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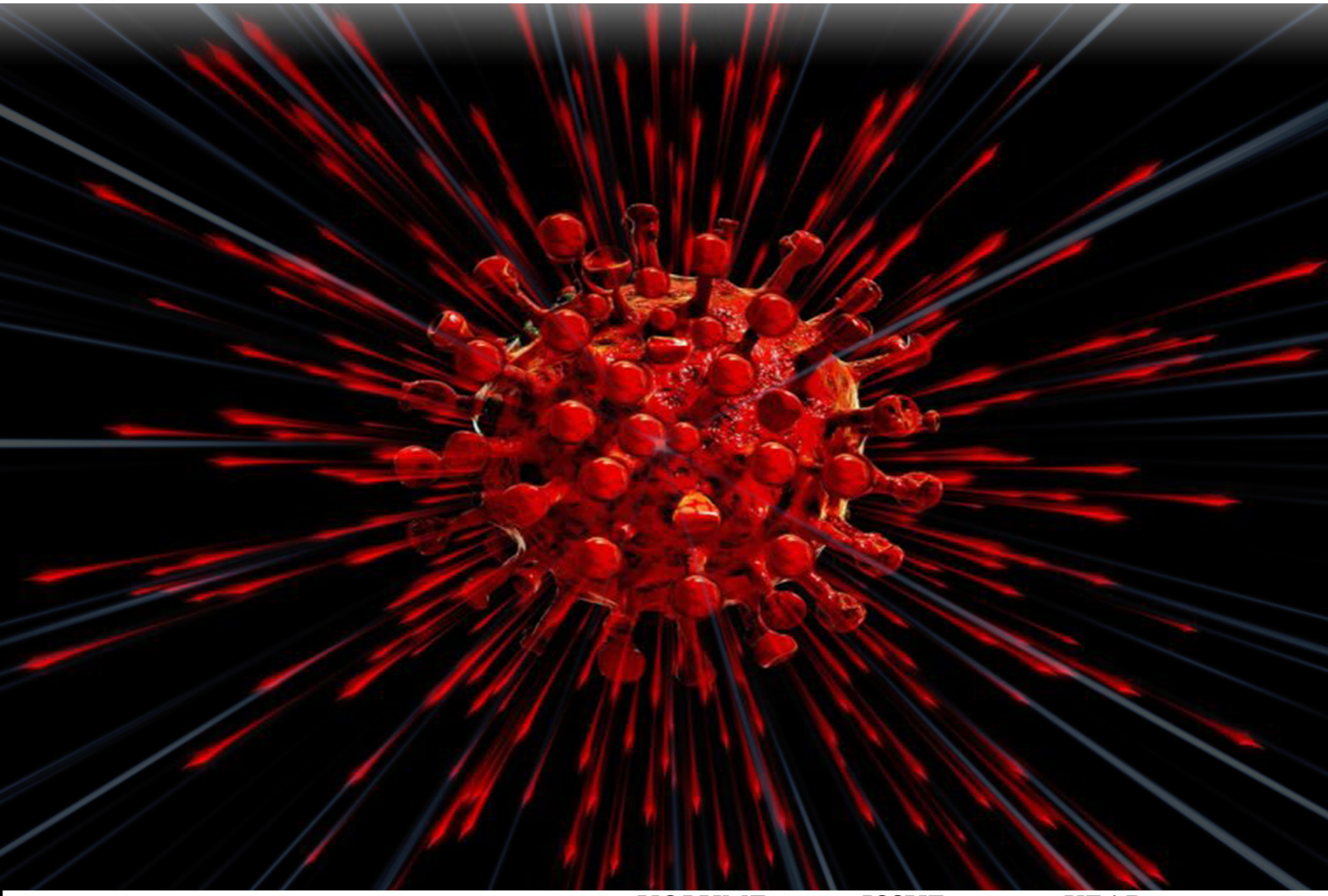

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Twenty years of research on total intravenous anesthesia (TIVA): bibliometric analysis and visual mapping with Web of Science data

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ABSTRACT

Aims: This study aims to determine the leading articles, countries, institutions, authors, funding sources and scientific collaborations by examining the scientific literature related to total intravenous anesthesia (TIVA) using bibliometric methods. It also aims to reveal the thematic structure and research trends of the field using keyword analysis.

Methods: A total of 494 English-language articles published in the Web of Science Core Collection (WoSCC) database were examined. Publication trends were evaluated using citation analyses, co-citation networks, and keyword co-occurrence analyses. Bibliometrix and VOSviewer programs were used for the analyses. In addition, thematic trends and keyword evolution were analyzed with Sankey diagrams and trend analysis.

Results: In total, 494 articles and 195 journals from 54 countries were evaluated. The most productive countries are the USA, China and South Korea, while institutions such as the National Defense Medical Center and Tri-Service General Hospital have come to the fore. Wu ZF, Lai HC and Lee MS have been identified as the most prolific authors. Anesthesiology has been the most cited journal, while pediatric anesthesia has been the most prolific journal. Among the most frequently used keywords were propofol, TIVA and anesthesia. After 2019, it has been observed that the interest in areas such as cancer surgery and recovery issues has increased. The studies of Nimmo and Wu ZF have been among the important references highlighting the oncological and postoperative advantages of TIVA.

Conclusion: This bibliometric study examines the scientific studies in the field of TIVA between 2003 and 2023. During this time, the number of publications has increased, and the USA has come to the fore as the country with the highest number of publications and citations. China and South Korea, on the other hand, are following the United States. National Defense Medical Center and Tri Service General Hospital are the prominent institutions. The most active authors are Wu ZF, Lai HC and Lee MS; Wu ZF in particular is the leader in both the number of publications and citations. Anesthesiology is the most cited and pediatric anesthesia is the most active journal. After 2019, there has been an increasing interest in the topics of "obstructive sleep apnea," "recovery," and "cancer surgery". The Sankey diagram indicates that topics such as "rocuronium," "cerebral oxygen saturation" and "surgery" were more focused during this period.

Keywords: Total intravenous anesthesia, bibliometric analysis, TIVA, propofol, anesthesia, volatile free anesthesia

INTRODUCTION

Total intravenous anesthesia (TIVA) is a method in which the anesthesia process is completely provided with intravenous drugs. TIVA, which was first started to be used in the 1870s, has become widespread especially with the introduction of propofol into clinical use in the early 1980s.[1] In traditional anesthesia methods, intravenous agents are usually used for anesthesia induction, while maintenance is usually provided with inhalation agents. In TIVA, both induction and maintenance are performed entirely with intravenous agents.[2] This approach reduces air pollution caused by inhalation agents in operating rooms.[3] Initially introduced for pediatric patients in the 1990s, it provides a safe option, particularly in airway management procedures, by reducing the risk of delirium during emergence and preventing respiratory complications such as laryngospasm, bronchospasm, and reactivity. This method, which is preferred in cases such as neuromuscular diseases, nuclear myopathies and muscular dystrophy, stands out with its minimal intervention and cost-effectiveness in neurological monitoring during surgery.[4,5] In addition, TIVA, which increases patient comfort by reducing nausea and vomiting after surgery, is increasingly widely used in pediatric patients today.[6] However, side effects such as infection, pain during injection, bradycardia and hypotension may be observed during TIVA administration, especially related to the use of propofol.[7,8] In addition, it has been shown in studies that in cases where monitors measuring the

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depth of anesthesia, such as BIS, are used, patient-based dose adjustment should be made and the optimal dose should be carefully determined.[9]

Bibliometric analysis is a critical tool for understanding research trends, evaluating academic achievement, and determining future research directions in the field of medicine. This analysis method contributes to the emergence of innovative and potential research areas in health sciences by measuring productivity and impact.[10] Bibliometrics determines the relevant journals, articles, authors and themes by systematically examining academic outputs and thus serves as a guide for defining our discipline. Developing a comprehensive understanding of the field provides an opportunity to monitor trends and decipher existing research gaps, while at the same time fostering a sense of belonging among those working in this field. In this way, bibliometric analysis stands out as an important tool that both directs scientific developments and strengthens the identity of the discipline.[11]

TIVA is a widely used technique in clinical anesthesia practice and is frequently encountered as a subject of study in the literature. However, literature reviews indicate that studies aimed at evaluating scientific publications related to TIVA using bibliometric methods are limited. This study aims to determine the leading articles, countries, institutions, authors, funding sources and scientific collaborations by examining the scientific literature related to TIVA using bibliometric methods, as well as to reveal the thematic structure and research trends of the field through keywords.

METHODS

Ethics

Ethics committee approval was not required because publicly available data was used.

Working Design

This study has been designed as a bibliometric research that examines the scientific publications published in the Web of Science Core Collection (WoSCC) database in the last 21 years between 2003 and 2023 on the topic of TIVA using bibliometric analysis methods. The aim of this study is to Decipher the scientific publications published in the WoSCC database. Since only publicly available data were used in the study, ethics committee approval was not required.

Data Sources, Registration and Search Strategy

The data were collected using the advanced search features of the WoSCC database. In order to select the articles in our study, author keywords (author keywords, AK) and title (title, TI) searches were performed. The following expressions have been deconstructed using Boolean operators in the search process:

TI=(total IV anesthesia) OR AK=(total IV anesthesia) OR TI=(volatile free anesthesia) OR AK=(volatile free anesthesia) OR TI=(TIVA) OR AK=(TIVA) OR TI=(TIVA) OR AK=(TIVA).

In this way, the most appropriate articles related to TIVA to be used in our research have been determined. In order to prevent data loss and to avoid being affected by future changes, bibliometric data for all articles in the WoSCC database were downloaded along with their references on September 25, 2024. For each article, detailed information such as publication year, title, country, institution, journal, DOI, author name and author keywords are transferred to Microsoft Excel and recorded.

In order to ensure data consistency, the determined studies were examined manually. Data with different spelling styles (for example, journal, country, institution, author name, keywords) are standardized in Excel and exported in BibTeX file format. The standardization of the data was carried out by two independent researchers in order to increase the reliability. In contradictory cases, the final decision was made by taking the opinion of a third researcher.

Inclusion Criteria

Scientific publications published in the WoSCC database between 2003 and 2023 were included in our study about TIVA. The articles in the English language and included in the science citation index expanded (SCI-Expanded) are defined as "article" and "review article" type articles.

Exclusion Criteria

Studies showing decoherence between non-human studies (for example, animal and veterinary research) and title and subject content were excluded.

Data Analysis and Statistical Analysis

In this study, in which the scientific contributions and effects in the field of TIVA were evaluated, regression analysis was performed to show the increase of studies by years. The countries, institutions, journals and authors contributing to TIVA research have been ranked according to the number of publications and the number of citations, and the leading individuals and organizations in the field have been identified.

In order to examine the literature related to TIVA, a co-citation network was established by using the 50 publications that received the most citations. The centrality criteria for this network were obtained with the Bibliometrix program, and the visual representation of the network was obtained with the VOSviewer program. Within the scope of document co-citation analysis, each article was grouped in a cluster and PageRank, betweenness and closeness centrality criteria were used to evaluate their roles and effects within the network. PageRank is calculated according to the number of links received by each article and the importance of these links. A high PageRank value has shown that an article is frequently referenced and establishes relationships with articles in other clusters. Betweenness refers to the degree to which an article acts as a bridge between articles in different clusters. The high betweenness value has shown that that article plays a key role in the flow of information and provides links between articles in different clusters. Closeness shows the average distance of an article from other articles on the network. A high closeness

value indicates that the article is centrally located among the articles in the network and provides quick access to other articles. A visual map of the co-citation of the studies related to TIVA was created with the VOSviewer co-citation analysis. In the created image, different clusters are shown in different colors, which helped us decipher the studies related to TIVA and the connections between these studies.

Keywords Co-Occurrence analysis was performed based on the most commonly used author keywords related to TIVA, and the degree of centrality and interaction capacity of each keyword in the network were evaluated using PageRank, betweenness and closeness criteria. In addition, the relationships between the words were visualized with the Keywords Co-Occurrence analysis performed with Bibliometrix. In order to decipher the evolution of the studies related to TIVA, trend topics analysis and Sankey diagram were used to determine the trending words between 2003-2023.

RESULT

Between 2003 and 2023, the 1.180 articles originally identified from the Web of science core collection on TIVA were reduced to 494 articles as a result of the exclusion criteria determined (**Figure 1**).

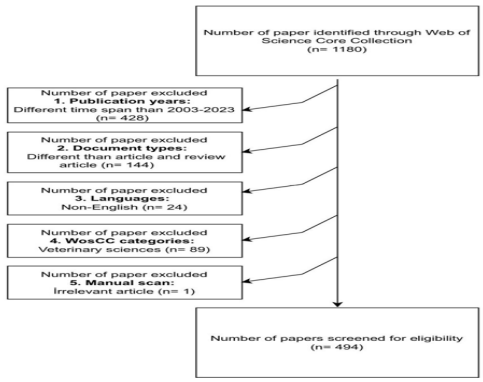

Figure 1. Flow chart

These studies were published in 195 different journals with the participation of 497 institutions and 2.544 authors from 54 countries, and 218 studies were funded by various organizations. It has been observed that publications and citations related to TIVA have increased between 2003 and 2023, and the highest number of publications was reached in 2021 (**Figure 2**).

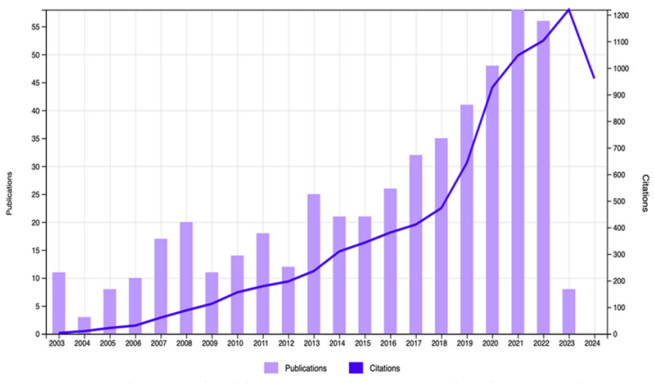

Figure 2. Distribution of publications and citations related to TIVA by year

Regression analysis applied to examine the change in the number of publications by year showed that the number of publications related to TIVA showed a continuous increase between 2003 and 2023, and there was an increase in the number of articles by 1.92 every year (**Figure 3**).

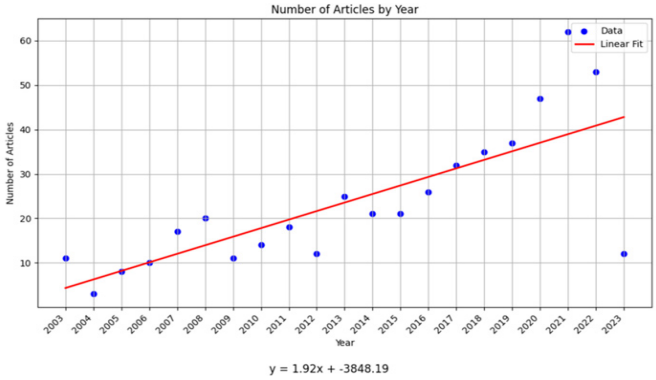

Figure 3. Linear regression analysis of the number of publications related to TIVA over the years

When the distribution of TIVA publications by country is examined, it is seen that the USA has been the most productive country with 101 publications in the last 20 years (**Table 1**). The United States was followed by China with 80 publications and South Korea with 15 publications, respectively. The most productive institutions are the National Defense Medical Center and Tri Service General Hospital with 15 publications each, followed by Seoul National University with 13 publications. While Pediatric Anesthesia was the most prolific journal, this journal was followed by Journal of Clinical Anesthesia with 25 publications and Medicine with 15 publications. The most prolific authors were Wu ZF with 15 publications, Lai HC with 12 publications and Lee MS with 10 publications.

The number of citations of countries, institutions, journals and authors related to TIVA between 2003 and 2023 was examined in **Table 2** and the 10 articles that received the most citations were examined in **Table 3.** China is one of the most cited countries with 19.2%. China is followed by the USA with 18% and Italy with 7.5%. The most cited journal is Anesthesiology with 9.91%, followed by Anesth Analg with 8.8% and Brit J Anesth with 8%. Wu ZF stands out among the most cited authors with 1.6%. Wu ZF is followed by Lai HC with 1.4% and Lee MS with 1.3%. The study titled "Guidelines for the Safe Practice of TIVA: Joint Guidelines from the Association of Anesthetists and the Society for Intravenous Anesthesia", published in the journal "Anesthesia" in 2019 and written by Nimmo AF et al., has been the most cited article.

In this study, a document co-citation network was created for the 50 most cited publications in TIVA literature. The centrality metrics of the publications and the structure of the field were examined by clustering analysis (**Table 4**). According to the results of clustering analysis 1. in the cluster, the article written by Wigmore TJ and colleagues in the journal Anesthesiology in 2016 is ranked first with a PageRank of 0.04 and a betweenness value of 428.22. In the

Table 1. Countries, institutions, journals and authors with the highest productivity in TIVA-related research

	Country	n (%)	Affiliations	n (%)	Journal	n (%)	Author	n
1	Usa	104 (21.1)	National Defense Medical Center	15 (3)	Pediatric Anesthesia	34 (6.9)	Wu Zf	15 (3)
2	China	80 (16)	Tri Service General Hospital	15 (3)	Journal of Clinical Anesthesia	25 (5.1)	Lai Hc	12 (2.4)
3	South Korea	50 (10.1)	Seoul National University Snu	13 (2.6)	Medicine	24 (4.8)	Lee Ms	10 (2)
4	Italy	40 (8.)	University of Texas System	12 (2.4)	Journal of Neurosurgical Anesthesiology	19 (3.8)	Lu Ch	8 (1.6)
5	Turkey	38 (7.7)	Capital Medical University	10 (2)	Journal of Cardiothoracic and Vascular Anesthesia	18 (3.6)	Anderson Bj	7 (1.4)
6	Germany	33 (6.7)	University of Colorado System	10 (2)	Journal of Anesthesia	16 (3.2)	Ansermino Jm	6 (1.2)
7	Canada	25 (5.)	University of Melbourne	10 (2)	Bmc Anesthesiology	13 (2.6)	Riedel B	6 (1.2)
8	Japan	22 (4.4)	Sichuan University	9 (1.9)	Anesthesia and Analgesia	12 (2.4)	Bagshaw O	5 (1)
9	Taiwan	22 (4.4)	University of British Columbia	9 (1.9)	Plos One	12 (2.4)	Boon M	5 (1)

Table 2. Countries, institutions, journals and authors with the highest number of citations in TIVA-related research

	Country	n (%)	Journal	n (%)	Author	n (%)
1	China	321 (19.2)	Anesthesiology	1592 (10)	Wu Zf	80 (1.6)
2	USA	301 (18)	Anesth Analg	1407 (8.8)	Lai Hc	68 (1.4)
3	Italy	125 (7.5)	Brit J Anaesth	1270 (8)	Lee Ms	63 (1.3)
4	Turkey	104 (6.2)	Pediatr Anesth	463 (2.9)	Lu Ch	51 (1)
5	South Korea	99 (6)	Anaesthesia	444 (2.8)	Lin C	39 (0.9)
6	Germany	74 (4.4)	Acta Anaesth Scand	344 (2.1)	Huang Ys	38 (0.8)
7	Canada	70 (4.2)	J Clin Anesth	235 (1.5)	Lin Kt	38 (0.8)
8	UK	66 (4)	Eur J Anaesth	211 (1.3)	Lou Ys	36 (0.7)
9	Australia	61 (3.7)	Can J Anaesth	186 (1.2)	Wong Cs	36 (0.7)
10	Japan	52 (3.1)	J Cardiothor Vasc An	184 (1.2)	Bagshaw O	33 (0.7)

Table 3. Top 10 publications by average citation number (citation/year after publication)

	Title	Journal	First author	Publication year	Number of citation
1	Joint guidelines from the association of anaesthetists and the society for intravenous anaesthesia	Anaesthesia	Nimmo, AF	2019	170
2	Volatile anesthetics versus total intravenous anesthesia for cardiac surgery	New England Journal of Medicine	Landoni, G	2019	161
3	Global onco-anesthesia research collaboration group. Anesthetic technique and cancer outcomes: a meta-analysis of total intravenous versus volatile anesthesia	Canadian Journal of Anesthesia	Yap, A	2019	151
4	Propofol-based total intravenous anesthesia is associated with better survival than desflurane anesthesia in colon cancer surgery	Anesthesiology	Wu, Zf	2018	141
5	Heart rate variability during total intravenous anesthesia: effects of nociception and analgesia. Auton Neurosci	Autonomic Neuroscience-Basic & Clinical	Jeanne, M	2009	129
6	The effect of the total intravenous anesthesia compared with inhalational anesthesia on the surgical field during endoscopic sinus surgery	American Journal of Rhinology	Wormald, PJ	2005	128
7	Remimazolam: non-clinical and clinical profile of a new sedative/anesthetic agent	Frontıers in Pharmacology	Kilpatrick, GJ	2021	115
8	Ultrasound-guided multilevel paravertebral blocks and total intravenous anesthesia improve the quality of recovery after ambulatory breast tumor resection	Anesthesiology	Abdallah, Fw	2014	114
9	Neuroendocrine stress response and heart rate variability: a comparison of total intravenous versus balanced anesthesia	Anesthesia and Analgesia	Ledowski, T	2005	114
10	Influence of nociceptive stimulation on analgesia nociception index (Anı) during propofol-remifentanil anaesthesia	British Journal of Anaesthesia	Gruenewald, M	2013	112

same cluster, the article published by Wu ZF and colleagues in the journal Anesthesiology in 2018 ranked seventh with a closeness value of 0.03 and a betweenness value of 232.65. 3. in the cluster, the article published by Kataria BK and others in the journal Anesthesiology in 1994 has the highest PageRank value (0.04) in this cluster and was found to be 0.00 and 0.002 in the betweenness and closeness criteria, respectively. In an article published by McFarlan CS and others in the journal pediatric anesthesia in 1999, the PageRank value was found to be 0.03, closeness value was found to be 0.002 and betweenness value was found to be 9.07002E.

In this study, the keyword co-occurrence network created using author keywords frequently used in publications on the topic of TIVA was also examined by network centrality criteria and clustering analysis (**Table 5**). It has become the most frequently used key term in TIVA literature.[2] This term, which is included in the cluster, has been repeated 327 times. This term has assumed the most central role in the literature with a betweenness value of 678.66. At the same time, the word "tiva" has 0.02 closeness and 0.21 PageRank values. Another keyword in the same cluster, "inhalation anesthesia", was used 57 times. It has been seen that the term "inhalation

Table 4. Centrality criteria of influential publications

	Title	Cluster	Betweenness	Closeness	PageRank
1	Wigmore TJ, Mohammed K, Jhanji S. Long-term survival for patients undergoing volatile versus iv anesthesia for cancer surgery: a retrospective analysis. Anesthesiology. 2016	3	428.22	0.004	0.04
2	Kataria BK, Ved SA, Nicodemus HF, et al. The pharmacokinetics of propofol in children using three different data analysis approaches. Anesthesiology. 1994	1	0.00	0.002	0.04
3	McFarlan CS, Anderson BJ, Short TG. The use of propofol infusions in paediatric anaesthesia: a practical guide. Paediatr Anaesth. 1999	1	9.07	0.002	0.03
4	Absalom A, Amutike D, Lal A, White M, Kenny GN. Accuracy of the 'Paedfusor' in children undergoing cardiac surgery or catheterization. Br J Anaesth. 2003	1	1.03	0.002	0.03
5	Marsh B, White M, Morton N, Kenny GN. Pharmacokinetic model driven infusion of propofol in children. Br J Anaesth. 1991	1	7.21	0.002	0.03
6	Minto CF, Schnider TW, Egan TD, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology. 1997	1	232.65	0.004	0.03
7	Wu ZF, Lee MS, Wong CS, et al. Propofol-based total intravenous anesthesia is associated with better survival than desflurane anesthesia in colon cancer surgery. Anesthesiology. 2018	3	0.91	0.003	0.03
8	Enlund M, Berglund A, Andreasson K, Cicek C, Enlund A, Bergkvist L. The choice of anaesthetic--sevoflurane or propofol--and outcome from cancer surgery: a retrospective analysis. Ups J Med Sci. 2014	3	10.23	0.004	0.03
9	Yoo S, Lee HB, Han W, et al. Total intravenous anesthesia versus inhalation anesthesia for breast cancer surgery: a retrospective cohort study. Anesthesiology. 2019	3	0.75	0.003	0.03
10	Jun IJ, Jo JY, Kim JI, et al. Impact of anesthetic agents on overall and recurrence-free survival in patients undergoing esophageal cancer surgery: a retrospective observational study. Sci Rep. 2017	3	0.63	0.003	0.03

Table 5. Top 20 most used author keywords and centrality metrics

	Author keywords	n	Cluster	Betweenness	Closeness	PageRank
1	Tiva	327	2	678.66	0.02	0.21
2	Propofol	137	3	170.18	0.02	0.12
3	Anesthesia	106	3	85.36	0.02	0.08
4	Remifentanil	58	3	12.52	0.01	0.05
5	İnhalation anesthesia	57	2	11.55	0.01	0.04
6	Sevoflurane	42	3	3.39	0.01	0.04
7	Pediatric anesthesia	30	3	2.08	0.01	0.03
8	Bispectral index	27	3	6.03	0.01	0.02
9	Target-controlled infusion	24	3	0.75	0.01	0.02
10	Dexmedetomidine	22	3	0.86	0.01	0.02
11	Desflurane	21	2	0.55	0.01	0.02
12	Neuromonitoring	20	2	0.75	0.01	0.02
13	Motor evoked potentials	18	2	1.11	0.01	0.02
14	Analgesia	17	2	0.06	0.01	0.01
15	Recovery	17	3	0.51	0.01	0.02
16	Cancer surgery	14	2	0.26	0.01	0.02
17	Pharmacokinetic	14	5	0.03	0.01	0.02
18	Volatile anesthetics	13	2	0.15	0.01	0.01
19	Postoperative nausea and vomiting	12	3	0.00	0.01	0.01
20	Cardiac surgery	11	2	0.12	0.01	0.01

anesthesia" has a betweenness of 11.55, closeness of 0.01 and PageRank value of 0.04.

In TIVA studies, "propofol" was the second most frequently used keyword, being used 137 times. According to the results of the clustering analysis of "propofol" 3. it took place in the cluster and exhibited a high centrality with a betweenness value of 170.18. This word, which has a closeness value of 0.02 and a PageRank value of 0.12, is an important component of studies in the field of TIVA. The keywords found in the same cluster include "remifentanil," "inhalation anesthesia" and "sevoflurane," and these words were used 58, 57 and 42 times, respectively. "Remifentanil" acquires a certain centrality with a betweenness value of 12.52, while "inhalation anesthesia" and "sevoflurane" have lower betweenness values (11.55 and 3.39, respectively).

The Paper Co-Citations analysis of the most influential studies in the literature related to TIVA has divided it into three main clusters (**Figure 4**). In this image, the works in the green cluster, especially Wigmore TJ and Wu ZF publications, are seen in the central location. The blue cluster is represented by authors such as Minto CF and McFarlan CS. The red cluster contains publications by Gupta and Apfel.

Keywords Co-Occurrence analysis of keywords has been performed in the literature related to TIVA (**Figure 5**). This analysis reveals the central positions of keywords such as

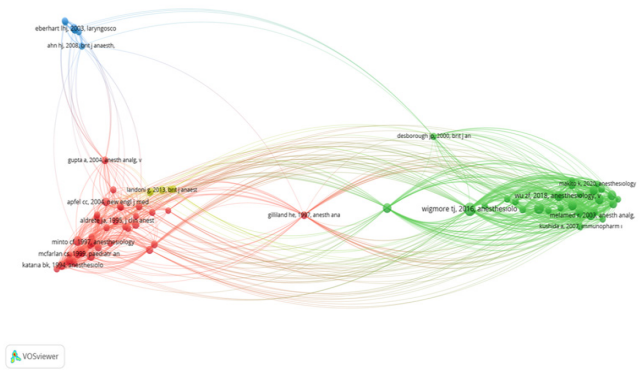

Figure 4. TIVA paper co-citations

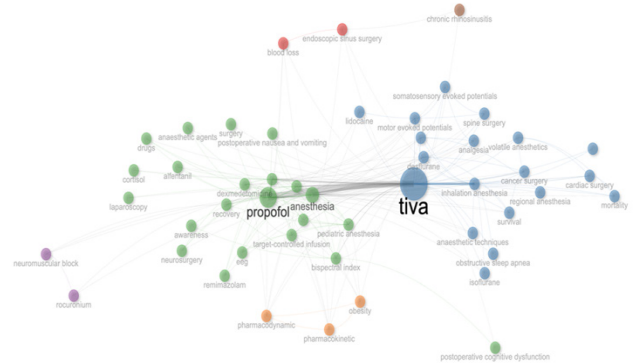

Figure 5. Keywords co-occurrence

"tiva," "propofol" and "anesthesia" in the literature and their connections with various related terms.

In this analysis, the associated words were divided into five different groups. In the blue cluster, the keywords "TIVA" and "propofol" were prominent. In the green cluster, the words "anesthesia" and again "propofol" were included. In the orange cluster, the terms "obesity" and "pharmacodynamic" appeared at the forefront. In the red cluster, the words "endoscopic sinus surgery" and "blood loss" attracted attention. Finally, the words "spine surgery" and "motor evoked potentials" stood out in the gray cluster.

Trend topics analysis has been performed to determine the key terms indicating the trends over time in the literature related to TIVA (**Figure 6**). It is observed that the words obstructive sleep apnea, remimazolam, ketofol, inhalation anesthesia, recovery, cancer surgery, volatile anesthetics, EEG, mortality and pharmacokinetic have come to the fore in the last 5 years.

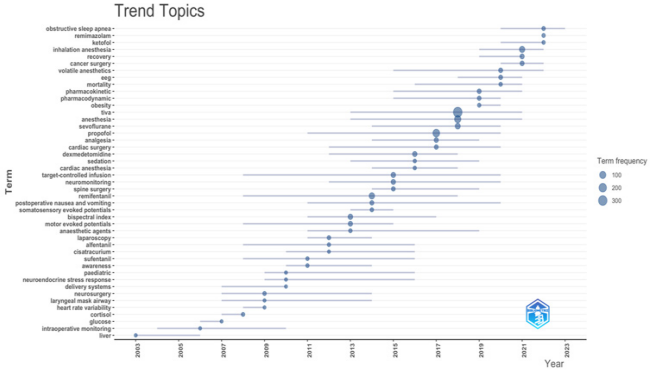

Figure 6. Trend topics

A Sankey diagram has been made in the TIVA literature, segmented at five-year intervals, showing how the key issues have evolved and are related to each other over the past 20 (**Figure 7**). Between the years 2003-2008, the terms 'neuromoniteurization' and 'inhalational anesthesia' came to prominence. Between 2009 and 2013, 'TIVA' appeared as an important theme, and topics such as 'emergence delirium', 'endoscopic sinus surgery' and 'neuromuscular block' attracted more attention. Between 2014 and 2018, 'TIVA' continued as a central theme, while terms such as 'analgesia,' 'cancer surgery,' 'target controlled infusion' and 'cerebral oxygen saturation' came to the fore more. During the years 2019-2023, 'TIVA' is still a subject of attention, but the terms 'surgery,' 'endoscopic sinus surgery,' 'rocuronium,' 'inhalational anesthesia' and 'analgesia' have been used frequently.

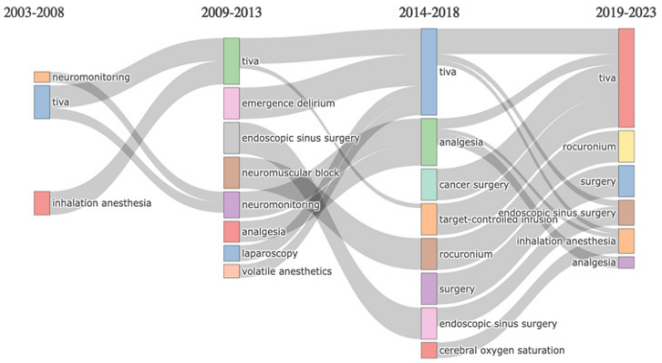

Figure 7. Sankey diagram

Centrality criteria, which are widely used in bibliometric analyses, have played an important role in the analysis of citation networks.[15]

DISCUSSION

There was a significant increase in TIVA-related publications between 2003 and 2023, with the highest number published in 2021. The findings of the bibliometric analysis reveal that there was a strong worldwide interest in TIVA-related research during this period and that this interest was supported not only in academic circles, but also through projects funded by various organizations. The most published countries about TIVA are the USA, China and South Korea, respectively, while the National Defense Medical Center and Tri Service General Hospital attract attention among the leading institutions of these countries. While the most prolific authors include Wu ZF, Lai HC and Lee MS, Wu ZF's top ranking in both publication and citation numbers shows his influential contributions in this field. The most cited journal is Anesthesiology, followed by Anesthesia & Analgesia and the British Journal of Anesthesia. This situation shows that authors prefer journals of American and European origin more for publishing, and these journals also stand out as the journals with the highest citation.

F. Nimmo et al.'s[1] study published in the journal Anesthesia, in order to ensure the safe application of TIVA in the practice of general anesthesia, the study in which Nimmo et al.recommended that all anesthesia and intensive care specialists be provided with education, training and practical experience on TIVA, has been the study that has received the most references in this literature.

The study of Landoni et al.[12] showed that volatile anesthetics in coronary artery bypass grafting surgeries did not make a significant difference on 1-year mortality compared to TIVA, but there was no difference in 30-day mortality and one-year mortality rates. These important findings have caused a wide resonance in the field of study and have attracted attention as the second most cited study in the literature.

A meta-analysis by Yap et al.[13] evaluating the effect of anesthesia technique on long-term outcomes in patients undergoing cancer surgery showed that propofol-based TIVA may have positive effects on recurrence-free survival and overall survival compared to inhalational volatile anesthesia. This study stands out as the third most cited study in the field.

A retrospective study by Wigmore TJ and colleagues[14] found that those who were administered volatile INHA in patients undergoing cancer surgery had a higher risk of death compared to those who received propofol-based TIVA. This study shows that it is frequently referenced with a high PageRank value, plays a key role in the information flow with a high betweenness value, and occupies a central position in the network with a high closeness value, providing quick access to other articles.

Similarly, Wu ZF's[15] study, in which he examined the effect of the type of anesthesia (propofol or desflurane) on survival in colon cancer surgery, reported that propofol anesthesia was associated with better survival compared to desflurane. This study, which is included in the same cluster as the work of Wigmore et al.[14], has also gained an important place in the literature with its high PageRank, betweenness and closeness values and has assumed a central role in the flow of information. In the VOSviewer images created by the Web of Science Paper Co-Citation analysis, it is seen that these studies are grouped in a green cluster and form a strong network of relationships based on studies co-cited in this cluster, consisting of studies conducted in patients with TIVA-related cancer.

Kataria's[16] study, in which she examined the pharmacokinetics of propofol in children using different data analysis methods, revealed that the pharmacokinetics of propofol are best described by a three-compartment model, and weight is an important variable in this model. This study, which is included in the red color cluster in the literature, has been frequently referenced with its high PageRank value and has been placed in a central position in the network with its high closeness value, providing quick access to other articles.[16]

In the study, which aims to create a practical guide for the use of propofol infusion in children, it was emphasized that higher propofol infusion rates are required in children compared to adults. This study reveals that it is frequently referenced in the literature with a high PageRank value, plays a key role in the flow of information with a high betweenness value, and is in a central position in the network with a high closeness value.[17]

In general, it was considered that these studies were included in the same cluster because they focused on pediatric patients.

Keywords co-occurrence network analysis has been used to automatically extract meaningful information from a large set of literature.[18] In the analysis conducted with VOSviewer, it is thought that propofol and its application areas (general anesthetic agents, postoperative nausea, pediatric anesthesia, target controlled infusion) are focused on the green cluster, TIVA, desflurane, inhalational anesthesia and survival studies in cancer surgery are focused on the blue cluster. Pharmacokinetic, pharmacodynamic and obesity studies are thought to be included in the orange cluster, blood loss, endoscopic sinus surgery and chronic rhinosinusitis in the red cluster, neuromuscular block and rocuronium in the purple cluster, and cognitive dysfunction studies after surgery in the light green cluster.

Trend topics analysis is often used to show the change of research topics over time.[19] When we examine the evolution of research areas related to TIVA, it is seen that terms such as "delivery systems", "cortisol" and "neurosurgery" came to the fore in the early 2000s, and terms such as "target-controlled infusion", "propofol", "pharmacokinetic" and "volatile anesthetics" became the focus in later years. Since 2019, it is noteworthy that topics such as "obstructive sleep apnea," "recovery" and "cancer surgery" have been studied with increasing interest.

The Sankey diagram has been used in similar studies to illustrate the evolution of literature over time.[20,21] In our study, topics such as "inhalation anesthesia," "neuromonitoring" and "TIVA" were prominent with the Sankey diagram in the period 2003-2008, while links with areas such as "endoscopic sinus surgery," "emergence delirium" and "neuromuscular block" increased in the period 2009-2013. In the period 2014-2018, orientation to application areas such as "cancer surgery," "target-controlled infusion" and "analgesia" has been observed. In the period 2019-2023, more specific issues such as "rocouronium," "cerebral oxygen saturation" and "surgery" were focused on. We think that the information obtained from trend topics and Sankey diagrams indicates that TIVA research is becoming more specific and focused.

Limitations

Among the strengths of this study is that it offers guidance to studies in this field due to a comprehensive dataset and visualization of data. The limitations are that studies in other databases and in different languages are excluded due to the examination of English-only publications in the WoSCC database. Being a retrospective analysis, it may not fully reflect the latest developments in the field of TIVA. In addition, although bibliometric analyses evaluate scientific productivity, they cannot measure the scientific quality and clinical effects of articles. However, this study provides valuable guidance to scientists who will conduct research in the field of TIVA.

CONCLUSION

This bibliometric analysis has revealed the scientific productivity and research trends in the TIVA literature between 2003 and 2023. During this period, when the number of publications is constantly increasing, it has been seen that the United States is the leader in terms of both publications and citations, while China and South Korea are following the United States. Among the leading institutions, National Defense Medical Center and Tri Service General Hospital

attract attention. The most prolific authors are Wu ZF, Lai HC and Lee MS, and Wu ZF's superiority in both the number of publications and citations shows his important contributions to the field. The most cited journal has been Anesthesiology, and the most prolific journal has been Pediatric Anesthesia.

Trend Topics analysis showed that after 2019, interest in topics such as "obstructive sleep apnea," "recovery," and "cancer surgery" increased, while the Sankey diagram showed that the focus on specific topics such as "rocuronium," "cerebral oxygen saturation," and "surgery" increased during this period.

ETHICAL DECLARATIONS

Ethics Committee Approval
Ethics committee approval was not required because publicly available data was used.

Informed Consent
Informed consent was not required because publicly available data was used.

Referee Evaluation Process
Externally peer-reviewed.

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

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

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Frequency and risk factors of ulcerative colitis associated colorectal cancer referral center experience in non-endemic area

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ABSTRACT

Aims: The incidence of colorectal cancer (CRC) in ulcerative colitis (UC) patients varies across different geographical regions, with limited data available from non-endemic areas for sporadic CRC. This study aimed to evaluate the CRC rates and risk factors in UC patients in a non-endemic region for sporadic CRC.

Methods: A retrospective cohort study was conducted on UC patients who had at least 6 months of follow-up between June 1993 and February 2023 at a tertiary referral center in Turkey. Risk factors for CRC development were assessed, including age at UC onset, disease duration, extent of colitis, family history of CRC, and treatment response.

Results: A total of 875 UC patients were included in the study. The median age at diagnosis was 38 years, and the median follow-up period was 8.16 years. Of these patients, 133 (15.2%) had proctitis, 426 (48.7%) had left-sided colitis, and 316 (36.1%) had extensive colitis. CRC was histologically diagnosed in 5 (0.6%) UC patients, with a median UC onset age of 29.4 years and a total disease duration of 18 years. The median age at CRC diagnosis was 46 years. Three patients had extensive colitis, while two had left-sided colitis. Three patients had steroid dependence, two had thiopurine resistance, and one was biologic treatment-resistant. All UC-related CRC patients had persistent mild to moderate disease activity on colonoscopy during follow-up.

Conclusion: The low incidence of UC-associated CRC in non-endemic areas may be associated with some environmental and racial factors specific to the region.

Keywords: Colorectal cancer, ulcerative colitis, non-endemic area

MAIN POINTS

- The study showed a strong relationship between disease duration and CRC risk, with patients who developed colorectal cancer having a median overall disease duration of 18 years.
- Over a 30-year period, among 875 UC patients, resulting in a total incidence of CRC related to UC of 0.6%.
- The incidence of CRC linked to UC in our study was lower than that reported in earlier research.
- As current guidelines advice, initiating screening colonoscopy 8–10 years after the initial diagnosis in UC patients with more than one-third of the colon affected appears to be an appropriate approach in non-endemic areas.

INTRODUCTION

Ulcerative colitis (UC), an inflammatory colorectal disease, is characterized by a relapsing and remitting nature.[1] UC is associated with an elevated risk of colorectal cancer (CRC), particularly in patients with longer disease duration, extensive colitis, family history of CRC, concurrent primary sclerosing cholangitis, and younger age at diagnosis.[2-5] Compared to sporadic CRC, UC-associated CRC is typically diagnosed 15-20 years earlier.[6] In patients with chronic UC, CRC is a significant contributor to morbidity and mortality. Recent studies have documented an increased risk of CRC development in UC patients.[7]

CRC ranks as the third most diagnosed cancer in males and the second in females.[8,9] Compared to the general population, pancolitis is associated with a 5-to-15-fold increased risk of CRC, while left-sided colitis is associated with an approximately threefold relative risk. In contrast, the risk does not appear to be significantly elevated in proctitis or proctosigmoiditis alone.[10,11] The estimated incidence of colon cancer is approximately 0.5% per year for patients with disease duration between 10 and 20 years, increasing to 1% per year thereafter. The risk of colon cancer begins to rise approximately 8 to 10 years after the initial diagnosis of pancolitis and 15 to 20 years for left-sided colitis. The probability of developing cancer increases with disease

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duration and active inflammation, reaching as high as 30% in patients with pancolitis by the fourth decade of disease.[12-14]

The reduced rate of CRC in UC patients is primarily attributed to effective colonoscopic surveillance programs and aggressive control of disease activity through medical therapy. Colonic surveillance is recommended for UC patients to prevent the development of CRC.[15] Current guidelines advocate initiating screening colonoscopy with random biopsies every 10 cm of the intestine 8–10 years after the initial diagnosis in UC patients with more than one-third of the colon affected.[2] The potential association between clinical factors and CRC incidence in UC is not well understood, and there is a lack of knowledge regarding the risk factors and clinical characteristics of UC-associated CRC patients.

