2) ve tam yivli vida gruplarına (ortalama: 85.9) göre anlamlı derecede daha yüksekti (p=0.02). Talus'un üst yüzeyi ile anterior tibia tavanı arasındaki hizalanma açısından yarım ve tam yivli vida grupları arasında anlamlı fark bulunmadı. TBW grubunda yanlış hizalanmış eklem sayısı diğer gruplara göre anlamlı derecede daha yüksekti (p=0.000).

Sonuç: Radyolojik sonuçlar, yarım ve tam yivli kanüle vida tespiti gruplarında TBW tespiti grubuna göre daha iyiydi. AOFAS skorları, yarım yivli vida tespiti grubunda en yüksekti. Komplikasyonlar açısından gruplar arasında anlamlı fark bulunmadı. Çalışmada, kanüle vida tespitinin izole medial malleol kırıklarının tedavisinde TBW tespiti yöntemine göre daha güvenli ve etkili bir yöntem olduğu sonucuna varıldı.

Anahtar Sözcükler: Gergi bandı yöntemi; kanüle vida ile tespit; medial malleol kırığı.

SCIE DOI: 10.14744/scie.2024.03880
South. Clin. Ist. Euras. 2024;35(3):288-292

Original Article

The Predictive Power of Rapid Acute Physiology Score and Rapid Emergency Medicine Score in Mortality Risk of Diabetic Ketoacidosis Patients

Avni Uygar Seyhan,[1] Rohat Ak,[1] Yeşim Aylin Kalafat Demirdağ,[1] Ahmet Şahin,[1] Yunus Emre Erdoğan,[2] Burcu Ağırbaş,[3] Mukaddes Kübra Melemez,[4] Şevval Deke[5]

[1]Department of Emergency Medicine, University of Health Sciences, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Türkiye
[2]Department of Emergency Medicine, Medicana Çamlıca Hospital, İstanbul, Türkiye
[3]Department of Emergency Medicine, Elbistan State Hospital, Kahramanmaraş, Türkiye
[4]Department of Anesthesiology and Reanimation, University of Health Sciences, Haydarpaşa Numune Education and Research Hospital, İstanbul, Türkiye
[5]Department of Internal Medicine, University of Health Sciences, Sultan 2. Abdülhamid Han Education and Research Hospital, İstanbul, Türkiye

Submitted: 14.08.2024
Revised: 19.08.2024
Accepted: 27.08.2024

Correspondence: Avni Uygar Seyhan,
Department of Emergency Medicine, University of Health Sciences, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Türkiye
E-mail: uygarseyhan@gmail.com

Keywords: Diabetic ketoacidosis; early warning systems; emergency department.

ABSTRACT

Objective: This study aimed to evaluate the effectiveness of the Rapid Emergency Medicine Score (REMS) and the Rapid Acute Physiology Score (RAPS) in predicting mortality among patients with diabetic ketoacidosis (DKA) in the emergency department.

Methods: A retrospective cross-sectional study was conducted on 111 patients diagnosed with DKA who were admitted to the emergency department of a tertiary hospital between June 1, 2021, and June 1, 2022. Inclusion criteria were patients aged 18 years and older who met the diagnostic criteria for DKA as defined by the American Diabetes Association. Data on vital signs, laboratory results, and clinical outcomes were collected. The predictive power of the REMS and RAPS scores for mortality was assessed using Receiver Operating Characteristic (ROC) curve analysis to determine the area under the curve (AUC) for each score. Descriptive statistics and non-parametric tests were used to analyze the data.

Results: A total of 111 patients with DKA were included in this study. The cohort comprised 64 males (57.6%) and 47 females (42.3%), with a mean age of 51.86±20.27 years. Among the patients, 7 (6.31%) were discharged, 56 (50.45%) were admitted to the general ward, 35 (31.53%) to the intensive care unit (ICU), and 13 (11.71%) patients died. The REMS score demonstrated a higher predictive power for mortality in DKA patients, with an AUC of 0.712, compared to an AUC of 0.60 for the RAPS score.

Conclusion: The REMS score proved to be a more effective tool than the RAPS score in predicting mortality among DKA patients. Given its higher accuracy and reliability, the REMS score could be valuable as an early warning system in the management of DKA in emergency settings. Routine use of REMS in similar critical conditions is recommended.

INTRODUCTION

Diabetic ketoacidosis (DKA) is a metabolic emergency frequently observed in patients with type 1 diabetes and is potentially life-threatening. DKA is characterized by hyperglycemia, ketonemia, and metabolic acidosis as a result of insulin deficiency and increased levels of counter-regulatory hormones. This condition can lead to severe dehydration, electrolyte imbalances, and acid-base disturbances.[1-5] The diagnosis and management of DKA in emergency

departments are of great importance because the mortality rate is significantly high if not treated promptly and appropriately. Rapid and accurate recognition and management of DKA increase patients' chances of survival and reduce complications.

In critical conditions such as DKA, the implementation of scoring systems is indispensable for guiding clinical decision-making and optimizing patient care. DKA, marked by severe metabolic disturbances, including hyperglycemia, ketonemia, and acidosis, poses a significant risk of morbidity and mortality if not promptly and effectively managed. Scoring systems provide a structured approach to evaluating the severity of a patient's condition by quantifying vital physiological parameters. These tools allow clinicians to prioritize interventions based on the patient's risk profile, ensuring that those with the highest need receive timely and appropriate treatment. By offering a standardized method to assess and monitor disease progression, scoring systems are critical in improving outcomes in patients with life-threatening conditions like DKA.

The Rapid Emergency Medicine Score (REMS) and the Rapid Acute Physiology Score (RAPS) are two important scoring systems used in emergency departments to quickly assess the overall condition of patients and estimate their mortality risk.[6-8] In REMS, parameters such as age, mean arterial pressure, heart rate, respiratory rate, body temperature, and the Glasgow Coma Scale (GCS) are included. Each of these parameters is assessed with specific points, and the total score reflects the patient's overall condition and mortality risk.[9,10] In RAPS, parameters such as mean arterial pressure, heart rate, respiratory rate, and GCS are included, and similarly, it is used to quickly assess the patient's physiological condition.[11,12] These scores play a crucial role in clinical decision-making processes and can be applied quickly and effectively in emergency departments.

The aim of this study is to examine the predictive power of RAPS and REMS scores in estimating mortality in patients with DKA.

MATERIALS AND METHODS

This retrospective cross-sectional study includes patients diagnosed with DKA who presented to the emergency department of a tertiary hospital between June 1, 2021, and June 1, 2022. Ethics approval was obtained from Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee with the decision dated 30.06.2022 and numbered 2022/514/228/3. The study included patients over the age of 18 who presented to the emergency department and met the diagnostic criteria for DKA. The diagnostic criteria for DKA include hyperglycemia, ketonemia or ketonuria, and metabolic acidosis, as defined by the American Diabetes Association (ADA).[13] The data were obtained from the hospital's electronic patient record management system. Patients who did not meet the DKA diagnostic criteria, patients for whom REMS or RAPS scores could not be calculated, patients whose emergency department triage data could not be accessed through the electronic patient record management system, and patients transferred from another hospital were excluded from the study.

For all patients included in the study, age, gender, vital signs (blood pressure, heart rate, respiratory rate, body temperature), laboratory parameters (blood glucose, serum electrolytes, blood gases), and medical history were recorded digitally. Vital signs and laboratory results were evaluated as the initial data obtained at the time of the emergency department visit.

