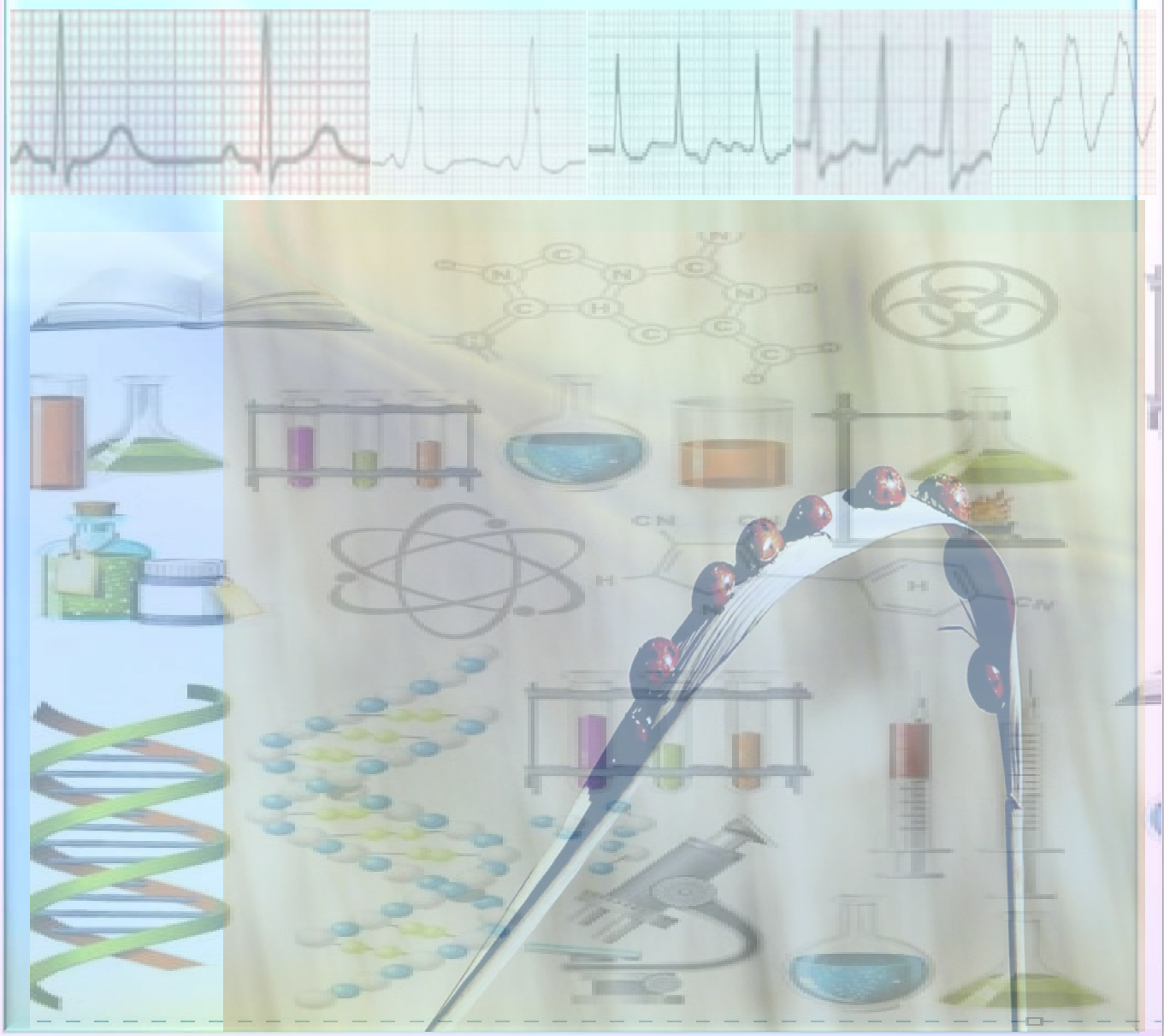
IJCMBS

International Journal of Current Medical and Biological Sciences

Volume 3 Issue 1 March-2023

e-ISSN:2791-8815



Journal Editorial Board

Overview

The International Journal of Current Medical and Biological Sciences is an international, peer-reviewed, open-access electronic and conventional published journal in the English language. The journal accepts clinical and experimental studies, editorial articles, technical and educational reviews, clinical case reports, original images, letters to the editor, and congress abstracts that contribute to general medicine and academic studies.

Information About the Journal

IJCMBS was established in 2021as open access and peer-reviewed journal that accepts articles in English. IJCMBS is published 3 times a year. Articles submitted should not have been previously published or be currently under consideration for publication any place else and should report original unpublished research results. The journal does not expect any fees for publication. All articles are available on the website of the journal with membership.

Journal Management Location and Address

Harran University Faculty of Medicine Osmanbey Campus Haliliye/ SANLIURFA/TURKIYE

Web: https://ijcmbs.com

E-mail: info@ijcmbs.com

Manuscript Preparation Guidelines

Author Guidelines

WRITING RULES

Manuscripts submitted for publication should be written in Microsoft Word. All text, figures and graphics should be sent electronically. Except for the cover page, the name of the institution and the authors should not be mentioned anywhere in the article. The cover page must be loaded separately.

ALL ARTICLES

Title page,

Turkish Abstract,

English Abstract,

Article Section,

Descriptions,

Referances,

Tables,

Figures and Pictures,

It should be arranged as subtitles.

Authors' Open Researcher and Contributor ID **(ORCID ID)** information must be uploaded to the system during article submission.

The article part (except for the abstract, references, table, figure and subtitles) of the research reviews should not exceed **3500 words**, the abstract part should not exceed **250 words,** the references should **not exceed 40**,

the number **of tables 5** and the number of **figures 5 should** not exceed. Case reports should consist of Turkish Title, English title, Turkish and English abstract, introduction, presentation of the case(s), discussion and references. Case reports should not exceed **5 pages** in total. Articles on technical and medical developments and image presentations of original topics should not **exceed 3 pages.**

PREPARATION OF ARTICLES

A plain and understandable writing language should be used in the text, scientific writing style should be adopted and unnecessary repetitions should be avoided. Writing; It should be written with 1.5 line spacing, Times New Roman 12 points. Pages should be numbered in the lower right corner. Manuscripts should be uploaded to the system in 2 files.

1 – Title PAGE

The title of the article should not exceed 100 characters (letters) in research articles and 80 characters in case reports. The title should be written in both English and Turkish. The names and surnames of the authors who contributed to the study should be written clearly.

If the study has been presented in any congress before, the congress name, time (day-month-year and congress place) should be specified.

The name, surname, full address, postal code, telephone e-mail address of the author to be contacted should be written at the bottom of the title page. **Reviewer recommendation:** Assists the editor when selecting a referee for a specific study. Include the names and contact details of at least **2 potential reviewer** on the title page.

2- FULL TEXT

The full texts to be reviewed by the referees during the evaluation process should be uploaded to the system as a single file. The full text file should be composed of the following parts and should be arranged in this order.

A) Abstract

Title of the Article; It should be short, easy to understand and describe the content of the article. Turkish (Abstract) and English (Abstract) abstracts should have Turkish and English titles at the beginning. It should not exceed **250** words in research reviews and **150** words in case reports.

Abstracts, Bacground, Materials and Methods, Results, Conclusion, Keywords in Turkish research articles; In English research papers, it should consist of Background, Materials and Methods, Results, Conclusions, Key words sections.

Case reports do not require these sections.

Keywords; At the end of the Turkish Abstract and English Abstract section, under the heading Keywords and Keywords, there should be a maximum of five keywords that capture the main titles of the scientific article and are written in accordance with the Index Medicus Medical Subject Headings (MeSH). Care should be taken to select the keywords from the Science Terms of Turkey (www.bilimterimleri.com).

Abbreviations in the text should be explained in parentheses where they are first used. Abbreviations should not be used in abstracts.

B) Article

It consists of Introduction, Material and method, Results, Discussion and Conclusion sections.

Introduction: Information that will explain the subject and the purpose of the study is given.

Material and method: The place, time, and planning of the study, as well as the elements and methods used,

should be reported. Data collection, characteristics of patients and individuals, characteristics of the experimental study, and statistical methods should be explained in detail.

Results: The obtained data should be given together with the statistical results.

Discussion: The results of the study should be evaluated by comparing with the literature data.

All spellings must comply with Turkish spelling rules and must be in accordance with punctuation marks. Abbreviations should be avoided as much as possible. References, figures, tables and pictures should be numbered in the order they appear in the text.

Conclusion: Findings from the study should be reported briefly without adding comments.

C) Referances

References should be written with 1.5 line spacing. Reference numbers should be given in ( ) without a period at the end of the sentence, and the period should be placed later. If more than one reference number is given, "," should be placed between them, and if more than two consecutive reference numbers are given, "-" should be placed between the numbers [eg. such as (1,2), (1-3)].

If the journal is used as a source: year, volume, issue, start and end pages are given.

If a book is used as a source: only year, start and end pages are given. The surnames and initials of the authors should be written in the references. If the number of authors is **3** or less in the references, all author names are written. If the name of the author is more than **3,** instead of the names of the following authors, "et al." is written in English sources and "et al." in Turkish sources. Journal names should be abbreviated according to Index Medicus. The way of writing the reference should be like the examples below. References should be arranged in the language of the article and as seen in the examples below.

Sources from journals: Tascanov MB, Tanriverdi Z, Gungoren F, et al. Comparisons of microbiota-generated metabolites in patients with young and elderly acute coronary syndrome. Anatol J Cardiol. 2020;24(3):175-82.

Books; 1. Wagner G. S. Marriott's Practical electrocardiography, Tenth ed. Lippincott Williams Publisher, 2000: 124-129

Web article: Abood S. Quality improvement initiative in nursing homes: The ANA acts in an advisory role. Am J Nurs [serial on the Internet] 2002 [cited 12 Aug 2002]. Available from: www.nursingworld.org/AJN/2002/june/wawatch.htm

Website; Cancer-pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources [updated 16 May 2002; cited 9 July 2002]. Available from: www.cancer-pain.org

Thesis; Gezer R: Morphological Characteristics and Individual Differences of Rugae Palatines. Master Thesis, Şanlıurfa: Harran University Institute of Health Sciences, 2016.

D) Explanations

Financial resources, contributing institutions, organizations and individuals, if any, should be specified in this section.

E) Tables

Tables should be written on a separate page with 1.5 line spacing, each table should have a number and an explanatory name. If there are abbreviations in the table, their expansions should be written in alphabetical order under the table. Table numbering (Table 1. , Table 2., ...) should be given consecutive numbers and Roman numerals should not be used. Tables should be uploaded in the article on a separate page.

F) Figures and Pictures

Figures and pictures must be named and numbered. Numbering (Figure 1., Figure 2., …) should be given consecutive numbers and Roman numerals should not be used. Images should be clear and have a minimum resolution of 300 dots per inch (dpi). Images should be uploaded within the article on a separate page. If abbreviations are used under the figure and picture, the explanation of the abbreviations should be stated under the subtitle in alphabetical order. The magnification and technique of microscopic images should be explained. The editorial board can make any changes it deems necessary without changing the essence of the article.

COMPLIANCE WITH PUBLICATION ETHICS

It is a must to prepare the manuscripts in accordance with research and publication ethics. The authors should state that they accept ethical principles in all human clinical research and that they conduct the research in accordance with these principles. Regarding these, in the Materials and Methods section: they obtained approval for each prospective and retrospective study from the ethics committee of the institution where the clinical research was conducted, and they obtained informed consent from the people who participated in the study or their guardians; In experimental studies on animals, they have to state that they protect animal rights and that they have received approval from the relevant experimental animal ethics committee. Regarding the results of experimental studies on humans or experimental animals, it is obligatory to submit an ethics committee approval document during the application to the journal. In the presence of the author(s), commercial link or institution providing financial support for the study; used commercial product, drug, company, etc. should inform the Editor on the presentation page. The absence of such a situation should also be stated on a separate page.

In studies that require ethics committee approval, the Ethics Committee Approval Document should be uploaded to the system during the article submission process, and the information about the permission (board name, date and issue number) should be stated in the material and method section, as well as in the explanations section after the discussion section of the article. Studies that require the approval of the Ethics Committee are as follows.

All kinds of research conducted with qualitative or quantitative approaches that require data collection from the participants by using survey, interview, focus group work, observation, experiment and interview techniques.

Use of humans and animals (including material/data) for experimental or other scientific purposes, Clinical studies on humans, Animal studies,

Retrospective studies in accordance with the law on the protection of personal data, (If requested, the permission document obtained from the institution where the study was carried out should also be uploaded to the system when the archive is scanned.)

The patient's clear identity should not be shared in the Case Report - Series.

EVALUATION AFTER THE REFEREE'S REPORT

Authors should write the topics that are requested to be corrected in the referee report as an answer in the answer section reserved for them. In addition, they should make the necessary changes in the article and resubmit them online by specifying (painting) them in the article

Contents

IJCMBS

THE INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND BIOLOGICAL SCIENCES e-ISSN: 2791-8815

Letter to The Editor

Where do we stand in predicting contrast-induced nephropathy?

Ertan AYDIN[1*]

[1] Department of Cardiology, Giresun university medical faculty training and research hospital/Giresun/TURKİYE

We read with great interest Toprak's research article on contrast-induced nephropathy, titled "Relationship between basal liver function test levels and contrast-induced nephropathy (CIN) in patients undergoing coronary angiography", published in your journal (1). A well-designed and presented article explores the possible relationship between preprocedural basal liver enzymes and contrast-induced nephropathy. It has been shown that high levels of basal liver enzymes Aspartate Alanine Aminotransferase (ALT) and especially Aminotransferase (AST) may predict the development of CIN. Multivariate logistic regression analysis revealed that AST level was an independent predictor of CIN (OR 1.006, 95% CI 1.003–1.009, p<0.001). AST level was found to be predictive for estimating CIN in ROC curve analysis, with optimal threshold value, AST ≥43 U/L, 77% sensitivity and 71% specificity (area under the curve: 0.764, 95% confidence interval [CI]: 0.712-0.817, p<0.001).

CIN has become a common morbidity and mortality due to increasing radiocontrast-mediated imaging (2). Therefore, it has become essential to predict the development of CIN and to take more intensive medical measures before contrast application. Although it is recommended today to predict the development of CIN, such as the Mehran Risk Score, increasing studies have shown that many important parameters other than the parameters of the Mehran score may be important in predicting CIN (3,4). We think that integrating simple, reproducible and quickly accessible parameters such as AST and ALT into the Mehran Risk Score will further increase the predictive value of contrast-induced nephropathy of the Mehran risk score.

Although hydration is currently the only proven treatment to prevent contrast nephropathy, CIN is still frequently encountered, especially after percutaneous coronary procedures, despite preprocedural and post-procedural hydration (5). It is seen more frequently in subjects prone to nephropathy such as diabetes, and kidney functions are affected more deeply than normal individuals after contrast application (6). Therefore, increasing the predictive value of the Mehran risk score would be particularly beneficial for such patients. In addition to all these, it has been shown that C-peptide may be protective against contrast nephropathy in diabetic patients in a recent article by Toprak (7). If these results are supported by large-scale randomized clinical trials, administration of C-peptide in high-risk patients may hold great promise in preventing the development of CIN.

Corresponding author:
Dr. Ertan AYDIN (MD)
Adress: Department of Cardiology, Giresun university medical faculty training and research hospital/Giresun/TURKİYE
E-mail: drertaydin@gmail.com **Received:** 20.11.2022 **Accepted:** 24.12.2022
Cite as: AYDIN. E Where do we stand in predicting contrast-induced nephropathy?. IJCMBS 2023;3(1):1-2
doi.org/ 10.5281/ 10.5281/zenodo.7487364

References

1. Toprak, K. Relationship between basal liver function test levels and contrast-induced nephropathy in patients undergoing coronary angiography: Basal liver function test levels and contrast-induced nephropathy. International Journal of Current Medical and Biological Sciences. 2, 1 (Mar. 2022), 47–55.
2. Rundback JH, Nahl D, Yoo V. Contrast-induced nephropathy. J Vasc Surg. 2011 Aug;54(2):575-9.
3. Mehran R, Aymong ED, Nikolsky E, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol. 2004; 44:1393–99.
4. Toprak K. Atherogenic Index of Plasma is an Independent Risk Factor for Contrast Induced Nephropathy in Patients With Non-ST Elevation Myocardial Infarction. Angiology. 2022;0(0).
5. Nijssen EC, Rennenberg RJ, Nelemans PJ, Essers BA, Janssen MM, Vermeeren MA, Ommen VV, Wildberger JE. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. Lancet. 2017 Apr 1;389(10076):1312-1322.
6. Heyman SN, Rosenberger C, Rosen S, Khamaisi M. Why is diabetes mellitus a risk factor for contrast-induced nephropathy? Biomed Res Int. 2013; 2013:123589.
7. Toprak K. Effect of Serum C-Peptide Levels on the Development of Contrast-Induced Nephropathy in Diabetic Patients Undergoing Coronary Angiography. Angiology. 2022;0(0).

Acknowledgements*: none*

Author Contributions: *Concept: E.A Literature Review: E.A Design: E.A Data acquisition: E.A Analysis and interpretation: E.A , Writing manuscript: E.A Critical revision of manuscript: E.A*

Conflict of Interest: *The author has no conflicts of interest to declare.*

Financial Disclosure: *Author declared no financial support.*

IJCMBS

THE INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND BIOLOGICAL SCIENCES e-ISSN: 2791-8815

Orgınal Article

Investigation of Anatomic and Orthopedic Properties of First Metatarsal Bone

Os Metatarsale'nin Anatomik ve Ortopedik Özelliklerinin Araştirilmasi

Berin Tuğtağ Demir[1*], Murat Üzel[2]

[1]Department of Anatomy, Ankara Medipol University, Faculty of Medicine, Ankara/TURKİYE

[2]Department of Orthopaedics and Travmatology, Kocaeli University, Faculty of Medicine, Kocaeli/ TURKİYE

Corresponding author:

Berin Tuğtağ Demir

Adress:
Hacı Bayram Mah, Talatpaşa Blv No: 4, 06050 Altındağ/ Ankara/TURKİYE

E-mail:
berin.tugtag@ankaramedipol.edu.tr

Received: 19.10.2022

Accepted: 01.11.2022

Cite as: DEMİR.TB, UZEL. M Investıgatıon of Anatomıc and Orthopedıc Propertıes of Os Metatarsale I IJCMBS 2023;3(1):3-12 doi.org/ 10.5281/zenodo.7266289

Highlights

- First metatarsal bone are important factors in the development of foot deformities.
- To detect feet at risk in terms of deformities such as hallux valgus, hallux varus, hallux rigidus in the early period and take precautions.

Abstract

Background: Structure most affected by the clinical deformities associated with lower extremity is the first metatarsal bone which may cause orthopedic problems and chronic pain on foot, because approximately 80% of the load from the talus and calcaneus is transmitted to the ground via medial arch. **Materials and Methods:** Our study was performed on lower extremities of 32 adult patients without any foot deformity, which were amputated due to circulation failure in the Department of Orthopaedics and Traumatology. Firstly, tibia length, foot length and foot width were measured. Subsequently, the dimensions and length of first metatarsus as well as proximal and distal articular surface dimensions of the first metatarsus were measured.**Results:** The average values were as follows: tibia length: 35.9 cm, foot length:22.7cm, foot width: 8 cm, length of first metatarsus: 5.8 cm. Statistical significance was found among the dimensions of proximal end, dimensions of distal head and the thinnest site of the bone ($p \leq 0.01$). **Conclusions:** Various external deforming forces cause variations in the medial longitudinal arch and lead foot pain. The length, shape of the head as well as the dimensions of the proximal and distal joint surfaces of the first metatarsal bone are important factors in the development of foot deformities. Since peroneus longus and tibialis anterior muscles insert onto the first metatarsal bone, the forces exerted by their tendons affect morphology of the bone. Therefore, dimensions of these muscles and their tendons in relation with the dimensions of first metatarsal bone are essential in the prevention and treatment of foot deformities.

Key Words: First metatarsal bone, Lower Extremity, Morphology, Anatomy, Orthopedics

ÖZ

Amaç: Alt ekstremite ile ilişkili klinik deformitelerden en çok etkilenen yapı, ortopedik problemlere ve ayakta kronik ağrıya neden olabilen birinci metatarsal kemiktir, çünkü talus ve calcaneus'tan gelen yükün yaklaşık %80'i arcus longitudinalis medialis pedis yoluyla yere iletilir. **Materyal ve Metod:** Çalışmamız Ortopedi ve Travmatoloji Anabilim Dalı'nda dolaşım yetmezliği nedeniyle ampute edilen ayak deformitesi olmayan 32 erişkin hastanın alt ekstremiteleri üzerinde yapıldı. İlk olarak tibia uzunluğu, ayak uzunluğu ve ayak genişliği ölçüldü. Daha sonra os metatarsale I uzunluğu ile proksimal ve distal eklem yüzey boyutları ölçüldü. **Bulgular:** Ortalama değerler; tibia uzunluğu: 35,9 cm, ayak uzunluğu: 22,7 cm, ayak genişliği: 8 cm, os metatarsale I uzunluğu: 5,8 cm olarak hesaplandı. Proksimal uç boy, distal baş ve kemiğin en ince yerinin boyutu kıyaslandığında birbirleriyle arasında istatistiksel anlamlılık bulundu ($p \leqslant 0,01$). Çeşitli dış deforme edici kuvvetler, arcus longitudinalis medialis pedis'te değişikliklere neden olur ve ayak ağrısına yol açar. Başın uzunluğu, şekli ve os metatarsale I'in proksimal ve distal eklem yüzeylerinin boyutları ayak deformitelerinin gelişiminde önemli faktörlerdir. **Sonuç:** Musculus peroneus longus ve musculus tibialis anterior, os metatarsale I üzerine tutunduğundan, tendonlarının uyguladığı kuvvetler kemiğin morfolojisini etkiler. Bu nedenle, ayak deformitelerinin önlenmesi ve tedavisinde bu kasların ve tendonlarının, os metatarsale I boyutlarına göre boyutları önemlidir.

Anahtar Kelimeler: Os metatarsale I, Alt ekstremite, Morfoloji, Anatomi, Ortopedi

Introduction

Compared to other metatarsals, the first metatarsal bone has a unique anatomical configuration and two main articular surfaces at its proximal and distal ends, whose angles have an important clinical impact in the management of hallux deformities. In addition, an articulation occurs between the base of the first metatarsal and the second metatarsal laterally, and this complex structure makes the first metatarsal bone an indispensable element in the preservation of the foot arch and dynamics (1).

Clinically; deformities such as hallux valgus, hallux varus, hallux rigidus and metatarsus adductus constitute the majority of foot deformities. It is thought that these deformities are directly or indirectly caused by the first metatarsal bone being longer or shorter than normal (2). While the reaction force in the metatarsophalangeal joint (MTPJ) is approximately 80% of the body weight in the pushing phase of gait, the load on the big toe in the heel rise phase corresponds to twice that of the other toes (3). This situation reveals that, first metatarsal bone is more prominent orthopedically and clinically in force transmission of the foot. Because morphometric factors such as the length and width of the first metatarsal bone, the width of the proximal and distal articular surfaces and the shape of the metatarsal head may disrupt the normal orthopedics of the foot as a deformity factor (4-6). As a result, it does not only cause deformities in the foot, but also causes many health problems by disrupting the holistic structure of the foot.

It is known that the diameters of the proximal and distal joint surfaces are important in the pronation of the metatarsal, and they also play an active role in the deformities that may occur with the effect of the muscles (7). In particular, the angulation of the proximal joint diameter with respect to the first metatarsal shaft and the role of this angle in the pathology of the first metatarsal are not clearly defined. The shape of the distal articular surface of the first metatarsal bone, which varies from flat or round to chevron, is believed to be a contributing factor to the hallux valgus deformity. Theoretically, the round head is considered the least stable, while the flat and zigzag head is more resistant to lateral displacement of the proximal phalanx over the metatarsal head (8).

Extremely long or short first metatarsal bone compared to second metatarsal bone has also been associated with these deformities, especially hallux valgus (9,10). In the literature, it is thought that the joints and muscles to which first metatarsal bone is attached, rather than its pure bone structure, are important in foot clinic (11). However, there are biomechanical studies state that the causes of deformities are not due to the excessive length or shortness of the first metatarsal bone alone, but to the shape of the metatarsal head, morphological features of the inserting muscles, or their medial protrusion (12,13).

With this viewpoint; we think that proximal and distal head of first metatarsal bone, distal head shape, also the tibialis anterior and the peroneus longus muscles which attach to its proximal part, also play role in the foot clinic by affecting the metatarsal. The aim of this study was to determine the length, width and articular surfaces of the first metatarsal bone in the anatomical position; to reveal the attachment sites and distances of peroneus tertius and tibialis anterior tendons attached to the metatarsal and to determine the relationships between them, also to examine the relationship between head shape and other morphometric features of first metatarsal bone.

Material and Method

Study place and design

This research was carried out as a result of the colloborative work of the Anatomy and Orthopedics Departments at Kahramanmaraş Sütçü İmam University.

Ethic approval

Permission was obtained from Kahramanmaraş Sütçü İmam University Ethics Committee for Non-Pharmaceutical Practices. (2013/12-5).

Dissection

This study was performed on 32 (12 female-20 male; age range 40-65 years) lower extremities which were amputated for ischemic reasons and had no congenital structural anomalies. After measuring the length and width of the foot, fine dissection was performed starting from the anterior and posterior of the leg, without damaging the tendons of tibialis anterior and peroneus longus muscles, to expose the dorsal and plantar aspects of the foot **(Figure 1).** All samples were sealed in airtight plastic bags and stored in a frost-free freezer (-20 °C). The samples were thawed at room temperature (+20 °C) 1 day before the process. After the skin was lifted, dissection of the peroneus longus and tibialis anterior was performed and the attachment sites to the first metatarsal bone were exposed. After the necessary measurements were made in the neutral position, deep dissection of the first metatarsal bone and measurements of the bone were made.

Data collection

Firstly, the lengths of tibialis anterior and peroneus longus tendons up to the point of insertion, the distal extension of the muscle fibers, their distance from the lateral and medial malleolus levels, and the dimensions of the tendons at the thinnest part and at the insertion were measured. Then; the first metatarsal bone was dissected and removed from the foot skeleton. Major parameters measured after dissection was completed:

- Foot size (Length-Width)
- Tibia size
- First metatarsal bone size (Length-Width)
- First metatarsal bone head type
- Proximal tip size (Height Width)
- The length of the metatarsal
- Distal head size (Height Width)
- Thinnest part size (Height Width)
- Diameter of the proximal articular surface
- Diameter of the distal articular surface
- Peroneus longus (PL) and Tibialis anterior (TA) tendon length
- Diameter of PL and TA tendon in origo, insertio and level of Tibiotalar Joint (TTJ)
- Distance of muscle fibers to insertion

Statistical analysis

After all measurements were made, statistical analyzes were performed in SPSS 15.0 for windows. Descriptive statistics were given as arithmetic mean ± standard deviation. Parametric tests were applied due to normal distribution (Independent t test). For the correlation analysis, Pearson correlation was performed and the significance levels were evaluated. Significance level was accepted as $p<0.05$.

RESULTS

Study groups were divided according to their gender and right-left distinction. Subsequently, foot lengths, foot widths, tibia and first metatarsal bone lengths were measured. Mean values obtained were as follows; tibia length 34.3 cm, foot length 21 cm, foot width 8 cm and first metatarsal bone length 5.6 cm for women, and tibia length 37.5 cm, foot length 24.5 cm, foot width 8.7 cm, and first metatarsal bone length 6 cm for men **(Figure 2).** It was observed that the right side was statistically larger than the left side in both genders, and there was a positive correlation between the length of the first metatarsal bone and tibia length (medium correlation), foot length and foot width (high correlation) ($p<0.05$). No correlation was found between the right and left sides, also between tibia length and foot length ($p>0.05$).

Morphometric results of first metatarsal bone

The results of the measurements obtained from the first metatarsal bone are shown in **Table 2**. In both genders, the proximal end size was larger than the distal head size, and the proximal articular surface size was larger than the distal articular surface size. Metaphyseal dimensions were taken from 1.5 cm distal to the proximal end, and distal metaphyseal dimensions were taken from 1.5 cm proximal to the distal end. While no difference was found between the proximal and distal metaphyses in women, it was observed that the distal metaphysis size was larger than the proximal in men. It was measured that the PL tendon was attached to an average of 9.1 mm proximal in women and 10.5 mm proximal in men, while the TA tendon descended from 12.7 mm proximal to distal in women and 13 mm proximal to distal in men **(Table 2).** Metatarsal length and foot width were found to be correlated. According to the correlation results between first metatarsal bone and related parameters **(table 2)**, there were correlation;

- Between metatarsal length and foot length (r=.426, $p<0.05$),
- Between proximal head height and foot length (r=.375, $p<0.05$),
- Between the thinnest ground width and metatarsal length (r=.391, $p<0.05$) and proximal head width (r=.544, $p<0.01$),
- Between the thinnest ground height and metatarsal length (r=.369) and proximal head height (r=.509),
- Between distal head height and foot length (r=.579, $p<0.01$), foot width (r=.463, $p<0.05$), metatarsal length (r=.403, $p<0.05$), and the thinnest ground height (r=,416, $p<0.05$),

- Between proximal joint surface diameter and foot length (r=.470, *p<0.05*), metatarsal length (r=.563, *p<0.01*), proximal head width (r=.419, *p<0.05*), proximal head height (r=.559, p<0.05),
- Between distal articular surface diameter (r=.396, *p<0.05*), foot length (r=.576, *p<0.01*), metatarsal length (r=.570, *p<0.01*) and distal head height (r=.468, *p<0.01*),
- Between head shape and tibia length (r=.39, *p<0.05*), metatarsal length (r=-0.19, *p<0.05*), thinnest ground elevation (r=.363, *p<0.05*)

Head shape results of first metatarsal bone

First metatarsal bone was found to be round-headed in 40.6% (13 individuals; 7 males 6 females), dome-shaped in 28.1% (9 individuals; 6 males 3 females) and had a flat head in 32% (10 individuals; 7 males 3 females) of the legs (Figure 3). As a result of the statistical analysis, using the Pearson correlation test, it was observed that there was a statistically negative level correlation between head shape and metatarsal length *(p<0.05*). One of the most striking statistical results regarding the head shape of the first metatarsal bone was that it showed a tight relationship with the dimensions of the PL tendon at the insertion point. In other words, the dimensions of the PL tendon are also effective in shaping the head of the metatarsal bone (*p<0.05*).

Relationship of PL and TA tendon Findings with First Metatarsal bone

In order to reveal the relationship of the PL and TA muscles with the first metatarsal bone; the tendon lengths of the muscles and tendons, the distance of the muscle fibers to the insertion, and the dimensions of the tendons at the insertion and TTJ level were measured, as shown in **Table 1**. The mean tendon length of PL was found to be 30.4 cm in women, 32 cm in men, and the mean tendon length of TA was found to be 20.3 cm in women and 20.6 cm in men. The mean size of the PL tendon at insertion was 10.2x4.4 mm in women, 9.2x4.5 mm in men, and the mean size of the TA tendon at insertion was 10.7x3.8 mm in women and 12.3x5.1 mm in men **(Table 3).**

It was observed that the dimensions of the PL muscle, the tendon at the insertion site, and the dimensions of the tendon at the TTJ level were larger on the left side in women, but there was no significant difference between the right and left sides in men. In the statistical analysis, no difference was found between male-female or right-left sides (*p>0.05*).

Although the PL and TA muscles were located in different parts of the leg, tendon lengths and sizes were related to each other. At the insertion points, both the place of attachment on the first metatarsal bone and their distance from the proximal end of the first metatarsal bone were related to each other.

It was observed that there was a significant correlation between the tendon lengths of PL and TA (r=0.48, *p<0.01*). In addition, a negative correlation was found between the lengths of the PL and TA tendons and their width at the TTJ level (r=-0.34, *p<0.05*). In other words, as the length of the tendon increased, the width at the level of the tibiotalar joint decreased. There was also a close correlation between the width at the insertion points and the width at the TTJ level (r=0.40, *p<0.01*). There was a negative correlation (r=-0.469, *p<0.05*) between foot width and PL tendon **(Table 4)**.

Table1. Results of informative parameters (proximal and distal head) from first metatarsal bone, Length of PL and TA tendon

Gender	Side	P 3D (mm)	Dimension of thin place (mm)	D head dimension (mm)	P metaphysical dimension (mm)	D metaphysical dimension (mm)	P articular surface dimension (mm)	D articular surface dimension (mm)	PL tendon distance (mm)	TA tendon distance (mm)
Female	right	26x22	14x15	22x21	20x18	20x19	27x15	19x20	9.3	13.5
	left	25x19	14x13	21x20	19x17	19x18	25x14	18x17	9	12
mean		25.5x 20.5	14x14	21.5x20.5	19.5x17.5	19.5x 18.5	26x14.5	18.5x 18.5	9.1	12.7
P		0.98	0.12	0.23	0.54	0.09	**0.04**	0.10	0.91	0.08
Male	right	30x22	15x15	24x25	23x20	25x23	29x16	23x20	13	14
	left	30x22	15x15	23x25	18x17	24x23	31x16	25x18	8	12
mean		30x22	15x15	23.5x25	20.5x 18.5	24.5x23	30x16	24x19	10.5	13
P		0.23	0.67	0.09	0.03	0.14	0.07	0.03	0.04	0.09

Test: Independent t test, p<0.05 P: Proximal, D: Distal, PL: Peroneus longus, TA: Tibialis anterior

Table 2. Correlation between informative parameters of First metatarsal bone

	FL	FW	TL	MTL	PTW	PTH	Th PW	Th PH	DH W	DHH	TA TL	DP AS	PAS H	DD AS	DA SH
FL	1.00														
FW	.33	1.00													
TL	.04	-.19	1.000												
MTL	.13	.42*	.026	1.00											
PTW	.22	.08	.129	.19	1.00										
PTH	.37*	.28	-.072	.28	.16	1.00									
ThPW	.25	-.00	.238	.39*	.54**	.28	1.00								
ThPH	.19	.19	.107	.36*	.34	.50**	.38*	1.00							
DHW	-.02	-.21	.177	.25	.59**	.25	.49**	.22	1.00						
DHH	.57**	.46**	.211	.40*	.26	.34	.26	.41*	.06	1.00					
TATL	.00	.04	.399	-.19	-.12	-.05	.07	-.12	.16	.32	1.00				
DPAS	.30*	.47**	-.125	.56**	.49*	.47**	.35*	.55**	.16	.53**	-.39	1.00			
PASH	.235	.32	-.42*	.19	.00	.40*	.24	.04	.17	.11	-.40	.46**	1.00		
DDAS	.39*	.57*	-.081	.57**	.21	.28	.13	.27	-.09	.46**	-.33	.75**	.36*	1.00	
DASH	.08	.01	.317	.226	.41*	.11	.39*	.28	.40*	.20	-.18	.19	.21	.19	1.00
HT	.39*	.18	.39*	-.19*	.20	.22	.28	.36*	.22	.32	.04	.31	.01	.14	.23

Aberrations: *p<0.05 P: Proximal, D: Distal, PL: Peroneus longus, TA: Tibialis anterior, FL:* Foot length, FW: foot width, TL:Tibia length, MTL: Metatars length, PTW: Proximal tip Width, PTH: Proximal tip height,ThPW: Thinnest part Width, ThPH: Thinnest part height, DHW: Distal head Width, DHH: Distal head height, TATL: TA tendon length, DPAS: Diameter of proximal articular surface, PASH: P articular surface height,DDAS: Diameter of the distal articular surface, DASH: D articular surface height, HT: Head type

Table 3. Averages of the data obtained from the measurements made in PL and TA tendon, according to sex

Gender	Side	Length of tendon (cm)		Distance of muscle fibers to insertion (cm)		Size of tendon at insertion (mm)		Tendon size at TTJ level (mm)	
		PL	TA	PL	TA	PL	TA	PL	TA
Female	**right**	27±5	19.7±3	20.4±3	13.3±2	9.3x4.3	11.1x 3.3	9.1x 3.7	9.1x3.6
	left	33.5±2	21±0.8	23.8±0.2	13.8±0.2	12.6x4.6	9.3x5.3	12.3x 4.3	7.6x3.8
Total mean		30.4±7	20.3±5	22.1±5	13.5±0.2	10.2x4.4	10.7x3.8	9.9x3.8	8.8x3.7
p		0.13	0.76	0.61	0.22	0.10	0.09	0.12	0.09
Male	**right**	32±5	20.2±4	19.9±3	11.75±1	9.5±1 x 4.4±0.9	12.6x4.7	9.2x3.9	8.6x3.7
	left	32±2	21.1±2	22.2±3.6	13.0±2	9x4.6	12x5.6	9.3x3.6	8.5x4
Total mean		32±6	20.6±4	21.5±3.6	12.3±1.8	9.2x4.5	12.6x5	9.2x3.7	8.5x3.6
p		0.15	0.56	0.77	0.31	0.20	0.11	0.09	0.13

Aberrations: *Test: Independent t test, p<0.05* TA: Tibialis anterior, PL: Peroneus longus, TTJ: Tibiotalar joint AO±SD

Table 4. Relationship between the PL and TA tendons properties and metatarsale I bone morphology

	FL	FW	TL	MTL	DPAS	DDAS	HT	TADTATO	PLTDTTJL	TATDTTJL	DPLTİ	DTATİ	LPLT
MTL	.154	.439*	-.095	1									
DPAS	.400*	.522**	-.292	.580**	1								
DDAS	399*	.581**	-.290	.554**	.670**	1							
HT	.382*	.210	.258	.199	.341	.154	1						
DTATO	-.183	-.069	-.345	.239	.115	-.067	-.193	1					
PLTDTTJL	-.127	-.387*	-.035	.119	-.201	-.161	-.164	.482**	1				
TATDTTJL	.103	.030	-.151	-.026	.128	.193	-.104	-.269	-.099	1			
DPLTİ	,533**	-.504**	-.123	.009	-.297	.231	.176	-.391*	-.221	.002	1		
DTATİ	.105	.203	.226	-.007	.400*	-.163	.086	-.180	.341	.187	-.137*	1	
LPLT	.020	.110	-.46	.081	-.022	.134	.677	.102	-.34*	.309	.099	.056	1
LTAT	.125	.172	-.26	.314	.256	.678	.812	.400*	.211	-.34*	.122	.78	.48*