The varying rates reported worldwide demonstrate how factors such as geographic location, genetics, and environmental variables can influence the risk of CRC. Asians have a distinct genetic makeup for UC compared to Caucasians, which may impact the risk of disease development, including colon cancer. This study aimed to determine the risk factors and frequency of CRC development in long-term follow-up of UC patients in the Turkish population.

METHODS

Ethics

The study was conducted with the permission of Ankara Bilkent City Hospital Scientific Researches Ethics Committee (Date: 25.01.2023, Decision No: E1/23/3219). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study Design and Patient Population

We conducted a retrospective cohort study of UC patients who received care at a tertiary referral center between June 1993 and February 2023. The inclusion criteria were: (1) a confirmed diagnosis of UC, (2) age ≥18 years at the time of diagnosis, (3) regular follow-up at our department, and (4) a minimum follow-up duration of 6 months. Patients with missing data or those who had less than six months of follow-up were excluded from the study.

Data Collection and Outcome Measures

Data were retrospectively collected from electronic medical records and the national health system. The information gathered included demographics (age, gender), laboratory variables (hemoglobin, C-reactive protein, albumin), medical and surgical history, treatments (mesalazine, steroids, thiopurines, biological therapies), duration from UC onset to CRC diagnosis, endoscopic findings, and partial Mayo scores. Smoking habits were assessed at the time of UC diagnosis and noted in the patient's chart at the final visit. Patients were classified as current smokers, ex-smokers, or non-smokers. Family history of UC or CRC was also evaluated. The extent of the disease was determined using the Montreal classification (proctitis, left-sided colitis, or extensive colitis). Extraintestinal manifestations that developed at diagnosis and during follow-up were recorded. The primary outcome measure was the development of histologically confirmed adenocarcinoma during the follow-up period. The diagnosis of CRC was confirmed by histopathological examination of biopsy specimens obtained during colonoscopy or surgical resection.

Statistical Analysis

Statistical analysis was performed using SPSS 25.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were described using median and interquartile range (IQR), while categorical variables were expressed as numbers (n) and percentages (%). Patients were stratified based on the duration of the disease (<10 years, 10-19 years, 20-29 years, or ≥30 years) and the extent of the disease (proctitis, left-sided colitis, or extensive colitis). Baseline characteristics, including hemoglobin, CRP, albumin, and partial Mayo scores, were reported. The demographic and clinical variables of patients who developed CRC were analyzed separately. Comparisons between the group that developed CRC and the group that did not were performed using appropriate statistical tests, although no statistical differences were observed.

RESULTS

Patient Characteristics

During the study period, 991 UC patients were followed, of which 116 were excluded due to missing data and a short follow-up period. The final study population comprised 875 UC patients, with 547 (62.5%) being male. The median age at diagnosis was 38 years (IQR: 28-49), and the median follow-up duration was 8.16 years (IQR: 4.16-13.5). The disease duration was categorized as follows: <10 years, 532 (60.8%); 10–19 years, 246 (28.1%); 20–29 years, 79 (9%); and ≥30 years, 18 (2.1%). Regarding disease extent, 133 (15.2%) patients had proctitis, 426 (48.7%) had left-sided colitis, and 316 (36.1%) had extensive colitis (**Table 1**). The most commonly used medication was mesalazine (843 patients, 96.3%), followed by steroids (356, 40.7%), thiopurines (242, 27.7%), and biological therapies (144, 16.5%). Peripheral arthralgia was the most prevalent extraintestinal manifestation, affecting 174 (19.9%) patients, while primary sclerosing cholangitis was found in 11 (1.3%) patients. At baseline, the median hemoglobin level was 13.7 g/dl, median CRP was 4.45 mg/L (IQR: 1.45-10.27), median albumin was 4.5 g/dl (IQR: 4.2-4.7), and the median partial Mayo score was 6 (IQR: 5-7) (**Table 1**).

Colorectal Cancer Incidence and Patient Characteristics

During the study period, 5 (0.6%) histologically confirmed adenocarcinomas were detected. Among the patients who developed CRC, four were male. The median age at onset of UC was 29.4 years (IQR: 17-43), and the median total disease duration was 18 years (IQR: 4.8-28.5). The median age at CRC diagnosis was 46 years (IQR: 34.5-54.5) (**Table 2**). Three patients were nonsmokers, while the remaining two were former smokers. One patient had a family history of colon cancer.

Regarding disease extent, three patients had extensive colitis, and two had left-sided involvement. Three patients had steroid dependence, two had thiopurine resistance, and one had a biologically resistant condition. One patient had poor compliance with medical treatment. All UC-related CRC

Table 1. Demographic characteristics of patients with ulcerative colitis

	Ulcerative colitis (n=875)
Age at onset of UC (years)	38 (28-49)
Total disease duration (years)	8.16 (4.16-13.5)
Disease duration	
<10 years	532 (60.8%)
10-19 years	246 (28.1%)
20-29 years	79 (9%)
≥30 years	18 (2.1%)
Colorectal cancer	5 (0.6%)
Duration from onset of UC to colorectal cancer (years)	8.41 (4.2-28.37)
Gender, male	547 (62.5%)
Smoking (current/ex/none)	105 (12%)/294 (33.6%)/476 (54.4%)
Family history of UC	103 (11.8%)
Appendectomy	16 (1.8%)
UC (disease extension)	
Proctitis	133 (15.2%)
Left-sided colitis	426 (48.7%)
Extensive colitis	316 (36.1%)
Extra-intestinal manifestations	
Peripheral arthralgia	174 (19.9%)
Peripheral arthritis	36 (4.1%)
Ankylosing spondylitis	33 (3.8%)
Sacroiliitis	11 (1.3%)
Erythema nodosum	9 (1%)
Pyoderma gangrenosum	2 (0.2%)
Aphthous ulcer	119 (13.6%)
Uveitis	11 (1.3%)
Episcleritis	2 (0.2%)
Primary sclerosing cholangitis	11 (1.3%)
Medication (conventional)	
Mesalazine	843 (96.3%)
Sulfasalazine	68 (7.8%)
Steroids	356 (40.7%)
Thiopurine	242 (27.7%)
Biological therapy	144 (16.5%)
Baseline CRP (mg/L)	4.45 (1.45-10.27)
Baseline HB (g/dl)	13.7 (12.2-15)
Baseline albumin (g/dl)	4.5 (4.2-4.7)
Baseline partial MAYO score	6 (5-7)

Variables are reported as median (1st quartile-3rd quartile) or frequency (%). UC: Ulcerative colitis, IQR: Interquartile range, CRP: C-reactive protein, HB: Hemoglobin

patients had persistent mild to moderate disease activity on colonoscopy (**Table 3**). CRC developed in three patients with a disease duration of less than 9 years. One patient (aged 34) developed CRC after two years of having pancolitis. Another patient, also aged 34, had left-sided involvement and developed CRC.

Several factors were proportionally higher in the group that developed CRC, including male gender, younger age at UC onset, longer total disease duration, extensive colitis, steroid dependency, thiopurine resistance, and biologic agent resistance. However, no statistically significant differences were observed between the CRC and non-CRC groups for these variables (**Table 4**).

DISCUSSION

This study, conducted at a tertiary center in Turkey, included a long-term follow-up of UC patients and reported a low incidence rate of CRC. Over a 30-year period, five cases of CRC were identified among 875 UC patients, resulting in a total incidence of CRC related to UC of 0.6%. This finding emphasizes the importance of performing surveillance colonoscopies to detect dysplasia early and prevent the development of CRC. The present study demonstrated a strong relationship between disease duration and CRC risk, with patients who developed CRC having a median overall disease duration of 18 years. This observation is consistent with the hypothesis that chronic inflammation and mucosal damage secondary to prolonged disease activity trigger the neoplastic process.[16]

Chronic inflammation is known to release cytokines that are involved in various stages of cancer development, including angiogenesis, metastasis, tumor promotion, and initiation.[17,18] The current study supports this concept, as steroid dependency, resistance to immunomodulators, and biological agents, which are indicators of chronic inflammation, were more prevalent in the patient group that developed CRC.

Previous studies have identified several factors that increase the risk of CRC in UC patients, including the presence of pancolitis, prolonged disease duration, moderate-to-severe or persistent inflammatory activity, smoking, and age.[19,20] In line with these findings, the current study observed that male gender, younger age at UC onset, longer total disease duration, and extensive colitis were more common among patients who developed CRC. However, no statistically significant differences were found between the CRC and non-CRC groups, possibly due to the relatively low number of patients who developed CRC in this cohort.

Based on previous studies, UC patients have a cumulative risk of developing CRC ranging from 2% to 10% over a ten-year period.[7] CRC is a major cause of mortality and morbidity among UC patients, accounting for 10% to 15% of deaths.[21] Several confirmed risk factors for colitis-associated CRC include concomitant primary sclerosing cholangitis, disease duration and severity, the severity of colitis, and a family history of CRC.[7]

The risk of developing CRC varies depending on the extent of the disease. Patients with pancolitis have the highest risk, while those with left-sided colitis have a moderate risk.[7] Disease extent and duration are widely recognized as risk factors for CRC in UC patients. Most malignancies originate in extensive colitis, and proctitis is generally considered to carry little to no increased risk, while left-sided colitis has an intermediate risk of cancer In elderly-onset UC, a less aggressive phenotype with primarily left-sided colitis and less extensive colitis has been observed.[22,23] Our study findings are consistent with the literature, as two patients with UC-CRC had left-sided UC, and three patients had extensive UC. According to meta-analyses that included IBD patients of all ages, the age at UC diagnosis in adults does not affect the relative risk of CRC.[24]

Previous Turkish studies reported a prevalence rate of UC-associated CRC of 1.1% between 1994 and 2008[25] and 0.7% between 1993–2016.[26] In our study, CRC affected 0.6% of the incident UC population between 1993 and 2023. The incidence of CRC linked to UC in our study was lower than that reported in earlier research. This finding is in line with the recent trend of decreasing CRC prevalence in UC patients, although it remains a significant concern.[27] As current guidelines advocate, initiating screening colonoscopy 8–10 years after the initial diagnosis in UC patients with more than

Table 2. Characteristic features of ulcerative colitis patients with colorectal cancer

	1. case	2. case	3. case	4. case	5. case	Total
Age at onset of UC (years)	43	32	28	27	17	29.4 (17-43)
Total disease duration (years)	19.5	4.8	28.5	9.3	28.2	18 (4.8-28.5)
Gender	M	M	F	M	M	
Smokers (ex/none)	Ex	None	None	None	Ex	
Family history of IBD	-	-	-	+	-	
Age at onset of colon cancer (years)	51.7	34.5	57.3	33.6	46.2	46 (34.5-54.5)
Duration from onset of UC to colorectal cancer (years)	8.41	2	28.5	6.41	28.25	8.41 (4.2-28.37)
Family history of colorectal cancer (yes +/no -)	-	-	-	+	-	
Uncontrolled disease activity	+	+	+	+	+	
UC (disease extension)						
Left-sided colitis	-	-	-	+	+	
Extensive colitis	+	+	+	-	-	
Extra-intestinal manifestations	-	-	+	-	-	
Medication (conventional)						
Mesalazine oral	+	+	+	+	+	
Mesalazine enema	-	-	+	+	-	
Mesalazine suppository	-	-	-	+	-	
Sulfasalazine	-	-	-	-	+	
Budesonide	-	-	-	+	-	
Steroids	-	+	+	+	-	
Thiopurine	+	+	+	+	-	
Steroid dependence/resistance	-	+/-	+/+	+/+	-	
Thiopurine resistance	-	-	-	+	-	
Biological therapy	-	-	ADA-VEDO	-	-	
Biologic resistance						
Adalimumab	-	-	+	-	-	
Baseline CRP (mg/L)	8	50	32	25.6	1.4	25.6 (4.68-41)
Baseline HB (g/dl)	12.8	11.2	10.1	15	11.9	11.9 (11.2-12.8)
Baseline albumin (g/dl)	4	2.8	4	4.9	4.3	4 (4-4.3)
Baseline endoscopic MAYO	2	3	3	3	3	2.8 (2-3)
Baseline partial MAYO score	5	7	8	7	8	7 (7-8)
Baseline total MAYO score	6	11	10	10	12	10 (10-11)

Variables are reported as median (1st quartile-3rd quartile) or frequency (%) UC: Ulcerative colitis, IBD: Inflammatory bowel disease, CRP: C-reactive protein, HB: Hemoglobin. (+=Yes) and (-=No). M: Male, F: Female, ADA: Adalimumab, VEDO: Vedolizumab

Table 3. Colorectal cancer risk factors in patients with ulcerative colitis

	CRC (+) (n=5)	CRC (-) (n=737)	p-value
Age at onset of UC (years)	28 (22-37.5)	37 (27-49)	0.129
Total disease duration (years)	19.5 (7.08-28.38)	8.5 (4.25-14.17)	0.074
Gender, male	5 (100)	459 (62.3)	0.163
UC (disease extension)			0.656
Left-sided colitis	2 (40)	424 (57.5)	
Extensive colitis	3 (60)	313 (42.5)	
Extra-intestinal manifestations	1 (20)	258 (35)	0.663
Steroid dependence	3 (60)	225 (30.5)	0.172
IM resistance (thiopurine, MTX)	1 (20)	89 (12.1)	0.477
Biological resistance	1 (20)	54 (7.3)	0.320
Baseline partial MAYO score	7 (6-8)	6 (5-7)	0.111
Baseline total MAYO score	10 (8-11.5)	8 (7-10)	0.148

UC: Ulcerative colitis, CRC: Colorectal cancer, IM: Immunomodulatory, MTX: Methotrexate

Table 4. Univariate and multiple variate logistic regression analysis of predictors of colorectal cancer in ulcerative colitis

	Univariate analysis				Multiple variate analysis			
		95% CI				95% CI		
	OR	Lower	Upper	p	OR	Lower	Upper	p
Age at onset of UC (years)	0.943	0.872	1.021	0.150	0.951	0.862	1.048	0.309
Total disease duration (years)	1.087	1.006	1.174	0.034	1.072	0.981	1.172	0.125
Gender, male	>100	0	-	0.994	-	-	-	-
UC (disease extension)								
Left-sided colitis	1	-	-	-	-	-	-	-
Extensive colitis	2.032	0.388	12.233	0.439	-	-	-	-
Extra-intestinal manifestations	0.464	0.052	4.174	0.493	-	-	-	-
Steroid dependence	3.413	0.566	20.568	0.180	0.386	0.022	6.674	0.513
IM resistance (thiopurine, MTX)	1.820	0.201	16.468	0.594	-	-	-	-
Biological resistance	3.162	0.347	28.788	0.307	-	-	-	-
Baseline partial MAYO score	1.654	0.830	3.294	0.152	0.324	0.040	2.646	0.293
Baseline total MAYO score	1.355	0.860	2.135	0.191	3.173	0.803	12.535	0.100

UC: Ulcerative colitis, IM: Immunomodulatory, MTX: Methotrexate

one-third of the colon affected appears to be an appropriate approach in non-endemic areas.[1]

5-ASA compounds, the first-choice drugs in the treatment of UC, are also used at a dose of 2 g/day for CRC prophylaxis. In our clinical management of UC, we maintain prophylactic 5-ASA even in patients with mucosal healing, which may contribute to the low CRC rate observed in our study. In our practice, we promptly initiated immunomodulator or biological therapy for moderate-to-severe UC when required. Immunomodulators and biological agents have been associated with increased mucosal healing, which may have contributed to the decreased incidence of CRC in our study population.

The incidence of CRC in UC patients varies according to geographical location. A population-based cohort study of 96.447 UC patients in Denmark and Sweden between 1969 and 2017 reported a CRC incidence of 1.23%.[11] Another study by Bernstein et al.[28] in Canada found an even higher CRC incidence of 1.8% among 19,665 UC patients followed for 13 years. In contrast, our study demonstrated a lower risk of CRC in UC patients. There may be two logical explanations for the lower risk of CRC in UC patients in our study compared to the aforementioned studies. First, considering the follow-up dates of the above studies, immunomodulators and biologic agents, which have been shown to effectively suppress mucosal inflammation, were likely not used in the patients during their follow-up periods. Second, geographical differences, such as genetics, environmental factors, and nutritional habits, may contribute to the observed variation in CRC incidence.

The incidence of UC in Turkey is lower than in North-West Europe but similar to that in the Middle East. The low incidence rates of UC in Turkey, which are comparable to those in Western European countries, may be attributed to genetic factors, lifestyle, environmental variables, and even climate. Turkey, with a population of more than 80 million people, is predominantly young and has characteristics of both the east and west. However, CRC rates due to UC in Turkey have been observed to be more similar to those in the eastern region, rather than representing a transition between these regions. In our study, only five UC patients with CRC (0.6%) were identified. This low rate can be partially explained by the overall low incidence of CRC in the general Turkish population. These figures are similar to those observed in Asian research but much lower than those reported by Western countries.[29]

Limitations

The current study has several limitations that should be acknowledged. First, despite the long follow-up period, the number of patients who developed CRC was low, which may limit the generalizability of the findings and the power to detect significant differences in risk factors between the CRC and non-CRC groups. Second, the clinic where the study was conducted is an experienced referral center for inflammatory bowel diseases and follows an effective approach in applying immunomodulators and biological agents to patients with ongoing mucosal inflammation. This approach may not be representative of the general practice in other clinics throughout the country, where there may be hesitation about initiating immunomodulators and biological agents. Consequently, the incidence of CRC developing on the basis of UC in Turkey may be higher than what was observed in the current study. Third, the study's retrospective design is another limitation that should be considered when interpreting the results, as it may introduce selection and information biases.

Furthermore, the study did not assess the impact of disease severity, duration of inflammation, or the extent of mucosal healing on the risk of CRC development. These factors have been shown to influence the risk of CRC in UC patients and should be considered in future studies. Additionally, the study did not evaluate the adherence to surveillance colonoscopy guidelines or the quality of colonoscopies performed, which are essential factors in the early detection and prevention of CRC in UC patients.

Despite these limitations, the study also has notable strengths. The regular recording of patients' data by experienced gastroenterologists ensures the reliability and accuracy of the information collected. Moreover, the application of an accelerated step-up treatment approach for the effective treatment of mucosal inflammation may have contributed to the low incidence of CRC in the patients included in the study. The long follow-up period of 30 years is another strength, as it allows for the assessment of long-term outcomes and risk factors associated with CRC development in UC patients.

CONCLUSION

In conclusion, this study found a CRC frequency of 0.6% among UC patients in the non-endemic area, which is significantly lower than the rates reported in previous studies of UC cases. This lower incidence may be attributed to several factors, including the non-endemic nature of the region for sporadic CRC and inflammatory bowel disease, as well as certain environmental and racial factors specific to the non-endemic area.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of Ankara Bilkent City Hospital Scientific Researches Ethics Committee (Date: 25.01.2023, Decision No: E1/23/3219).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Prediction of mortality in patients admitted to the intensive care unit due to respiratory failure; use of nutritional screening tools mNUTRIC and NRS-2002*

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ABSTRACT

Aims: The objective of this study was to examine the effectiveness of the nutritional screening tools modified nutrition risk in the critically ill (mNUTRIC) and nutrition risk screening-2002 (NRS-2002) in predicting mortality among patients admitted to the intensive care unit (ICU) with acute respiratory failure (ARF) and to determine if their effectiveness varies by respiratory failure (RF) type.

Methods: This prospective, cohort, descriptive study was initiated after ethics committee approval. During a 6-month period, all adult patients (aged ≥18 years) admitted to the tertiary ICUs with acute RF, with type 1 and type 2 RF, who stayed for more than 48 hours were included. Patients were divided into two groups: survivors and non-survivors. Nutritional screening was performed with mNUTRIC and NRS-2002. Scores of 5 points or more on any of the nutritional tools were considered to indicate high nutritional risk. Multiple logistic regression analysis was used to test data predicting 1-month (30-day) and 3-month (90-day) mortality. Relative risk (RR) values of the nutritional tools on mortality were calculated.

Results: Among 525 patients, 35.4% had type 1 RF, and 64.6% had type 2 RF. The mortality rates were 44.2% at one month and 62.5% at three months, with higher mortality observed in type 1 RF in both periods. The mNUTRIC score, the presence of inotropic support, type 1 RF, and admission from the ward were identified as independent variables with a significant association with mortality at 1 and 3 months. The mNUTRIC score emerged as the variable most strongly associated with mortality in both periods. When the mNUTRIC score was evaluated in isolation, the optimal cut-off value was determined to be 6 (1-month mortality AUC: 0.77, 3-month mortality AUC: 0.82). Patients with nutritional risk, as identified by mNUTRIC, exhibited a fourfold elevated risk of mortality within one month (RR=4.2; 95% CI: 2.56–6.95; p<.001) and three months (RR=4.6; 95% CI: 3.04–7.15; p<.001). Combining mNUTRIC and NRS-2002 scores did not significantly enhance predictive accuracy compared to mNUTRIC alone.

Conclusion: In patients with RF, the mNUTRIC score is the most powerful parameter for identifying the high-risk group. The prognosis is worse in patients with type 1 RF compared to type 2. Especially in the group of patients with high mNUTRIC score, in need of inotropic support, type 1 RF findings, and the need for ICU during hospitalization, early intervention and management in terms of nutrition is important to improve the duration of intensive care stay and mortality rates.

Keywords: Acute respiratory failure, intensive care unit, mortality, mNUTRIC, NRS-2002

*Our study was previously presented as an oral presentation at the 24th International Intensive Care Symposium with the first 1-month preliminary data.

INTRODUCTION

Acute respiratory failure (ARF) is the most common reason for intensive care unit (ICU) admission of critically ill patients.[1] The clinical syndrome of ARF can be associated with a variety of acute illnesses, yet there is no universally accepted definition. Consequently, quantifying the true incidence of ARF poses a significant challenge.[2] A substantial proportion of ICU patients, ranging from 40% to 65%, require mechanical ventilation (MV) during their stay in the ICU.[3] The acute disruption of gas exchange between the lungs and blood leads to two possible outcomes: hypercapnia or hypoxia without hypercapnia.[4] Hypoxic respiratory failure (RF) (type 1 RF) is characterized by an arterial partial

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pressure of oxygen (PaO_2) less than 60 mmHg or an arterial blood oxygen saturation (SaO_2) less than 88% in room air at sea level, without hypercapnia. This condition may result from ventilation/perfusion (V/P) mismatch, shunting, hypoventilation, diffusion restriction, or low inspired oxygen pressure.[5] Hypercapnic RF (type 2 RF) is characterized by an arterial partial pressure of carbon dioxide ($PaCO_2$) ≥45 mmHg and a potential hydrogen (pH) of less than 7.35 in room air at sea level. Potential etiologies include alveolar hypoventilation, increased dead space ratio, or increased carbon dioxide production.[5] Given the overlap between the mechanisms causing hypoxemia and hypercapnia, some patients may have both disorders (mixed RF).

Evaluating nutritional status in ICUs presents significant challenges for healthcare professionals due to the diverse range of patient profiles, including variations in diagnoses, ages, comorbidities, and disease severities. Early identification of patients with poor nutritional status and heightened risk of adverse outcomes is crucial during the initial stages of ICU admission.[6] Providing adequate nutrition to critically ill individuals anticipated to remain in the ICU for over 48 hours is a widely recognized standard of care.[7] Among the available tools, the nutrition risk screening-2002 (NRS-2002)[8] and the nutritional risk in critically ill patients (NUTRIC)[9] scores are considered the most suitable for nutritional risk assessment in ICU patients, as they account for the influence of underlying diseases.[9] Nevertheless, no nutritional scoring system has been specifically validated for exclusive use in the ICU setting.[10] The NRS-2002 was not developed with the specific intention of assessing critically ill patients, and the NUTRIC does not incorporate any nutritional parameters.[10]

Although the NRS-2002 includes nutritional parameters such as body-mass index (BMI) below 20.5 kg/m², recent weight loss, and reduced food intake, it was not originally designed for critically ill patients.[9] It also integrates clinical metrics like the severity of illness and the acute physiology and chronic health evaluation II (APACHE II) score.[9] Conversely, the NUTRIC score was explicitly developed to identify ICU patients at nutritional risk who might benefit from intensive nutritional intervention.[9] This tool incorporates variables such as APACHE II and sequential organ failure assessment (SOFA) scores, patient age, comorbidities, hospitalization duration prior to ICU admission, and serum interleukin-6 (IL-6) levels.[9] Given the limited availability of IL-6 in clinical practice, a modified version of the NUTRIC score (modified NUTRIC (mNUTRIC)) excludes this parameter.[11] The mNUTRIC categorizes patients into low-risk (0–4) and high-risk (5–9) groups, with the latter indicating a poorer prognosis.[9,12]

Although both mNUTRIC and NRS-2002 have been proposed, there is no evidence on which scale should be prioritized in the nutritional care protocol of critically ill patients in resource-limited settings. The clinical outcomes of these tools in predicting mortality in the ICU general population have been explored in a limited number of studies, with no existing literature on their use in ICU patients with ARF.[2,12] The present study was designed with the hypothesis that the combined use of NRS-2002 and mNUTRIC scores would outperform the use of these tools alone in predicting mortality in a cohort of ICU patients with ARF. The objective of this study was twofold: first, to evaluate the performance of nutritional screening tools, both as standalone measures and in combination, in predicting 1-month and 3-month mortality in critically ill patients admitted to the ICU with ARF; and second, to assess whether the prognostic performance of these tools varies according to the type of RF.

METHODS

Ethics

This prospective cohort descriptive study was initiated after approval from the Clinical Researches Ethics Committee of Health Sciences University, Ankara Atatürk Sanatorium Training and Research Hospital (Date: 08.02.2023, Decision No: 2012-KAEK-15/2627) and clinicaltrials.gov registration number: NCT06115525. All procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and the Declaration of Helsinki revised in 2013. Our hospital is a regional medical facility specializing in the treatment and follow-up of patients with RF.

Study Design and Patients

The study population included all patients over the age of 18 years who were hospitalized with ARF in the tertiary ICUs of the anesthesiology and reanimation department of our hospital between February 15, 2023 and August 15, 2023. Informed consent was obtained from all participants or their first-degree relatives. Patients with a diagnosis of malignancy whose treatment process was terminated due to lack of response to treatment, patients with diagnosed neurodegenerative diseases (Alzheimer's and other dementias, Parkinson's, Prion, Motor neuron, Huntington's, Spinocerebellar ataxia, Spinal muscular atrophy), patients with mixed type (hypoxia and hypercapnia) RF, pregnant women, and those who refused to give written consent by themselves or their first-degree relatives were excluded from the study. Furthermore, patients who remained in the ICU for less than 48 hours and subsequently expired within 48 hours were excluded from the study. In the event of recurrent ICU hospitalizations, patient follow-up was maintained throughout the study period, with data from the patient's initial hospitalization being considered.

Patients who met the inclusion criteria were included in the study after the 48th hour of ICU hospitalization and were followed up through their medical records until discharge from the hospital or death. The data utilized in this study were obtained from physical and electronic records, as well as from the patients themselves, the care team, family members, and/or companions. No changes were made to patients' treatment while in hospital. The study was terminated at the completion of three months (90-day) of follow-up (November 12, 2023), based on the date the last patient was included (August 15, 2023).

The study was developed in accordance with the strengthening the reporting of observational studies in epidemiology (STROBE) statement.

Overall Evaluation

The clinical and demographic characteristics of patients admitted with ARF were obtained from the medical records. These characteristics included the patients' age, gender, weight, height, BMI, mode of admission (emergency, ward (clinical service, palliative, second step ICU), outpatient center), presence/absence of comorbidities, and history of malignancy. SOFA scores were calculated at admission, and APACHE II scores were calculated at the 24th hour of hospitalization. These scores were obtained from the medical records. Patients were weighed at admission and discharge from the ICU and recorded in the follow-up file. The following clinical outcome measures were recorded: length of ICU stay, ICU readmission, MV use, inotrope support intake, 1-month mortality, and 3-month mortality. All patients were followed up until they were discharged from the hospital or died, and discharged patients were contacted one month and three months later, and their mortality status was recorded by telephone.

ARF was defined as the presence of respiratory complaints during the patient's ICU hospitalization. Patients with PaO_2 levels below 60 mmHg or SaO_2 levels below 88% in room air during their ICU admission were classified as type 1 RF. Patients with $PaCO_2$ levels of 45 mmHg or higher (50 mmHg or higher in patients with chronic obstructive pulmonary disease (COPD)) and a pH level below 7.35 in room air were classified as type 2 RF. Patients exhibiting both of these RF types were designated as mixed type RF.[5,13]

Nutrition Screening

The nutritional status of patients admitted to our ICUs with RF was assessed by a trained nutritionist (working in the nutritional outpatient clinic of our hospital) using two tools, NRS-2002 and mNUTRIC, within 72 hours after admission to the ICU. These two tools are developed for the evaluation of ICU patients and are scores calculated without the need for patient cooperation. Additionally, both tools can be utilized in intubated patients, and the necessary data can be obtained from the patient's relatives and/or family.[10] The NRS-2002 tool assesses the nutritional risk of patients based on the following five variables: (1) unexplained weight loss in the last three months, (2) appetite, (3) body-mass index, (4) disease stressors (comorbidities), and (5) age greater than 70 years.[14] The mNUTRIC score (without IL-6) employs the following criteria for patient classification: (1) age, (2) APACHE II score, (3) SOFA score, (4) comorbidities, and (5) days of previous hospitalization prior to ICU admission.[8] Patients were defined as being at high nutritional risk when they scored ≥5 points (on one or both of these screening tools).[12]

Outcome

The primary outcome measure of the study was the ability of the NRS-2002 and mNUTRIC screening tools to predict mortality in ICU patients with ARF. The secondary outcome measure was the ability of these two screening tools, when used in combination, to predict mortality in ICU patients with ARF. The study also examined whether the predictive capability of nutritional screening tools differed based on the type of RF.

Statistical Analysis

The data obtained were analyzed with the Statistical Package for the Social Sciences 24.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as number of cases (n), percentage (%), mean±standard deviation ($\overline{X}$±SD) or median (Q1-Q3), minimum value (min), and maximum value (max). Categorical and demographic data were tabulated as n and %. The Chi-square test was employed to compare two rates. The distribution of the obtained data was evaluated using the Shapiro-Wilk test. Subsequent to the evaluation of the distribution outcomes of the numerical data, a comparison of paired groups was executed through the implementation of the Student-T test and the Mann-Whitney U test. The comparison of categorical data between groups was performed using Pearson Chi-Square test or Fisher exact test. Nutritional risk was assessed by the NRS-2002 and mNUTRIC, and then categorized as dichotomous data as <5 or ≥5 points. Univariate analysis was assessed at 1-month (30-day) and 3-month (90-day) periods, distinguishing between survivors and non-survivors. Multiple logistic regression analysis was used to calculate the relative risk (RR) and the associated 95% confidence intervals (CIs) by type of RF for mortality at 1-month and 3-month periods. Furthermore, a receiver operating characteristic (ROC) curve was constructed to compare the predictive capability of mNUTRIC and NRS-2002 scores, both individually and in combination, for 1-month and 3-month mortality. Statistical significance was set at $p<0.05$.

In the univariate analysis, logistic regression analysis was performed using statistically significant variables in terms of 1-month and 3-month ICU mortality and variables that were not statistically significant but had a p value less than 0.2. For the 1-month mortality outcome, it was determined that 14 variables could potentially be included in the multivariate logistic regression model. To assess the potential for multicollinearity, all variables were evaluated using correlation analysis, variance inflation factors, and tolerance values. However, subsequent to this analysis, it was determined that the duration of ICU stay and MV use were to be excluded from the model, as they exhibited a high correlation with the duration of MV use. SOFA score and APACHE II score were excluded from the model due to their high correlation with mNUTRIC score. The residual and Cook distance values were controlled. No data were excluded from the set. BMI (likelihood ratio (LR) test X^2 values 0.005), presence of comorbidities (LR test X^2 values 0.527) and high nutritional risk (mNUTRIC+NRS-2002) (LR test X^2 values 0.053) were excluded from the model because their contribution was too low. The final model incorporated seven variables: age, sex, mode of admission, mNUTRIC score, type of RF, duration of MV, and inotrope support intake. The overall fit of the model was confirmed by omnibus testing ($p<.001$). The model demonstrated an accuracy power of 50% (Nagelkerke $R^2=0.5058$). The multivariable logistic regression model for 3-month mortality developed with the potential inclusion of fifteen variables. To assess the potential for multicollinearity, all variables were evaluated using correlation analysis, variance inflation factors, and tolerance values. However,

subsequent to the analysis, it was determined that the duration of ICU stay and MV use were to be excluded from the model due to their high correlation with the duration of MV. Furthermore, high nutritional risk, as measured by SOFA score, APACHE II score, and mNUTRIC, was excluded from the model due to its high correlation with mNUTRIC score. Similarly, high nutritional risk as measured by NRS-2002 was excluded from the model due to its high correlation with the NRS-2002 score. Finally, high nutritional risk in terms of mNUTRIC+NRS-2002 was excluded from the model due to high correlation with mNUTRIC and NRS-2002 score. The residual and Cook distance values were controlled. No data were excluded from the set. The LR test X^2 values for age (0.838) and duration of MV (0.797) were found to be minimal contributors to the model, leading to the exclusion of these parameters. The final model incorporated six variables: mode of admission, presence of comorbidity, mNUTRIC score, NRS-2002 score, type of RF, and inotrope support intake. The overall fit of the model was confirmed by omnibus testing (p<.001). The model demonstrated an accuracy power of 55% (Nagelkerke R^2=0.5552).

RESULTS

A total of 525 patients who were hospitalized in the ICU for more than 48 hours with type 1 or type 2 ARF were included in the study. The mean age of the patients was 72±13 years, and the mean BMI was 25.2±5.9 kg/m^2. Of these patients, 327 (62.3%) were male and 463 patients (88.1%) had a chronic comorbidity. 186 (35.4%) had type 1 RF, while 339 (64.6%) had type 2 RF. The mean SOFA score was 6.7±2.2, and the mean APACHE II score was 22.9±6.7. 304 patients (57.9%) were identified as having high nutritional risk according to NRS-2002 screening (NRS-2002 ≥5), and 413 patients (78.6%) were identified as having high nutritional risk according to mNUTRIC screening (mNUTRIC ≥5). Furthermore, 250 patients (47.6%) exhibited high nutritional risk according to both screening tools (NRS-2002 ≥5 and mNUTRIC ≥5). 41.3% of patients were admitted from the emergency department. The mean length of ICU stay was 9±8 days, and the mean length of hospitalization was 20±15 days. During any period of ICU hospitalization, 295 patients (56.2%) received invasive MV support and 187 patients (35.6%) received inotropic support. Tracheostomy was observed in 15 patients (2.8%). 124 patients (23.6%) were readmitted to the ICU. The mortality rate at one-month follow-up was 232 patients (44.2%), and the mortality rate at three-month follow-up was 328 patients (62.5%).

1-Month Mortality

When 1-month mortality was evaluated, demographic and clinical characteristics between survivors and non-survivors are presented in **Table 1**. Demographically, higher mortality rates were observed in the older age group, male gender, those with higher disease severity (APACHE II, SOFA), those with comorbidities, and those hospitalized in the ward (p<0.05). Clinically, a higher mortality rate was observed in patients with high mNUTRIC scores, type 1 RF, invasive MV, and inotrope support (p<0.05). Furthermore, the duration of invasive MV and ICU hospitalization was found to be significantly prolonged in non-survivors (p=0.002).

The findings of the logistic regression analysis for 1-month mortality are delineated in **Table 2**. The multivariate analysis revealed that a high mNUTRIC score, the presence of inotropic support, male gender, type 1 RF, and admission to the ICU were independent variables that were significantly associated with 1-month patient mortality. The LR analysis revealed that the mNUTRIC score contributed the most to the model, with LR test X^2 values of 49.6 and a p-value of <.001. The diagnostic performance of the model was 80.9% sensitivity and 79.6% specificity, with an area under the ROC curve (AUC) of 0.86 (**Figure 1**). When the mNUTRIC score, the most significant contributor to the model, was considered individually, the AUC for 1-month mortality was 0.77; the best cut-off value was 6 (sensitivity and specificity 79% and 62%, respectively) and the youden index was 0.41.

The RR of 1-month mortality in patients with RF according to mNUTRIC, NRS-2002, or both is detailed in **Table 3**. In patients categorized as at high nutritional risk according to mNUTRIC (score ≥5), the 1-month mortality risk was found to be 8 times higher in patients with type 1 RF and 3 times higher in patients with type 2 RF (p<.001). Conversely, in patients assessed to be at high nutritional risk according to NRS-2002 (score ≥5), no statistically significant increase in the risk of death was observed in either type of RF (p values; 0.640, 0.923, respectively). With respect to the complementarity of these tools, the 1-month mortality risk of patients classified as at nutritional risk according to both mNUTRIC and NRS-2002 scores was not statistically significantly increased in the type 1 RF group (p=0.115), but was 1.45 times higher in the type 2 RF group (p=0.010).

3-Month Mortality

Table 4 presents the demographic and clinical characteristics of 3-month survivors and non-survivors. Demographically, higher mortality rates were observed in the older age group, those with higher disease severity (APACHE II, SOFA), those with comorbidities, and those hospitalized in the ward (p<0.05). Clinically, a higher mortality rates were observed in patients with elevated mNUTRIC scores, severe NRS-2002 scores, type 1 RF, invasive MV, and inotrope support (p<0.05). Furthermore, the duration of invasive MV and ICU hospitalization was found to be significantly prolonged in non-survivors (p<.001).

The findings of the logistic regression analysis for 3-month mortality are delineated in **Table 5**. The multivariate analysis revealed that a high mNUTRIC score, the presence of inotropic support, type 1 RF, the presence of comorbidity, and admission to the ICU were independent variables that were significantly associated with 3-month patient mortality. The LR analysis revealed that the mNUTRIC score contributed the most to the model, with LR test X^2 values of 70.1 and a p-value of <.001. The diagnostic performance of the model was 89.2% sensitivity and 74.4% specificity, with an AUC of 0.89 (**Figure 2**). The AUC for 3-month mortality considering the mNUTRIC score alone, the highest contributor to the model, was 0.82; the best cut-off value was 6 (sensitivity and specificity 76% and 76%, respectively), and the youden index was 0.52.