The REMS includes parameters such as age, mean arterial pressure, heart rate, respiratory rate, body temperature, and GCS. The RAPS, on the other hand, includes parameters such as mean arterial pressure, heart rate, respiratory rate, and GCS. These scores are used to estimate the overall condition and mortality risk of patients. Higher REMS and RAPS indicate worse clinical outcomes and a higher risk of mortality.

The primary aim of the study is to evaluate the effectiveness of REMS and RAPS in predicting mortality in DKA patients presenting to the emergency department.

Statistical Analysis

Statistical analyses were performed using the SPSS version 25 statistical software package. Descriptive statistical methods (mean, frequency, percentage) were used to summarize the data during the evaluation of the study findings. The normality distribution of continuous variables was assessed using the Shapiro-Wilk test. Since the assumption of normal distribution was not met, the Mann-Whitney U test was applied to examine differences between the two groups. Relationships between two continuous variables were investigated using Spearman's rho correlation coefficients. To determine the predictive power of the scores used in identifying patient mortality, ROC analysis was performed. A p-value of <0.05 was considered statistically significant for all tests.

RESULTS

In this study, 111 patients diagnosed with DKA who met the inclusion criteria were included. Of these patients, 64 (57.6%) were male, and 47 (42.3%) were female, with a mean age of 51.86±20.27 years (range 19-90 years). Seven patients (6.31%) were discharged, 56 (50.45%) were admitted to the ward, and 35 (31.53%) were admitted to the intensive care unit (ICU), with 13 (11.71%) patients who died. Patients admitted to the ward stayed an average of 5.81±4.86 days (range 0-23), while those in the ICU stayed an average of 6.04±3.69 days (range 1-18). The demographic information of the patients, along with their hospital admission, non-survivor, and discharge statuses, is presented in Table 1.

The statistical data for the criteria used in the REMS and RAPS, including age, mean arterial pressure, heart rate, respiratory rate, oxygen saturation, and GCS values, which were used to predict patient mortality, are summa-

Table 1. Basic statistics of categorical variables of patients

Variable	Frequency	Percentage
Sex		
Man	64	57.66
Woman	47	42.34
Outcome		
Outpatient	7	6.31
Inpatient Unit	56	50.45
Intensive Care Unit	35	31.53
Non-survivor	13	11.71

rized in Table 2.

A ROC analysis was performed to compare the power of the RAPS and REMS in predicting patient mortality. This analysis identified the appropriate positivity threshold, critical values, and the quality of mortality prediction for each score. According to the ROC analysis results presented in Table 3, the area under the curve (AUC) for the RAPS was 0.60 ($p>0.05$), which was not statistically significant. For the REMS, the AUC was 0.712 ($p<0.05$), which was statistically significant (Tables 3-4).

The sensitivity of correctly identifying non-survivor patients was higher for the REMS, while the specificity of correctly identifying non-survivor patients was higher for the RAPS. Based on the Youden J index, the discriminatory ability of the REMS in predicting mortality was higher than that of the RAPS. Additionally, when considering the non-survivor criteria, it was observed that a RAPS greater than 4 and a REMS greater than 5 were associated with a higher likelihood of non-survival (Tables 3-4).

DISCUSSION

The key findings of this study reveal that REMS and RAPS scores have different levels of effectiveness in predicting mortality in DKA patients. It was observed that the REMS score could be used with higher accuracy for mortality prediction. ROC analyses demonstrated that the REMS score has higher sensitivity and specificity rates, while the RAPS score did not exhibit sufficient performance in this regard. These findings suggest that the REMS score may be a more effective tool in the management of DKA patients in emergency departments.

Scoring systems in emergency departments play a crucial role in the rapid and accurate assessment of patients' clinical conditions. These tools provide healthcare profession-

Table 2. Basic statistics of vital values of patients

Variable	Mean	Standard Deviation	Minimum-Maximum
Age (years)	51.86	20.27	19-90
Mean arterial pressure (mmHg)	93.11	46.86	36.67-156.67
Pulse rate (/min)	99.40	19.48	64-160
Respiratory rate (/min)	20.95	7.76	12-40
Oxygen Saturation (%)	95.92	5.74	50-100

Table 3. Predictive performance of RAPS in terms of severity in diabetic ketoacidosis patients

AUROC (95% CI)	Youden J	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	p value
0.600 (0.503-0.692)	0.283	>4	46.2 (35.3-65.5)	89.8 (67.5-94.6)	0.3367

RAPS: Rapid Acute Physiology Score; AUROC: Area under the receiver operating characteristic; CI: Confidence interval.

Table 4. Predictive performance of REMS in terms of severity in diabetic ketoacidosis patients

AUROC (95% CI)	Youden J	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	p value
0.712 (0.619-0.794)	0.3760	>5	69.2 (45.7-77.5)	68.4 (49.2-84.3)	0.0134

REMS: Rapid Emergency Medicine Score; AUROC: Area under the receiver operating characteristic; CI: Confidence interval.

als with a standardized method to evaluate the severity of illness, prioritize treatment, and make informed decisions about patient management. By quantifying various physiological parameters, scoring systems such as the REMS allow for early identification of high-risk patients, ensuring timely intervention. The integration of these systems into routine practice not only enhances patient outcomes but also optimizes the allocation of limited resources in the fast-paced and high-stakes environment of emergency care.

In critical conditions such as DKA, the use of scoring systems is essential for assessing the severity of the patient's condition and guiding clinical management. DKA is a life-threatening metabolic emergency that requires prompt and precise treatment to prevent complications and reduce mortality. Scoring systems like REMS or the RAPS score enable clinicians to systematically evaluate the physiological derangements associated with DKA, such as electrolyte imbalances, acid-base disturbances, and organ dysfunction. By providing a quantifiable measure of illness severity, these tools help prioritize interventions and monitor the patient's response to treatment, ultimately improving the chances of survival in such critical scenarios.

DKA is a common and serious complication, particularly in type 1 diabetes. Diagnosing and managing DKA in emergency departments is critical to increasing patients' chances of survival. DKA is characterized by hyperglycemia, ketonemia, and metabolic acidosis due to insulin deficiency and elevated counter-regulatory hormone levels. Hyperglycemia leads to severe dehydration and electrolyte loss through osmotic diuresis. This condition, especially when combined with potassium imbalance and metabolic acidosis, increases the risk of cardiac and neurological complications. Ketonemia and ketonuria result from increased lipolysis and the production of ketone bodies, which are the primary causes of metabolic acidosis. The pathophysiology of DKA is a complex process requiring prompt and appropriate treatment, and managing this condition in emergency departments is crucial for reducing patient mortality and morbidity. Treatment generally focuses on insulin replacement, fluid therapy, and electrolyte balance. However, the rapid and accurate assessment of patients' clinical conditions enhances the effectiveness of the treatment process and helps prevent complications.[14-16]