Aberrations:*p<0.05 P: Proximal, D: Distal, PL: Peroneus longus, TA: Tibialis anterior FL:* Foot length, FW: foot width, TL:Tibia length, MTL: Metatars length, DPAS: Diameter of proximal articular surface, DDAS: Diameter of the distal articular surface, HT: Head type, DTATO: Diameter of TA tendon in origo, PLTDTTJL: PL Tendon diameter at TTJ level, TATDTTJL:TA Tendon diameter at TTJ level, DPLTİ: Diameter of PL tendon in insertion, DTATİ: Diameter of TA tendon in insertion, LPLT: Length of PL tendon, LTAT: Length of TA tendon

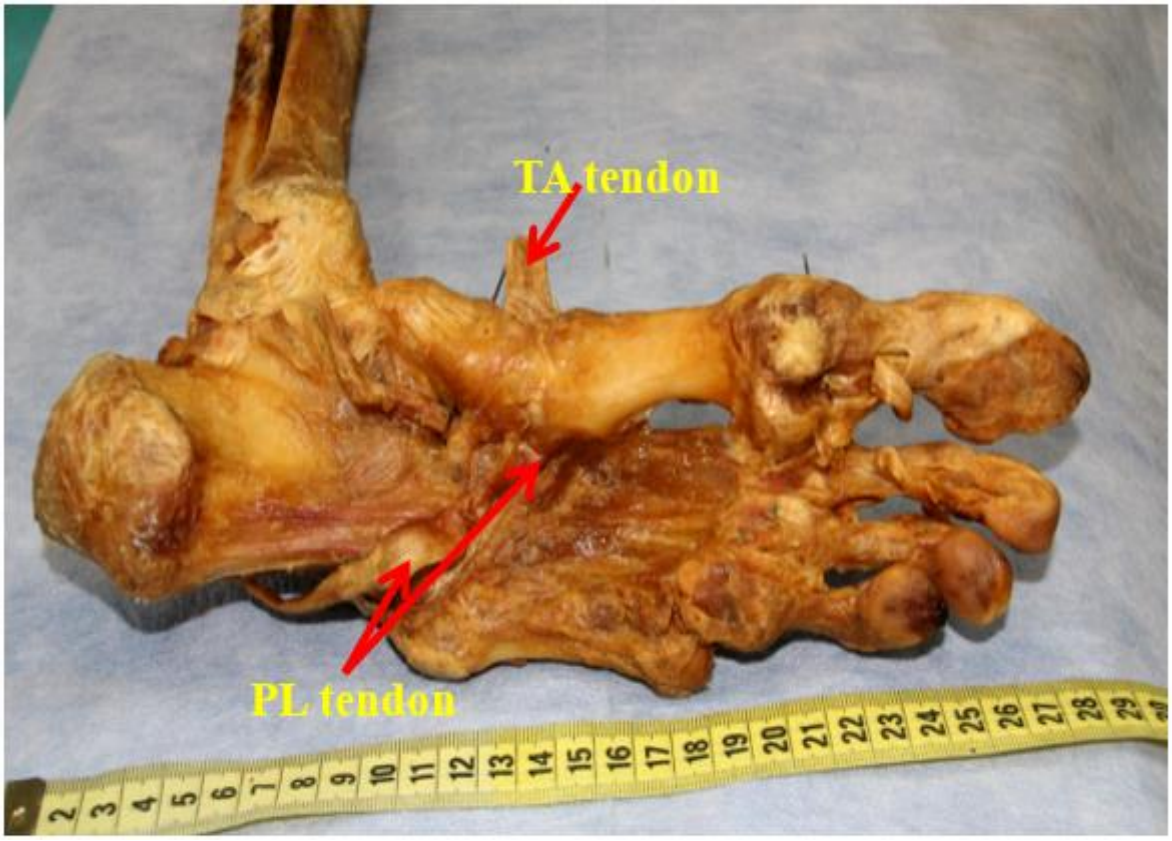
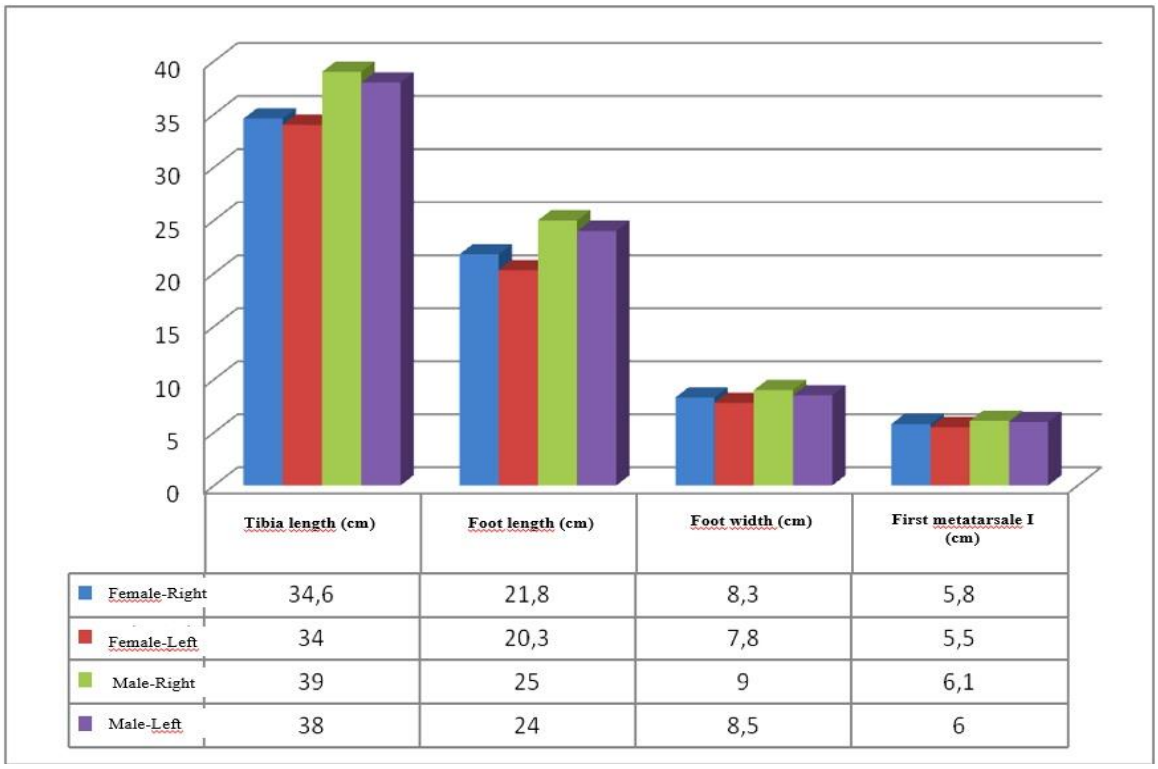


Figure 1: Deep plan view of the foot from the plantar face. The PL tendon was exposed by lifting the muscle and fascia on the plantar aspect of the foot. (TA: Tibialis anterior PL: Peroneus longus)



	Tibia length (cm)	Foot length (cm)	Foot width (cm)	First metatarsale I (cm)
Female-Right	34,6	21,8	8,3	5,8
Female-Left	34	20,3	7,8	5,5
Male-Right	39	25	9	6,1
Male-Left	38	24	8,5	6

Figure 2. Comparison of Tibia, Foot length, Foot width and First metatarsal bone

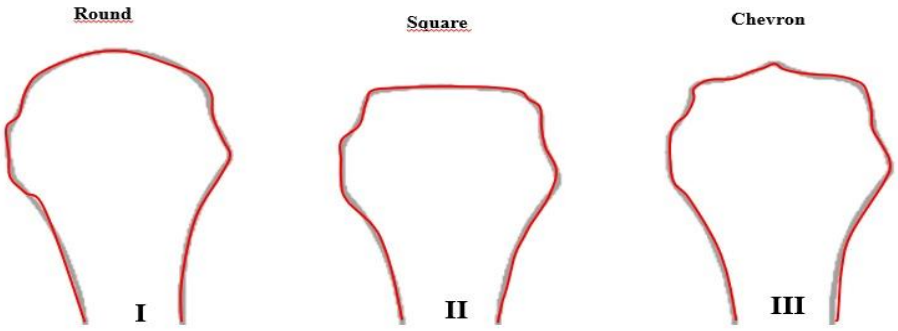


Figure 3: First metatarsal bone head shapes

Disscussion

Our first parameter of clinical significance of first metatarsal bone was its longitudinal length. Because in various studies, it has been stated that the first metatarsal bone being shorter or longer than normal plays a role in the etiology of hallux valgus (14). In studies on metatarsal shortness, it has been reported that the short metatarsal may cause difficulty in standing and walking due to the insufficiency of the metatarsal arch. Recent advances in orthopedic surgery have already shown that any defect in the feet, especially shortness, can be corrected with improved surgical techniques. Some investigators have reported that the pain and cosmetic problem caused by brachymetatarsia can be relieved by lengthening the short metatarsal and thus satisfactory results can be obtained (15,16). In our study, the length of the first metatarsal bone was determined with the help of the line drawn perpendicular to its longitudinal axis passing through the most extreme point of the

proximal and distal ends and the diaphysis/metaphyseal intersection (17). Beeson et al. (2009) reported the mean length of the first metatarsal bone as 6.0 cm in their study in which they performed the radiological evaluation of hallux rigidus on 180 individuals aged between 18 and 70 (18). In a similar study; Coughlin et al. (1999) measured the mean length of the first metatarsal bone as 6.3 cm (19). In the study of Doğan et al. (8.89±0.79 mm in men and 7.83±0.72 mm in women) the first metatarsal was found to be the shortest (13). Abdel et al. reported the mean length of this bone as 5.11 cm in women and 6.4 cm in men (20). In our study, the mean length of the first metatarsal bone was found to be 5.6 cm in women and 6 cm in men. Our results were found to be similar to the literature.

According to many researchers, long metatarsals cause metatarsus primus adductus and hallux rigidus as it will increase the pressure on the joint. Especially if it is longer than the second metatarsal, it is an important factor in the etiopathogenesis of hallux rigidus (21). Bryant et al. (2000) stated that there is a relationship between long metatarsal and tibia length (22). Mancuso et al. (2003) reported that a long first metatarsal would prevent the dorsiflexor ability of the first metatarsophalangeal joint since it is prevented from falling under the second metatarsal, and this may lead to functional metatarsus primus elevatus and subluxation of the first metatarsophalangeal joint over time (23). As a result of our statistical analysis based on these statements, we could not find any significant relationship between metatarsal length and tibia length, but we found a positive correlation between foot width and metatarsal length. As a result, it will be more vital to have data on metatarsal lengths, which will be more important for any surgical intervention. In addition, in procedures that require surgical shortening of the metatarsal, the amount of shortening is thought to depend on the length of the metatarsal and the articular surfaces (24).

While the proximal articular surface plays a decisive role for the metatarsophalangeal joint angle, the distal joint angle plays an active role in the transmission of power to the phalanxes (25). Brenner et al. (2003) examined the dimensions of the proximal and distal heads of the first metatarsal bone and found the mean proximal head size of the first metatarsal bone as 22x30 mm (26). They stated that there is no correlation between metatarsal heads and metatarsal or foot lengths in adults (26). We found the mean proximal tip size as 22x20 mm in women and 30x22 mm in men. However, in our results, there was a close relationship between proximal head articular surface and metatarsal length. The increase in the metatarsophalangeal angle, which is called the proximal metatarsal joint angle, causes an increase in the degree of hallux valgus.

Proximal and distal head size is associated with the proximal and distal articular surfaces, and it is known that the articular surface is the main factor that plays a role in the activity of the metatarsal. Because the size of the articular surface is effective on the pronation of the metatarsal, and the smaller the articular surface, the more restricted the movement of the metatarsal (27). El Said et al (2006) studied 478 metatarsal bones to examine the anatomical variations of first metatarsal bone. They examined the length and width of the bone, the middle region of the shaft, the proximal and distal joint angles. They stated that these angles were related to the proximal and distal head size (8). On the other hand, Coughlin (1999) reported that the proximal articular surface was correlated with the proximal head diameter, and also emphasized that as the area of the articular surface in the proximal and distal head increases, the metatarsal length may increase. Similarly, we determined that there is a positive correlation between proximal articular surface diameter and proximal head width, foot length and metatarsal length. We could not find a study in the literature that gives the relationship between head width and articular surfaces of first metatarsal bone with metatarsal and foot length.

Metatarsal shortening surgery is related to both metatarsal length and joint surfaces, and it has been reported that osteotomy of more than 6 mm will cause disproportionate load distribution in the joints (24). Therefore, we think that knowing the size and diameter of the joint surfaces is important in osteotomy surgery.

All the articles we identified state that the first metatarsal head has three types, and all authors associate each head type with the diagnosis of a foot pathology such as hallux valgus or hallux rigidus (28,29). Among the first metatarsal heads, the most common ones are round and then square ones (30). van Deventer et al. (2020) reported that the round shape was the most common (60.6%) and the chevron shape was the rarest (7.1%); They argued that reference values should be established in order to confirm the morphological typing of the head of first metatarsal bone and to defend its clinical use (29). In our study, first metatarsal bone was found to be round-headed in 40.6% (13 individuals; 7 men, 6 women), chevron in 28.1% (9 individuals; 6 men, 3 women), and had a flat (square) head in 32% (10 individuals; 7 men, 3 women). According to our results, there was a negative correlation between head shape of first metatarsal bone and metatarsal length. In other words, shortening of the metatarsal length was observed due to the change of the head of the first metatarsal bone from round to square. In a similar study, it was stated that as the metatarsal length increases, damage occurs in the MTPJ angle and the head shape becomes flat (18). In other words, it is believed that the round head of the first metatarsal bone is associated with the long metatarsal and predisposes to the development of

hallux valgus deformity, whereas a square-shaped head resists deforming forces (10). In summary, long metatarsal and round metatarsal head shapes are risk factors for hallux valgus formation.

While explaining the etiology of hallux valgus, Mann and Coughlin argued that the flat or square metatarsal head is more resistant to the deforming forces caused by the use of shoes, while the round metatarsal head is more prone to the development of hallux valgus (19). In addition, one of the most striking results statistically regarding the head shape of first metatarsal bone in our study was that it showed a close relationship with the dimensions of the insertion point of the PL tendon. In other words, besides the angle of the metatarsophalangeal joint, the dimensions of the PL tendon are also effective in shaping the head of the metatarsal bone (31).

As a result of our study, we found that the length of the PL tendon also affects the metatarsal length, and that the distance of attachment of the PL tendon to the first metatarsal bone and the size of the place where it is attached can affect both the length of the metatarsal and the diameter of the proximal articular surface directly. The size of the TA tendon at insertion increased in direct proportion to the diameter of the distal articular surface. We also believe that it is necessary to know how many cm the PL and TA tendons extend to the distal of the first metatarsal bone and their diameters at the insertion. Because, the larger the PL insertion tendon is and the more distally it extends, also the smaller the TA tendon and the more proximal it is, the greater the predisposition to metatarsus adductus and hallux valgus. In summary, TA pulls the metatarsal base medially and PL pulls laterally to balance each other.

Conclusion

In conclusion, we think that the length, proximal and distal articular surfaces and dimensions, also head shape of the first metatarsal bone are important factors in the development of foot deformities. Although various external deforming forces disrupt the medial arch and cause pain and deformities in the foot, we think that many foot deformities can be corrected if the dimensions of the PL and TA tendons at the insertion point and their relationship with the first metatarsal bone are precisely determined. Thus, it will be possible to detect feet at risk in terms of deformities such as hallux valgus, hallux varus, hallux rigidus in the early period and take precautions. When PL and TA muscles are evaluated biomechanically in selected clinical cases, we think that the results will confirm the anatomical data of our study.

Study Limitation

The small number of samples in the study and the inability to confirm the results biomechanically constitute the most important limitation of the study.

Acknowledgements: None

Ethical Approval: *Permission was obtained from Kahramanmaraş Sütçü İmam University Ethics Committee for Non-Pharmaceutical Practices. (2013/12-5).*

Author Contributions: *Concept: BTD Literature Review: BTD Design: MÜ Writing manuscript: BTD, MÜ Critical revision of manuscript: MÜ*

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

Financial Disclosure: *Authors declared no financial support.*

References

1. Glasoe WM, Nuckley DJ, Ludewig PM. hallux valgus and the first metatarsal arch segment: a theoretical biomechanical perspective. Physical Therapy. 2010;90(1):110–120.
2. Nawoczenski DA, Saltzman CL, Cook TM. The effect of foot structure on the three-dimensional kinematic coupling behavior of the leg and rear foot. Phys Ther. 1998; 78:404–16.
3. Xu R, Zuo H, Ji Y, et al. Effects of short-term limitation of movement of the first metatarsophalangeal joint on the biomechanics of the ıpsilateral hip, knee, and ankle joints during walking. Med Sci Monit. 2021;27: e930081.
4. Dawoodi AIS, Perera A. Radiological assessment of metatarsus adductus. Foot And Ankle Surgery. 2012; 18:1–8.
5. Easley ME, Darwish HH, Schreyack DW, et al. hallux valgus: proximal first metatarsal osteotomies. International Advances in Foot And Ankle Surgery. 2012:11-25.
6. Jastifer JR, Coughlin MJ, Schutt S, et al. comparison of radiographic and anatomic distal metatarsal articular angle in cadaver feet. Foot Ankle Int. 2014; 35:389.
7. Cavalheiro CS, Arcuri MH, Guil VR, et al. Hallux valgus anatomical alterations and ıts correlation with the radiographic findings. Acta Ortop Bras. [Online]. 2020;28(1):12-5.

8. Elsaid AG, Tisdel C, Donley B, et al. First metatarsal bone: an anatomic study. Foot Ankle Int. 2006;27(12):1041-1048.
9. Sung W, Kluesner AJ, Irrgang J, et al. Radiographic outcomes following primary arthrodesis of the first metatarsophalangeal joint in hallux abducto-valgus deformity. The Journal of Foot &Ankle Surgery. 2010; 49:446–451.
10. Ünal KO. Birinci metatars başı şeklinin halluks valgus deformitesi ile ilişkisi. Doktora Tezi, Ankara: Gazi Üniversitesi Tıp Fakültesi Ortopedi ve Travmatoloji Anabilim Dalı, 2008.
11. Perera AM, Mason L, Stephens MM. The Pathogenesis of hallux valgus. J Bone Joint Surg Am. 2011;93(17):1650-1661.
12. Coughlin MJ, Roger A, Mann Award. Juvenile hallux valgus: etiology and treatment. Foot Ankle Int. 1995;16(11):682-697.
13. Dogan A, Uslu M, Aydinlioglu A, et al. Morphometric study of the human metatarsals and phalanges. Clinical Anatomy. 2007; 20:209–214.
14. Munuera PV, Polo J, Rebollo J. Length of The First metatarsal and hallux in hallux valgus in the ınitial stage. International Orthopaedics (SICOT). 2008; 32:489–495.
15. Song HR, Oh CW, Kyung HS, et al. Fourth brachymetatarsia treated with distraction osteogenesis. Foot Ankle Int. 2003;24(9):706-711.
16. Tomic S, Krajcinovic O, Dakic N. Use of ılizarov mini-fixator in the treatment of congenital brachymetatarsia. Rev Chir Orthop Reparatrice Appar Mot. 2000;86(2):204-208.
17. Srivastava, S, Chockalingam, N, El Fakhri, Radiographic measurements of hallux angles: a review of current techniques. Foot (Edinb). 2010;20(1):27-31.
18. Beeson P, Phillips C, Corr WS, et al. hallux rigidus: a cross-sectional study to evaluate clinical parameters. Foot (Edinb). 2009;19(2):80-92.
19. Coughlin MJ, Carlson RE. Treatment of hallux valgus with an ıncreased distal metatarsal articular angle: evaluation of double and triple first ray osteotomies Foot Ankle Int. 1999;20(12):762-70.
20. Abdel Moneim WM, Abdel Hady RH, Abdel Maaboud RM, et al. Identification of sex depending on radiological examination of foot and patella. Am J Forensic Med Pathol. 2008;29(2):136-140.
21. Calvo A, Viladot R, Giné J, et al. The importance of the length of the first metatarsal and the proximal phalanx of hallux in the etiopathogeny of the hallux rigidus. Foot Ankle Surg. 2009;15(2):69-74.
22. Bryant A, Tinley P, Singer K. A Comparison of Radiographic Measurements in Normal, Halluks Valgus, and Hallux Limitus Feet. J Foot Ankle Surg. 2000;39(1):39-43.
23. Mancuso JE, Abramow SP, Landsman MJ, et al. The zero-plus first metatarsal and its relationship to bunion deformity. J Foot Ankle Surg. 2003;42(6):319-326.
24. Geng X, Shi J, Chen W, et al. Impact of first metatarsal shortening on forefoot loading pattern: a finite element model study. BMC Musculoskelet Disord. 2019;20(1):625.
25. Feldman V, Nyska M, Marom N, et al. Measurement of transverse forces between the first and second metatarsals: a cadaveric study. J Orthop Surg Res. 2016;11(1):121.
26. Brenner E. The intersesamoidal ridge of the first metatarsal bone: anatomical basics and clinical considerations. Surg Radiol Anat. 2003;25(2):127-131.
27. Kilmartin TE, Flintham C. Hallux valgus surgery: a simple method for evaluating the first-second intermetatarsal angle in the presence of metatarsus adductus. J Foot Ankle Surg. 2003;42(3):165-166.
28. Okuda R, Kinoshita M, Yasuda T, et al. The shape of the lateral edge of the first metatarsal head as a risk factor for recurrence of hallux valgus. J Bone Joint Surg Am. 2007;89(10):2163-2172.
29. van Deventer SJ, Strydom A, Saragas NP, et al. Morphology of the first metatarsal head as a risk factor for hallux valgus interphalangeus. Foot Ankle Surg. 2020;26(1):105-109.
30. Stein G, Pawel A, Koebke J, et al. Morphology of the first metatarsal head and hallux rigidus: a cadaveric study. Surg Radiol Anat. 2012;34(7):589-592.
31. Babacan S, Kafa IM. Morphometric Analysis of Tibial Plateau for Knee Arthroplasty and Prosthesis Design. IJCMBS. 2022;2(1):57-63

IJCMBS

THE INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND BIOLOGICAL SCIENCES e-ISSN: 2791-8815

Orgınal Article

Relationship Between Primary Tumor, Metastasis and Blood Type in Patients with Malignancy Receiving Palliative Care

Palyatif Bakim Alan Malignansli Hastalarda Primer Tümör, Metastaz ve Kan Tipi Arasindaki İlişki

Onur ÖZTÜRK*[1], Mikail ÖZDEMİR[2], Ebru ERGE[3], Muhammed Emin GÖKTEPE[4], Latife Merve YILDIZ[5], Merve SAGUŞ[6], Muhammet Ali ORUÇ[7]

Corresponding author:

Onur ÖZTÜRK

Adress:

Samsun Education and Research Hospital, Department of Family Medicine/ Samsun/TURKİYE

E-mail:

dr.onurozturk@yahoo.com

Received: 05.11.2022

Accepted: 19.12.2022

Cite as: OZTURK. O et al. Relationship Between Primary Tumor, Metastasis and Blood Type in Patients with Malignancy Receiving Palliative Care. IJCMBS 2023;3(1):13- 8

doi.org/ 10.5281/zenodo.7479158

[1]Samsun Education and Research Hospital, Department of Family Medicine/Samsun/TURKİYE

[2]Oğuzeli District Health Directorate, Department of Public Health/Gaziantep/TURKİYE

[3]Çiftlik Family Healthcare Center/ Samsun/TURKİYE

[4]Giresun University Training and Research Hospiatal, Department of Family Medicine/Giresun/TURKİYE

[5]Samsun University, Faculty of Medicine, Department of Family Medicine/Samsun /TURKIYE

[6]Manisa Sarigol State Hospital, Department of Family Medicine/ Manisa /TURKİYE

[7]Samsun University, Faculty of Medicine, Department of Family Medicine/Samsun/TURKİYE

Highlights

- Patients with blood group A had a lower incidence of CNS and breast cancers than patients with other blood groups
- There was no relation between metastases status and ABO/Rh blood groups.

Abstract

Background: The blood type is known to be associated with the risk of cancer. This study aimed to evaluate the relationship between oncological diagnoses and blood groups of inpatients receiving palliative care. **Material and methods:** This retrospective study was conducted with patients receiving palliative care at our hospital between December 2019 and December 2020. The records of patients receiving comprehensive palliative care during this 1-year period were obtained from the hospital archive, and patients diagnosed with a malignant disease were included in the study. **Results:** Overall, 176 patients were included in the study. No association was found between the cancer type and ABO/Rh blood groups. The incidence of central nervous system (CNS) and breast cancers was lower in patients with blood group A than in those with other blood groups ($p = 0.028$). Moreover, the focus and site of metastasis and the ABO/Rh blood group were not related. In addition, the comparisons between blood groups in terms of the presence and site of metastasis revealed no significant relationship. **Conclusions:** Patients with blood group A had a lower incidence of CNS and breast cancers than patients with other blood groups, and there was no relation between metastases status and ABO/Rh blood groups.

Keywords: Tumor, Metastasis, Blood Group, Palliative Care

ÖZ

Amaç: Kan grupları kanser riski ile ilişkilendirilmektedir. Bu çalışmanın amacı, ilgili serviste yatarak tedavi gören hastaların onkolojik tanılarının kan grupları ile ilişkisini değerlendirmektir. **Gereç ve Yöntem:** Çalışma retrospektif veri taramasına dayalıdır. Kapsamlı palyatif bakım servisine Aralık 2019- Aralık 2020 tarihleri arasındaki 1 yıllık süreçte yatışı olan hastaların kayıtları hastane arşivi vasıtası ile incelenmiştir. Herhangi bir malignansi tanısı olan hastalar veri setini oluşturmuştur. **Bulgular:** Totalde 176 hasta çalışmaya dahil edilmiştir. Kanser çeşidinin kan grubu ve Rh ile ilişkisi bulunmamıştır. A kan grubuna sahip olanlarda diğer kan gruplarına kıyasla SSS ve meme kanseri görülme sıklığının daha düşük olduğu görülmüştür ($p=0,028$). Metastaz varlığı ve odağının kan grubu ve Rh ile ilişkisi bulunmamıştır. Metastaz varlığı ve odağı açısından kan grupları kendi arasında kıyaslandığında anlamlı bir ilişki saptanmamıştır. **Sonuç:** A kan grubuna sahip olanlarda diğer kan gruplarına kıyasla SSS ve meme kanseri görülme sıklığının daha düşük olduğu görülmüştür. Metastaz durumunun ise kan grubu ve Rh ile ilişkisi bulunmamıştır.

Anahtar Kelimeler: Tümor, Metastaz, Kan Grubu, Palyatif Bakım

Introduction

Globally, malignancy is recognised as one of the leading causes of death. Cancer is known to develop because of the interaction between genetic and environmental factors. Moreover, most cancers are caused by environmental factors, and some of these factors include smoking, diet, obesity, radiation and infections (1-3). Although hereditary cancers are rare, some blood groups have been associated with an increased risk of such cancers (2,3).

ABO blood groups are inherited through genes on chromosome 9q34, and this chromosome encodes glycotransferases that catalyse the transfer of nucleotide donor sugars onto the H antigen to form the ABO blood group antigens. The A allele encodes a glycosyltransferase that causes the binding of α-N-acetylgalactosamine to the D-galactose end of the H antigen, thereby producing the A antigen (2). Many hypotheses on the relationship between the blood group and the risk of developing cancer have been proposed; however, there is no established mechanism for the same (1-5).

This study aimed to evaluate the relationship between oncological diagnoses and blood groups of inpatients receiving palliative care.

Materials and methods

Subjects

This retrospective study was conducted with patients receiving palliative (n=176) care at our hospital between December 2019 and December 2020.

The comprehensive palliative care unit of our hospital has a capacity of 24 beds and cares for approximately 5000 adult patients, including those registered with the home health services of the provincial health directorate and those who are not registered with these services but are being treated at various clinics within our hospital. A significant proportion of the patients treated in this unit have terminal-stage malignancies.

The records of patients receiving comprehensive palliative care during this 1-year period were obtained from the hospital archive, and patients with a diagnosis of any malignant disease were included in the study. Patients with an unknown blood group or missing information were excluded from the study. Moreover, patients with repeated admissions were evaluated only once based on the most recent admission. In these patients, age, diagnosis, place of birth, place of residence, addictive habits, personal and family history and metastases were examined. The included patients were not requested to undergo any additional tests, and personal details, such as name and Turkish Identification Number, were kept confidential.

Statistical analysis

All data were analysed using the SPSS version 20.0 software. Categorical variables were presented as number and percentage. For categorical variables, the chi-square test was used to determine the relationship between the groups. A p-value of <0.05 was considered statistically significant in all analyses.

Results

In total, 63.64% of patients were men, 35.80% had blood group A Rh(+), 82.82% had Rh(+) blood group, 34.66% had respiratory system cancer, 76.70% had metastatic disease and 50.41% had a family history of cancer (Table 1). There was no relationship between cancer type ($p = 0.092$) and ABO/Rh blood group ($p = 0.053$) (Table 2). The incidence of central nervous system (CNS) and breast cancers was lower in those with blood group A than in those with other blood groups ($p = 0.028$) (Table 3). There was no relationship between the presence and site of metastases and the ABO/Rh blood groups ($p > 0.05$ for all) (Table 4). Moreover, the comparisons between blood groups in terms of the presence and site of metastasis revealed no significant relationship ($p > 0.05$ for all) (Table 5).

Table 1. Demographic data

		n	%
Gender	Female	64	(36.36)
	Male	112	(63.64)
Place of birth	Samsun	136	(77.27)
	Other provinces	40	(22.73)
Blood group	A Rh+	63	(35.80)
	A Rh−	14	(7.95)
	B Rh+	10	(5.68)
	B Rh−	2	(1.14)
	AB Rh+	8	(4.55)
	AB Rh−	3	(1.70)
	O Rh+	55	(31.25)
	O Rh−	8	(4.55)
	Unknown	13	(7.39)
Blood group	O	63	(38.65)

	A	77	(47.24)
	B	12	(7.36)
	AB	11	(6.75)
Rh	–	28	(17.18)
	+	135	(82.82)
Cancer type	Respiratory system	61	(34.66)
	Central nervous system	9	(5.11)
	Urogenital	25	(14.20)
	Gastrointestinal system	71	(40.34)
	Breast	10	(5.68)
	Other	0	(0.00)
Metastasis	No	41	(23.30)
	Yes	135	(76.70)
Focal metastasis	No	41	(23.30)
	One	63	(35.80)
	More than one	72	(40.90)
Family history	Positive	61	(50.41)
	Negative	60	(49.59)
Smoking	Yes	45	(38.46)
	No	45	(38.46)
	Previous history of smoking	27	(23.08)
Occupation	Not working/Unemployed	36	(30.77)
	White collar	11	(9.40)
	Blue collar	70	(59.83)

Table 2. The relationship between cancer type and ABO/Rh blood group

		Cancer type										P
		Respiratory system		Central nervous system		Urogenital		Gastrointestinal system		Breast cancer		
		n(%)	%95 CI	n (%)	%95 CI	n (%)	%95 CI	n (%)	%95 CI	n (%)	%95 CI	
Blood group	**0**	20(37.74)	(25.62-51.15)	3(33.33)	(10.42-65.22)	7(28.00)	(13.49-47.28)	25(37.88)	(26.9-49.9)	8(80.00)	(49.72-95.59)	0.053
	A	25(47.17)	(34.18-60.46)	2(22.22)	(4.93-54.38)	16(64.00)	(44.49-80.47)	33(50.00)	(38.15-61.85)	1(10.00)	(1.1-38.13)	
	B	3(5.66)	(1.62-14.34)	2(22.22)	(4.93-54.38)	1(4.00)	(0.44-17.21)	6(9.09)	(3.88-17.78)			
	AB	5(9.43)	(3.69-19.45)	2(22.22)	(4.93-54.38)	1(4.00)	(0.44-17.21)	2(3.03)	(0.63-9.37)	1(10.00)	(1.1-38.13)	
Rh	-	10(18.87)	(10.14-30.89)	4(44.44)	(17.3-74.59)	6(24.00)	(10.69-42.94)	7(10.61)	(4.87-19.7)	1(10.00)	(1.1-38.13)	0.092
	+	43(81.13)	(69.11-89.86)	5(55.56)	(25.41-82.7)	19(76.00)	(57.06-89.31)	59(89.39)	(80.3-95.13)	9(90.00)	(61.87-98.9)	

Chi-square test

Table 3. Comparison between blood groups according to cancer type

	Cancer type										P
	Respiratory system		Central nervous system		Urogenital		Gastrointestinal system		Breast cancer		
	n(%)	%95 CI	n(%)	%95 CI	n(%)	%95 CI	n(%)	%95 CI	n(%)	%95 CI	
Blood group 0	20(37.74)	(25.62-51.15)	3(33.33)	(10.42-65.22)	7(28)	(13.49-47.28)	25(37.88)	(26.9-49.9)	8(80)	(49.72-95.59)	0.073
Other groups	33(62.26)	(48.85-74.38)	6(66.67)	(34.78-89.58)	18(72)	(52.72-86.51)	41(62.12)	(50.1-73.1)	2(20)	(4.41-50.28)	
Blood group A	25(47.17)	(34.18-60.46)	2(22.22)	(4.93-54.38)	16(64)	(44.49-80.47)	33(50)	(38.15-61.85)	1(10)	(1.1-38.13)	0.028
Other groups	28(52.83)	(39.54-65.82)	7(77.78)	(45.62-95.07)	9(36)	(19.53-55.51)	33(50)	(38.15-61.85)	9(90)	(61.87-98.9)	
Blood group B	3(5.66)	(1.62-14.34)	2(22.22)	(4.93-54.38)	1(4)	(0.44-17.21)	6(9.09)	(3.88-17.78)	-	-	0.327
Other groups	50(94.34)	(85.66-98.38)	7(77.78)	(45.62-95.07)	24(96)	(82.79-99.56)	60(90.91)	(82.22-96.12)	10(100)	-	
Blood group AB	5(9.43)	(3.69-19.45)	2(22.22)	(4.93-54.38)	1(4)	(0.44-17.21)	2(3.03)	(0.63-9.37)	1(10)	(1.1-38.13)	0.203
Other groups	48(90.57)	(80.55-96.31)	7(77.78)	(45.62-95.07)	24(96)	(82.79-99.56)	64(96.97)	(90.63-99.37)	9(90)	(61.87-98.9)	

Chi-Square Test

Blood group A- Other groups P values	**Central nervous system**	**Urogenital**	**Gastrointestinal system**	**Breast cancer**
Respiratory system	0.163	0.165	0.759	0.029
Central nervous system		**0.031**	0.117	0.466
Urogenital			0.232	0.004
Gastrointestinal system				0.018

Table 4. The relationship between the presence and focus of metastasis and the ABO/Rh blood group

		Metastasis				p	Focal metastasis						p
		Negative		Positive			Negative		One		More than one		
		n (%)	%95 CI	n (%)	%95 CI		n (%)	%95 CI	n (%)	%95 CI	n (%)	%95 CI	
Blood group	0	18(47.37)	(32.17-62.95)	45(36)	(27.98-44.66)	0.473	18(47.37)	(32.17-62.95)	21(35.59)	(24.3-48.26)	24(36.36)	(25.54-48.35)	0.822
	A	16(42.11)	(27.46-57.9)	61(48.8)	(40.15-57.51)		16(42.11)	(27.46-57.9)	30(50.85)	(38.31-63.31)	31(46.97)	(35.28-58.92)	
	B	3(7.89)	(2.27-19.59)	9(7.2)	(3.62-12.73)		3(7.89)	(2.27-19.59)	4(6.78)	(2.33-15.32)	5(7.58)	(2.95-15.81)	
	AB	1(2.63)	(0.29-11.65)	10(8)	(4.19-13.73)		1(2.63)	(0.29-11.65)	4(6.78)	(2.33-15.32)	6(9.09)	(3.88-17.78)	
Rh	-	7(18.42)	(8.64-32.8)	21(16.8)	(11.04-24.08)	0.817	7(18.42)	(8.64-32.8)	10(16.95)	(9.06-27.98)	11(16.67)	(9.19-26.99)	0.973
	+	31(81.58)	(67.2-91.36)	104(83.2)	(75.92-88.96)		31(81.58)	(67.2-91.36)	49(83.05)	(72.02-90.94)	55(83.33)	(73.01-90.81)	

Chi-Square Test

Table 5. Comparison between blood groups according to the presence and focus of metastasis

	Metastasis				p	Focal metastasis						p
	Negative		Positive			Negative		One		More than one		
	n (%)	%95 CI	n (%)	%95 CI		n (%)	%95 CI	n (%)	%95 CI	n (%)	%95 CI	
Blood group 0	18(28.6)	(18.6-40.5)	45(71.4)	(59.5-81.4)	0.208	18(28.6)	(18.6-40.5)	21(33.3)	(22.6-45.5)	24(38.1)	(26.9-50.4)	0.450
Other groups	20(20)	(13.1-28.6)	80(80)	(71.4-86.9)		20(20)	(13.1-28.6)	38(38)	(28.9-47.8)	42(42)	(32.7-51.8)	
Blood group A	16(20.8)	(12.9-30.8)	61(79.2)	(69.2-87.1)	0.469	16(20.8)	(12.9-30.8)	30(39.0)	(28.6-50.1)	31(40.3)	(29.8-51.4)	0.700
Other groups	22(25.6)	(17.3-35.5)	64(74.4)	(64.5-82.7)		22(25.6)	(17.3-35.5)	29(33.7)	(24.4-44.1)	35(40.7)	(30.8-51.3)	
Blood group B	3(25)	(7.6-52.9)	9(75)	(47.1-92.4)	0.886	3(25)	(7.6-52.9)	4(33.3)	(12.5-61.2)	5(41.7)	(18.1-68.8)	0.976
Other groups	35(23.2)	(17-30.4)	116(76.8)	(69.6-83)		35(23.2)	(17-30.4)	55(36.4)	(29.1-44.3)	61(40.4)	(32.8-48.4)	
Blood group AB	1(9.1)	(1-35.3)	10(90.9)	(64.7-99)	0.248	1(9.1)	(1-35.3)	4(36.4)	(13.7-65.2)	6(54.6)	(27.0-80.0)	0.450
Other groups	37(24.3)	(18.1-31.6)	115(75.7)	(68.4-82.0)		37(24.3)	(18.1-31.6)	55(36.2)	(28.9-44.0)	60(39.5)	(32.0-47.4)	

Chi-square test

Discussion

The relationship between blood group and cancer type has been investigated in several epidemiological studies (1-5). However, the studies investigating the relationship between metastasis and blood groups are limited. Therefore, we believe that the results of the present study conducted at the palliative care unit will contribute to the literature and provide up-to-date data.