Table 1. Demographic and clinical characteristics of 1-month survivors and non-survivors

		Survivors, (n=293)	Non-survivors, (n=232)	p-value
Age, year, median (Q1-Q3)		72 (64-82)	75 (66-84)	0.019
Gender, n (%)	Female	124 (62.6%)	74 (37.4%)	0.014
	Male	169 (51.7%)	158 (48.3%)	
BMI, kg/m², median (Q1-Q3)		25.9 (21.5-29.1)	24.2 (22-27.6)	0.088
APACHE II score, median (Q1-Q3)		20 (17- 24)	26 (20-31)	**<.001**
SOFA score, median (Q1-Q3)		5 (5-6)	8 (6-9)	**<.001**
Presence of comorbidity	No, n (%)	42 (67.7%)	20 (32.3%)	**0.044**
	Yes, n (%)	251 (54.2%)	212 (45.8%)	
mNUTRIC score, median (Q1-Q3)		5 (4-6)	7 (6-8)	**<.001**
mNUTRIC score	<5, n (%)	98 (87.5%)	14 (12.5%)	**<.001**
	≥5, n (%)	195 (47.2%)	218 (52.8%)	
NRS-2002 score, median (Q1-Q3)		5 (4-5)	5 (4-5)	0.976
NRS-2002 score	<5, n (%)	125 (56.6%)	96 (43.4%)	0.767
	≥5, n (%)	168 (55.3%)	136 (44.7%)	
mNUTRIC+NRS-2002 score	<5, n (%)	175 (63.6%)	100 (36.4%)	**<.001**
	≥5, n (%)	118 (47.2%)	132 (52.8%)	
Mode of admission	Emergency, n (%)	135 (62.2%)	82 (37.8%)	**<.001**
	Ward, n (%)	60 (39.2%)	93 (60.8%)	
	Outpatient center, n (%)	98 (63.2%)	57 (36.8%)	
Respiratory failure	Type 1, n (%)	74 (39.8%)	112 (60.2%)	**<.001**
	Type 2, n (%)	219 (64.6%)	120 (35.4%)	
Invasive MV	No, n (%)	206 (89.6%)	24 (10.4%)	**<.001**
	Yes, n (%)	87 (29.5%)	208 (70.5%)	
Invasive MV duration, day, median (Q1-Q3)		0 (0-3)	3 (1-9.7)	**<.001**
Inotrope support	No, n (%)	242 (71.6%)	96 (28.4%)	**<.001**
	Yes, n (%)	51 (27.3%)	136 (72.7%)	
ICU readmission	No, n (%)	223 (55.6%)	178 (44.4%)	0.869
	Yes, n (%)	70 (56.4%)	54 (43.6%)	
Length of ICU stay, day, median (Q1-Q3)		5 (3-10)	6 (4-14.2)	0.002

Continuous variables are expressed as either the mean±standard deviation (SD) or median (Q1-Q3) and categorical variables are expressed as either frequency (percentage). Continuous variables were compared with Student-t test or Mann-Whitney U test, and categorical variables were compared using Pearson's Chi-square test or Fisher exact test.
APACHE II: Acute physiologic assessment and chronic health evaluation, BMI: Body-mass index, ICU: Intensive care unit, mNUTRIC: Modified nutritional risk in critically ill patients, MV: Mechanical ventilation, NRS-2002: Nutrition risk screening-2002, SD: Standard deviation, SOFA: Sequential organ failure assessment

Table 2. Univariate and multivariate logistic regression modeling for 1-month mortality

Prediction variable	Unadjusted			Adjusted		
	OR	95% CI	p-value	OR	95% CI	p-value
mNUTRIC score	2.28	1.89-2.75	<.001	2.21	1.72-2.82	<.001
Inotropic support, yes	9.89	5.97-16.38	**<.001**	6.75	3.65-12.48	**<.001**
Gender, male	1.79	1.17-2.73	**0.007**	2.55	1.44-4.50	**<.001**
Respiratory failure, type 1	2.59	1.71-3.93	**<.001**	1.98	1.16-3.37	**0.012**
Mode of admission, ward	2.57	1.63-4.07	**<.001**	2	1.12-3.56	**0.018**
Age, year	1.02	1-1.04	**0.002**	0.98	0.96-1	0.108
Invasive MV duration, day	1.05	1.02-1.08	**<.001**	0.98	0.94-1.01	0.251

mNUTRIC: Modified nutritional risk in critically ill patients, MV: Mechanical ventilation, OR: Odds ratio, CI: Confidence interval

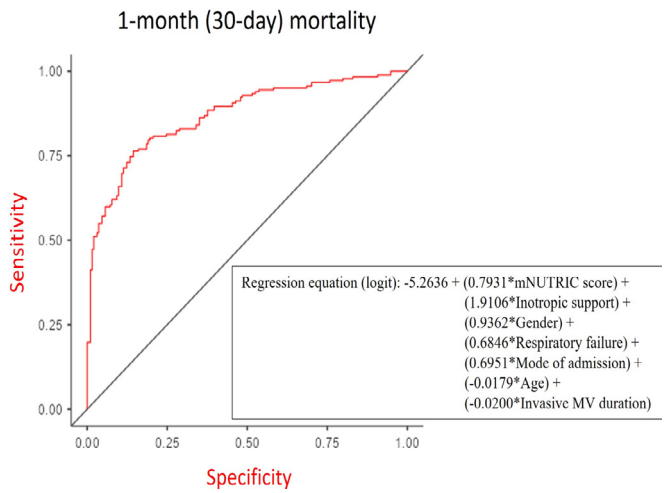

Figure 1. Area under the receiver operating characteristic curve of the model for predicting 1-month mortality in patients hospitalized with respiratory failure in the intensive care unit

Table 3. Relative risk values for 1-month mortality according to types of respiratory failure according to mNUTRIC, NRS-2002 or both

	RR	95% CI	p-value
All			
mNUTRIC ≥5	4.2	2.56-6.95	**<.001**
NRS-2002 ≥5	1.03	0.84-1.25	0.768
mNUTRIC+NRS-2002 ≥5	1.45	1.19-1.76	**<.001**
Type-1 RF			
mNUTRIC ≥5	8.14	2.15-30.84	**0.002**
NRS-2002 ≥5	0.94	0.74-1.20	0.640
mNUTRIC+NRS-2002 ≥5	1.22	0.95-1.57	0.115
Type-2 RF			
mNUTRIC ≥5	3.15	1.83-5.44	**<.001**
NRS-2002 ≥5	0.98	0.73-1.31	0.923
mNUTRIC+NRS-2002 ≥5	1.45	1.09-1.93	**0.010**

mNUTRIC: Modified nutritional risk in critically ill patients, NRS-2002: Nutrition risk screening-2002, RF: Respiratory failure, RR: Relative risk, CI: Confidence interval

The RR of 3-month mortality in patients with RF according to mNUTRIC, NRS-2002, or both is detailed in **Table 6**. In patients categorized as at high nutritional risk according

Table 4. Demographic and clinical characteristics of 3-month survivors and non-survivors

		Survivors, (n=197)	Non-survivors, (n=328)	p-value
Age, year, median (Q1-Q3)		70 (63-80)	76 (65-85)	<.001
Gender, n (%)	Female	78 (39.4%)	120 (60.6%)	0.491
	Male	119 (36.4%)	208 (63.6%)	
BMI, kg/m², median (Q1-Q3)		25.9 (21.3-29.1)	24.5 (22-27.9)	0.350
APACHE II score, median (Q1-Q3)		19 (17-23)	24.5 (19-29)	**<.001**
SOFA score, median (Q1-Q3)		5 (5-6)	7 (6-9)	**<.001**
Presence of comorbidity	No, n (%)	36 (58%)	26 (42%)	**<.001**
	Yes, n (%)	161 (34.8%)	302 (65.2%)	
mNUTRIC score, median (Q1-Q3)		5 (4-5)	6 (6-7)	**<.001**
mNUTRIC score	<5, n (%)	94 (84%)	18 (16%)	**<.001**
	≥5, n (%)	103 (24.9%)	310 (75.1%)	
NRS-2002 score, median (Q1-Q3)		5 (4-5)	5 (4-5)	**0.039**
NRS-2002 score	<5, n (%)	94 (42.5%)	127 (57.5%)	**0.043**
	≥5, n (%)	103 (33.9%)	201 (66.1%)	
mNUTRIC+NRS-2002 score	<5, n (%)	140 (50.9%)	135 (49.1%)	**<.001**
	≥5, n (%)	57 (22.8%)	193 (77.2%)	
Mode of admission	Emergency, n (%)	111 (51.2%)	106 (48.8%)	**<.001**
	Ward, n (%)	33 (21.6%)	120 (78.4%)	
	Outpatient center, n (%)	53 (34.2%)	102 (65.8%)	
Respiratory failure	Type 1, n (%)	40 (21.5%)	146 (78.5%)	**<.001**
	Type 2, n (%)	157 (46.3%)	182 (53.7%)	
Invasive MV	No, n (%)	152 (66.1%)	78 (33.9%)	**<.001**
	Yes, n (%)	45 (15.3%)	250 (84.7%)	
Invasive MV duration, day, median (Q1-Q3)		0 (0-1)	3 (1-8)	**<.001**
Inotrope support	No, n (%)	181 (53.5%)	157 (46.5%)	**<.001**
	Yes, n (%)	16 (8.6%)	171 (91.4%)	
ICU readmission	No, n (%)	158 (39.4%)	243 (60.6%)	0.110
	Yes, n (%)	39 (31.5%)	85 (68.5%)	
Length of ICU stay, day, median (Q1-Q3)		5 (3-8)	6 (4-15)	<.001

Continuous variables are expressed as either the mean±standard deviation (SD) or median (Q1-Q3) and categorical variables are expressed as either frequency (percentage). Continuous variables were compared with Student-t test or Mann-Whitney U test, and categorical variables were compared using Pearson's Chi-square test or Fisher exact test.
APACHE II: Acute physiologic assessment and chronic health evaluation, BMI: Body-mass index, ICU: Intensive care unit, mNUTRIC: Modified nutritional risk in critically ill patients, MV: Mechanical ventilation, NRS-2002: Nutrition risk screening-2002, SD: Standard deviation, SOFA: Sequential organ failure assessment

Table 5. Univariate and multivariate logistic regression modeling for 3-month mortality

Prediction variable	Unadjusted			Adjusted		
	OR	95% CI	p-value	OR	95% CI	p-value
mNUTRIC score	2.80	2.24-3.51	<.001	2.48	1.93-3.19	<.001
Inotropic support, yes	15.96	7.48-34.06	**<.001**	8.63	3.66-20.3	**<.001**
Respiratory failure, type 1	2.95	1.88-4.64	**<.001**	3.1	1.68-5.71	**<.001**
Mode of admission, ward	2.86	1.67-4.89	**<.001**	2.25	1.13-4.46	**0.020**
Presence of comorbidity, yes	2.64	1.01-6.86	**0.046**	4.11	1.06-15.98	**0.041**
NRS-2002 score	1.19	0.92-1.54	0.170	0.68	0.47-1.00	0.055

mNUTRIC: Modified nutritional risk in critically ill patients, NRS-2002: Nutrition risk screening-2002, OR: Odds ratio, CI: Confidence interval

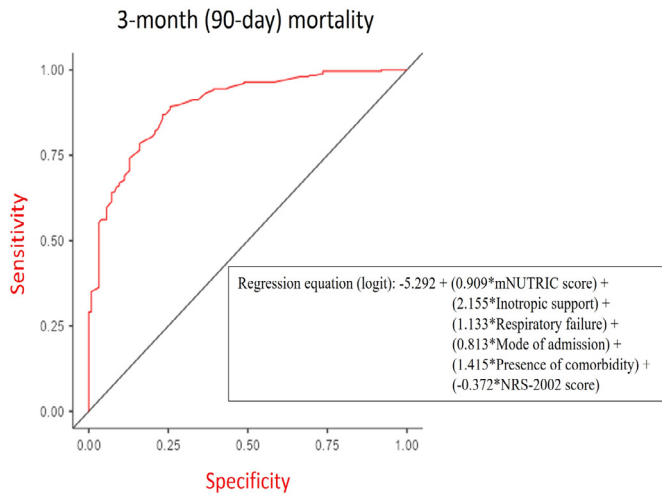

Figure 2. Area under the receiver operating characteristic curve of the model for predicting 3-month mortality in patients hospitalized with respiratory failure in the intensive care unit

Table 6. Relative risk values for 3-month mortality according to types of respiratory failure according to mNUTRIC, NRS-2002 or both

	RR	95% CI	p-value
All			
mNUTRIC ≥5	4.6	3.04-7.15	**<.001**
NRS-2002 ≥5	1.15	1.00-1.32	**0.048**
mNUTRIC+NRS-2002 ≥5	1.57	1.37-1.80	**<.001**
Type-1 RF			
mNUTRIC ≥5	10.66	2.82-40.25	**<.001**
NRS-2002 ≥5	1.00	0.85-1.18	0.929
mNUTRIC+NRS-2002 ≥5	1.31	1.10-1.56	**0.002**
Type-2 RF			
mNUTRIC ≥5	3.63	2.31-5.71	**<.001**
NRS-2002 ≥5	1.17	0.96-1.44	0.115
mNUTRIC+NRS-2002 ≥5	1.63	1.34-1.99	**<.001**

mNUTRIC: Modified nutritional risk in critically ill patients, NRS-2002: Nutrition risk screening-2002, RF: Respiratory failure, RR: Relative risk, CI: Confidence interval

to mNUTRIC (score ≥5), the 3-month mortality risk was found to be 10 times higher in patients with type 1 RF and 3 times higher in patients with type 2 RF (p<.001).

Conversely, in patients assessed to be at high nutritional risk according to NRS-2002 (score ≥5), no statistically significant increase in the risk of death was observed in either type of RF (p values; 0.929, 0.115, respectively). With respect to the complementarity of these tools, the 3-month mortality risk of patients classified as at nutritional risk according to both mNUTRIC and NRS-2002 scores was 1.31 times higher in the type 1 RF group (p=0.002) and 1.63 times higher in the type 2 RF group (p<.001).

DISCUSSION

In the present study, we identified the mNUTRIC score as a robust predictor of 1-month and 3-month mortality in a cohort of patients admitted to a tertiary ICU with type 1 and type 2 RF. Furthermore, the mortality rates were found to be higher in patients with type 1 RF compared to those with type 2 RF, both at one month and three months following admission. Multivariate logistic regression analysis revealed that a high mNUTRIC score, the presence of inotropic support, type 1 RF, and admission to the ward were strongly associated with 1-month and 3-month mortality. Tertiary intensive care beds, defined as those with high occupancy rates resulting from an aging population and advancements in medical technology, are a priority allocation of hospital beds. The ICU length of stay for patients is consistently costly and rising.[15] mNUTRIC and NRS-2002 are the most frequently employed nutritional screening instruments in clinical practice.[12] The utilization of these tools facilitates the early identification of nutritional risk, thereby enabling the timely implementation of specialized and comprehensive nutritional therapy, which is particularly beneficial for patients with severe malnutrition.[9] While our study was conducted in a cohort of patients with RF, the importance of nutrition and its screening in terms of mortality in critically ill patients is clear. The findings of this study indicate that addressing nutritional adequacy may be a crucial measure to reduce mortality in patients with RF.

RF is among the most prevalent etiologies for hospitalization and ICU admissions, with a wide range of underlying causes. Data demonstrate that ARF is present in 32% of patients admitted to the ICU and 24% of patients develop ARF during their ICU stay.[16] The underlying pathophysiology of RF can be multifaceted, involving various mechanisms such as hypoventilation, diffusion impairment, shunting, ventilation-perfusion mismatch, or a combination of these factors.[17] The necessity for ventilatory support is observed in 43-63% of ICU admissions with RF.[2,3,16] Nutritional management of patients with ARF necessitates a multidisciplinary approach.[18] Nutritional status is intricately linked to respiratory function, and a comprehensive understanding of these interrelationships holds therapeutic potential. Malnutrition has been demonstrated to be associated with impaired mechanical function of the lung in both chronic and acute RF.[19] Appropriate and effective patient care and treatment have been shown to reduce complications, shorten ICU and hospital stays, and improve survival rates.[17] The present study examined a cohort of 525 patients, with 186 (35.4%) experiencing type 1 RF and 339 (64.6%) encountering type 2 RF. The necessity for invasive MV support during ICU hospitalization was observed in 56.2% of patients, a finding that aligns with literature data. The mortality rates at one and three months were found to be high in patients with type 1 RF. This underscores the need for enhanced patient care and nutritional interventions to minimize mortality, particularly among patients with type 1 RF who require inotrope and MV support.

The efficacy of early nutritional intervention in critically ill patients is well-documented.[9,20] Recent studies have proposed the use of screening tools and nutritional assessment in conjunction with multiple screening tools for ICU patients.[21] A cross-sectional study of 159 patients compared the predictive power of mNUTRIC and Subjective Global Assessment (SGA), used alone or in combination, to predict the 28-day mortality risk in the ICU. The study revealed that patients classified by mNUTRIC as at nutritional risk (score ≥4) exhibited a 7-fold higher risk of death at the 28-day assessment.[21] Another study of 439 ICU patients evaluated the correlation between mNUTRIC and SGA and showed that the combination of the two has better, significant predictive capacity for in-hospital mortality.[22] The NRS 2002 and NUTRIC scores have been developed to incorporate severity of illness, making them potentially suitable for use in critically ill patients.[20] The NRS 2002 has gained the most traction as a screening instrument to identify hospitalized patients who may benefit from nutritional support.[8] The NRS 2002 is notable for its ease of calculation and the minimal time and data points required for its implementation. The association between the nutritional risk ascertained by the NRS-2002 tool and adverse clinical outcomes, including sepsis and mortality, has been demonstrated.[23,24] The American society for parenteral and enteral nutrition (ASPEN) guidelines have demonstrated the NRS-2002's capacity to differentiate between critically ill patients based on clinical characteristics and outcomes.[24] Furthermore, patients assessed by NRS-2002 to be at high nutritional risk (score ≥3) were reported to have a 2.10-fold increased risk of death in the ICU.[24] Conversely, the NUTRIC score, a tool developed and validated in the intensive care setting, was designed to identify patients who would benefit from aggressive nutritional support, thereby improving adverse clinical outcomes.[9] In a retrospective study, Canales et al.[20] investigated the association of NUTRIC and NRS 2002 scores with macronutrient deficiency in critically ill patients. The study found that NUTRIC scores were associated with macronutrient deficiency in ICU patients, while NRS 2002 scores were not associated with macronutrient deficiency. In their study comparing mNUTRIC and NRS 2002, Machado et al.[12] found a high nutritional risk in 48.4% of NRS-2002 and 54.4% of mNUTRIC in ICU patients. In their 28-day mortality study, they found that the risk of death in the ICU increased 1.41-fold in patients who were assessed to be at high nutritional risk (score ≥5) by NRS-2002, and the risk of death in the ICU increased 3.01-fold in patients who were assessed to be at high nutritional risk (score ≥5) by mNUTRIC.[12] In the present study, which evaluated both 1-month and 3-month mortality in patients admitted to the ICU with RF, the mNUTRIC score emerged as the most robust predictor of mortality. According to the NRS-2002 score, 57.9% of patients exhibited high nutritional risk, while the proportion increased to 78.6% when the mNUTRIC score was considered. This figure exceeded

the rates reported in the extant literature. Furthermore, the prevalence of high nutritional risk (score ≥5) varied according to the specific type of RF. In type 1 RF, the NRS-2002 score identified high nutritional risk in 65.5% of patients, while the mNUTRIC score identified high nutritional risk in 87.1% of patients. In contrast, in type 2 RF, these values were 53.6% according to the NRS-2002 score and 74% according to the mNUTRIC score. These findings underscore the critical importance of nutritional management in patients with RF, particularly in hypoxic patients with type 1 RF, within ICUs. The NRS-2002 score demonstrated no statistical significance in the 1-month mortality assessment. However, a marked increase in mortality was observed, reaching 4.2-fold, in patients evaluated as being at high nutritional risk (score ≥5) by mNUTRIC. In the 3-month mortality assessment, the mortality rate increased 1.15-fold in patients assessed to be at high nutritional risk (score ≥5) by NRS-2002 and 4.6-fold in patients assessed by mNUTRIC. These findings were consistent across different types of RF. The mNUTRIC score emerges as a valuable tool for evaluating patients hospitalized in ICU with RF, applicable to both types of RF. It is noteworthy that the NRS-2002, despite its ease of administration relative to the mNUTRIC, did not demonstrate significant outcomes in ICU patients with RF, particularly in terms of short-term mortality assessment and management.

Limitations

It is imperative to acknowledge the limitations inherent in the present study. Firstly, the study design was observational, single-center, and consequently, the possibility of residual confounding due to unmeasured factors influencing the observed associations cannot be excluded. Furthermore, the inclusion of patients with RF, along with the exclusion of those with mixed-type RF, was a deliberate strategy employed to provide a clear assessment of the outcomes associated with hypoxic and hypercarbic RF. Additionally, the dietary intake of patients was not analyzed in this study. However, the NRS-2002 nutrition screening tool, which includes criteria such as decreased food intake in the last week and recent weight loss, addresses this aspect. It is also important to note that the administration of these screening tools is carried out by a trained nutrition nurse, with direct supervision ensuring the integrity of the process. Therefore, we excluded ICU hospitalizations of less than 48 hours. Furthermore, the present sample included ICU patients with RF, and therefore, the results cannot be generalized to all ICU patients or hospitalized patients. Finally, the study was not designed to conduct a therapeutic analysis, and as such, data regarding treatment management was not available for analysis.

CONCLUSION

The findings of this study indicate that nutritional management is of critical importance in patients hospitalized in the tertiary ICU with RF. In such cases, the utilization of the mNUTRIC nutrition screening tool emerges as a more valuable method for evaluating patients than the NRS-2002 score or both scores in combination. While the NRS-2002 nutrition screening tool is more straightforward to administer, the mNUTRIC tool provides more meaningful results, particularly in the context of short-term mortality assessment and management in ICU patients with type 1 RF. Despite the mNUTRIC score's inclusion of additional parameters, it can be readily derived from the initial data of ICU patients and is the most effective parameter in identifying the high-risk group when the data from our study are considered. In addition to the mNUTRIC score, the presence of inotropic support, type 1 RF, and ward admission are predictors strongly associated with 1-month and 3-month mortality in patients with RF. The prognosis for patients with type 1 RF is worse than for those with type 2, and nutritional management is much more important in this patient group. Especially in patients with high mNUTRIC score, need for inotropic support, and need for ICU while hospitalized with type 1 RF, early intervention and management in terms of nutrition is important to improve the duration of ICU stay and mortality rates.

ETHICAL DECLARATIONS

Ethics Committee Approval

This prospective cohort descriptive study was initiated after approval from the Clinical Researches Ethics Committee of Health Sciences University, Ankara Atatürk Sanatorium Training and Research Hospital (Date: 08.02.2023, Decision No: 2012-KAEK-15/2627).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The diagnostic value of eosinophil-to-lymphocyte ratio in predicting contrast-induced nephropathy in patients with ST-segment elevation myocardial infarction

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ABSTRACT

Aims: Inflammation is considered a major contributor to the development of contrast-induced nephropathy (CIN). The purpose of this study was to assess the effectiveness of eosinophil-to-lymphocyte ratio (ELR) as a predictor of CIN among patients who experienced percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI).

Methods: The study involved 440 patients diagnosed with STEMI who underwent primary PCI. The participants were categorized into two classes based on whether they had CIN or not. ELR was calculated by dividing the eosinophil count by the lymphocyte count.

Results: The group with CIN (+) showed significantly higher ELR levels (0.134±0.063 vs. 0.069±0.037, p<0.001). According to the ROC curve assessment, the best threshold level of ELR to predict CIN development was identified as 0.093, with 75.9% sensitivity and 79.1% specificity (AUC: 0.836; 95% CI: 0.783–0.889; p<0.001). Logistic regression analysis revealed that estimated glomerular filtration rate (eGFR), C-reactive protein, left ventricular ejection fraction, and ELR were independent predictors of CIN.

Conclusion: ELR could be an effective and reliable marker to predict CIN development in individuals with STEMI who undergo primary PCI. Early prediction of CIN risk is critical to provide intensive preventive measures for high-risk patients.

Keywords: Eosinophil-to-lymphocyte ratio, contrast-induced nephropathy, percutaneous coronary intervention, ST-segment elevation myocardial infarction

INTRODUCTION

Contrast-induced nephropathy (CIN) represents a significant complication that occurs after percutaneous coronary intervention (PCI).[1] High-risk conditions such as diabetes and hypertension, combined with the increasing number of invasive cardiac procedures, CIN remains a clinically significant concern. CIN is characterized by an elevation in serum creatinine concentrations of a minimum of 0.5 mg/dl or a 25% rise from baseline, taking place within 72 hours following exposure to contrast agents.[2] Based on current studies, the risk of developing CIN after PCI varies between 6% and 24%.[3] The primary cause of CIN is pre-existing chronic kidney disease (CKD). Additionally, patients with triggering factors such as acute coronary syndrome, hypotension, nephrotoxic drug use, and anemia have an increased likelihood of experiencing CIN. CIN can lead to extended hospital stays, escalating treatment costs, and an increase in mortality rates.[4]

While the exact mechanism behind CIN remains unclear, there is a strong connection between inflammation and the onset of CIN.[5] As a result, biomarkers associated with inflammation are currently a focal point of intense study in this field. Eosinophils are actively involved in the processes of inflammation, endothelial injury, and vascular thrombosis.[6] The cytotoxic granules they release (such as major basic protein-1) and the various enzymes, cytokines, and chemokines they produce contribute to the progression or resolution of inflammation. Reduced lymphocyte counts are closely tied to inflammation and significantly influence both the onset and progression of atherosclerosis.[7] An increase in eosinophils and low lymphocyte levels reflect systemic inflammation. The eosinophil-to-lymphocyte ratio (ELR) is an inflammatory marker that takes into account both eosinophil and lymphocyte counts. Recent studies have

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indicated that ELR is connected to clinical outcomes in a range of cardiovascular conditions.[8,9]

CIN is linked to adverse clinical outcomes.[10] By implementing existing preventive strategies before the PCI procedure, we can significantly lower the risk of developing CIN and effectively prevent its progression. Therefore, identifying patients at higher risk early is essential for significantly improving clinical outcomes. This research sought to assess the effectiveness of ELR as a predictor of CIN among patients who experienced PCI for ST-elevation myocardial infarction (STEMI).

METHODS

Ethics

The study protocol received approval from Yozgat Bozok University Non-interventional Clinical Researches Ethics Committee (Date: 18.12.2024, Decision No: 2024-GOKAEK-2415_2024.12.18_251). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Participants' formal informed permission was not acquired because the study was a retrospective design.

Study Design

An overall of 440 consecutive STEMI patients, who were admitted to the cardiology unit and underwent PCI from January 2023 to October 2024, were part of this cross-sectional, single-center study. According to current clinical practice guidelines, STEMI was diagnosed when there was ST-segment elevation in two or more adjacent leads on the electrocardiography or the presence of newly developed left bundle branch block, along with signs of ischemia and/or increased levels of cardiac biomarkers indicating myocardial injury.[11] The exclusion criteria were: patients who received thrombolytic therapy before PCI, those with end-stage renal failure [estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m^2] or undergoing dialysis, evidence of active infection or active malignancy, chronic liver disease, a history of hematologic disorders, autoimmune, allergic, or chronic inflammatory diseases, those on chronic steroid or immunosuppressant/immunomodulatory therapy, those using nephrotoxic drugs, those who had contrast-enhanced imaging other than coronary angiography in the previous days, and those who did not undergo PCI.

All demographic details, such as gender, age, smoking status, and coronary artery disease (CAD) history, were collected from the hospital's record system. Additionally, data related to vital signs at admission, including both systolic and diastolic blood pressure readings, was documented for the research.

Laboratory Measurements

Venous blood samples for routine analysis were drawn from all subjects before undergoing coronary angiography. Complete blood count parameters were evaluated using an automated cell counter (Beckman Coulter LH 750; Beckman Coulter Inc., USA). Biochemical tests, which included measurements of serum glucose, lipid levels, and creatinine, were conducted using established laboratory methods (Beckman Coulter Inc., USA). In all patients analyzed, serum creatinine was assessed once daily during their hospital stay, both before and after primary PCI. The equation from the CKD epidemiology collaboration (CKD-EPI) was employed to compute the eGFR.[12] The ELR was calculated by taking the eosinophil count and dividing it by the lymphocyte count. Left ventricular ejection fraction (LVEF) was identified using Simpson's method through standard transthoracic echocardiography (Vivid 7 GE Medical System) within 24 hours following the PCI.

CIN was defined by an elevation in serum creatinine levels, specifically a rise of at least 0.5 mg/dl or 25% over the baseline, occurring within 72 hours following exposure to contrast agents.[2] Based on this standard, the subjects were divided into two classes: CIN (+) and CIN (-).

Angiographic Analysis

Based on the operator's choice, coronary angiography was conducted using the Standard Judkins technique, via either femoral or radial access. The PCI procedures were carried out following international guidelines, with Iohexol used as the contrast agent. Each patient was administered a loading dose of acetylsalicylic acid (300 mg) along with a P2Y12 receptor inhibitor, which included a loading dose of either 600 mg of clopidogrel, 60 mg of prasugrel, or 180 mg of ticagrelor before the procedure. Following the administration of a 70 IU/kg bolus of unfractionated heparin during the PCI procedure, the operator had the option to use tirofiban to block the platelet glycoprotein IIb/IIIa receptor.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS for Windows version 23.0 (SPSS Inc., Chicago, IL, USA). The distribution patterns of variables were assessed with the Kolmogorov-Smirnov test. Categorical variables were presented as frequencies and percentages, while continuous variables were expressed as mean±standard deviation or median with interquartile range (IQR), depending on the data distribution. The Mann-Whitney U test was used to compare nonparametric continuous variables, and categorical variables were evaluated using Pearson's Chi-square test. Logistic regression analysis was carried out to determine factors independently correlated with CIN. The receiver operating characteristic (ROC) curve was also employed to determine the most accurate ELR cutoff for predicting CIN. A p-value under 0.05 was considered statistically significant.

RESULTS

This research encompassed 440 STEMI patients (average age: 59.2±13.0, 73% male) who underwent primary PCI, with 58 (13.1%) of them developing CIN. Based on the occurrence of CIN, the population was separated into two categories, with their demographic and clinical characteristics are illustrated and contrasted in **Table 1**. The CIN (+) group was older than the other group (70.9±12.5 vs. 57.4±12.2, p<0.001). Notable distinctions were not identified among the groups concerning gender, frequency of hyperlipidemia, history of CAD, medicines taken before to and during hospitalization, blood pressure at the time of admission, or body-mass index. Patients in the CIN (+) group exhibited a greater incidence

Table 1. Comparison of demographic, clinical and laboratory characteristics of patients

Variables	CIN (-) (n:382)	CIN (+) (n:58)	p
Age (years)	57.4±12.2	70.9±12.5	<0.001
Gender (male), n (%)	284 (74.3)	37 (63.8)	0.092
Diabetes mellitus, n (%)	108 (28.3)	24 (41.4)	0.042
Hypertension, n (%)	133 (34.8)	35 (60.3)	<0.001
Hyperlipidemia, n (%)	115 (30.1)	15 (25.9)	0.509
Current smoker, n (%)	211 (55.2)	10 (17.2)	<0.001
Body-mass index (kg/m²)	28.0±4.2	27.7±4.9	0.243
History of coronary artery disease, n (%)	56 (14.7)	10 (17.2)	0.608
Systolic blood pressure (mmHg) (at admission)	128.6±23.2	128.0±30.1	0.781
Diastolic blood pressure (mmHg) (at admission)	78.1±13.7	77.4±17.1	0.929
LVEF (%)	47.9±9.5	40.0±10.2	<0.001
Pre-hospital medications			
Statin, n (%)	36 (9.4)	7 (12.1)	0.527
ACE-İ/ARB, n (%)	86 (22.5)	18 (31.0)	0.155
Beta blocker, n (%)	58 (15.2)	12 (20.7)	0.285
Oral antidiabetic, n (%)	82 (21.5)	17 (29.3)	0.183
In-hospital medications			
Statin, n (%)	356 (93.2)	53 (91.4)	0.615
ACE-I/ARB, n (%)	298 (78.0)	40 (69.0)	0.128
Beta blocker, n (%)	339 (88.7)	50 (86.2)	0.574
MRA, n (%)	32 (8.4)	4 (6.9)	0.702
Glucose (mg/dl)	126 (107-170)	135 (108-234)	0.144
Creatinine (mg/dl) (at admission)	1.05±0.25	1.38±0.43	<0.001
eGFR (mL/min/1.73m²) (at admission)	76±19	51±20	<0.001
Triglyceride (mg/dl)	139 (95-199)	141 (80-201)	0.660
Total cholesterol (mg/dl)	195±45	187±51	0.149
HDL-cholesterol (mg/dl)	40±8	40±11	0.741
LDL-cholesterol (mg/dl)	125±40	121±40	0.517
C-reactive protein (mg/L)	0.56 (0.29-0.97)	0.83 (0.43-1.44)	0.005
WBC (x10³/μL)	10.4±2.9	10.5±3.4	0.810
Neutrophil (x10³/μL)	6.4±2.4	6.9±2.5	0.135
Lymphocyte (x10³/μL)	3.0±1.2	2.4±1.3	<0.001
Eosinophil (x10³/μL)	0.19±0.12	0.31±0.18	<0.001
Hemoglobin (g/dl)	14.4±1.6	13.0±2.4	<0.001
Platelet (x10³/μL)	230 (194-268)	245 (196-326)	0.068
ELR	0.069±0.037	0.134±0.063	<0.001

Data are shown as mean±standard deviation, median (25th and 75th interquartile range), and number (%), CIN: Contrast-induced nephropathy, ACE-I: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, ASA: Acetylsalicylic acid, eGFR: Estimated glomerular filtration rate, ELR: Eosinophil/lymphocyte ratio, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, LVEF: Left ventricular ejection fraction, MRA: Mineral corticosteroid receptor antagonists, OAD: Oral antidiabetic, WBC: White blood cell

of diabetes and hypertension, along with reduced LVEF and smoking rates compared to those in the CIN (-) group. The groups exhibited no notable differences regarding admission serum glucose, white blood cell (WBC) count, neutrophil and platelet levels, or serum lipid profile. In the CIN (+) group, the admission serum creatinine level, C-reactive protein (CRP), and eosinophil count were significantly higher, while lymphocyte count, eGFR, and hemoglobin levels were lower. Moreover, the ELR was notably elevated in the CIN (+) group when compared to the CIN (-) group (0.134±0.063 vs. 0.069±0.037; p<0.001) (**Figure 1**).

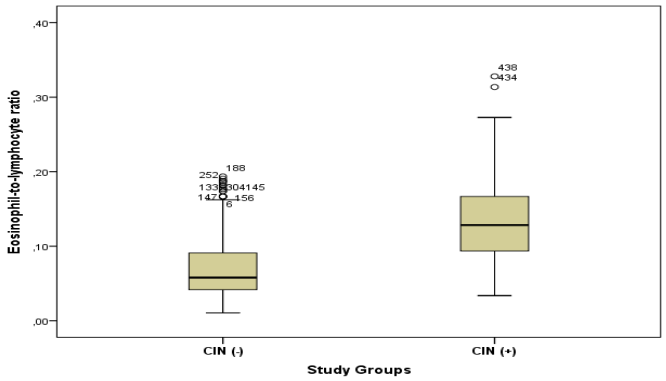

Figure 1. Comparison of ELR of the study groups
ELR: Eosinophil-to-lymphocyte ratio

The angiographic characteristics of the subjects are presented in **Table 2**. We detected statistically no remarkable differences in terms of the culprit coronary artery, total contrast volume, stent length, and stent diameter between the two groups. While the incidence of multivessel disease was slightly greater in the CIN (+) cohort compared to the CIN (-) cohort, this disparity did not achieve statistical significance (62.1% vs. 50.5%; p=0.101).

The multivariate logistic regression analysis revealed that elevated ELR levels (OR:1.251, 95% Confidence Interval (CI):1.149-1.362; p<0.001) were an independent predictor of CIN. Furthermore, lower eGFR (OR:0.961, 95%CI: 0.937-

Table 2. Angiographic features of patients according to the presence or absence of contrast nephropathy

Variables	CIN (-) (n:382)	CIN (+) (n:58)	p
Culprit coronary artery, n (%)			
LAD	166 (43.5)	28 (48.3)	0.491
LCX	70 (18.3)	14 (24.1)	0.294
RCA	146 (38.2)	16 (27.6)	0.118
Total amount of contrast media (ml)	167±71	170±72	0.822
Multivessel disease, n (%)	193 (50.5)	36 (62.1)	0.101
Stent length (mm)	25.0±11.9	26.5±10.8	0.127
Stent diameter (mm)	3.2±0.4	3.0±0.3	0.109

Data are shown as mean±standard deviation, CIN: Contrast-induced nephropathy, LAD: Left anterior descending artery, LCX: Left circumflex artery, RCA: Right coronary artery

0.985; p=0.002), higher CRP levels (OR:1.555, 95%CI: 1.164-2.077; p=0.003), and reduced LVEF (OR:0.943, 95%CI: 0.904-0.984; p=0.006) were also found to be independent predictors of CIN (**Table 3**).

Based on the ROC curve analysis, the best ELR threshold level for predicting CIN development was 0.093, demonstrating a sensitivity of 75.9% and specificity of 79.1% [area under curve (AUC): 0.836; 95% CI: 0.783–0.889; p<0.001] (**Figure 2**).

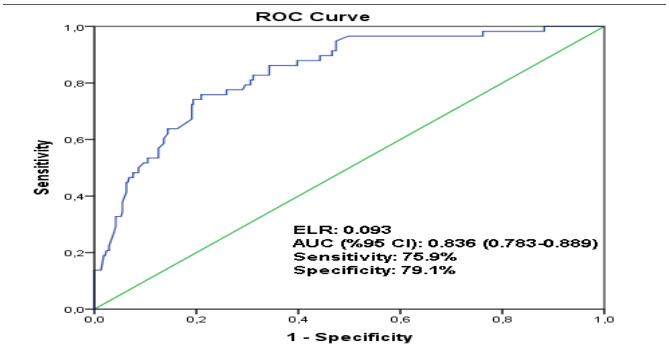

Figure 2. ROC curves analysis of CIN prediction using ELR
ROC: Receiver Operating Charasteristics, CIN: Contrast-induced nephropathy, ELR: Eosinophil-to-lymphocyte ratio

DISCUSSION

The findings of this study indicated that ELR independently predicts the occurrence of CIN in STEMI patients undergoing primary PCI. Furthermore, eGFR, CRP, and LVEF were identified as factors linked to the onset of CIN.

Earlier studies have pinpointed various risk elements contributing to the onset of CIN. However, due to the nephrotoxic effects of contrast agents can vary significantly from one individual to another, predicting CIN can sometimes be challenging in clinical settings. In STEMI patients, CIN occurs at higher rates compared to elective PCI patients due to the more complex nature of primary PCI, increased contrast usage, hemodynamic instability, and the limited applicability of preventive measures.[13] In our research, the rate of CIN among STEMI patients was found to be 13.1%.

The pathophysiology of CIN involves complex mechanisms that are likely influenced by multiple factors. Previous research has indicated that potential causes include direct damage to tubular epithelial cells, constriction of blood vessels within the kidneys, hypoxia in the medulla, endothelial dysfunction, and reactive oxygen species.[5,14] Contrast agents lead to prolonged vasoconstriction of renal blood vessels by directly affecting vascular smooth muscle cells and triggering the release of inflammatory mediators at the cellular level. Additionally, they reduce water reabsorption, leading to an increase in interstitial pressure. This leads to a reduction in eGFR and exacerbation of medullary hypoxia. Moreover, contrast agents increase blood viscosity, which raises resistance to blood flow by reducing the deformability of red blood cells. The formation of intravascular sludge can result in localized ischemia and trigger the production of reactive oxygen products. This process contributes to cellular damage within the tubules, which is associated with the progression of acute kidney injury. On the other hand, contrast agents activate inflammatory pathways, which can result in acute kidney injury.[15] Studies in experimental animals supporting this mechanism have illustrated that inflammatory cytokines, such as TNF-α, IL-1, and IL-6, rise markedly right following exposure to contrast agents, resulting in acute tubular damage.[16] A prospective study conducted by Kwasa et al.[5] showed that individuals with CIN exhibited elevated CRP levels in contrast to those without. These findings indicate that inflammation is considered a major contributor to the emergence of CIN.[5,14] High eosinophil levels and low lymphocyte levels reflect systemic inflammation. ELR is an inflammatory marker that considers both eosinophil and lymphocyte counts. Our study found ELR and CRP, inflammatory markers, as independent predictors of CIN.

Numerous indices based on complete blood counts have been created recently to examine the connection between inflammation and cardiovascular disorders. Eosinophils are multipurpose white blood cells that contribute to the emergence of several inflammatory diseases, including cancer, allergic disorders, and systemic and local infections.[17] Eosinophils perform a vital role, particularly in vascular inflammation and thrombosis.[6] A study conducted by Colon et al.[18] demonstrated that eosinophils accumulating in the renal interstitium could trigger renal fibrosis by modulating the inflammatory response and eosinophil peroxidase activity. A study conducted by Kielar et al.[19] demonstrated that individuals with CKD and high eosinophil levels encountered

Table 3. Logistic regression analysis of potential predictors for contrast nephropathy

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.086 (1.060-1.112)	<0.001		
Diabetes mellitus	1.791 (1.015-3.160)	0.044		
Hypertension	2.849 (1.617-5.021)	<0.001		
C-reactive protein	1.363 (1.161-1.600)	<0.001	1.555 (1.164-2.077)	0.003
ELR	1.295 (1.213-1.382)	<0.001	1.251 (1.149-1.362)	<0.001
Current smoker	0.169 (0.083-0.344)	<0.001		
Hemoglobin	0.690 (0.598-0.797)	<0.001		
LVEF	0.923 (0.896-0.952)	<0.001	0.943 (0.904-0.984)	0.006
eGFR	0.940 (0.924-0.955)	<0.001	0.961 (0.937-0.985)	0.002
Eosinophil	1.631 (1.363-1.951)	<0.001		
Lymphocyte	0.628 (0.474-0.833)	0.001		

OR: Odds ratio, CI: Confidence interval, eGFR: Estimated glomerular filtration rate, ELR: Eosinophil/lymphocyte ratio, LVEF: Left ventricular ejection fraction

a heightened likelihood of progressing to end-stage renal disease. In contrast, lymphocytes are essential in regulating inflammatory responses. Lower lymphocyte counts, associated with increased inflammation and lymphocyte apoptosis, make STEMI patients more susceptible to endothelial dysfunction, platelet activation, and thrombosis.[20] Low lymphocyte levels (lymphopenia) have been linked to heightened increased inflammatory activity and adverse cardiovascular events.[21]

ELR is a new inflammatory biomarker based on serum eosinophil and lymphocyte counts. Recent research has highlighted a notable connection between ELR and adverse outcomes in cancer patients.[22] Furthermore, the predictive value of this index has been investigated across various cardiovascular diseases, including CAD, heart failure, isolated coronary artery ectasia, microvascular angina, and slow coronary flow.[8,9,23-25] However, the relationship between ELR and CIN has not been previously explored. Given that an elevated ELR is strongly linked to inflammatory processes and atherosclerosis, our research sought to determine whether ELR correlates with CIN in STEMI patients. The findings from this study suggest that ELR serves as an independent predictor for CIN occurrence following the PCI procedure.

As the occurrence of CIN results in considerable morbidity and mortality, it is essential to identify useful biomarkers to decrease the rate of CIN through preventive strategies. ELR, a practical and reliable indicator that can be straightforwardly derived from complete blood analysis, could serve as a predictor of CIN. Preventive strategies, such as prophylactic hydration and/or using low-dose iso-osmolar contrast agents, can be easily applied to subjects with elevated ELR levels, regardless of kidney function.

Limitations

Our investigation has some constraints. To begin with, the analysis is retrospective, conducted at a single center, and possesses a restricted sample size. Consequently, the results need to be further validated and confirmed in larger populations. Second, only a baseline ELR value was determined in the study; temporal measurements of ELR values could provide additional data. Finally, because changes in serum creatinine may extend beyond the 72-hour time frame due to delayed effects of the contrast agent, kidney function deterioration may have occurred after hospital discharge in some subjects; therefore, the correct rate of CIN may have been overlooked.

CONCLUSION

Inflammation has been identified as a crucial factor in the progression of CIN, with various inflammation-related biomarkers recognized as being associated with its occurrence. This study emphasizes the correlation between the emergence of CIN in individuals with STEMI and ELR, a relatively new inflammatory marker. This index could assist clinicians in identifying high-risk patients who would benefit from preventive strategies prior to and following the primary PCI procedure.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Yozgat Bozok University Non-interventional Clinical Researches Ethics Committee (Date: 18.12.2024, Decision No: 2024-GOKAEK-2415_2024.12.18_251).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Morphometry of the masseter muscle and topographic location of the masseteric nerve: anatomical study in terms of BTX-A and facial reanimation applications

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ABSTRACT

Aims: The aim of this study was to investigate the morphometry of the masseter muscle (MM) and the topography of the masseteric nerve (MN) innervating the MM.