REMS and RAPS are important tools used in patient assessment and triage processes in emergency departments. REMS includes parameters such as age, mean arterial pressure, heart rate, respiratory rate, body temperature, and GCS. These parameters reflect the patient's overall physiological condition and are used to determine mortality risk. For example, the age factor indicates that older patients have a higher mortality risk compared to younger ones. Mean arterial pressure is an indicator of hemodynamic stability, with low pressures associated with a higher risk of mortality. Heart rate and respiratory rate assess the status of cardiac and respiratory functions. Body temperature can indicate the presence of infection or a systemic inflammatory response. GCS provides a rapid assessment of neurological status, with lower scores associated with poor prognosis. The RAPS, on the other hand, includes mean arterial pressure, heart rate, respiratory rate, and GCS parameters and is similarly used for quickly assessing the patient's physiological condition. However, it has been observed that the REMS offers a more comprehensive evaluation and, therefore, may have broader applicability in emergency departments.[17]

In the literature, there are various studies on the use and effectiveness of REMS and RAPS scores in different clinical scenarios. Many studies have demonstrated that the REMS is a reliable tool for predicting mortality in conditions such as sepsis, trauma, and other critical illnesses. For instance, a study conducted by Imhoff et al.[18] reported that the REMS had high accuracy in predicting mortality among trauma patients. This study showed that the REMS was particularly effective in predicting mortality in trauma patients at the time of hospital admission.[18] Similarly, in the study conducted by Ruangsomboon et al.,[19] the use of the REMS in patients with suspected sepsis was examined, and it was shown to have higher accuracy in predicting mortality compared to other early warning systems. These studies support the broad applicability of the REMS in various critical situations. Additionally, studies on the use of the RAPS in emergency departments have shown that it can be a useful tool for quick assessment. However, it has been determined that the REMS offers higher accuracy and reliability.

This research faces certain limitations. Firstly, as it is a retrospective study, there is an inherent risk of inaccuracies in data collection and recording. Additionally, since the study was conducted at a single center, the results may not be widely applicable to other settings. Furthermore, the relatively small sample size could limit the strength of the conclusions, indicating that larger studies might yield more definitive results. To address these issues, future research should focus on prospective and multicenter studies to confirm and expand upon these findings.

Conclusion

This study evaluated the effectiveness of REMS and RAPS in predicting mortality in DKA patients. The findings indicate that the REMS is more effective in predicting mortality in DKA patients. The REMS can be used as a rapid and accurate assessment tool in emergency departments and may play a significant role in patient management. Therefore, it is recommended that the routine use of the REMS be considered in DKA and similar critical conditions.

Ethics Committee Approval

The study was approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 30.06.2022, Decision No: 2022/514/228/3).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: A.U.S., R.A.; Design: A.U.S., R.A.; Supervision:

A.U.S.; Fundings: A.U.S. ;Materials: Y.A.K.D., Y.E.E., A.Ş., B.A., Ş.D., M.K.M.; Data: Y.A.K.D., Y.E.E., A.Ş., B.A., Ş.D., M.K.M.; Analysis: Y.E.E., Ş.D.; Literature search: M.K.M., Y.A.K.D., B.A.; Writing: A.U.S., R.A., Y.A.K.D., A.Ş., B.A.; Critical revision: A.U.S., R.A., Y.E.E., S.D., M.K.M.

Conflict of Interest

None declared.

REFERENCES

1. Calimag APP, Chlebek S, Lerma EV, Chaiban JT. Diabetic ketoacidosis. Dis Mon 2023;69:101418. [CrossRef]
2. Long B, Lentz S, Koyfman A, Gottlieb M. Euglycemic diabetic ketoacidosis: Etiologies, evaluation, and management. Am J Emerg Med 2021;44:157–60. [CrossRef]
3. Alışkan H, Kılıç M. The relationship between initial lactate levels and outcomes in patients diagnosed with diabetic ketoacidosis in the emergency department. J Surg Med 2022;6:991–3. [CrossRef]
4. Dhatariya KK, Glaser NS, Codner E, Umpierrez GE. Diabetic ketoacidosis. Nat Rev Dis Primers 2020;6:40. [CrossRef]
5. Evans K. Diabetic ketoacidosis: Update on management. Clin Med (Lond) 2019;19:396–8. [CrossRef]
6. Nakhjavan-Shahraki B, Baikpour M, Yousefifard M, Nikseresht ZS, Abiri S, Mirzay Razaz J, et al. Rapid acute physiology score versus rapid emergency medicine score in trauma outcome prediction; A comparative study. Emerg (Tehran) 2017;5:e30.
7. Chang SH, Hsieh CH, Weng YM, Hsieh MS, Goh ZNL, Chen HY, et al. Performance assessment of the mortality in emergency department sepsis score, modified early warning score, rapid emergency medicine score, and rapid acute physiology score in predicting survival outcomes of adult renal abscess patients in the emergency department. Biomed Res Int 2018;2018:6983568. [CrossRef]
8. Ustaalioğlu İ, Ak R, Öztürk TC, Koçak M, Onur Ö. Investigation of the usability of the REMS, RAPS, and MPM II0 scoring systems in the prediction of short-term and long-term mortality in patients presenting to the emergency department triage. Ir J Med Sci 2023;192:907–13. [CrossRef]
9. Garkaz O, Rezazadeh F, Golfiroozi S, Paryab S, Nasiri S, Mehryar H, et al. Predicting the 28-day mortality of non-trauma patients using REMS and RAPS; A prognostic accuracy study. Arch Acad Emerg Med 2022;10:e52.
10. Khari S, Zandi M, Zarmehrparirouy M, Adel Ramawad H, Yousefifard M. Prognostic value of physiological scoring systems in COVID-19 patients: A prospective observational study. Adv Emerg Nurs J 2023;45:77–85. [CrossRef]
11. Olsson T, Lind L. Comparison of the rapid emergency medicine score and APACHE II in nonsurgical emergency department patients. Acad Emerg Med 2003;10:1040–8. [CrossRef]
12. Olsson T, Terent A, Lind L. Rapid Emergency Medicine score: A new prognostic tool for in-hospital mortality in nonsurgical emergency department patients. J Intern Med 2004;255:579–87. [CrossRef]
13. Chung WK, Erion K, Florez JC, Hattersley AT, Hivert MF, Lee CG, et al. Precision medicine in diabetes: A Consensus Report from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2020;63:1671–93. [CrossRef]
14. Barski L, Golbets E, Jotkowitz A, Schwarzfuchs D. Management of diabetic ketoacidosis. Eur J Intern Med 2023;117:38–44. [CrossRef]
15. Karslioglu French E, Donihi AC, Korytkowski MT. Diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome: Review of acute decompensated diabetes in adult patients. BMJ 2019;365:l1114. [CrossRef]
16. Cashen K, Petersen T. Diabetic ketoacidosis. Pediatr Rev 2019;40:412–20. [CrossRef]
17. Hung SK, Ng CJ, Kuo CF, Goh ZNL, Huang LH, Li CH, et al. Comparison of the Mortality in Emergency Department Sepsis Score, Modified Early Warning Score, Rapid Emergency Medicine Score and Rapid Acute Physiology Score for predicting the outcomes of adult splenic abscess patients in the emergency department. PLoS One 2017;12:e0187495. [CrossRef]
18. Imhoff BF, Thompson NJ, Hastings MA, Nazir N, Moncure M, Cannon CM. Rapid Emergency Medicine Score (REMS) in the trauma population: A retrospective study. BMJ Open 2014;4:e004738. [CrossRef]
19. Ruangsomboon O, Boonmee P, Limsuwat C, Chakorn T, Monsomboon A. The utility of the rapid emergency medicine score (REMS) compared with SIRS, qSOFA and NEWS for Predicting in-hospital Mortality among Patients with suspicion of Sepsis in an emergency department. BMC Emerg Med 2021;21:2. [CrossRef]

Diyabetik Ketoasidoz Hastalarında Mortalite Riskinin Belirlenmesinde Hızlı Akut Fizyoloji Skoru ve Hızlı Acil Tıp Skorunun Öngörü Gücü

Amaç: Bu çalışma, acil serviste diyabetik ketoasidoz (DKA) hastalarında mortalite tahmininde Rapid Emergency Medicine Score (REMS) ve Rapid Acute Physiology Score (RAPS) skorlarının etkinliğini değerlendirmeyi amaçladı.