A previous study compiled the distribution of ABO and Rh (D) groups over 6 years in Istanbul (Turkey's most populous province) and analysed more than 100,000 blood donors (4). The study found that approximately 42% of the participants had blood group A, 35% had blood group O, 15% had blood group B and 8% had blood group AB; moreover, a total of 85% of the participants had a Rh (D)-positive blood group (4). In addition, Salduz et al. (2015) investigated blood groups in Istanbul and reported similar results (5). Remarkably, the distribution of ABO/Rh blood groups in the present study was consistent with that reported in the relevant literature. This suggests that the higher number of patients with blood groups A and Rh (+) is due to the blood group distribution of the study population rather than a specific finding of malignancy.

It has been reported that the incidence of gastrointestinal cancer is higher in people with blood group A and lower in people with blood group O. Moreover, some studies have reported that blood group A increases the risk of developing breast cancer and that patients with blood group O demonstrate better prognosis (1-3). Wolpin et al. compared ABO genotypes using data from 12 prospective cohorts and found that compared to patients with blood group O, an increased probability of pancreatic cancer is observed in patients with blood groups A, AB and B (6). In addition, Iodice et al. reported that in patients with exocrine pancreatic cancer, blood group O was detected at a lower rate than the other blood groups; however, there was no significant difference in blood groups of patients with endocrine pancreatic, other gastrointestinal, breast, prostate and blood cancers (1). According to a study conducted in Taiwan, where the most common blood group is O, when all cancer types were examined together, blood groups AB and A were found to be more common in men and women, respectively, among patients with cancer. This positive relationship is mainly due to lung

and gastrointestinal cancer in men and liver and gastrointestinal cancer in women (2). A case-control study conducted in China reported an increased risk of hepatocellular carcinoma in men with blood group A and chronic hepatitis B (7). Regarding other studies conducted in Turkey with similar geographical and hereditary characteristics, a multicentre retrospective study by Urun et al. reported that the risk of lung cancer was higher in patients with non-O blood groups (8). Tam et al. reported that the incidence of thyroid malignancy was higher in patients with blood group A (9). However, Gömeç and Özden reported no significant relationship between any cancer type and blood group (10). Because of the advances in transportation, industrialisation and technology as well as increased mobility and migration around the world, changes in population groups and blood types are currently more common. The distribution of blood groups is one of the strongest evidences of population mixing in humans (11). The palliative care unit at our hospital cares for patients from the Black Sea region, and these patients mainly reside in Samsun. In the present cross-sectional study, we observed that the incidence of CNS and breast cancers decreased in patients with blood group A. This finding is inconsistent with the literature (1-3), and further cohort or case-control studies are needed to validate these findings.

Kahramanca et al. examined blood group characteristics of patients with colon cancer, and they found a significant relationship between ABO blood groups and susceptibility to liver metastases (12). The susceptibility was more common in patients with blood group A, but it was not associated with Rh antigen (12). Nakagoe et al. reported that the risk of lymph node metastasis was increased in patients with blood group A and colorectal cancer (13). Moreover, some studies have reported that Rh antigen positivity is associated with liver metastasis in patients with colorectal cancer and lymph node metastasis in patients with breast cancer (3,14). However, in the present study, the presence and focus of metastases were not associated with blood group and Rh.

The single-centre design and inability to comprehensively analyse the risk factors were some of the limitations of the current study. The limited sample size was another limitation.

Conclusions

Patients with blood group A had a lower incidence of CNS and breast cancers than patients with other blood groups. Moreover, there was no relation between metastases status and ABO/Rh blood groups. Future studies with larger participation may shed light on this issue.

Acknowledgements: None

Ethical Approval: *Ethical approval was obtained from the local ethics committee (protocol number: GOKA/2020/7/23).*

Author Contributions: *Concept: O.Ö. Literature Review: O.Ö, E.E, M.E.G, L.M.Y. Design: O.Ö, M.Ö. Data acquisition: O.Ö, E.E, M.E.G, L.M.Y, Analysis and interpretation: M.Ö. Writing manuscript: O.Ö. Critical revision of manuscript: M.S, M.A.O*

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

Financial Disclosure:*All Authors declared no financial support.*

References

1. Iodice S, Maisonneuve P, Botteri E, et al. ABO blood group and cancer. Eur J Cancer. 2010; 46(18):3345-50. doi: 10.1016/j.ejca.2010.08.009.
2. Hsiao LT, Liu NJ, You SL, et al. ABO blood group and the risk of cancer among middle-aged people in Taiwan. Asia-Pacific Journal of Clinical Oncology. 2015; 11: 31–6
3. Parlak Ö, Kocaöz S. Meme Kanseri Hastalarında ABO ve Rhesus Kan Grubunun Klinikopatolojik Etkisi: Retrospektif Çalışma. Ankara Med J. 2019; 1:152-6 DOI: 10.17098/amj.542143.
4. Yanasik M, Tunc T, Huslu M, et al. The overall distribution of ABO and Rh (d) groups in the most populous city Istanbul as representing the complex ethnicity of Turkey. Med J Bakirkoy. 2020; 16(4):363-8.
5. Salduz ZİY, Çetin G, Karatoprak C, et al. ABO and Rh Blood Distribution in İstanbul Province (Turkey). İstanbul Med J. 2015; 16: 98-100.
6. Wolpin BM, Kraft P, Gross M, et al. Pancreatic cancer risk and ABO blood group alleles: results from the pancreatic cancer cohort consortium. Cancer Res. 2010; 70:1015–23.
7. Li Q, Yu CH, Yu JH et al. ABO blood group and the risk of hepatocellular carcinoma: a case-control study in

patients with chronic hepatitis B. PLoS ONE. 2012; 7: e29928.

8. Urun Y, Utkan G, Cangir AK, et al. Association of ABO blood group and risk of lung cancer in a multicenter study in Turkey. Asian Pac J Cancer Prev. 2013; 14: 2801–3.
9. Tam AA, Özdemir D, Fakı S, et al. ABO Blood Groups, Rh Factor, and Thyroid Cancer Risk: To 'B'or Not to 'B'. Endocrine research. 2020; 45(2):137-46.
10. Gömeç M, Özden H. Distribution of AB0 and Rh blood groups in cancer patients; is A Rh (+) blood group a risk factor in colorectal cancer development? Cumhuriyet Medical Journal. 2021; 43(2): 182-8.
11. Akın G, Dostbil N. Türkiye'de Kan Grubu Araştırmaları. Ankara Üniversitesi Dil ve Tarih-Coğrafya Fakültesi Dergisi. 2005; 45: 2: 1-15.
12. Kahramanca Ş, Anuk T, Yıldırım AC, et al. Blood Group Characteristics in Colorectal Cancers. Türk Kolon ve Rektum Hastalıkları Dergisi. 2018; 28(2): 76-9. 10.4274/tjcd.00378
13. Nakagoe T, K Fukushima, A Nanashima, et al. Comparison of the expression of ABH/Lewis-related antigens in polypoid and non-polypoid growth types of colorectal carcinoma. J Gastroenterol Hepatol. 2001; 16:176-83.
14. Halvorsen TB. ABO blood groups, rhesus types, and colorectal adenocarcinoma. A retrospective study of 747 cases. Scand J Gastroenterol. 1986; 21(8):979-83.

IJCMBS

THE INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND BIOLOGICAL SCIENCES e-ISSN: 2791-8815

Orgınal Article

An example from non-traumatic emergency patient group in a post-conflict low-income region: Dialysis patients applying to the emergency department in northwest Syria

Çatışma sonrası düşük gelirli bir bölgede travmatik olmayan acil hasta grubundan bir örnek: Kuzeybatı Suriye'de acil servise başvuran diyaliz hastaları

Bahadır Karaca[1], Murat Tepe[2], Hakan Güner[3], Burak Çelik[4], Mustafa Çetin[5]

[1]Department of Emergency, Sancaktepe Şehit Prof. Dr. Ilhan Varank Training and Research Hospital, Istanbul, Türkiye
[2]Department of Emergency, Kilis Prof. Dr. Alaeddin Yavaşca State Hospital, Kilis, Türkiye
[3]Department of Emergency, Midyat State Hospital, Mardin, Türkiye
[4]Department of Emergency, Kırsehir Training and Research Hospital, Kırşehir, Turkey
[5]Department of Internal Medicine, Hitit University Erol Olcok Training and Research Hospital, Corum, Türkiye

Corresponding author:

Burak Çelik

Address:

Kirsehir Training And Research Hospital, Kervansaray, 2019. Sk. No: 1, Özbağ/Kırşehir Merkez/Kırşehir/TURKİYE

E-mail: burakcelik57@gmail.com

Received: 19.10.2022

Accepted: 01.11.2022

Cite as: KARACA.B et al. An example from non-traumatic emergency patient group in a post-conflict low-income region: Dialysis patients applying to the emergency department in northwest Syria IJCMBS 2023;3(1):19-24 doi.org/ 10.5281/zenodo.7556471

Abstract

Background: In this study, we aimed to investigate the demographic characteristics, comorbidities and reasons for applying to emergency dialysis in Syrian hemodialysis patients who applied to the emergency department.

Material Method: This study was conducted at Azez Vatan and Marea Hospitals in northwestern Syria. This study included end-stage renal failure (ESRD) patients and underwent emergency hemodialysis as a result of emergency department visits between January 1, 2022, and March 31, 2022. Demographic data, vital signs, laboratory results, concomitant diseases, and indications for emergency dialysis were investigated retrospectively and analyzed statistically.

Results : In this study has been detected that the mean age of the participants was 58 years and 34 (59.6%) of the patients were male and 23 (40.4%) were female. The patients who received two dialysis sessions per week older the patients who received three dialysis sessions per week (p=0.030). The presence of hypertension was found to be significantly higher in patients who received three sessions per week (p=0.004). Emergency dialysis was performed in 26.3% of patients due to hypervolemia, in 14.1% due to hyperkalemia, in 29.8% due to uremic findings, and in 29.8% due to metabolic acidosis. When the laboratory parameters have been investigated only sodium values were found to be significantly higher in patients who received two sessions of hemodialysis (p=0.004).

Conclusion: It may suggest that further increasing the hemodialysis service in northwest Syria may contribute to reaching the peak benefit to decrease the emergency dialysis patients.

Keywords: emergency department, hemodialysis, post-conflict area, Syria

ÖZ

Amaç: Bu çalışmada acil servise başvuran Suriyeli hemodiyaliz hastalarının demografik özelliklerini, böbrek yetmezliği nedenlerini, komorbiditelerini ve acil diyalize başvurma nedenlerini araştırmayı amaçladık.

Materyal ve Metod: Bu çalışma kuzeybatı Suriye'deki Azez Vatan ve Marea Hastaneleri'nde yürütülmüştür. Bu çalışmaya 1 Ocak 2022 - 31 Mart 2022 tarihleri arasında acil servise başvuran ve acil hemodiyaliz uygulanan son dönem böbrek yetmezliği (ESRD) hastaları dahil edildi. Demografik veriler, vital bulgular, laboratuvar sonuçları, eşlik eden hastalıklar ve acil diyaliz endikasyonları retrospektif olarak incelendi ve istatistiksel analizleri yapıldı.

Bulgular: Bu çalışmada katılımcıların yaş ortalamasının 58 olduğu ve hastaların 34'ünün (%59,6) erkek, 23'ünün (%40,4) kadın olduğu saptandı. Haftada iki diyaliz seansı alan hastalar, haftada üç diyaliz seansı alan hastalardan daha yaşlıydı (p=0,030). Haftada üç seans alan hastalarda hipertansiyon varlığı anlamlı olarak yüksek bulundu (p=0,004). Hastaların %26,3'üne hipervolemi, %14,1'ine hiperkalemi, %29,8'ine üremik bulgular ve %29,8'ine metabolik asidoz nedeniyle acil diyaliz uygulandı. Laboratuvar parametreleri incelendiğinde iki seans hemodiyaliz alan hastalarda sadece sodyum değerleri anlamlı olarak yüksek bulundu (p=0,004).

Sonuç: Kuzeybatı Suriye'de hemodiyaliz hizmetinin daha da artırılması, acil diyaliz hastalarını azaltmaya katkı sağlayabilir.

Anahtar Kelimeler: Acil servis, çatışma sonrası bölge, hemodiyaliz, Suriye

Highlights

- The emergency dialysis patients from Northwest Syria who received two dialysis sessions per week were older than the patients who received three times.
- The emergency dialysis patients who received three sessions per week in northwest Syria have more hypertension comorbidity.
- Metabolic acidosis and uremic findings are more frequent indications for emergency dialysis than hypervolemia and hyperkalemia in a post-conflict area like Northwest Syria.
- The sodium values of the patients who received two sessions of dialysis in emergency dialysis patients were higher than those who received three sessions of hemodialysis.

Introduction

Chronic renal failure (CRF) has become a public health problem with increasing prevalence worldwide. During disease progression and treatment, quality of life is significantly affected, and treatment costs are gradually increasing (1). Renal replacement therapies (RRT) are used in patients with CRF. RRT methods include hemodialysis, peritoneal dialysis, and kidney transplantation (2). According to reports from the European Renal Association-European Dialysis and Transplant Association (ERAEDTA), 81,714 RRTs were initiated for CRF in 2018, representing an incidence rate of 129 per million population (3).

Although hospitalization rates for patients with end-stage renal failure (ESRF) have decreased in recent years, emergency department visits have increased. The reason for this may be the increase in the duration of observation in the emergency department. Renal failure patients are about eight times more likely to be admitted to the emergency department compared with the general population (4). Repeated visits of dialysis patients to the emergency department cause unnecessary healthcare costs and disrupt the planning of treatment services (5). According to a study conducted in the United States of America, spending on dialysis patients is approximately $36 billion annually and accounts for 7.2% of all healthcare spending (6).

Treating ESRD patients requires trained healthcare workers, various medications, and advanced technology medical equipment. Wars make access to all these medical needs impossible or difficult (7). Therefore, an increase in the number of dialysis patients admitted to emergency departments is inevitable in countries where there is war or civil unrest and no regular health care. According to the United Nations Office for the Coordination of Humanitarian Affairs, the ongoing conflict in Yemen since March 2015 has had a serious negative impact on hospital dialysis centers. The number of dialysis sessions in hospitals has been significantly reduced to one session every two weeks, and the duration of sessions has been reduced from five to three hours (8).

In regions where civil unrest continues after the war, such as northern Syria, attempts are being made to address most of the problems of this patient group palliatively with emergency services. There are no studies in the literature on dialysis patients' emergency department visits in northern Syria after the civil war. Identifying these patient profiles could help reduce emergency department visits and the need for acute medical care. This could guide health services in similar regions. In this study, we aimed to investigate the demographic characteristics, comorbidities, and reasons for applying to emergency dialysis in Syrian hemodialysis patients who applied to the emergency department.

Materials and Methods

Study Design

This study was conducted at Azez Vatan Hospital and Marea Hospitals in northwestern Syria, where Turkey provides consultation services. This study included 57 ESRD patients who were routinely undergoing hemodialysis and underwent emergency hemodialysis as a result of emergency department visits between January 1, 2022, and March 31, 2022. The patients' data were retrospectively analyzed. Approval was also obtained from the administrations of the hospitals concerned and Ethics committee approval was obtained from the Hatay Mustafa Kemal University Non-Interventional Research Ethics Committee (Meeting date: 30.06.2022 and Decision number: 04).

Location of the study

There are hospitals in northern Syria where Turkey provides consultation services. Syrian doctors, nurses, other medical professionals, and support staff work in these hospitals. The population living in the region receives services from these hospitals. This study was conducted at Azez Vatan Hospital and Marea Hospital in Northern Syria.

Azez Vatan Hospital: Azez is a city south of Kilis, on the border with Turkey. It has about 300 thousand inhabitants and part of the population lives in tent cities. Azez Vatan Hospital is located in the west of the city

and has a capacity of 186 beds. It has specialized departments such as the general intensive care unit, pediatric intensive care unit, neonatal intensive care unit, and dialysis unit (9,10). It has 6 hemodialysis machines and regularly provides dialysis services for patients with end-stage renal failure (10).

Marea Hospital: The city of Marea is located in the south of Kilis province and currently has a population of approximately 50,000. Marea Hospital has a capacity of 75 beds and has specialized departments such as the general intensive care unit, neonatal intensive care unit, and dialysis unit. The dialysis department treats ESRD patients with 13 hemodialysis machines (11).

Selection of patients

Among routine hemodialysis patients admitted to the emergency department, patients aged 18 years and older who underwent emergency hemodialysis were included in the study. Patients with missing data and patients younger than 18 years were excluded from the study.

Obtaining the data

Demographic data, vital signs, laboratory results, concomitant diseases, and indications for emergency dialysis were obtained from previously prepared patient record forms.

Statistics

Statistical analyzes for the study were performed using Statistical Package for Social Sciences version 28.0 software for Windows (IBM SPSS Statistics for Windows, version 28.0. Armonk, NY: IBM Corp., USA). Normality assumptions for the quantitative variables were made using Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics of the variables are reported as mean∓standard deviation, median (min-max), and n(%). The chi-square test, Fisher's exact test, Mann-Whitney U test, Kruskal-Wallis test, and independent t-test were used depending on the type of variables and whether the assumptions were met.

Results

A total of 57 subjects participated in the study. 34 (59.6%) of the patients were male and 23 (40.4%) were female. The mean age of the participants was 58 years, the youngest was 18 years old, and the oldest was 85 years old. The difference between the mean age of patients who received 2 dialysis sessions per week and the mean age of patients who received 3 dialysis sessions per week was statistically significant (p=0.030). The mean age of patients who received 2 sessions per week was higher (Table 1). Among male patients, 19 (55.9%) received 2 dialysis sessions per week and 15 (44.1%) received 3 dialysis sessions per week. Among female patients, 14 (60.4%) received 3 dialyzes 9 and (39.1%) received 2 sessions per week. The association between the number of hemodialysis visits and gender was not statistically significant (p=0.215).

Table 1: Mean and median ages according to the number of weekly hemodialysis sessions

	Total	**2 Sessions/Week (n=28)**	**3Sessions/Week (n=29)**	**p**
Age	52.61±16.57 58 (18-85)	56.32±17.79 62 (18-85)	49.03±14.73 50 (24-75)	0.030*

*: Mann Whitney U test

When the comorbidities of the patients were analyzed, 64.9% had hypertension (HT), 45.6% (n=26) had diabetes mellitus (DM), and 3.5% had congestive heart failure (CHF). When patients who received 2 dialysis sessions per week were compared with patients who received 3 dialysis sessions per week in terms of comorbidity, the presence of HT was found to be significantly higher in patients who received 3 sessions per week (p=0.004). The relationship between the number of sessions and comorbidity is shown in Table 2.

Table 2: The relationship between the number of hemodialysis sessions and comorbidity

	Total	**2 Sessions / Week**	**3 Sessions / Week**	**p**
Diabetes Mellitus	Yes 26 %45,6)	15(%53.6)	11(%37.9)	0.236*
Hypertension	Yes 37(%64.9)	13(%46.4)	24(%82.8)	0.004*
Heart Failure	Yes 2(%3.5)	1(%3.6)	1(%3.4)	1.000#

*: Chi Square test, #: Fisher Exact Test

The association between emergency dialysis indications and the number of sessions was not statistically significant (p=0.948). The number of weekly dialysis sessions did not affect the indications for emergency hemodialysis. Emergency dialysis was performed in 29.8% due to uremic findings, in 29.8% due to metabolic acidosis, in 26.3% of patients due to hypervolemia, and in 14.1% due to hyperkalemia (Table 3).

Table 3: Distribution of indications for emergency hemodialysis

	Hypervolemia	Hyperkalemia	Hyperuremia	Met. Acidosis	p
Two Sessions /Week	%53.3 (n=8)	%50 (n=4)	%41.2 (n=7)	%52.9 (n=9)	0.948[#]
Three Sessions /Week	%46.7 (n=7)	%50 (n=4)	%58.8 (n=10)	%47.1 (n=8)	
Total	%26.3 (n=15)	%14.1 (n=8)	%29.8 (n=17)	%29.8 (n=17)	

#: Fisher Exact Test

When various laboratory parameters of the patients were compared between patients who received 2 and 3 weekly hemodialysis sessions, only sodium (Na) values were found to be significantly higher in patients who received 2 sessions of hemodialysis (p=0.004). No statistically significant difference was found in terms of other parameters. When the hemoglobulin values of the patients were examined, the values of both the group receiving 2 sessions (9.75∓1.45 g/dl) and the group receiving 3 sessions (9.98∓ 1.70 g/dl) were below the normal values, but there was no statistically significant difference between the two groups (p=0.588)(Table 4). When the causes of end-stage renal failure were analyzed, no statistically significant difference was found between men and women (p=0.843). In the analysis of mean age by etiology of renal failure, no significant difference was found between groups (p=0.223)

Table 4: The relationship between the laboratory parameters of the patients and the number of hemodialysis sessions

Parameters	2 Sessions / Week	3 Sessions / Week	p#
Hemoglobin (gr/dL)	9.75±1.45 10.20(5.9-11.6)	9.98±1.70 9.80(6.9-13.4)	0.588
Leukocyte (x10^6/L)	7.13±2.68 6.75(3.60-13.20)	7.21±2.37 6.56(4.10-12.81)	0.684
Platelets (x10^6/L)	200.50±58.47 191.50(99.0-322.0)	190.22±83.50 192.0(2.43-408.0)	0.594
Glucose (mg/dL)	132.33±76.61 102.0(55.0-431.5)	152.91±129.50 110.0(52.0-713.0)	0.719
Urea (mg/dL)	179.60±58.32 166.5(88.0-307.0)	161.35±45.38 148.0(83.0-261.0)	0.192
Creatinine (mg/dL)	7.36±2.39 7.34(2.92-12.80)	8.48±2.64 8.36(4.77-13.50)	0.098
Na (Sodium) (mmol/L)	139.46±3.45140.0(133. 0-147.0)	136.13±4.72 137.0(122.0-143.0)	0.004
K (Potassium) (mmol/L)	4.90±0.83 4.73(3.66-6.70)	5.02±0.63 4.93(3.83-6.40)	0.541
Ca (Calcium) (mmol/L)	8.09±1.14 7.94(6.37-10.89)	8.27±0.89 8.38(5.99-9.80)	0.514
P (phosphor)(mmol/L)	5.11±1.78 5.67(1.13-7.37)	5.89±1.18 6.0(3.07-7.60)	0.056
Alanine aminotransferase (U/L)	17.85±11.52 15.2(7.0-57.0)	16.51±9.15 15.0(6.0-46.6)	0.604
Aspartate aminotransferase (U/L)	17.96±14.64 14.0(5.0-71.0)	17.79±11.47 14.80(7.0-53.7)	0.731

#: Fisher Exact Test

Discussion

In this study, emergency admissions of chronic kidney failure patients in a post-conflict region in northwest Syria were evaluated. HT was the most common comorbidity in these patients, while metabolic acidosis and uremic findings were found to be the most common emergency dialysis indications.

Since the routine use of hemodialysis treatment in the 1940s, a significant increase in life expectancy has been observed in ESRD patients (12). As the survival rate of ESRD patients has increased, so has the number of patients undergoing routine hemodialysis. With this increase, the number of hemodialysis centers has also increased, and guidelines for hemodialysis have been established and attempts have been made to facilitate patient follow-up through regular updates of the guidelines (13). A reputable technical infrastructure and the presence of trained personnel are essential for hemodialysis centers. Access to trained personnel and technical

infrastructure can be easily damaged during natural disasters and war. There is not much information in the literature on how ESRD patients are affected in war zones (14).

This study analyzed data from 57 routine hemodialysis patients aged 18 years and older who underwent emergency hemodialysis after being admitted to the emergency departments of the hospitals. Of the patients included in this study, 59.6% were male and 40.4% were female. In a study by Aktepe et al, who examined patients with hemodialysis indication in the emergency department, 37.9% of patients were female and 62.1% were male, which is parallel to this study (2). Similarly, in a study by Özpolat et al. that examined patients with emergency hemodialysis indications in the emergency department, 56.6% of patients were male and 43.4% were female. (15). Of the patients included in this study, 64.9% had HT, 45.6% had diabetes mellitus, and 3.5% had CHF. In a study by Gülle et al. that investigated the need for emergency hemodialysis in routine hemodialysis patients, 63.1% had HT, 47.1% of patients had DM, and 33% had CHF (16). In a study by Özpolat et al, 66.3% had HT, 47.6% of dialysis patients had DM, and 37.1% had cardiac disease (15). In a study by Kaplan et al., 35% of dialysis patients most commonly had HT, and secondly, 27% had DM (17). Similarly, HT and DM were the most common comorbidities in three studies.

Of the patients enrolled in this study, 28 (49.1%) received 2 hemodialysis sessions per week and 29 (50.9%) received 3 sessions per week. In a study conducted by Gürsu et al. evaluating Syrian refugees living in Turkey who received routine hemodialysis, the proportion of patients who received 3 sessions per week was 91.9%, which is different from this study (18). In a study conducted by Isreb et al. on Syrian refugee hemodialysis patients living in Jordan, the rate of patients receiving 3 sessions of hemodialysis per week was approximately 57%, which is similar to this study (19). When the indications for hemodialysis of the patients in this study were investigated, 29.8% of patients were admitted for emergency hemodialysis due to metabolic acidosis, 29.8% due to uremic findings, 26.3% due to hypervolemia, and 14.1% due to hyperkalemia symptoms. In the study by Gülle et al, the indications for emergency hemodialysis were 31.8% hypervolemia, 22.7% hyperkalemia, 21% uremic findings, and 19.2% metabolic acidosis, and their rates were not parallel with this study (16). When the indications for emergency hemodialysis in routine hemodialysis patients were examined in the study by Özpolat et al, hypervolemia ranked first at 53.1% and metabolic acidosis ranked last at 4.1% (15). This study differs from this study in terms of emergency hemodialysis indications. In addition, the indications for emergency hemodialysis were compared between patients who received 2 sessions per week and patients who received 3 sessions per week in this study, and no statistically significant result was found. When we looked at the literature, we could not find any relevant data. Various laboratory parameters of patients were compared between patients who received 2 and 3 dialysis sessions per week, and it was found that only sodium levels (Na+) were significantly higher in the group of patients who received 2 dialysis sessions. No relevant data could be found in the literature. No statistically significant difference was found in the other parameters. Hemoglobin level was 9.75∓1.45 gr/dl in the group receiving 2 sessions per week and 9.98∓1.70 gr/dl in the group receiving 3 sessions per week. There was no statistically significant difference between the two groups, and the values were lower than in healthy subjects. Anemia is commonly observed in patients with renal failure. The most important reason is erythropoietin deficiency. In addition, hemorrhage, hemolysis, chronic inflammation, and shortening of erythrocyte life span due to oxidative stress are other causes of anemia (20).

Conclusion

In a post-conflict region such as northwest Syria, patients with chronic renal failure present to the emergency department. It was observed that patients who applied to the emergency department twice a week had less hypertension and were older. Geriatric patients may be receiving dialysis in fewer numbers due to difficulties in accessing dialysis in post-conflict areas, and these patients with more comorbidities may have a shorter life expectancy. It may suggest that further increasing the hemodialysis service in northwest Syria may contribute to reaching the peak benefit.

Acknowledgments: *The authors would like to thank Prof. Dr. Özkan GORGULU (Kırşehir Ahi Evran University, Faculty of Medicine, Biostatistics and Medical Informatics Department) for his assistance in the statistical analysis of the study*

Ethical Approval: *Permission was obtained from Hatay Mustafa Kemal University Non-Interventional Research Ethics Committee (2022/30-6 Decision number:04).*

Author Contributions: *Concept: BK, MT, HG, BÇ, MÇ Literature Review: BK, MT, HG, BÇ, MÇ Design: BK, MT, HG, BÇ, MÇ. Data acquisition: BK, MT, BÇ, MÇ Analysis and interpretation: BK, MT, HG, BÇ, MÇ Writing manuscript: BK, MT, HG BÇ, MÇ Critical revision of manuscript: BK, MT, HG, BÇ, MÇ*

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

Financial Disclosure: *Authors declared no financial support.*

References

1. Foley RN, Wang C, Ishani A, et al. NHANES III: influence of race on GFR thresholds and detection of metabolic abnormalities. Journal of the American Society of Nephrology. 2007;18(9), 2575-82.
2. Aktepe M, Akdeniz YS, İpekci A, et al. Acil Serviste Hemodiyaliz Endikasyonu Konulan Hastaların Analizi. Phoenix Medical Journal. 2020;2(3), 145-51.
3. Kramer A, Boenink R, Stel VS, et al. The ERA-EDTA registry annual report 2018: a summary. Clinical Kidney Journal, 2021;14(1), 107-23.
4. Han G, Bohmart A, Shaaban H, et al. (2021). Emergency Department Utilization Among Maintenance Hemodialysis Patients: A Systematic Review. Kidney medicine.
5. Loran MJ, McErlean M, Eisele G, et al. The emergency department care of hemodialysis patients. Clinical Nephrology. 2002;57(6), 439-43.
6. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2019 Annual Data Report: epidemiology of kidney disease in the United States. Am J Kidney Dis. 2020;75(1 suppl 1):S1–S64.
7. Vanholder R, Gallego D, Sever MS. Wars and kidney patients: a statement by the European Kidney Health Alliance related to the Russian-Ukrainian conflict. Journal of Nephrology. 2022;1-4.
8. Official Website of Office for the Coordination of Humanitarian Affairs. 'Yemen's Dialysis patients fear for their lives amid medical shortages'. (Cited: 19 Jan 2017) Available from: https://www.unocha.org/story/yemen%E2%80%99s-dialysis-patients-fear-their-lives-amid-medical-shortages. (Date of access:18.11.2022)
9. Karaca B, Çelik B. (2022). Can 4C Score Predict Mortality due to COVID-19 Pneumonia in Syria? An Observational Study. Southern Clinics of Istanbul Eurasia, 33(3).
10. Kilis İl Sağlik Müdürlüğü Suriye Görev Gücü Başkanlığı [homepage on the Internet] Azez Vatan Hastanesi [updated 14 Apr 2021; cited 18 Nov 2022]. Available from: https://kilissgg.saglik.gov.tr/TR,69179/azez-vatan-hastanesi.html#
11. Kilis İl Sağlik Müdürlüğü Suriye Görev Gücü Başkanlığı [homepage on the Internet] Marea Hastanesi [updated 14 Apr 2021; cited 20 Nov 2022]. Available from: https://kilissgg.saglik.gov.tr/TR-69176/mare-hastanesi.html#
12. US Renal Data System. (2013). USRDS 2013 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Digestive and Kidney Diseases, Vol. 2014.
13. Daugirdas JT, Depner TA, Inrig J, et al. KDOQI clinical practice guideline for hemodialysis adequacy: 2015 update. American Journal of Kidney Diseases. 2015;66(5), 884-930.
14. Sekkarie MA, Zanabli AR, Rifai AO, et al. The Syrian conflict: assessment of the ESRD system and response to hemodialysis needs during a humanitarian and medical crisis. Kidney International. 2015;87(2), 262-5.
15. Özpolat Ç, Altunbaş E. Retrospective Analysis of Patients with Emergency Hemodialysis Indication in the Emergency Department. Anatolian Journal of Emergency Medicine. 2022;5(3), 124-7.
16. Gülle S, Yıldırım M, Karakaş B, et al. Evaluation of Urgent Hemodialysis in Maintenance Hemodialysis Patients: A 2-Year Retrospective Single Center Study. Turkish Nephrology, Dialysis and Transplantation Journal, 2016;25(3), 289-95.
17. Kaplan NB., Arık N. (2022). Evaluation of polypharmacy and adherence to the phosphorus binding treatment in hemodialysis patients: Evaluation of polypharmacy and adherence in hemodialysis patients. International Journal of Current Medical and Biological Sciences, 2(3), 157-64.
18. Gursu M, Arici M, Ates K, et al. Hemodialysis experience of a large group of Syrian refugees in Turkey: all patients deserve effective treatment. Kidney and Blood Pressure Research. 2019;44(1), 43-51.
19. Isreb MA, Kaysi S, Rifai AO, et al. The effect of war on Syrian refugees with end-stage renal disease. Kidney International Reports. 2017;2(5), 960.
20. Aydın Z, Gürsu M, Uzun S, et al. (2012). Evaluation of the Relationship of Hepcidin Levels with Anemia and Inflammatory Markers in Patients on Peritoneal Dialysis: A Controlled Study. Turkish Nephrology, Dialysis and Transplantation Journal. 2012;21(1), 66-71.

IJCMBS

THE INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND BIOLOGICAL SCIENCES e-ISSN: 2791-8815

Orgınal Article

Investigation of the Effects of Cyclooxygenase I and Cyclooxygenase II Inhibitors on Angiogenesis in a Random-Pattern Rat Abdominal Skin Flap

Random Bazlı Sıçan Karın Derisi Flebinde Siklooksijenaz 1 ve Siklooksijenaz 2 İnhibitörlerinin Anjiyogenez Üzerine Etkilerinin Araştırılması

Ayhan Sönmez[1], Tekin Şimşek[2]

[1] Department of Plastic Reconstructive and Aesthetic Surgery, Samsun Education and Research Hospital, Samsun, Türkiye
[2]Department of Plastic Reconstructive and Aesthetic Surgery, 19 Mayıs University, Samsun, Türkiye

Corresponding author:

Dr. Ayhan Sönmez

Adress:

Samsun Eğitim ve Araştırma Hastanesi Plastik , Rekonstrüktif ve Estetik Cerrahi Departmanı, Samsun, Türkiye

E-mail:

sonmezayhan19@gmail.com

Received: 14.12.2022

Accepted: 29.01.2023

Cite as: Sonmez A, Şimşek T. Investigation of the Effects of Cyclooxygenase I and Cyclooxygenase II Inhibitors on Angiogenesis in a Random-Pattern Rat Abdominal Skin Flap IJCMBS 2023;3(1):24-32 doi.org/ 10.5281/zenodo.7581676

Abstract

Background: Cyclooxygenase (COX) inhibiting agents are already in use before, during and after flap surgery due to their analgesic and anti-inflammatory properties and they are known to improve flap viability. We have investigated the influence of COX1 and COX2 inhibitor drugs in the neoangiogenesis of random pattern flaps.

Methods: Forty-eight rats were divided into 4 groups and their lateral based inguinal flaps measuring 3x3 cm were used as the experimental flap models. Group 1 was the control group so no agents were administered. In groups 2, 3 and 4; Celecoxib (selective COX2 inhibitor), Metamizole Sodium (nonselective COX1 and COX2 inhibitor) and Paracetamol (selective to COX2 in the periphery) were administered, respectively. Clinical observations, radiological studies and histopathological analyses were undertaken in order to demonstrate and compare the individual agents' influence in flap viability and neoangiogenesis. **Results:**Groups 2 and 4 displayed lesser neoangiogenesis when compared with the control group by the end of the first week. The vessel intensities of groups 3 and 1 were not significantly different at the end of the first week; however, by the end of the third week, group 3 yielded a significantly better neoangiogenesis rate ($p<0,05$). Metamizole sodium is proven to significantly enhance vascularization by the end of 3 weeks.

Conclusion: This study has shown that Metamizole Sodium, a collectively inhibiting COX1 and COX2 significantly improves flap vascularity, and when postoperative analgesia is required following a flap surgery, it is a suitable drug of choice.

Keywords: Random pattern flap, Neoangiogenesis, Celecoxib, Paracetamol, Metamizole Sodium

ÖZ

Giriş: Siklooksijenaz (COX) inhibe edici ajanlar, analjezik ve antiinflamatuar özellikleri nedeniyle flep cerrahisi öncesinde, sırasında ve sonrasında sıkça kullanılmaktadır ve onların flep viabilitesini etkilediği bilinmektedir. Biz çalışmamızda random paternli flep beslenmesi üzerine COX-1 ve COX–2 inhibisyonu yapan ilaçların etkilerini araştırırdık.

Materyal ve Metot: 48 rat 4 gruba ayrıldı ve lateral tabanlı 3x3 cm boyutlarındaki inguinal flepler deneysel flep modeli olarak kullanıldı. Birinci deney grubu kontrol grubu olduğundan dolayı herhangi bir ilaç kullanılmadı. Sırasıyla 2. 3. ve 4. gruplarda Selekoksib (selektif COX–2 inhibitörü), Metamizol Sodyum (COX–1 ve COX–2 nonselektif inhibitörü), Parasetamol (periferal COX–2 selektif inhibitörü) uygulandı. Sonrasında bu belirtilen ajanların flep canlılığı ve neoanjiyogenez üzerindeki etkisini göstermek ve karşılaştırmak için klinik gözlemler, radyolojik çalışmalar ve histopatolojik analizler yapıldı.**Bulgular:** Grup 2 ve 4'te birinci haftanın sonunda kontrol grubuyla karşılaştırıldığında daha az neoanjiyogenez görüldü. Birinci haftanın sonunda grup 1 ve 3'ün damar yoğunlukları arasında anlamlı bir fark yoktu; ancak grup 3'te üçüncü haftanın sonunda neoanjiyogenez açısından anlamlı olarak fark görüldü. ($p<0,05$). Metamizol sodyumun 3 haftanın sonunda vaskülarizasyonu önemli ölçüde arttırdığı gözlendi. **Sonuç:**Bu çalışma COX1 ve COX2'yi birlikte inhibe eden Metamizol Sodyum'un flep vaskülaritesini önemli ölçüde iyileştirdiğini ve bir flep cerrahisini takiben postoperatif analjezi gerektiğinde, tercih edilebilir uygun bir ilaç olduğunu göstermiştir.