Methods: The MM and MN were examined on 18 sides (female: 4, male: 5) of formaldehyde-fixed adult cadavers in the laboratory of Kocaeli University Faculty of Medicine, Department of Anatomy. The MM and its surroundings were exposed by dissection. The morphometric measurements of the MM were obtained using a digital caliper. Tragus and lateral canthus landmarks were used for the location of the motor nerve of the MM.

Results: In this study, morphometric measurements of the MM were presented. A statistically significant difference was found between sexes in morphometric measurements related to the height and width of the muscle ($p<0.05$). MM thickness was measured as 6.47 (6.06-6.50) mm. The median value of the distance between the tragus and lateral canthus was 76.04 (72.36-79.02) mm. Accordingly, the branching point of the MN; the vertical distance from the midpoint of the distance between the tragus and lateral canthus to the nerve was 42.72 (39.09-44.50) mm.

Conclusion: We believe that determining the topographic location of the MN using standard anatomical landmarks will make important contributions to both facial reanimation and BTX-A applications.

Keywords: Masseter muscle, masseteric nerve, facial reanimation, botulinum toxin type A, masseter muscle hypertrophy

INTRODUCTION

One of the clinically important problems associated with the masseter muscle (MM) is masseteric muscle hypertrophy (MMH).[1,2] Botulinum toxin type A (BTX-A) application stands out as a safer and more effective option compared to invasive methods such as partial surgical resection and osteotomy for the treatment of this condition, which may cause aesthetic concerns.[3,4] BTX-A reduces muscle activity by creating a transient synaptic blockade at the neuromuscular junction. However, the contractile function of the muscle begins to gradually return within a few weeks depending on the cellular regeneration process and although this process shows individual differences, it usually ends with the muscle reaching its pretreatment strength in approximately 6 months.[1] In order to perform BTX-A application safely and effectively, it is of great importance to know the anatomical structure of the MM and the location of the masseteric nerve (MN), the nerve innervating this muscle, in detail.

On the other hand, facial paralysis is a complex disease with variable etiology and severity and may lead to both physical and psychological complications.[5,6] In the treatment of this condition, various surgical options are available for facial reanimation. However, timing is critical in these operations because intervention should be performed within a certain period of time in order to connect the damaged facial nerve to another intact nerve.[5] The potential role of the MN in facial rehabilitation was first described in 1978 and its use in facial reanimation became widespread in the following years.[7-9] MN transfer is surgically advantageous due to its low morbidity rate and close location to the facial nerve. In addition, faster recovery compared to contralateral facial nerve graft makes this method attractive. However, despite all these advantages, surgeons report that dissection of this nerve is technically challenging.[10] Therefore, the identification of reliable and reproducible anatomical landmarks that will facilitate the surgical detection of the MN may significantly help surgeons.

The MN is increasingly used in facial reanimation through three primary approaches: direct motor neurotization, babysitter and double innervation techniques, and the

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innervation of neuromuscular transplants. In direct motor neurotization, the MN is directly coapted to the facial nerve branches. Its location within the "subzygomatic triangle," formed by the zygomatic arch, anterior border of the temporomandibular joint, and frontal branch of the facial nerve, allows for precise and efficient identification. In babysitter procedures, the MN temporarily innervates the facial nerve during long reinnervation periods to prevent muscle atrophy, and in some cases, it remains as a permanent coaptation to enhance facial movements. For neuromuscular free tissue transfers, the MN is commonly used to power free muscle grafts, such as gracilis muscle transfers, for smile reanimation, often leading to quicker functional recovery, with initial movement observed within 2–4 months.[11]

In the literature, studies on the MN, the motor nerve of the MM, are limited compared to other cranial nerves and the anatomical, topographic and functional data on this nerve are not comprehensive enough. This study aims to examine the detailed anatomical structure and morphometric parameters of the MM and to define the topographic localization of the motor point of the muscle with reliable and reproducible anatomical landmarks that are highly usable in surgical procedures. The findings obtained in this direction are expected to provide intraoperative guidance in surgical applications and to increase surgical success by reducing complications in neurological rehabilitation and nerve transfer procedures.

METHODS

Ethics

Approval for this study was obtained from Kocaeli University Faculty of Medicine Non-interventional Clinical Researches Ethics Committee (Date: 19.12.2024, Decision No: GOKAEK 2024-/21.01). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. In this study, the MM was examined on 4 female and 5 male (total 18 sides) fixed cadavers. Cadavers with previous deformations or surgical procedures in the examined area were not included in the study.

Dissection Stages

Skin, superficial musculoaponeurotic tissue and adipose tissue were removed. The MM and surrounding structures were preserved and dissected carefully. Measurements were taken to determine the morphometric properties of the MM (**Figure 1**). The thickness of the MM was measured at the most bulging point of the muscle. Digital caliper was used for measurements.

Defined measurement points:

A: The highest point of the anterior edge of the superficial part of the MM

B: The highest point of the posterior edge of the superficial part of the MM

C: The highest point of the posterior edge of the deep part of the MM

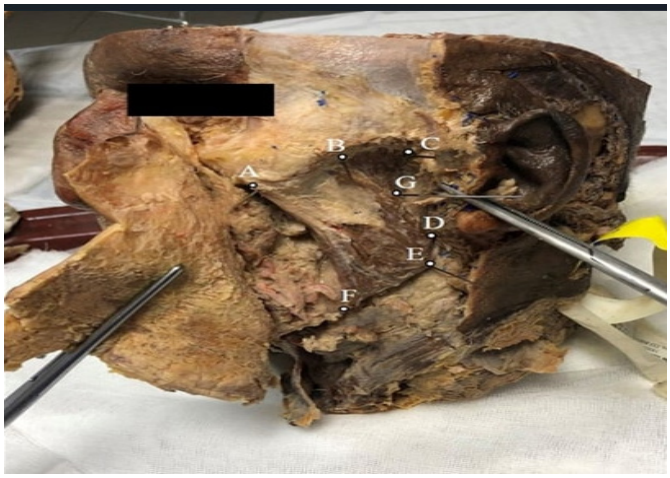

Figure 1. Measurement points used for the MM

D: The lowest point of the posterior edge of the superficial part of the MM

E: The gonion point

F: The lowest point of the anterior edge of the superficial part of the MM

G: The lowest edge of the deep part of the MM

Morphometric measurements related to the MM:

A-B: Upper edge length of the superficial part of the MM

A-F: Anterior edge length of the superficial part of the MM

B-C: Superficial upper edge of the deep part of the MM

B-D: Posterior edge length of the superficial part of the MM

B-G: Superficial anterior edge of the deep part of the MM

C-G: Posterior edge length of the deep part of the MM

E-D: Lower posterior edge length of the superficial part of the MM

F-E: Lower anterior edge length of the superficial part of the MM

To expose the MN, the MM was freed from its origin under the zygomatic arch and its insertion at the masseteric tuberosity. The muscle was reflexed from back to front and the branching point of the MN and the motor nerve entering the superficial and middle part of the muscle were identified (**Figure 2**). The branching point of the nerve was marked on the skin. Tragus and lateral canthus landmarks were determined on the skin to determine the entry point of the nerve into the muscle. The distance between the tragus and the lateral canthus (a) and the vertical distance from the midpoint of this line to the branching point of the MN were measured with a digital caliper (**Figure 3**).

Statistical Analysis

The data analyses of the study were performed with IBM SPSS Statistics 25.0 (IBM Corp. Armonk, New York, USA). Descriptive statistics of the variables in the study are given

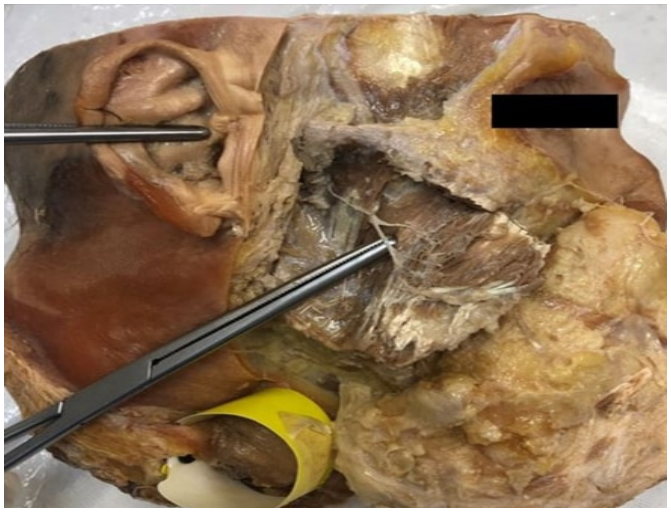

Figure 2. Branching point of the MN

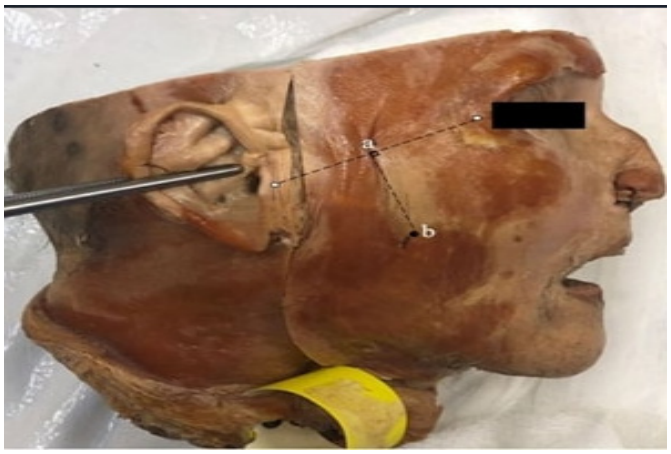

Figure 3. Topographic location of the MN (**a**. Midpoint of the distance between the tragus and lateral canthus, **b**. Branching point of the MN)

as number of units, median and quartile values. Mann-Whitney-U test was used for comparisons between sexes and Wilcoxon test was used for comparisons between right/left sides. Statistical significance level was accepted as α=0.05.

RESULTS

The mean age of the 9 fixed cadavers used in the study was 67.56 (±8.443) years. The number of units, median and quartile values of the variables measured for the morphometry of the MM are given in Table 1 and Table 2. There was a statistically significant difference between the sexes in the morphometric measurements of the MM A-F, B-C, B-D, B-G, E-D, F-E (Table 1). When the measurements of the muscle were compared between the right and left sides, a statistically significant difference was found only in the E-D measurement (Table 2).

The thickness values of the MM are presented as medians in Table 3. The median value of the muscle thickness was 6.47 (6.06-6.50) mm. There was no statistically significant difference in muscle thickness between the right and left sides and between sexes (p>0.05). The vertical distance from the midpoint of the distance between the tragus and the lateral canthus to the nerve (point b) was 42.72 (39.09-44.50) mm (Table 4). There was no statistically significant difference between sexes and between right and left sides (p>0.05).

DISCUSSION

The MM and MN are important anatomical structures for many applications such as BTX-A, facial reanimation and acupuncture. In this study, morphometric measurements of the MM and the topographic location of the MN were presented. A statistically significant difference was found between the sexes in the measurements expressing the length and width of the MM (p<0.05). Additionally, the study determined that a vertical line descending from the midpoint of the distance between the tragus and the lateral canthus reaches the branching point of the MN. There was no statistically significant difference in this measurement, which reports the topographic location of the nerve, according to sex and side (p>0.05). Thus, the measurement point determined for the nerve can be used regardless of sex and side.

The MM, which consists of three parts—superficial, middle, and deep—was found to have smaller dimensions in women (p<0.05). This difference may be attributed to variations in the mastication process based on sex. Previous studies have reported that men exhibit a higher chewing frequency and shorter chewing duration compared to women.[12,13] Furthermore, we believe that the statistically significant difference observed in only one variable between the right and left sides in morphometric measurements of the muscle does not affect the overall results of our measurements.

In the literature, a study by Lee et al.[14] reported the width of the superficial part of the MM as 33.3±4.4 mm, the width of the deep part as 18.5±4.0 mm, the anterior length of the muscle as 64±5.4 mm, and the posterior length as 49.9±4.6 mm. Recently, muscle thickness has been considered an indicator of masticatory muscle function. Muscle thickness is associated with various factors, including bone morphology and physical activity.[15] A direct relationship has been observed between MM thickness and different skeletal structures: the muscle is thicker in individuals with short faces and thinner in those with long faces.[16]

In the literature, MM thickness has been measured using various radiological imaging methods.[15,17,18] Differences in measured muscle thickness exist among imaging methods. Studies have shown that the relaxed muscle thickness measured using ultrasonography is smaller than that measured with MRI.[18] Ultrasonography is considered an accessible, reliable, and practical tool among imaging methods in clinical settings. However, measurement errors can occur due to the position of the probe or excessive pressure applied to the skin.[19] Standardization of methods and parameters is required to prevent measurement errors.

In a study by Rani et al.[15], using ultrasonography, men were found to have a thicker MM. In the present study, no significant difference in MM thickness was found between sexes. Additionally, smaller muscle thickness values were observed compared to the study by Rani et al.[15] Considering that formaldehyde causes tissue shrinkage, the differences in findings between the two studies may be due to the measurement methods used.

There are multiple treatment options available for MMH. To avoid postoperative complications, BTX-A injections are

Table 1. Comparison of morphometric measurement values of MM between sexes

Parameters	Total (n=9) median (25.Q-75.Q) (mm)	Sex		p*
		Female (n=4) median (25.Q-75.Q) (mm)	Male (n=5) median (25.Q-75.Q) (mm)	
A-B	32.55 (29.74-34.68)	32.55 (31.60-33.39)	32.92 (27.20-35.78)	0.897
A-F	65.42 (61.47-65.91)	61.47 (60.27-62.39)	65.76 (65.44-67.74)	<0.001***
B-C	18.56 (16.36-19.31)	16.46 (15.40-18.57)	18.97 (18.34-21.03)	0.027***
B-D	49.23 (46.12-51.78)	45.98 (44.69-51.81)	49.56 (49.16-51.97)	0.034***
B-G	26.87 (22.49-27.10)	23.23 (22.26-26.42)	27.03 (25.83-27.58)	0.016***
C-G	21.46 (19.77-22.26)	19.52 (16.42-23.33)	21.46 (20.99-21.71)	0.573
E-D	22.21 (18.89-23.51)	23.21 (22.33-23.90)	19.33 (17.78-20.59)	0.006***
F-E	23.88 (22.87-31.95)	22.74 (21.60-23.70)	31.63 (23.88-32.61)	0.001***

A-B: Upper edge length of the superficial part of the MM, A-F: Anterior edge length of the superficial part of the MM, B-C: Superficial upper edge of the deep part of the MM, B-D: Posterior edge length of the superficial part of the MM, B-G: Superficial anterior edge of the deep part of the MM, C-G: Posterior edge length of the deep part of the MM, E-D: Lower posterior edge length of the superficial part of the MM, F-E: Lower anterior edge length of the superficial part of the MM, MM: Masseter muscle, p*: Comparison between sexes (Wilcoxon test). ***p<0.05 there is a statistically significant difference

Table 2. Comparison of morphometric measurement values of MM between sides

Parameters	Total (n=9) median (25.Q-75.Q) (mm)	Side		p*
		Right (n=9) median (25.Q-75.Q) (mm)	Left (n=9) median (25.Q-75.Q) (mm)	
A-B	32.55 (29.74-34.68)	33.31 (28.30-34.57)	32.20 (29.52-34.72)	0.514
A-F	65.42 (61.47-65.91)	65.45 (61.06-66.03)	65.42 (61.82-66.47)	0.440
B-C	18.56 (16.36-19.31)	18.97 (16.13-19.09)	18.56 (16.23-19.88)	0.260
B-D	49.23 (46.12-51.78)	49.16 (45.54-52.56)	49.56 (46.24-51.83)	0.678
B-G	26.87 (22.49-27.10)	26.87 (22.59-27.17)	26.91 (22.49-27.10)	0.906
C-G	21.46 (19.77-22.26)	21.29 (19.10-21.87)	21.46 (19.11-22.47)	0.314
E-D	22.21 (18.89-23.51)	22.13 (18.23-23.24)	22.47 (18.71-23.72)	0.021***
F-E	23.88 (22.87-31.95)	23.59 (22.67-32.23)	24.62 (22.98-32.13)	0.373

A-B: Upper edge length of the superficial part of the MM, A-F: Anterior edge length of the superficial part of the MM, B-C: Superficial upper edge of the deep part of the MM, B-D: Posterior edge length of the superficial part of the MM, B-G: Superficial anterior edge of the deep part of the MM, C-G: Posterior edge length of the deep part of the MM, E-D: Lower posterior edge length of the superficial part of the MM, F-E: Lower anterior edge length of the superficial part of the MM, MM: Masseter muscle, p*: Comparison between sides (Wilcoxon test). ***p<0.05 there is a statistically significant difference

Table 3. Comparison of MM thickness by sex and side (mm)

Parameters	Total (n=9) median (25.Q-75.Q) (mm)	Sex			Side		
		Female (n=4) median (25.Q-75.Q) (mm)	Male (n=5) median (25.Q-75.Q) (mm)	p*	Right (n=9) median (25.Q-75.Q) (mm)	Left (n=9) median (25.Q-75.Q)(mm)	p**
Muscle thickness	6.47 (6.06-6.50)	6.48 (6.47-6.67)	6.09 (5.63-6.48)	0.055	6.47 (6.25-6.63)	6.47 (5.44-6.48)	0.400

MM: Masseter muscle, p*: Comparison between sexes, (Mann-Whitney test), p**: Comparison between parties, (Wilcoxon test)

Table 4. The distance between the tragus and the lateral canthus (a) and the vertical distance from the midpoint of this line to the branching point of the MN (a-b distance) by sex and side (mm)

Parameters	Total (n=9) median (25.Q-75.Q) (mm)	Sex			Side		
		Female (n=4) median (25.Q-75.Q) (mm)	Male (n=5) median (25.Q-75.Q) (mm)	p*	Right (n=9) median (25.Q-75.Q) (mm)	Left (n=9) median (25.Q-75.Q) (mm)	p**
Distance between tragus and lateral canthus	76.04 (72.36-79.02)	72.29 (71.55-78.71)	76.56 (75.85-79.02)	0.083	75.85 (72.67-79.59)	76.56 (72.29-78.75)	0.767
a-b distance	42.72 (39.09-44.50)	42.94 (42.70-45.93)	40.71 (34.78-44.80)	0.101	42.89 (37.29-45.22)	42.68 (37.98-44.81)	0.483

MN: Masseteric nerve, b: Branching point of the MN. p*: Comparison between sexes, (Mann-Whitney test), p**: Comparison between sides, (Wilcoxon test)

frequently used as an alternative to surgical operations.[12] Since 1994, intramuscular BTX-A injections have become the standard non-surgical method for treating MMH. Although it is the standard method, there is no consensus on the most effective injection technique. Some studies recommend using single or low-point injection techniques instead of multi-point injections due to their reduced pain and faster administration.[20]

The optimal dosage of BTX-A varies due to differences in variables, ethnic backgrounds, or relevant morphometric data in studies.[21] Anatomical studies of the region can contribute to the literature by aiding in the determination of effective injection techniques and the appropriate number of injection points.

Botulinum toxin-A (BTX-A) is considered a reliable method for the treatment of MMH; however, complications such as bruising, swelling, and muscle weakness may occur if the injection is administered to the wrong area.[22] Preventing such complications requires a detailed understanding of the MM and the surrounding anatomical structures. In the literature, various anatomical landmarks and entry points have been described for BTX-A injection.

Kim and colleagues[23] proposed a method involving two points along a line drawn between the tragus and the angle of the mouth (chelion), along with two additional points located 1 cm above and below this line. Additionally, injections performed at 1 cm intervals in the lower third of the muscle are also commonly used techniques.[24] Anatomical landmarks described in the literature for identifying the motor nerve of the MM serve as crucial guides for determining injection reference points for BTX-A. Furthermore, the diversity of available techniques provides clinicians with the flexibility to choose the method that best suits their needs and preferences.

On the other hand, the MN is utilized in facial reanimation procedures.[5,25] Facial reanimation is a challenging field, with various nerve transfer options available, such as the hypoglossal nerve, the contralateral facial nerve, and the MN.[5] Studies suggest that the MN is a more advantageous option compared to other nerves due to factors such as its anatomical location, relative reliability, strong motor impulses, and low morbidity.[11] Additionally, the literature includes evidence that combining multiple nerve transfers can provide greater benefits.[26,27]

There are studies regarding the location of the MN, which innervates the MM. Previous research has provided guidance for identifying the location of this nerve.[28,29] Cotrufo et al.[28] defined the masseteric region using the mandibular notch and the zygomatic arch to locate the MN. Additionally, Kaya et al.[30] measured the distance between the tragus and lateral canthus as 8.4±1.8 cm, while Ganapathy et al.[3] reported the preauricular to lateral canthus distance as 7.25 cm on the right and 6.95 cm on the left. The measurements in this study yielded similar results. Thus, the anatomical landmarks used for the nerve are consistent with the literature, reliable, and applicable.

Using two standard anatomical landmarks—the tragus and the lateral canthus—the branching point of the MN was identified. This allowed for determining the topographic location of the MN without requiring any imaging device. These standard anatomical landmarks are easily identifiable points, enabling the motor point of the MM to be located on the skin without any prior preparation.

Limitations

The limitation of this study is the low number of cadavers. Future studies could examine the relationship of the MN with nearby nerve branches and conduct clinical investigations for a more detailed analysis of the MN.

CONCLUSION

Knowing the topographic location of the MN is crucial for accurately performing interventions such as facial reanimation and BTX-A injections. In this study, the method used to locate the MN through the skin is considered to be highly repeatable. The study proposes a repeatable, reliable, and easily understandable location for identifying the nerve without requiring prior preparation.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approval for this study was obtained from Kocaeli University Faculty of Medicine Non-interventional Clinical Researches Ethics Committee (Date: 19.12.2024, Decision No: GOKAEK 2024-/21.01).

Informed Consent

This study was conducted using human cadaveric material provided by the anatomy laboratory of Kocaeli University Medicine Faculty, in accordance with ethical guidelines and institutional regulations.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Morphometric and morphologic analysis of the mental foramen using cone beam computed tomography

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ABSTRACT

Aims: It is critical to know the localization, anatomy and dimensions of mental foramen (MF) to avoid nerve damage during surgical procedures in the mandibular anterior region and to ensure complete local anesthesia for dental procedures. The aim of our study was to retrospectively evaluate the morphological and morphometric features of MF using cone-beam computed tomography (CBCT) and to contribute to the existing data.

Methods: In our study, the location of the MF, its horizontal diameter, its vertical diameter, the distance of the MF to the alveolar crest, the distance to the lower border of the mandible, the distance to the apex of the adjacent tooth and the distance to the midline were evaluated in the CBCT images of 500 patients between the ages of 18-65. In addition, the types of exit of the mental nerve from the MF were examined. Pearson Chi-square test was used to analyze categorical variables. Normally distributed characteristics were compared using the student t test.

Results: In our study, CBCT images of 500 cases, 250 (50%) of which were male and 250 (50%) of which were female were examined (mean age: 37.12±11.91). No significant relationship was found between MF location and gender ($p>0.05$). In the right mandibular region, a statistically significant difference was found between the vertical and horizontal diameters of the MF (higher in males), the distance to the alveolar crest (higher in males), the distance of the MF to the lower border of the mandible (higher in males), the distance to the midline (higher in males) and gender ($p<0.05$). No statistically significant relationship was found between MF exit types and gender in the right and left mandibular regions ($p>0.05$).

Conclusion: It is important to examine the localization, size and distance of MF to neighboring anatomical structures, the presence and dimensions of alveolar loop (AL) with CBCT before procedures with high risk of complications in the interforaminal region.

Keywords: Mental foramen, alveolar loop, CBCT

INTRODUCTION

Anterior mandibular region has been considered a safe area for many years, but with the widespread use of implant surgery in the interforaminal region, which has been considered a safe area for many years, more detailed morphometric analysis of the anatomical formations and variations in this region is needed.[1] The mandibular canal origins from the mandibular foramen on the medial surface of the ramus and courses anteriorly, then ends at the mental foramen (MF) on the vestibule surface of the premolar region.[1,2] Knowing the localization, anatomy and dimensions of MF is critical to avoid nerve damage during surgical procedures in the relevant region and to successfully perform local anesthesia for dental procedures.[1,3] The location of MF on the jaw varies according to race and gender.[4] Horizontal and vertical diameters of MF have been measured in various studies.[1,5-8] In studies conducted with cone beam computed tomography (CBCT), the horizontal diameter of MF was reported to be between 3.2-4.08 mm and the vertical diameter was reported to be between 3-3.45 mm.[5,7]

Mental nerve, which is a branch of the inferior alveolar nerve; at the terminal end of the mandibular canal, it continues its course in different ways as it exits the MF.[9,10] After the mental nerve leaves the MF, it distributes in the chin and lip region in the form of horizontal, vertical, alveolar loop (AL) exit types and provides innervation to the surrounding tissue.[2,9] In the

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AL type, the mental canal leaves the MF by bending upwards and backwards.[11] The incidence of AL has been found to be between 7% and 93.57% in the literature.[9,12,13] Another important issue to consider in patients in whom AL is detected is AL lengths. In literature anterior extension of AL has been reported to be 0.11-11 mm, and its caudal extension to be 2.68-11.27 mm.[9,13,14]

The diagnostic method to be chosen is important for correct diagnosis and treatment. Panoramic radiographs, which are routinely used in dentistry, have disadvantages such as providing evaluation in only two dimensions, creating magnifications in the image, and not being able to prevent superpositions.[1,7] The disadvantages of traditional projections have been eliminated with the use of computerized tomography (CT) devices that provide three-dimensional imaging in dentistry. However, the use of CT devices in dentistry has been limited due to features such as high radiation dose, cost and long time to obtain images. Cone beam computed tomography (CBCT) provides three-dimensional data acquisition in a single rotation and with a very low radiation dose.[15] CBCT, which provides images to be obtained more quickly with lower radiation dose and lower cost compared to CT, is especially useful in evaluating bones because it has high resolution.[14,15]

In our study, the location, dimensions and distance of MF to adjacent anatomical structures were evaluated with CBCT. Additionally, the exit types of the mental artery from MF were examined. The purpose of our study is to retrospectively investigate the morphological and morphometric features of MF with CBCT and to contribute to the existing data.

METHODS

This research was conducted with the approval of the Harran University Faculty of Dentistry Ethics Committee (Date: 07.02.2022, Decision No: 22/03/23). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. In our study, the morphological and morphometric features of MF were retrospectively examined in CBCT images of cases aged 18 and over who applied to the Department of Dentomaxillofacial Radiology of Harran University Faculty of Dentistry in 2023 for various reasons.

G power 3.1 was used for power analysis. When α=0.05 and 1-β=0.90 were accepted, the sample size was found to be 375. In our study, CBCT images of 500 cases between the ages of 18-65 were analyzed. Images of patients aged 18 and over who did not have any defects, lesions or pathologies in the anterior mandibular region, did not have a jaw fracture, did not undergo any surgical procedure, and did not have a systemic or genetic disease that would affect the jaw bones were included in the study. Low-resolution images with patient- or device-related artifacts that prevented the examination of anatomical structures in the relevant region were excluded from the study. Images were examined and evaluated in multiplanar (axial, sagittal, coronal) planes and their variations were analyzed morphologically and morphometrically.

In our study, it used blocked randomization to ensure that the groups being compared were of equal size and to increase the power of the statistical procedure to reject the null hypothesis, in resulting randomly selected 250 female and 250 male patients. CBCT images were obtained with the Castellini X-Radius Trio Plus CBCT device (imola, ITALY) using irradiation parameters of 16 mAs and 90 kVp. CBCT images size of 0.3 mm and a field of view (FOV) of 13x16 cm were created reconstruction images with slice thickness of 1 mm using the IRYS viewer 15.1 software program. The reconstruction algorithm used was "filtered back projection" because it is simple and can be quickly implemented on modern computers. In this technique, each projection was processed with filtering to reduce high-frequency noise and to highlight the edges of objects. The filtered projections were projected back into the original image space, thus obtaining a complete cross-sectional image. In this way, cross-sectional images of the object were created using projection data taken from different angles. All images were examined by a single observer and evaluated on a full HD display with a maximum screen resolution of 1920x1080 and a screen size of 15.6 inches. Multiplanar reconstructions ensured to depict the anatomic structures in flattened curved or linear transaxial planes, enable linear measurements in images. In this way, it was possible to ensure consistency and repeatability, especially of millimetric measurements.

MF location, horizontal diameter, vertical diameter, distance of MF to the alveolar crest, distance to the lower border of the mandible, distance to the adjacent tooth apex and distance to the midline were evaluated. MF is divided into six separate groups according to its location:

Location 1: Situated anterior to the 1. premolar

Location 2: In level with the 1. premolar

Location 3: Between the 1. and 2. premolars

Location 4: In level with 2. premolar

Location 5: Between 2. premolar and 1. molar

Location 6: In level with 1. molar (**Figure 1**).

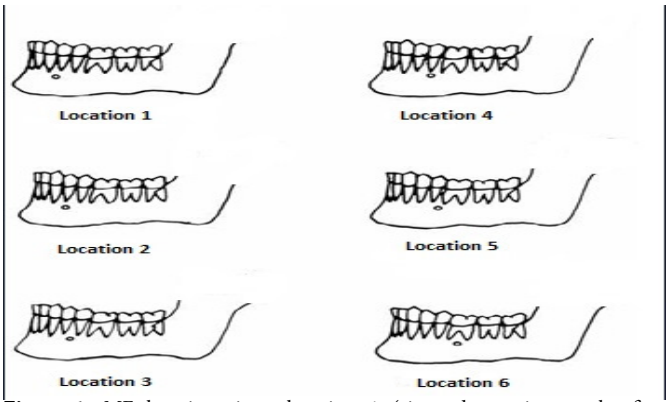

Figure 1. MF location tipes: location 1 (situated anterior to the first premolar), location 2 (in line with the first premolar), location 3 (between the first and second premolars), location 4 (in line with second premolar), location 5 (between second premolar and first molar), location 6 (in line with first molar)

The different exit types of the mental canal as it exits the bone from the MF were examined in sagittal, axial and coronal planes. These output types are divided into three groups: horizontal, vertical and AL (**Figure 2**). In images where AL

was detected, anterior alveolar loop (aAL) length and caudal alveolar loop (cAL) length were measured.

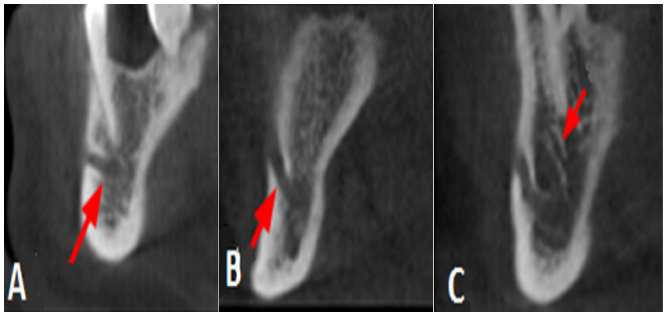

Figure 2. MF output types; horizontal (**A**), vertical (**B**), anterior loop (**C**)

Statistical Analysis

The Kolmogorov-Smirnov test was used to test whether the data were normally distributed. Normally distributed characteristics were compared using the student t test. Pearson Chi-square test was used to analyze categorical variables. To investigate intraobserver agreement, approximately 20% of the total number of patients (n: 100) were remeasured at two-week intervals and an intraclass correlation test was applied. In our study, the statistical confidence level was found to be high (0.87). Statistical analysis was performed using SPSS Windows version 23.0 package program and $p<0.05$ was considered statistically significant.

RESULTS

CBCT images of 500 cases between the ages of 18-65 were examined and it was determined that 250 (50%) of the cases were females, 250 (50%) were male and the average age was 37.12±11.91.

The relationship between MF localization in the right and left mandibular region and gender is shown in Table 1. MF localization in the right region was most frequently observed at the line of the 2. premolar teeth in male, and in the region between the 1. and 2. premolar teeth in females. MF localization in the left region was most frequently detected between the 1. and 2. premolar teeth in males and females. No significant relationship was observed between MF localization in the right and left mandibular regions and gender ($p>0.05$).

Table 2 shows the comparison of the horizontal diameter, vertical diameter of the MF, the distance of the MF to the alveolar crest, the distance to the lower border of the mandible, the distance to the adjacent tooth apex, and the distance to the mandibular midline according to gender.

Table 2. Comparison of the horizontal and vertical diameters of the MF, the distances of the MF to the alveolar crest, the lower border of the mandible, the apex of the adjacent teeth and the mandibular midline according to gender

	Male mean±SD	Female mean±SD	Total mean±SD	p
Right				
Horizontal diameter (mm)	3.12±0.86	2.81±0.87	2.92±0.91	0.046*
Vertical diameter (mm)	2.87±0.82	2.39±0.59	2.61±0.68	0.001*
MF-alveolar crest (mm)	13.45±2.89	12.37±2.43	12.91±2.72	0.035*
MF-lower border of the mandible (mm)	13.91±2.01	12.08±1.53	12.97±1.97	0.001*
MF-adjacent tooth apex (mm)	4.09±2.49	3.48±1.74	3.87±2.62	0.328
MF-mandibular midline (mm)	26.12±2.01	24.93±2.87	25.51±2.72	0.001*
Left				
Horizontal diameter (mm)	3.11±0.80	2.91±0.86	2.99±0.87	0.210
Vertical diameter (mm)	2.80±0.77	2.15±0.72	2.52±0.78	0.001*
MF-alveolar crest (mm)	13.25±3.11	12.78±2.71	12.94±2.67	0.204
MF-lower border of the mandible (mm)	13.71±1.62	11.57±1.53	12.83±1.64	0.001*
MF-adjacent tooth apex (mm)	4.04±2.01	3.69±1.57	3.89±2.11	0.362
MF-mandibular midline (mm)	24.38±2.05	24.01±1.91	24.23±1.95	0.128

MF: Mental foramen, SD: Standart deviation

The horizontal diameter of MF in the right mandibular region was found to be higher in males (3.12±0.86 mm) than in females (2.81±0.87) ($p=0.046$). The horizontal diameter of MF in the left mandibular region was found to be 3.11±0.80 mm in males and 2.91±0.86 mm in females ($p=0.210$). The mean vertical diameter of MF in the right mandibular region was calculated to be higher in males (2.87±0.82 mm) than in females (2.39±0.59 mm) ($p=0.001$). The mean vertical diameter of MF on the left side was found to be higher in males (2.80±0.77 mm) than in females (2.15±0.72 mm) ($p=0.001$).

Table 1. Location of MF on the right and left sides according to gender

	Male n (%)	Female n (%)	Total n (%)	p
Right				
Situated anterior to the first premolar	0 (0%)	0 (0%)	0 (0%)	0.812
In line with the first premolar	8 (44.4%)	10 (55.6%)	18 (100%)	
Between the first and second premolars.	94 (45%)	115 (55%)	209 (100%)	
In line with second premolar	114 (55.1%)	93 (44.9%)	207 (100%)	
Between second premolar and first molar	34 (51.5%)	32 (48.5%)	66 (100%)	
In line with first molar	0 (0%)	0 (0%)	0 (0%)	
Left				
Situated anterior to the first premolar	0 (0%)	0 (0%)	0 (0%)	0.894
In line with the first premolar	10 (62.5%)	6 (37.5%)	16 (100%)	
Between the first and second premolars.	118 (47.4%)	131 (52.6%)	249 (100%)	
In line with second premolar	101 (51.8%)	94 (48.2%)	195 (100%)	
Between second premolar and first molar	21 (56.8%)	16 (43.2%)	37 (100%)	
In line with first molar	0 (0%)	0 (0%)	0 (0%)	

MF: Mental foramen

The average distance of the MF to the alveolar crest was determined to be 13.45±2.89 mm in males and 12.37±2.43 mm in females in the right mandibular region (p=0.035). The average distance of the MF in the left mandibular region to the alveolar crest was reported as 13.25±3.11 mm in males and 12.78±2.71 mm in females (p=0.204).

In the right mandible, the distance of the MF to the lower border of the mandible was measured to be greater in males (13.91±1.01 mm) than in females (12.08±1.53 mm) (p=0.001). The average distance of the MF on the left side to the lower border of the mandible was calculated as 13.71±1.62 mm in males and 11.57±1.53 mm in females (p=0.001).

The average distance of the MF to the adjacent tooth apex was measured as 4.09±2.49 mm in males and 3.48±1.74 mm in females in the right mandibular region (p=0.328). In the left mandibular region, the distance of the MF to the adjacent tooth apex was reported as 4.04±2.01 mm in males and 3.69±1.57 mm in females (p=0.362).

The distance of the MF to the mandibular midline was measured higher on the right side in males (26.12±2.01 mm) than in females (24.93±2.87 mm) (p=0.001). The average distance of the MF in the left mandibular region to the mandibular midline was determined as 24.38±2.05 mm in males and 24.01±1.91 mm in females (p=0.128).

Comparison of MF exit types in the right and left mandibular region according to gender is shown in **Table 3**. AL type was detected in 125 (25.0%) of 500 cases. Of these, 86 (68.8%) were unilateral and 39 (31.2%) were bilateral. No statistically significant relationship was found between MF outlet types and gender in the right and left mandibular regions (p>0.05). Of the ALs observed in the right mandibular region, 51 were detected in males and 42 in females and in the left mandibular region, 34 were observed in males and 37 in females.

Table 3. Comparison of MF exit types in the right and left mandibular regions according to gender

	Male n (%)	Female n (%)	Total n (%)	p
Right				
Horizontal	77 (55.4%)	62 (44.6%)	139 (100.0%)	0.481
Vertical	122 (45.5%)	146 (54.5%)	268 (100.0%)	0.143
Alveolar loop	51 (54.8%)	42 (45.2%)	93 (100.0%)	0.395
Left				
Horizontal	81 (52.9%)	72 (47.1%)	153 (100.0%)	0.798
Vertical	135 (48.9%)	141 (51.1%)	276 (100.0%)	0.833
Alveolar loop	34 (47.9%)	37 (52.1%)	71 (100.0%)	0.912

MF: Mental foramen

Table 4 shows the comparison of the anterior and caudal extensions of the AL in the right and left mandibular regions according to gender. According to the measurements, the average cAL length in the right mandibular region was calculated as 3.82±1.03 mm in males and 3.65±1.40 mm in females (p=0.648). The average cAL length measurements in the left mandibular region were 3.64±0.93mm in males and 3.49±1.03mm in females (p=0.705). The average aAL length measurements on the right side were calculated as 2.75±0.81 mm in males and 3.43±1.29 mm in females (p=0.379). On the left side, the average aAL length was measured as 3.01±0.64 mm in males and 3.28±0.96 mm in females (p=0.559).

Tablo 4. Comparison of anterior and caudal extensions of AL in the right and left mandibular regions according to gender

	Male mean±SD	Female mean±SD	Total mean±SD	p
Right				
cAL (mm)	3.82±1.03	3.65±1.40	3.77±1.21	0.648
aAL (mm)	2.75±0.81	3.43±1.29	3.56±1.19	0.379
Left				
cAL (mm)	3.64±0.93	3.49±1.03	3.55±1.46	0.705
aAL (mm)	3.01±0.64	3.28±0.96	3.31±0.97	0.559

AL: Alveolar loop, SD: Standart deviation, cAL: Caudal extension of anterior loop, aAL: Anterior extension of anterior loop

DISCUSSION

Before surgical procedures involving the MF, it is of great importance to know the structures and variations of this region. Examining the location, size and distance of the MF before interventional applications in the region is important in order to prevent complications such as permanent or temporary loss of sensation, bleeding or severe pain that may arise during the procedure.[2,3,16]

There are various skull, panoramic, CBCT and magnetic resonance imaging (MRI)-based studies in the literature regarding MF localization, dimensions and distance to surrounding tissues.[1,17-23] Studies have reported that CBCT is more successful than panoramic radiography in measuring the localization, dimensions and distance of MF to surrounding anatomical structures and allows more accurate measurements.[1,7] With panoramic radiographs that provide imaging in two dimensions, small-sized MFs can be overlooked or incorrect measurements can be made. Unreliable measurements can be made as a result of artifacts such as magnification and superposition in panoramic radiographs that are not positioned in the optimum position. More accurate measurements can be obtained in CBCT studies due to the elimination of such artifacts and the acquisition of three-dimensional data.[7,22,23]

While there are studies in the literature reporting that MF localization is most common among the premolar teeth,[1,4,6,7] there are also studies that detect MF most frequently at the line of the 2. premolar teeth.[2,18,24,25] In the 500 CBCT images examined in our study, MF was most frequently detected between the 1. and 2. premolar teeth in the right and left mandibular regions, and second most frequently at the level of the 2. premolar tooth. When MF localization was examined by gender, no significant difference was detected. It is thought that ethnic changes may cause differences in MF localization.[2,4,26,27] Santini and Alayan[27] evaluated MF localization in a total of 155 Chinese, European and Indian skulls in their anthropometric study. While MF was most frequently observed between the premolar teeth in European and Indian samples, it was most frequently detected at the 2. premolar tooth level in Chinese samples. In studies evaluating the Arab population, MF was most frequently reported at the 2. premolar tooth level.[2,28,29] Kalender et al.[7] evaluated MF localization using CBCT in the Turkish population and Gungor et al.[1] obtained a result consistent with our study and reported MF most frequently between premolar teeth.

Kalender et al.[7] in their study examining the Turkish population using CBCT, found the average vertical diameter to be 3.7±0.7 mm and the horizontal diameter to be 3.4±0.8 mm. Ertuğrul et al.[21] reported the mean vertical diameter as 2.78 mm and horizontal diameter as 2.95 mm. In their morphometric head analysis, Neiva et al.[17] the horizontal diameter was 3.59 mm and the vertical diameter was 3.47 mm, Apinhasmit et al.[30] calculated the average horizontal diameter as 2.80±0.70 mm, Oğuz and Bozkır[20] calculated the horizontal diameter as 2.98 mm on the right mandibular region, 3.14 mm in the left mandibular region, and the vertical diameter as 2.38 mm on the right side and 2.64 mm on the left side. Elmansori et al.[26] They determined the vertical diameter on the right side as 3.15±0.78 mm and the horizontal diameter as 3.45±1.08 mm, and on the left side the vertical diameter as 3.46±0.86 mm and the horizontal diameter as 3.85±1.27 mm.