Gereç ve Yöntem: Retrospektif kesitsel bir çalışma, 1 Haziran 2021 - 1 Haziran 2022 tarihleri arasında bir üçüncü basamak hastanenin acil servisine başvuran ve DKA tanısı alan 111 hasta üzerinde gerçekleştirildi. Dahil edilme kriterleri, Amerikan Diyabet Derneği tarafından tanımlanan DKA tanı kriterlerine sahip 18 yaş ve üzeri hastaları içeriyordu. Vital bulgular, laboratuvar sonuçları ve klinik sonuçlara ilişkin veriler toplandı. REMS ve RAPS skorlarının mortaliteyi tahmin etme gücü, her bir skor için eğri altındaki alanı (EAA) belirlemek amacıyla ROC (Receiver Operating Characteristic) eğrisi analizi kullanılarak değerlendirildi. Verilerin analizi için tanımlayıcı istatistikler ve parametrik olmayan testler kullanıldı.

Bulgular: Bu çalışmaya toplam 111 DKA hastası alındı. Kohort, 64 erkek (%57.6) ve 47 kadından (%42.3) oluşmakta olup, yaş ortalaması 51.86±20.27 yıldır. Hastalardan 7'si (%6.31) taburcu edilirken, 56'sı (%50.45) servise, 35'i (%31.53) yoğun bakım ünitesine (YBÜ) kabul edilmiş ve 13 hasta (%11.71) hayatını kaybetmiştir. REMS skoru, DKA hastalarında mortaliteyi öngörmede RAPS skoruna kıyasla daha yüksek bir prediktif güce sahip olup, EAA değeri 0.712 iken, RAPS skoru için bu değer 0,60 olarak bulunmuştur.

Sonuç: REMS skoru, DKA hastalarında mortaliteyi tahmin etmede RAPS skorundan daha etkili bir araç olarak öne çıktı. Yüksek doğruluğu ve güvenilirliği göz önüne alındığında, REMS skoru, acil servislerde DKA yönetiminde erken uyarı sistemi olarak değerli olabilir. REMS skorunun benzer kritik durumlarda rutin kullanımının değerlendirilmesi önerilmektedir.

Anahtar Sözcükler: Acil servis; diyabetik ketoasidoz; erken uyarı sistemler.

SCIE DOI: 10.14744/scie.2024.21549
South. Clin. Ist. Euras. 2024;35(3):293-297

Original Article

Management of Thoracolumbar Fracture Dislocation Resulting from High Energy Trauma: Clinical Case Series

Ali Börekçi,[1] Pınar Kuru Bektaşoğlu,[1] Julide Hazneci,[1]
Ali Fatih Ramazanoğlu,[2] Erhan Çelikoğlu[1]

[1]Department of Neurosurgery, University of Health Sciences, Fatih Sultan Mehmet Education and Research Hospital, Istanbul, Türkiye
[2]Department of Neurosurgery, University of Health Sciences, Umraniye Training and Research Hospital, Istanbul, Türkiye

Submitted: 18.05.2024
Revised: 27.06.2024
Accepted: 12.07.2024

Correspondence: Pınar Kuru Bektaşoğlu, Department of Neurosurgery, University of Health Sciences, Fatih Sultan Mehmet Education and Research Hospital, İstanbul, Türkiye
E-mail: pnr.kuru@gmail.com

Keywords: Spinal trauma; surgical management; thoracolumbar fracture dislocation.

ABSTRACT

Thoracolumbar fracture dislocations are important cause of morbidity in patients with a history of accidents causes high energy trauma. In this type of spinal trauma, all three columns of the spine affect due to high-energy and may cause serious neurological deficits. There is two major surgical options when stabilization is indicated. Short segment and long segment stabilization options have their own advantages and disadvantages. In this brief report we will present the outcomes of our case series with thoracolumbar fracture dislocations that were managed with long segment stabilization. In our case series, neurological recovery was achieved in 4 of 6 patients to whom we applied emergency surgical treatment within 8 hours. We showed that reduction, stabilization and decompression performed with emergency surgical treatment had positive effects on the neurological recovery of patients.

INTRODUCTION

Thoracolumbar fractures are the most common injuries to the spine and account for more than 50% of all traumatic spine cases. However, fracture dislocations are rare and occur in less than 3%. Thoracolumbar fracture dislocations are an important cause of morbidity and mortality in these patients.[1] Neurological deficit is observed in the majority of cases and always requires urgent surgical reduction and stabilization.[2] In this study, cases in which thoracolumbar fracture dislocation was detected as a result of high-energy trauma and urgently operated on in our clinic are discussed in light of the literature.

In our case series, there were 5 male and 1 female patient. Their ages varied between 14 and 62. Most of the time, a fall from height was the mechanism of the accident. All patients were indicated for surgery, and we operated on them and stabilized the vertebrae with long-segment posterior fixation (Table 1).

CASE REPORT

Case 1

A 24-year-old male patient was injured as a result of falling from a height. He was brought to the emergency department with complaints of waist and back pain and weakness in both lower extremities. On neurological examination, both lower extremities were paraplegic and anesthetized

Table 1. Demographic characteristics of the patients

No	Age, Gender	Trauma	Preop Neurological examination	Pathology	Additional pathology	Surgery	Postop Complication	Follow -up	Last Neurological examination
1	24, M	Fall from height	ASIA-A	T10-T11 fracture dislocation	Right pulmonary contusion	T8-L2 posterior stabilization and reduction	(-)	8 year	ASIA-B
2	24, M	Blunt trauma	ASIA-A	T8-9 fracture dislocation	Sternum fracture, multiple costa fracture and left hemothorax	T5-T12 posterior stabilization and reduction T8 total laminectomy, duraplasty	(-)	4 year	ASIA-A
3	62, M	Fall from height	ASIA-A	T12-L1 fracture dislocation	(-)	T9-L4 posterior stabilizasyon, redüksiyon	(-)	4 year	ASIA-E
4	14, W	Fall from height	ASIA-A	L1-2 fracture dislocation, L5 comperssion fracture	(-)	T10-S1 posterior stabilization and reduction, L2 total laminectomy, duraplasty	(-) (-)	4 year	ASIA-D
5	52, M	Fall from height	ASIA-A	T11-T12 fracture dislocation	(-)	T7-L4 posterior stabilization and reduction	CSF	5 year	ASIA-A
6	23, M	Car accident	ASIA-A	T11-12 fracture dislocation	Right hemothorax	T8-L3 posterior stabilization and reduction T12 total laminectomy, duraplasty	Fistula, abscess	2 year	ASIA-D

below the T11 level (ASIA A). In the patient's spinal computed tomography (CT) scans, a fracture dislocation (AO Spine Type C injury) was detected at the T10-T11 level (Figure 1A-1B), and a contusion in the right lung was detected in the thorax CT. The patient, whose general condition was stable, was taken into emergency surgery. T8-L2 posterior stabilization was performed (Figure 1C-1D). The patient was transferred to the physical therapy clinic on the 3rd postoperative day. The follow-up period was 8 years. His last neurological examination was observed as ASIA-B.