Anahtar Sözcükler: Random bazlı flep, Neoanjiogenez, Selekoksib, Parasetamol, Metamizol Sodyum

Highlights

- The objective of flap surgery is to close complex tissue defects with similar tissues in a functional and aesthetically pleasing manner and with minimal donor area deformity
- Analgesic and antiinflammatory drugs are frequently used during the perioperative period in patients undergoing flap repair.
- A common feature of most NSAIDs is that they inhibit cyclooxygenase (COX)-1 and COX-2 enzymes, which catalyze the formation of prostaglandins and some other eicosanoids from arachidonic acid in tissues.
- In this experimental study MS did not affect neoangiogenesis in the seventh day but significantly increased it in the twenty- first day.
- Non-selective NSAIDs should be preferred in patients who have undergone flap surgery, especially in delayed flap surgery, if there is no contraindication.

Introduction

Flaps are frequently used in plastic surgery in the reconstruction of tissue defects to achieve the most appropriate functional and aesthetic result. The objective of flap surgery is to close complex tissue defects with similar tissues in a functional and aesthetically pleasing manner and with minimal donor area deformity (1,2).

Flap surgery is constantly evolving, and new approaches are being introduced. So far, experimental studies have focused on the effects of delayed procedures, microsurgical methods of additional arterial and vein anastomoses, physical applications, anticoagulants, antiadrenergic drugs, sympathetic receptor blockers, vasodilating drugs acting directly on smooth muscles, agents that change the rheological properties of blood, and agents that increase ischemia tolerance on skin flap viability (3).

Analgesic and antiinflammatory drugs are frequently used during the perioperative period in patients undergoing flap repair. A common feature of most NSAIDs is that they inhibit cyclooxygenase (COX)-1 and COX-2 enzymes, which catalyze the formation of prostaglandins and some other eicosanoids from arachidonic acid in tissues (3-8).

In the present study, the selective COX-2 inhibitor celecoxib, metamizole sodium (MS), which non-selectively inhibits COX-1 and COX-2, and paracetamol, which is used non-selectively but is selective for COX-2 enzyme in the periphery, were used to investigate the effects on angiogenesis in the random-pattern flap model.

The effects of celecoxib, MS, and paracetamol on neoangiogenesis were compared based on clinical, radiological, and pathological findings in a random-pattern skin flap model. The aim of the study was to recommend or not recommend different drug treatments during flap surgery depending on the positive or negative effects of different antiinflammatory drugs on the random-pattern flap.

Materials and Methods

Approval for this study was obtained from the Animal Care and Ethics Committee of 19 Mayıs University (HADYEK-PYO.TIP.1904.12.009). A total of 48 adult female Sprague–Dawley rats weighing 200–250 grams were used. All the rats were kept in the same room and fed the same diet.

Anesthesia was induced in rats via intraperitoneal administration of Ketamine HCl 75 mg/kg and xylazine 0.2 mL/kg. The animals were placed in the supine position, and their abdominal wall hair was shaved. Flap dimensions were drawn with a skin pen. A 3 x 3 cm rectangular flap was designed

in the left inguinal region of the rat with a lateral base distally parallel to the midline and top and bottom borders 90 degrees to this line **(Figure 1)**. After drawing the flap, the surgical area was stained with povidone–iodine solution. The surgical procedure was started after proper surgical dressing was done. Superficial epigastric artery and the descending branches of lateral thoracic artery were cut to make the flap random-based.

Figure 1. **A)** Photo of flap design. **B)** Photo of flap dissection

For 7 and 21 days, orogastric gavage was used to administer 50 mg/kg/day of celecoxib in distilled water, 100 mg/kg/day of MS in distilled water, and 200 mg/kg/day of paracetamol dimethyl sulfoxide solution (9-11). The rats were divided into four main groups. Each group was further divided into two (7 and 21 days).

Group 1a (Control Group): A random-pattern abdominal flap was performed without the use of any medical agents. Rats were monitored for 7 days.

Group 1b (Control Group): A random-pattern abdominal flap was performed without the use of any medical agents.Rats were monitored for 21 days.

Group 2a (Celecoxib Group): Starting 1 day before the operation, a single daily dose of 50 mg/kg of celecoxib was given in distilled water for 7 days, followed by the application of a random-pattern abdominal skin flap.

Group 2b (Celecoxib Group): Starting 1 day before the operation, a single daily dose of 50 mg/kg of celecoxib was administered for 21 days, followed by the application of a random-pattern abdominal skin flap.

Group 3a (MS Group): Starting 1 day before the operation, a single daily dose of 100 mg/kg of MS was administered for 7 days, followed by the application of a random-pattern abdominal skin flap.

Group 3b (MS Group): Starting 1 day before the operation, a single daily dose of 100 mg/kg of MS was administered for 21 days, followed by the application of a random-pattern abdominal skin flap.

Group 4a (Paracetamol Group): Starting 1 day before the operation, a single daily dose of 200 mg/kg of paracetamol was administered for 7 days, followed by the application of a random-pattern abdominal skin flap.

Group 4b (Paracetamol Group): Starting 1 day before the operation, a single daily dose of 200 mg/kg of paracetamol was administered for 21 days, followed by the application of a random-pattern abdominal skin flap.

On the 7th and 21st days after surgery, 1 x 1 cm skin specimens were taken from the living part of the flaps of three rats from each group.

The samples were fixed in 10% buffered formalin solution, trimmed after 24 hours, and post-fixed. Samples were evaluated under a Nikon Eclipse E600W light microscope, and microscopic photographs were taken using a Nikon DS Camera Head DS-5M. Hematoxylin-Eosin was used for histopathological evaluation. Immunohistochemical staining was done with CD31.

For angiographic evaluation, the vascular bed was washed with heparinized SF, and a solution containing 75–100 mL of contrast material (lead oxide and gelatin) was given for 3–5 minutes.

It was observed that the solution containing contrast material outflowed from the raised flap edges and the foot incision. Then, the flap pedicle was cut, placed on moist gauze, and wrapped to avoid folding. The samples were then kept in a refrigerator at +4°C for 24 hours. X-rays were taken on a mammography device (Mammo Diagnost UC, Philips, Germany) from a distance of 66 cm under 24 kV and 8 mAs.

The vessel density in the tissues was measured using the “VesSeg Tool” vessel segmentation software program **(Figure 2)**.

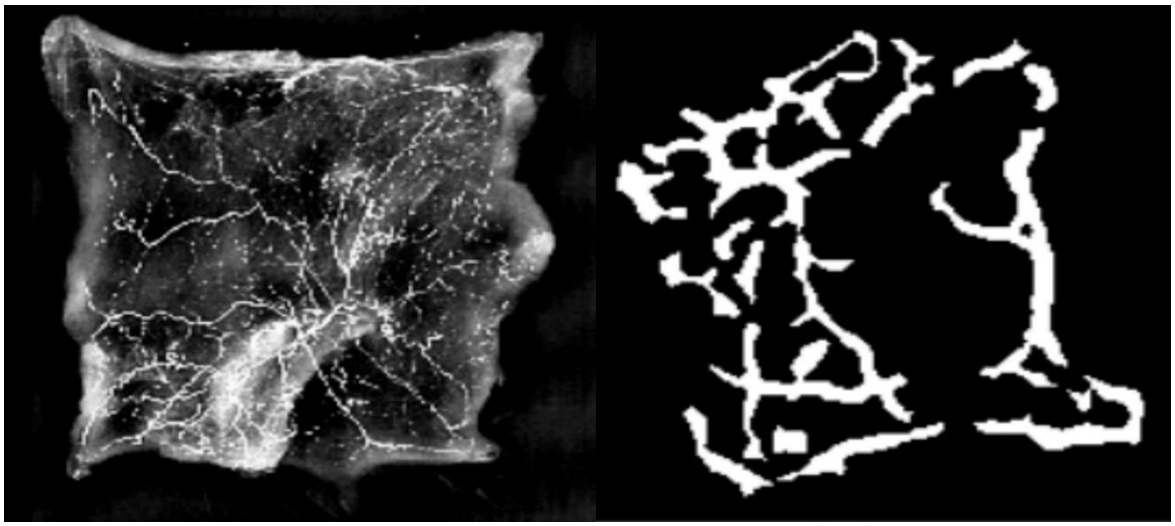


Figure 2. **A)** Photo of microangiography image of the flap of the control group. **B)** Photo of condensed area for pixel analysis

Stastical Analysis

Descriptive statistical analysis of the measurement values was performed using the "VesSeg Tool" vessel segmentation software program. To evaluate the differences between the groups, a factorial analysis of variance organized according to time was performed. The Student's t test was used to compare the effects of drugs over time. Analyses were conducted using the "SAS" statistical package program.

Results

In rats treated with celecoxib, wound dehiscence was more severe after surgery, and when specimens were taken for pathological evaluation after 21 days, excessive seroma accumulation was observed under the flap. Wound healing was rapid and uneventful in all rats treated with metamizole **(Figure 3).**

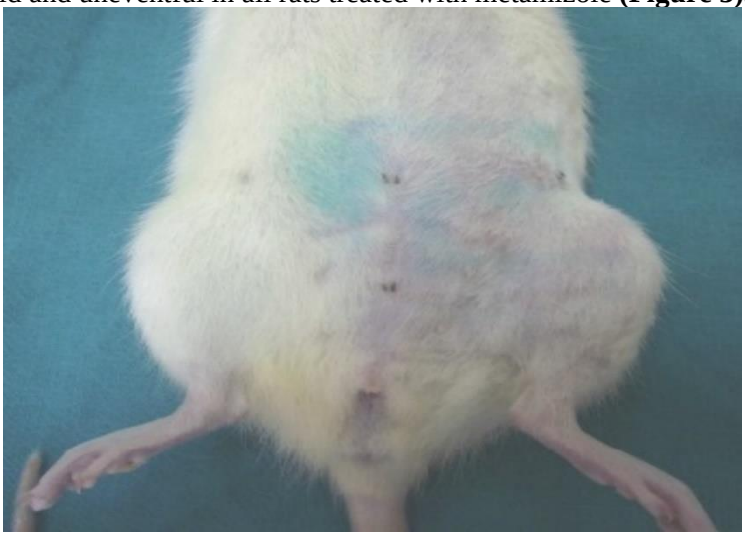
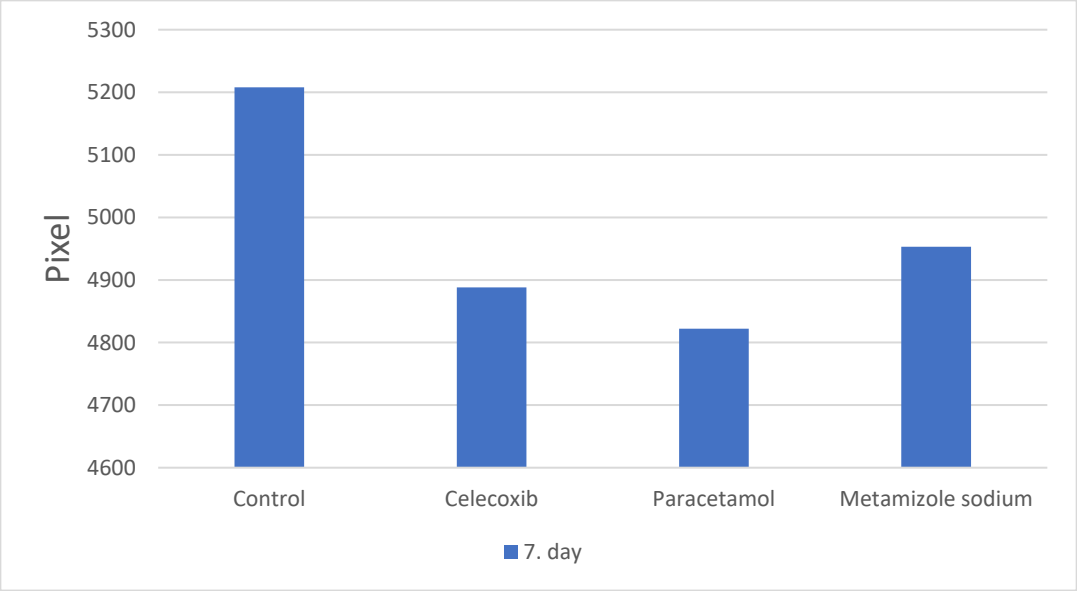


Figure 3. Photo of wound healing in a rat belonging to the Metamizole Sodium group at the end of the 21st day

Comparisons of total area values between groups on day 7:

When the groups were evaluated separately for neoangiogenesis after 7 days of follow-up, no statistically significant difference was found between the MS and control groups ($p > 0.05$, **Table 1**).

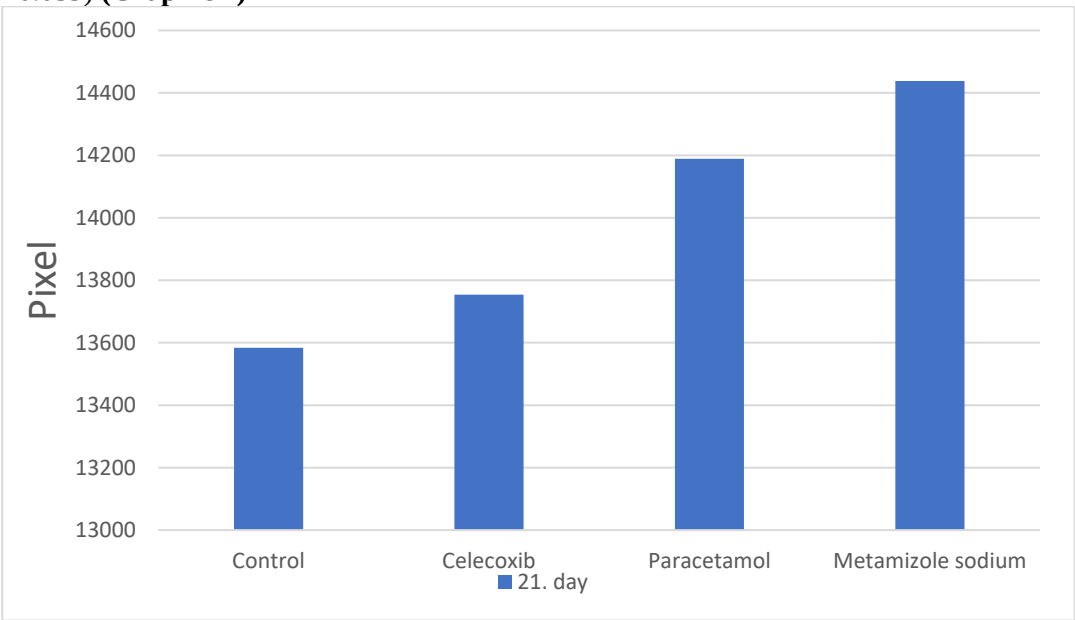
Although not statistically significant, the total vessel area was lower in the celecoxib and paracetamol groups than in the control group ($p > 0.05$, **Graphic 1**).



Graphic 1. Angiogenesis densities between groups on day 7

Comparisons of total area values between groups on day 21:

When the groups were evaluated separately for neoangiogenesis after 21 days of follow-up, a statistically significant difference was found, and vessel formation was increased in the MS group compared to the control group (p = 0.039) **(Graphic 2)**



Graphic 2. Angiogenesis densities between groups on day 21

Table 1. Angiogenesis densities in the experimental groups

Groups	**7th day**				
	Mean Area	Standard Deviation	Min/Max	C.V %	P
Control	5208	75.17	5124-5358	2.5	>0,05
Celocoxib	4888	176.168	4539-50101	6.24	>0,05
Metamizole Sodium	4953	25.67	4902-4980	0.89	>0,05
Paracetomole	4822	102.8	4628-4978	3.69	>0,05
	21st day				

Control	13584	360.14	13158-14300	4.59	>0,05
Celocoxib	13754	566.77	12621-14351	7.13	>0,05
Metamizole Sodium	14438	184.23	14078-14686	2.21	0.039
Paracetomole	14189	210.69	13787-14499	2.57	>0,05

Px: pixel c.v: coefficient of variation

Although not statistically significant, the total vessel area was higher in the paracetamol and celecoxib groups than in the control group ($p > 0.05$) **(Table 1).**

Sections taken on the 7th and 21st days after surgery were evaluated histopathologically in terms of neoangiogenesis and inflammatory cell density.

Inflammatory cell density was scored as 1–10, 11–100, 101–1000, and >1000, and the groups were compared accordingly. Neoangiogenesis was scored as 0–20, 20–40, 40–60, and >60. The "hotspot" method described by Weidner was used for neovascularization (12).

When the groups were compared in terms of neoangiogenesis, it was found that MS did not increase neoangiogenesis compared to the control group at the end of the 1st week, whereas a significant increase was observed at the end of the 3rd week compared to the control group.

On the contrary, celecoxib and paracetamol decreased neoangiogenesis compared to the control group at the end of the 1st week, whereas a slight increase in angiogenesis was observed at the end of the 3rd week compared to the control group (**Graphic 1,2**) **(Figure 4)**

No difference was found between the groups in terms of inflammatory cell density at the end of the 1st week. At the end of the 3rd week, inflammatory cell density was significantly reduced in all groups.

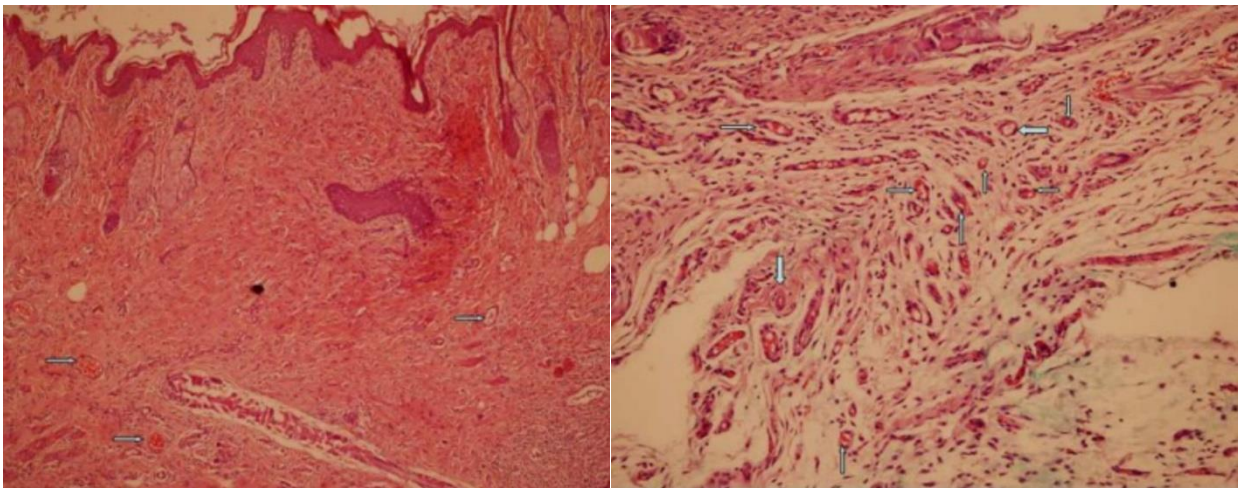


Figure 4. A) Photo of histopathological appearance of a flap in the control group after one week.
B) Photo of histopathological appearance of a flap belonging to metamizole sodium group after 21 days

Discussion

Flap surgery is constantly developing, and new approaches are being introduced. The evidence on the effects of COX-1 and COX-2 inhibitors on flap survival is increasing, but studies investigating the effects on angiogenesis are limited (4).

Repeated interventions may be required when flap necrosis occurs. This increases morbidity, length of hospital stay, and medical costs. Certain surgical and medical applications have been used for a long time to prevent these problems and improve flap success (3).

Most of the medical applications to increase skin flap viability remained in the experimental stage and were not used in routine clinical practice. Random-pattern skin flaps have been generally used in the literature to investigate the effects of medical agents on flap viability. Random-pattern flaps have no known axial vessels and are fed predominantly from the subdermal plexus (3).

The random flap model was used in this experimental study. Using this flap model, the effects of celecoxib, MS, and paracetamol on flap viability and neoangiogenesis were compared based on clinical, radiological, and pathological findings. This will allow us to determine the positive or negative effects of different antiinflammatory drugs on the random flap and to recommend or not recommend different drug treatments.

The mechanism of action of celecoxib depends on the inhibition of prostaglandin synthesis via the inhibition of the COX-2 enzyme. Celecoxib belongs to the group of selective COX-2 inhibitors. In the present study, celecoxib was used with the hypothesis that it would decrease flap viability by reducing neoangiogenesis as a result of inhibiting the COX-2 enzyme in the periphery of random-pattern flaps. When COX-2 is stimulated, the production of epidermal growth factor, vascular endothelial growth factor, and fibroblast growth factor increases (13). Studies on NSAIDs and COX-specific inhibitors showed inhibition of angiogenesis in epithelial tumors (14-16). In another study, Ballerini et al. reported that selective COX-2 inhibitors reduced vascularity, especially in cancerous tissues (17). Mark et al. investigated the effects of COX-2 inhibitors on viability and revascularization of the fasciocutaneous flap. No adverse effects were found on ischemia and flap viability, and it was reported that COX-2 inhibitors had the same effect on flap revascularization as the control group and did not cause flap loss (4). In the present study, celecoxib decreased neoangiogenesis to some extent at the end of the 1st week, but neoangiogenesis was increased at the end of the 3rd week compared to the control group. While reduced angiogenesis in the 7th day is consistent with the literature, it is increased rather than decreased by celecoxib in the 21st day. It can be considered as an option in flap surgery.

Paracetamol causes weaker COX-1 and COX-2 enzyme inhibition than other NSAIDs (16,18). There is no study in the literature investigating the effects of paracetamol on flap viability or revascularization. The difference between paracetamol and celecoxib is that paracetamol only inhibits COX-2 in the periphery. In the present study, paracetamol's effects on neoangiogenesis by inhibiting the COX-2 enzyme in the periphery of random-pattern flaps were the same as those of celecoxib. Similarly to celecoxib, it reduced neovascularization in the 7th day and increased it in the 21st day compared to the control group. Paracetamol, which is used safely in pregnant women, children, and adults, may be an alternative drug for patients undergoing flap surgery.

MS, used in the present study, inhibits the COX enzyme and exerts analgesic, antipyretic, antiinflammatory, and antispasmodic effects. Even though metamizole sodium is commonly used in the clinical aplications, there is no clinical study in the literature about its effect of randomized flap viability. Metamizole sodium is frequently used clinically, although it can cause kidney problems such as fluid and electrolyte disorders, acute renal failure, nephrotic syndrome, tubular necrosis and interstitial nephritis. It has been shown that significant histopathological changes occur in distant organs due to oxidative stress in lower extremity ischemia-reperfusion (19). Side effects of metamizole sodium should be considered in patients undergoing lower extremity surgery. Its analgesic effect is stronger than acetylsalicylic acid. Although the cyclooxygenase inhibitor and antiinflammatory effects of MS are low, it has strong pain-relieving properties (8). MS was used in the present study with the hypothesis that it would increase neoangiogenesis by inhibiting both COX-1 and COX-2 enzymes in random-pattern flaps.

Daniel RK et al. reported that ibuprofen, a non-selective NSAID, increased flap viability in rat skin (3). For flap viability to increase, neoangiogenesis should also increase. The results obtained in the present study showed that MS had no positive or negative effect on neoangiogenesis after the 1st week. However, it significantly increased neoangiogenesis at the end of the 3rd week. The results showed that MS has similar effects to other non-selective COX-inhibiting NSAIDs in terms of neoangiogenesis. These findings are consistent with the literature. Given that MS increases angiogenesis, non-selective antiinflammatory drugs can contribute positively to flap viability by increasing neangiogenesis, especially in delayed flaps. If antiinflammatory drugs are used in patients with flaps, drugs that inhibit COX-1 and COX-2 non-selectively are preferable.

In the present study, all groups had the same inflammatory cell density values as the control group during the acute period. After 21 days, however, all groups had significantly reduced inflammatory cell density.

Conclusion

In this experimental study MS did not affect neoangiogenesis in the seventh day but significantly increased it in the twenty- first day. Non-selective NSAIDs should be preferred in patients who have undergone flap surgery, especially in delayed flap surgery, if there is no contraindication. Effective use of medication can improve flap vitality and help reduce losses and failures after surgery.

Ethical Approval: *Permission was obtained Animal Care and Ethics Committee of 19 Mayıs University (HADYEK-PYO.TIP.1904.12.009).*

Author Contributions: *Concept: AS, TŞ. Literature Review: AS, TŞ. Design: AS, TŞ.. Data acquisition: AS. Analysis and interpretation: AS, TŞ. Writing manuscript: AS. Critical revision of manuscript: TŞ.*

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

Financial Disclosure: *Authors declared no financial support.*

References

1. Geddes CR., Morris SF., Neligan PC. Perforator flaps evolution, classification, andapplications. Ann Plast Surg. 2003; 1:90-9.
2. Rahpeyma A, Khajehahmadi S. Submental flap donor site morbidity in pediatric patients. Int J Otorhinolaryngol. 2018:113-305
3. Daniel RK, Kerrigan CL. Principles and physiology of skin surgery. In: McCarthy JG. (Ed). Plastic Surgery. Philadelphia. WB Saunders, 1990: 275-328.
4. Mark K. Wax, Douglas D. Reh, Melissa M. Levack. Effect of Celecoxib on Fasciocutaneous Flap Survival and Revascularization. Arch Facial Plast Surg. 2007:9:120-24.
5. Sade A, Tunçay S, Cimen I, et al. Banerjee S. Celecoxib reduces fluidity and decreases metastatic potential of colon cancer cell lines irrespective of COX-2 expression. Biosci Rep. 2012; 2:35-44
6. Gelincik A, Büyüköztürk S, İşsever H, et al. Analjezik intoleransında parasetamol ve propifenazonun yeri. Asthma Allergy Immunol 2009; 7:32-8
7. Arslan Y. Koroner Arter Baypas Cerrahisi Sonrası Parasetamol, Diklofenak Sodyum ve Tramodolün Postoperatif Analjezide Kullanımı. (Uzmanlık Tezi, Tez danışmanı: Aykaç Z). İstanbul – 2008
8. Gülmez SE, Serel S, Uluç A, et al. Dipyrone increases the blood flow of arterial dorsal skin flaps. Aesthetic Plast Surg. 2008; 9;:766-70
9. Nıederberger E, Tegeder I, Vetter G, et al. Celecoxib loses its anti-inflammatory efficacy at high doses through activation of NF-kappa B. Faseb J. 2001;15: 1622-24
10. Taylor J, Mellstrom B, Fernaud I, et al. Metamizol potentiates morphine effects on visceral pain and evokedc-Fos immunoreactivity in spinal cord. European Journal of Pharmacology.1998;351:39-47
11. Lavie L. Obstructive sleep apnoea and acetaminophen safety is the liver at risk? Exp Physiol. 2009; 94:199–200
12. Tataroğlu C, Polat, A., Kargı, et al. Kolorektal karsinomlarda invazyon derinliğinin neovaskülarizasyon, peritümöral nk hücresi, makrofaj ve eozinofil lökositlerle ilişkisinin araştırılması. Turk path derg. 2005:21: 49-53
13. Perkins D.J, Kniss DA. Rapid and transient induction of cyclooxygenase 2 byepidermal growth factor in human amnion-derived WISH cells. Biochem J. 1997; 21:677-81
14. Leahy KM, Ornberg R.L, Wang Y, et al. Cyclooxygenase-2 inhibition by celecoxib reduces proliferation and induces apoptosis in angiogenic endothelial cells in vivo. Cancer Res. 2002; 62:625-31
15. Masferrer J.L, Leahy K.M, Koki A.T, et al. Antiangiogenic and antitumor activities of cyclooxygenase-2 inhibitors. Cancer Res. 2000; 60:1306-11
16. Leahy K.M., Koki A.T. Role of cyclooxygenase in angiogenesis. Curr Med Chem. 2000; 7:1163-70
17. Ballerini P, Contursi A, Bruno A, et al. Inflammation and Cancer: From the Development of Personalized Indicators to Novel Therapeutic Strategies. Front Pharmacol. 2022;3;13.
18. Robak J. Adjuvant-induced and carrageenin-induced inflammation and lipid peroxidation in rat liver spleen and lungs. Biochem Pharmacol.1978;27:531-3
19. Büyükfırat E, Aydoğan H, Yalçın Ş, Karahan MA, et al. Comparison of Effects of Dexmedetomidine and Thymoquinone on Kidney at Hind Limb Ischemia - Reperfusion Generated Rats: Effects of Dexmedetomidine and Thymoquinone at Hind Limb Ischemia – Reperfusion Injury. İJCMBS 2022;2(1):30-8.

IJCMBS

THE INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND BIOLOGICAL SCIENCES e-ISSN: 2791-8815

Orgınal Article

The Effect of the SARS-CoV-19 Virus on Sperm Parameters of Patients with Male Infertility

Erkek İnfertilitesi Olan Hastalarda SARS-CoV-2 Virüsünün Sperm Parametreleri Üzerine Etkisi

Eyup Dil[1*]

[1]Department of Urology, Recep Tayyip Erdogan University, Rize, Türkiye

**Corresponding author:*

Eyup Dil

Adress:

Recep Tayyip Erdogan University the Faculty of Medicine, Islampasa, 53020, Rize, Turkiye

E-mail: eyup.dil@erdogan.edu.tr

Received: 27.11.2022

Accepted: 07.01.2023

Cite as: DİL. E The Effect of the SARS-CoV-19 Virus on Sperm Parameters of Patients with Male Infertility IJCMBS 2023;3(1):33-7 doi.org/ 10.5281/zenodo.7581768

Highlights

- Investigate the effects of COVID-19 disease in spermiogram parameters in male infertilitiy.
- SARS-CoV-2 virus can affect male fertility by resulting in deterioration of sperm volume, pH and morphology

Abstract

Background: Although Coronavirus Disease 2019 mainly affects the pulmonary system, the related studies on male reproductive health are limited. We aimed to investigate the effect of COVID-19 disease in spermiogram parameters of patients with male infertility.

Material and Methods: 39 outpatients with male infertility diagnosed with COVID-19 disease between 1st March 2020 and 31st March 2022 in our andrology policlinic were analysed, retropspectively. We evaluated the demographic data of the patients and the spermiogram analyzes before and after the COVID-19 disease.**Results:** The mean age of the patients were 33,44±7,52 years and body mass index (BMI) was 27,05±3,38 kg/m^2. The mean time between PCR test and second semen analysis was 3,95±3,59 months. There were statistically significant reduction in semen volüme ($p<0,03$) and significant deterioration in sperm morphology ($p<0,014$), but no detect alteration on sperm motility.

Conclusion: We observed adversly effects of SARS-CoV-2 virus on spermiogram parameters in patients with male infertility. Deterioration of spermiogram after COVID-19 disease may results with male infertility.

Keywords: Semen, COVID-19, Male infertiliy, SARS-CoV-2, Spermatogenesis

ÖZ

Amaç: Koronavirus hastalığı 2019 (COVID-19) esas olarak pulmoner sistemi etkilemesine rağmen, erkek üreme sağlığı üzerine çalışmalar sınırlıdır. Bizim kliniğimize erkek infertilitesi ile başvuran hastalarda COVID-19 hastalığının (virusunun) sperm parametrelerine etkisini araştırmayı amaçladık.

Gereç ve Yöntem: Bizim androloji kliniğimize 1 Mart 2020 ve 31 Mart 2022 tarihleri arasında başvuran ve daha öncesinde COVID-19 hastalığı tanısı almış 39 erkek infertilite hastası retrospektif olarak analiz edildi. Hastaların demografik verileri, COVID-19 hastalığı öncesi ve sonrası spermiogramları değerlendirildi. Bu verileri kaydettik ve istatistiksel olarak karşılaştırdık.**Bulgular:** Hastaların ortalama yaşı 33,44±7,52 yıl ve vücut kitle indeksi (BMI) 27,05±3,38 kg/m^2 olarak saptandı. PCR testi ile ikinci semen analizi arasındaki ortalama süre 3,95±3,59 ay olarak ölçüldü. Semen morfolojinde($p< 0,014$) önemli bozulma ve semen volümünde ($p<0,03$) önemli azalma istatiksel olarak gözlememize rağmen sperm motilitesi açısından anlamlı farklılık saptanmadı.

Sonuç: Erkek infertilite hastalarında spermiogram parametreleri üzerine SARS-CoV-2 virüsünün olumsuz etkisi olduğunu gözlemledik. COVID-19 hastalığından sonra spermiogramdaki bozulma erkek infertilitesi ile sonuçlanabilir.

Anahtar Kelimeler: Semen, COVID-19, Erkek infertilitesi, SARS-CoV-2, Spermatogenez

Introductıon

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and also known as corona virus disease 2019 (COVID-19) is a single strained RNA viruses belong to the coronaviridae family (1) Since it was first seen in Wuhan, China to the July of 2022, ıt has been reported resulting more than 6.5 million deaths and 623 million cases in the World (2). Recently, with increasing knowledge, COVID-19 has been defined as a systemic disease that most commonly affects the lungs, but can also affect more than one organ (3,4). SARS-CoV-2 uses the angiotensin-converting enzyme II receptor (ACE2) to enter the host cell similar to SARS-CoV. Angiotensin converting enzyme 2 (ACE2) is not just an enzyme, but a functional receptor highly expressed in heart, kidney, and lung cells. However, studies have shown that ACE2 receptors are abundantly expressed in spermatogonia, Leydig and Sertoli cells in testis (5,6). Another study showed that COVID-19 disease affect men 2.5 times more than women, and may cause changes in testoterone levels (7). Therefore, the human testis is a potential target for SARS-CoV-2 infection. The virus can directly damage the organs, as well as it may cause organ failure with systemic effects. In many studies on male infertility, it has been reported that COVID-19 disease may have unfavorable influence on semen parameters (8–12). Although the long-term effects of SARS-CoV-2 on male reproductive health are not known, it is inevitable that it will be an important health problem for humanity (13). There are limited studies on the effects of COVID-19 disease in spermiogram parameters in the literature. Therefore, we aimed to investigate effects of COVID-19 disease on spermiogram parameters in patients who applied our clinic with male infertility.

Materials and Methods

The data of the study were recorded after the ethics committee approval was obtained from the local Non-Interventional Clinical Research Ethics Committee (Decision No: 2022/35, date: 23.02.2022). We designed a single-center, retrospective, cohort study between March 2020 and March 2022. After detailed history and physical examination of patients, sexually active male patients between the ages of 18-50 who diagnosed COVID-19 disease with nasopharyngeal or oropharyngeal swab test and have spermiogram analyses before the diagnosis of COVID-19 disease were included in the study. Second spermiogram tests were performed after COVID-19 disease recovered. Patients' age, body mass index (BMI), semen analysis, and the times between COVID-19 infection and second semen analysis were recorded. Patients younger than 18 years old, older than 50 years old, using medication affecting spermatogenesis, diagnosed with endocrinological disease affecting spermatogenesis, presence of genetic diseases, with gender disorders, history of varicocele or cryptorchidism operations, having only one sample and diagnosed azoospermia according to the spermiogram analyses were excluded from the study. After exclusison criteria, total 39 patients' data recorded and analysed.

Swab samples of all patients were studied by reverse transcription polymerase chain reaction (RT-PCR) method in the medical microbiology laboratory of our university.

Spermiogram analyses

All semen samples obtained by masturbation after at least 2-7 days of sexual abstinence were evaluated in the andrology laboratory of our faculty according to the World Health Organization (WHO) laboratory manual instructions. In the evaluation, first of all, after the semen sample reached the laboratory, it was placed on the shaker to ensure complete liquefaction at room temperature at a certain cycle. After full liquefaction, macroscopic and microscopic examinations were performed by experienced laboratory workers within 30-60 minutes. In macroscopic and microscopic examination, liquefaction, viscosity, color, volume, pH, sperm concentration (10^6/ml), motility (%), round cells and morphology (%) parameters were examined. For the evaluation of sperm concentration and motility, 8-10 µl semen sample was placed in the Makler counting chamber (Sefi Medical Instruments, Israel) and examined under a phase contrast microscope at 100x magnification. Then, diff-quick staining set (bes-quick) was used to evaluate sperm morphology. For evaluation, 200 cells at 1000 x magnification were examined under a phase contrast microscope (Plan Apo 100 x 1.45 Oil; Nikon, Japan). Spermatozoa were classified as having normal or abnormal morphological features according to WHO criteria (14).

Statistical Analyse

SPSS v23.0 statistical package programme was used for all statistical analyses (SPSS, Inc., Chicago, IL). Shapiro-Wilk test was used to evaluate the distrubition of variables. Descriptive statistic methods were evaluated with the mean±standart deviation and median±interquartile range. Student-t paired test was used to compare

the variables with normal distribution before and after the diagnosis of COVID-19 disease, and Wilcoxon signed-rank test was used for variables that did not show normal distribution. $p<0.05$ was considered as criterion for the statistical significance.

Results

Demographic characteristics were shown in Table 1. Mean age of the patients were 33,44±7,52 years and body mass index (BMI) was 27,05±3,38 kg/m^2. The mean time between PCR test and second semen analysis was 3,95±3,59 months. Semen parameters of the participants were summarized on table-2. We observed that sperm volume was decreased ($p<0,03$) and sperm morphology was impaired ($p<0,014$) after COVID-19 disease. Other main semen parameters such as pH and motility was not change after COVID-19 disease.