Caglayan et al.[31] calculated the right vertical diameter as 3.29±0.6 mm, the vertical diameter as 3.36±0.9 mm, the right horizontal diameter as 3.83±0.99 mm, and the left horizontal diameter as 3.8±1.01 mm. In our study, the horizontal diameter of the MF was measured as 2.92±0.91 mm in the right mandibular region and 2.99±0.87 mm in the left mandibular region. The vertical diameter of the MF was determined as 2.61±0.68 mm on the right side and 2.52±0.78 mm on the left side. The reason for these different results between studies is that anatomical structures may differ from region to region and from person to person. In addition, different results can be obtained because the number of data evaluated in the studies and the device and technique used may also vary.

In our study, when the horizontal and vertical lengths of the MF were compared between genders in the right and left mandibular regions, they were reported to be higher in males than in females, consistent with previous studies.[2,6,7,26,30]

Gungor et al.[1] in their study measured the distance to the alveolar crest as 13.36±2.84 mm on the right side and 13.22±2.76 mm on the left side. Caglayan et al.[31] determined the distance to the alveolar crest as 11.86±2.75 mm on the right side and 12.08±3.12 mm on the left side. Udhaya et al.[18] also stated that the distance measurements to the alveolar crest in the right and left mandibular regions were 12.02±2.48 mm and 12.21±2.61 mm, respectively. Singh et al.[8] calculated this distance as 17.82±1.87 mm and 17.91±1.16 mm on the right and left sides, respectively. Haktanir et al.[32] reported the average distance to the alveolar crest as 14.2 mm in their multidetector CT study. In our study, the average distance of the upper border of the MF to the alveolar crest was found to be 12.91±2.72 mm in the right mandibular region and 12.94±2.67 mm in the left mandibular region. When the results of our study are similar to the some studies in the literature,[18,31] but there are differences between them.[1,8] This may be because the alveolar crest region does not have a stable structure and is heavily affected by bone resorptions.[7,12]

When the average distance of the MF to the alveolar crest is evaluated according to gender; On the right side, it was found to be higher in males (13.45±2.89 mm) than in females (12.37±2.43 mm). On the left side, no significant difference was found between genders in the distance of the MF to the alveolar crest. However, higher measurements were obtained in males than in females on both sides. There are studies in the literature where the distance to the alveolar crest is found to be higher in males.[1,7,31,32] Since the mandible is smaller in females, it is an expected result that the distance to the alveolar crest is also smaller.[7,26] Additionally, metabolic diseases such as osteoporosis are more common in females and can cause increased crest resorption.[33]

In morphometric skull analysis, Neiva et al.[17] the distance to the lower border of the mandible was 12 mm on average, Apihasmit et al.[30] this value; They found the average length to be 15.40±1.73 mm in males and 13.89±1.40 mm in females. In CBCT-based studies conducted in the Turkish population, the distance to the lower border of the mandible; Gungor et al.[1], 12.75±2.19 mm on the right side, 12.65±1.88 mm on the left, Çağlayan et al.[31] reported it as 12.86±1.55 mm on the right and 13.13±1.89 mm on the left. In our study, the distance of the MF to the lower border of the mandible was evaluated according to the lower border of the MF, and the average was calculated as 12.97±1.97 mm on the right side and 12.83±1.64 mm on the left side.

In our study, the distance between the lower border of the MF and the lower border of the mandible was calculated to be higher in males than in females on the right and left sides. In the literature, higher measurements were found in males compared to females in terms of distances.[6,7,30,31]

Al-Mahalawy et al.[34] found the average distance between the MF and the adjacent tooth apex to be 3.1 mm in their study. Von Arx et al.[6] found the distance to the adjacent tooth apex to be higher than 5 mm. Kalender et al.[7] found the average distance to the adjacent tooth apex as 4.2±2.4 mm in their study. In our study, the average distance of the MF to the adjacent tooth apex was measured as 3.87±2.62 mm on the right and 3.89±2.11 mm on the left. Since anatomical structures may vary from region to region and from person to person, it is thought that these in studies differences can be considered normal in various ethnic groups.

In the literature, the distance of MF from the mandibular midline is; Neiva et al.[17] 27.61±2.29 mm, Apinhasmit et al.[30] 28.52±2.52 mm and Udhaya et al.[18] also calculated it as 25.79±1.78 mm in the right mandibular region and 25.29±2.29 mm in the left mandibular region. Haktanır et al.[32] reported this value as an average of 24.9±2.1 mm in their CT-based study. Singh et al.[8] found this distance to be 28.87±1.45 mm on the right side and 28.38±1.44 mm on the left side. In our study conducted with CBCT, this value was found to be 25.51±2.72 mm on the right side and 24.23±1.95 mm on the left side. Our findings regarding the distance of the MF to the midline of the mandible are in line with the results of Udhaya et al.[18] and Haktanır et al.[32], while the study by Singh et al.[8], the study by Neiva et al.[17] and the study by Apinhasmit et al.[30] showed a difference. Anatomical structures may vary depending on different populations, the number of data, and the device and technique used. In addition, one reason for these differences may be that different evaluations were made in different axial sections of CBCT images.

The average distance of the MF from the midline of the mandible was calculated to be higher in males than in females.

It can be said that the reason for this is that the mandible in males is larger than in females. In statistical evaluation, a significant difference between genders was observed for the right side, while no significant difference was found for the left side. It is possible that a significant difference will be shown for the left side as the number of data increases.

More studies have been conducted on the AL exit type, which is clinically more important and is formed by the mental nerve bending upwards and backwards, compared to other types.[9,11,12,14] There are studies aimed at detecting the clinically important AL exit type and knowing its dimensions before implant applications or other surgical procedures such as apical resection.[11,14,35] AL studies in the literature include macroscopic cadaveric examinations, conventional radiography, and advanced imaging techniques such as CT and CBCT.[11-14,36] In these studies, the prevalence of AL has been reported in a wide range, between 7% and 93.57%.[17,37,38] Soman et al.[9] They reported the prevalence of AL in the Saudi population as 4.24%. Rodricks et al.[39] They reported this rate as 57.5% in the Indian population. Shahman et al.[12] found the prevalence of AL to be 28.5% in their study in the Turkish population. AL exit type was found in 125 (25.0%) of 500 CBCT images evaluated in our study. Of the detected ALs, 86 (68.8%) were unilateral and 39 (31.2%) were bilateral. In our study, the prevalence of AL was calculated to be higher in males on the right side and higher in females on the left side. However, this difference was not found to be statistically significant. Studies have generally reported that the prevalence of AL is higher in males than in females, even if it is not statistically significant.[11,14,39,40]

The reason why the prevalence of AL is observed in such wide ranges as a result of studies in the literature may be ethnic differences, the number of data used in studies, and different imaging methods used. When the techniques used in these studies are evaluated, it is accepted that anatomical macroscopic examinations and CT/CBCT studies reflect measurements more accurately than conventional imaging techniques such as panoramic and periapical.[9,41] Uchida et al.[11] compared anatomical measurements with CBCT measurements in their study and found similar values in the results, except for minor differences.

In the literature, the average aAL length has been reported to be between 0.15 and 11 mm, while the average cAL length has been reported to be between 7.8 and 15.1 mm.[9,12,17,39,42] In our study, aAL measurements were calculated as 3.56±1.19 mm on the right side and 3.31±0.97 mm on the left side. In our study, cAL measurements were found to be 3.77±1.21 mm on the right side and 3.55±1.46 mm on the left side. In comparison between genders, cAL length in the right and left mandibular regions was found to be higher in men, and aAL length in females. In other studies in the literature, aAL was generally calculated to be higher in males than in females.[11,12,35,42] The reason why these results do not correlate with the literature may be the variety of devices used, different measurement methods and the number of data, in addition to the fact that studies were conducted in different populations. In addition, the fact that this study was single-centered, there was no ethnic diversity, and the measurements were made by a single observer may be the reasons for the significant difference in cAL length.

In the presence of AL in the interforaminal region, the main issue is that implants placed mesial to the MF may cause various complications if the AL dimensions are not taken into consideration.[9,11,39] To prevent possible complications, different researchers have recommended various distances (between 1 mm and 6 mm) that should be left between the distal surface of the implant and the mesial border of the MF.[43] Considering that TAL may have various sizes, instead of determining a standard distance in order to prevent complications, evaluating the presence and dimensions of AL in multiplanar sections with pre-implant CBCT application will be effective in treatment planning.

Since CBCT is insufficient in diagnosing the contents of the anatomical structures in the anterior mandible region, we think that detecting the neurovascular tissues in this region and evaluating them with MR imaging in cases where they need to be analyzed in more detail will increase the success before interventional procedures.[44] Another limitation of our study is that since it is single-centered, the measurements represent a local region. In future studies, studies involving many centers can be planned.

CONCLUSION

It is important to know the localization, size and distance of the MF before treatments such as regional anesthesia, root canal treatment, implant surgery, periodontal surgery, osteotomy, genioplasty and apical resection applied to the lower jaw. In order to prevent complications that may occur in the presence of AL, the presence and size of AL must be evaluated with CBCT before each operation. Using CBCT images instead of standard panoramic radiographs before procedures with high risk of complications will help to clearly monitor the area and make correct treatment planning.

ETHICAL DECLARATIONS

Ethics Committee Approval

This research was conducted with the approval of the Harran University Faculty of Dentistry Ethics Committee (Date: 07.02.2022, Decision No: 22/03/23).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The effects of Tai Chi exercise on motor functions in mild-to-moderate Parkinson's disease

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ABSTRACT

Aims: Motor symptoms of Parkinson's disease (PD) adversely impact patients' quality of life. Exercise and physical therapy are important in reducing disability and increasing the quality of life in patients. Data on which type of exercise is more effective in the management of the disease is controversial. We aimed to examine the effect of Tai Chi exercises on motor functions in patients with PD and compare them with classical stretching-strengthening exercises.

Methods: This study comprised 51 participants with PD. The patients were divided into 3 groups as the Tai Chi group, the strengthening-stretching exercises group, and the control group. The first 2 groups exercised for 50 minutes 3 days a week for 12 weeks. Berg Balance Scale (BBS), The Timed Up and Go test, The freezing of Gait Questionnaire and the 10-meters walk test (10 MWT) were applied to 3 groups at the beginning and end of the study.

Results: The mean BBS scores of the Tai Chi group were higher than those of the control group. The mean timed up and go test and 10 MWT scores of the Tai Chi group were lower than those of the control group.

Conclusion: Tai Chi exercises can be an adjunctive treatment method for improving motor functions in patients with PD, as they are easy to apply, have high patient compliance and do not show serious side effects.

Keywords: Parkinson's disease, exercise, Tai Chi, quality of life

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder marked by dopaminergic cell loss in the substantia nigra, disrupting cortico-striatal networks. These networks are essential for the regulation of cognitive functions and movement. The disease's prevalence increases with age, with a mean age of onset of 50–60 years. PD is distinguished by both motor and non-motor symptoms.[1]

The quality of life is significantly impacted by both sorts of illnesses. Nevertheless, the motor symptoms resulting from physical handicaps significantly impaire the patient's capacity to carry out their daily life tasks. As the condition advances, patients have a decline in postural stability and encounter balance difficulties. For this reason, especially in elderly patients, frequent falls and associated complications reduce patients' quality of life and life expectancy and increase health expenditures.[2]

Over time, non-medical therapies have been used to delay the course of PD, control symptoms, and lessen impairment. Previous studies investigating the relationship between PD and exercise have shown that exercises that include physical therapy methods such as strength training, aerobic training, Tai Chi or dance therapy delays the onset of symptoms and slows the disease progression.[3,4] Recent evidence indicates that exercise or physical therapy can effectively alleviate both motor and non-motor symptoms, thereby enhancing the quality of life for patients with PD.[3,5] In a review investigating various types of exercise, it was reported that exercises such as walking training, balance training, virtual reality interventions, Tai Chi and dance all create short-term beneficial effects, and their beneficial effects can continue in the long term.[6] Therefore, a safe and well-tolerated exercise program is a promising complementary therapy for preventing the development and delaying the progression of PD.

Although the neurobiological mechanisms underlying the impact of physical exercise on PD remain inconclusive, many hypotheses have been proposed. The prevailing consensus

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is that exercise prevents mitochondrial dysfunction and oxidative stress.[7-9] Exercise has been shown to be beneficial in PD by improving muscle flexibility and balance and positively influencing the patient's emotional state.[10] In addition, positron emission tomography showed increased blood flow in the basal ganglia and heightened activity in the cerebellum and motor regions of the brain during dance exercises.[11]

Classic stretching-strengthening exercises have been recommended and applied by physiotherapists to Parkinson's patients for years. It is stated that it increases the quality of life of patients and reduces the life difficulties caused by immobility.[12] In addition to classical physical therapy methods, Tai Chi is a mind-body exercise that combines breath control with continuous, curved, and spiraling body motions. Tai Chi exercises reduce stress and anxiety in adults, as well as improve aerobic capacity, muscle strength, balance and motor control.[13-17]

There is no clear answer as to which type of exercise may be more effective in improving motor functions in PD patients. In our study, we aimed to examine the effect of Tai Chi exercises on motor function in early Parkinson's patients and compare the efficacy of typical stretching–strengthening and Tai Chi exercises.

METHODS

Ethics

Sakarya University Faculty of Medicine Non-interventional Ethics Committee approved the study (Date: 27.11.2023, Decision No: 376). Throughout the study of the investigation, the researchers strictly followed the principles delineated in the Declaration of Helsinki.

Patients

This study was structured as a randomized controlled trial (RCT) encompassing 51 patients aged 50 to 80 diagnosed with idiopathic PD and monitored at the neurology outpatient clinic. The sample size was determined by calculating that 51 people needed to be contacted, with a 90% confidence level and an alpha level of.05.[18] Patients with Hoehn and Yahr stages 1-3 were included in the study. This staging system was developed in 1967 to easily define the severity of the disease for both the patient and clinician and to evaluate its progression. Stages 1 and 2 are classified as 'mild,' stage 3 as 'moderate,' and stages 4 and 5 as 'severe'.[19]

In order to guarantee that patients' characteristics were balanced, they were randomly assigned to one of three categories through computer-assisted block randomization.

Group 1 (n=18): Patients performing Tai Chi exercises,

Group 2 (n=17): Patients performing strengthening and stretching exercises,

Group 3 (n=16): Control group (no home exercises).

Randomization was conducted by a research assistant who was blinded to the study, ensuring unbiased group allocation.

Intervention

Patients in Groups 1 and 2 followed a prescribed home exercise program supervised by a physical therapist. Over 12 weeks, these patients performed their respective activities for 50 minutes three days a week. Group 1 engaged in Tai Chi exercises, while group 2 performed strengthening and stretching exercises. Both groups were monitored weekly via phone calls to ensure adherence. Patients in the control group (group 3) did not participate in any exercise program but were reassessed after 12 weeks.

Data Collection

Demographic information and medical records were obtained from the hospital's automation system by the attending physician. Motor assessments were conducted at the beginning and end of the study by a physical therapist.

Inclusion Criteria

Aged between 50 and 80 years,

Diagnosed with idiopathic PD,

Hoehn and Yahr stages 1-3,

Receiving ongoing medical treatment for PD without any changes in the last three months,

No physical therapy or exercise programs in the past three months,

Able to participate in a supervised 12-week Tai Chi or standard home exercise program.

Exclusion Criteria

Secondary parkinsonism,

Neurological or orthopedic conditions that could impair participation in the exercise program,

Advanced heart disease (aortic stenosis, atrial fibrillation, or pacemaker) or lung disease,

Visual or auditory impairments that could affect participation in the exercise program.

Clinical Evaluation

The participants' balance scores were obtained using the Berg Balance Scale (BBS). The BBS is a test that consists of 14 items and measures the dynamic balance of patients. Items are scored between 0 and 4 (0 represents the poorest performance and 4 signifies optimal performance). The maximum score that can be obtained is 56, with higher scores indicating better balance.[20]

The functional mobility of participants in the randomized groups was assessed using the Timed Up and Go test (TUGT). The patients were instructed to rise from their chairs, walk three meters, then return to their seats. The duration was measured in seconds.[21] The patient is at a low risk of collapsing and is able to walk independently if the time interval is 10 seconds or less. If the duration exceeds 30 seconds, it suggests that there is a high risk of collapsing and an occasional need

for assistance. This is due to the fact that results exceeding 11.5 seconds have been associated with a high fall risk in Parkinson's patients.[22]

The freezing of gait questionnaire (FOG-Q) consists of 6 items and was used to evaluate freezing episodes and severity. A score between 0 and 4 is given for each item. Of these 6 items, 4 assess freezing in general and 2 assess freezing during walking. High scores indicate severe freezing-of-gait attacks.[23]

The 10-metre walk test (10 MWT) was used to evaluate the patients' walking abilities. This test is easy to apply in Parkinson's patients and measures changes in walking speed. First, the patient's normal walking speed is recorded in m/s. The initial 2 meters of walking are considered the acceleration phase and the last 2 meters the deceleration phase, with measurements being made on a 14 meter-long track.[24] All assessments were conducted twice for each participant across the three randomized groups: at baseline (prior to starting the intervention) and after the 12-week exercise program. These standardized measures ensured consistency and allowed for the evaluation of intervention effects between the Tai Chi group, the strengthening and stretching group, and the control group.

Statistical Analysis

IBM SPSS Statistics 27 was employed to conduct the statistical analysis. The Shao method was employed to analyze the data's normality distribution.[25] The data were regularly distributed, with skewness and kurtosis values ranging from -1.5 to +1.5. Parametric tests were used because the data were normally distributed. Since there were 3 groups in total, the differences between the pre- and post-exercise groups were evaluated using one-way analysis of variance (ANOVA) test. For comparison of pre- and post-treatment means, repeated measures ANOVA was used. Therefore, the differences between the groups before and after the exercises could be evaluated using a ANOVA test. Homogeneity between groups was assessed using Levene's test, which resulted in an $\alpha>0.05$, indicating a homogeneous distribution. Next, the direction of the difference between the paired groups in the BBS, FOG-Q, TUGT and 10 MWT was examined using the Tukey post-hoc test. The Pearson Chi-square significance test was used to determine the relationship between the variables based on the underlying assumptions.

RESULTS

There were 30 female, and 21 male individuals diagnosed with PD included in the study. The demographic characteristics of the study participants are shown in **Table 1**. The patients were divided into 2 exercise groups (stretching strengthening and Tai Chi) and 1 control group.

Variance analysis ANOVA was employed to assess the differences among groups. There was no significant difference between the stretching strengthening, Tai Chi and control groups in terms of BBS, FOG-Q, TUGT and 10 MWT before exercise ($p>0.05$ for all) (**Table 2**).

Repeated Measures ANOVA test was used to compare the 3 groups before and after treatment. Within group comparison showed that the patients' BBS scores increased after exercise, while their TUGT and 10 MWT scores decreased (p=0.004, 0.000, 0.001, respectively). However, no significant difference was observed in the FOG-Q scores before and after exercise (p=0.174) (**Table 3**).

Table 1. Participants' demographic information

		n	%
Gender	Female	30	58.8
	Male	21	41.2
Marital status	Married	37	72.5
	Single	2	3.9
	Widow	11	21.6
Alcohol use	Yes	0	0
	No	51	100
Smoking	Yes	5	9.8
	No	46	90.2
Education status	Illiterate	4	7.8
	Primary school	33	64.7
	High school	10	19.6
	University	4	7.8

*A frequency test was performed using the SPSS program to analyze the participants' descriptive information

Table 2. The difference between the pre-exercise BBS, FOG-Q, TUGT, and 10 MWT scores of the stretching strengthening, Tai Chi and control groups

	F	p
BBS	0.137	0.872
FOG-Q	0.836	0.439
TUGT	1.249	0.296
10 MWT	1.245	0.297

BBS: Berg Balance Scale, FOG-Q: Freezing of Gait Questionnaire, TUGT: Timed Up and Go test, 10 MWT: 10-metre walk test
*Analysis of variance ANOVA was used to test the difference between groups

It was observed that the patients' BBS scores increased after exercise compared to before exercise, while their TUGT and 10 MWT scores decreased (p=0.004, 0.000, 0.001, respectively). However, no significant difference was observed in the FOG-Q scores before and after exercise (p=0.174) (**Table 3**).

There was no statistically significant difference between the BBS, FOG-Q, TUGT and 10 MWT scores before and after the exercise period according to gender (**Table 4**).

Given the homogeneous distribution of the data, the directional differences between the matched groups in BBS, FOG-Q, TUGT, and 10 MWT were analyzed using the Tukey Post-Hoc test. The average BBS scores of the Tai-Chi group exceeded those of the control group ($p<0.05$). The average TUGT and 10 MWT scores of the Tai-Chi group were inferior to those of the control group ($p<0.05$) (**Table 5**).

DISCUSSION

The PD patients in our study were evaluated before and after exercise, and it was observed that the BBS, TUGT and 10 MWT scores significantly improved after 12 weeks of exercise therapy. As a result, we may infer that short-term exercise improves balance function, lowers the chance of falling, and increases walking speed in PD patients. Although we have a low patient population to generalize the findings, patients who exercise regularly under expert supervision show better motor functions.

It was observed that the FOG-Q scores of the patients were similar before and after exercise. Longer and regular

Table 3. Participants' pre- and post-exercise BBS, FOG-Q, TUGT and 10 MWT scores

		Pre-exercise			Post-exercise			
	n	Min	Max	X±SD	Min	Max	X±SD	p
BBS	51	16.00	56.00	38.72±11.55	18.00	65.00	42.35±12.77	0.004*
FOG-Q	51	0.00	23.00	9.74±6.86	00.00	41.00	8.80±8.04	0.174
TUGT	51	10.00	39.00	18.54±6.46	8.00	42.00	16.41±6.90	0.000*
10 MWT	51	29.00	153.00	54.41±21.81	24.00	160.00	49.09±22.70	0.001*

BBS: Berg Balance Scale, FOG-Q: Freezing of Gait Questionnaire, TUGT: Timed Up and Go test, 10 MWT: 10-metre walk test, Min: Minimum, Max: Maximum, SD: Standard deviation
*Repeated measures ANOVA test was used to compare the 3 groups pre- and post-exercises

Table 4. Comparison of BBS, FOG-Q, TUGT and 10 MWT scores before and after exercise between genders

	Before exercise			After exercise		
Test	Female (30)	Male (21)	p	Female (30)	Male (21)	p
BBS	42.89±10.66	36.20±15.65	0.081	43.44±11.96	38.55±16.70	0.237
FOG-Q	9.34±7.13	10.30±7.34	0.651	7.55±7.15	8.85±7.04	0.533
TUGT	18.68±7.48	17.20±4.79	0.437	16.58±7.40	15.25±5.27	0.491
10 MWT	47.10±2.92	47.20±13.40	0.980	41.93±11.46	42.95±14.12	0.782

BBS: Berg Balance Scale, FOG-Q: Freezing of Gait Questionnaire, TUGT: Timed Up and Go test, 10 MWT: 10-metre walk test
*Independent samples t-Test was used to compare other parameters according to gender before and after exercise

Table 5. Comparison of post-exercise BBS, FOG-Q, TUGT and 10 MWT scores between stretching-strengthening, tai chi and control groups

Test	Group	n	mean	SD	F	p	Tukey
BBS	Tai Chi (1)	18	46.61	12.50	4.044	0.024*	1>3
	Stretching–strengthening (2)	17	44.41	12.36			
	Control (3)	16	35.37	11.21			
TUGT	Tai Chi (1)	18	13.00	3.58	5.760	0.006*	3>1
	Stretching–strengthening (2)	17	16.29	6.04			
	Control (3)	16	20.37	8.63			
10 MWT	Tai Chi (1)	18	39.38	10.53	4.093	0.023*	3>1
	Stretching–strengthening (2)	17	48.70	19.49			
	Control (3)	16	60.43	30.61			

BBS: Berg Balance Scale, FOG-Q: Freezing of Gait Questionnaire, TUGT: Timed Up and Go test, 10 MWT: 10-metre walk test, SD: Standard deviation
*Since the data were homogeneously distributed, the direction of the difference between the paired groups in BBS, FOG-Q, TUGT and 10 MWT was examined with the Tukey Post-Hoc test

exercise programs may be more effective in affecting freezing symptoms and disease severity. In our study, the exercise program given to the patients in a short period of time may not have affected these long-term symptoms.

Over the past 30 years, studies have shown that exercise can protect against PD, with some studies stating that this protective effect is higher in men than in women.[26,27] In a publication on Tai Chi, it was reported that Tai Chi exercises were more beneficial for low-educated women.[28] Building on these findings, we also investigated whether there was a gender difference in the effect of short-term exercise on PD patients. We observed that the well-being of the patients after the exercise program did not discriminate between genders. Our study was conducted with a small patient group, and we anticipate that studies with large patient series that will also consider gender and age distributions will shed light on this issue.

A meta-analysis that evaluated the impact of various forms of physical exercise on the severity of motor symptoms and quality of life in adults with PD. It was observed that the evidence regarding the effects of stretching-strengthening training is still ambiguous. No significant side effects were documented in any of the studies as a consequence of the meta-analysis. In the review of PD patients, there was evidence of beneficial effects for the majority of physical exercise types. However, there was minimal evidence of differences between the varieties of exercise.[29] In another meta-analysis, consistent evidence was discovered to suggest that Tai Chi is a relatively safe program that results in improvements in bradykinesia and balance, as well as increased overall motor function. Nevertheless, no statistically significant advantages were observed in terms of functional mobility or quality of life. Accordingly, it was determined that additional investigation is required regarding this matter.[30] In another study, older adult patients with mild cognitive impairment were followed for 36 weeks and performed Tai Chi exercises, and it was concluded that their cognitive functions were better compared to the other group doing fitness walking.[28] In addition, Tai Chi exercises have been shown to have positive effects on psychiatric diseases such as depression and anxiety disorders.[31] Tai Chi exercises seem promising in PD, which is a disease that is frequently accompanied by cognitive and psychiatric symptoms.

At the end of our study, we found that the BBS scores were lower and the TUGT and 10 MWT scores were higher in the Tai Chi exercise group compared to the control group after a 12-week exercise program. These results could be interpreted as showing that patients have better balance and walking functions after Tai Chi exercises and that their risk of falling is reduced. Notably, no statistically significant benefits were observed in the patient group who performed stretching–strengthening exercises.

Limitations
The limitations of our study include the small patient group, short exercise duration, and not including the patients' treatment protocols in the study.

CONCLUSION
Tai Chi exercises can be an adjunctive treatment method in improving motor functions in PD patients, as they are easy to apply, can be done at home by themselves, exhibit high patient compliance and do not show serious side effects. Multicenter studies with longer follow-up periods and larger patient series on this subject will contribute to the existing literature.

ETHICAL DECLARATIONS
Ethics Committee Approval
Sakarya University Faculty of Medicine Non-interventional Ethics Committee approved the study (Date: 27.11.2023, Decision No: 376).

Informed Consent
All patients signed and free and informed consent form.

Referee Evaluation Process
Externally peer- reviewed.

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

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

Author Contributions
All the authors declare that they have all participated in the design, execution, analysis of the paper and that they have approved the final version.

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Original Article

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Effect of internal ligation on the occurrence of trocar site hernia after laparoscopic sleeve gastrectomy

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ABSTRACT

Aims: Nowadays, laparoscopic sleeve gastrectomy (LSG) has become the most commonly performed bariatric surgical method. One of the complications seen after LSG is trocar site hernia (TSH). The aim of this study is to identify the risk factors for TSHs after LSG and to investigate the effect of internal ligation of the trocar entry site using energy-based vessel-sealing device (LigaSure™) on preventing TSH occurrence.

Methods: The records of 841 patients who underwent LSG between January 2021 and October 2023 at Altınbaş University Faculty of Medicine Medicalpark Hospital were reviewed. A total of 244 patients were included in the study. All surgeries were performed by the same surgical team under identical conditions. In all patients, the right trocar site used to remove the stomach from the abdomen was expanded with a Kocher clamp. The right and left 12 mm trocar entry sites were ligated internally using LigaSure. The patients' age, gender, body-mass index (BMI), diabetes mellitus (DM), hypertension (HT), dyslipidemia, wound site infections, smoking status, chronic obstructive pulmonary disease (COPD), and constipation were evaluated. All patients were followed up at the 3rd, 6th, and 12th months following the LSG surgery. Physical examinations and ultrasound scans were performed to detect the presence of TSH.

Results: In the analysis of 244 patients, 150 (61.5%) were female, 94 (38.5%) were male, and their ages ranged from 18 to 72 years old. The average age was 39.28±12.27 years old. The BMI ranged from 35.1 kg/m² to 63.9 kg/m², with an average of 43.16±5.40 kg/m². HT was present in 32% of the cases, diabetes in 35.2%, dyslipidemia in 38.9%, and COPD in 6.1%. Constipation was reported in 26.6% of the patients, and 41.4% were smokers. Wound infections were seen in 2 cases (0.8%). At the 3-month follow-up, no TSHs were detected. At the 6-month post-surgical follow-up, one patient had a TSH, and one more was detected in an ultrasound scan performed after 1 year of the LSG surgery. The hernias identified were at the right trocar site, and none of them were symptomatic. There was no statistically significant correlation between gender, BMI, HT, diabetes, dyslipidemia, smoking, and the occurrence of hernia ($p>0.05$). The mean age of patients with a detected hernia (66.0±2.83 years) was statistically significantly higher than that of patients without hernia (39.06±12.07 years) ($p:0.020$; $p<0.05$). The hernia rate in COPD patients (13.3%) was statistically significantly higher compared to those without COPD (0%) ($p: 0.004$; $p<0.05$). Although the hernia rate in patients with constipation (3.1%) was higher than in those without constipation (0%), this difference was not statistically significant ($p: 0.070$; $p>0.05$). The hernia rate in patients with wound site infections was statistically significantly higher than in those without wound site infections ($p: 0.016$; $p<0.05$). In literature, studies report that the incidence of TSH ranges from 4% to 39%. In our study, this rate was less than 1%.

Conclusion: Advanced age, COPD, constipation, and wound site infection were identified as risk factors for TSH. Internal ligation of the trocar entry site after LSG is an effective method for reducing the rate of TSH.

Keywords: Laparoscopy, sleeve gastrectomy, trocar site hernia, wound infection

INTRODUCTION

Obesity is a chronic and complex disease characterized by excessive fat accumulation that can impair the body's health. Obesity increases the risk of type 2 diabetes, hypertension (HT), fatty liver disease, cardiovascular disease, joint disorders, sleep apnea, depression, and certain cancers. According to the World Health Organization's 2022 data, one in eight people worldwide lives with obesity.[1]

In the treatment of obesity, diet and exercise are initially recommended. However, in patients who are unable to lose

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weight despite diet and exercise while having a body-mass index (BMI) over 40 kg/m^2, or a BMI over 35 kg/m^2 with obesity-related comorbidities, bariatric surgery is indicated. Various bariatric surgical methods have been described. However, today laparoscopic sleeve gastrectomy (LSG) is the most frequently performed bariatric surgery method.

LSG is a restrictive method. The stomach is mobilized along the greater curvature, and 75-80% of the stomach is resected, forming a tube-shaped stomach.

Complications that can arise in patients after LSG are divided into early and late complications (**Table 1**). Hemorrhage is the most common early complication. Staple line leaks in the early period can be a fatal complication. Nutritional deficiencies are the most common late complications. Trocar site hernia (TSH) is a late complication that can also occur. TSH is an incisional hernia that can occur at the trocar entry sites following various laparoscopic surgeries.

Table 1. Possible complications of sleeve gastrectomy surgery

Early complications (<30 days)	Late complications (>30 days)
Bleeding	Gastric stenosis
Staple line leaks	Nutritional deficiencies
Intraabdominal abscess	Gastroesophageal reflux
Wound site infections	
Acute pancreatitis	
Pulmonary emboli	Trocar site hernia
Thrombophlebitis	Eating disorders
Rhabdomyolysis	Mental disorders
Acute kidney insufficiency	
Partial spleen infarct	

TSH may sometimes be an overlooked complication because it usually has a slow clinical course. While it can manifest asymptomatically in some patients, it can cause serious morbidity and mortality due to bowel strangulation risk in others.

In obese patients, due to the excess subcutaneous fat tissue, diagnosing TSH by inspection and physical examination is difficult. Therefore, it is recommended to evaluate the trocar site with superficial ultrasound. Various studies have used imaging methods to detect abdominal wall defects postoperatively in obese patients. In these studies, TSH was detected in up to 39% of cases.[2-4] These values make TSH an important complication after bariatric surgeries, especially LSG.

Current literature supports closing trocar sites larger than 10 mm due to the risk of incisional hernia, while stating that it is unnecessary to suture the abdominal fascia when 5 mm trocars are used.

Closing the trocar entry incision in laparoscopic surgery, especially in patients with morbid obesity, is a challenging procedure. Various techniques and devices have been proposed to close trocar wounds and therefore minimize the risk of hernia formation. To date, the most suitable closure technique for closing trocar site incisions after LSG has not been clearly defined.

Our procedure for closing the trocar entry site is relatively simple, safe, less time-consuming, and cost-effective.

The aim of our study is to determine the risk factors for TSHs after LSG surgery and to investigate the preventive effect of internally ligating the trocar entry site with a Ligasure device on the development of TSH.

METHODS

The study was initiated with the approval of the Altınbaş University Health Sciences Scientific Researches Ethics Committee (Date: 14.11.2024, Decision No: 1). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The records of 841 patients who underwent LSG at Altınbaş University Faculty of Medicine Medical Park Hospital between January 2021 and October 2023 were reviewed. 244 patients were included in the study.

All surgeries were performed by the same surgical team under the same conditions. A standard LSG was applied to all patients.

Two 12 mm trocars were inserted through the right and left midclavicular lines, one 11 mm trocar through the umbilicus within the left rectus muscle, one 5 mm trocar through the epigastric region, and one 5 mm trocar through the left anterior axillary line (**Figure 1**). The right trocar region used for stomach extraction was expanded with a Kocher clamp in all patients (**Figure 2-3**). The 12 mm right and left trocar entry sites were internally ligated with a energy-based vessel-sealing device (LigaSure™) (**Figure 4**). The sealing was done circumferentially, ensuring the trocar entry site opening was 5 mm or smaller (**Figure 5-6-7**).

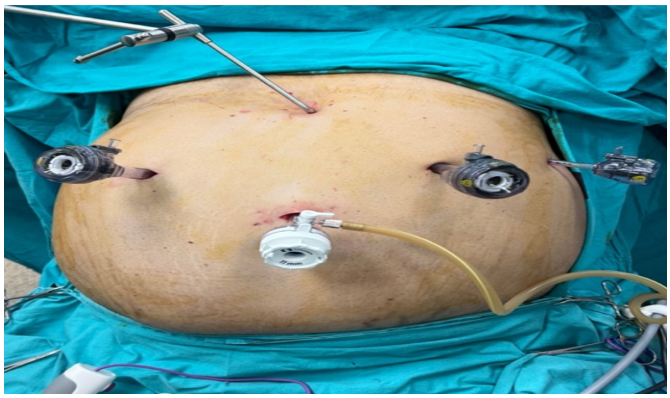

Figure 1. Trocar placement

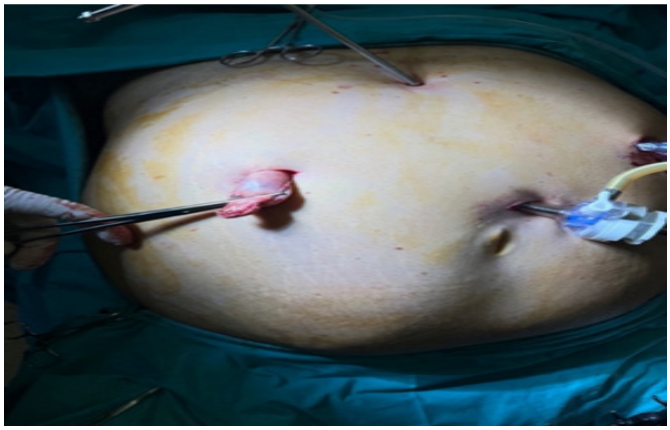

Figure 2. Right trocar used for stomach extraction

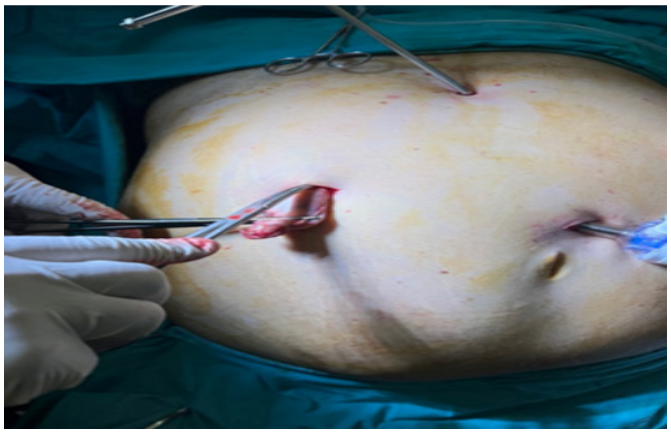

Figure 3. Right trocar used for stomach extraction

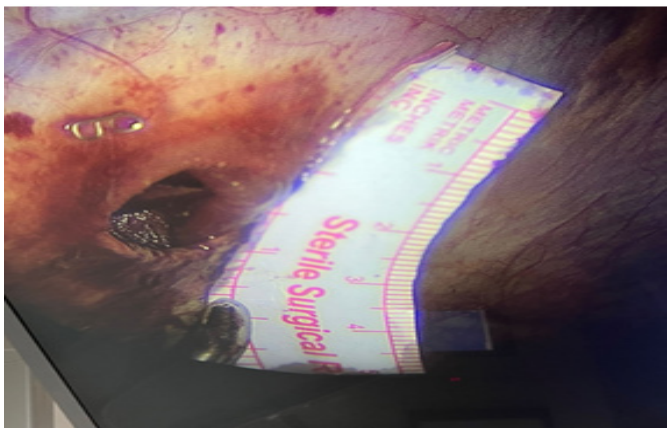

Figure 4. Measuring trocar entry site

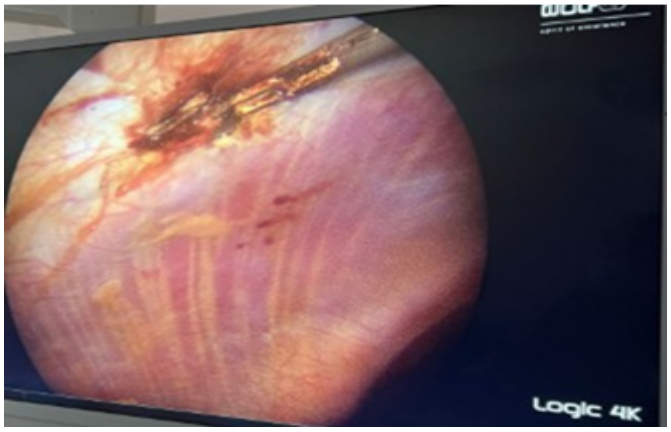

Figure 5. Internal ligation of the trocar entry site

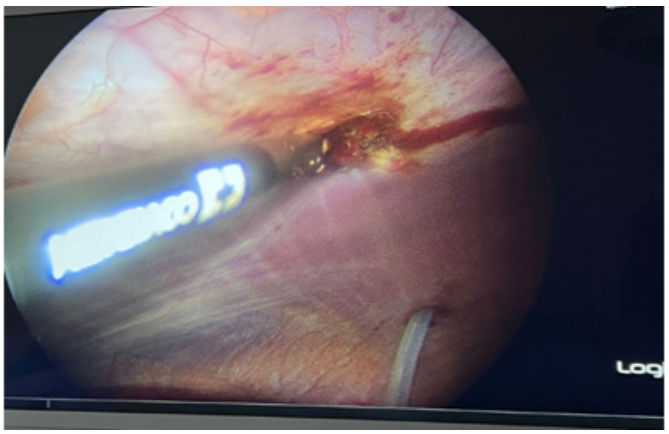

Figure 6. Internal ligation of the trocar entry site

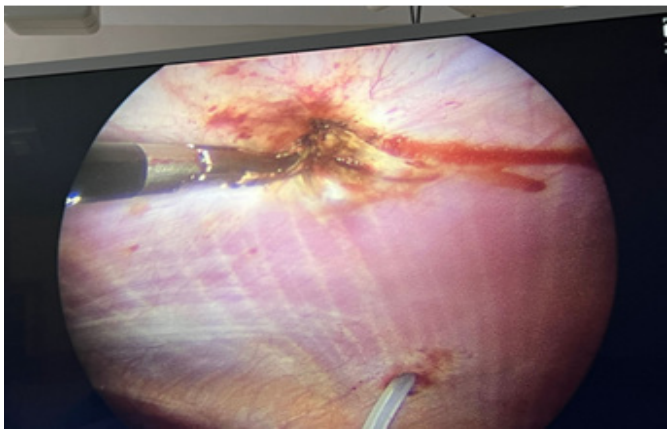

Figure 7. Internal ligation of the trocar entry site

Patients' age, gender, BMI, diabetes mellitus (DM), HT, dyslipidemia, wound site infections, smoking, chronic obstructive pulmonary disease (COPD), and presence of constipation were evaluated.

In addition to routine follow-ups, all patients were checked at 3, 6, and 12 months post-LSG surgery for the presence of TSH through physical examination and ultrasound controls. All ultrasound checks were performed by the same radiologist.

Findings and statistical results were compared with the literature to analyze the effect of internally ligating the trocar entry site using a LigaSure device.