Case 2

A 24-year-old male patient was brought to the emergency room with an injury caused by a concrete pump hitting his back during construction. In his neurological examination, his bilateral lower extremities were paraplegic and anesthetized below the T8 level (ASIA A). The patient had a T8-9 fracture dislocation (AO Spine Type C injury) (Figure 1E-1F), sternum fracture, multiple rib fractures, and left hemothorax, which were detected in the CT examinations. A tube thoracostomy was performed. The patient, whose general condition was stable, was urgently operated on, and T5-T12 posterior stabilization was performed. T8 total laminectomy was performed (Figure 1G-1H), bone fragments compressing the spinal cord were removed, and duraplasty was performed. The patient was transferred to the physical therapy unit on the 7th postoperative day. The follow-up period was 4 years. His last neurological examination was evaluated as ASIA-A.

Case 3

A 62-year-old male patient was brought to the emergency room after falling from a height. On neurological examination, both lower extremities were paraplegic and anesthetized below the L1 level (ASIA A). Spinal CT scans revealed a fracture dislocation (AO Spine Type C injury) at the T12-L1 level (Figure 2A-2B). The patient, who had no additional pathology and whose general condition was stable, was operated on urgently. The patient, who underwent posterior stabilization between T9-L4 (Figure 2C-2D), was transferred to the physical therapy unit on the 3rd postoperative day. The follow-up period was 4 years.

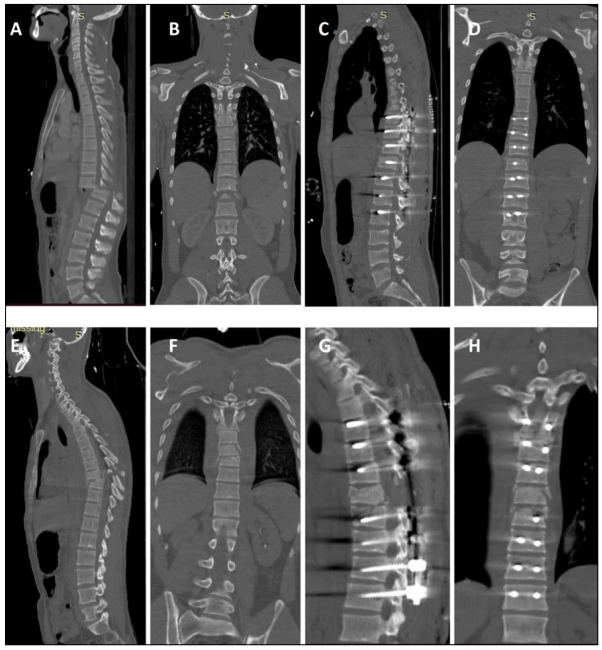

Figure 1. (a) Preoperative sagittal thoracolumbar computed tomography (CT) image of Case 1, **(b)** Preoperative coronal thoracolumbar CT image of Case 1, **(c)** Postoperative sagittal thoracolumbar CT image of Case 1, **(d)** Postoperative coronal thoracolumbar CT image of Case 1, **(e)** Preoperative sagittal thoracolumbar CT image of Case 2, **(f)** Preoperative coronal thoracolumbar CT image of Case 2, **(g)** Postoperative sagittal thoracolumbar CT image of Case 2, **(h)** Postoperative coronal thoracolumbar CT image of Case 2.

His last neurological examination was observed as intact, ASIA-E.

Case 4

A 14-year-old girl was brought to the emergency department after falling from a height. On neurological examination, both lower extremities were paraplegic and anesthetized below the L2 level (ASIA A). The patient, whose spinal CT examination revealed L1-2 fracture dislocation (AO Spine Type C injury) and L5 partial compression, was taken into surgery urgently (Figure 2E-2F). Posterior stabilization was performed between T10-S1. L2 total laminectomy was performed, bone fragments in the spinal canal were removed, and duraplasty was performed (Figure 2G-2H). She was transferred to the physical therapy unit on the 5th postoperative day. The follow-up period was 4 years. Her last neurological examination was evaluated as ASIA-D.

Case 5

A 52-year-old male patient was brought to the emergency room due to a fall from a height. His neurological examination revealed paraplegia in both lower extremities and anesthesia below the T11 level (ASIA A). The patient, whose examinations revealed a T11-T12 fracture dislocation (AO Spine Type C injury) (Figure 3A-3B), was operated on urgently, and a T7-L4 posterior stabilization and

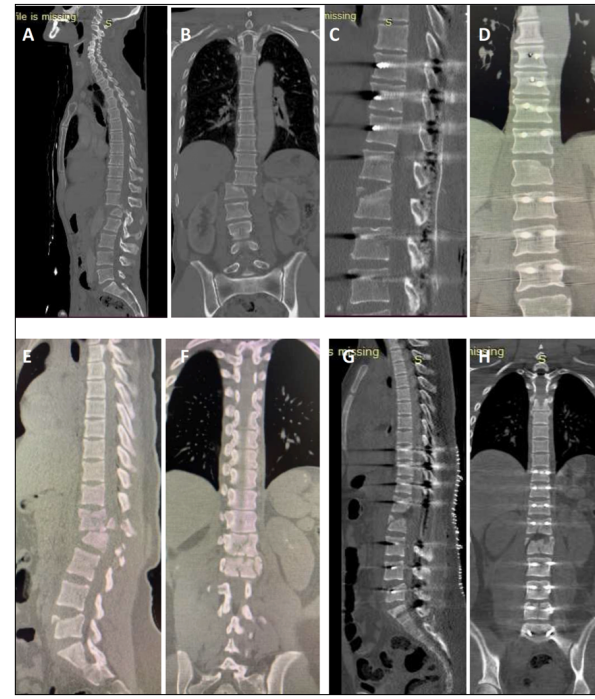

Figure 2. (a) Preoperative sagittal thoracolumbar CT image of Case 3, **(b)** Preoperative coronal thoracolumbar CT image of Case 3, **(c)** Postoperative sagittal thoracolumbar CT image of Case 3, **(d)** Postoperative coronal thoracolumbar CT image of Case 3, **(e)** Preoperative sagittal thoracolumbar CT image of Case 4, **(f)** Preoperative coronal thoracolumbar CT image of Case 4, **(g)** Postoperative sagittal thoracolumbar CT image of Case 4, **(h)** Postoperative coronal thoracolumbar CT image of Case 4.

reduction operation was performed (Figure 3C-3D). The follow-up period was 5 years. His last neurological examination was evaluated as ASIA-A.