Table 1. Demografic characteristics of the patients

	Count	Mean	Sd
Age	39	34	7
BMI	39	27.12	3.56
Covid-19 Time(mounth)	39	3.95	3.59

BMI: Body Mass Index Sd: Standard Deviation

Table 2. Semen parameters characteristics of patients according to the spermiograme analyse

	Pre- COVID-19	**Post- COVID-19**	**P**
Semen volume, *mL (mean±Sd)*	4.09±1.91	3.63±1.63	0.030
Semen pH, *mean±Sd.*	7.58±0.37	7.36±0.63	0.049
Total sperm count, *million±Sd*	151.70±148.30	135.53±160.21	0.081
Total sperm motility, *(mean±Sd) %*	33.46±14.74	34.95±15.76	0.488
Progressive sperm motility (a+b), *(mean±Sd) %*	32.26±14.60	32.05±15.86	0.424
Non-progressive sperm motility (c+d), *(mean±Sd) %*	63.74±14.60	65.05±15.76	0.276
Morphologically normal forms, *(mean±Sd) %*	2.97±2.88	2.21±2.37	0.014

Sd: Standard Deviation

Discussion

Today, after the pandemic period, there is a little information about the impact of the SARS-CoV-2 virus on semen. There are limited studies on male infertility after COVID-19 disease. In this study, we observed that SARS-CoV-2 virus can affect male fertility by resulting in deterioration of sperm volume, pH and morphology. When the effects of the SARS-CoV-2 virus on semen parameters in men are examined, it is estimated that the direct effect of the infection and the social restrictions caused by the pandemic process have possible negative psychophysiological effects on male reproductive health (15) It has been shown that many viruses such as mumps virus, herpes simplex virus (HSV), human immunodeficiency virus (HIV), human papilloma virus (HPV), hepatitis B virus, hepatitis C virus and SARS CoV-2 virus adversely affect the male reproductive system and sperm quality (16–18). In studies examining the pathophysiology of viruses on testicles, It has been reported that the direct tissue damage of the virus, the inflammation and temperature increase that develop as a result of the immune response against the virus may damage the testicular tissue (19). We consider that virus may effect testicles by direct tissue damage or inflammation that may result with decreased semen volume and impaired sperm morphology in our study, as well. We could not detect virus directly on semen, because of the design of the study, but our results can support this theory indireclty.

It has been showed that the ACE2 receptor is a functional receptor for coronaviruses to enter the virus into the host and it is also commonly found in spermatogonia, sertoli and Leydig cells (20). Studies on infertile men found high levels of ACE2 receptors and it was stated that this could cause infertility through its activation (21). It has been shown that SARS-CoV-2 virus can be found in the semen of patients with COVID-19, as well as in

the male reproductive system through systemic and local inflammation (22). There is TMPRSS2, which can increase viral transmission through the ACE2 receptor in sperm cells. SARS-CoV-2 abolishes phosphoinocyte 3-kinase and protein kinase B by targeting spike protein at ACE2 receptor, reducing sperm viability by causing sperm apoptosis. In addition, it is thought that the decrease in sperm motility and count may be related to this pathway (23–25). Decreased sperm volume and deteriorated sperm morphology in our study also may be related with these pathways.

Although SARS-CoV-2 RNA was not detected in the semen of patients with acute stage and recovered COVID-19, it caused deterioration in sperm concentration, total sperm count, and total motility in moderately ill patients. It has been found to be associated with a disorder in semen parameters in those with severe disease (26). In another study using data collected from 41 men, a significant decrease was observed in sperm concentration, total sperm count and morphology of patients after COVID-19 infection (27). Erbay G. et al., in their study, divided the patients diagnosed with COVID-19 into mild and moderate severity, and examined the spermiogram tests performed before the disease and at the 3rd month after the disease. It was determined that progressive motile sperm, total motility and vitality were decreased in patients with mild disease. In those with moderate disease, deterioration was observed in all sperm parameters. They observed that there was no difference between the groups with and without fever in the disease (28). Although we could not separate the patients by the severity of the COVID-19 disease, we observed similar results in terms of sperm volume and morphology, but the sperm motility was not affected by the COVID-19 disease in our study.

This study also has some limitations. First, we could not compare the infertile men with healthy men. Deterioration on semen after SARS-CoV-2 virus infection may be different in healthy men. Second, we could not detect SARS-CoV-2 virus mRNA on spermiogram analyses. Detection of SARS-CoV-2 on semen analyse coud be more valuable in terms of the effect on fertility. Despite all this, we think that the results of our study contribute to the studies on the effects of SARS-CoV-2 virus on male infertility.

Conclusıons

Since the COVID-19 disease entered our daily practice with the pandemic, its effects on male reproductive health are not yet well-known. There is a limited number of studies on this subject, and both the literature and the study we conducted show that this disease adversely affects male reproductive health in the short term. Although our study showed negative effects in the short term, long-term follow-up and results of the effects of the disease on male reproductive health are needed.

Acknowledgements: *None*

Ethical Approval: *Permission was obtained from Recep Tayyip Erdogan University Ethics Committee for Non-Interventional Clinical Research Ethics Committee. (2022/35).*

Author Contributions: *Concept: E.D Literature Review: E.D Design: E.D Data acquisition: E.D Analysis and interpretation: E.D Writing manuscript: E.D Critical revision of manuscript: E.D*

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

Financial Disclosure: *Authors declared no financial support.*

References

1. Omolaoye TS, Adeniji AA, Cardona Maya WD, et al. SARS-COV-2 (Covid-19) and male fertility: Where are we? Reprod Toxicol. 2021 Jan 1 ;99:65–70.
2. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data [Internet]. Available from: https://covid19.who.int/
3. Jain U. Effect of COVID-19 on the Organs. Cureus . 2020 Aug 4 ;12(8).
4. Çelik B, Karaca B, ÇELİK Adress B, et al, Hospital Kırşehir R. New regular candidates to the emergency department; lasting symptoms after COVID -19: the example of northwestern Syria. International Journal of Current Medical and Biological Sciences . 2022;2(2):96–102.
5. Yao L, Lu L, Ma W. Immunopathological changes, complications, sequelae and immunological memory in COVID-19 patients. Heliyon . 2022 Apr 1 ;8(4).
6. Beyerstedt S, Casaro EB, Rangel ÉB. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. Eur J Clin Microbiol Infect Dis . 2021 May 1 ;40(5):905–19.
7. Xu J, Zhao S, Teng T, et al. Systematic Comparison of Two Animal-to-Human Transmitted Human Coronaviruses: SARS-CoV-2 and SARS-CoV. Viruses . 2020 ;12(2).
8. Illiano E, Trama F, Costantini E. Could COVID-19 have an impact on male fertility? Andrologia . 2020 Jul 1 ;52(6).
9. Navarra A, Albani E, Castellano S, et al. Coronavirus Disease-19 Infection: Implications on Male Fertility and Reproduction. Front Physiol . 2020 Nov 17;11.

10. Li H, Xiao X, Zhang J, Zafar MI, Wu C, Long Y, et al. Impaired spermatogenesis in COVID-19 patients. EClinicalMedicine [Internet]. 2020 Nov 1 [cited 2022 Oct 21];28. Available from: https://pubmed.ncbi.nlm.nih.gov/33134901/
11. Anifandis G, Messini CI, Daponte A, et al. COVID-19 and fertility: a virtual reality. Reprod Biomed Online [Internet]. 2020 Aug 1 ;41(2):157–9.
12. Dutta S, Majzoub A, Agarwal A. Oxidative stress and sperm function: A systematic review on evaluation and management. Arab J Urol . 2019 Apr 3 ;17(2):87–97.
13. Pan F, Xiao X, Guo J, et al. No evidence of severe acute respiratory syndrome-coronavirus 2 in semen of males recovering from coronavirus disease 2019. Fertil Steril . 2020 Jun 1 [cited 2022 Oct 21];113(6):1135–9.
14. WHO. World Health Organization. WHO laboratory manual for the examination and processing of human semen. 6th ed. World Health Organization, Department of Reproductive Health and Research. Geneva, Switzerland. WHO Press [Internet]. 2021; Available from: https://www.who.int/publications/i/item/9789240030787
15. Temiz MZ, Dincer MM, Hacibey I, et al. Investigation of SARS-CoV-2 in semen samples and the effects of COVID-19 on male sexual health by using semen analysis and serum male hormone profile: A cross-sectional, pilot study. Andrologia . 2021 Mar 1 ;53(2).
16. Batiha O, Al-Deeb T, Al-zoubi E, et al. Impact of COVID-19 and other viruses on reproductive health. Andrologia . 2020 Oct 1 ;52(9).
17. Kharbach Y, Khallouk A. Male genital damage in COVID-19 patients: Are available data relevant? Asian J Urol . 2021 Jul 1 ;8(3):324–6.
18. Xu J, Qi L, Chi X, et al. Orchitis: a complication of severe acute respiratory syndrome (SARS). Biol Reprod . 2006 Feb ;74(2):410–6.
19. Dejucq N, Jégou B. Viruses in the mammalian male genital tract and their effects on the reproductive system. Microbiol Mol Biol Rev . 2001 Jun ;65(2):208–31.
20. Yang M, Chen S, Huang B, et al. Pathological Findings in the Testes of COVID-19 Patients: Clinical Implications. Eur Urol Focus . 2020 Sep 15 ;6(5):1124–9.
21. Shen Q, Xiao X, Aierken A, et al. The ACE2 expression in Sertoli cells and germ cells may cause male reproductive disorder after SARS-CoV-2 infection. J Cell Mol Med . 2020 Aug 1 ;24(16):9472–7.
22. Li D, Jin M, Bao P, et al. Clinical Characteristics and Results of Semen Tests Among Men With Coronavirus Disease 2019. JAMA Netw Open [Internet]. 2020 May 1 ;3(5):e208292.
23. He Y, Wang J, Ren J, et al. Effect of COVID-19 on Male Reproductive System - A Systematic Review. Front Endocrinol (Lausanne) . 2021 May 27 ;12.
24. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet . 2020 Feb 22 ;395(10224):565–74.
25. Yuan M, Wu NC, Zhu X, et al. A highly conserved cryptic epitope in the receptor binding domains of SARS-CoV-2 and SARS-CoV. Science . 2020 May 8 ;368(6491):630–3.
26. Holtmann N, Edimiris P, Andree M, et al. Assessment of SARS-CoV-2 in human semen-a cohort study. Fertil Steril . 2020 Aug 1 ;114(2):233–8.
27. Hamarat MB, Ozkent MS, Yilmaz B, et al. Effect of SARS-CoV-2 infection on semen parameters. Can Urol Assoc J . 2022 Mar 1 ;16(3).
28. Erbay G, Sanli A, Turel H, et al. Short-term effects of COVID-19 on semen parameters: A multicenter study of 69 cases. Andrology . 2021 Jul 1;9(4):1060–5.
1.

IJCMBS

THE INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND BIOLOGICAL SCIENCES e-ISSN: 2791-8815

Orgınal Article

The Efficacy of Large-Focused and Controlled-Unfocused (Radial) Extracorporeal Shock Wave Therapies in the treatment of Patellar Tendinopathy: A randomized sham-controlled single-blind trial

Patellar Tendinopati tedavisinde Geniş Odaklı ve Kontrollü Odaksız (Radyal) Ekstrakorporeal Şok Dalgası Tedavilerinin Etkinliği: Randomize sham-kontrollü tek kör çalışma

Volkan Şah[1*], Veysel Delen[2]

[1]Department of Sports Medicine, Faculty of Medicine, Yüzüncü Yıl University, Van, Türkiye
[2] Department of Physical Therapy and Rehabilitation, Faculty of Medicine, Harran University, Sanliurfa, Türkiye

Corresponding author:

Volkan Şah

Adress:

1Department of Sports Medicine, Yüzüncü Yıl University, Faculty of Medicine, Van /TÜRKİYE

E-mail: volkansah@yyu.edu.tr

Received: 29.12.2022

Accepted: 29.01.2023

Cite as: SAH. V et al. The Efficacy of Large-Focused and Controlled-Unfocused (Radial) Extracorporeal Shock Wave Therapies in the treatment of Patellar Tendinopathy: A randomized sham-controlled single-blind trialIJCMBS 2023;3(1):38-44 doi.org/ 10.5281/zenodo.7581892

Abstract

Background: Although Extracorporeal Shock Wave Therapy (ESWT) is a widely used treatment option in patellar tendinopathy (PT), treatment protocols are not clearly defined. There is no consensus on the type of shock wave or the energy level, number of shocks, pressure, and frequency values. For this reason, this study will, on the one hand, aim to contribute to the confusion of whether ESWT is effective in the treatment of PT and, on the other hand, try to define the most effective ESWT protocol in the treatment of PT, rather than choosing one at random. **Methods:** Eighty-six patients with PT randomised to 'Controlled Unfocused/Radial' ESWT (r-ESWT), 'Large-Focused' ESWT (f-ESWT) and sham ESWT (s-ESWT) groups and the data of seventy-eight patients who could reach the last control were evaluated statistically. The patients received the ESWT application once a week for a total of three sessions. Patients were evaluated with Visual Analog Scale (VAS) and Victorian Institute of Sports Assessment-Patella (VISA-P) scores just before the treatment (baseline), one day after the end of treatment (week 3), one month after the end of treatment (week 7) and three months after the end of treatment (week 15).**Results:** VAS and VISA-P scores have significantly improved at *3th, 7th, and 15th weeks* in the r-ESWT group ($p<0.05$) and at *7th, and 15th weeks* in the f-ESWT group ($p<0.05$). In terms of *baseline-3th week, baseline-7th week and baseline-15th* week differences of VAS and VISA-P scores, r-ESWT was superior to f-ESWT ($p<0.05$). **Conclusions:** Although both r-ESWT and f-ESWT were effective in the treatment of PT according to the results of this study, the efficacy of r-ESWT was superior to f-ESWT.

KeyWords: patellar tendinopathy, extracorporeal shock wave therapy, radial, focused

ÖZ

Amaç: Patellar tendinopati (PT) tedavisinde yaygın olarak kullanılmasına rağmen Vücut Dışı Şok Dalga Tedavisi-Extracorporeal Shock Wave Therapy (ESWT) 'nin tedavi protokolleri net olarak tanımlanmamıştır. Şok dalgasının türü (odaklanmış veya radyal), enerji seviyesi, atım sayısı, basınç ve frekans değerleri hakkında fikir birliği sağlanamamıştır. Bu nedenle bu çalışma bir yandan ESWT'nin PT tedavisinde etkili olup olmadığı konusundaki karışıklığa katkıda bulunmayı, diğer yandan PT tedavisinde rastgele bir ESWT tedavisi seçmek yerine en etkili ESWT protokolünü tanımlamayı amaçlamaktadır. **Yöntemler:** Seksen altı PT hastası; Radial-Radyal ESWT (r-ESWT), Focused-Odaklı ESWT (f-ESWT) ve Sham-Plasebo ESWT (s-ESWT) gruplarına randomize edildi ve son kontrole ulaşabilen yetmiş sekiz hastanın verileri istatistiksel olarak değerlendirildi. ESWT, birer hafta arayla uygulanan toplam üç seans olarak uygulandı. Hastalar tedaviden hemen önce (başlangıçta), tedavi bitiminden bir gün sonra (3. hafta), tedavi bitiminden bir ay sonra (7. hafta) ve tedavi bitiminden üç ay sonra (15. hafta) Görsel Analog Skala-Visual Analogue Scale (VAS) ve Viktorya Enstitüsü Spor Değerlendirme-Diz kapağı-Victorian Institute of Sports Assessment-Patella (VISA-P) skorları ile değerlendirildi. **Bulgular:** VAS ve VISA-P skorları, r-ESWT grubunda 3., 7. ve 15. haftalarda ($p<0.05$), f-ESWT grubunda ise 7. ve 15. haftalarda anlamlı olarak iyileşti ($p<0.05$). VAS ve VISA-P skorlarının başlangıç-3. hafta, başlangıç-7. hafta ve başlangıç-15. hafta farkları açısından r-ESWT, f-ESWT'den üstündü ($p<0.05$). s-ESWT grubunda takip haftalarının hiçbirinde VAS ve VISA-P skorlarında anlamlı değişiklik olmadı ($p>0,05$). **Sonuç:** Bu çalışmanın sonuçlarına göre PT tedavisinde hem r-ESWT hem de f-ESWT etkili olsa da r-ESWT'nin etkinliği f-ESWT'den üstün bulundu.

Anahtar Kelimeler: patellar tendinopati, vücut dışı şok dalga terapisi, radyal, odaklı

Highlights

• ESWT is a promising option in the treatment of patellar tendinopathy.

• Finding out which ESWT type is more effective in the treatment of patellar tendinopathy is important for treatment success.

INTRODUCTION

Patellar Tendinopathy (PT) is an injury that causes pain and dysfunction in the patellar tendon and is usually caused by overload (1). A localized pain is usually felt in the proximal patellar tendon during jumping and squatting activities (2). Although the overall prevalence among competitive elite athletes is 14%, it can reach 45% among volleyball and basketball players (3).

The conservative treatment of PT is carried out with two options: active and passive. Active conservative treatment includes eccentric, isometric, and resistance exercises. Passive treatment options include NSAIDs, corticosteroid and platelet-rich plasma (PRP) injections, iontophoresis, topical glyceryl trinitrate (GTN), low-energy laser, therapeutic ultrasound (US), and extracorporeal shockwave therapy (ESWT) (4).

ESWT is a high-energy sound wave therapy that enhances the healing of damaged tissues. It was first used in the treatment of kidney stones and has been used in the treatment of musculoskeletal disorders of tendons, ligaments, muscles, joints, and bones since the 1990s (5).

It is very encouraging that, in a systematic review, approximately 74.7% of those who underwent ESWT in the treatment of PT had improvements in pain and knee function, and no serious side effects were reported (6). However, in some other studies, its effectiveness has not been proven (7,8) and this makes it difficult to reach a definite conclusion. In addition, ESWT treatment protocols have not been clearly established. In different studies, the type of shock wave (radial (r-) ESWT or focused (f-) ESWT), energy level, number of shocks, pressure, and frequency values varied. (9–12). Only one study has compared the r- and f- waves in the treatment of PT (13).

For this reason, this study will, on the one hand, aim to contribute to the confusion of whether ESWT is effective in the treatment of PT and, on the other hand, try to define the most effective ESWT protocol in the treatment of PT, rather than choosing one at random.

MATERIALS AND METHODS

Ethical Considerations

All patients were informed verbally before the study, and all of them filled out written informed consent forms in accordance with the Declaration of Helsinki. Yüzüncü Yıl University Clinical Research Ethics Committee approval was obtained (Decision No: 02; Date: June 06, 2022) and registered on 'Clinicaltrials.gov' with the number NCT05423366.

Study Design

This study was carried out at the University of Van Yüzüncü Yıl, Faculty of Medicine, Department of Sports Medicine, and it was a prospective, single-blind, randomized, and sham-controlled clinical trial with three parallel treatment groups; Controlled-Unfocused (Radial) ESWT (r-ESWT), Large-Focused ESWT (f-ESWT), and Sham ESWT (s-ESWT). The study lasted for fifteen weeks, of which the first three weeks were the treatment period. Patients in all three groups were given isometric knee exercises as a home program until the end of the ESWT sessions (during the first 3 weeks of the study). Patients were evaluated with Visual Analog Scale (VAS) and Victorian Institute of Sports Assessment-Patella (VISA-P) scores just before the treatment (baseline), one day after the end of treatment (week 3), one month after the end of treatment (week 7) and three months after the end of treatment (week 15). In patients with bilateral knee pain, treatments were applied to both sides, but evaluations were made based on the most painful knee.

Estimation of Sample Size

The study power and sample size were calculated with a study power of 80% and a 5% type 1 (α) error with the G*Power statistical program (version 3.1.9.7).

Participants

A total of 100 patients (66 volleyball athletes and 34 basketball athletes) were evaluated in terms of inclusion and exclusion criteria. Eighty-six patients, who accepted to participate in the study and met the criteria, randomised to 'Controlled Unfocused/Radial' ESWT (r-ESWT), 'Large-Focused' ESWT (f-ESWT) and sham ESWT (s-ESWT) groups. The statistical results of 78 patients that were able to be evaluated at the last control were analyzed. Figure 1 shows the flowchart of the study participants.

Inclusion criteria were: being 18-40 years old, doing sports at least once a week, and being diagnosed with PT. The PT was diagnosed by the physiatrist in the presence of the following findings: knee pain in the patellar tendon or its insertion, tenderness along the patella tendon or in the insertion of the tendon into the patella, symptoms for more than 8 weeks, VISA-P score at the baseline (before treatment) less than 80, pain that limited to the tendon or tendon-bone junction during loading and does not radiate to the entire patellar region (to differentiate PT and patellofemoral pain). In bilateral complaints, treatment was applied to both knees, but the most painful knee was included in the study. Exclusion criteria were: acute knee injury, chronic inflammatory joint diseases (such as rheumatoid arthritis), the other co-existing knee pathologies, use of corticosteroid drugs in the past 6 months, history of knee surgery (on the anterior cruciate ligament or patellar tendon), a recent injection of the knee (including corticosteroid) within one month, contraindications for ESWT treatment (e.g., malignancy, coagulopathy, pregnancy), and participants who had previously received ESWT (as they couldn't be blinded to ESWT).

Randomisation

The patients were assigned to the treatment groups by "block randomization" with the help of the "Random Allocation Software (ver.1.0)" package program.

Blinding

The patients were not informed about the sequence of procedures and their differences from each other. They did not realize which treatment group they were included in since ESWT had never been applied to them before, and similar pulse sounds were heard in all three groups of treatment.

Interventions

The patients received the ESWT application once a week for a total of three sessions. The probe was applied to the most painful point on the patellar tendon when the patient brought the knee to full extension in the supine position with an ultrasound gel, and without using local anesthesia. The same ESWT device was used in all sessions and in both treatment groups (Pagani Elettronica, made in Italy) and it has an electro-pneumatic system and produces both r- and f- waves. The frequency, pressure, energy, pulse, and duration values when hip osteoarthritis diagnosis is selected on the screen were automatically assigned by the device.

The f-ESWT was applied to the first group as two consecutive parts in each session; part 1 (5 Hz, 1.6 Bar, 500 pulses, 0.02-0.60 mJ/mm2, 1 minutes and 40 seconds) + part 2 (8 Hz, 1.8 Bar, 1800 pulses, 0.02-0.60 mJ/mm2, 3 minutes and 45 seconds. The r-ESWT was applied to the second group as two consecutive parts in each session; part 1 (5 Hz, 1.4 Bar, 1400 pulses, 0.168 mJ/mm2, 4 minutes and 40 seconds) + part 2 (8 Hz, 1.5 Bar, 1800 pulses, 0.180 mJ/mm2, 3 minutes and 45 seconds). The s-ESWT was applied to the third group. For the s-ESWT application, using an r-ESWT probe, the frequency (Hz), pressure (Bar) values, and time intervals are the same as the r-ESWT, but the energy value (joule) was manually set to 0 (zero) so that there was no energy transfer to the patient.

Outcome Measures

The pain intensity of the patients at rest was evaluated by the VAS. This scale consists of a horizontal line, the value of 0 (zero-no pain) at the beginning of the line, and the value of 10 (ten-unbearable pain) at the end.

The VISA-P questionnaire is an outcome assessment scale for PT patients (14) and is used to evaluate pain and activity level. It is scored between 0 and 100 (no activity/maximum pain = 0 and maximum activity/no pain = 100). The Turkish validity and reliability was demonstrated by Çelebi et al. (15).

Statistical analysis

After the normal distribution control for continuous measurements was evaluated with the Shapiro-Wilk ($n<50$) and Skewness-Kewness tests, parametric tests were applied for measurements that were found to be normally distributed. Descriptive statistics for continuous variables are expressed as a mean (mean), standard deviation (SD), number (n), and percentage (%). The "Independent T-test" and "One-Way ANOVA" were used to compare continuous measurement values according to the treatment groups. The "paired T-test" was used to compare the VAS and VISA-P changes over time. The statistical significance level was taken as $p<0.05$ in calculations, and SPSS (IBM SPSS for Windows, ver.26) statistical package program was used for analysis.

RESULTS

Table 1 presents the participants' characteristics. The groups were similar with respect to baseline characteristics (age, gender, height, weight, body mass index, distribution of sport type, and symptom duration) (for all, $p>0.05$) (Table 1). Also, the three groups were similar in terms of baseline VAS and VISA-P scores (for all, $p>0.05$) (Tables 2-3).

Intra-group comparisons

VAS and VISA-P scores have significantly changed (improved) at all follow-up points (*3^{th}, 7^{th}, and 15^{th} weeks*) compared with baseline (0^{th} week), in the r-ESWT group ($p<0.05$). VAS and VISA-P scores have significantly

changed (improved) at two follow-up points (*7th, and 15th weeks*) compared with baseline (0th week), in the f-ESWT group (p<0.05). VAS and VISA-P scores have not significantly changed in any of the follow-up points in the s-ESWT group (p>0.05) (Tables 2-3).

Table 1. Statistical analysis of the participants characteristics.

		f-ESWT		r-ESWT		s-ESWT		*P
		n	%	n	%	n	%	
Gender	Female	15	34.1%	15	34.1%	14	31.8%	*0.930*
	Male	11	32.4%	13	38.2%	10	29.4%	
Sports Type	Basketball	10	29.4%	12	35.3%	12	35.3%	*0.710*
	Volleyball	16	36.4%	16	36.4%	12	27.3%	
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	***P**
Age		26.22	5.57	24.76	4.58	26.55	5.10	*0.397*
Height (meter)		1.77	0.10	1.77	0.08	1.77	0.09	*0.941*
Weight (kg)		74.42	14.07	71.35	12.24	70.97	13.39	*0.592*
Body Mass Index (kg/m^2)		23.60	2.26	22.70	2.23	22.35	2.35	*0.135*
Symptom Duration (week)		23.88	12.33	23.46	12.64	28.00	13.37	*0.386*

** chi-square test; ** independent T-test f-ESWT: Focused Extracorporeal Shock Wave Therapy. r-ESWT: Radial Extracorporeal Shock Wave Therapy s-ESWT: Sham Extracorporeal Shock Wave Therapy*

Table 2. Statistical analysis for the VAS scores.

	f-ESWT			r-ESWT			s-ESWT			*p.
	Mean	**SD**	***p.**	**Mean**	**SD**	***p.**	**Mean**	**SD**	***p.**	
Base VAS	5.85	1.22		5.75	1.27		5.58	1.32		*0.762*
Week3 VAS	5.81a	1.36		3.04b	2.03		5.00a	1.64		***0.001***
Week7 VAS	4.62a	1.27		1.64b	1.66		5.25a	1.33		***0.001***
Week 15VAS	4.23b	1.24		1.07c	1.70		5.21a	1.47		***0.001***
Change (Base-Week3 VAS	0.04b	1.18	*0.870*	2.71a	2.49	***0.001***	0.58b	1.56	*0.080*	***0.001***
Change (Base-Week7 VAS	1.23b	1.07	***0.001***	4.11a	2.17	***0.001***	0.33c	0.92	*0.088*	***0.001***
Change (Base-Week 15 VAS	1.62b	1.10	***0.001***	4.68a	2.28	***0.001***	0.38c	0.97	*0.071*	***0.001***

** ANOVA test (inter-groups comparisons) ** Dependent (paired) T-test (inta-group comparisons).VAS: Visual Analog Scale. f-ESWT: Focused Extracorporeal Shock Wave Therapy. r-ESWT: Radial Extracorporeal Shock Wave Therapy.. s-ESWT: Sham Extracorporeal Shock Wave Therapy*

Table 3. Statistical analysis for the VISA-P scores.

	f-ESWT			r-ESWT			s-ESWT			*p.
	Mean	**SD**	***p.**	**Mean**	**SD**	***p.**	**Mean**	**SD**	***p.**	
Base VISA-P	55.89	10.26		56.75	11.36		56.54	10.43		*0.955*
Week3 VISA-P	56.95b	11.75		74.25a	11.44		60.21b	12.40		*0.001*
Week7 VISA-P	66.87b	10.24		83.18a	9.33		57.71c	10.34		*0.001*
Week15 VISA-P	72.85b	11.47		89.36a	8.64		57.08c	10.95		*0.001*
Change (Base-Week3 VISA-P	-1.05a	8.01	*0.508*	-17.50b	15.76	*0.001*	-3.67a	11.44	*0.130*	*0.001*
Change (Base-Week7 VISA-P	-10.98b	9.33	*0.001*	-26.43c	14.97c	*0.001*	-1.17a	7.25	*0.439*	*0.001*
Change (Base-Week15 VISA-P	-16.96b	10.47	*0.001*	-32.61c	14.88	*0.001*	0-.54a	5.93	*0.659*	*0.001*

** ANOVA test (inter-groups comparisons). ** Dependent (paired) T-test (inta-group comparisons). VISA-P: The Victorian Institute of Sport Assessment-Patella. f-ESWT: Focused Extracorporeal Shock Wave Therapy. r-ESWT: Radial Extracorporeal Shock Wave Therapy. s-ESWT: Sham Extracorporeal Shock Wave Therapy*

Inter-groups comparisons

In terms of *baseline-3th week. baseline-7th week and baseline-15th* week differences of VAS and VISA-P scores. r-ESWT was superior to s-ESWT (p<0.05). In terms of *baseline-7th week and baseline-15th week* differences of VAS and VISA-P scores. f-ESWT was superior to s-ESWT (p<0.05). Importantly. in terms of *baseline-3th week. baseline-7th week and baseline-15th* week differences of VAS and VISA-P scores. r-ESWT was superior to f-

ESWT ($p<0.05$) (Tables 2-3). Mild erythema. which improved one day after the first session. was detected in 3 patients in the f-ESWT group and in 1 patient in the r-ESWT group. but this side effect did not occur in the other sessions that followed.

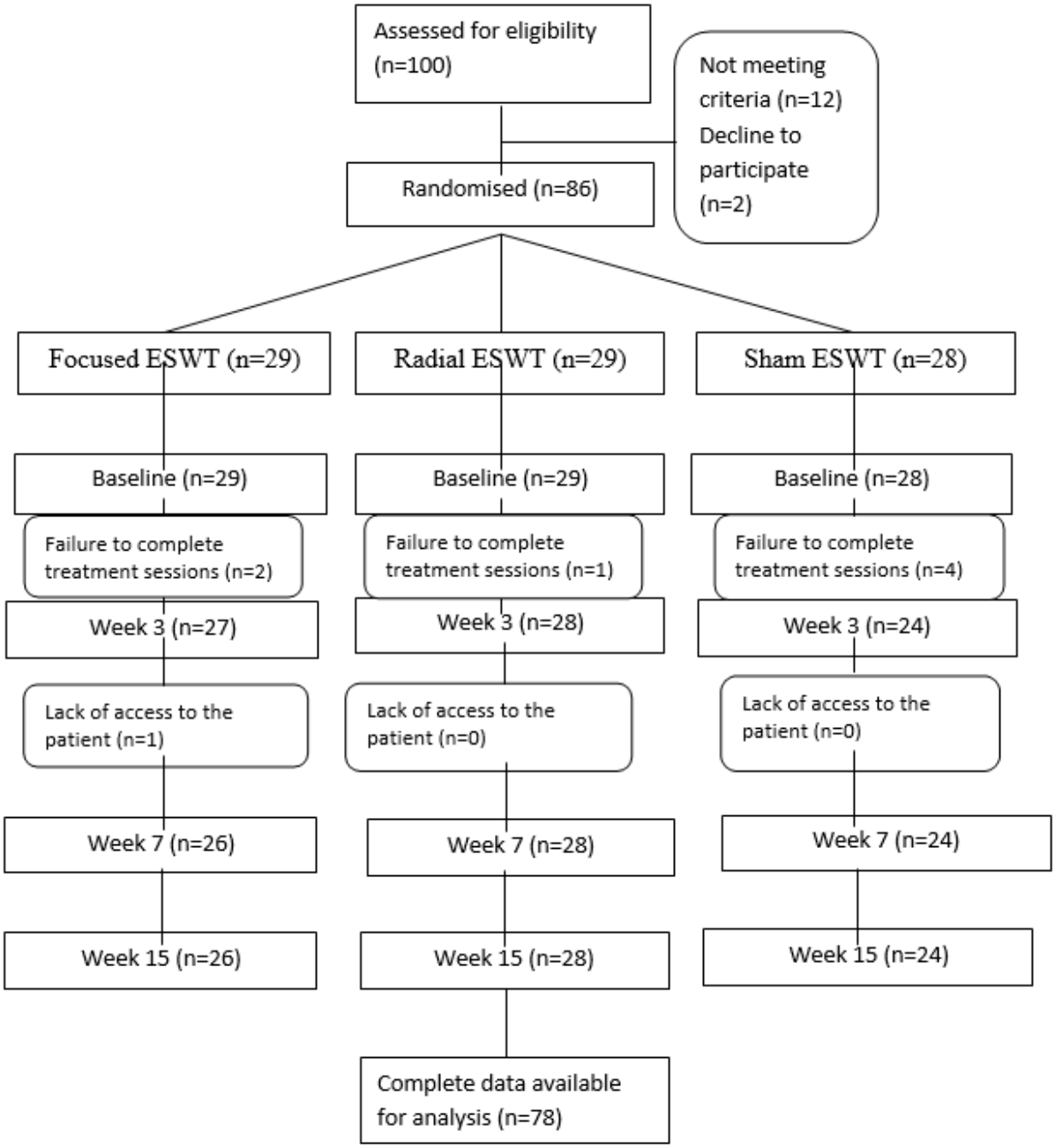


Figure 1. Flowchart of the study participants.

DISCUSSION

This randomized. controlled. single-blind study demonstrated that ESWT might be an effective and safe option for treating patients with patellar tendinopathy. According to pain and activity level assessment based on VAS and VISA-P scores. both the f-ESWT and r-ESWT were found to be effective in the treatment of patellar tendinopathy. However; the f-ESWT provided a superior improvement in these scores compared to the r-ESWT based on mid-term outcomes.

Despite conflicting results on the effectiveness of ESWT. it is widely used in sports injuries. The precise mechanisms of ESWT's pain-relieving effect are unknown; however. it has been proposed that ESWT improves

tissue healing by increasing TGF1 and IGF-1 expression. and that it may also induce neovascularization by increasing the release of endothelial nitric oxide synthase and vascular endothelial growth factor (16). However. ESWT could also have some side effects such as dysesthesia. swelling. ecchymosis and/or petechiae. bruising. and a throbbing sensation (17).

The therapeutic efficacy of ESWT for patellar tendinopathy is unclear (18). The studies in a systematic review about the efficacy of ESWT in the treatment of patellar tendinopathy indicated that ESWT produced both short- and long-term improvements (19). However. another systematic review is available in the literature with contradictory results. concluding that ESWT is not superior to standard conservative treatments (20).

In the study conducted to treat patellar tendinopathy patients consisting of volleyball. basketball. and handball athletes. f-ESWT was applied three sessions per week at a frequency of 4 Hz per session. with 2000 shocks and energy flow up to a maximum of 0.58 mJ/mm2 (according to the pain tolerance of each patient). Although the patients' symptoms decreased in the first week. it was revealed that there was no positive change in the pain and function evaluations at the 12^{th} and 22^{nd} weeks (7). Cheng et al. in their study on athletes with patellar tendinopathy. compared the r-ESWT (16 weekly sessions. 2000 shocks per session; 1.5 to 3.0 bar pressure; 9 to 12 Hz frequency) and the control group (patients receiving physical therapy such as acupuncture. ultrasonic wave. and microwave therapy). Significant improvements in pain and muscle strength scores were demonstrated in both treatment groups at week 16 (21).

The first comparison study of the r-ESWT and f-ESWT in the treatment of patellar tendinopathy was conducted by Van der Worp et al. A significant improvement in VAS and activity scores was observed at 14 weeks in both the group given eccentric exercise + three sessions of r-ESWT and the group given eccentric exercise + three sessions of f-ESWT. but no statistically significant difference was found between the groups (13).

The studies in which PT was treated with either r-ESWT or f-ESWT predominate in the literature (7.19–21). Only one trial has examined the comparative effects of r-ESWT and f-ESWT in the treatment of PT. and it became a milestone in further identifying the most effective ESWT type for each musculoskeletal disease. In this study. researchers applied f-ESWT at a frequency of 4 Hz and an energy level of 0.12 mJ/mm^2. and r-ESWT at a frequency of 8 Hz and a pressure of 2.4 bars. Both groups received electro-magnetic ESWT once a week for a total of 3 sessions and 2000 shocks per session (13). In our trial. unlike this study. we found r-ESWT to be superior to the f-ESWT. Since our frequency. energy and pressure values were similar. the difference could be considered in our study that the number of pulses per session is higher in the r-ESWT (3200 pulses) than in the f-ESWT (2300 pulses). and that our device was electro-pneumatic. unlike their electro-magnetic device.

Due to their characteristics. f-ESWT waves reach higher energy levels in deeper tissues. while r-ESWT gives its maximum energy just near the probe tip (22). In our study. although the energy density could increase up to 0.60 mj/mm2 in certain sequences during the f-ESWT session. the fact that r-ESWT was more effective may be related to the superficial location of the patellar tendon. In addition. because our electro-pneumatic device (Pagani Elettronica. Italy) delivered 3200 shocks per session in the r-ESWT group and 2300 shocks in the f-ESWT group. a higher number of pulses may have resulted in more positive treatment results. Pressure (bar) and frequency (Hz) values were similar in both treatment groups. suggesting that they did not have an effect on different treatment outcomes.

Limitations

This study had some limitations. The treatment groups were non-homogeneous as they included both men and women. No radiological imaging (X-ray. MRI. etc) was taken from the patients. For follow-up. no athletic performance tests were used. Further studies can be conducted with larger patient series and longer follow-up periods.

CONCLUSIONS

In terms of VAS and VISA-P scores. both the r-ESWT which created a significant difference at the 3^{th}.5^{th} and 17^{th} weeks. and the f-ESWT which created a significant difference at the 5^{th} and 17^{th} weeks. were found to be effective in the treatment of PT. However. the r-ESWT produced a superior improvement at follow-up points (3^{th}.5^{th} and 17^{th} weeks) compared to the f-ESWT.

Acknowledgements: *The author would like to thank Dr. Hamza Özsayım for his assistance in data collection. Dr. Şeyhmus Kaplan for distributing patients to groups. and Dr. Sadi Elasan for evaluating the results and statistics*.