Statistical Analysis

The findings obtained in the study were analyzed using the IBM SPSS Statistics 22 program. The suitability of the parameters to normal distribution was evaluated using the Kolmogorov-Smirnov test, and it was determined that the parameters did not show normal distribution. Descriptive statistical methods (minimum, maximum, mean, standard deviation, median, frequency) were used in the evaluation of the study data. Mann-Whitney U test was used for comparisons of quantitative data between two groups. Fisher's Exact Chi-square test was used for the comparison of qualitative data. OR (odds ratio) was calculated for univariate risks. Significance was evaluated at the $p<0.05$ level.

RESULTS

The study was conducted with 244 cases, including 150 (61.5%) females and 94 (38.5%) males, aged between 18 and 72 years. The mean age was 39.28±12.27 years. BMI levels ranged from 35.1 kg/m^2 to 63.9 kg/m^2, with a mean of 43.16±5.40 kg/m^2 (**Table 2**).

HT was present in 32% of the cases; diabetes in 35,2%; dyslipidemia in 38,9%; and COPD in 6.1%. Constipation was reported in 26.6% of the patients, and 41.4% were smokers. Wound infections were observed in 2 cases (0.8%).

Hernia was detected in 2 cases (0.8%) in the ultrasound performed after 1 year of the LSG surgery, with one of the detected hernias being symptomatic.

There was no statistically significant relationship between gender and hernia ($p>0.05$).

Table 2. Distribution of the study parameters

		n	%
HT	Yes	78	32
	No	166	68
DM	Yes	86	35.2
	No	158	64.8
Dyslipidemia	Yes	95	38.9
	No	149	61.1
COPD	Yes	15	6.1
	No	229	93.9
Constipation	Yes	65	26.6
	No	179	73.4
Smoking	Yes	101	41.4
	No	143	58.6
Wound site infection	Yes	2	0.8
	No	242	99.2
Ultrasound scan 1 year later	TSH	2	0.8
	No TSH	242	99.2

HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, TSH: Trocar site hernia

No statistically significant relationship was found between HT, diabetes, and dyslipidemia with hernia (p>0.05).

No statistically significant relationship was found between smoking and hernia (p>0.05).

In patients with COPD, the incidence of hernia (13.3%) was statistically significantly higher than in patients without COPD (0%) (p:0.004; p<0.05). The hernia risk in cases with COPD was 1.154 times higher (OR:1.154; 95% CI:0.946-1.407).

The incidence of hernia in cases with constipation (3.1%) was higher than in cases without constipation (0%); however, this difference was near significance but not statistically significant (p:0.070; p>0.05). The hernia risk in cases with constipation was 1.032 times higher (OR:1.032; 95% CI:0.988-1.077).

In cases with wound site infection, the incidence of hernia (50%) was statistically significantly higher than in cases without wound site infection (0.4%) (p:0.016; p<0.05). The hernia risk in cases with wound site infection was 241 times higher (OR:241; 95% CI:8.066-7200.466).

The mean age of cases with hernia detected by ultrasound (66.0±2.83) was statistically significantly higher than those without hernia (39.06±12.07) (p:0.020; p<0.05). The hernia risk in older cases was 1.251 times higher (OR:1.251; 95% CI:1.008-1.553).

There was no statistically significant difference in BMI averages between cases with and without hernia detected by ultrasound (p>0.05) (**Table 3**).

Table 3. Evaluation of parameters affecting ultrasound findings

		Ultrasound scan 1 year later	
		TSH (n=2)	No TSH (n=242)
		n	%
Gender	Female	2 (1.3%)	148 (98.7%)
	Male	0 (0%)	94 (100%)
HT	Yes	2 (2.6%)	76 (97.4%)
	No	0 (0%)	166 (100%)
DM	Yes	2 (2.3%)	84 (97.7%)
	No	0 (0%)	158 (100%)
Dyslipidemia	Yes	1 (1.1%)	94 (98.9%)
	No	1 (0.7%)	148 (99.3%)
COPD	Yes	2 (13.3%)	13 (86.7%)
	No	0 (%0)	229 (100%)
Constipation	Yes	2 (3.1%)	63 (96.9%)
	No	0 (0%)	179 (100%)
Smoking	Yes	2 (2%)	99 (98%)
	No	0 (0%)	143 (100%)
Wound site infection	Yes	1 (50%)	1 (50%)
	No	1 (0.4%)	241 (99.6%)
Age $_{\text{mean±SD (median)}}$		66.0±2.83 (66)	39.06±12.07 (38)
BMI $_{\text{mean±SD (median)}}$		45.40±1.10 (45.4)	43.15±5.42 (42.3)

Fisher's Exact test, +Mann Whitney U Test, *p<0.05
HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, TSH: Trocar site hernia, SD: Standard deviation

DISCUSSION

In this study, the factors influencing the development of TSH and the effect of internally ligating the trocar entry site on hernia development are discussed.

Various risk factors for TSH have been identified. These may be related to patient factors (such as advanced age, smoking status, obesity, comorbidities like diabetes)[5], technical and perioperative factors (such as surgery duration, trocar size), and postoperative factors like wound infection.[6]

There are many patient and procedure-related risk factors that predispose individuals to TSHs. Obesity is highlighted as an important factor increasing the risk of TSH. Due to the increased intra-abdominal pressure, obese patients are more likely to develop a weakness in the abdominal wall at the trocar entry site.[7] The higher intra-abdominal pressure and thicker subcutaneous fat tissue make obesity a significant predisposition factor for TSH, which also complicates full-thickness closure of the trocar site. Furthermore, during LSG, manipulation of the port site with an instrument or finger while removing the resected stomach piece from the 12 mm trocar site theoretically increases the risk of herniation. A study reports that excessive manipulation of the trocar site during specimen removal is a significant risk factor for TSH.[8] Additionally, a multivariate analysis revealed that advanced age (over 60) is significantly associated with hernias, potentially due to decreased fascial strength. It is also known that postoperative wound infection at the trocar entry site increases the risk.[9,10]

Our study findings, similar to the literature, show that advanced age, COPD, constipation, and wound site infection increase the risk of developing TSH. However, no risk was identified with gender, HT, and diabetes. One of the two patients who developed wound site infection also developed TSH, consistent with the literature. The prevalence of TSH is uncertain.[9] Especially in obese patients, clinically detecting a small TSH embedded in thick subcutaneous fat tissue is difficult.[11,12] Ultrasound and CT scans can diagnose more TSH efficiently and help clarify the diagnosis when TSH is clinically suspected.[13,14] For example, the incidence of TSH in laparoscopic bariatric surgery is generally reported as low single-digit percentages, according

to studies detecting asymptomatic TSH with physical examination only. However, a prospective cohort series with ultrasound follow-up in one study population observed TSH development in 34% of patients at one or more trocar sites.[3] Karampinis et al.[13] reported in a meta-analysis that the incidence of TSH was significantly higher in studies with follow-up periods of 12 months compared to those shorter than 12 months. In our study, ultrasound follow-ups detected one case of TSH at 6 months and one at 1 year, with patients being asymptomatic. In both cases, the TSH developed at the 12 mm trocar site on the right midclavicular line. It is known that manipulation of the port site during the removal of the stomach piece from this port influences hernia development. Post-surgical wound site infection was present in one of the hernia cases. We believe the lower detection of TSH in these follow-ups supports the effectiveness of our closure method.

It is generally accepted that closing umbilical trocar sites, most midline trocar sites of 10 mm or larger, and any port sites enlarged for specimen extraction is a good practice.[15] An international consensus group agreed by 86.8% that 15 mm ports should be closed in all patients.[16] In our study, 5 mm trocar sites were also internally ligated with a Ligasure device for bleeding control. The 10 mm and 12 mm trocar entry sites were also ligated, reducing their openings to 5 mm or less. We believe the lower incidence of hernia development in our study, consistent with the literature, is due to reducing the opening to 5 mm.

In bariatric surgery, a review stated that the general incidence of TSH is 3.2%. This review showed that the incidence of TSH is significantly higher in studies using imaging for diagnosis compared to those using clinical examination or without specific follow-up regimens (16.2% vs. 1.3%). A recent case series of 79 patients undergoing laparoscopic gastric sleeve procedures reported a 21.5% incidence of TSH at the umbilical removal site when examined with CT after a mean follow-up of 37 months. This emphasizes that the true incidence of TSHs is likely underestimated.

We had the chance to observe the trocar entry sites previously ligated with a Ligasure tool in two patients we operated on for gallstones 10 months after their sleeve gastrectomy surgeries. The trocar entry sites were found to be closed (**Figure 8-9**).

Figure 8. The trocar entry sites after 10 months

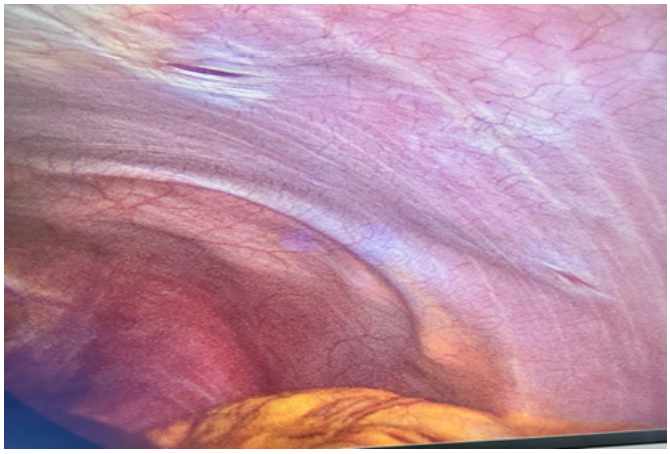

Figure 9. The trocar entry sites after 10 months

Internally ligation with a Ligasure device is commonly used by many surgeons for port site hemostasis. Similarly, ligating and reducing the opening of the trocar entry sites is an easily applicable, cost-effective, and time-saving method. In our method, where patients were followed up for 1 year and their trocar entry sites were checked with ultrasound, the significantly lower TSH rate compared to the literature demonstrates the method's effectiveness.

Limitations

Our study has observational limitations due to its retrospective design and the data obtained from a specific patient group. Larger sample groups and prospective studies are necessary to demonstrate the effectiveness of internal ligation with a Ligasure device in the prevention of TSH.

CONCLUSION

Advanced age,COPD,constipation and wound site infection were identified as risk factors for TSH.Internal ligation of the trocar entry site after LSG is an effective method for reducing the rate of TSH.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of the Altınbaş University Health Sciences Scientific Researches Ethics Committee (Date: 14.11.2024, Decision No: 1).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

ANATOLIAN CURRENT MEDICAL

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The effect of 0.24% hyaluronic acid gel used after diode laser-assisted labial frenectomy on postoperative pain level and periodontal parameters: a randomized clinical research

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ABSTRACT

Aims: Diode lasers are popular dental soft tissue lasers due to their bleeding-free and sutureless surgery advantages. Although diode lasers offer benefits in surgery, their application in frenectomy procedures for pediatric patients remains limited. Hyaluronic acid gel (HA) is a commonly used natural biopolymer for treating symptoms of wound healing. No studies have examined the effect of 0.24% HA gel on postoperative pain and periodontal outcomes after laser-assisted frenectomy in children. This research aimed to evaluate the effect of 0.24% HA gel on the healing trajectory and postoperative pain management in pediatric patients undergoing diode laser-assisted labial frenectomy.

Methods: Two groups were formed for the study: a control group consisting of 20 participants aged 8 to 14 who underwent diode laser-assisted frenectomy with sterile saline and an experimental group of 20 participants, also aged 8 to 14, who received diode laser-assisted frenectomy supplemented with HA gel. A frenectomy was performed using diode laser assistance. After the surgery, the pain level was evaluated using the visual analog scale for one week. Plaque index, gingival index, pocket depth, bleeding on probing, keratinized gingival width, and attached gingival thickness values were observed and evaluated for three months.

Results: No difference in pain levels between HA gel and the control group after one week on days 1 and 2; the group that used HA gel reported lower pain levels ($p>0.05$). The control group reported lower pain levels during the third and fourth days ($p>0.05$). During days 5-7, the group treated with HA gel reported lower pain levels ($p>0.05$). Between days 5 and 7, the HA gel participants experienced decreased pain levels. The test group also showed no significant changes in all periodontal parameters.

Conclusion: Applying 0.24% HA gel post-laser-assisted frenectomy reduced pain, although this effect did not reach statistical significance compared to the control group. Future studies should involve larger sample sizes and extended follow-up periods to investigate further HA gel's effects, particularly formulations with higher concentrations.

Keywords: Frenectomy, hyaluronic acid, diode laser, labial frenulum, Visual Analog Scale

INTRODUCTION

The labial frenulum refers to a fold of mucous membrane that consists of connective tissue and muscle fibers.[1] This mucosal membrane connects the upper lip to the gums and underlying bone through the periosteum. Frenectomy refers to the surgical procedure of removing the frenulum.[2]

If the labial frenulum prevents breastfeeding movements in newborns and babies, they should be surgically removed. It should be removed if it restricts lip movements, disrupts nourishment, and complicates oral hygiene maintenance in childhood.[3]

Indications for frenectomy include several functional and aesthetic considerations. Insufficient labial mobility can hinder effective utensil use, particularly forks and spoons. The presence of a prominent labial frenulum may disrupt the articulation of bilabial consonants—specifically /b/, /f/, /m/, /p/, and /w/. Additionally, the normal frenulum structure plays a role in preventing mouth breathing by restricting the closure of the upper and lower lipsh From an oral hygiene perspective, a restrictive frenulum can obstruct access to the vestibular sulcus, particularly in the incisors, thereby increasing the risk of caries due to compromised cleaning. Clinical indications for frenectomy also include the presence of a midline diastema greater than 2 mm, gingival recession, and aesthetic concerns such as diminished lip fullness and altered smile lines in adults. Furthermore, instability of prosthetic restorations in

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adults can necessitate surgical intervention to enhance both function and appearance.[3,5-7]

The use of the traditional scalpel for surgical procedures has become widely accepted. The classic scalpel method has been used for years to perform labial frenectomies.[1] Surgeries using scalpels often lead to patient complaints due to bleeding, use of local anesthetic, and suturing.[8]

The reliability of lasers for dental procedures, marketed as an alternative to scalpel surgery, has been confirmed by numerous studies.[2] Studies show that lasers like Nd: YAG, CO_2, Er: YAG, Er, and Cr; YSGG are used for surgical procedures like gingivectomy, gingivoplasty, harvesting free gingival graft, operculectomy, and frenectomy.[9] Diode lasers are specifically designed for soft tissue surgery and have proven effective.[10] Operating on soft tissue, diode laser offers coagulation, evaporation, cutting, and sterilization features for ease of use by both operator and patient.[5,11]

Diode lasers offer key benefits in frenectomy procedures by reducing the risk of damage to surrounding tissue and minimizing bleeding. They also lower scar tissue formation and postoperative pain, improving patient comfort. With a pre-programmed wavelength and pulse power, diode lasers ensure precise targeting of tissue while protecting adjacent structures from injury.[9,12] Diode lasers in sutureless surgery can reduce plaque accumulation, minimize stress, and speed up recovery.[13] Protecting against secondary trauma from speech and chewing, rapid recovery can significantly enhance patient comfort.[14]

Numerous wound care products have been developed to maintain cleanliness in the wound area and speed up healing.[15] This helps enhance patient comfort by promoting faster recovery during the postoperative period and enables the patient to return to their preoperative routine sooner.[16] Chlorhexidine is the most well-known.[14] While sodium hypochlorite, hydrogen peroxide, and povidone-iodine are commonly used, they are cytotoxic to epithelial cells.[14,17] Although there is still controversy surrounding the use of topical drugs in pediatrics, the primary concern is the ability to swallow the drugs.[18] Swallowable wound care products made with natural ingredients have gained popularity due to safety concerns.[15,19] Hyaluronic acid (HA), which has gained popularity in dentistry recently, was first discovered and isolated in the vitreous humor of the eye in 1934 and named "Hyaluronan." HA is the most fundamental glycosaminoglycan form.[16] HA is a naturally occurring biopolymer with biocompatibility and moisture-retaining properties.[20] In dentistry, it effectively manages gingivitis and periodontitis, aids in papillary reconstruction, and promotes wound healing in periodontal tissues, enhancing tissue regeneration.[21-23] It is also helpful in accelerating bone healing in the socket after tooth extraction, aiding in regenerating the temporomandibular joint, treating oral aphthous ulcers, and providing symptomatic relief as a teething gel for infants and young children.[16] Although there is a recommendation to use HA gel for these pathologies, there are only a limited number of studies evaluating its use after frenectomy. Only one research has assessed the use of HA gel in frenectomies carried out with a diode laser.[14]

In this research, the null hypothesis is that using 0.24% HA during frenectomies performed with diode laser will decrease postoperative pain levels in patients and improve periodontal parameters compared to the group not receiving HA treatment.

METHODS

The study was conducted with the approval of Afyonkarahisar University of Health Sciences Clinical Researches Ethics Committee (Date: 14.06.2019, Decision No: 2019/7) between April 2019 and August 2020. The research conducted follows the ethical principles outlined in the Declaration of Helsinki. We used G-Power version 3.1 (Informer Tech Inc. Germany) to determine the number of research participants. We considered an effect size of 0.5.[24] It was determined that each group should have 16 individuals for 95% power at a 5% significance level. Despite this, the research included total 40 pediatric patients during the selected dates. However, 12 out of the 40 patients were excluded at the end of the research. Eventually, the control and experimental groups consisted of 14 patients each.

Inclusion Criteria

Children who have not received any antibiotic treatment in the past four months. Children who do not have any underlying systemic diseases. Children who are not required to take medication regularly. Both girls and boys between the ages of 8 and 14. Children and their parents willing to participate in the study and attend the control session one week later were included.

Exclusion Criteria

The patient presents with periodontal disease. Children with cognitive disabilities, including autism and attention deficit hyperactivity disorder, as well as those with mental health conditions such as cerebral palsy and Down syndrome. Children and their parents who do not meet the specified criteria were excluded from the study.

Frenectomy was indicated, and informed consent forms were obtained from willing parents. At the end of the research, only 28 patients could participate fully. This was due to some patients not accurately completing the Visual Analog Scale (VAS) (**Figure 1**), being unable to apply the HA Gel as instructed, and failing to attend their follow-up appointments.

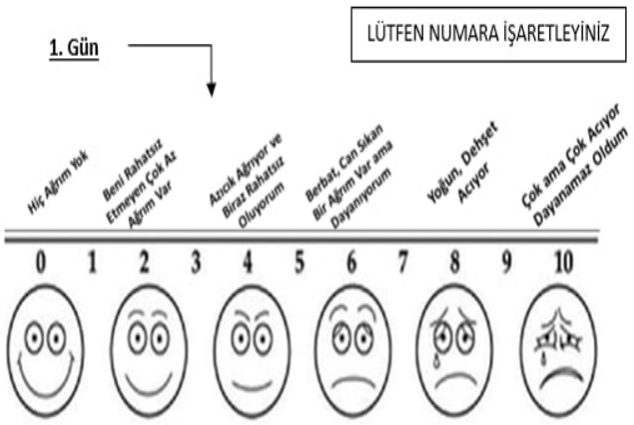

Figure 1. Visual analog scale

According to the behavioral guidance protocol, the researcher ÖD informed the patients about the procedures and assisted them in getting comfortable in the dental chair.[25] In the research, various periodontal parameters such as plaque index[26] (PI), gingival index[26] (GI), pocket depth (PD), bleeding on probing (BOP), keratinized gingival width[11] (KGW), and attached gingival thickness[11] (AGT) were measured for all patients. These measurements were performed using a periodontal probe (HuF No:15, Hu Friedy, Chicago, IL, USA) on both the maxillary right incisor (11) and the maxillary left incisor (21).[11,14] PI, GI, and PD values were measured from 6 different points of teeth 11-21: mesiobuccal, buccal, distobuccal, distopalatinal, palatal, and mesiopalatinal. The obtained values were averaged to create a single value.[11,14] Another researcher who performed periodontal measurements who did not complete the frenectomy, conducted the frenectomy.[3,4,13,27]

Before topical anesthesia, pediatric patients' frenectomy areas were wiped with a dry cotton pellet and dried. Topical anesthesia was achieved using locanest spray, which contains 10% lidocaine (Avixa İlaç San. in Başakşehir, İstanbul, Turkey). The topical anesthesia solution was applied to cotton pads and left on the right and left areas of the frenulum attachment for 1 minute to provide topical anesthesia. The frenulum area was injected with 2% articaine solution containing 1:100,000 adrenaline, 0.5 ml to the right and left for local anesthesia.[14]

The usage protocol for the diode laser was initiated after a wait of around 10 minutes. In this research, the diode laser used was the BIOLASE Epic10™ (BIOLASE INC., CA, USA). The laser interface has been set to "Frenectomy" mode. The features of the frenectomy mode are shown in **Table 1**.

Table 1. Parameters of BIOLASE epic 10™ diode soft tissue laser

BIOLASE epic 10™ diode soft tissue laser	
Wavelength	940±10
Maximum power of the equipment	10 Watts (W)
Operating mode	Puls mode
Used power	1.0 W
Irradiation mode	The activation occurs once the pedal is pressed and the targeted tissue is contacted.
Used optic fiber tip diameter	400 micrometer/7 mm
Pulse duration	1 millisecond
Pulse interval	1 millisecond
Peak power	2.0 W
Average	1.0 W

After the patient and the operator wore protective glasses, environmental safety measures were taken before the frenectomy procedure, following the guidelines in **Table 1**.

Using brushing movements, the laser was applied to the frenulum's upper and lower parts near the hemostat. It also removed the remaining muscular attachments of the periosteum to eliminate the periosteal adhesion. The remaining ablated tissue was cleared using a moistened gauze with a sterile saline solution.[10,11] The average time taken for the procedure was 120 seconds with the diode laser (**Figure 2**). Post-surgical instructions for participants included guidelines for the application of HA gel. Individuals in the 0.24% HA cohort received seven disposable blister packs, each containing aftamed child gel (0.24% HA, Aktident, Üsküdar, Istanbul, Turkey). Patients were directed to apply the HA gel to the wound site three times daily for one minute following the instructions for use, starting each application with a fresh blister pack.[28] They were also advised to abstain from ingestion of food or liquids for 10 to 15 minutes following each application to optimize the gel's efficacy.[14]

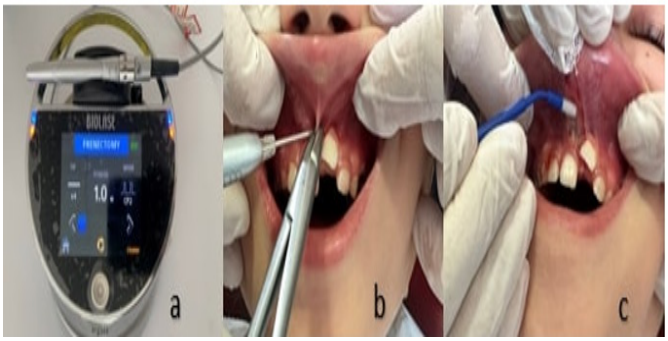

Figure 2. The stages of a frenectomy procedure that utilizes the diode laser. **a.** The epic 10 diode laser. **b.** Surgical procedure of the diode laser assisted-frenectomy. **c.** The application of 0.6% HA gel for demonstration for parents
HA: Hyaluronic acid

Parents of patients who had frenectomy were instructed on completing the VAS.[29] A visual VAS was given to patients to rate their pain level each evening, including the night of the frenectomy. According to this scale, 0 means I have no pain, and 10 means I have unbearably great pain. (**Figure 1**) From the evening of the transaction day, the VAS was completed for seven consecutive evenings, with a numerical value assigned to each entry.[5,10] It was decided not to measure the periodontal parameters again after the first week to avoid discomfort for the children with inflamed wound areas. During the 1st week of control after the frenectomy, the patients were given oral hygiene training again and were called back for control at the end of the 3rd month. Patients with scheduled 3rd-month follow-up appointments were reminded by phone and encouraged to attend. At the end of the third month, another operator repeated the PI, GI, PD, BOP, KGW, and AGT values without verifying whether the patient belonged to the control or test groups. The patients and their parents were reminded about oral hygiene training and informed that the research had been completed (**Figure 3**).

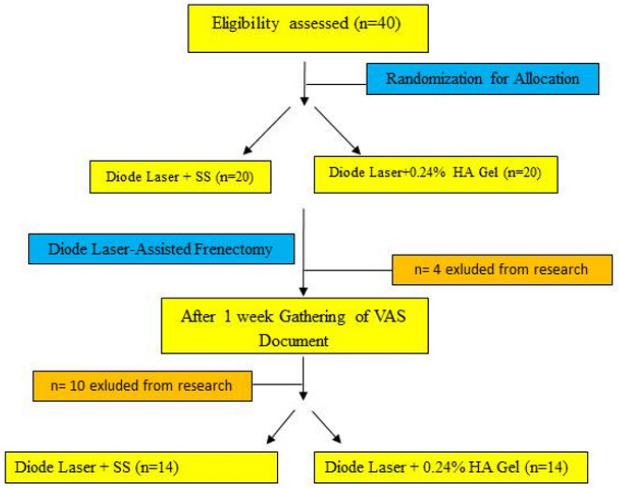

Figure 3. Flow diagram of the research

Statistical Analysis

The data analysis was conducted using the SPSS version 21 program. Descriptive statistics such as standard deviation and median (minimum-maximum) were utilized to analyze quantitative variables. The Fisher exact test examines the relationship between two qualitative variables the Repeated Measures ANOVA test was used to compare measurements within groups. A significance level of 0.05 was set for statistical analysis.

RESULTS

In the diode laser+SS group, there was a significant difference in VAS measurements taken at seven different time points (p<0.001). The mean VAS score was highest on day one and lowest on day seven. It is observed that the significant difference between the first and fourth day is the highest among all pairs of days (p=0.017), first-sixth day (p=0.007), first-seventh day (p=0.007), second-six day (p=0.043), and second-seventh day (p=0.043) (**Figure 4**).

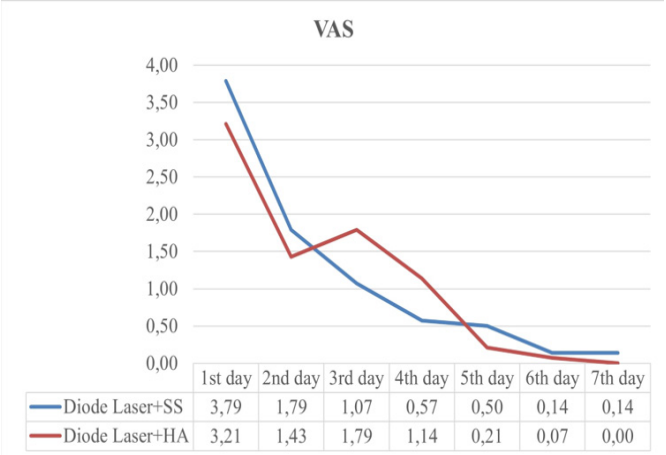

Figure 4. The time-dependent changes in VAS for the diode laser+SS and diode laser+HA groups
VAS: Visual analog scale, HA: Hyaluronic acid

There was a significant difference in the VAS measurements taken seven times in the group that received diode laser+HA. de laser+HA (p<0.001). The mean VAS score was highest on the first day and lowest on the seventh. It is observed that the significant difference between the seven days occurs between the first and fifth days (p=0.034), first-sixth day (p=0.012), first-seventh day (p=0.010), second-fifth day (p=0.029), second-sixth day (p=0.009), and second-seventh day (p=0.016) (**Figure 4**).

Table 1 shows no significant difference in variables between the two groups (p>0.05). Three monthly changes showed no difference in the diode laser+SS group. An increase in PI value was observed in 21.4% of patients in the diode laser+HA group, while a decrease was observed in 7.1%. (p=0.098) When compared monthly, there was a 7.1% decrease in the PI value of tooth number 21 for patients in the diode laser+SS group. In the diode laser+HA group, 14.3% of the patients experienced a decrease in PI value, while 7.1% experienced an increase (p=0.596).

During the first three months, 7.1% of diode laser+SS group patients showed a decrease in GI value for tooth number 11. 7.1% of patients in the diode laser+SS group showed a decrease in GI value from the beginning to 3 months in tooth 11. (p=0.730). 7.1% of patients in the diode laser+SS group showed a decrease in GI value in tooth 21 during the first three months. In the diode laser+HA group, 14.3% of patients experienced a decrease in GI value, while 7.1% experienced an increase. (p=0.596) (**Table 2**).

Table 2. Comparisons of baseline-3 month changes in variables between two groups

Variables		Diode laser+SS	Diode laser+HA	p
PI 11	No change	14 (100.0)	10 (71.5)	0.098[a]
	Decrease	0 (0.0)	1 (7.1)	
	Increase	0 (0.0)	3 (21.4)	
PI 21	No change	13 (92.9)	11 (78.6)	0.596[a]
	Decrease	1 (7.1)	2 (14.3)	
	Increase	0 (0.0)	1 (7.1)	
GI 11	No change	13 (92.9)	11 (78.6)	0.730[a]
	Decrease	1 (7.1)	1 (7.1)	
	Increase	0 (0.0)	2 (14.3)	
GI 21	No change	13 (92.9)	11 (78.6)	0.596[a]
	Decrease	1 (7.1)	2 (14.3)	
	Increase	0 (0.0)	1 (7.1)	
PD 11	No change	12 (85.7)	11 (78.6)	0.108[a]
	Decrease	2 (14.3)	0 (0.0)	
	Increase	0 (0.0)	3 (21.4)	
PD 21	No change	12 (85.8)	11 (78.6)	1.000[a]
	Decrease	1 (7.1)	1 (7.1)	
	Increase	1 (7.1)	2 (14.3)	
BOP 11	No change	12 (92.3)	9 (75.0)	0.390[a]
	Decrease	1 (7.7)	2 (16.7)	
	Increase	0 (0.0)	1 (8.3)	
BOP 21	No change	12 (92.3)	11 (91.7)	1.000[a]
	Decrease	1 (7.7)	1 (8.3)	
	Increase	-	-	
KGW 11	No change	11 (78.6)	10 (71.4)	0.648[a]
	Decrease	1 (7.1)	0 (0.0)	
	Increase	2 (14.3)	4 (28.6)	
KGW 21	No change	13 (92.9)	12 (85.7)	1.000[a]
	Decrease	-	-	
	Increase	1 (7.1)	2 (14.3)	
AGT 11	No change	13 (92.9)	12 (100.0)	1.000[a]
	Decrease	-	-	
	Increase	1 (7.1)	0 (0.0)	
AGT 21	No change	13 (92.9)	12 (100.0)	1.000[a]
	Decrease	-	-	
	Increase	1 (7.1)	0 (0.0)	

HA: Hyaluronic acid, a: Fisher-exact test

Only 14.3% of patients in the diode laser+SS group showed decreased PD value when comparing tooth 11 from baseline to 3 months. An increase in pocket depth was only observed in 21.4% of patients in the diode laser+HA group. (p=0.108). After examining the PD change in tooth 21 from baseline to 3 months, it was noticed that 7.1% of the patients in the diode laser+SS group experienced a decrease in PD value, while 7.1% saw an increase in their pocket depth value. A decrease in PD was observed in 7.1% of patients who received diode laser+HA, while an increase was observed in 14.3%. (p=1.000) (**Table 2**).

When analyzing the first 3-month change in BOP of tooth #11, 7.7% of patients in the diode laser+SS group had a decrease in BOP value. In the group that received diode laser therapy plus HA, 16.7% of patients experienced a decrease in BOP value, while 8.3% experienced an increase in BOP value (p=0.390). 7.7% of patients in the diode laser+SS group showed a decrease in BOP value in tooth 21 during the initial 3-month period.

An 8.3% decrease in BOP value was observed among patients in the diode laser+HA group (p=1.000) (**Table 2**).

The KGW change in tooth 11 from the initial to the third month showed that 7.1% of patients in the diode laser+SS group had a reduction in KGW value, while 14.3% showed an increase in KGW value. An increase in KGW value was observed in 28.6% of patients who received diode laser and HA treatment. (p=0.648). 7.1% of patients in the diode laser+SS group showed increased KGW value in tooth number 21 during the initial three months. An increase in the KGW value was observed in 14.3% of the patients in the diode laser+HA group (p=1.000) (**Table 2**).

After three months, the change in AGT values in tooth number 11 was observed in 7.1% of patients in the diode laser+SS group. No changes were observed in the AGT value of patients in the diode laser+HA group (p=1.000). There was an increase in AGT value for 7.1% of patients in the diode laser+SS group when comparing AGT at the initial and three months later in tooth number 21. No changes were observed in the AGT value of patients in the group treated with diode laser and HA (p=1.000) (**Table 2**).

DISCUSSION

It was found that using 0.24% HA gel during frenectomy diode laser-assisted surgery did not significantly reduce patient pain levels. After frenectomy, it was found that 0.24% HA did not significantly improve periodontal parameters. Based on the results, the research's null hypothesis was rejected.

The research included children aged 8 to 14 to increase treatment success. While anxiety and fear are often used interchangeably, they are distinct experiences. Dental anxiety is the fear of experiencing pain or discomfort during dental procedures. Dental anxiety is a common fear of dental procedures, including stimuli, devices, tools, and needles.[30] Previous studies have revealed that dental anxiety among children falls within the range of 21.3% to 23.5%.[31] This anxiety disorder experienced in pediatric patients poses a challenge, especially in surgical procedures performed under local anesthesia. Behavioral guidance techniques are used for older children instead of sedation/general anesthesia during surgical procedures.[25]

Children perceive and express pain differently than adults.[32] Pain perception is affected by physiological, psychological, behavioral, and developmental factors, which make its expression complex.[33] It is easier to define and measure the pain level in adolescents than in newborns and young children, who often experience difficulty in expressing their pain and determining its level.[34] During studies on frenectomy, the degree of post-operative pain was primarily assessed using VAS.[5,11,14,35] The pain level of pediatric patients was evaluated using VAS in this research.[29]

Diode laser, widely used in soft tissue-related procedures, has recently gained popularity.[10] Solid-state semiconductor diode lasers are composed of aluminum, gallium, and arsenide. It produces light in the near-infrared spectral region with a wavelength range of 808-980 nm.[36] Frenectomy surgeries can have difficult bleeding control, and sutures can impede healing and make patients uncomfortable during recovery.[37] Cleaning a wound with sutures and plaque can slow post-op healing and affect speech and chewing.[11]

High molecular weight HA gel exhibits high viscosity, elasticity, and negative energy charge. It has been widely used in dentistry for the past decade. HA gel has several beneficial properties, including bacteriostatic, fungistatic, anti-inflammatory, antiedematous, osteoinductive, and proangiogenic effects.[38-40] It was recommended to alleviate symptoms of gingivitis, periodontitis, bone healing, oral ulcers, and teething and improve the aesthetics of the lips and jawline.[41] Despite its recommendation after surgical procedures, there are still limited studies on the effectiveness of topical HA gel after frenectomy in pediatric patients.[14,42]

In this research on labial frenectomy-assisted diode laser, periodontal parameters, including PI, GI, BOP, PD, KGW, and AGT, were measured and monitored over three months. However, no significant changes were detected in any of these parameters for either the control or test groups. Previous studies have revealed no significant differences in the periodontal parameters evaluated compared to the current results.[5,10,11,14]

Öztürk Özener et al.[10] found no significant change or recurrence in the KGW parameter after a 12-month follow-up for frenectomy operations using diode laser or conventional scalpel surgery. In related research, Sezgin et al.[5] found no significant change in the KGW parameter over a 12-month follow-up period. In this research, an analysis of the KGW values for teeth numbers 11 and 21 revealed an increase in the KGW values within the 0.24% HA treatment group; however, this increase did not reach statistical significance. Uraz et al.[11] found that the AGT parameters no significant change in AGT over six months, consistent with present research. This study's application of 0.24% HA demonstrated no significant alteration in AGT levels following a diode laser frenectomy procedure.

Limitations

There are some limitations to this research. The research's most significant limitation is the number of patients enrolled. Researchers faced a considerable challenge when conducting the research with a larger participant pool. In the group of young patients, keeping them calm and relaxed during dental procedures was quite challenging, especially when using a laser. One of the reasons for this challenge is that the patients needed to be administered sedation. Another factor to consider is the behavioral disorder caused by wearing protective equipment, including glasses. Many patients refuse to regularly use HA gel and SS provided in 10cc syringes, resulting in fewer research participants. The parents of certain patients expressed this situation to the researchers. These patients were excluded from the research. Due to the COVID-19 pandemic, many participants canceled their procedures or missed follow-up appointments.

The follow-up for participants in this research after one month was conducted similarly to previous studies.[5,10,11,14] At the end of the research, the participants' periodontal parameter values in the 1st and 3rd months were almost identical. To

simplify the statistical analysis and improve the readability of the research, only the initial and 3rd-month periodontal parameter results are presented. Studies with longer follow-ups focus on the KGW parameter in the literature; only one research by Uraz et al.[11] three reported recurrence in a few patients following diode laser-assisted frenectomy. However, Pie-Sanchez et al.[43], Sezgin et al.[5], and Öztürk Özener et al.[10] stated no recurrence in the KGW parameter after 12 months of follow-up. It is important to note that all of these studies were conducted on adult patients. If the follow-up period is shorter, it may be easier to fully understand the reasons for parameter changes as pediatric patients continue to grow and develop. This study employed a non-blinded design, wherein all control procedures were carried out by the same clinicians (SSAD and NCK). A potential limitation of this approach is the likelihood that the findings may have been influenced by the inherent characteristics of the study design.

CONCLUSION

The 0.24% HA Gel Diode was ineffective in reducing pain perception after a laser-assisted frenectomy. Furthermore, it did not contribute to improving any other periodontal parameters that were assessed. Using higher concentrations of HA gel in future studies can validate the results and determine the effective concentration after frenectomy with the diode laser.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the approval of Afyonkarahisar Health Sciences University Clinical Researches Ethics Committee (Date: 14.06.2019, Decision No: 2019/7).

Informed Consent

Parents of all patients signed a free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Comparison of outcomes of banding, nail brace, and Winograd techniques in the treatment of Heifetz stage 2 ingrown toenails

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ABSTRACT

Aims: This study aims to evaluate the clinical outcomes of three commonly used treatment methods—banding, nail brace, and the Winograd procedure—in patients with Heifetz stage 2 ingrown toenails. Parameters such as recurrence rate, infection rate, postoperative pain, and patient satisfaction were assessed to guide clinical decision-making.

Methods: This retrospective study included 91 patients diagnosed with Heifetz stage 2 ingrown toenail, who were treated using one of three methods. Patients were divided into three groups: banding, nail brace, and Winograd procedure. Visual Analog Scale (VAS) scores were recorded on the third postoperative day to assess pain levels. The short-term outcomes, recurrence rates, and complications were analyzed. Ethical approval was obtained and the study adhered to the principles of the Declaration of Helsinki.

Results: The nail brace method showed a significantly shorter return-to-work duration (mean 10.2±9.5 days) compared to the Winograd procedure (19.0±6.4 days, $p<0.001$). Postoperative pain levels were significantly lower in the nail brace group (VAS score: 4.1±1.3) than in the Winograd group (6.0±1.5, $p<0.001$). Recurrence rates were similar across the nail brace (25.0%), Winograd (15.0 %), and banding (26.1%) groups ($p=0.472$). No significant differences were observed in the postoperative infection rates between the two methods ($p=0.571$).

Conclusion: The nail brace method offers faster recovery, shorter return-to-work durations, and lower postoperative pain, making it a less invasive alternative to the Winograd technique, which has longer recovery times. Despite these differences, both methods show similar recurrence rates, highlighting the need for treatment selection based on patient characteristics and preferences. Further studies with larger samples are required to assess long-term outcomes.

Keywords: Ingrown toenail nail brace, Winograd technique, recurrence, postoperative pain

INTRODUCTION

Ingrown toenails (onychocryptosis) are a common yet often debilitating condition affecting millions worldwide.[1] This condition not only causes significant pain and discomfort but also leads to restricted mobility and impaired quality of life. In severe cases, it can result in secondary infections, chronic inflammation, and even surgical intervention.[2] Despite various treatment options, there is still no universal consensus on the most effective approach, making this condition a crucial subject of clinical research.[3]

Despite various treatment options, the management of ingrown toenails remains a challenge due to the lack of consensus on the most effective approach.[4] Conservative methods, such as banding and nail bracing, aim to realign the nail and provide symptom relief, but recurrence rates remain high.[5] Surgical techniques, such as the Winograd procedure, offer a more definitive solution by excising the affected nail portion and matrix, yet they are associated with increased postoperative pain and longer recovery times.[6] The absence of a standardized treatment protocol underscores the need for further comparative studies to determine the optimal approach.

The Heifetz classification system is frequently used to grade the severity of ingrown toenails.[7] Stage 3 represents the most advanced stage and often necessitates surgical intervention owing to chronic pain, inflammation, and the potential for infection.[8] Despite the availability of various treatment options, there is no consensus on long-term outcomes, particularly in terms of recurrence rates, patient satisfaction, and complication profiles.

Despite various treatment options, the optimal approach for treating Heifetz stage 2 ingrown toenails remains uncertain. The lack of consensus on recurrence rates, patient satisfaction, and complication profiles highlights the need for comparative studies. This study aims to evaluate and compare the clinical

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outcomes of three commonly used treatment methods—banding, nail brace, and the Winograd technique. We hypothesize that the nail brace method will provide a balance between effectiveness and minimal invasiveness, offering faster recovery and lower postoperative pain compared to the Winograd procedure while maintaining similar recurrence rates.

METHODS

Ethics

This study was approved by the Scientific Researches Ethics Committee of the Adana City Training and Research Hospital (Date: 05.12.2024, Decision No: 270). The committee reviewed the study and confirmed that it did not involve any ethical concerns. The study was conducted at the Adana City Training and Research Hospital and included 91 patients diagnosed with ingrown toenails who were deemed eligible for treatment. All patients were thoroughly informed before the study, and written informed consent was obtained from each participant. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. All patient data included in this study were anonymized and de-identified prior to the analysis to ensure confidentiality. No personal identifiable information was collected or shared. This study complied with the ethical standards regarding patient privacy and confidentiality.