Case 6

A 24-year-old male patient was brought to the emergency room after an in-car traffic accident. In his neurological examination, his bilateral lower extremities were paraplegic and anesthetized below the L1 level (ASIA A). A spinal CT scan revealed a T11-T12 fracture dislocation (AO Spine Type C injury) and hemothorax in the right lung (Figure 3E-3F). A tube thoracostomy was performed on the right lung. The patient, whose general condition was stable, was taken into emergency surgery. Posterior stabilization was performed between T8-L3 (Figure 3G-3H). With T12 total laminectomy, bone fragments that were compressing the spinal cord from the anterior were pushed anteriorly, and duraplasty was performed. External lumbar drainage was installed in the patient, who was found to have a CSF fistula during postoperative follow-up. Vancomycin and Meropenem treatment were started for the patient, who had fever, neck stiffness, and pus from the wound on the 12th postoperative day. When pan-resistant Klebsiella pneumoniae grew in the CSF culture, Polymyxin, Fosfomycin, and Meropenem treatment was started. Due

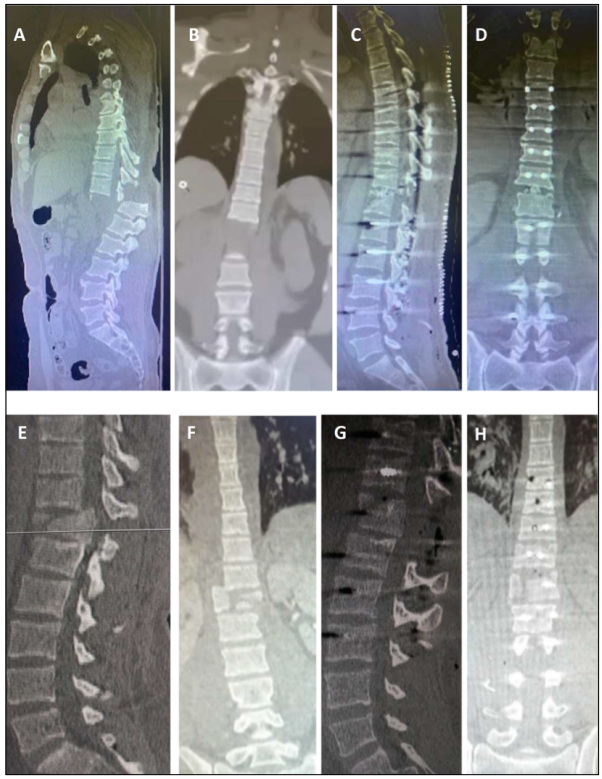

Figure 3. (a) Preoperative sagittal thoracolumbar CT image of Case 5, **(b)** Preoperative coronal thoracolumbar CT image of Case 5, **(c)** Postoperative sagittal thoracolumbar CT image of Case 5, **(d)** Postoperative coronal thoracolumbar CT image of Case 5, **(e)** Preoperative sagittal thoracolumbar CT image of Case 6, **(f)** Preoperative coronal thoracolumbar CT image of Case 6, **(g)** Postoperative sagittal thoracolumbar CT image of Case 6, **(h)** Postoperative coronal thoracolumbar CT image of Case 6.

to the development of an abscess in the operation area in the control MRI, the patient was taken into re-operation, and abscess drainage was performed and the CSF fistula was repaired. The patient, whose antibiotic treatment was completed, was transferred to the physical therapy unit at the 8th postoperative week. The follow-up period was 2 years. His last neurological examination was evaluated as ASIA-D.

DISCUSSION

Thoracolumbar fracture dislocations are treated surgically with long-segment posterior stabilization. While surgical fixation allows early rehabilitation, the chance of neurological recovery is rare. Many cases of thoracolumbar fracture dislocations without spinal cord injury have been reported in the literature. This is an issue that needs to be taken into consideration in terms of the risk of neurological deficits during the transfer of the patient to the operating table and during surgical treatment. Kanna et al.[3] reported in their case series of 36 thoracolumbar fracture dislocation cases without spinal cord injury that they divided these injuries radiologically into four types: coronal translation (Type 1), sagittal translation (Type 2), anterior-combined translation (Type 3a), and posterior-combined translation (Type 3b). They reported that translation can occur in one or two planes, depending on the variability in the distortion of the posterior ligamentous structures and facet joints.[3] Three of our cases were sagittal translation (Type 1) and three were posterior-combined (Type 3b) injuries.

Chokshi et al.[1] applied short-level posterior stabilization, including the fracture level, to 50 patients who were operated on with the diagnosis of thoracolumbar fracture dislocation. Their average follow-up period was 18.4 months, and they argued that including the fracture level in short-segment fixation in thoracolumbar fracture dislocations could eliminate the need for traditional long-segment fixation.[1] Similarly, Mittal et al.[4] reported that 12 of the 26 cases with thoracolumbar fracture dislocation were stabilized at a long level, two levels above and two levels below the fracture level, and applied short-level posterior stabilization to 14 of them, one level above and one level below, including the fracture level. Their follow-up period was 8.64 months, and they reported that short-segment stabilization can be used in the treatment of thoracolumbar fracture dislocations because short-segment stabilization is associated with less blood loss, shorter intraoperative time, and has similar radiological and clinical results to long-segment fixation.[4]

Wang et al.[5] reported that due to the high level of instability, early surgical treatment with decompression, reduction, and stabilization is the best policy in patients with thoracolumbar fracture dislocation, and they recommended long-level stabilization in these cases due to higher rigidity.[5] We preferred reduction and fusion with long-level stabilization in all our cases. In a series of 53 thoracolumbar fracture dislocation cases, Farooque et al.[6] applied interbody fusion with fragmented autogenous bone grafts to the fracture level after long-level fixation. They achieved 90.56% fusion at the end of one-year follow-up. They also stated that one upper and one lower short-segment instrumentation at the fracture level could provide 360-degree fusion and adequate spinal stability in non-ambulatory patients.[6]

Although it is known that the prognosis of patients with incomplete spinal cord injury is much better, it has been reported that patients with complete injuries can also benefit from early surgical decompression within 24 hours. Regarding the timing of surgical decompression after acute spinal cord injury, it has been emphasized that the optimal duration should be 8 hours, especially in animal experiments.[7] In our case series, neurological recovery was achieved in 4 of 6 patients to whom we applied emergency surgical treatment within 8 hours.

Conclusion

Thoracolumbar fracture dislocations are spinal traumas that affect all three columns of the spine due to high-energy traumas and cause serious neurological deficits. We

showed that reduction, stabilization, and decompression performed with emergency surgical treatment may have positive effects on the neurological recovery of patients.

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: A.B.; Design: A.B.; Supervision: E.Ç.; Materials: A.B., J.H., A.F.R.; Data: A.B., P.K.B., J.H., A.F.R., E.Ç.; Analysis: P.K.B.; Literature search: A.B., P.K.B.; Writing: A.B., P.K.B.; Critical revision: E.Ç.

Conflict of Interest

None declared.

REFERENCES

1- Chokshi JJ, Shah M. Outcomes of including fracture level in short-segment fixation for Th oracolumbar fracture dislocation. Asian Spine J 2019;13:56–60.

2- Eastlack RK, Bono CM. Fractures and dislocations of the thoracolumbar spine. In: RW, Heckman JD, Court-Brown CM, editors. Rockwood and Green's Fractures in Adults. Philadelphia: Lippincott Williams Wilkins; 2001. p. 1543–80.

3- Kanna RM, Raja DC, Shetty AP, Rajasekaran S. Thoracolumbar fracture dislocations without spinal cord injury: Classification and principles of management. Global Spine J 2021;11:63–70.

4- Mittal S, Ifthekar S, Ahuja K, Sarkar B, Singh G, Rana A, et al. Outcomes of thoracolumbar fracture-dislocation managed by short-segment and long-segment posterior fixation: A single-center retrospective study. Int J Spine Surg 2021;15:55–61.