Ethical Approval: *All patients were informed verbally before the study. and all of them filled out written informed consent forms in accordance with the Declaration of Helsinki. Yüzüncü Yıl University Clinical Research Ethics Committee approval was obtained (Decision No: 02; Date: June 06. 2022) and registered on 'Clinicaltrials.gov' with the number NCT05423366.*

Author Contributions: *Concept: VŞ. Literature Review: VŞ. VD Design: VŞ. VD. Data acquisition: VŞ. VD Analysis and interpretation: VŞ. VD Writing manuscript: VŞ Critical revision of manuscript: VŞ. VD*

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

Financial Disclosure: *Authors declared no financial support.*

REFERENCES

1. Scott A. Squier K. Alfredson H. et al. ICON 2019: International Scientific Tendinopathy Symposium Consensus: Clinical Terminology. Br J Sports Med. 2020;54(5):260–2.
2. Cook JL. Khan KM. Kiss ZS. et al. Patellar tendinopathy in junior basketball players: a controlled clinical and ultrasonographic study of 268 patellar tendons in players aged 14-18 years. Scand J Med Sci Sports. 2000 Aug;10(4):216–20.
3. Lian ØB. Engebretsen L. Bahr R. Prevalence of jumper's knee among elite athletes from different sports: A cross-sectional study. Am J Sports Med. 2005;33(4):561–7.
4. Challoumas D. Pedret C. Biddle M. et al. Management of patellar tendinopathy: A systematic review and network meta-analysis of randomised studies. BMJ Open Sport Exerc Med. 2021;7(4):1–11.
5. Romeo P. Lavanga V. Pagani D. et al. Extracorporeal shock wave therapy in musculoskeletal disorders: A review. Med Princ Pract. 2013;23(1):7–13.
6. Van Leeuwen MT. Zwerver J. Van Den Akker-Scheek I. Extracorporeal Shockwave therapy for patellar tendinopathy: A review of the literature. Br J Sports Med. 2009;43(3):163–8.
7. Zwerver J. Hartgens F. Verhagen E. et al. No effect of extracorporeal shockwave therapy on patellar tendinopathy in jumping athletes during the competitive season: a randomized clinical trial. Am J Sports Med. 2011 Jun;39(6):1191–9.
8. Thijs KM. Zwerver J. Backx FJG. et al. Effectiveness of shockwave treatment combined with eccentric training for patellar tendinopathy: A double-blinded randomized study. Clin J Sport Med. 2017;27(2):89–96.
9. Chung B. Wiley JP. Extracorporeal shockwave therapy: A review. Sport Med. 2002;32(13):851–65.
10. Ogden JA. Tóth-Kischkat A. Schultheiss R. Principles of shock wave therapy. Clin Orthop Relat Res. 2001 Jun;(387):8–17.
11. Furia JP. Rompe JD. Extracorporeal shock wave therapy in the treatment of chronic plantar fasciitis and Achilles tendinopathy. Curr Opin Orthop. 2007;18(2):102–11.
12. Sems A. Dimeff R. Iannotti JP. Extracorporeal shock wave therapy in the treatment of chronic tendinopathies. JAAOS-Journal Am Acad Orthop Surg. 2006;14(4):195–204.
13. van der Worp H. Zwerver J. Hamstra M. et al. No difference in effectiveness between focused and radial shockwave therapy for treating patellar tendinopathy: a randomized controlled trial. Knee Surg Sports Traumatol Arthrosc. 2014;22(9):2026–32.
14. Visentini PJ. Khan KM. Cook JL. et al. The VISA score. J Sci Med Sport. 1998;22–8.
15. Çelebi MM. Köse SK. Akkaya Z. et al. Cross-cultural adaptation of VISA-P score for patellar tendinopathy in Turkish population. Springerplus. 2016;5(1).
16. Lee S. Lee D. Park J. Effects of extracorporeal shockwave therapy on patients with chronic low back pain and their dynamic balance ability. J Phys Ther Sci. 2014;26(1):7–10.
17. Roerdink RL. Dietvorst M. Van der Zwaard B. et al. Complications of extracorporeal shockwave therapy in plantar fasciitis: Systematic review. Int J Surg. 2017;46:133–45.
18. van der Worp H. van den Akker-Scheek I. Van Schie H. Zwerver J. ESWT for tendinopathy: technology and clinical implications. Knee Surgery. Sport Traumatol Arthrosc. 2013;21(6):1451–8.
19. Mani-Babu S. Morrissey D. Waugh C. et al. The effectiveness of extracorporeal shock wave therapy in lower limb tendinopathy: A systematic review. Am J Sports Med. 2015;43(3):752–61.
20. Korakakis V. Whiteley R. Tzavara A. et al. The effectiveness of extracorporeal shockwave therapy in common lower limb conditions: a systematic review including quantification of patient-rated pain reduction. Br J Sports Med. 2018;52(6):387–407.
21. Cheng L. Chang S. Qian L. et al. Extracorporeal shock wave therapy for isokinetic muscle strength around the knee joint in athletes with patellar tendinopathy. J Sports Med Phys Fitness. 2019 May;59(5):822–7.
22. Wu YT. Chang CN. Chen YM. et al. Comparison of the effect of focused and radial extracorporeal shock waves on spastic equinus in patients with stroke: A randomized controlled trial. Eur J Phys Rehabil Med. 2018;54(4):518–25.

IJCMBS

THE INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND BIOLOGICAL SCIENCES e-ISSN: 2791-8815

Orgınal Article

The Prognostic Role of the Systemic Inflammatory Index (SII) in Heart Failure Patients

Kalp Yetmezliği Hastalarında Sistemik İnflamatuvar İndeksin (SII) Prognostik Rolü

Yasin Özen[1*], M. Akif Erdöl[2], Mustafa Bilal Ozbay[3], Mehmet Erdoğan[2]

[1] Sivas Numune Hospital, Department of Cardiology, Sivas, Turkey
[2] Ankara City Hospital, Training and Research Hospital, Cardiology, Ankara, Turkey
[3] Metropolitan Hospital Center New York Medical College, Internal Medicine, New York, USA

**Corresponding author:*
Yasin Özen
Adress:
Sivas Numune Hospital, Department of Cardiology, Sivas /TÜRKİYE
E-mail: volkansah@yyu.edu.tr
Received: 08.01.2023
Accepted: 20.02.2023
Cite as: OZEN. Y et al. The Prognostic Role of the Systemic Inflammatory Index (SII) in Heart Failure Patients. IJCMBS 2023;3 (1):45-50 doi.org/ 10.5281/zenodo.7657891

Abstract

Background: The prevalence of heart failure (HF) is increasing worldwide with new treatment methods (percutaneous, medical) that improve survival in heart diseases. Inflammation plays a central role in the development of HF, and many inflammatory markers have been studied to determine HF survival. In this study, we aimed to investigate the relationship between Systemic Immune-Inflammation Index and survival in patients with HF.

Material Method: A total of 672 HF were included in this retrospective and observational study. The primary end-point of the study was all-cause mortality. The median follow-up duration of the study patients was 21 (8-42) months.

Results : 672 patients were analyzed, and all-cause mortality developed in 278 of these patient groups during the follow-up period. The number of all-cause mortality was 113 (34%) in the low SII group, and the number of all-cause mortality was 165 (49%) in the high SII group.

Conclusion: This is the first and only study in the literature showing the relationship between the SII index and survival in patients with HF. In addition, the main finding of our study is that the SII index is an independent predictor of mortality in patients with HF.

Keywords: Systemic immune-inflammation index, heart failure, inflammatory markers

ÖZ

Amaç: Kalp hastalıklarında sağkalımı artıran yeni tedavi yöntemleri (perkütan, medikal) ile kalp yetersizliği (KY) prevalansı dünya çapında artmaktadır. Enflamasyon, KY gelişiminde merkezi bir rol oynar ve KY sağkalımını belirlemek için birçok inflamatuar belirteç incelenmiştir. Bu çalışmada KY hastalarında Sistemik İmmün-İnflamasyon İndeksi (SII) ile sağkalım arasındaki ilişkiyi araştırmayı amaçladık.

Materyal ve Metod: Bu retrospektif ve gözlemsel çalışmaya toplam 672 KY dahil edildi. Çalışmanın primer sonlanım noktası, tüm nedenlere bağlı ölümlerdi. Çalışmaya alınan hastaların median takip süresi 21 (8-42) aydı.

Bulgular:672 hasta analiz edildi ve bu hasta gruplarının 278' inde takip süresince tüm nedenlere bağlı ölüm gelişti. Düşük SII grubunda tüm nedenlere bağlı ölüm sayısı 113 (%34), yüksek SII grubunda tüm nedenlere bağlı ölüm sayısı 165 (%49) idi.

Sonuç: Literatürde KY' li hastalarda SII indeksi ile sağkalım arasındaki ilişkiyi gösteren ilk ve tek çalışmadır. Ayrıca çalışmamızın ana bulgusu, SII indeksinin KY hastalarında mortalitenin bağımsız bir göstergesi olduğudur.

Anahtar Kelimeler: Sistemik immün-inflamasyon indeksi, kalp yetmezliği, inflamatuar belirteçler

Highlights

- SII may have prognostic significance in the follow-up of HF patients.

INTRODUCTION

The prevalence of heart failure (HF) is increasing worldwide with new treatment methods (percutaneous, medical) that increase survival in heart diseases(1-3). Despite the development of new medical and mechanical treatments, 5-year mortality due to HF exceeds that of many cancers by 42-60%(4-6). Inflammation plays a central role in HF development, and many inflammatory markers have been studied to determine HF survival(7-11). Inflammation-related biomarkers have gained a particular interest in the cardiovascular era(7, 12-15).

The Systemic Immune-Inflammation Index (SII) consists of a combination of 3 inflammatory parameters (neutrophils, lymphocytes, and platelets) and can be calculated based on a complete blood count (CBC)(16). In addition, the SII is a strong prognostic indicator of adverse outcomes in various types of cancer(17, 18). In addition, SII was demonstrated to predict mortality in infective endocarditis and coronary artery disease(19, 20). In recent years, it has been shown that SII is associated with mortality in coronary artery disease, valve disease and myocardial infarction(20-23).

In this study, we aimed to identify the relationship between SII and survival in patients with HF.

Materials and Methods

Study Design and Systemic Immune-Inflammation Index (SII)

A total of 672 HF were included in this retrospective and observational study. SII was determined as absolute platelet count × absolute neutrophile count/lymphocyte count(20). The SII value of all patients was calculated, and the median value was calculated. The patient group with more than the median value constituted the high SII group, while the group with less than the median value formed the low SII group. The primary end-point of the study was all-cause mortality. The median follow-up duration of the study patients was 21 (8-42) months. The patients were split into two groups during the follow-up period: those with all-cause mortality and those without The patients were split into two groups during the follow-up period: those with all-cause mortality and those without all-cause mortality. Cumulative survival rates were determined by the Kaplan-Meier analysis and compared between the two groups using the log-rank test. The clinical and laboratory characteristics linked to heart failure mortality were analyzed using the Cox proportional hazard model.

Statistics analysis

All analyses were carried out using IBM SPSS Statistics for Macintosh, Version 26.0 (IBM Corp., Armonk, New York, USA). During the follow-up period, patients were divided into two groups as those who developed all-cause mortality and those who did not. Kolmogorov–Smirnov test was used to determine the distribution of numerical variables. The Student's t-test was implemented to the continuous variables, which conforms to the normal distribution, and the results were presented as mean and standard deviation. Conversely, the Mann-Whitney-U test was performed for the non-normal distributed variables. According to the results of this test, the median and interquartile range values were given. The Chi-squared test was applied for categorical variables, and data presented as numbers and percentages. Cumulative survival rates were determined by the Kaplan-Meier analysis and compared between the two groups using the log-rank test. Kaplan-Meier analysis was performed for the two groups according to the median SII value. Comparisons between groups were made according to the Log-rank test. Cox proportional hazard model was applied to clinical and laboratory features which are thought to be related to mortality for heart failure. The significance level of the results obtained was interpreted with the P value at the 95% confidence interval. A P value of < 0.05 was considered statistically significant.

Results

After the application of exclusion criteria, finally, 672 patients were analyzed, and all-cause mortality developed in 278 of these patient groups during the follow-up period (Table 1). The median SII value of the patients was calculated as 666 x 10^3. Mortality rates in the two groups constructed based on this value were compared. The number of all-cause mortality was 113 (34%) in the low SII group, and the number of all-cause mortality was 165 (49%) in the high SII group (Figure 1). Median survival time in the whole study population was 59 (42-77, 95% CI) months**,** whereas median survival time in the low and high SII groups was 85 months (54-117, 95% CI), 42 months (29-55, 95% CI) respectively (P<.001) (Figure 2). The male gender was statistically significantly higher in the mortality group (288 (53%) vs. 254 (91%)) . In addition, while left ventricular ejection fraction (20 (18-26) vs. 20 (15-22)) was found to be lower in the mortality group, systolic pulmonary artery pressure was 42 (35-54) vs. 48 (40-58)) and functional capacity class was higher in the mortality group (P<.001 in all

parameters). Urea nitrogen, NT-proBNP, and SII were significantly higher in the mortality group (P<.001 in all parameters). Time-dependent Cox regression analysis revealed that a high SII (≥666x10^3) level was found to be an independent predictor of mortality (Table 2).

Table 1. Baseline characteristics of study populations

Variables (n=672)	**All-Cause Mortality**		
	Without event (n= 394)	**With event (n= 278)**	**P value**
Demographic and clinical features			
Age (years)	49 (39-54)	50 (41-57)	.014
Gender (male)	288 (53%)	254 (91%)	<.001
Diabetes mellitus (n=600)	92 (27%)	71 (27%)	.815
Hypertension (n=651)	56 (15%)	36 (13%)	.535
Atrial fibrillation (n=657)	129 (34%)	80 (29%)	.355
Implantable cardiac defibrillator (n=670)	306 (78%)	196 (70%)	.026
Etiology (ischemic) (n=661)	141 (37%)	97 (35%)	.611
Left ventricular ejection fraction (%)	20 (18-26)	20 (15-22)	<.001
Systolic pulmonary artery pressure (mmHg)	42 (35-54)	48 (40-58)	<.001
NYHA (New York Heart Association) functional capacity class			<.001
Class I	63 (16%)	18 (6%)	
Class II	157 (40%)	65 (23%)	
Class III	140 (36%)	110 (40%)	
Class IV	34 (8%)	85 (31%)	
Laboratory findings			
Glucose (mg/dl)	102 (90-123)	99 (88-116)	.027
Urea nitrogen (mg/dl)	40 (31-51)	48 (37-66)	<.001
Creatinin (mg/dl)	1.06 (0.87-1.25)	1.03 (0.86-1.16)	.066
Aspartate transaminase (SGOT) (U/L)	23 (18-30)	27 (20-35)	<.001
Alanine transaminase (SGPT) (U/L)	21 (16-32)	25 (16-41)	.009
Total bilirubin (mg/dl)	0.92 (0.59-1.54)	1.59 (0.92-2.40)	<.001
NT-proBNP (pg/mL) (n= 387)	903 (284-2467)	1605 (722-4090)	<.001
Hemoglobin (g/dL)	13.9±1.9	13.1±1.9	<.001
Hematocrit (%)	43.1±5.5	40.9 ± 5.5	<.001
White cell count (10^3/mm^3)	8.20 (6.88-9.40)	7.82(6.69-9.25)	.111
Neutrophil count (10^3/mm^3)	5.17 (4.01-6.30)	5.20 (4.37-6.40)	.138
Lymphocyte count (10^3/mm^3)	1.90 (1.44-2.40)	1.60 (1.26-2.10)	<.001
Platelet count (10^3/mm^3)	229 (190-280)	220 (180-272)	.111
Systemic immune-inflammation index (x10^3)	607 (420-919)	732 (499-1068)	<.001

Table 2. Time dependent Cox-regression analysis for all-cause mortality

Variables	**All-cause mortality**		
	Hazard ratio	**95% CI**	**P value**
Age	1.02	1.01-1.03	.002
Gender	1.39	0.85-2.29	.414
Left ventricular ejection fraction, %	0.95	0.92-0.97	<.001
Ischemic cardiomyopathy	0.88	0.67-1.16	.362
Diabetes mellitus	0.81	0.61-1.08	.156
Hypertension	1.01	0.69-1.47	.972
Implantable cardiac defibrillator	0.73	0.55-0.97	.028
Aspartat transaminase	1.01	1.00-1.01	<.001
High SII (≥666x10^3)	1.51	1.19-1.92	.001

SII= Systemic immun-inflammtion index

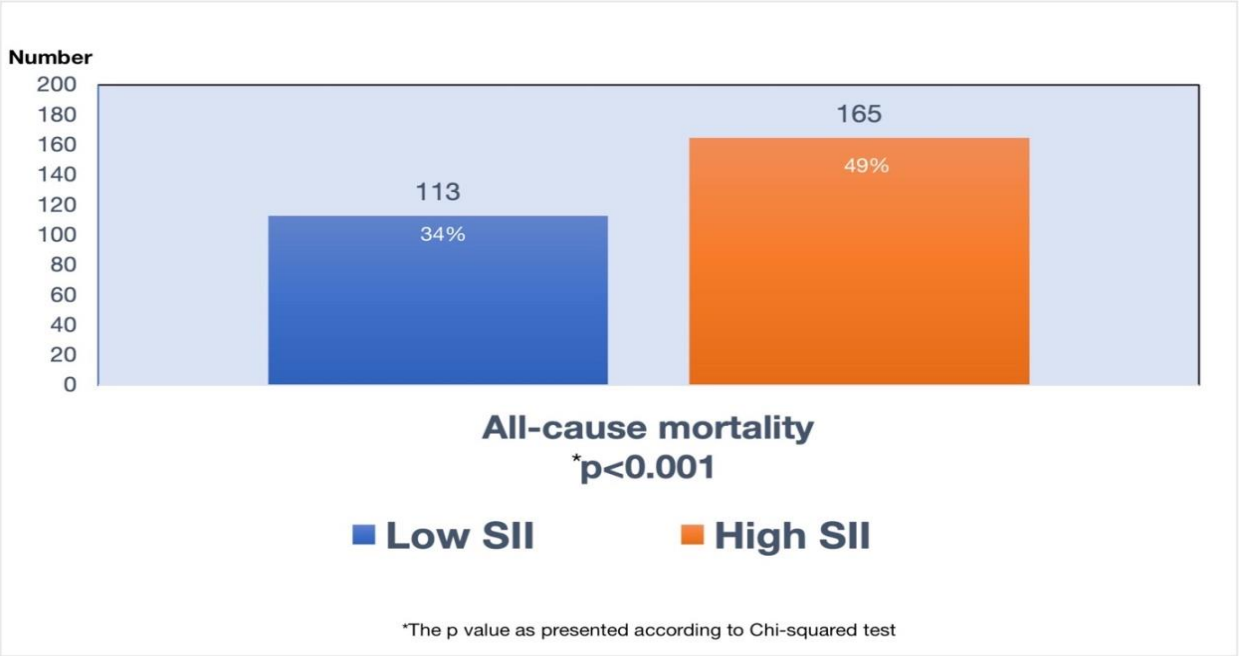


Figure 1. Number of all-cause mortality in both groups.

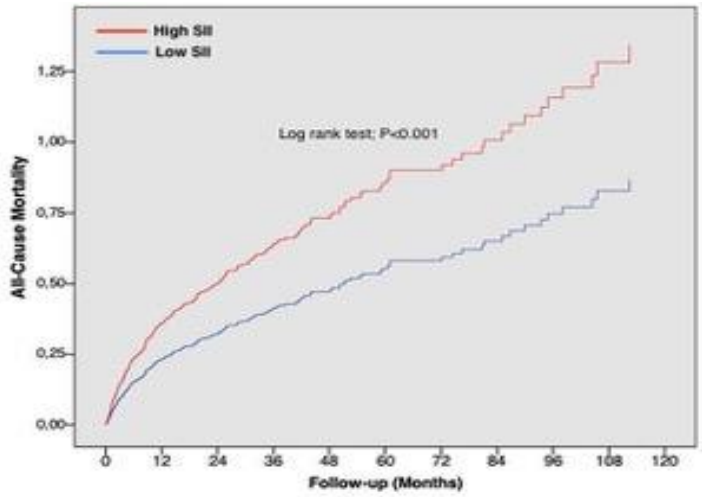


Figure 2. Kaplan meier survival analysis

Discussion

As far as we are concerned, this is the first and only study that has assessed the relationship between the SII index and survival in HF patients. In addition, the main finding of our study is that the SII index is an independent predictor of mortality in patients with HF.

HF is the final common path of all heart diseases, rising in incidence and prevalence, and to a pandemic (24). Despite the many advances in the current pharmacotherapy and mechanical device therapy strategies, HF remains one of the most common causes of hospitalization. It is the most important cause of hospitalization and death in elderly patients in Western countries (12). Therefore, it seems necessary to investigate new pathophysiological mechanisms for possible new opportunities in the treatment of HF, thereby improving survival and slowing disease progression. The immune system's role in the development and course of HF has been determined. In HF, there is an imbalance between several proinflammatory and anti-inflammatory markers. In the past decade, many inflammatory markers have been associated with cardiovascular disease. Toprak et al. showed that the monocyte/HDL-C ratio could predict multivessel disease in patients with the acute coronary

syndrome (25). Interleukin-33 levels are elevated in HF patients, according to research by Segiet et al.(12). Similar to this, Traxler et al. shown that sST2 (soluble suppression of tumorigenicity 2), HSP27, and hs- CRP may be used to predict cardiovascular mortality and HF hospitalization(26). Kuster et al. emphasized that sST2 and growth differentiation factor-15 (GDF-15) may help evaluate the prognosis in patients with HF (27).
The immunothrombosis model provides evidence of balanced interactions between the immune and coagulation systems(28). The SII, an inflammation marker that has emerged in recent years, was developed to simultaneously assess patients' inflammatory and immunothrombotic status based on platelet count and neutrophil-to-lymphocyte ratio (NLR) The SII was initially thought to be a prognostic indicator for various malignancies(17, 29). Thanks to the combination of three inflammatory parameters (neutrophile, lymphocyte, and platelet) in a single index, SII can be considered a sensitive parameter in predicting inflammatory conditions in the patient. This has attracted the attention of cardiologists, and several studies have shown that it is superior to NLR and platelet-to-lymphocyte ratio (PLR) alone in determining the inflammatory state of cardiovascular diseases(30-36). The SII index has been the subject of numerous recent studies since it has proven to be an independent predictor of numerous unfavorable cardiovascular outcomes(20-22, 37). Erdogan et al.'s study on fractional flow reserve (FFR) in patients with chronic coronary syndrome revealed that the SII was superior to the NLR and PLR in predicting hemodynamically severe coronary stenosis(20). The authors of this study found in a recent study that in patients undergoing transcatheter aortic valve implantation for severe aortic stenosis, SII is an independent predictor of postprocedural contrast nephropathy(16). Similarly, the findings of this study demonstrated that SII is an independent predictor of survival in HF patients.

Limitations

Apart from the mentioned strengths of our study, it had some limitations because it was a single-center and recorded by file scanning. In addition, due to the retrospective study, missing data on other inflammatory markers could not be reached, which prevented us from comparing SII with other inflammatory markers. Another limitation of our study is that patients with heart failure with preserved ejection fraction were not included in the study.

Conclusion

To the best of our knowledge, this is the first and only study to evaluate the relationship between SII and survival in patients with heart failure. A high SII level is an independent predictor of mortality in patients with HF. The complete blood count is a readily accessible, inexpensive, routine examination that provides correct and reproducible information.

Acknowledgements: *This study was presented at the 37th Turkish Cardiology Congress with International Participation. 20 November 2021/ Kaya Palazzo Hotel- Antalya..*

Ethical Approval: *The study protocol was approved by the Ankara City Hospital Clinical Trials and Ethics Committee (Ethics number: E1-23-3189).*

Author Contributions: *Concept: YÖ, MAÖ Literature Review: YÖ, MBÖ,ME, Design: YÖ, MBÖ,MAE,ME. Data acquisition: YÖ, MBÖ,MAE,ME Analysis and interpretation: ME Writing manuscript YÖ, MBÖ,MAE,ME Critical revision of manuscript: YÖ, MBÖ,MAE,ME*

Conflict of Interest: *The author(s) do not have any potential conflict of interest regarding the research, authorship and/or publication of this article.*

Financial Disclosure: *Authors declared no financial support.*

REFERENCES

1. Groenewegen A, Rutten FH, Mosterd A, et al. Epidemiology of heart failure. 2020;22(8):1342-56.
2. Bytyçi I, Bajraktari G. Mortality in heart failure patients. Anatol J Cardiol. 2015;15(1):63-8.
3. Gatzov P, Monsuez JJ, Agoston G, et al. Heart Failure 2019 Insights from the National Society of Cardiology journals. Turk Kardiyol Dern Ars. 2021;49(4):341-3.
4. 4.Ajayi AA, Sofowora GG, Ladipo GO. Explaining Heart Failure Hyper-mortality in Sub Saharan Africa: Global Genomic and Environmental Contribution Review. Journal of the National Medical Association. 2020;112(2):141-57.
5. Lüscher TF. Classification of heart failure: A farewell to ejection fraction? Anatol J Cardiol. 2021;25(1):2-6.
6. Yılmaz MB, Aksakal E, Aksu U, et al. Snapshot evaluation of acute and chronic heart failure in real-life in Turkey: A follow-up data for mortality. Anatol J Cardiol. 2020;23(3):160-8.
7. Murphy SP, Kakkar R, McCarthy CP, et al. Inflammation in Heart Failure: JACC State-of-the-Art Review. Journal of the American College of Cardiology. 2020;75(11):1324-40.
8. Rubio-Gracia J, Demissei BG, Ter Maaten JM, et al. Prevalence, predictors and clinical outcome of residual congestion in acute decompensated heart failure. International journal of cardiology. 2018;258:185-91.
9. Çavuşoğlu Y, Alper AT, Altay H, et al. Natriuretic Peptides in Clinical Practice. Anatolian journal of cardiology. 2019;21(Suppl 1):1-40.

10. Ural D, Çavuşoğlu Y, Eren M, et al. Diagnosis and management of acute heart failure. Anatol J Cardiol. 2015;15(11):860-89.
11. Ural D. How to Manage Heart Failure Patients with Not Reduced Ejection Fraction Based on Available Evidence? Turk Kardiyol Dern Ars. 2022;50(4):237-8.
12. Segiet OA, Romuk E, Nowalany-Kozielska E, et al. The concentration of interleukin-33 in heart failure with reduced ejection fraction. Anatolian journal of cardiology. 2019;21(6):305-13.
13. Ozmen N, Cebeci BS, Kardeşoğlu E. Inflammatory markers in heart failure]. Anadolu Kardiyol Derg. 2006;6(1):51-4.
14. Wang S, Zhang J, Wang Y ,et al. NLRP3 inflammasome as a novel therapeutic target for heart failure. Anatol J Cardiol. 2022;26(1):15-22.
15. Cengel A, Sahinarslan A. Nitric oxide and cardiovascular system. Anadolu Kardiyol Derg. 2006;6(4):364-8.
16. Ertem AG, Ozen Y, Yuksekkaya B, et al. Association of the novel inflammatory marker systemic immune-inflammation index and contrast-induced nephropathy in patients undergoing transcatheter aortic valve replacement for severe aortic stenosis. 2022;73(5):422-30.
17. Hu B, Yang XR, Xu Y, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research. 2014;20(23):6212-22.
18. Huang Y, Gao Y, Wu Y, et al. Prognostic value of systemic immune-inflammation index in patients with urologic cancers: a meta-analysis. Cancer cell international. 2020;20:499.
19. Agus HZ, Kahraman S, Arslan C, et al. Systemic immune-inflammation index predicts mortality in infective endocarditis. Journal of the Saudi Heart Association. 2020;32(1):58-64.
20. Erdoğan M, Erdöl MA, Öztürk S, et al. Systemic immune-inflammation index is a novel marker to predict functionally significant coronary artery stenosis. Biomarkers in medicine. 2020;14(16):1553-61.
21. Erdoğan M, Öztürk S, Kardeşler B, et al. The relationship between calcific severe aortic stenosis and systemic immune-inflammation index. Echocardiography (Mount Kisco, NY). 2021;38(5):737-44.
22. Esenboğa K, Kurtul A, Yamantürk YY, et al. Systemic immune-inflammation index predicts no-reflow phenomenon after primary percutaneous coronary intervention. Acta cardiologica. 2022;77(1):59-65.
23. Yılmaz MB. Heart rate in heart failure with mid-range ejection fraction. Anatol J Cardiol. 2019;21(2):75.
24. Usalp S. The Role of Gender in Heart Diseases: Gender and Heart. International Journal of Current Medical and Biological Sciences. 2021;1(1):1-6.
25. Toprak K. Akut Koroner Sendrom ile Gelen Hastalarda Çok Damar Hastalığı ile Monosit/HDL-C Oranı Arasındaki İlişki. Harran Üniversitesi Tıp Fakültesi Dergisi. 2022; 19(1): 98-104.
26. Traxler D, Zimmermann M, Simader E, et al. The inflammatory markers sST2, HSP27 and hsCRP as a prognostic biomarker panel in chronic heart failure patients. Clinica chimica acta; international journal of clinical chemistry. 2020;510:507-14.
27. Kuster N, Huet F, Dupuy AM, et al. Multimarker approach including CRP, sST2 and GDF-15 for prognostic stratification in stable heart failure. ESC heart failure. 2020;7(5):2230-9.
28. Engelmann B, Massberg S. Thrombosis as an intravascular effector of innate immunity. Nature reviews Immunology. 2013;13(1):34-45.
29. Zhong JH, Huang DH, Chen ZY. Prognostic role of systemic immune-inflammation index in solid tumors: a systematic review and meta-analysis. Oncotarget. 2017;8(43):75381-8.
30. Huang J, Zhang Q, Wang R, et al. Systemic Immune-Inflammatory Index Predicts Clinical Outcomes for Elderly Patients with Acute Myocardial Infarction Receiving Percutaneous Coronary Intervention. Medical science monitor : international medical journal of experimental and clinical research. 2019;25:9690-701.
31. Yang YL, Wu CH, Hsu PF, et al. Systemic immune-inflammation index (SII) predicted clinical outcome in patients with coronary artery disease. European journal of clinical investigation. 2020;50(5):e13230.
32. Gülgün M. Analysis of platelet-to-lymphocyte ratio requires methodological consideration. Anatol J Cardiol. 2017;17(2):162-3.
33. Akyel A, Yayla Ç, Erat M, et al. Neutrophil-to-lymphocyte ratio predicts hemodynamic significance of coronary artery stenosis. Anatol J Cardiol. 2015;15(12):1002-7.
34. Kundi H, Gök M, Çetin M, et al. Relationship between platelet-to-lymphocyte ratio and the presence and severity of coronary artery ectasia. Anatol J Cardiol. 2016;16(11):857-62.
35. Acet H, Ertaş F, Akıl MA, et al. Novel predictors of infarct-related artery patency for ST-segment elevation myocardial infarction: Platelet-to-lymphocyte ratio, uric acid, and neutrophil-to-lymphocyte ratio. Anatol J Cardiol. 2015;15(8):648-56.
36. Kundi H, Balun A, Çiçekcioğlu H, et al. Association between platelet to lymphocyte ratio and saphenous vein graft disease in patients with stable angina pectoris. Anatol J Cardiol. 2016;16(5):349-53.
37. Yılmaz E, Güllü A, Karakayalı M, et al. The Relationship between SYNTAX Score and Resting/Post-exercise Ankle-Brachial index in Patients with Acute Coronary Syndrome. International Journal of Current Medical and Biological Sciences. 2022;2(2):117-26.

IJCMBS

THE INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND BIOLOGICAL SCIENCES e-ISSN: 2791-8815

Orginal Article

Evaluation of Knowledge and Attitudes of Family Medicine Residents on Traditional and Complementary Medicine: A descriptive comparative study

Aile Hekimliği Asistanlarının Geleneksel ve Tamamlayıcı Tıp Konusunda Bilgi ve Tutumlarının Değerlendirilmesi: Tanımlayıcı ve karşılaştırmalı bir çalışma

Mahmut Isik[1], Murat Altuntas[2], Ali Timucin Atayoglu[3*]

[1] Department of Family Medicine, Beylikduzu Family Health Center No:4, Istanbul, Turkiye

[2] Department of Family Medicine, Health Sciences University, Bagcilar Training and Research Hospital, Istanbul, Turkiye

[3] Department of Family Medicine, Istanbul Medipol University, International School of Medicine, Istanbul, Turkiye

Corresponding author:
Asst.Prof. Ali Timucin ATAYOGLU
Adress:
Istanbul Medipol University, International School of Medicine, Department of Family Medicine, Beykoz, Istanbul/TURKİYE
E-mail: atatayoglu@medipol.edu.tr

Received: 17.01.2023
Accepted: 20.02.2023
Cite as: ISIK.M et al. Evaluation of Knowledge and Attitudes of Family Medicine Residents on Traditional and Complementary Medicine: A descriptive comparative study. IJCMBS 2023;3 (1):51-8 doi.org/ 10.5281/zenodo.7658058

ABSTRACT

Background: The World Health Organization urges to integrate traditional medicine into health services particularly primary health care services. The aim of this study is to evaluate the knowledge and attitudes of residents on Traditional and Complementary Medicine (T&CM) and compare the ones in the department of Family Medicine with the others.

Materials and Methods: A descriptive comparative study. Residents in a training and research hospital in Istanbul were divided into three groups as Family Medicine, Surgical specialities, and other Medical specialities. A questionnaire consisting of 23 questions was prepared and applied to the residents at the hospital, using a face-to-face interview technique.

Results: In this study, 245 residents from different departments participated. Among them, 68.9% (n=169) stated that T&CM applications might contribute to modern medicine. It was determined that the most known applications were Acupuncture, Cupping therapy, and Hirudotherapy. Among the participants, 11.0% (n=27) of the residents had a certificate of a T&CM applications. According to 69.2% of the residents in Family Medicine the main role of T&CM is in wellness and preventive healthcare. Among the residents in the Family Medicine, the number of participants using T&CM applications in the treatment of their own health problems was found to be higher than the ones in the other medical and surgical specialities; 38.5%, 9.6% and 10.1%, respectively ($p<0.001$).

Conclusion: Compared to other medical and surgical specialities, residents in family medicine seem to have a more positive attitude towards T&CM practices. Further education and training are required for resident physicians to enhance their understanding of the possible efficacy and adverse effects of T&CM practices.

Key words: Family Medicine, Preventive Healthcare, Traditional and Complementary Medicine

ÖZ

Amaç: Dünya Sağlık Örgütü, geleneksel tıbbın sağlık hizmetlerine entegre edilmesini teşvik etmektedir, özellikle de birinci basamakta. Bu çalışmanın amacı, asistan hekimlerin Geleneksel ve Tamamlayıcı Tıp (GETAT) konusundaki bilgi ve tutumlarını değerlendirmek ve bu konuda Aile Hekimliği asistanlarını diğerleriyle karşılaştırmaktır.

Yöntem: Tanımlayıcı-karşılaştırmalı bir çalışma. Bir eğitim ve araştırma hastanesindeki asistanlar aile hekimliği, cerrahi branşlar ve diğer tıp dalları olmak üzere üç gruba ayrıldı. 23 sorudan oluşan bir anket hazırlanarak hastanedeki asistanlara yüz yüze görüşme tekniği kullanılarak uygulandı.

Bulgular: Bu çalışmaya farklı bölümlerden 245 asistan hekim katılmıştır. Hekimlerin %68,9'u (n=169) GETAT uygulamalarının modern tıbba katkı sağlayabileceğini belirtmiştir. En çok bilinen uygulamaların Akupunktur, Kupa terapi ve Hirudoterapi olduğu belirlendi. Katılımcı asistanların arasında %11'inin (n=27) bir GETAT uygulama belgesi bulunmaktaydı. Aile hekimliği asistanlarının %69,2'sine göre GETAT uygulamalarının temel rolü iyilik halinin devamı ve koruyucu sağlık hizmetidir. Aile hekimliği asistanlarında kendi sağlık sorunlarının tedavisinde GETAT uygulamalarını kullananların sayısı diğer dahili ve cerrahi uzmanlık dallarına göre daha fazla bulunmuştur; bu oran sırasıyla %38,5, %9,6 ve %10,1 şeklindedir ($p<0,001$).

Sonuç: Aile hekimliği asistanlarının diğer dahili ve cerrahi uzmanlık dallarına göre GETAT uygulamalarına karşı daha olumlu bir tutuma sahip oldukları görülmektedir. Asistan hekimlere yönelik T&CM uygulamalarının potansiyel etki ve yan etkileri üzerine daha fazla eğitim ve öğretime gereksinim vardır.

Anahtar kelimeler: Aile Hekimliği, Koruyucu Sağlık Hizmeti, Geleneksel ve Tamamlayıcı Tıp

Highlights

- Family medicine residents have relatively more positive attitude towards Traditional & Complementary Medicine.
- According to the family medicine residents, the main role of Traditional & Complementary Medicine should be in wellness and prevention.
- Education and training are required for resident physicians to enhance their understanding of the possible efficacy of Traditional & Complementary Medicine.

Introduction

There has been an increasing interest in Traditional and Complementary Medicine (T&CM) methods all over the world, among the general public and the healthcare professionals (1-3).

In response to that ever-increasing use of T&CM therapies, the US Congress established the National Center for Complementary and Alternative Medicine (NCCAM) as a component of the National Institutes of Health (NIH) in 1998 to explore CAM practices (1). In Europe, CAMbrella which is a European research network for complementary and alternative medicine (CAM) conducted a research programme into the situation of CAM in Europe between 2010 and 2012, coming forward with recommendations as to its viability and place within the established EU healthcare system. CAMbrella Project substantiated the fact that CAM is an established part of healthcare in Europe (2). The findings of the CAMbrella Project noted a high demand for and widespread use of CAM treatments by the people in Europe and highlighted the lack of its integration into national public health systems. The World Health Organization (WHO) urges to integrate traditional medicine into health services particularly primary health care services, within the scope of its 2014-2023 strategy (3-5).

Based on the 2014-2023 strategy of the WHO, Turkish Ministry of Health focused on integration of traditional medicine with modern medicine and the Regulation on Practices of Traditional and Complementary Medicine entered into force in 2014. It promotes integration of T&CM into the national health care system, in accordance with the recommendation of WHO. The Regulation states 15 separate methods of T&CM including acupuncture, apitherapy, maggot therapy, hirudotherapy, phytotherapy, homeopathy, cupping therapy, prolotherapy, ozone therapy, mesotherapy, hypnotherapy, reflexology, music therapy, chiropractic, and osteopathy (6). The Regulation introduced a system of authorization certificates, restricting who may practice T&CM. It is notable that some universities in Turkey have already begun activities with respect to the T&CM.