Patient Groups and Method Description

All the patients included in the study were classified as having stage 2 ingrown toenails. Patients were divided into three groups based on the treatment method applied: banding, nail brace, and Winograd procedure. In the banding method, the ingrown portion of the nail is separated from the nail bed using a band to alleviate localized pressure. The band was replaced at regular intervals and patients were provided with guidance to manage the treatment process. In the nail brace method, a U-shaped wire is placed on the lateral and medial edges of the nail, and the tension created by the wire corrects the curvature of the ingrown nail. This method aims to maintain a corrective effect throughout the natural growth of the nails. The Winograd procedure involved surgical intervention, in which the ingrown portion of the nail was excised, and the nail matrix and bed were curetted. Suturing was performed postoperatively, and all patients were prescribed oral antibiotics for one week to reduce the risk of infection (**Figure**).

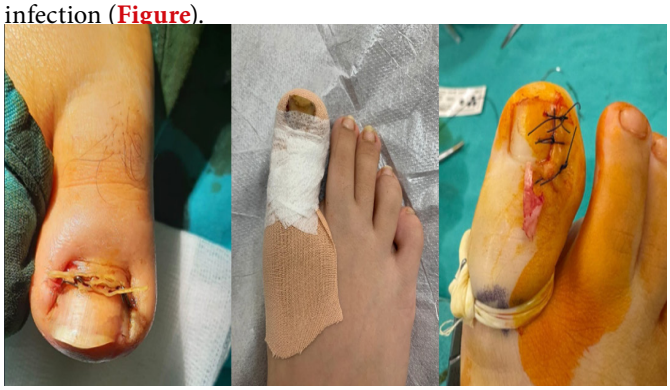

Figure. Treatment techniques for ingrown toenails: nail brace, banding, and Winograd procedure

Inclusion and Exclusion Criteria

Patients included in this study were diagnosed with Heifetz stage 2 ingrown toenail and were treated with one of the three methods: banding, nail brace, or the Winograd procedure. Eligible participants were between 18 and 65 years old and had complete medical records, allowing for thorough postoperative evaluation. Patients were excluded if they had Heifetz stage 1 or stage 3 ingrown toenails, as these cases require different management strategies. Additionally, those with a history of previous ingrown toenail surgery on the same toe were not included to ensure that treatment outcomes were not influenced by prior interventions. Patients with systemic conditions affecting wound healing, such as diabetes mellitus, peripheral vascular disease, or immunosuppressive disorders, were also excluded, as these factors could impact postoperative recovery and infection rates. Furthermore, individuals with traumatic nail deformities or congenital nail abnormalities were not considered, as these conditions could confound the study results. Finally, patients with poor compliance to follow-up or those lost to follow-up were excluded to ensure the reliability of postoperative outcome assessments.

Procedure and Evaluation

All patients were regularly monitored after the procedure. To assess the impact of treatment on pain levels, Visual Analog Scale (VAS) scoring was performed on the third postoperative day. The short-term outcomes of the treatment methods were compared, and the recovery process and complication rates were analyzed in detail.

Statistical Analysis

All statistical analyses were performed using SPSS 27.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Normally distributed continuous data are presented as mean±standard deviation, whereas non-normally distributed continuous variables are reported as median (minimum–maximum). Categorical variables were expressed as counts (percentages). For comparisons between two groups, the Independent Samples t-test was used for normally distributed variables, whereas the Mann-Whitney U test was applied for non-normally distributed variables. For comparisons among three groups, One-Way analysis of variance (ANOVA) was performed for parametric data, followed by Tukey's post-hoc test if a significant difference was detected. For non-parametric data, the Kruskal-Wallis test was used, and if a significant difference was found, Dunn-Bonferroni post-hoc test was conducted to determine intergroup differences. Categorical variables were analyzed using the chi-square test, and in cases where the expected cell frequency was greater than 20%, Fisher's Exact test was applied. Missing data were handled using listwise deletion, and cases with incomplete records were excluded from the analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

The mean age of the participants was 21.7±10.5 years, with an average Body-mass index (BMI) of 22.7±3.4 kg/m^2. The mean postoperative VAS score was recorded as 4.6±1.9, while

the mean return-to-work duration was calculated as 16.5±8.8 days (Table 1).

Table 1. Demographic and clinical characteristics of patients

	Mean±SD
Age (years)	21.7±10.5
BMI (kg/m²)	22.7±3.4
Post op VAS score	4.6±1.9
Return to work duration (days)	16.5±8.8

The data in the table are presented as mean±standard deviation. Abbreviations: VAS: Visual Analog Scale, BMI: Body-mass index, SD: Standard deviation

The majority of participants were male (60.4%), and most were unilateral (right: 41.8%, left: 49.5%). The most commonly applied treatment method was the Winograd procedure (44.0%), followed by nail wire (30.8%) and nail bandage (25.3%). Treatment success was achieved in 78.0% of the cases, while recurrence was observed in 20.9%. Postoperative infections were noted in only 9.9% of the cases (Table 2).

Table 2. Distribution of patient characteristics and treatment outcomes

		Count	Column n %
Sex	Female	36	39.6%
	Male	55	60.4%
Affected side	Bilateral	8	8.8%
	Right	38	41.8%
	Left	45	49.5%
Treatment method	Winograd	40	44.0%
	Nail bandage	23	25.3%
	Nail wire	28	30.8%
Treatment result	Success	71	78.0%
	Failed	20	22.0%
Postop infection	Yes	9	9.9%
	No	82	90.1%
Recurrence	Yes	19	20.9%
	No	72	79.1%

The data in the table are presented as count (percentage)

No significant differences were found in sex distribution or the affected side across the groups (p<0.05). The highest treatment success rate was observed in the Winograd group (85.0%), followed by the nail bandage (73.9%), and nail wire (71.4%) groups, with no statistically significant differences (p=0.355). The postoperative infection rates were also comparable between the groups (Winograd, 12.5%; bandage, 4.3%; nail wire, 10.7%; p=0.571). Similarly, the recurrence rates were not significantly different, ranging from 15.0% in the Winograd group to 26.1% in the bandage group (p=0.472) (Table 3).

No significant differences were observed in age and BMI (p=0.405 and p=0.493, respectively). However, the postoperative VAS scores showed a statistically significant difference, with the highest scores recorded in the Winograd group (6.0±1.5), followed by the nail wire group (4.1±1.3), and the lowest in the bandage group (2.7±1.2; p<0.001). Similarly, the return-to-work duration was significantly longer in the Winograd (19.0±6.4 days) and nail wire (18.0±8.9 days) groups compared to the bandage group (10.2±9.5 days; p<0.001) (Table 4).

No significant difference was found in age between patients with recurrence (23.3±15.0 years) and those without recurrence (21.3±9.0 years; p=0.718). However, patients who experienced recurrence had a significantly higher BMI (24.3±4.0 kg/m²) compared to those without recurrence (22.2±3.1 kg/m²; p=0.033). Although this difference was not statistically significant, higher BMI has been clinically associated with an increased risk of recurrence and infection in ingrown toenail cases. Excess weight may contribute to greater pressure on the toes, altered nail growth patterns, and compromised wound healing, all of which could predispose patients to higher recurrence and infection rates following treatment. Postoperative VAS scores were similar between the groups (4.3±1.7 vs. 4.7±2.0; p = 0.291). In contrast, the return-to-work duration was significantly longer in patients with recurrence (21.6±10.8 days) than in those without recurrence (15.1±7.7 days; p=0.001) (Table 5).

Table 3. Comparison of demographic and clinical outcomes among treatment methods

		Winograd (n=40)	Bandage (n=23)	Nail wire (n=28)	
		Count (%)	Count (%)	Count (%)	p value
Sex	Female	17 (42.5)	8 (34.8)	11 (39.3)	0.833
	Male	23 (57.5)	15 (65.2)	17 (60.7)	
Affected side	Bilateral	4 (10.0)	3 (13.0)	1 (3.6)	0.697
	Right	15 (37.5)	9 (39.1)	14 (50.0)	
	Left	21 (52.5)	11 (47.8)	13 (46.4)	
Treatment result	Success	34 (85.0)	17 (73.9)	20 (71.4)	0.355
	Failed	6 (15.0)	6 (26.1)	8 (28.6)	
Postop infection	Yes	5 (12.5)	1 (4.3)	3 (10.7)	0.571
	No	35 (87.5)	22 (95.7)	25 (89.3)	
Recurrence	Yes	6 (15.0)	6 (26.1)	7 (25.0)	0.472
	No	34 (85.0)	17 (73.9)	21 (75.0)	

The data in the table are presented as count (percentage)

Table 4. Comparison of age, BMI, postoperative pain, and recovery time across treatment methods

	Winograd (n=40)	Bandage (n=23)	Nail wire (n=28)	
	Mean±SD	Mean±SD	Mean±SD	p value
Age (years)	23.4±13.8	20.0±6.0	20.7±7.1	0.405
BMI (kg/m²)	22.2±3.3	23.23.5	22.9±3.6	0.493
Post op VAS score	6.0±1.5	2.71.2	4.1±1.3	**<0.001**
Return to work duration (days)	19.0±6.4	10.29.5	18.0±8.9	**<0.001**

The data in the table are presented as mean±standard deviation. Statistically significant p-values are highlighted in bold. Abbreviations: VAS: Visual Analog Scale, BMI: Body-mass index, SD: Standard deviation

Table 5. Comparison of demographic and clinical parameters between patients with and without recurrence

	Recurrence (n=19)	No recurrence (n=72)	
	Mean±SD	Mean±SD	p value
Age (years)	23.3±15.0	21.3±9.0	0.718
BMI (kg/m²)	24.3±4.0	22.2±3.1	**0.033**
Post op VAS score	4.3±1.7	4.7±2.0	0.291
Return to work duration (days)	21.6±10.8	15.1±7.7	**0.001**

The data in the table are presented as mean±standard deviation. Statistically significant p-values are highlighted in bold. Abbreviations: VAS: Visual Analog Scale, BMI: Body-mass index, SD: Standard deviation

DISCUSSION

This study aimed to evaluate the clinical outcomes of different treatment methods for ingrown toenails. Significant differences were observed between treatment methods in terms of pain level and return-to-work duration. The banding method had lower postoperative pain levels and shorter recovery times than the other treatments. In contrast, higher

pain scores and prolonged recovery times were noted with Winograd and nail brace methods. These findings suggest that more invasive treatments have a more pronounced impact on recovery and highlight the need for careful pain management using such methods. Additionally, BMI was found to be associated with recurrence, indicating that individual factors such as obesity may influence treatment success. Our study found that patients with recurrence had a significantly higher BMI (24.3±4.0 kg/m^2) than those without recurrence (22.2±3.1 kg/m^2; p=0.033). Although this difference was not statistically significant, it aligns with previous studies, such as Arica et al.[9], who identified obesity as a key risk factor for ingrown toenail development. Higher BMI is known to contribute to increased mechanical stress on the toes, chronic microtrauma, and altered nail growth patterns, all of which may predispose patients to higher recurrence rates and postoperative complications. Furthermore, obesity is often linked to impaired circulation and delayed wound healing, which could prolong inflammation and increase susceptibility to postoperative infections. Given this association, BMI should be considered an essential factor in the treatment selection process for ingrown toenails. The differences in pain scores and return-to-work duration observed between treatment methods can be attributed to several factors. The Winograd procedure, being a surgical intervention involving partial nail and matrix excision, is inherently more invasive than conservative methods such as banding and nail bracing. This increased invasiveness likely contributes to higher postoperative pain levels and prolonged recovery times. Furthermore, individual patient factors such as BMI and overall health status may also play a role in postoperative recovery. Patients with higher BMI may experience increased mechanical stress on the surgical site, delayed wound healing, and prolonged discomfort, which could extend their recovery period. Additionally, postoperative care adherence, including wound hygiene and appropriate footwear, may influence pain perception and overall healing time. Understanding these contributing factors is crucial in guiding treatment selection and optimizing patient outcomes. The study's findings underscore the importance of a patient-centered approach in treatment selection, highlighting the strengths and limitations of each method.

An ingrown toenail is a common ailment that can disrupt daily life and social engagement.[10,11] Various factors contribute to this condition, including wearing tight footwear; improper trimming of toenails such as cutting them too short or not in a straight line; excessive curvature of the nail causing internal pressure; and health-related issues such as arthritis, structural deformities, diabetes, obesity, and age-related nail variations.[10-14] Heifetz outlined three primary stages of ingrown toenails.[15] In stage I, the mildest form, the symptoms include swelling, redness, slight edema, and pain when pressure is applied. Stage II is more severe, featuring increased swelling, seropurulent discharge, persistent wounds that do not heal, signs of infection, and development of granulation tissue. The most severe stage III is characterized by chronic inflammation, more pronounced granulation, and a hardened area around the lateral nail fold.[16,17] The progression or regression between these stages can vary based on how the ingrown toenail is managed.[17] A variety of treatment options exist for ingrown toenails, ranging from basic conservative measures to more advanced surgical interventions. Each treatment option has different recurrence rates.[10,11,13,18] For stage II and III ingrown toenails, surgical methods are often recommended over conservative treatments, which, although effective for stage I, have higher failure and recurrence rates for more severe stages.[10,11,14,16,19,20] It's worth noting that experts have not yet unified on an optimal surgical technique for ingrown toenails.[19,21] However, a combination of techniques, such as partial nail plate avulsion coupled with chemical cauterization or wedge excision alongside phenol cauterization, has been identified as particularly effective for managing this condition. In this context, our study compared the Winograd technique with the nail brace method and observed significant differences in postoperative pain scores and return-to-work duration. Notably, the nail brace method demonstrated a shorter return-to-work duration (10.2±9.5 days) and lower postoperative pain levels, suggesting that this conservative approach could be a more patient-friendly option. However, the longer recovery period associated with the more invasive nature of the Winograd technique is evident. Our findings align with those of Güler et al.[21], who reported that nail braces provided a shorter return-to-work duration and lower postoperative pain levels compared to the Winograd technique. However, while their study found similar recurrence rates between the two methods, our study suggests that recurrence may be influenced by patient-specific factors such as BMI rather than the procedure itself. This highlights the importance of a patient-centered approach when selecting a treatment method, considering factors such as BMI, severity of the condition, and patient preference. Future research should focus on prospective studies with larger sample sizes to further explore the impact of BMI and other patient-related factors on treatment outcomes. Additionally, investigating preventive strategies such as weight management and customized postoperative care could help reduce recurrence rates and improve long-term patient satisfaction. Our findings align with those in the literature and emphasize the importance of considering individual needs, particularly in stage II patients, when planning treatment strategies.

In a study conducted by Güler et al.[21], clinical parameters such as patient satisfaction, return-to-work duration, and recurrence rates were compared between nail braces and the Winograd technique. Their study reported that the nail brace method provided a shorter return-to-work duration (mean 4.15±1.07 days) and higher patient satisfaction (94.6%). Similarly, in our study, the nail brace method demonstrated an advantage in terms of return-to-work duration (mean 10.2±9.5 days) and lower postoperative pain. However, while Güler et al.[21] observed similar recurrence rates for both methods (8.1% vs. 9.4%), our study showed that the recurrence rates were associated with individual factors, particularly BMI. Regarding postoperative pain scores, Güler et al.[21] found that the nail brace method resulted in lower pain scores, which aligns with our findings that nail braces provided lower pain levels than other methods. Both studies highlighted that the invasive nature of the Winograd technique led to prolonged recovery times, which

is a consistent finding. These results align with the literature, emphasizing that conservative treatments, such as nail braces, can be a preferable option due to their shorter recovery times and higher patient satisfaction. However, the need to consider individual patient characteristics during treatment selection was clearly demonstrated.

Limitations

This study has several limitations. First, as the study utilized a retrospective design, the retrospective collection of data introduces potential risks of data gaps and bias. Additionally, because the study was conducted at a single center, the generalizability of the findings to different patient populations may be limited. Furthermore, the follow-up duration was relatively short, making it difficult to assess long-term outcomes, particularly recurrence rates and their impact on permanent recovery. Lastly, while evaluating subjective outcomes, such as postoperative pain and patient satisfaction, it was not possible to fully control for individual variations.

CONCLUSION

The nail brace method demonstrated faster recovery, shorter return-to-work durations, and lower postoperative pain levels compared to the Winograd technique, making it a favorable option for patients seeking a less invasive treatment. However, recurrence rates were comparable between both methods, suggesting that treatment selection should be tailored to patient characteristics. Surgical interventions like the Winograd procedure may be preferable for patients with severe or recurrent cases, while conservative approaches such as nail bracing may be more suitable for those prioritizing shorter recovery times and reduced postoperative discomfort. Further studies with larger sample sizes are needed to assess long-term outcomes and refine treatment guidelines.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Scientific Researches Ethics Committee of the Adana City Training and Research Hospital (Date: 05.12.2024, Decision No: 270).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Gastrointestinal tumors of the small bowel: prognostic roles of tumor stage and inflammatory markers

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ABSTRACT

Aims: Small bowel tumors are a heterogeneous group of malignancies, including gastrointestinal stromal tumors (GISTs), adenocarcinomas, neuroendocrine tumors (NETs), and myofibroblastic tumors, each with distinct prognostic implications. While tumor stage is a well-established prognostic factor, patient survival outcomes and systemic inflammatory markers also play a crucial role in disease progression. This study evaluates these factors comprehensively to enhance prognostic assessment in small bowel malignancies.

Methods: This retrospective study analyzed 25 patients diagnosed with small bowel tumors, including various histological subtypes. The prognostic significance of tumor stage (T and N classification), systemic inflammatory markers (neutrophil-to-lymphocyte ratio [NLR], platelet-to-lymphocyte ratio [PLR], albumin, and C-reactive protein [CRP]), and overall survival was assessed. Kaplan-Meier survival analysis was conducted to evaluate the association between tumor stage, inflammatory markers, and patient outcomes. Statistical analyses included independent sample t-tests, Mann-Whitney U tests, and Chi-square tests.

Results: The median age of the cohort was 63 years (range: 47–81). The most common histological subtype was GIST (52%), followed by adenocarcinoma (24%), NET (20%), and myofibroblastic tumors (4%). Kaplan-Meier survival analysis revealed a significant association between tumor stage and patient survival ($p=0.036$), with advanced-stage tumors (T3–T4) demonstrating significantly lower survival rates compared to early-stage tumors (T2). Lymph node involvement (N stage) was also a significant predictor of reduced survival ($p=0.013$). Although inflammatory markers such as NLR, PLR, albumin, and CRP were assessed, they did not show statistically significant associations with survival outcomes ($p>0.05$).

Conclusion: This study highlights the importance of evaluating both tumor stage and patient survival when determining prognosis in small bowel tumors. The Kaplan-Meier analysis underscores the strong prognostic impact of tumor staging and lymph node involvement on survival outcomes. Although systemic inflammatory markers did not show significant prognostic value in this cohort, their role in risk stratification warrants further investigation in larger studies. These findings contribute to a broader understanding of small bowel tumor prognosis beyond staging alone, supporting the need for a multidimensional approach in clinical assessment and treatment planning.

Keywords: Gastrointestinal stromal tumors (GISTs), inflammatory markers, tumor stage, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), survival analysis, gastrointestinal tumors, prognostic factors

INTRODUCTION

Small bowel tumors are rare but clinically significant neoplasms that represent a diverse spectrum of histological subtypes, including gastrointestinal stromal tumors (GISTs), adenocarcinomas, neuroendocrine tumors (NETs), and myofibroblastic tumors.[1,2] These tumors, though uncommon compared to those arising in other parts of the gastrointestinal (GI) tract, pose significant diagnostic and therapeutic challenges due to their nonspecific symptoms and delayed diagnosis.[3] Each histological subtype exhibits unique biological behaviors, prognostic implications, and therapeutic considerations.

GISTs are the most common mesenchymal neoplasms of the GI tract and are typically characterized by activating mutations in KIT or PDGFRA.[1] These mutations make GISTs amenable to targeted therapy with tyrosine kinase inhibitors, such as imatinib, which has significantly improved outcomes in these patients. Adenocarcinomas, in contrast, are epithelial tumors often presenting at advanced stages due to their insidious onset, leading to poor survival outcomes despite surgical and chemotherapeutic advancements.[2] NETs of the small bowel arise from enteroendocrine cells and frequently present with distinct clinical syndromes, such as carcinoid

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syndrome, necessitating a multidisciplinary approach for optimal management.[3,4] Myofibroblastic tumors, while rare, contribute to the heterogeneity of small bowel tumors and are often associated with inflammatory processes, further complicating their diagnosis and treatment.[5]

Prognosis in small bowel tumors is influenced by several factors, including tumor stage, histological subtype, and systemic inflammatory response.[6,7] Tumor stage, particularly the presence of lymph node or distant metastases, is a well-established prognostic factor in GI cancers, with advanced-stage tumors demonstrating significantly worse survival.[8,9] Histological subtypes also play a crucial role in determining prognosis and response to treatment. For instance, GISTs respond favorably to targeted therapies, while adenocarcinomas often require aggressive multimodal treatment with limited success.[10]

In recent years, systemic inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have emerged as potential prognostic indicators in various cancers, including GI tumors.[11,12] These markers are thought to reflect the interaction between the tumor and host immune response, as well as systemic inflammation, which can promote tumor progression. Additionally, albumin levels and C-reactive protein (CRP) have been explored as markers of nutritional and inflammatory status, with low albumin and elevated CRP often associated with worse survival in cancer patients.[13,14]

While previous studies have evaluated these markers individually, few have analyzed their combined prognostic significance across multiple histological subtypes of small bowel tumors. Moreover, given the rarity of these tumors, data on their prognostic factors remain limited, and most studies have focused primarily on GISTs, leaving other subtypes underrepresented in the literature.[15]

Small bowel tumors represent a heterogeneous group of malignancies, including GISTs, adenocarcinomas, NETs, and myofibroblastic tumors, each with distinct biological behavior and prognostic implications. While GISTs are the most well-known mesenchymal neoplasms of the GI tract, other histological subtypes also significantly impact disease progression and patient outcomes. This study evaluates the prognostic significance of tumor stage, overall patient survival, histological subtypes, and systemic inflammatory markers, such as NLR, PLR, albumin, and CRP, across multiple small bowel tumor subtypes. By adopting a comprehensive approach, this research aims to provide deeper insights into the factors influencing survival beyond tumor staging alone. Furthermore, the findings contribute to the growing body of evidence supporting the integration of inflammatory markers into clinical practice for improved risk stratification and personalized treatment planning in small bowel malignancies.

METHODS

This study was approved by the Ethics Committee of Haydarpaşa Numune Training and Research Hospital (Date: 01/09/2023, Decision No: 771/01/2021). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The retrospective data of 25 patients diagnosed with small bowel tumors, including GISTs, adenocarcinomas, NETs, and myofibroblastic tumors, were analyzed. The ages, genders, histological subtypes, and clinical parameters of the included patients were evaluated. Neutrophil, lymphocyte, and platelet counts, as well as the NLR, PLR, albumin levels and CRP levels, are recorded. The normal reference ranges for the laboratory parameters were as follows: neutrophils ($2.5–10\times10^9$/L), lymphocytes ($1.0–3.0\times10^9$/L), platelets ($150–450\times10^3$/μL), albumin (3.5–5.0 g/dl), and CRP (<5 mg/L). Additionally, the tumor stages (T and N stages), tumor locations, and clinical presentations of the patients were analyzed. Computed tomography (CT) imaging findings were also reviewed. Follow-up times and survival statuses were calculated using the Kaplan-Meier method. Statistical analyses were performed using independent Sample t-tests, Mann-Whitney U tests, and Chi-square tests. $p<0.05$ was considered statistically significant.

Statistical Analysis

The descriptive statistics of the data are presented as mean, standard deviation, median, minimum, maximum, frequency, and percentage values. The distribution of the variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Variables with a normal (Gaussian) distribution, such as age, the NLR, and the PLR, are reported as mean±standard deviation, while variables with non-normal distribution, such as lymphocyte counts and CRP, were reported as median and interquartile range (IQR). For the analysis of quantitative independent data, independent sample t-tests and Mann-Whitney U tests were used. For the analysis of qualitative independent data, the Chi-square test was used, and Fisher's exact test was applied when the Chi-square test assumptions were not met. The Kaplan-Meier method was used for a survival analysis. All analyses were performed using SPSS version 28.0.

RESULTS

This study analyzed the clinical and demographic characteristics of 25 patients with GI tumors to evaluate the prognostic significance of various parameters, including age, gender, histological subtypes, inflammatory markers, and tumor stage. The results are summarized as follows:

Patient Demographics

The median age of the cohort was 63 years (range: 47–81 years), with a mean age of 62.7±9.1 years. Of the 25 patients, 14 (56%) were male, and 11 (44%) were female. The statistical analysis revealed no significant association between age, gender, and survival outcomes ($p>0.05$).

Histological Subtypes

The cohort included patients with GISTs (52%, n=13), adenocarcinomas (24%, n=6), NETs (20%, n=5), and myofibroblastic tumors (4%, n=1). Histological subtype was not significantly associated with survival outcomes ($p=0.546$) (**Table 1**).

Table 1. General clinical and demographic characteristics of patients with gastrointestinal tumors

		Min-Max	Medyan	Mean±SD/n %
Age		47.0-81.0	63.0	62.7±9.1
Sex	Female			11/44.0%
	Male			14/56.0%
Histoloji	Adenocarsinom			6/24.0%
	GIST			13/52.0%
	Myofibrobastik tumor			1/4.0%
	NET			5/20.0%
Neutrophil		2810.0-24500.0	8140.0	9216.4±5142.2
Lymphocyte		700.0-4100.0	1180.0	1595.6±863.0
Platelet (x10^3)		131.0-399.0	260.0	265.5±73.9
NLR		1.2-35.0	5.7	7.6±7.1
PLR		80.2-500.0	180.5	201.3±100.9
Albumin		2.0-4.5	3.3	3.3±0.7
CRP		0.2-30.0	4.4	6.5±6.9
T stage	II			11/44.0%
	III			7/28.0%
	IV			7/28.0%
N stage	0			16/64.0%
	I			6/24.0%
	II			3/12.0%
Presentation	Chron			2/8.0%
	Hematochezia			1/4.0%
	Incidental			1/4.0%
	Ischemia			3/12.0%
	Abdominal pain			4/16.0%
	Melena			5/20.0%
	Obstruction			6/24.0%
	Perforation			2/8.0%
	Jaundice			1/4.0%
Tumor area	Duedoneum			1/4.0%
	İleum			12/48.0%
	Jejeneum			12/48.0%
CT screening	Intramural hematoma			1/4.0%
	Tumor			15/60.0%
	Tumor+perforation			1/4.0%
	Mezenter ischemia			2/8.0%
	Obstruction			5/20.0%
	Perforation			1/4.0%

GIST: Gastrointestinal stromal tumor, NET: Neuroendocrine tumor, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CRP: C-reactive protein, CT: Computed tomography, Min: Minimum, Max: Maximum, SD: Standard deviation

Inflammatory Markers

The mean NLR was 7.6±7.1, and the mean PLR was 201.3±100.9. While both the NLR and PLR tended to be elevated in patients with advanced-stage tumors, these differences were not statistically significant in relation to survival outcomes (NLR: p=0.352; PLR: p=0.106) (Table 1).

Albumin and CRP

Albumin and CRP levels were analyzed. The mean albumin level was 3.3±0.7 g/dl, and the mean CRP level was 6.5±6.9 mg/L. Neither the albumin nor CRP levels showed significant associations with survival outcomes (albumin: p=0.358; CRP: p=0.956) (Table 1).

Tumor Staging (T and N Stages)

Tumor staging revealed that 44% of the patients (n=11) were classified as T stage II, 28% (n=7) were classified as T stage III, and 28% (n=7) were classified as T stage IV. The Kaplan-Meier survival analysis demonstrated that tumor stage significantly influenced survival outcomes, with the patients in T stage II showing a cumulative survival time of 123.2 months compared to 56.2 months for in the patients T stages III-IV (p=0.036).

For N stage, 64% of the patients (n=16) had no lymph node involvement (N0), while 24% (n=6) were classified as N1, and 12% (n=3) were classified as N2. The patients with N0 had significantly better survival outcomes than with N1 or N2 (p=0.013) (Table 2).

Tumor Location

Tumor location was categorized as the duodenum (4%, n=1), ileum (48%, n=12), and jejunum (48%, n=12). The statistical analysis showed no significant differences in survival outcomes based on tumor location (p=0.821) (Table 1).

Survival Outcomes

By the end of the study, 72% (n=18) of the patients were still alive, while 28% (n=7) were deceased. The median follow-up time was 34.9 months (range: 0.1–133.9 months), with a mean follow-up time of 53.0±45.0 months (Table 3,4).

Table 2. Comparative analysis of clinical and demographic characteristics in patients with T stage II and T stage III-IV gastrointestinal tumors

		T stage II		T stage III- IV		p
		Mean±SD/n-%	Medyan	Mean±SD/n-%	Medyan	
Age		65.7±9.8	65.0	60.3±7.9	62.0	0.139[t]
Sex	Female	4/36.4%		7/50.0%		0.495[X²]
	Male	7/63.6%		7/50.0%		
Histologia						
Adenocarsinom		2/18.2%		4/28.6%		0.546[X²]
GIST		7/63.6%		6/42.9%		0.302[X²]
Myofibrobastik tumor		1/9.1%		0/0.0%		0.440[X²]
NET		1/9.1%		4/28.6%		0.227[X²]
Neutrophil		9466.4±3400.4	8710.0	9020.0±6310.9	6025.0	0.352[m]
Lymphocyte		1895.5±979.5	1500.0	1360.0±707.8	1070.0	0.055[m]
Platelet (x10³)		275.9±81.1	295.0	257.3±69.7	251.5	0.543[t]
NLR		5.7±2.6	6.1	9.0±9.1	5.3	0.956[m]
PLR		164.4±62.7	152.0	230.3±117.1	215.3	0.106[t]
Albumin		3.1±0.7	2.9	3.4±0.8	3.6	0.358[t]
CRP		5.7±4.5	5.9	7.1±8.4	4.0	0.956[m]
N stage	0	10/90.9%		6/42.9%		0.013[X²]
	I	1/9.1%		5/35.7%		
	II	0/0.0%		3/21.4%		
Location	Duedonum	0/0.0%		1/7.1%		1.000[X²]
	İleum	5/45.5%		7/50.0%		0.821[X²]
	Jejenum	6/54.5%		6/42.9%		0.561[X²]
Ex	(-)	10/90.9%		8/57.1%		0.062[X²]
	(+)	1/9.1%		6/42.9%		
Following time		74.7±47.2	87.7	36.0±36.3	27.0	0.055[m]

GIST: Gastrointestinal stromal tumor, NET: Neuroendocrine tumor, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CRP: C-reactive protein, CT: Computed tomography, SD: Standard deviation, t: Independent sample t test, m: Mann-Whitney U test, X^2: Ki-kare test (Fischer test)

Table 3. Survival status and follow-up duration of patients

		Min-Max	Medyan	Mean±SD/n %
Ex	(-)			18/72.0%
	(+)			7/28.0%
Following time		0.1-133.9	34.9	53.0±45.0

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

Table 4. Cumulative survival time by tumor stage in patients with gastrointestinal tumors

		Cumulative survival time (mounth)	% 95 GA	p
T grade	II	123.2	103.6-142.8	*0.036*
	III-IV	56.2	30.5-81.9	
Total		94.2	70.0-118.4	

Kaplan Meier (log rank)

Table 3 provides a summary of survival distributions, highlighting the percentage of patients with favorable versus poor outcomes. These data allow for a better understanding of survival trends within the cohort, despite the limitations posed by the sample size. **Table 2** presents detailed analyses of prognostic factors, including tumor stage, histological subtypes, and systemic inflammatory markers such as NLR and PLR. While some markers did not reach statistical significance due to the small cohort, the trends observed align with findings in larger studies and warrant further investigation.

Kaplan-Meier Analysis Section

To provide a comprehensive prognostic evaluation, we assessed not only tumor stage but also overall patient survival using Kaplan-Meier survival analysis. As shown in **Table 4**, survival outcomes significantly varied based on tumor stage, with patients diagnosed at T stage II demonstrating markedly improved survival compared to those with more advanced-stage disease (p=0.036). Furthermore, lymph node involvement (N stage) was strongly associated with reduced survival, reinforcing its prognostic importance (p=0.013).

DISCUSSION

GISTs represent a unique subset of GI neoplasms, distinguished primarily by the presence at the KIT mutation, which has profound implications for treatment and prognosis.[16] In this study, we aimed to evaluate the clinical characteristics, prognostic markers, and survival outcomes of patients with GI tumors, focusing on the impact of tumor stage, inflammatory indices, and histological subtypes on survival. Our findings contribute to the growing body of literature suggesting that both tumor biology and systemic inflammatory responses are significant determinants of patient outcomes.[17]

One of the key findings of our analysis is the strong association between tumor stage and survival outcomes. Patients with T stage II tumors demonstrated significantly longer survival than with stage III or IV tumors (p=0.036). This result is consistent with that of previous studies, emphasizing the critical role of early-stage diagnosis in improving the long-term prognosis of GISTs and other GI tumors.[18] Early-stage tumors are often localized, making complete surgical resection more feasible, whereas advanced-stage tumors frequently exhibit metastasis or lymph node involvement, complicating surgical interventions and overall management.[19]

Another important aspect of our study is the evaluation of inflammatory markers, including the NLR and PLR. Elevated NLRs and PLRs have been shown to correlate with worse survival outcomes in a variety of cancers, including GI malignancies.[20] In our study, although the NLR and PLR were

elevated in more advanced stages, the differences between the stages were not statistically significant. This may be due to the relatively small sample size, limiting the statistical power to detect subtle differences. However, the trend observed is consistent with the hypothesis that systemic inflammation plays a role in cancer progression and may be associated with poorer outcomes.

The role of systemic inflammation in cancer progression is well established. Elevated NLRs and PLRs are indicative of a heightened inflammatory state, which may promote tumor growth and metastasis by creating a favorable microenvironment for cancer cells.[21] Although our study did not find statistically significant differences in the NLR and PLR between stages, the potential prognostic value of these markers should not be overlooked. Larger studies are warranted to further explore the utility of these markers in clinical practice.

Albumin, a well-known marker of nutritional status and systemic inflammation, was another variable of interest in our study. Low albumin levels are commonly associated with poor prognosis in cancer patients due to their correlation with malnutrition and systemic inflammation.[22] Our results show no significant differences in albumin levels between early and advanced stages, which may again be due to the small sample size. However, low albumin levels were more frequently observed in patients with advanced disease, aligning with the literature that suggests a relationship between hypoalbuminemia and worse clinical outcomes.

CRP, another inflammatory marker, was also assessed in our study. Elevated CRP levels have been linked to poor outcomes in various cancers, including GI tumors.[23] Although CRP levels were higher in patients with more advanced disease in our cohort, these differences were not statistically significant. Nonetheless, CRP remains a valuable marker in clinical practice, particularly in assessing systemic inflammation and guiding treatment decisions.

Histological subtype is another critical factor influencing the prognosis of GI tumors. GISTs, which made up the majority of cases in our study, are generally more responsive to targeted therapies such as tyrosine kinase inhibitors than adenocarcinomas or NETs.[24] This is largely due to the presence of at KIT mutation, which can be specifically targeted with drugs such as imatinib.[25] In our study, patients with GISTs had generally better survival than those with adenocarcinoma or NETs, although the differences were not statistically significant. This observation is consistent with other reports suggesting that the molecular characteristics of GISTs confer a more favorable prognosis when treated appropriately.

Our study also examined the impact of lymph node involvement (N stage) on survival. Patients without lymph node metastasis (N0) had significantly better survival outcomes than those with lymph node involvement (N1 or N2) (p=0.013). This finding aligns with that of previous research indicating that lymph node involvement is a strong negative prognostic factor of GI cancers.[26] The presence of metastatic lymph nodes often reflects more aggressive disease and may reduce the effectiveness of surgical resection, leading to poorer outcomes.[27,28]

Our findings highlight the necessity of evaluating prognosis beyond tumor stage alone. The significant differences in survival outcomes observed between early and advanced tumor stages indicate that overall survival should be a key consideration when assessing disease prognosis. The Kaplan-Meier survival analysis in our study confirms that lymph node involvement and advanced T stage correlate with poorer patient outcomes, a finding consistent with previous research on GI malignancies. These results underscore the importance of integrating both tumor stage and patient survival data when determining prognostic indicators for small bowel tumors.

Limitations

Despite the valuable insights provided by this study, several limitations should be noted. First, the retrospective nature of the study introduces potential biases, including selection bias and incomplete data. Additionally, the relatively small sample size limits the generalizability of the findings and reduces the statistical power to detect differences in some variables, particularly inflammatory markers such as the NLR, the PLR, albumin, and CRP. Future studies with larger cohorts and prospective designs are needed to validate these findings and explore the potential for integrating inflammatory markers into routine prognostic assessments for GI tumors.

CONCLUSION

Our study highlights the critical role of tumor stage in determining survival outcomes in patients with GI tumors. Early detection and appropriate staging are essential for improving prognosis. While systemic inflammatory markers such as the NLR, the PLR, and CRP were not found to be significantly associated with survival in this cohort, their potential utility as prognostic tools warrants further investigation. Targeted therapies, particularly for GISTs, continue to play a key role in improving outcomes, and the presence of lymph node involvement remains a significant negative prognostic factor. Future research should aim to refine the prognostic models for GI tumors, incorporating both traditional factors such as tumor stage and emerging biomarkers of systemic inflammation.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ethics Committee of Haydarpaşa Numune Training and Research Hospital (Date: 01/09/2023, Decision No: 771/01/2021).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The effect of Buzzy application on pain and comfort level during heel stick in newborns: a randomized controlled study

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ABSTRACT

Aims: The aim of this study was to evaluate the effects of the Buzzy device application on pain levels and comfort in newborns during heel stick procedures.

Methods: This randomized controlled experimental study was conducted at a Family Health Centre affiliated with the Public Health Directorate in a province in eastern Turkey between September and November 2024. The sample included 80 newborns born at 37–42 weeks of gestational age within the first 28 days of life (Buzzy group: n=40; control group: n=40). In the Buzzy group, the Buzzy device was applied approximately 30 seconds before the heel stick procedure. In the control group, the procedure was performed without any intervention. Data collection tools included the neonatal introduction form, the neonatal infant pain scale (NIPS), and the neonatal comfort behavior scale (NCBS). Ethical principles were adhered to throughout the study.

Results: Pain levels and comfort scores during the heel stick procedure were significantly better in the Buzzy group compared to the control group ($p<0.001$). Analysis revealed that, in the control group, pain levels increased significantly, and comfort levels decreased markedly during the procedure. In contrast, the Buzzy group exhibited a more limited increase in pain levels and a less pronounced decrease in comfort. After the procedure, the pain scores were significantly lower, and comfort levels were higher in the Buzzy group compared to the control group ($p<0.001$).

Conclusion: The Buzzy device was found to be an effective method for significantly reducing pain and maintaining comfort in newborns during heel stick procedures. These findings suggest that the Buzzy device can be a valuable tool for pain management and enhancing comfort in clinical settings. Future studies could explore the effectiveness of the device in larger populations and compare it with other pain management strategies.

Keywords: Buzzy, newborn, pain, comfort, heel stick, nursing

INTRODUCTION

Heel stick blood collection is a critical preventive health service performed globally.[1] However, it causes significant pain and stress in newborns[2], which disrupts their comfort.[3] Invasive procedures that impair comfort can negatively affect the biopsychosocial development of newborns.[2] Due to their higher density of nociceptors compared to adults, neonates perceive pain more intensely[4,5], making pain a more pronounced stressor for this age group.[6,7]

Pain during medical procedures can lead to adverse physiological consequences, including decreased blood oxygen saturation (SpO_2), increased heart rate, heightened oxygen demand, and elevated intracranial pressure, which raises the risk of intraventricular haemorrhage.[8] Furthermore, pain and stress can weaken an infant's immune system, increasing susceptibility to infections.[5] Research indicates that painful experiences during infancy may negatively affect brain development and predispose individuals to inadequate pain responses later in life. Repeated exposure to pain in early life may also hinder the healthy development of organs.[9,10]

Reports suggest that newborns undergo approximately 98 painful procedures within the first 14 days of life, with most performed without drug-based or non-drug pain management interventions.[11] Evidence highlights that healthcare providers address pain management in only 20% of these procedures[12], and more than half are performed without any measures to alleviate pain.[5,13] Heel pricking is a common painful procedure used for screening, diagnostics, and emergencies. Repeated punctures may have long-term negative effects on pain processing and stress responses in infants.[5,14]

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Non-pharmacological interventions have demonstrated efficacy in reducing pain and regulating physiological and cognitive responses in infants.[15-17] However, many non-pharmacological methods are underutilised by healthcare professionals due to the need for preparation, complexity of application, and the potential to extend procedural time.[18,19] The Buzzy device offers a simple, time-efficient solution. This device combines vibration and cold application to naturally block pain within seconds. By physiologically suppressing pain signals through the combination of cold and vibration, the Buzzy device effectively reduces acute procedural pain.[20-22] The Buzzy device has been found to be effective in minimizing pain and anxiety during immunizations, blood draws, and sample collections in children aged 2 to 18 years.[20,23-25] However, there is limited information in the literature on its use in infants under 2 years of age.[26]

Based on the gate control theory, vibratory stimuli compete with pain signal transmission along the spinal cord-thalamic pathway, potentially reducing the perception of pain in neonates.[27] Providing comfort, ensuring safety, and protecting health are core professional and ethical responsibilities of nurses, particularly when caring for neonates. However, effectively reducing pain and maintaining comfort in newborns continues to be a major difficulty for nurses.[3,27,28] Among pain management strategies, drug-free methods are prioritized in neonatal nursing.[25]

Thus, this study aims to evaluate how effective the device is in this age group, focusing on newborns' pain experience and overall comfort. In this regard, it seeks to provide scientific evidence for the potential application of Buzzy as a drug-free pain relief method in neonatal nursing.

Study hypotheses;

H_1: There is a notable variation in the pain measurements of newborns in the Buzzy group relative to the control group.

H_2: There is a notable variation in the comfort levels of newborns in the Buzzy group relative to the control group.