5- Wang F, Zhu Y. Treatment of complete fracture-dislocation of thoracolumbar spine. J Spinal Disord Tech 2013;26:421–6.

6- Farooque K, Sharma V, Kar S. Morcellized local grafts as cost effective option for interbody fusion in thoracolumbar fracture dislocation: Seven years follow up of 53 patients. J Orthop 2022;31:33-39.

7- Kale A, Emmez H. Travmatik omurilik yaralanmasında cerrahi tedavi. Turk Nöroşir Derg 2020;30:475–477.

Yüksek Enerjili Travma Sonucu Oluşan Torakolomber Kırıklı Çıkıkların Yönetimi: Klinik Vaka Serisi

Torakolomber kırıklı çıkıklar, yüksek enerjili travmaya neden olan kaza öyküsü olan hastalarda önemli bir morbidite nedenidir. Bu tür omurga travmalarında omurganın üç sütunu da yüksek enerji nedeniyle etkilenir ve ciddi nörolojik defisitlere neden olabilir. Stabilizasyon endike olduğunda iki ana cerrahi seçenek vardır. Kısa segment ve uzun segment stabilizasyon seçeneklerinin kendilerine göre avantaj ve dezavantajları bulunmaktadır. Bu raporda uzun segment stabilizasyonu ile tedavi edilen torakolomber kırıklı çıkıklı olgu serimizin sonuçlarını sunacağız. Olgu serimizde acil cerrahi tedavi uyguladığımız 6 hastanın 4'ünde 8 saat içinde nörolojik iyileşme sağlandı. Acil cerrahi tedavi ile yapılan redüksiyon, stabilizasyon ve dekompresyonun hastaların nörolojik iyileşmesi üzerine olumlu etkileri olduğunu gösterdik.

Anahtar Sözcükler: Cerrahi tedavi; spinal travma; torakolomber kırıklı çıkık.

SCIE DOI: 10.14744/scie.2024.39269
South. Clin. Ist. Euras. 2024;35(3):298-300

Case Report

Lung Adenocarcinoma's Rare Metastasis: Tongue Metastasis

Saibe Fulya Elmastaş Akkuş

Department of Pulmonology, University of Health Sciences Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Türkiye

Submitted: 22.07.2024
Revised: 03.08.2024
Accepted: 05.08.2024

Correspondence: Saibe Fulya Elmastaş Akkuş, Department of Pulmonology, University of Health Sciences Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Türkiye

E-mail: flyelmastas@hotmail.com

Keywords: Adenocarcinoma; lung; metastasis; tongue.

ABSTRACT

When examining oral cavity tumors, the incidence of metastatic tumors is quite low. Most of these metastases occur in the mandible, with only a small portion involving soft tissues. Generally, the most common sites for metastases from lung cancer are the brain, adrenal glands, bones, and the contralateral lung, while the incidence of metastases to the tongue is reported to be approximately 0.2% to 1.6%. Patients with tongue metastases from lung cancer usually have a poor prognosis, making early diagnosis important. This case presentation aims to discuss a 62-year-old male patient with lung adenocarcinoma who presented with dysphagia and was found to have tongue metastasis. No distant metastases were detected apart from the tongue and cervical lymph node metastases. Systemic treatment was initiated for the patient diagnosed with stage 4 lung adenocarcinoma.

INTRODUCTION

Lung cancer ranks first among cancer-related deaths worldwide.[1] Symptoms, diagnosis, treatment approach, and survival in lung cancer vary depending on the location, invasion, and local or distant metastasis of the tumor. While the brain, liver, adrenal glands, bone, bone marrow, contralateral lung, and kidneys are the most common sites of metastasis in lung cancer, it can metastasize to any part of the body, though this is rare.[2] Metastasis to the oral cavity is very rare and accounts for approximately 1% of all oral malignancies.[3] Among metastatic oral cavity tumors, primary lung malignancy accounts for 0.1%.[4] Metastases in the oral cavity are most commonly seen in the mandible, with soft tissue metastases being rarer.[5] Although metastasis to the tongue is rare, advanced investigations should be planned when a lesion is detected on the tongue due to the generally poor prognosis and alteration of disease stage in patients with lung cancer.[6]

CASE REPORT

A 62-year-old male patient with a history of known peripheral artery disease presented to our Ear, Nose, and Throat clinic with unintentional weight loss and swelling in the left cervical area. The patient, who had a smoking history of 55 pack-years, was found to be an active smoker. On physical examination, a fixed, hard, painless lymph node approximately 2x1 cm in size was palpated in the left cervical area, and another lymph node approximately 1x1 cm in size was palpated in front of the sternocleidomastoid muscle on the right side. Laboratory tests revealed no abnormalities in complete blood count and biochemistry values.

Ultrasonography revealed multiple spherical-shaped pathological lymph nodes without fatty hilum in bilateral submandibular and cervical chains, with the largest being 12x11 mm in size in the upper cervical chain on the left side. Fine-needle aspiration biopsy taken from the left cervical lymph node supported a malignant epithelial tumor, with the thyroid and lung considered as the primary focus, prompting a Positron Emission Tomography-Computer

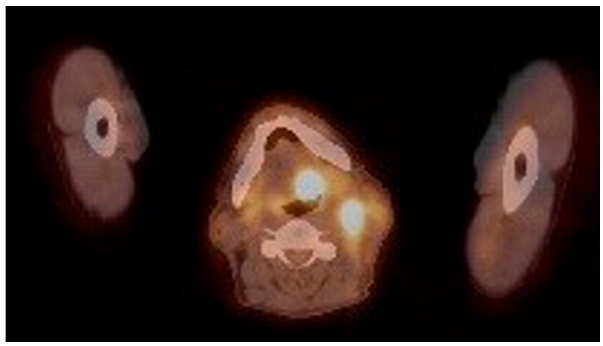

Figure 1. Lesion on the posterior segment of the left lateral tongue and cervical lymph nodes on PET-CT.

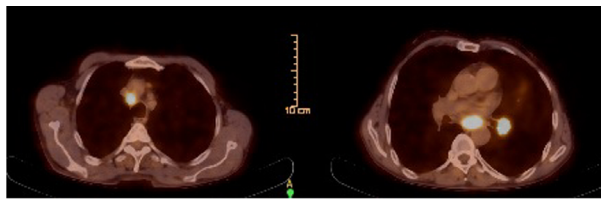

Figure 2. Lesion in the left hilum, right upper paratracheal and subcarinal lymphadenopathy on PET-CT.

Tomography (PET-CT) scan (Figure 1). The PET-CT scan revealed a lesion measuring 15x20 mm with maximum standardized uptake value (SUVmax):11.1 in the posterior segment of the left lateral tongue, conglomerate lymph nodes with SUVmax:9.6 at cervical levels 2, 3, and 5A, with the largest being approximately 18x12 mm, and lymph nodes with a diameter of 1 cm and SUVmax:3.6 at level 4 on the right side (Figure 2). In the thoracic and mediastinal sections, a lesion measuring 2 cm with SUVmax:10.5 in the left lung hilum was observed, and nodules with significant fluorodeoxyglucose uptake in the left lower lobe and lymphadenopathies in the right upper paratracheal, subcarinal, and left hilar areas, with the largest measuring 25x15 mm with SUVmax:11.2, were observed. Diagnostic endobronchial ultrasound (EBUS) was planned for the lesions described in the lung and mediastinum.