The aim of this study is to evaluate the knowledge and attitudes of residents on T&CM and compare the ones in the department of Family Medicine with the other medical and surgical specialities.

Materials and Methods

Design of the Study: This was a descriptive comparative study. Residents in a training and research hospital were divided into three groups as Family Medicine, Surgical specialities, and other Medical specialities at the Bagcilar Training and Research Hospital of the University of Health Sciences in Istanbul, Turkey between the 1st and 31st October 2019.

The study determined the necessary sample size using priori power analysis by G*Power software (ver. 3.1.9.4; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). The study required a minimum sample size of 226 with a minimum power of 80%, assuming an effect size of 0.23 and a Type I error rate of 0.05. Participants were asked to choose one of three options, "No," "Yes," or "I'm not sure," regarding their opinion on whether T&CM applications contribute to modern medical practices.. Considering that there will be 8% data loss in the responses of the minimum participants, it was decided that a minimum of 245 participants should be included in the study.

Data Collection: A questionnaire consisting of 23 questions was prepared and applied to the residents using a face-to-face interview technique. In the questionnaire, age, gender, place of birth, specilization, status of having certificate on T&CM, opinion on the T&CM methods as a contributer to modern medicine, and who should perform T&CM applications were evaluated. The data were used in a Family Medicine specialization thesis (7).

Ethical Committee Approval: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of the University of Health Sciences, Bagcilar, Istanbul, Turkey (protocol code: 2019.09.2.01.063.r1.067 and date of approval: 20/09/2019). Informed consent was obtained from all subjects involved in the study.

Statistical Analysis: The obtained data were analyzed in the Statistical Package for the Social Sciences (SPSS) version 25.0 package program. Descriptive findings were presented with frequency and percentage distributions n (%). Comparisons were made between groups of residents from different departments. Chi-square test was used in the analysis of qualitative data. Statistical significance was evaluated at the $p<0.05$ level.

Results

The total number of resident physicians who were the target of the study was 257. Twelve of them (4.7%) reported that they were not available for face-to-face interviews to answer the questionnaire during the study period. The study group consisted of 245 residents (Participation rate: 95.3%).

Among the residents 51.8% (n=127) were male and 48.2% (n=118) were female. The distribution of the physicians' places of birth by region was determined as follows: 24.5% Marmara, 18.8% Central Anatolia, 13.5% Black Sea, 12.2% Eastern Anatolia, 8.9% Mediterranean, 7.7% Aegean, 6.1% Southeast Anatolia and 8.2% abroad. Of the 245 residents participating in the study, 52 (21.2%) were in Family Medicine, 94 (38.4%) were in surgical specialities, and 99 (40.4%) were in other medical specialities (Figure 1).

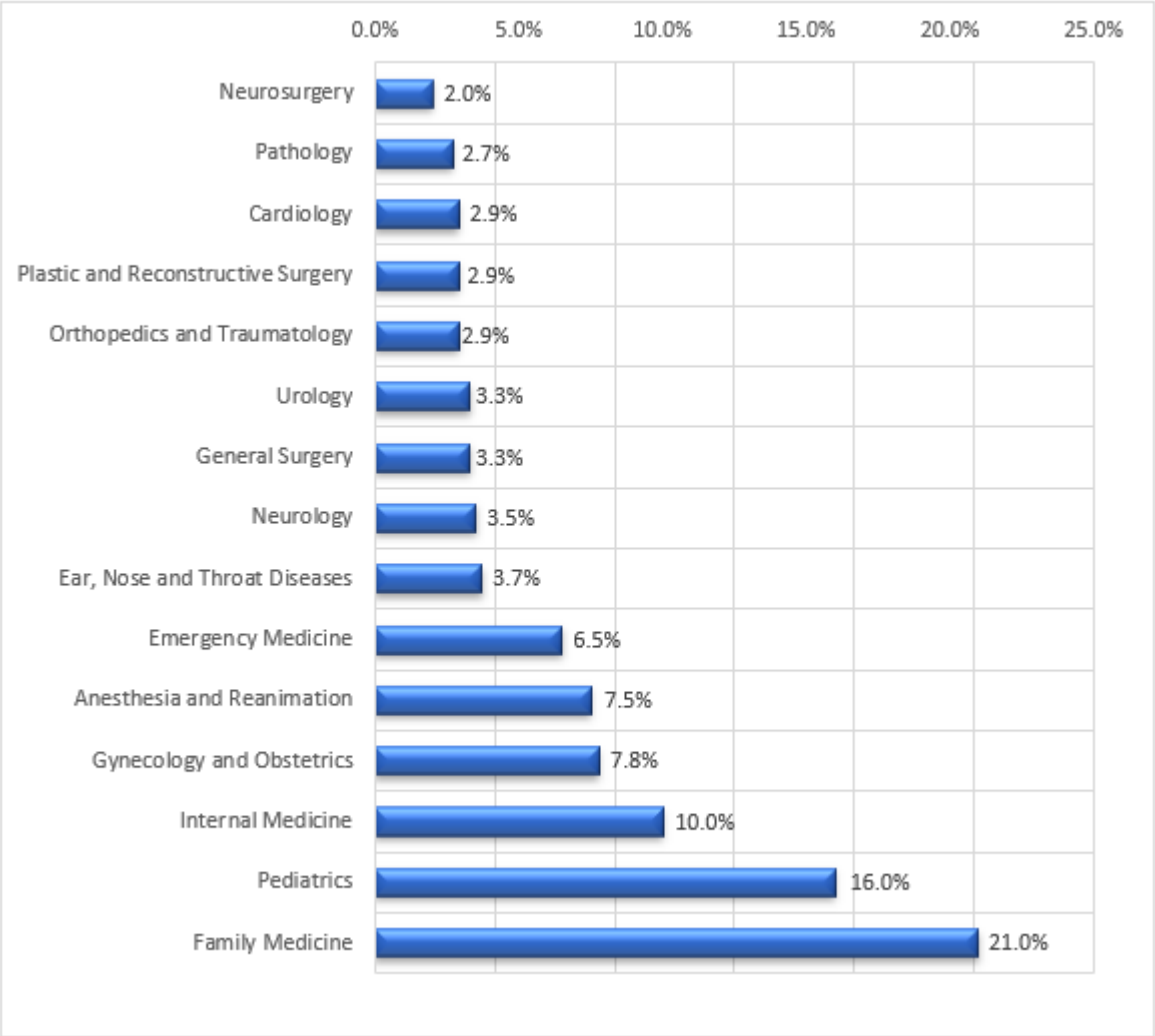


Figure 1. Distribution of physicians by clinics.

In the query made to evaluate the knowledge and attitudes of 245 physicians participating in the study towards T&CM applications; The rate of those who thought that the T&CM methods could contribute to modern medicine was 68.9%, the rate of those who did not think was 13.5%, and the rate of those who were not sure was 17.6%.

Table 1 presents a comparison of views on the contribution of T&CM applications to modern medical practices. The contribution of T&CM to modern medicine was recognized by 76.9% of family physicians, 71.3% of

surgical specialties, and 85.9% of other medical specialties, respectively. However, the difference in proportions among the three groups was not statistically significant (p>0.05).

Table 1. Comparison of the opinions of residents in Family Medicine and other specialties that T&CM applications may contribute to conventional medicine.

		Surgical specialities (n=94)		**Other medical specialities (n= 99)**		**Family Medicine(n= 52)**		
		n	**%**	**n**	**%**	**n**	**%**	**X^2; p***
Whether T&CM may contribute to conventional medicine	*No*	19	20.2	7	7.1	7	13.5	7.802; 0.099
	Yes	67	71.3	85	85.9	40	76.9	
	Not sure	8	8.5	7	7.1	5	9.6	

*Chi-square test was used in the analysis of qualitative data. Statistical significance was evaluated at the p<0.05 level.

Table 2. Comparison of opinions of residents in Family Medicine and other specialties about the main use of T&CM applications.

		Surgical specialities (n=94)		**Other medical specialities (n= 99)**		**Family Medicine (n= 52)**		
		n	**%**	**n**	**%**	**n**	**%**	**X^2; p***
The main purpose of using T&CM	*Diagnostic*	7	7.4	11	11.1	5	9.6	10.375; 0.035
	Treatment	37	39.4	20	20.2	11	21.2	
	Wellness & Prevention	50	53.2	68	68.7	36	69.2	

*Chi-square test was used in the analysis of qualitative data. Statistical significance was evaluated at the p<0.05 level.

The physicians were surveyed regarding their familiarity with traditional and complementary medicine practices recognized by the Ministry of Health. The recognition rate of the three most widely recognized traditional and complementary medicine (T&CM) practices, namely acupuncture, cupping therapy, and leech therapy, was found to be 97%, 88%, and 77% respectively. Comparison of opinions about the main use of T&CM applications in Family Medicine, other medical Specialities and surgical specialities is presented in Table 2. Residents of surgical specialties were the most likely (39.4%) to believe that the primary objective of T&CM practices was for treatment. However, a higher proportion of family physicians and other medical specialties believed that promoting a wellness and prevention was the main goal of T&CM practices (69.2% and 68.7%, respectively) compared to surgical specialties (53.2%), and this difference was statistically significant (p<0.05).

Considering that personal experiences may change their perspective on T&CM applications, physicians were asked whether they have ever applied any of the T&CM applications in their personal lives. Only 15.9% of all physicians answered "yes". Among these, acupuncture is the most common one with 38.5%; cupping therapy is the second one with 36%; hirudotherapy and mesotherapy were the third with 8%.

Comparison of frequency of use of the T&CM applications in is presented in Table 3. The utilization rate of any T&CM intervention for self-treatment among residents in family medicine, surgical specialties, and other medical specialists was found to be 38.5%, 9.6%, and 10.1%, respectively, with a statistically significant difference (p<0.001). While 61.2% (n= 150) of the physicians participating in the study stated that T&CM practices should be included in the basic medical education curriculum; 59.2% (n= 145) reported that T&CM training should not be given to any health personnel except physicians.

Physicians were queried on their beliefs regarding the prevalence of complications in traditional and complementary medicine (T&CM) compared to modern medical practices. 49% of the physician participants responded affirmatively to this question, Of the total participants, 11.0% (n=27) were residents with certification in a T&CM method.

Table 3. Comparison of the residents in Family Medicine and other specialties on being treated with T&CM applications.

		Surgical specialities (n=94)		Other medical specialities (n= 99)		Family Medicine (n= 52)		
		n	**%**	**n**	**%**	**n**	**%**	**X^2; p***
Whether the resident has ever received T&CM treatments for any reason	*No*	85	90.4	89	89.9	32	61.5	25.074; <0.001
	Yes	9	9.6	10	10.1	20	38.5	

*Chi-square test was used in the analysis of qualitative data. Statistical significance was evaluated at the $p<0.05$ level.

Discussion

The number of studies on T&CM practices is growing, and it is crucial for physicians to have knowledge in this field to minimize the risks and maximize the benefits of T&CM. The holistic approach of T&CM, similar to the biopsychosocial model in family medicine, and the integration with other medical fields are key issues. Ensuring that T&CM practices are carried out by certified physicians in approved centers, as regulated, will prevent adverse effects and promote cost-effective and preventive healthcare, reducing the burden on secondary and tertiary health institutions. To progress and develop T&CM practices further, based on evidence, physicians interested in T&CM must be trained, and the infrastructure for this needs to be established.

Previous studies have explored the opinions of physicians regarding T&CM. A survey was carried out in the United States in 1995, which involved 295 family physicians and aimed to explore their opinions on T&CM. The data showed that most of the physicians reported that they either use T&CM practices themselves or refer their patients to them (8). In this current research, it was found that 68.9% of medical practitioners had the perspective that T&CM practices can serve as a complementary adjunct to conventional medicine. Hence, it can be deduced that a substantial portion of the physicians in our study held a favorable viewpoint towards T&CM practices. This perspective aligns with the national regulations regarding T&CM practices, which state that these practices should not be utilized as a replacement for conventional medicine (6). In a previous study, among the family physicians in Istanbul, the majority (70.1%) reported a preference for integrating T&CM practices with conventional medicine (9). In the current study, the perceptions regarding the contribution of T&CM practices to conventional medicine were assessed among three groups, and no significant differences were observed among these groups ($p>0.05$). Considering the holistic health approach and the biopsychosocial approach of family physicians compared to other medical specialities, it could be expected that they would be more prone to T&CM applications; however, our study did not provide any evidence that family medicine residents think differently than residents of other specialties.

In the present investigation, acupuncture was found to be the most widely utilized traditional and complementary medicine practice, with a utilization rate of 97%. Cupping therapy was identified as the second most prevalent, with a utilization rate of 88%, followed by hirudotherapy (leech therapy) with a utilization rate of 77%. Strong evidence supports the efficacy of acupuncture in reducing nausea and pain syndromes, including migraine (10). A meta-analysis determined that the combination use of cupping therapy was significantly more efficacious in treating patients with conditions such as herpes zoster, facial nerve paralysis, acne vulgaris, and cervical spondylosis, in comparison to single modality treatments (11). Hirudotherapy has been shown to be successful in evacuating hematomas and resolving complications following scalp replantation or flap transfers in head and neck reconstructive surgery, as well as enhancing the venous system through non-surgical means (12).

The individual's attitude and interest towards traditional medicine practices are greatly influenced by factors such as family structure, environmental conditions, religious convictions, cultural customs, and traditions of the society. The prevalence of cupping therapy and hirudotherapy in the country may be attributed to the long-standing presence of these practices in the society, as they have been sustained due to religious beliefs and/or cultural traditions. In a previous study, among the family physicians in Istanbul, cupping therapy was the most widely recognized T&CM technique; it was also the most frequently recommended method by physicians (9).

In the curent study, the majority of the participants (71.6%) had no formal T&CM training, and 66.4% reported inquiring about T&CM in their patient consultations. Over half of the physicians (56.79%) believed that T&CM methods should be used in preventive medicine.

According to the systematic review and meta-analysis study of Tozun et al. (13), it has been determined that the most known and used T&CM applications are massage, herbal therapy and acupuncture. The fact that the most used and known applications are compatible with each other suggests that applications are learned based on usage rather than theoretical knowledge. It is not surprising that the most well-known practices are the methods that are in the tradition of the country and the legislation is the oldest. Studies on this subject reflect cultural and

traditional differences. The most commonly used practices in the United States are spiritual healing methods (prayer, etc.), vitamins and herbs, and mind/body approaches (14). In a systematic review of studies from various countries, the most commonly used practices are herbal therapy, chiropractic, massage, and homeopathy (15). In a study conducted in Canada (16), physicians were most knowledgeable about acupuncture (71%), chiropractic (59%) and hypnosis (55%) among T&CM practices; It is reported that the order of the applications that physicians think most useful is the same.

In the present investigation, according to majority of the residents in Family Medicine the main role of T&CM is in "wellness and preventive", while for the residents in surgical specialities the role in the "treatment" was more prominent ($p<0.05$). It is remarkable that physicians know or think that T&CM applications are used not only in treatment, but also in preventive medicine, which is one of the main areas of use, that they can be carried out in a more integrated way with modern medicine. The results of the study can be interpreted by associating it with the 'problem prevention' oriented approach in medical specialties such as family medicine, while 'problem solving' is at the forefront of those in surgical specialties.The study also assessed whether physicians utilized T&CM practices for themselves, with only 15.9% responding in the affirmative. Of these, acupuncture was the most frequently utilized, at 38.5%, followed by cupping therapy at 36%. Hirudotherapy and mesotherapy ranked third, with 8%. The finding that acupuncture was the most commonly used T&CM practice by physicians is in line with the country's early legislation and historical context. Cupping therapy, with its religious and traditional background, likely contributes to its popularity among physicians. Thus, our results are consistent with expectations.

A group of researchers, evaluating the views of physicians on T&CM practices in England and its reflection on health practice, conducted a study with 2748 physicians, 79% of whom worked in the national health system, and 32% of the physicians working in the national health system reported that they use the T&CM applications in their personal life. In addition, it was stated in the study that the most preferred areas of T&CM were acupuncture, aromatherapy and manipulative medicine (17). In a study of health plan members in Minnesota in US, the frequency of use of at least one T&CM was reported as 42% (18). In a study of healthcare workers in Egypt, it was reported that 4.12% of participants usually used T&CM and 38.1% used it sometimes (19). In our study, the frequency of using T&CM by physicians (15.9%) was quite low compared to some other studies. In our study, the frequency of family medicine residents using a T&CM application in their own treatment was found to be higher than the residents in the other two groups. This finding suggests that family medicine residents are more inclined to use T&CM than other physicians. This is an expected result related to the health perspective of family medicine disciplines and practices. In another study conducted in Iran in 2015, 94% of the physicians had a positive attitude towards T&CM applications (20). In a study in Germany, 74% of family physicians stated that basic T&CM training should be given to family physicians (21).

In the current study, 61% of the physicians stated that T&CM practices should be included in the basic medical education curriculum. It is understood from the legislation that these practices are taken from untrained people and only trained physicians are authorized (6). According to the results of the systematic compilation and meta-analysis study carried out by Tozun et al. The prevalence value of the meta-analysis was determined as 21% for physicians or health professionals who received training on T&CM practices. In 19 studies included in the meta-analysis, the opinion of willingness to receive education ranged from 21.9% to 85.3% (13). However, the opinion that T&CM courses should be included in the curriculum of medical and other health schools was reported between 36.7% and 90.4% in 22 studies. In our study, only 11% of the physicians received T&CM training, while 89% did not. This is a fairly low frequency. In a study conducted on primary care physicians in the country, it was determined that the majority of physicians (96%) did not have training on T&CM applications, and 74% wanted additional training on these issues (22). It is recognized that there is a growing interest among physicians in T&CM and that they are seeking training in this area. This has led to calls for T&CM training to be incorporated into the curriculum. It is anticipated that this demand for T&CM education will increase over time.The results of the current study suggest that physicians' demands for training on T&CM and inclusion of T&CM in the curriculum and the competent authorities on these issues should tighten their infrastructure inspections even more.

The biopsychosocial health model, which is one of the basic principles in family medicine, and the holistic health approach in T&CM have similarities. In this context, family medicine practice and T&CM applications seem to have a basic common denominator for the integration as recommended by WHO. The activity of traditional medical practitioners must meet the requirements and standards set forth under the Regulation, including safety, effectiveness and quality. Tozun et al. (23) conducted a comprehensive evaluation of the ethical dimension of the Regulation on T&CM practices. Their assessment reveals that T&CM practices are undergoing a transitional phase both in Turkey and globally. The authors suggest that as the body of scientific evidence

supporting T&CM practices grows, there is potential for these practices to be effectively integrated into modern medicine.

The study has certain limitations. The foremost limitation is that the study's sample size was relatively limited. Additionally, it was carried out at a singular medical facility, which could potentially impact the generalizability of the findings.

Conclusion

This study showed that a majority of the physicians believed that T&CM practices contributed to modern medicine, however only a small number reported using T&CM applications in their own treatment. The majority of the physicians believed that T&CM practices should be included in medical education. According to the majority of the residents in family medicine, the main role of T&CM should be in wellness and prevention.

Compared to other medical and surgical specilities, residents in family medicine seem to have a more positive attitude towards T&CM practices. The biopsychosocial health model, which is one of the basic principles in family medicine, and the holistic health approach in T&CM have similarities. In this context, family medicine practice and T&CM applications seem to have a basic common denominator for the integration as recommended by WHO. Based on the results of the study, it can be suggested that there is a need for further education and training for resident physicians in T&CM practices. Additionally, there is a need for further research to increase understanding of the role and impact of T&CM practices in modern medicine and to address the concerns regarding potential complications. Furthermore, it could be recommended to consider including T&CM practices in the medical education curriculum.

Acknowledgements: *The authors would like to thank all residents who devoted their time to participate in this study. They are warmly acknowledged for the helpful and wholehearted support of Dr. Muhammet Zahid Oncu and Dr. Sercan Bulut. The authors would like to express their gratitude to Prof. Mustafa Tozun from the Department of Public Health and Prof. Ferhan Elmali from the Department of Biostatistics, in Izmir Katip Celebi University for their insightful comments and consultancy in statistical methods.*

Ethical Approval: *The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of the University of Health Sciences, Bagcilar, Istanbul, Turkey (protocol code: 2019.09.2.01.063.r1.067 and date of approval: 20/09/2019).*

Author Contributions: *Concept: MI, MA; Literature Review: MI, ATA; Design: MI; Data acquisition: MI; Analysis and interpretation: MI, MA, ATA; Writing manuscript: MI, ATA; Critical revision of manuscript: ATA*

Conflict of Interest: *The author(s) do not have any potential conflict of interest regarding the research, authorship and/or publication of this article.*

Financial Disclosure: *Authors declared no financial support.*

References

1. National Center for Complementary and Alternative Medicine: Expanding horizons of healthcare: five-year strategic plan 2001–2005. Available from: http://nccam.nih.gov/ strategic/ (cited 30 December 2022). [homepage on the Internet]
2. CAMbrella: A European research network for CAM. Available from: https://cam-europe.eu/library-cam/cambrella-research-reports/ mfa (cited 30 December 2022).
3. World Health Organization. WHO global report on traditional and complementary medicine 2019. Available from: https://apps.who.int/iris/handle/10665/312342 (cited 30 December 2022).
4. World Health Assembly 67. Sixty-seventh World Health Assembly, Geneva, 19-24 May 2014: resolutions and decisions: annexes. Geneva; 2014. Available from: https://apps.who.int/iris/handle/10665/260211 (cited 30 December 2022).
5. World Health Organization. WHO traditional medicine strategy 2002-2005. Available from: https://apps.who.int/iris/handle/10665/67163 (cited 30 December 2022).
6. Regulation on Practices of Traditional and Complementary Medicine; by Turkish Health Ministry. Available from: https://www.resmigazete.gov.tr/eskiler/2014/10/20141027-3.htm (cited 30 December 2022).
7. Işık M. Evaluation of the Knowledge and Attitudes of Residents Trained at the Bağcılar Health Application and Research Center of the Health Sciences University Regarding Traditional and Complementary Medicine Methods. [Istanbul]: Family Medicine Specialization Thesis: Istanbul Health Sciences University, 2020 (Thesis no: 644424). Available from: https://tez.yok.gov.tr/UlusalTezMerkezi/tezSorguSonucYeni.jsp
8. Berman BM, Singh BK, Lao L, et al. Physicians' attitudes toward complementary or alternative medicine: a regional survey. J Am Board Fam Pract. 1995;8(5):361–66.
9. Atayoglu AT, Tokac M, Doğan S, et al. Traditional and complementary medicine perspectives of family physicians in Istanbul. J Fam Pract Palliat Care. 2023; 8(1): 16-23.

10. Allais G, Chiarle G, Sinigaglia S. et al. Acupuncture treatment of migraine, nausea, and vomiting in pregnancy. Neurol Sci. 2019; 40 (Suppl 1), 213–15
11. Cao H, Li X, Liu J. An Updated Review of the Efficacy of Cupping Therapy. PLoS ONE. 2012;7(2): e31793.
12. Heinz P, Tvrdý P, Pink R, et al. Hirudotherapy In Reconstructive Surgery: Case-Reports And Review. Acta Chirurgiae Plasticae. 2020 ;62(3-4):95-102.
13. Tozun M, Bag HK, Pektas M, et al. Knowledge, Attitudes, and Opinions of Health Professionals and Students on Traditional and Complementary Medicine Practices in Turkey: A Systematic Review and Meta-Analysis. Eur J Environ Public Health. Modestum LTD; 2022;6(2):0115.
14. Paltiel O, Avitzour M, Peretz T, et al. Determinants of the use of complementary therapies by patients with cancer. J Clin Oncol. J Clin Oncol; 2001;19(9):2439–48.
15. Frass M, Strassl RP, Friehs H, et al. Use and acceptance of complementary and alternative medicine among the general population and medical personnel: a systematic review. Ochsner J. 2012;12(1):45-56.
16. Verhoef MJ, Sutherland LR. Alternative medicine and general practitioners. Opinions and behaviour. Can Fam Physician. 1995; 41:1005-11.
17. Lewith GT, Hyland M, Gray SF. Attitudes to and use of complementary medicine among physicians in the United Kingdom. Complement Ther Med. Complement Ther Med; 2001;9(3):167–72.
18. Gray CM, Tan AWH, Pronk NP, et al. Complementary and alternative medicine use among health plan members. A cross-sectional survey. Eff Clin Pract. 2002;5(1):17–22.
19. ElOlemy AT, Radwan NM, Dawood W, et al. Complementary and Alternative Medicine use among Health Workers in Mid-Delta, Egypt -. Majmaah J Health Sci. Majmaah University; 2013;1(2):35–42.
20. Barikani A, Beheshti A, Javadi M, Yasi M. Knowledge, Attitude and Practice of General Practitioners toward Complementary and Alternative Medicine: a Cross-Sectional Study. Acta Med Iran. 2015;6;53(8):501–6.
21. Joos S, Musselmann B, Szecsenyi J, et al. Integration of complementary and alternative medicine into family practices in Germany: results of a national survey. Evid Based Complement Alternat Med. 2011; 2011:495813.
22. Ozcakir A, Sadikoglu G, Bayram N, et al. Turkish general practitioners and complementary/alternative medicine. J Altern Complement Med; 2007 Nov 1;13(9):1007-10.
23. Tozun M. Consideration of Traditional and Complementary Medicine Practices in Türkiye in Terms of the Development of Health Policies and Evaluation of the Ethical Dimension of These Practices: J Tradit Complem Med. 2022;5(2):151-9

IJCMBS

THE INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND BIOLOGICAL SCIENCES e-ISSN: 2791-8815

Orgınal Article

Is very advanced maternal age associated with increased prevalence of placenta previa?

Çok ileri anne yaşı, artmış plasenta previa prevalansı ile ilişkili midir?

Muhammet Serhat Yildiz [1*], Meral Tugba Cimsir [2]

[1] Alanya Özel Anadolu HastanesiAntalya/TÜRKİYE
[2] Alanya Özel Şifa Tıp Merkezi

Corresponding author:
Muhammet Serhat YILDIZ
Adress:
Alanya Özel Anadolu Hastanesi
Antalya/TÜRKİYE
E-mail:
m.serhatyildiz@hotmail.com
Received: 24.01.2023
Accepted: 20.02.2023
Cite as: YILDIZ.M.S et al. Is very advanced maternal age associated with increased prevalence of placenta previa? IJCMBS 2023;3 (1):59-63 doi.org/ 10.5281/zenodo.7658823

Abstract

Background: Pregnancies of advanced maternal age have been increasing worldwide in recent years. Advanced maternal age pregnancies have adverse obstetric, perinatal, and neonatal outcomes. This study aims to investigate the frequency of placenta previa in pregnant women of very advanced maternal age and to examine the relationship between advanced maternal age and placenta previa using statistical methodologies.

Methods: This retrospective study includes 140 pregnant women aged 46-48 years who applied to the hospital between September 2018 and December 2019 in our clinic. Patients were divided into two groups according to the mode of delivery: (i) normal vaginal delivery (NVD) (n=99) and (ii) cesarean section (C-section) (n=41). Demographic characteristics, pregnancy outcomes, C-Section rates, preterm delivery rates, fetal growth restriction rate, neonatal outcomes, and C-Section indications were recorded.

Results: A significant difference was found in infant birth weight and the gestational week at delivery between the NVD and C-section groups ($p<0.05$ for both). According to the independent samples t-test, infant birth weight was significantly higher in the NVD group compared to the C-section group ($p<0.05$). Placenta previa was detected in 8 (19.5%) patients in the C-Section group.

Conclusion: The results indicate that placenta previa, which is one of the location anomalies of the placenta, is more common in pregnancies of very advanced maternal age than in pregnancies of normal reproductive age and that having a less fertile uterus at an older age can cause to adverse pregnancy outcomes.

Keywords: Advanced maternal age, Placenta previa, Normal vaginal delivery, Cesarean section

ÖZ

Amaç: Son yıllarda dünya çapında ileri anne yaşındaki gebelikler artmaktadır. İleri anne yaşındaki gebeliklerin olumsuz obstetrik, perinatal ve neonatal sonuçları vardır. Bu çalışmanın amacı çok ileri anne yaşındaki gebelerde plasenta previa sıklığını araştırmak ve ileri anne yaşı ile plasenta previa arasındaki ilişkiyi istatistiksel yöntemlerle incelemektir.

Materiyal ve metod: Bu retrospektif çalışma, kliniğimizde Eylül 2018 ile Aralık 2019 tarihleri arasında hastaneye başvuran 46-48 yaş arası 140 gebeyi içermektedir. Hastalar çalışma şekline göre iki gruba ayrılmıştır. doğum: (i) normal vajinal doğum (n=99) ve (ii) sezaryen (n=41). Demografik özellikler, gebelik sonuçları, Sezaryen oranları, erken doğum oranları, fetal büyüme geriliği oranı, neonatal sonuçlar ve Sezaryen endikasyonları kaydedildi.

Bulgular: Normal vajinal doğum ve sezaryen grupları arasında bebeğin doğum ağırlığı ve doğumdaki gebelik haftası açısından anlamlı bir fark bulundu (her ikisi için de $p<0.05$). Bağımsız örneklem t-testine göre bebek doğum ağırlığı normal vajinal doğum grubunda sezaryen grubuna göre anlamlı olarak daha yüksekti ($p<0.05$). Sezaryen grubunda 8 (%19,5) hastada plasenta previa saptandı.

Sonuç: Sonuçlar, plasentanın yerleşim anomalilerinden biri olan plasenta previa'nın çok ileri anne yaşındaki gebeliklerde normal üreme çağındaki gebeliklere göre daha sık görüldüğünü ve ileri yaşta daha az fertil bir uterusa sahip olmanın olumsuz gebelik sonuçlarına neden olabileceğine işaret etmektedir.

Anahtar Kelimeler: İleri anne yaşı, Plasenta previa, Normal vajinal doğum, Sezaryen

INTRODUCTION

Working women prefer to give birth between the ages of 35 and 44 due to their desire to gain financial stability and their aim for a successful career, thus leading to a substantial increase in pregnancies at advanced maternal age. Furthermore, the failure of traditional family planning methods and housewives' desire to have a larger family has resulted in a rise in advanced maternal age in the regions with low socioeconomic status.

Although many researchers define advanced maternal age as an age of 35 years and above (1-6), the term "advanced maternal age" in the medical literature is often defined as an age over 40 years (7-10).

The birth rate of mothers aged 35 to 39 and 40 to 45 years is gradually increasing throughout the world, while this rate has notably increased within the last three years in women aged 35 to 40 years. In turn, these increasing trends lead to raised cesarean delivery rates and serious complications associated with advanced maternal age (11,12).

Placenta previa is a severe complication of pregnancy that caused adverse outcomes for maternal and fetal health, including adherence to the placenta, antepartum hemorrhage, intrauterine growth restriction, postpartum hemorrhage, malpresentation, preterm labor, septicemia, and thrombophlebitis (13) Therefore, pregnancies complicated by placenta previa have a higher risk for adverse maternal and neonatal outcomes (14).

The present study aims i) to evaluate the effect of very advanced maternal age which becomes a crucial social problem, on pregnancy and neonatal outcomes, ii) to investigate whether pregnancy outcomes, neonatal outcomes, and delivery patterns of pregnant women are associated with very advanced maternal age. These results will be beneficial for clinicians performing antenatal follow-ups of pregnant women at very advanced maternal age.

Methods

Research population and design

This single-center retrospective study included 140 pregnant women aged between 46-48 years who were followed up in our clinic between September 2018 and December 2019. Patients were divided into two groups according to the mode of delivery: (i) normal vaginal delivery (NVD) (n=99) and (ii) cesarean section (C-section) (n=41). Both groups were further divided into three subgroups according to maternal age: (1) 46 years, (2) 47 years, and (3) 48 years.

All criteria for inclusion were singleton pregnancy, age 46 years and over, non-smoking, ongoing use of iron, folic acid, multivitamin replacement, and regular antenatal pregnancy follow-up. Patients with prior use of Assisted Reproductive Techniques (ART) and those aged 45 years and younger were excluded from the study. Demographic characteristics, pregnancy outcomes, gestational week, infant birth weight, neonatal outcomes, mode of delivery, and C-Section indications were recorded for each patient.

Statistical analysis

The data was analyzed using SPSS for Windows version 22.0 (Armonk, NY: IBM Corp.). The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as frequencies (n) and percentages (%). Continuous variables were compared using the Independent Samples *t*-test, and categorical variables were compared using the Chi-square test. A *p-value* of <0.05 was considered significant.

Results

The findings indicated a significant difference between the NVD and C-section groups in terms of infant birth weight and gestational week at delivery ($p<0.05$ for both) (Table 1). However, there was no significant difference concerning maternal age ($p>0.05$).

Table 1. Distribution of delivery weeks

Gestational week at delivery	C-Section (N=41)	NVD (N=99)
32	1 (2.4%)	0 (0%)
33	1 (2.4%)	0 (0%)
35	4 (9.8%)	1 (1%)
36	4 (9.8%)	3 (3%)
37	8 (19.5%)	31 (31.3%)
38	16 (39%)	46 (46.5%)
39	4 (9.8%)	12 (12.1%)
40	3 (7.3%)	6 (6.1%)

C-Section: Cesarean Section, NVD: Normal vaginal delivery

Independent Samples t-test showed that infant birth weight was significantly higher in the NVD group compared to the C-section group ($p<0.05$) (Table 2).

Table 2. Descriptive statistics and analysis results

Maternal age (years)	**C-Section (n=41)**	**NVD (n=99)**	***p***
46	19 (46.3%)	53 (53.5%)	[b]0.731
47	12 (29.3%)	22 (22.2%)	
48	7 (17.1%)	14 (14.1%)	
49	3 (7.3%)	10 (10.1%)	
Mean maternal age (years)	46.85 ± 0.96	46.81 ± 1.03	[a]0.808
Mean infant birth weight (kg)	3055.4 ± 766.6	3360.1 ± 471.1	*[a]0.022**
Gestational week at delivery			
32-36	10 (24.4%)	4 (4.0%)	*[b]0.003**
37	8 (19.5%)	31 (31.3%)	
38	16 (39.0%)	46 (46.5%)	
39-40	7 (17.1%)	18 (18.2%)	

C-Section: Cesarean Section, NVD: Normal vaginal delivery, *$p<0.05$; [a] Independent Samples t-test; [b] Chi-square test

According to Chi-Square test results, no significant difference was found in the mode of delivery between the gestational weeks of 38 and 39-40, while the proportion of patients who gave delivery at the week of 37 was significantly higher in the NVD group compared to the C-section group (31.5% vs. 19.5%) ($p<0.05$). In contrast, the rate of patients with a gestational period of 32-36 weeks was significantly higher in the C-section group compared to the NVD group (24.4% vs. 4%) ($p<0.05$) (Tables 1 and 2). Among the C-Section indications, placenta previa was detected in 8 (19.5%) patients (Table 3).

Table 3. Distribution of C-Section indications

Cesarean indications	C-Section (N=41)
Previous C-Section	17 (41.5%)
Fetal distress	7 (17.1%)
Non-progressive labor	2 (4.9%)
Umbilical cord prolapse	1 (2.4%)
Breech presentation	3 (7.3%)
Placental abruption	1 (2.4%)
Placenta previa	8 (19.5%)
Preeclampsia	2 (4.9%)

Discussion

Advanced maternal age is becoming more common nowadays, which increases the risk of complications during pregnancy. Uterine blood flow decreases, and uteroplacental perfusion impairs in line with the physiological changes were associated with aging. In turn, having a less fertile uterus at an older age all by itself contributes to higher risks of adverse pregnancy outcomes [15]. In this retrospective study, we examined the relationship between advanced maternal age and placenta previa using statistical methodologies, as well as to investigate the frequency of placenta previa in pregnant women of very advanced maternal age by evaluating obstetric, perinatal, and neonatal outcomes.

The greatest strength of the present study is its number of participants. Placenta previa is a rare pregnancy complication, and large sample size is needed to detect such a situation. Our data were obtained from Sanliurfa Training and Research Hospital, where the fertility rate is the highest in Turkey (4.29 children per woman) according to the 2017 data of the Turkish Statistical Institute and where 73,000 births occur annually (16).

Literature indicates that with advancing age, both uterine function and pelvic compliance decrease, leading to prolonged labor. This situation results in increased cesarean delivery rates (17). Our findings were consistent with literature showing that very advanced maternal age alone could form an indication for C-Section. One of the reasons for the increase in cesarean delivery rates in advanced maternal age pregnancies is the location anomalies of the placenta. Placenta previa comes on in 0.3% to 2% of women of reproductive age (6) and in 18.8% of women aged 35 or older (18). The results showed that the prevalence of placenta previa was significantly higher in advanced age pregnancies than the prevalence of pregnancies in women of reproductive

age reported by Bi et al. (19). In the present study, placenta previa was detected in 8 out of 41 patients in the C-Section group, which suggests that the frequency of placenta previa may be closely related to the increased maternal age. A meta-analysis including 23 different studies reported that there was a relationship between advanced maternal age and placenta previa (6). Our findings are compatible with this meta-analysis and underscore the necessity of recommending early diagnosis and adequate treatment to pregnant women in advanced stages of pregnancy. Although most studies conducted on advanced maternal age (7-11) have been included pregnant women over 35 years, only a few studies have investigated the association between very advanced maternal age (> 40) and placenta previa (18-20). In this respect, present study is of high value since it examined the pregnancy outcomes of pregnant women aged 46-48 years in a single center.

Available evidence suggests that advanced maternal age is associated with increased pregnancy complications and adverse neonatal outcomes, including cesarean delivery, preterm labor, low birth weight, preeclampsia, gestational diabetes, maternal mortality, and perinatal mortality (11,21-25). However, most studies have focused on the results of pregnancies over the age of 35 and 40, while the studies conducted with very advanced maternal age groups (>45 years) are highly limited. A study conducted in Australia evaluated the results of 217 pregnant women aged over 45 years (26), and another study evaluated 924 pregnant women aged over 45 years out of 367,417 pregnant women from 149 different Japanese tertiary hospitals (11). Accordingly, the present study is highly specific since it evaluated 140 pregnant women aged 46 and over from a single center.

In addition, most of studies available in the literature were published approximately 20 years ago (11,27-29). Today, both male and female infertility are highly common in the society and thus the need for ART is greater and couples spend huge amounts of time and money to achieve a healthy pregnancy. As a result, the proportion of advanced-age mothers in the general population increases day by day (30). Depending on the studies in the literature investigating the poor obstetric and neonatal outcomes of ART pregnancies, we did not include ART pregnancies in our study (31).

Conclusion

Very advanced maternal age is associated with the increased risk of placenta previa and raised cesarean delivery rates. Therefore, further large-scale studies investigating advanced maternal age are needed to elucidate the adverse outcomes of very advanced maternal age.

Acknowledgements: *None*

Ethical Approval: *Ethical approval was obtained from Alaaddin Keykubat University Research Ethics Committee (Approval No: 10354421-2020/25-21), and signed informed consent was obtained from each participant. Study protocols were conducted following the principles of the Declaration of Helsinki and the principles of Good Clinical Practice.*

Author Contributions: *Concept: MYS; Literature Review: MSY, MTC; Design: MSY; Data acquisition: MSY; Analysis and interpretation: MSY, MTC; Writing manuscript: MSY, MTC; Critical revision of manuscript: MSY*

Conflict of Interest: *The author(s) do not have any potential conflict of interest regarding the research, authorship and/or publication of this article.*

Financial Disclosure: *Authors declared no financial support.*

REFERENCES

1. National Center for Complementary and Alternative Medicine: Expanding horizons of healthcare: five-year strategic plan 2001–2005. Available from: http://nccam.nih.gov/ strategic/ (cited 30 December 2022). [homepage on the Internet]
2. CAMbrella: A European research network for CAM. Available from: https://cam-europe.eu/library-cam/cambrella-research-reports/ mfa (cited 30 December 2022).
3. World Health Organization. WHO global report on traditional and complementary medicine 2019. Available from: https://apps.who.int/iris/handle/10665/312342 (cited 30 December 2022).
4. World Health Assembly 67. Sixty-seventh World Health Assembly, Geneva, 19-24 May 2014: resolutions and decisions: annexes. Geneva; 2014. Available from: https://apps.who.int/iris/handle/10665/260211 (cited 30 December 2022).
5. World Health Organization. WHO traditional medicine strategy 2002-2005. Available from: https://apps.who.int/iris/handle/10665/67163 (cited 30 December 2022).
6. Regulation on Practices of Traditional and Complementary Medicine; by Turkish Health Ministry. Available from: https://www.resmigazete.gov.tr/eskiler/2014/10/20141027-3.htm (cited 30 December 2022).
7. Işık M. Evaluation of the Knowledge and Attitudes of Residents Trained at the Bağcılar Health Application and Research Center of the Health Sciences University Regarding Traditional and Complementary Medicine Methods. [Istanbul]: Family Medicine Specialization Thesis: Istanbul Health Sciences University, 2020. Available from: https://tez.yok.gov.tr/UlusalTezMerkezi/tezSorguSonucYeni.jsp
8. Berman BM, Singh BK, Lao L, et al. Physicians' attitudes toward complementary or alternative medicine: a regional survey. J Am Board Fam Pract. 1995;8(5):361–66.

9. Atayoglu AT, Tokac M, Doğan S, et al. Traditional and complementary medicine perspectives of family physicians in Istanbul. J Fam Pract Palliat Care. 2023; 8(1): 16-23.
10. Allais G, Chiarle G, Sinigaglia S. et al. Acupuncture treatment of migraine, nausea, and vomiting in pregnancy. Neurol Sci. 2019; 40 (Suppl 1), 213–15
11. Cao H, Li X, Liu J. An Updated Review of the Efficacy of Cupping Therapy. PLoS ONE. 2012;7(2): e31793.
12. Heinz P, Tvrdý P, Pink R, et al. Hirudotherapy In Reconstructive Surgery: Case-Reports And Review. Acta Chirurgiae Plasticae. 2020 ;62(3-4):95-102.
13. Tozun M, Bag HK, Pektas M, et al. Knowledge, Attitudes, and Opinions of Health Professionals and Students on Traditional and Complementary Medicine Practices in Turkey: A Systematic Review and Meta-Analysis. Eur J Environ Public Health. Modestum LTD; 2022;6(2):0115.
14. Paltiel O, Avitzour M, Peretz T, et al. Determinants of the use of complementary therapies by patients with cancer. J Clin Oncol. J Clin Oncol; 2001;19(9):2439–48.
15. Frass M, Strassl RP, Friehs H, et al. Use and acceptance of complementary and alternative medicine among the general population and medical personnel: a systematic review. Ochsner J. 2012;12(1):45-56.
16. Verhoef MJ, Sutherland LR. Alternative medicine and general practitioners. Opinions and behaviour. Can Fam Physician. 1995; 41:1005-11.
17. Lewith GT, Hyland M, Gray SF. Attitudes to and use of complementary medicine among physicians in the United Kingdom. Complement Ther Med. Complement Ther Med; 2001;9(3):167–72.
18. Gray CM, Tan AWH, Pronk NP, et al. Complementary and alternative medicine use among health plan members. A cross-sectional survey. Eff Clin Pract. 2002;5(1):17–22.
19. ElOlemy AT, Radwan NM, Dawood W, et al. Complementary and Alternative Medicine use among Health Workers in Mid-Delta, Egypt -. Majmaah J Health Sci. Majmaah University; 2013;1(2):35–42.
20. Barikani A, Beheshti A, Javadi M, Yasi M. Knowledge, Attitude and Practice of General Practitioners toward Complementary and Alternative Medicine: a Cross-Sectional Study. Acta Med Iran. 2015;6;53(8):501–6.
21. Joos S, Musselmann B, Szecsenyi J, et al. Integration of complementary and alternative medicine into family practices in Germany: results of a national survey. Evid Based Complement Alternat Med. 2011; 2011:495813.
22. Ozcakir A, Sadikoglu G, Bayram N, et al. Turkish general practitioners and complementary/alternative medicine. J Altern Complement Med; 2007 Nov 1;13(9):1007-10.
23. Tozn M. Consideration of Traditional and Complementary Medicine Practices in Türkiye in Terms of the Development of Health Policies and Evaluation of the Ethical Dimension of These Practices: J Tradit Complem Med. 2022;5(2):151-9

IJCMBS

THE INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND BIOLOGICAL SCIENCES e-ISSN: 2791-8815

Orgınal Article

Investigation of Complementary and Alternative Medicine Use in Turkish Patients with Epilepsy

Epilepsili Türk Hastalarda Tamamlayici ve Alternatif Tip Kullaniminin Araştirilmasi

Ulkuhan DUZGUN [1*], Faruk YESILTAS [2], Omer KARADAS [3], Cengiz BEYSAN [1], Oktay SARI

[1] Neurology department, Health Sciences University, Gulhane training and research hospital Ankara/Türkiye

[2]TOBB University of Economics and Technology Hospital Traditional and Complementary Medicine Application Center Ankara/Türkiye

[3]Neurology department, Health Sciences University, Gulhane Faculty of Medicine Ankara/Türkiye

[4]Family Medicine, Health Sciences University, Gulhane Faculty of Medicine Ankara/Türkiye

**Corresponding author:*
Ulkuhan DUZGUN

Adress:
Neurology department, Health Sciences University, Gulhane training and research hospital Ankara/Türkiye

E-mail:
ulkuhanduzgun@hotmail.com

Received: 08.01.2023
Accepted: 20.02.2023
Cite as: DUZGUN. U. et al. Investigation of Complementary and Alternative Medicine Use in Turkish Patients with Epilepsy. IJCMBS 2023;3 (1):64-71 doi.org/ 10.5281/zenodo.7676250

Abstract

Background: New generation antiepileptic drugs, adopted in treating epilepsy in recent years, yield better results. Yet, patients may perceive themselves as helpless due to the burden of epilepsy and, thus, seek any treatment approach to relieve their problems. Complementary/alternative medicine (CAM) has recently become preferred among patients worldwide. In this study, we attempted to investigate CAM use among Turkish patients with epilepsy and their knowledge, attitude, and behavior profiles regarding CAM. **Materials and Methods:** We carried out this prospective cross-sectional study with epileptic patients aged 18 years and older. After noting down their demographic and clinical characteristics, we inquired the patients about CAM methods. In addition, we collected the data using the Perception of Health Scale (PHS), the Dispositional Hope Scale (DHS), and the Problem-Solving Inventory (PSI).**Results:** There were 135 patients with epilepsy, 45.92% males and 54.1% females, with a median age of 29 years (IQR=22-42). While 81.5% of the patients had focal-onset, 18.5% had generalized-onset seizures. The mean disease duration was 9 years (IQR=4-19). About one-third (29%) used at least one CAM method. The most common CAM methods reported by the patients were massage therapy (30.2%), herbal therapy (25.2%), and hijamat-cupping (18.6%). In addition, 78.95% stated the CAM method they used was helpful. Finally, we found disease duration to be significantly higher among CAM users (p=0.02). **Conclusion:** CAM use was prevalent among patients with epilepsy, and those with prolonged disease duration used CAM more; therefore, patients should be inquired about CAM use. Further research may consider scientifically evaluating all aspects of CAM use and methods. **Keywords:** Complementary and alternative medicine; CAM; Traditional medicine; Epilepsy; Turkish patients; Perception of health scale; Dispositional hope scale; Problem-solving inventory

ÖZ **Amaç:**Son yıllarda epilepsi tedavisinde kullanılmaya başlanan yeni kuşak antiepileptik ilaçlar, epilepsi tedavisinde hem yan etki profili hemde etkililik açısından daha iyi sonuçlar vermektedir. Ancak epilepsinin kendi hastalık yükü, gerekse de ilaçların yan etkileri nedeniyle hastalar hem fiziksel hem de psikososyal olarak kendilerini çaresiz görmekte, çözüm olabilecek her türlü tedavi yaklaşımını araştırma yoluna gitmektedirler. Tamamlayıcı/Alternatif Tıp (TAT) da ülkemizde ve dünyada hastaların tercih ettikleri modern tıp dışı yöntemlerden biridir. Bu çalışmada TAT yöntemlerinin kullanım sıklığını ve bu yöntemler konusundaki bilgi, tutum ve davranış profilini araştırmayı amaçladık.**Materyal ve Metod:** Bu prospektif tanımlayıcı kesitsel çalışmaya nöroloji polikliniğinde takipli 18 ve üstü, gönüllü hastalar dahil edildi. Hastaların demografik ve klinik bilgileri kaydedildi. Hastalara TAT yöntemlerini kullanım durumları, bilgi düzeyleri ve TAT yöntemleri konusundaki düşüncelerinin sorgulandığı sorular soruldu. Ayrıca Sağlık Algısı Ölçeği (SAÖ), Sürekli Umut Ölçeği (SUÖ), Problem Çözme Envanteri (PÇE) hastalara anket yöntemi ile uygulandı.

Bulgular: Çalışmaya dahil edilen 135 epilepsi hastasının % 45,92'si (n=62) erkek, %54,1'i (n=73) kadın cinsiyete sahipti. Yaş ortalamaları 29 (IQR, 22-42) idi. Hastaların %81.5'i (n=110) fokal başlangıçlı, %18.5'i (n=25) jeneralize başlangıçlı nöbet tipine sahipti ve hastalık süresi ortalama 9 (IQR, 4-19) yıl idi. Hastaların %29'u (n=38) en az bir TAT yöntemini kullanmıştı. Hastaların en sık kullandıkları TAT yöntemleri masaj uygulaması (%30,2 (n=13)), bitkisel tedavi (%25.2 (n=11)) ve kupa- hacamat (%18.6 (n=8)) dı. Kullanan hastaların %78,95'i (n=30) TAT yönteminin faydalı olduğunu ifade etti. Hastalık süresi TAT kullananlarda anlamlı olarak yüksek saptandı (p=0.02).**Sonuç:** Epilepsi hastalarında TAT kullanımı yaygındır ve hastalık süresi uzun olan hastalar daha fazla TAT kullanmaktadır. Hastalar mutlaka TAT kullanımı açısından sorgulanmalıdır. Gelecekteki çalışmalar TAT kullanımının ve yöntemlerinin tüm yönleri ile bilimsel açıdan değerlendirilmesi yönünde olmalıdır.

Anahtar Kelimeler: Tamamlayıcı ve alternatif tıp; TAT; Geleneksel tıp; Epilepsi; Türk hastalar; Sağlık algısı ölçeği; Sürekli umut ölçeği; Problem çözme envanteri.

Highlights

- We reported that 29% of the patients used at least one CAM method.
- The most commonly used CAM methods were massage and herbal treatments.
- 79% of CAM users stated that they found CAM methods useful.
- As the duration of the disease increased, the use of CAM increased.

INTRODUCTION

Epilepsy is a chronic, non-communicable brain disease that is likely to affect people of all ages. It is considered among the most prevalent neurological disorders, affecting about 50 million people worldwide. Although a significant part of the seizures in people with epilepsy can now be controlled thanks to antiseizure drugs, patients still experience many psychosocial problems due to the disease burden and drug side effects (1,2). The declined academic and professional performance, decreased familial and environmental support, disease burden, seizure/fear of seizure, social stigma, and undesirable attitudes toward epilepsy patients lead to psychosocial issues in patients, making them isolated from society (3). Thus, epilepsy patients perceive themselves as helpless and seek every possible treatment approach to relieve their problems. Complementary/alternative medicine (CAM) has recently become preferred among patients worldwide (4,5,6).

According to the World Health Organization (WHO), traditional medicine refers to "the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, used in the maintenance of health and in the prevention, diagnosis, improvement or treatment of physical and mental illness." The terms "complementary medicine" or "alternative medicine" refer to a broad set of healthcare practices that are not part of a country's own tradition or traditional medicine and are not fully integrated into the prevailing health system in that country (7). According to the National Center for Complementary and Alternative Medicine (NCCAM), while the use of CAM practices with conventional medicine refers to complementary medicine, its use rather than conventional medicine practices is called alternative medicine (8). As a result of the recent discussions in Turkey based on the definition of WHO, it was decided that there is no alternative to medicine, but only an alternative to treatment, highlighting the definition of 'traditional and complementary medicine' (9).

The methods accepted in the Turkish traditional and complementary medicine (TCM) regulation are phytotherapy (herbal treatment), larva (Maggot) therapy, prolotherapy, music therapy, osteopathy, mesotherapy, chiropractic, homeopathy, reflexology, cupping, leech therapy, apitherapy, hypnotherapy, and acupuncture (10). For these practices, many universities and state hospitals have established TCM centers.

The literature hosts a paucity of research investigating CAM use and the factors affecting its use among Turkish epilepsy patients. Besides, to the best of our knowledge, research interest seems to have missed the use of CAM by analyzing the psychosocial states of individuals with epilepsy.Thus, the present study investigated the frequency of and factors affecting CAM use in epilepsy patients and their knowledge, attitude, and behavior profile regarding these methods.

Materials and Methods:

Study popilations

The sample of this descriptive cross-sectional study consisted of epilepsy patients aged 18 years and older having good cognitive functions and followed up in the neurology outpatient clinic of a tertiary healthcare center.

Data collection

We collected the demographic (age, sex, educational attainment, marital status, place of residence, family structure, income status, smoking-alcohol use) and clinical characteristics (disease duration, seizure type, frequency, and time, and antiseizure drug use), CAM use, and knowledge and opinions on CAM methods) of patients with epilepsy through face-to-face interviews. Then, the patients were administered the Perception of Health Scale (PHS), the Dispositional Hope Scale (DHS), and the Problem-Solving Inventory (PSI) to analyze psychosocial factors that might affect their CAM use. Besides, we used the 2017 International League Against Epilepsy (ILAE) classification to classify epileptic seizures (11).

Perception of Health Scale

Developed by Diamond et al., the PHS is a relatively novel instrument (12). Kadıoğlu and Yıldız (2012) adapted the PHS into the Turkish context (13). Fifteen items on the scale are covered by four subscales: center of control, self-awareness, certainty, and importance of health. The responses are scored on a five-point Likert-type scale ranging from 1 (strongly disagree) to 5 (strongly agree), and items with negative statements are reverse-coded. One may obtain a score ranging between 15 (min) and 75 (max).

Dispositional Hope Scale

The 12-item DHS was designed by Snyder et al. (14) and adapted into Turkish by Tarhan and Bacanlı (15). The pathways and agentic thinking subscales host four items each, and the other four consist of filler statements irrelevant to hope. Responses are scored on an eight-point Likert-type scale, and only the scores on the pathways (items 1, 4, 6, and 8) and agentic thinking (items 2, 9, 10, and 12) subscales are considered to calculate a total dispositional hope score. One may obtain a score ranging between 8 (min) and 64 (max).

Problem-Solving Inventory

Heppner and Peterson developed the PSI (16), and Şahin et al. carried out the validity and reliability study of its Turkish version (17). The 6-point Likert-type inventory consists of 35 items. While determining the total score, items 9, 22, and 29 are excluded from the calculation, and items 1, 2, 3, 4, 11, 13, 14, 15, 17, 21, 25, 26, 30, 32, and 34 are reversely scored. Therefore, one may obtain a score ranging between 32 (min) and 192 (max).

Ethical considerationsThe Ethics Committee of Gulhane Medical Faculty, Health Sciences University granted ethical approval to our study (No: 2019-115 dated 03.23.2019). In this study, we strictly followed the principles of the revised Declaration of Helsinki and obtained written informed consent from the patients.

Statistical analysis

While categorical variables are presented as percentages and numbers, continuous variables are shown as means ± standard deviations or medians (interquartile range). We used the Kolmogorov-Smirnov test to check the normality of the data distribution. Accordingly, we compared normally distributed data using an independent samples *t*-test and non-normally distributed data using a Mann-Whitney U test. In addition, categorical variables were compared with a chi-square test. We performed all statistical analyses on SPSS 22.0 and accepted a *p*-value < 0.05 as statistically significant.

RESULTS

Participants' demographic characteristics

We carried out this study with 135 patients with epilepsy, 45.92% (n=62) males and 54.1% (n=73) females, with a median age of 29 years (IQR = 22-42). Five (3.7%) patients were illiterate, 21.5% (n=29) were primary school graduates, 49.6% (n=67) held a high school diploma, and 25.2% (n=34) held a higher education degree. While 13.3% (n=18) lived in a rural area, 86.7% (n=117) were urban dwellers. Finally, 26.7% (n=36) of the patients had a smoking habit, and 9.6% (n=13) had alcohol consumption (Table 1).

Participants' clinical characteristics

The median disease duration among the participants was 9 years (IQR=4-19). Most of the patients (81.5%; n=110) had focal-onset seizures, while 18.5% (n=25) had generalized-onset seizures. Given the use of antiseizure drugs, 68.1% (n=92) were receiving monotherapy, and 31.8% (n=43) were receiving polytherapy. About 44.4% (n=60) had one year ≤ seizure-free, but 37.8% (n=51) had seizures less than once a month, and 17.8% (n=24) had more than one seizure per month (Table 1).

Participants' CAM use

We found that 29% (n=38) of the patients used at least one CAM method. The majority (78.95%; n=30) stated that the CAM method was helpful, but 21.05% (n=8) did not find it useful. When asking all patients, 'Do you think CAM use is helpful?', 47.7% (n=62) among the respondents (n=130) thought that CAM use was helpful, 28.5% (n=37) thought that the CAM methods were not helpful, and 23.8% (n=31) had no idea about CAM use. The most common sources of learning about CAM were physician advice (36.5%; n=72) and the internet (33.5%; n=66). Moreover, the participants thought CAM methods to be used for every disease/to prevent aging (22.8%; n=75) and for chronic conditions (19.5%; n=66). We also discovered that the patients preferred the following CAM methods the most: massage therapy (30.2%; n=13), herbal treatment (25.2%; n=11), and hijamat-cupping (18.6%; n=8) (Table 2).

The patients' PHS, DHS, and PSI scores

The participants' median PHS score was found to be 47 (IQR=44-52), which may correspond to a moderate perception of health. Moreover, they got a median score of 52 (IQR=46-56) on the DHS; therefore, we can assert that the participants had high dispositional hope. Finally, the median PSI score of the participants was found to be 97 (IQR=86-107), implying moderate problem-solving ability.

Comparison of the research variables by CAM use

Our findings revealed no significant difference between the patients' demographic characteristics (age, sex, educational attainment, place of residence, perceived income status) by CAM use (p=0.92, 0.46, 0.68, 0.23, and 0.36, respectively; Table 3). While we found that disease duration was significantly higher among the CAM users (p=0.02), the patients' other clinical characteristics (antiseizure drugs (monotherapy-polytherapy), seizure type, and frequency of seizures) did not significantly differ by CAM use (p=0.08, 0.06, and 0.15, respectively; Table 4). Finally, we discovered the patients' PHS, DHS, and PSI scores did not significantly differ by CAM use (p=0.79, 0.95, and 0.54, respectively; Table 5).

Table 1. Patients' demographic and clinical characteristics

Age, median (IQR)	29 (22-42)	
Sex (n=135)	n	%
Male	62	45.9
Female	73	54.1
Educational attainment (n=135)		
Illiterate	5	3.7
Primary school	29	21.5
High school	67	49.6
Higher education	34	25.2
Marital status (n=135)		
Married	60	44.4
Single	75	55.6
Place of residence (n=135)		
Rural area	18	13.3
Urban area	117	86.7
Family structure (n=135)		
Nuclear	115	85.2
Extended	20	14.8
Perceived income status (n=135)		
Very good	21	15.6
Good	76	56.3
Moderate	26	19.3
Poor	12	8.9
Smoking (n=135)		
Yes	36	26.7
No	83	61.5
Ceased	16	11.9
Alcohol consumption (n=135)		
Yes	13	9.6
No	122	90.4
Disease duration, median (IQR)	9 (4-19)	
Antiseizure drug (n=135)	n	%
Monotherapy	92	68.1
Polytherapy	43	31.8
Seizure frequency (n=135)		
One year ≤ seizure-free	60	44.4
Less than one per month	51	37.8
More than per month	24	17.8
Seizure type (n=135)		
Focal-onset	110	81.5
Generalized-onset	25	18.5
Seizure time (n=135)		
Daytime	45	33.3

Night	33	24.4
Daytime-night	57	42.2

IQR: Interquartile range.

Table 2. Patients' CAM use and views on CAM methods

		n	%
Have you used any or more of the CAM methods? (n=131)	Yes	38	29.0
	No	93	71.0
Have you found the CAM methods you use helpful? (n=389	Yes	30	78.95
	No	8	21.05
Do you think CAM use is helpful in general? (n=130)	Yes	62	47.7
	No	37	28.5
	No idea	31	23.8
Where have you learned about CAM methods? (n=199*)	Friends, family members, neighbors	34	17.3
	Internet	66	33.5
	TV, radio	18	9.1
	Physician advice	72	36.5
	Newspaper, magazine	7	3.6
In which conditions do you think CAM can be used? (n=329*)	For every disease	75	22.8
	In the case of no benefit from medical treatment	3	0.9
	In chronic conditions	64	19.5
	In malignancies	10	3.0
	In obesity	48	14.6
	For aesthetic purposes	54	16.4
	For preventing aging	75	22.8
What do you think are the purposes of CAM use? (n=170*)	I have heard the success of these methods	67	39.4
	My medical treatment has failed	15	8.8
	Due to concerns about the side effects of medical treatments	17	10.0
	Alternative treatment methods are safer	30	17.6
	Physician advice	41	24.1
Which CAM methods have you heard/do you know?* (n=150*)	Massage therapy	37	24.7
	Herbal treatment	35	23.3
	Hijamat	29	19.3
	Acupuncture	25	16.7
	Ozone therapy	10	6.7
	Energy healing	4	2.7
	Homeopathy	3	2.0
	Other	7	4.7
Please specify CAM methods you use.* (n=43)	Massage therapy	13	30.2
	Herbal treatment	11	25.6
	Hijamat	8	18.6
	Acupuncture	5	11.6
	Ozone therapy	3	7.0
	Homeopathy	2	4.7
	Meditation	1	2.3

Table 3. Comparison of the patients' demographic characteristics by CAM use

		CAM Use		*p**
		YES (n=38)	NO (n=93)	
Age, years	Median (IQR)	28.50 (24-42.5)	30 (22-42.5)	0.92
Sex	Male	19 (14.5%)	40 (30.5%)	0.46

	Female	19 (14.5%)	53 (40.5%)	
Educational attainment	Illiterate	2 (1.5%)	3 (2.3%)	0.68
	Primary school	6 (4.6%)	23 (17.6%)	
	High school	19 (14.5%)	44 (33.6%)	
	Higher education	11 (8.4%)	23 (17.6%)	
Place of residence	Rural area	7 (5.3%)	10 (7.6%)	0.23
	Urban area	31 (23.7%)	83 (63.4%)	
Perceived income status	Very good	4 (3.1%)	16 (12.2%)	0.36
	Good	26 (19.8%)	48 (36.6%)	
	Moderate	5 (3.8%)	20 (15.3%)	
	Poor	3 (2.3%)	9 (6.9%)	

Table 4. Comparison of the patients' clinical characteristics by CAM use

		CAM Use		*p**
		YES (n=38)	NO (n=93)	
Disease duration, years	Median (IQR)	13.50 (5-22.5)	8 (4-17)	0.02
Antiseizure drug	Monotherapy	22 (16.8%)	68 (51.9%)	0.08
	Polytherapy	16 (12.2%)	25 (19.1%)	
Seizure type	Focal-onset	27 (20.6%)	79 (60.3%)	0.06
	Generalized-onset	11 (8.4%)	14 (10.7%)	
Seizure frequency	One year ≤ seizure-free	12 (9.2%)	45 (34.4%)	0.15
	Less than one per month	19 (14.5%)	31 (23.7%)	
	More than one per month	7 (5.3%)	17 (13.0%)	

* $p < 0.05$; IQR: Interquartile range.

Table 5. Patients' PHS, DHS, and PSI scores by CAM use

	CAM Use	Median (IQR)	*p*
PHS (n=126)	Yes (n=37)	47.00 (44-52)	0.79
	No (n=87)	47.00 (44-52)	
DHS (n=122)	Yes (n=37)	100.00 (88.75-104.25)	0.54
	No (n=87)	96.00 (85-108)	
PSI (n=124)	Yes (n=37)	52.50(43.50-55.75)	0.95
	No (n=87)	51.00 (46.00-56.00)	

DHS: Dispositional Hope Scale; PHS: Perception of Health Scale; PSI: Problem-Solving Inventory. IQR: Interquartile range.

Discussion

Our findings uncovered that about one-third of the patients with epilepsy used at least one CAM method. The most preferred CAM methods were determined to be massage therapy, herbal treatment, and hijamat-cupping. Moreover, 78.95% of CAM users stated that the CAM method they used was helpful. Yet, we could not establish a significant relationship between CAM use and the patients' demographic and clinical (except for disease duration) characteristics. Similarly, we could not detect a significant relationship between the patients' scores on the PHS, DHS, and PSI, which were administered to assess their psychosocial status.

The literature documented varying frequencies of CAM use among patients with epilepsy. A review study including 30 studies reported the percentage of CAM use ranging between 7.5%-73.3% (4). In India, Tandon et al. and Bhalerao et al. reported it to be 32% and 7.7%, respectively (18-19). The frequency of CAM use was found to be 76% by Tan et al. among patients living Erzurum and 22.6% by Goker et al. in a Turkish pediatric sample (6,20). It was also reported as 56.6% in a Nigerian pediatric sample and 27.5% among pediatric patients in a multi-ethnic population (21-22). Hartmann et al. pronounced CAM use as 13% in pediatric patients in a university hospital, while Girgis et al. reported it to be 7.9% (23-24). It was uttered to be 26.8% in a university hospital in Poland and 58% by Farrukh et al. (25-26). The inconsistencies in the prevalence of CAM use in the

literature may be attributed to population- or culture-specific differences, different applications in healthcare systems, or the reluctance of patients to explain it.

The type of CAM used may also differ due to differences in cultural norms and healthcare environments. Ayurveda (18), herbal preparations, herbs, multivitamins, dietary regime, ginseng, antioxidants (6,22,25,26,27), prayer, spirituality (20-21,27), energy healing, cannabis (25), homeopathy, osteopathy (18,23), acupuncture, and chiropractic (22,26) are frequently adopted CAM methods by patients with epilepsy in previous studies. In an analysis of 16 studies, Farrukh et al. reported the most common types of CAM to be herbal practices, prayer/ spirituality, and yoga/exercise (4). Besides, hijamat-cupping is a type of CAM mostly adopted in Muslim communities and was reported among epilepsy patients in Oman being with the least frequency (29). The high frequency of this method in our study may be because it is already widely adopted in Turkey and performed by experienced physicians with the permission of the Ministry of Health (30).

Massage therapy, which was found to be preferred the most frequently in this study, may be helpful in terms of providing relaxation to patients with epilepsy, who are often under intense psychosocial stress, besides their medical treatment. Moreover, the unconscious and inappropriate use of herbal treatment, another mostly preferred method, may interact with antiseizure drugs and cause changes in their effects and increase the risk of seizures by showing a proconvulsant effect. It can also cause life-threatening organ dysfunction (26,31,32). Neurologists should be aware of this issue, and patients should be inquired about the CAM methods they use.

We also explored the factors affecting CAM use and discovered a relationship between disease duration and CAM use. Accordingly, the patients with prolonged disease duration tended to use CAM methods more. Similarly, Bosak et al. examined patients with epilepsy in a university hospital in Poland and determined disease duration to be an independent predictor of CAM use (25). Contrary to what we expected, there were no significant relationships between CAM use and other variables such as seizure frequency, which indicates disease severity, and polypharmacy. Moreover, we evaluated the patients' perception of health, dispositional hope, and problem-solving skills to explore their psychosocial status but could not show their effects on CAM use. Our findings uncovered that about one-third of the patients with epilepsy used at least one CAM method. The most preferred CAM methods were determined to be massage therapy, herbal treatment, and hijamat-cupping. We showed that those with prolonged disease duration had significantly more CAM use. To the best of our knowledge, this is a pioneering study to explore CAM use among epilepsy patients with their psychosocial status.

Limitations

Despite uncovering significant findings, our study is not free of a few limitations. First, a few patients were reluctant to respond to some questions on the scales, further limiting the data for the relatively small number of patients. Secondly, the sample included only adult patients followed in our neurology clinic and, therefore, may not be representative of the general population.

Conclusion

CAM use was prevalent among our patients with epilepsy, and those with prolonged disease duration used CAM more. In this sense, healthcare professionals should be aware of CAM use, and patients should be inquired about the CAM methods they use. Future studies should be in the direction of scientific evaluation of all aspects of CAM use and methods among patients with epilepsy.

Acknowledgements: *None*

Ethical Approval: *The Ethics Committee of Gulhane Medical Faculty, Health Sciences University granted ethical approval to our study (No: 2019-115 dated 03.23.2019).*

Author Contributions: *Concept: ÜD, OS Literature Review: ÜD Design: ÜD, OS. Data acquisition: ÜD, ÖK, CB Analysis and interpretation: ÜD, FY, OS Writing manuscript: ÜD Critical revision of manuscript: FY, ÖK, OS.*

Conflict of Interest: *The author(s) do not have any potential conflict of interest regarding the research, authorship and/or publication of this article.*

Financial Disclosure: *Authors declared no financial support.*

REFERENCES

1. WHO.int [homepage on the Internet]. Geneve: World Health Organization Epilepsy Fact Sheet [updated 9 Feb 2022; cited 18 Jan 2023].Available from: https://www.who.int/en/news-room/fact-sheets/detail/epilepsy
2. Yadav J, Singh P, Dabla S, et al. Psychiatric comorbidity and quality of life in patients with epilepsy on anti-epileptic monotherapy and polytherapy. Tzu Chi Med J. 2021;34(2):226-31.
3. Görgülü Ü, Fesci H. Epilepsi ile yaşam: Epilepsinin psikososyal etkileri. Göztepe Tıp Dergisi. 2011;26(1):27-32.
4. Farrukh MJ, Makmor-Bakry M, Hatah E, et al. Use of complementary and alternative medicine and adherence to antiepileptic drug therapy among epilepsy patients: a systematic review. Patient Prefer Adherence. 2018; 12:2111-121.

5. Tanrıverdi G, Gürsoy MY, Şen HM, et al. Epilepside Geleneksel Tıp Uygulamaları: Çanakkale Örneği. Epilepsi. 2013;19(1):29-33
6. Tan M, Kavurmaci M. Complementary And Alternative Medicine Use In Turkish Patients With Epilepsy. Altern Ther Health Med. 2021;27(4):19-23.
7. Who.int [homepage on the Internet]. WHO Traditional Medicine Strategy 2014-2023. Online Resources [cited 21 Jan 2023]. Available from: https://www.who.int/initiatives/who-global-centre-for-traditional-medicine
8. Nccih.nih.gov [homepage on the Internet]. Complementary, alternative, or integrative health: what's in a name? [cited 8 Feb 2023]. Available from: https://www.nccih.nih.gov/health/complementary-alternative-or-integrative-health-whats-in-a-name
9. Mollahaliloğlu S, Uğurlu FG, Kalaycı MZ, et al. The new period in traditional and complementary medicine. Ankara Medical Journal. 2015;15(2):102-5.
10. Resmigazete.gov.tr [homepage on the Internet] Geleneksel ve Tamamlayıcı Tıp Uygulamaları Yönetmeliği, [updated 27 Oct 2014; cited 20 Jan 2023]. Available from: http://www.resmigazete.gov.tr/eskiler/2014/10/20141027-3.htm
11. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512-21.
12. Diamond GS, Reis BF, Diamond GM, et al. "Attachment-based family therapy for depressed adolescents: A treatment development study." J Am Acad Child Adolesc Psychiatry 2002;41(10):1190-196.
13. Kadioğlu H, Yildiz A. "Validity and reliability of Turkish version of perception of health scale." Türkiye Klinikleri Tip Bilimleri Dergisi 2012;32(1):47-53.
14. Snyder CR, Harris C, Anderson JR, et al. The will and ways: Development and validation of an individual-differences measure of hope. J Pers Soc Psychol. 1991;60(4):570-85.
15. Tarhan S, Bacanlı H. Adaptation of dispositional hope scale into Turkish: Validity and reliability study. The Journal of Happiness & Well-Being. 2015:3(1):1-14.
16. Heppner PP, Petersen CH. The development and implications of a personal problem-solving inventory. Journal of counseling psychology. 1982;29(1):66-75.
17. Sahin NH, Sahin N, Heppner P. Psychometric properties of the problem solving inventory in a grup of Turkish university students. Cognitive Therapy Research. 1993; 17:379–96.
18. Tandon M, Prabhakar S, Pandhi P. Pattern of use of complementary/alternative medicine (CAM) in epileptic patients in a tertiary care hospital in India. Pharmacoepidemiol Drug Saf. 2002;11(6):457-63
19. Bhalerao MS, Bolshete PM, Swar BD, et al. Use of and satisfaction with complementary and alternative medicine in four chronic diseases: a cross-sectional study from India. Natl Med J India. 2013;26(2):75-8.
20. Goker Z, Serin HM, Hesapcioglu S. Complementary and alternative medicine use in Turkish children with epilepsy. Complement Ther Med. 2012;20(6):441-6.
21. Lagunju IA. Complementary and alternative medicines use in children with epilepsy in Ibadan, Nigeria. Afr J Med Med Sci. 2013;42(1):15-23.
22. Chen C, Chong YJ, Hie SL, et al. Complementary and alternative medicines use among pediatric patients with epilepsy in a multiethnic community. Epilepsy Behav. 2016; 60:68-74.
23. Hartmann N, Neininger MP, Bernhard MK, et al. Use of complementary and alternative medicine (CAM) by parents in their children and adolescents with epilepsy- Prevelance, predictors and parents' assessment. Eur J Paediatr Neurol. 2016;20(1):11-9.
24. Girgis MMF, Fekete K, Homoródi N, et al. Use of Complementary and Alternative Medicine Among Patients With Epilepsy and Diabetes Mellitus, Focusing on the Outcome of Treatment. Front Neurosci. 2022; 15:787512.
25. Bosak M, Słowik A. Use of complementary and alternative medicine among adults with epilepsy in a university epilepsy clinic in Poland. Epilepsy Behav. 2019;98(Pt A):40-44.
26. Farrukh MJ, Makmor-Bakry M, Hatah E, et al. Impact of complementary and alternative medicines on antiepileptic medication adherence among epilepsy patients. BMC Complement Med Ther. 2021;21(1):50.
27. Koh MY, Khor SB, Lim KS, et al. Use of complementary and alternative medicine among adult with epilepsy-experiences from a single epilepsy center in Malaysia. Neuroscience Research Notes.2022;5(1):109-109.
28. Peebles CT, Mcauley JW, Roach J, et al. Alternative medicine use by patients with epilepsy. Epilepsy Behav. 2000;1(1):74–77.
29. Al Asmi A, Al Maniri A, Al-Farsi YM, et al. Types and sociodemographic correlates of complementary and alternative medicine (CAM) use among people with epilepsy in Oman. Epilepsy Behav. 2013;29(2):361-6.
30. Kılıç KN, Soylar P. Geleneksel ve Tamamlayıcı Tıp Uygulamalarına Başvuran Bireylerin Tutumları, Başvurma Nedenleri ve Memnuniyet Düzeylerinin İncelenmesi. J Tradit Complem Med. 2019;2(3):97-105.
31. Schachter SC. Botanicals and herbs: a traditional approach to treating epilepsy. Neurotherapeutics. 2009;6(2):415-20.
32. Sari O. Fitoterapi. Eds. Aydın Çiftçi, Adem Özkara, Serkan Tursun, Bulut Demirel, Murat Kekili. Bütüncül Tıp (Birinci Basamakta ve Aile Hekimliğinde Güncel Tanı- Tedavi). Bölüm 4: Geleneksel Tamamlayıcı Tıp Uygulamaları. Ankara Nobel Tıp Kitapevleri 2019: 193-95.