During the EBUS procedure, transbronchial needle aspiration was performed three times from oval, well-defined hypoechoic lymphadenomegaly (LAM) with a short axis of 1.3 cm seen in the right lower paratracheal area and oval, heterogeneous LAM with a well-defined border and a short axis of 1.4 cm seen in the left hilar area. Pathological examination revealed lung adenocarcinoma. Since the patient also experienced swelling in the tongue and impairment in articulation and swallowing functions, multiple deep punch biopsies were taken from the mass seen on the left lateral aspect of the tongue during simultaneous endolaryngeal microsurgery and direct laryngoscopy. Pathological examination supported the diagnosis of lung adenocarcinoma metastasis. Treatment was initiated for stage 4 lung adenocarcinoma, and the patient was found to be deceased approximately 3 months after diagnosis during follow-up.

DISCUSSION

Symptoms of primary lung cancer often include cough, sputum, and hemoptysis due to irritation of the respiratory mucosa. However, when tongue metastasis occurs, it typically results in dysphagia.[7] In our case, the patient presented primarily with swelling in the neck, and a biopsy of the lesion in the tongue was performed when dysphagia developed during follow-up, leading to the diagnosis of lung adenocarcinoma metastasis. Similarly, in the case presented by Cheng et al.,[8] the patient's admission to the hospital was due to hemoptysis and chronic cough, and the diagnosis of metastasis was made when the patient noticed swelling and pain in the tongue. Therefore, when investigating patients for lung cancer, dysphagia should also be considered. According to the literature, the rates of tongue metastasis in patients diagnosed with lung cancer are approximately 0.2% to 1.6%.[9] In a study by Zegarelli et al.,[6] 12 cases of tongue metastasis were detected in autopsies of 6,881 malignant patients, with a rate of 0.2%. Among all malignancies, 579 were primary lung cancer, and tongue metastasis was detected in only 2 cases (0.3%). In the study by Baden et al.,[10] it was reported that the metastases to the tongue were 21% lung, 21% kidney, and 17% skin-derived. Tongue metastases are usually located in the base of the tongue. The reason for this is thought to be the richness of the base of the tongue in vascular and lymphatic structures and its relative immobility.[11] As in our case and in the case presented by Cheng et al.,[8] metastasis was observed at the base of the tongue. Additionally, since metastasis was also detected in the cervical lymph nodes in our case, the metastasis at the base of the tongue suggests that lymphatic spread may be the primary route. However, there are also case presentations in the literature showing metastasis to the anterior part of the tongue.[11,12] This indicates that advanced investigations should be planned when a suspicious lesion of metastasis is detected regardless of its location in the oral cavity. Regarding treatment, surgery can be performed for patients with oligometastatic disease only if metastasis is limited to the tongue, but systemic treatment is more appropriate if metastasis occurs elsewhere. As in our case and in the case presented by Güven et al.,[13] systemic treatment was administered to patients due to metastases to the cervical lymph nodes and the base of the tongue. According to the study by Baden et al.,[10] the prognosis is poor in patients with tongue metastasis, with an average estimated survival time of six months. This is presumed to be due to the fact that metastasis to other sites usually occurs until the disease has metastasized to the head and neck region, indicating an advanced stage. Similarly, during follow-up of our case, the patient was found to be deceased approximately 3 months after diagnosis.

Conclusion

In conclusion, with this case presentation, we aimed to emphasize that tongue metastases in lung cancers should be taken into consideration due to their rarity and poor

prognosis. And although it is rare, it should be noted that dysphagia may be a signal of tongue metastasis.

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Conflict of Interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108. [CrossRef]
2. Savaş R, Alper H. Akciğer kanserlerinde radyolojik görüntüleme. In: Haydaroğlu A, editor. Akciğer Kanserleri: Tanı ve Tedavi. İzmir: Ege Üniversitesi Basımevi; 2000. p. 121–37.
3. Zachariades N. Neoplasms metastatic to the mouth, jaws and surrounding tissues. J Craniomaxillofac Surg 1989;17:283–90. [CrossRef]
4. Hirshberg A, Buchner A. Metastatic tumours to the oral region. An overview. Eur J Cancer B Oral Oncol 1995;31B:355–60. [CrossRef]
5. Yoshii T, Muraoka S, Sano N, Furudoi S, Komori T. Large cell carcinoma of the lung metastatic to the mandibular gingiva. J Periodontol 2002;73:571–4. [CrossRef]
6. Zegarelli DJ, Tsukada Y, Pickren JW, Greene GW Jr. Metastatic tumor to the tongue. Report of twelve cases. Oral Surg Oral Med Oral Pathol 1973;35:202–11. [CrossRef]
7. Majumder KR, Karmakar R, Alam MM, Rahman T. Carcinoma tongue Clinicopathological presentation. Mymensingh Med J 2015;24:787–93.
8. Cheng X, Hu Z, Han YP, Bai C. A case report of tongue metastasis from lung squamous cell carcinoma and literature review. Medicine (Baltimore) 2017;96:e8208. [CrossRef]
9. Terashima T, Matsuzaki T, Kawada I, Nishida J, Tanaka Y, Morishita T, et al. Tongue metastasis as an initial presentation of a lung cancer. Intern Med 2004;43:727–30. [CrossRef]
10. Baden E, Duvillard P, Micheau C. Metastatic papillary endometrial carcinoma of the tongue. Case report and review of the literature. Arch Pathol Lab Med 1992;116:965–8.
11. Mavili E, Oztürk M, Yücel T, Yüce I, Cağli S. Tongue metastasis mimicking an abscess. Diagn Interv Radiol 2010;16:27–9.
12. Jeba J, Backianathan S, Ishitha G, Singh A. Oral and gastrointestinal symptomatic metastases as initial presentation of lung cancer. BMJ Case Rep 2016;2016:bcr2016217539. [CrossRef]
13. Güven M, Öcal S, Eyibilen A, Aladağ İ, Köseoğlu D. Lung adenocarcinoma: A rare metastasis to the tongue. Balkan Med J 2010;2010:218–20.

Akciğer Adenokarsinomunun Nadir Metastazı: Dil Metastazı

Oral kavite tümörleri incelendiğinde metastatik tümör görülme oranı oldukça düşüktür. Bu metastazların çoğu mandibulaya olmakla beraber az bir kısmı yumuşak dokuya olmaktadır. Genel olarak akciğer kanserinin metastazlarına bakıldığında ise en sık beyin, sürrenal, kemik, karşı akciğer metastazı görülürken dile metastaz oranları yaklaşık olarak %0.2-1.6 olarak bildirilmiştir. Dilde metastaz saptanan akciğer kanseri tanılı hastaların genellikle prognozu kötü seyretmektedir. Bu sebeple erken tanı konulması önemlidir. Bu olgu sunumunda tarafımıza disfaji ile başvuran dil metastazı saptanan akciğer adenokarsinomlu 62 yaşında erkek hasta sunulması amaçlandı. Hastada dil ve servikal lenf nodu metastazları dışında uzak metastazı saptanmadı. Evre 4 akciğer adenokarsinomu tanısı konulan hastaya sistemik tedavi başlandı.

Anahtar Sözcükler: Akciğer adenokarsinom; dil; metastaz.