METHODS

Ethics

Ethical approval was granted by the Van Yüzüncü Yıl University Non-interventional Clinical Researches Ethics Committee (Date: 16.06.2023, Decision No: 2023/06-02). Written and verbal informed consent was obtained from the parents. The randomized controlled study followed CONSORT guidelines, ensuring adherence to ethical principles throughout the research. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Design

This research utilized a randomized controlled experimental design.

Place and Time

The research was carried out between September and November 2024 in a Family Health Centre, selected through a lottery method, under the Public Health Directorate in an eastern region of Turkey.

Population and Sample

The study population consisted of 80 newborns registered at the Family Health Centre, born at 37–42 weeks of gestation, and presenting at the health institution for routine heel prick blood collection within the first 28 days of birth.

The sample size was estimated with the G-power 3.1 software. Considering an effect size of 0.5 and a power of 0.95, at least 35 infants were required per group. To account for potential losses and ensure group homogeneity, the final sample size included 40 infants in both the control and Buzzy groups (**Figure 1**).

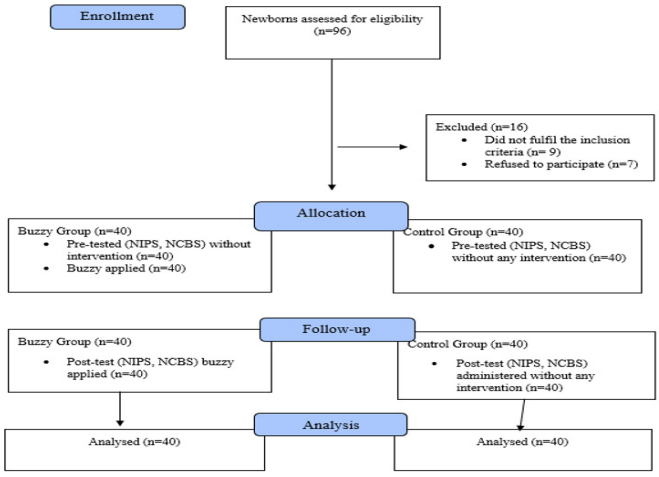

Figure 1. CONSORT 2022 flow diagram[29]

Inclusion Criteria

Newborns fulfilling the following conditions were enrolled in the research: neonates aged 0–28 days, having a gestational age ranging from 37 to 42 weeks, with vital signs within normal limits, and whose parents voluntarily consented to take part in the study.

Exclusion Criteria

Infants were excluded from the study if they had compromised skin integrity at the application site of the device, if they exhibited nerve impairment or deformity in the limb where the heel blood was to be drawn, or if they had inherited conditions, congenital abnormalities, metabolic disorders, or osteogenesis imperfecta. Additionally, infants who required cardiopulmonary resuscitation, had failed the first attempt at heel blood collection, had received analgesics within the last six hours, or had other conditions deemed unsuitable for the study were excluded.

Data Collection Tools

The instruments used for data collection comprised the neonatal introduction form, the neonatal infant pain scale (NIPS), and the neonatal comfort behaviour scale (NCBS).

The Neonatal Introduction Form

The Neonatal Introduction Form was created based on an analysis of existing studies in the field.[18,22,27] This form

includes questions regarding gestational age, gender, type of delivery, length, birth weight and the age of the mother.

The Neonatal Infant Pain Scale (NIPS)

The NIPS, created by Lawrence et al.[30], assesses pain responses in preterm and term newborns. Scores range from 0 to 7, with values above 3 indicating pain. The Turkish adaptation, validity, and reliability of the NIPS were established by Akdovan[31], with Cronbach's alpha values reported as 0.83 before and during the procedure, and 0.86 afterward.

Neonatal Comfort Behaviour Scale (NCBS)

NCBS, created by Ambuel et al.[32], evaluates comfort, pain, and stress in neonates on mechanical ventilation in intensive care. The Turkish adaptation of the scale was validated by Kahraman et al.[33] It includes items rated from 1 to 5. A total score below 13 indicates comfort, while 14 or higher suggests discomfort, requiring further intervention.

Implementation of the Intervention

The heel blood collection room was specially prepared to ensure the comfort of the infants and their stability during the procedure. The room temperature was kept between 24-26°C, and measures were taken against air flow and sudden temperature changes to prevent babies from getting cold. Lighting was adjusted so that it was neither too bright nor inadequate, and harsh lights shining directly into the infants' faces were avoided. Instead, diffused and soft light sources were used to create an environment that does not disturb the eyes of the babies. A comfortable environment was created for the babies, and care was taken to ensure that the babies could not see each other during the procedure. Parents were allowed to be with their babies throughout the process. The procedure took place in the unit's designated blood collection room. Infants meeting the sampling criteria were initially assessed by a family physician.

In order to ensure equal distribution between the groups, buzzy and control groups were determined by simple randomisation method using Random Allocation Software.[34]

Buzzy Group

Mothers of eligible infants for heel prick were informed by the observation nurse, and verbal and written consent were obtained. The procedure's purpose and details were explained. Then, the data collection form was completed. For Buzzy use, a deep-frozen ice pack was left at room temperature for 10 minutes before being attached to the device. During the procedure, it was placed below the knee, aligning with the sural nerve, 30 seconds before the heel prick. One nurse performed the procedure, while another recorded videos before, during (15-20 seconds), and five minutes after.[35] These recordings were evaluated by two experts NIPS and the NCBS to analyze the effectiveness of the procedure. After use, the ice pack was cleaned with 70% alcohol and placed back in the deep freezer for re-freezing (**Figure 2**).

Control Group

No pain relief device or method was used for the control group during the heel prick. The first nurse performed the procedure by collecting blood directly from the heel, while the second nurse recorded videos before, during (15-20 seconds), and five minutes after. Two experts analyzed the recordings using NIPS and NCBS to evaluate pain levels and comfort in the control group infants.

Figure 2. Buzzy device

Statistical Analysis

All statistical analyses were conducted using SPSS 26.0 for Windows. Continuous variables were summarized as mean, standard deviation, minimum, and maximum values, while categorical variables were presented with frequency and percentage distributions. Chi-square analysis was used to compare categorical variables between the control and Buzzy groups. The skewness and kurtosis values of the study scales were within ±1.5 in both groups, indicating normal distribution. Therefore, an Independent-samples T-test was applied to compare scale scores between groups. ANOVA was used to analyze variations in scale scores before, during, and after the heel prick, with the Bonferroni test applied for post-hoc comparisons. A p-value of <.05 was considered statistically significant.

Clinical Study Registration

The randomized controlled study was registered on the ClinicalTrials.gov website under ClinicalTrials ID No. NCT06773325 (https://www.clinicaltrials.gov) on January 2, 2025, with the Clinical Trial Registry.

RESULTS

In the control group, 30% of the babies were born at the 38th and 40th gestational weeks, 57.5% were female, 57.5% were born vaginally, 72.5% weighed between 3000-3490 g, and 85% had a birth length between 46-50 cm. Additionally, 65% of the mothers were aged between 26-35 years. In the Buzzy group, 32.5% of the babies were born at 39 weeks, with a 50% distribution between girls and boys, 55% were born by caesarean section, 65% weighed between 3000-3490 grams, and 85% were 46-50 cm tall. Furthermore, 67.5% of the mothers in the Buzzy group were aged between 26-35 years.

These findings revealed that there was no statistically significant difference between the Buzzy and control groups in variables such as gestational week, gender, mode of delivery, birth weight, birth length, and maternal age, indicating a general similarity between both groups (p>0.05, **Table 1**).

There was no significant difference between the NIPS scores observed before the heel prick in the control and Buzzy groups, with both groups having a pain level of zero. However,

Table 1. Demographic characteristics of the participants

Variable	Category	Control group		Buzzy group		Total		X^2	p
		n	%	n	%	n	%		
Gestational week	37th week	6	15.0	6	15.0	12	15.0	.820	.845
	38th week	12	30.0	12	30.0	24	30.0		
	39th week	10	25.0	13	32.5	23	28.7		
	40th week	12	30.0	9	22.5	21	26.3		
Gender	Girl	23	57.5	20	50.0	43	53.8	.453	.501
	Boy	17	42.5	20	50.0	37	46.3		
Birth type	Vaginal birth	23	57.5	18	45.0	41	51.2	1.251	.263
	Cesarean birth	17	42.5	22	55.0	39	48.8		
Weight	2500-2990 g	6	15.0	8	20.0	14	17.5	.540	.763
	3000-3490 g	29	72.5	26	65.0	55	68.8		
	3500-4000 g	5	12.5	6	15.0	11	13.8		
Length	46-50 cm	34	85.0	34	85.0	68	85.0	.000	1.000
	51 cm and above	6	15.0	6	15.0	12	15.0		
Mother's age	18-25 years	9	22.5	10	25.0	19	23.8	.571	.751
	26-35 years	26	65.0	27	67.5	53	66.3		
	36 years and above	5	12.5	3	7.5	8	10.0		

when the pain levels during the procedure were analyzed, the NIPS scores of the infants in the control group (6.00±0.93) were significantly higher than the NIPS scores of the infants in the Buzzy group (3.33±0.73) (t=14.276; p<0.001). Similarly, the NIPS scores of the infants in the control group (4.57±0.84) were significantly higher than the NIPS scores of the infants in the Buzzy group (1.58±0.68) (t=17.557; p<0.001). The ANOVA test results also indicated significant differences between the measurement times for both groups (p<0.001). The Bonferroni multiple comparison test following the repeated measures ANOVA test revealed the time periods during which these differences occurred.

These findings show that the pain level during the procedure was lower in the Buzzy group compared to the control group, and the pain decreased more after the procedure (**Table 2**).

Table 2. Comparison of NIPS scores of control and Buzzy groups

Time	Control group $\bar{X}$±SD	Buzzy group $\bar{X}$±SD	t	p
Before heel stick procedure	a.00±.00	a.00±.00		
During heel stick procedure	b6.00±.93	b3.33±.73	14.276	<.001*
After heel stick procedure	c4.57±.84	c1.58±.68	17.557	<.001*
F	942.896	417.309		
P	<.001*	<.001*		
Difference	a<c<b	a<c<b		

*p<.05, a,b,c.: Indicates the statistical difference between procedures according to the Bonferroni multiple test result, NIPS: Neonatal infant pain scale, SD: Standard deviation

It was determined that the NCBS scores of the babies before the heel stick blood collection were significantly lower in both the control (6.53±0.87) and Buzzy (6.78±0.92) groups, and the comfort levels of the babies were statistically similar (p>0.05). When the NCBS scores during the procedure were analysed, it was found that the mean score of the infants in the control group (26.43±2.39) was significantly higher than the mean score of the infants in the Buzzy group (13.73±1.54) (t=28.319; p<0.001). These results show that the comfort levels of the infants in the control group during heel prick were significantly lower than those in the Buzzy group. In fact, the mean score of the Buzzy group (13.73±1.54) was smaller than the cut-off score of 14 for the scale, and it was concluded that the comfort of the babies in this group did not deteriorate at all according to the scale evaluation criteria.

Similarly, the NCBS scores of the infants in the control group (17.15±3.01) were significantly higher than the mean score of the infants in the Buzzy group (9.63±1.85) after the procedure (t=13.233; p<0.001). These results show that the comfort levels of the babies in the control group were significantly lower than those in the Buzzy group after the procedure (**Table 3**).

Table 3. Comparison of comfort-NCBS scores of control and Buzzy groups

Time	Control group $\bar{X}$±SD	Buzzy group $\bar{X}$±SD	t	p
Before heel stick procedure	a6.53±.87	a6.78±.92	-1.245	.217
During heel stick procedure	b26.43±2.39	b13.73±1.54	28.319	<.001*
After heel stick procedure	c17.15±3.01	c9.63±1.85	13.233	<.001*
F	4588.194	229.135		
P	<.001*	<.001*		
Difference	a<c<b	a<c<b		

*p<.05, a,b,c.: Indicates the statistical difference between procedures according to the Bonferroni multiple test result, NCBS: Neonatal comfort behavior scale, SD: Standard deviation

In addition, according to the ANOVA test results, it was observed that there were significant differences between the measurement times for both groups in NCBS (p<0.001). The Bonferroni multiple comparison test performed after the

repeated measures ANOVA test determined between which time periods this differentiation occurred. The decrease in comfort level was less in the Buzzy group compared to the control group. Furthermore, it was found that the comfort level in the Buzzy group reached a level closer to the pre-procedure level in the post-procedure period (**Table 3**).

DISCUSSION

Heel stick is one of the most painful procedures performed in newborns.[36] The fact that their nervous systems are not fully developed makes newborns vulnerable to the neurodevelopmental effects of pain.[5] Various non-drug techniques are commonly utilized to manage pain during heel stick blood collection. These include swaddling, breastfeeding, heel warming, non-nutritive sucking, skin-to-skin contact, positioning strategies, therapeutic touch, foot massage, reflexology, and vibration therapy.[35,37-44] However, these applications may create additional time, effort, and stress on parents and nurses.[45]

Therefore, research supports the use of Buzzy, a device that is easy to use, reusable, cost-effective, and fast, as it has positive effects on pain management, especially by combining mechanical vibration and cold application. These mechanisms are believed to block pain messages and temporarily alleviate pain.[20,46,47] These effects can be explained within the framework of the pain gate theory, which suggests that the brain has the ability to 'switch off' or 'switch on' pain signals, and that external stimuli (e.g., cold or mechanical vibration) can influence this process.[48] The Buzzy device appears to alleviate pain based on this theory, with newborns reporting lower pain scores during procedures.[49,50] Buzzy has been found effective in managing pain in children and has been used in various settings such as intramuscular[20,51], subcutaneous[21], intravenous[47], blood sampling[48,52] and dental extractions.[53] There are also studies that demonstrate pain reduction with mechanical vibration alone[35,54] or cooling alone.[55,56]

However, no studies have been found in the literature evaluating the effectiveness of the Buzzy device in alleviating pain during the heel prick procedure. In this study, the Buzzy device was observed to significantly reduce pain during and after the procedure compared to the control group ($p<0.05$) (**Table 2**). These results support the hypothesis H1: "There is a notable variation in the pain measurements of newborns in the Buzzy group relative to the control group". It is believed that this effect can be explained by the gate control theory, which prevents the transmission of pain messages to the nervous system. Additionally, this device was found to be effective in alleviating pain in newborns during the heel prick procedure and is expected to make a significant contribution to the literature on this topic.

In neonatal nursing care, ensuring the comfort of the baby is a basic requirement to prevent the negative effects of pain and stress.[57] Many non-drug methods used during painful procedures in newborns help enhance comfort by alleviating pain.[58] Some studies have shown that skin contact, auditory interventions, holding, breastfeeding, foot massage, and heel warming effectively enhance infant comfort during heel blood collection.[3,43,59-61] Newborns react to pain severity with body movements such as crying, alertness, and changes in muscle tone. Tension in the body, along with facial and bodily movements, plays a key role in assessing their comfort. Multisensory stimuli have been found effective in soothing newborns and enhancing comfort during painful procedures.[60,61]

This study found that the Buzzy device significantly improved neonatal comfort levels compared to the control group during and after the procedure ($p<0.001$) (**Table 3**). These findings support the research hypothesis. H2: "There is a notable variation in the comfort levels of newborns in the Buzzy group relative to the control group" The Buzzy device was found to be effective in providing comfort to newborns by blocking pain messages with mechanical vibration and cold applications, and this effect is thought to be supported by the pain gate theory.

Limitations

This study possesses several notable strengths. First, it employed a randomized controlled trial design, widely regarded as the gold standard for evaluating intervention effectiveness. The sample size was calculated using robust statistical methods to ensure sufficient power, and strict inclusion criteria were applied to minimize confounding variables. The use of validated tools such as the NIPS and NCBS ensured the reliability and validity of the findings. Moreover, the analysis of video recordings by two independent evaluators enhanced the objectivity of the data.

However, the study is not without limitations. The sample was derived from a single center, which may limit the generalizability of the results to other settings or populations. The short follow-up period restricted the ability to assess the long-term effects of the Buzzy device on neonatal pain perception and comfort. Additionally, the intervention was not blinded, as the use of the Buzzy device was visually apparent, which could introduce observer bias despite independent evaluation. Finally, the study did not consider the psychological or physiological responses of parents, which could have provided a more comprehensive understanding of the intervention's broader impact.

CONCLUSION

This study demonstrated that the Buzzy device effectively reduced pain and enhanced comfort in newborns during heel blood collection. These findings suggest that the Buzzy device should be integrated into neonatal pain management protocols in clinical settings The pain-relieving and comfort-enhancing effects of mechanical vibration and cold applications, which influence the nervous system according to the pain gate theory, support the clinical use of the device. The preference of healthcare professionals for such non-pharmacological interventions in painful procedures can significantly contribute to minimizing pain and stress in newborns. Future studies should investigate its effectiveness in procedures such as venipuncture, lumbar puncture, or vaccination. Widespread use of the Buzzy device in nursing care could enhance care quality, improve pain management, and increase patient satisfaction.

ETHICAL DECLARATIONS

Ethics Committee Approval
Ethical approval was granted by the Van Yüzüncü Yıl University Non-interventional Clinical Researches Ethics Committee (Date: 16.06.2023, Decision No: 2023/06-02).

Informed Consent
Written and verbal informed consent was obtained from the parents.

Referee Evaluation Process
Externally peer-reviewed.

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

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

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Evaluation of children with allergic and non-allergic rhinitis and the effect of obesity/overweight in patients with allergic rhinitis

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ABSTRACT

Aims: Allergic rhinitis (AR) and obesity are two of the most prevalent chronic health diseases in children. This report aims to investigate to types of allergic and non-allergic rhinitis (NAR) and the association between the frequency and severity of rhinitis symptoms in AR patients with and without overweight/obesity.

Methods: Patients aged 5-18 years with rhinitis symptoms who were referred to Sincan Training and Research Hospital pediatric immunology and allergy outpatient clinic were retrospectively evaluated. Demographic, clinical and laboratory characteristics of patients were recorded.

Results: The study included 385 children with a median age of 11 years (IQR8-14) (53.5% males). 31 (8.1%) of patients had atopic dermatitis and 22 (5.7 %) of patients had asthma. 283 (73.5%) patients were in the AR group. Total IgE level and eosinophil count were found significantly higher in AR group [256 (113-995) vs. 280 (160-480)] than NAR group [64 (25.5-210) vs. 170 (90-310)] (p=0.002 vs. p=<0.001). 61.3 % of patients were sensitized to grass pollen, 21% to cat, and 9.9% to house dust-mite. The number of patients with moderate-to-severe rhinitis were higher in AR group (65%) compared to NAR group (35%) (p=0.005). Nasal congestion (77.7%), sneezing (75.3%), rhinorrhea (42.6%) were more common symptoms. Postnasal drip, snoring-mouth breathing and adenoid hypertrophy were more common in the NAR group compared to AR group (p=0.011, p=0.013 and p<0.001, respectively). Among patients with AR, there were 79 (28%) patients with overweight/obesity. The rate of moderate-to-severe rhinitis was 68.4% in obese/overweight group and 63.7% in the non-obese/overweight group.

Conclusion: Our study found that moderate-to-severe rhinitis was higher in the AR group than the NAR group. No difference was found between the frequency and severity of rhinitis symptoms and aeroallergen sensitivities in patients with and without obesity/overweight.

Keywords: Rhinitis, allergic, severity, children, obesity

INTRODUCTION

Rhinitis is defined as a group of symptoms such as rhinorrhea, nasal congestion, sneezing and itching, that are caused by inflammation and/or dysfunction of the nasal mucous membranes. Roughly, rhinitis can be classified as allergic rhinitis (AR), infectious rhinitis and non-allergic, non-infectious rhinitis.[1,2] Several criteria can be used to classify phenotypes, including severity of disease (mild, moderate or severe), frequency of symptoms (intermittent/persistent), dominant symptom (nasal congestion, runny nose, sneezing, etc.) and trigger of symptoms (infectious agents, allergens, etc.).[1,2] The prevalence of AR in childhood ranges from 0.8% to 45%[3] and nowadays, it has become a very widespread disease in allergy clinics.

It is well established that obesity represents a significant global health problem. Obesity and AR are the most prevalent chronic health diseases in childhood. The frequency of both conditions is rising globally, leading to a reduction in quality of life and becoming an important public health problem. Many reports have shown the association between obesity and the development of asthma.[4,5] The effect of obesity on AR has been of interest in studies because the pathogenesis of AR and asthma is similar. It has been suggested that there is a relationship between AR and obesity, but this relationship has not been definitively proven.[6,7]

Obesity is a low-grade systemic inflammatory state characterized by altered levels of adipokines, bioactive molecules secreted by adipose tissue.[8,9] These immunological changes may decrease immunological tolerance to allergens and cause a shift toward a T Helper 2 cell immune response, which increases the risk of atopic diseases.[10] Basically, physical inactivity and lifestyle disorders occur in obesity, can lead to

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various harmful effects on the immune system. This condition may increase the incidence of allergic diseases such as AR.[11]

Obesity and AR are significant public health problems in the world therfore, determining the relationship between obesity and AR is crucial. We aimed to investigate the clinical features of patients with AR and NAR. In addition, we evaulated the relationship the severity, frequency and allergen sensitivity of rhinitis in AR patients, between overweight/obesity and non-overweight/obesity groups.

METHODS

Ethics

The present report was organised within the framework of the principles of the Declaration of Helsinki. Approval for this retrospective study was obtained from the Scientific Studies Ethics Committee of Ankara Atatürk Sanatorium Training and Research Hospital (Date: 09.10.2024, Decision No: 2024-BÇEK/151).

Study Population and Data Collection

The study included children aged 5-18 years with rhinitis who were being followed at pediatric immunology and allergy outpatient clinic at Sincan Training and Research Hospital between December 2023 and December 2024. We evaluated demographic information (age, gender, family history, etc.), anthropometric measurements, allergy history, clinical features, presence of atopic comorbidities (AD, FA, OFS), allergy tests positivity, laboratory features (total IgE values, eosinophil, neutrophil counts) from the patients' medical records. Exclusion criteria were the presence of chronic inflammatory or systemic diseases.

Determination and Classification of Patients with Rhinitis

In cases where clinical signs of rhinitis were evident, the skin prick test (SPT) and/or allergen-specific IgE were assessed. Positive values were classified as indicative of AR and negative values were classified as NAR.[12] Patients with rhinitis were divided as AR group and NAR group. AR is categorised according to symptom frequency and severity and classification were made according to ARIA criteria. Patients with AR symptoms occurring shorter than four days per week or less than four weeks were classified as having intermittent AR, while those with symptoms occuring more than four days per week or more than four weeks were categorised as having persistent AR. AR patients with at least one of the following symptoms: impairment in routine daily and sports activities, sleep disorder, impaired school performance and unpleasant symptoms are classified as moderate-severe AR while patients with none of these symptoms were categorised as mild AR.[13]

Skin Prick Tests

The SPTs were conducted using a panel of common aeroallergens [grass pollen mix (*Lolium perenne*, *Dactylis glomerata*, *Poa pratensis* ,*Phleum pratense*), *Cynodon dactylon, Dermatophagoides farinea, Dermatophagoides pteronyssinus,* cat, dog, *Alternaria alternata*, *Cladosporium herbarum,* a weed pollen mix (*Artemisia vulgaris*, *Wall pellitory, Chenopodium album), a* tree pollen mix (*Betula pendula, Corylus avellana*, *Olea europaea, cupressus)]* in the routine practice of the pediatric immunology and allergy outpatient clinic on patients with rhinits symptoms. Allergen extracts [Lofarma®, (Italy)] were performed on the volar surface of the forearm with positive and negative controls and assessed after fifteen minutes. Positive results were identified as a mean wheal diameter three mm greater than the negative control.[14,15]

Anthropometric Assessment

The body-mass index (BMI) was defined as body weight (kg) divided by height (m) and BMI (kg/m^2) was optimised as a measurement of obsesity. According to WHO growth reference values, obesity was determined as a BMI z-score greater than two standard deviations and overweight was determined as a BMI z-score greater than 1 standard deviation in children aged 5-19 years.[16]

Statistical Analysis

The statistical data analysis was conducted using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). We conducted descriptive analysis to define the demographical, immunological, clinical, and laboratory characteristics and data. We showed the values as the median and min-max for data not normally distributed. We used Pearson's Chi-square or Fisher's exact tests, Mann–Whitney U tests between-group comparisons. All statistical tests were two-sided, a p-value less than 0.05 was considered statistically significant.

RESULTS

Study Population

The study included 385 children with a median age of 11 years (IQR8-14) (53.5% males). 31 (8.1%) of patients had atopic dermatitis, 22 (5.7%) of patients had asthma, 6 (1.6%) of patients had OFS, and 4 (1%) of patients had FA. 165 (42.9%) patients had a family history of atopic diseases and 110 (28.6%) patients had a family history of AR (**Table 1**).

Comparison of Patients between AR and NAR Groups

102 (26.5%) patients were in the NAR group and 283 (73.5%) patients were in the AR group. The age of onset of AR symptoms was 6 years (IQR 4-10). There were 110 (28.6%) obese/overweight patients in all study groups. The number of patients with and without obesity/overweight was not statistically different. The family history of AR rate was higher 89 (31.4%) in the AR group than NAR group 21 (20.6%) (p=0.037). Total IgE level and eosinophil count were significantly higher in the AR group [256 (IQR 113-995) vs. 280 (IQR 160-480)] than in the NAR group [64 (IQR 25.5-210) vs. 170 (IQR 90-310)] (p=0.002 vs. p=<0.001). Age, gender and age at onset of rhinitis symptoms were not statistically different. When rhinitis severity was evaluated, the number of patients with moderate-to-severe rhinitis were higher in the AR 184 (65%) group compared to the NAR 99 (35%) group (p=0.005). There was no difference in frequency of rihinits symptomps (**Figure 1a**). Intermittent mild rhinitis (33% vs. 46.1%), intermittent moderate-to-severe rhinitis (33.6% vs. 18.6%), persistent mild rhinitis (2.1% vs.4.9%) and persistent

Table 1. The characteristics of the study group and its subgroups according to AR and NAR groups

	Total group (n=385)	NAR (n=102)	AR (n=283)	*p value
Age, year¶	11 (8-14)	10 (8-13.25)	11 (8-14)	0.321
Gender-male, n (%)	206 (53.5)	49 (48)	157 (55.5)	0.197
Breast milk intake	349 (90.6)	93 (91.2)	256 (90.5)	0.831
AD, n (%)	31 (8.1)	9 (8.8)	22 (7.8)	0.738
FA, n (%)	4 (1)	1 (1)	3 (1)	0.558
Asthma n (%)	22 (5.7)	3 (2.9)	19 (6.7)	0.159
OFS, n (%)	6 (1.6)	1 (1)	5 (1.8)	0.582
Obese-overweight	110 (28.6)	31 (30.4)	79 (27.9)	0.635
Rhinits, age at onset, year¶	6 (4-10)	6 (3-9)	6 (4-10)	0.225
Phenotypes (according to ARIA classification)				0.010
Intermittent mild	140 (36.4)	47 (46.1)	93 (33)	
Intermittent moderate-to-severe	114 (29.6)	19 (18.6)	95 (33.6)	
Persistent mild	11 (2.9)	5 (4.9)	6 (2.1)	
Persistent moderate-to-severe	120 (31.2)	31 (30.4)	89 (31.4)	
Laboratory values of patients				
Total IgE (kU/L)¶	201 (77-568)	64 (25.5-210)	256 (113-995)	0.002
Eosinophil (n)¶	250 (140-420)	170 (90-310)	280 (160-480)	<0.001
Neutrophil (n)¶	3785 (3042-5195)	4400 (3210-5790)	3740 (2951-4830)	0.249
Familial AR history, n (%)	110 (28.6)	21 (20.6)	89 (31.4)	0.037
Familial atopy history, n (%)	165 (42.9)	37 (36.3)	128 (45.2)	0.117

¶median, IQR (interquartile range); AR: Allergic rhinitis, NAR: Non-allergic rhinitis, FA: Food allergy, AD: Atopic dermatitis, OFS: Oral food syndrome, ARIA: Allergic rhinitis and its impact on asthma guidelines, *Chi-square test and Mann–Whitney U-test was used.

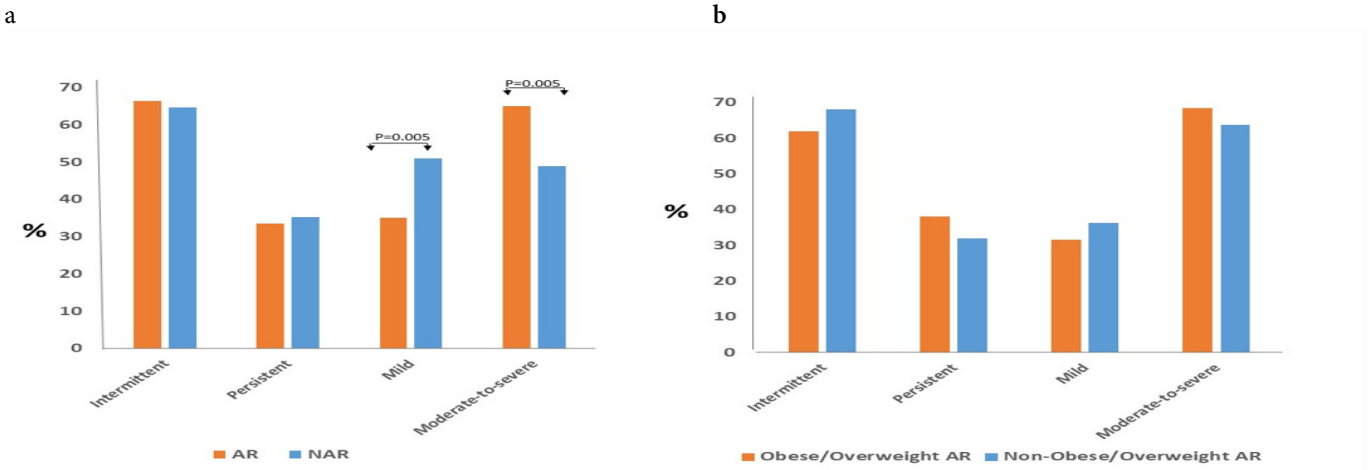

Figure 1. The comparison of severity and frequency of rhinits symptomps according to ARIA classification according to AR-NAR group (**1a**) and obese/overweight and non-obese/overweight group (**1b**)
ARIA: Allergic rhinitis and its impact on asthma guidelines, AR: Allergic rhinitis, NAR: Non-allergic rhinitis

moderate-to-severe rhinitis (31.4% vs.30.4%) were detected in AR and NAR groups, respectively (p=0.010) (Table 1).

When the symptoms of rhinitis were evaluated, nasal congestion 299 (77.7%), sneezing 289 (75.3%), and rhinorrhea 164 (42.6%) were more common symptoms in patients with rhinitis, respectively. Postnasal drip (30.4% vs. 18.4%), snoring-mouth breathing (12.7% vs. 5.3%) and adenoid hypertrophy (17.6% vs. 4.2%) were more frequent in the NAR group compared with the AR group, respectively (p=0.011, p=0.013 and p<0.001). Itchy eyes (27.6% vs.18.6%) were more frequent in the AR group compared with the NAR group (p=0.075) (Table 2).

Comparison of Patients between Obese/Overweight Group and Non-Obese/Overweight

79 (28%) obese/overweight patients were present in AR group. The age of onset of AR symptoms was lower in the obese/overweight group [6 years (IQR 3-8)] than non-obese/overweight group [7 years (IQR 4-10)] (p=0.081). Family history of atopy rate was higher (49%) in the non-obese/overweight group than obese/overweight group (35.4%) (p=0.040) (Table 3). The number of patients with moderate-to-severe rhinitis were 68.4% in obese/overweight group and 63.7% in the non-obese/overweight group. There was no statistical difference in severity and frequency of rhinits

Table 2. Allergic rhinitis symptoms of the study group and its subgroups

	Total group (n=385)	NAR (n=102)	AR (n=283)	p value	Obese/overweight AR group (n=79)	Non-obese/overweight AR group (n=204)	*p value
Nasal congestion, n (%)	299 (77.7)	78 (76.5)	221 (78)	0.736	61 (77.2)	160 (78.4)	0.824
Sneezing, n (%)	289 (75.3)	73 (71.6)	216 (76.3)	0.341	52 (67.1)	163 (80)	0.023
Rhinorrhea, n (%)	164 (42.6)	45 (44.1)	119 (42)	0.717	39 (49.4)	80 (39.2)	0.121
Cough, n (%)	130 (33.8)	34 (33.3)	96 (34)	0.914	32 (40.5)	64 (31.4)	0.145
Itchy nose, n (%)	116 (30.1)	31 (30.4)	85 (30)	0.946	22 (27.8)	63 (31)	0.617
Itchy eyes, n (%)	97 (25.2)	19 (18.6)	78 (27.6)	0.075	19 (24)	59 (29)	0.411
Watery eyes and redness in eyes, n (%)	96 (24.9)	21 (20.6)	75 (26.5)	0.237	16 (20.3)	59 (29)	0.138
Postnasal drip, n (%)	83 (21.6)	31 (30.4)	52 (18.4)	0.011	20 (25.3)	32 (15.7)	0.061
Snoring, mouth breathing, n (%)	28 (7.3)	13 (12.7)	15 (5.3)	0.013	6 (7.6)	29 (4.4)	0.284
Adenoid hypertrophy, n (%)	30 (7.8)	18 (17.6)	12 (4.2)	<0.001	2 (2.5)	10 (4.9)	0.375

* Chi-square test was used. AR: Allergic rhinitis, NAR: Non-allergic rhinitis

Table 3. The characteristics of the obese/overweight and non-obese/overweight groups

	Obese/overweight AR group (n=79)	Non-obese/overweight AR group (n=204)	*p value
Age, year¶	10 (8-12)	11 (8-14)	0.122
Gender-male, n (%)	42 (53.2)	115 (56.4)	0.626
Breast milk intake, n (%)	71 (89.9)	185 (90.7)	0.835
Height (cm)¶	142 (131-162)	145.5 (130-162)	0.809
Weight (kg)¶	48 (35-68)	39 (26-54)	<0.001
BMI (kg/m^2)¶	23.4 (21-25)	17.7 (15-19)	<0.001
AR, age at onset, year¶	6 (3-8)	7 (4-10)	0.081
Phenotypes (according to ARIA classification)			0.640
Intermittent mild	24 (30.4)	69 (33.8)	
Intermittent moderate-to-severe	25 (31.6)	70 (34.3)	
Persistent mild	1 (1.3)	5 (2.5)	
Persistent moderate-to-severe	29 (36.7)	60 (29.4)	
Familial AR history, n (%)	22 (27.8)	67 (32.8)	0.417
Familial atopy history, n (%)	28 (35.4)	100 (49)	0.040

¶median, IQR (interquartile range), AR: Allergic rhinitis, ARIA: Allergic rhinitis and its impact on asthma guidelines,* Chi-square test and Mann–Whitney U-test was used.

symptoms (Figure 1b). When the symptoms of rhinitis were evaluated, there was a higher frequency of sneezing (80% vs. 67%) in the non-obese/overweight group compared with the obese/overweight group. No statistically significant difference was observed in the number of other symptoms of rhinitis (Table 2).

Aeroallergen Sensitivity and Skin Prick Tests

SPTs were applied in the whole group with rhinits symptoms and the presence of aeroallergen sensitivity was shown in 283 (73.5%) patients. 61.3% of patients were sensitized to grass pollen, 54.5% to weed pollen, 31.2% to tree mix, 21% to cat, and 9.9% to house dust mite. There was no statistically significant difference in aeroallergen sensitivity between the obese/overweight group and the non-obese/overweight group. Figure 2 shows the aeroallergen sensitivities observed in the obese/overweight and non-obese/overweight groups.

Treatment

265 (68.8%) patients were treated with antihistamines and 43 (11.1%) of them had prolonged antihistamine treatment. 97(25%) were treated with nasal steroids. 132 (34.3%) patients received leukotriene receptor antagonist treatment. Leukotriene receptor antagonist treatment was found to be higher in the obese/overweight group (40.5%) than non-obese/overweight group (29.4%) (p=0.074). One patient received immunotherapy treatment due to severe AR symptoms. There was no statistical difference in the number of receiving all treatments between AR and NAR groups and obese/overweight group and non-obese/overweight groups.

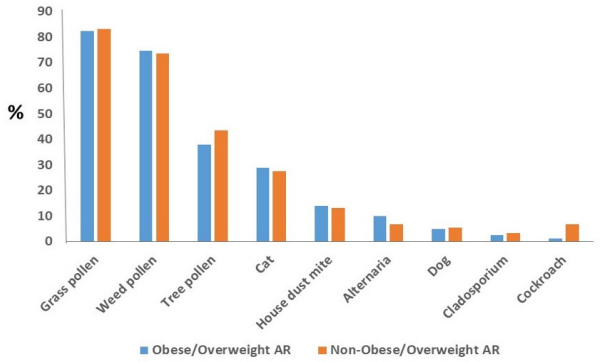

Figure 2. Distribution of aeroallergen sensitivities in obese/overweight group and non-obese/overweight group

DISCUSSION

AR and obesity are very common diseases and major public health problems worldwide. A link between obesity and increased risk of asthma has been observed.[5] However, the relationship between obesity and other atopic conditions such as AR is not clear. In this study, most of the patients presenting to our outpatient clinic with rhinitis symptoms were diagnosed with AR. Nasal congestion, sneezing and rhinorrhea were prevalent and these symptoms were detected at similar rates in both AR and NAR groups. Moderate-to-severe rhinitis was higher in the AR group than in the NAR group. Our findings indicated no significant difference in the frequency and severity of rhinitis symptoms between patients with and without obesity/overweight.

Only one in four to five patients with rhinitis referred to allergy clinics is diagnosed with NAR, but this estimation is biased due to the specific nature of referrals to such clinics. The prevalence of NAR is higher in the general population and accounts for approximately 50 per cent of all cases of rhinitis.[17] In our study, we detected 26.5% NAR in patients with rhinits. This can be related that the study was conducted in the allergy clinic as mentioned. A second reason may be that, non-allergic rhinitis (NAR) usually affects adults. In children the most frequent form of NAR is infectious rhinitis[18] in the present study, we eavulated the paediatric patients.

Differently from AR, atopy is not detected in NAR and patients with NAR have negative results for skin test reactivity, allergen specific IgE and nasal allergen challenges with allergen. Patients with NAR do not have symptoms triggered by contact with allergens.[18,19] In this study, we detected atopy in 75.5% patients with rhinitis. Male gender, birth in the pollen season, antibiotic treatment at an early age, maternal smoking, exposure to household allergens, high IgE levels (>100 IU/ml) before the age of six, detection of allergen-specific IgE and family history of atopy have been shown as risk factors for AR.[20,21] In this report, similarly, 55% of patients were male in AR group. Family history of AR rate, Total IgE level and eosinophil count were detected significantly higher in AR group than NAR group.

Most people with asthma have AR. We detected that 5.7% of patients had asthma in patients with rhinitis, although not statistically significant, the percentage of asthma was higher in the allergic individuals than non-allergic individuals. The incidence of AR significantly raises the probability of asthma: up to 40% of people with AR have or will have asthma.[22,23] The presence of AR complicates the control of asthma and is related to increased frequency of attacks and hospitalisation. Eriksson et al.[24] found that the prevalence of AR in asthmatic patients was 64% and the prevalence of asthma in patients with rhinitis was 20%. The frequency of oral allergy syndrome in patients with AR has been reported as 8.8%.[25] We found fewer OFS patients (1.8%) in the AR group compared to the literature.

Symptoms of NAR and AR are sometimes similar. Distribution symptoms of rhinitis were similar between subgroups in our study population and we found nasal congestion, sneezing, rhinorrhea were more common symptoms in patients. In a study involving 303 children with rhinitis, rinore and nasal congestion were found to be similar in AR and NAR patients. Nasal itching, sneezing and oculer findings were more common in patients with AR.[26] Adenoid hypertrophy, which is reported as one of the most common co-morbidities of AR, has been associated with the severity of AR.[27] We reported that adenoid hypertrophy was more frequent in the NAR group compared with the AR group.

In children, sensitisation begins as early as 4 years of age to aeroallergens (such as house dust mites, cat-dog allergens) that are constantly present in the indoor environment before the AR clinic develops and then develops against pollen and other inhalant allergens.[28] For this reason, SPTs were applied on patients aged 5-18 years with rhinitis symptoms in our study. Grass pollen sensitisation was the most common sensitisation. Cat and house dust mite sensitisation were common indoor allergens in our study. In our country, house dust mite is the most frequent indoor allergen and grass pollen is the most frequent outdoor allergen in aeroallergen sensitisation.[15]

In non-allergic patients, symptoms are usually perennial, sneezing and itchy nose are mild or absent. Patients complain of chronic nasal congestion and/or runny nose triggered by temperature and humidity, smell. Patients with AR have symptoms triggered by contact with allergens.[19,29] We reported that the number of patients with moderate-to-severe rhinitis were higher in the AR group compared to the NAR group. There was no difference in frequency of symptoms. A systematic search evaluated 171 studies and 33.843 patients to describe AR and NAR and found that symptoms were more severe in AR than NAR on Visual Analogue Scale (VAS) ($p<0.001$).[30]

A relationship between high BMI and AR has been hypothesised but has not been clearly demonstrated. Obesity is a risk factor for atopic allergic disorders in childhood. In this study, 28% of patients with AR were obese or overweight. We evaluated the severity and frequency of rhinitis symptoms in the AR group and found no statistically significant difference between obese/overweight group and Non-obese/overweight group. Previous reports have found that increased BMI is significantly associated with the occurrence of AR in childhood.[31-33] A meta-analysis of 30 observational reports showed a statistically significant association between obesity and the risk of AR in paediatric patients.[33] Previous studies supported that obese children with AR exhibit more severe clinical symptoms.[34]

Contrary to these studies, several reports show no significant difference or negative correlation between AR and obese paediatric patients.[35-37] Kusunoki et al.[36] investigated the relationship between obesity and several allergic conditions in children and reported a negative relationship between high BMI and allergic conjunctivitis and AR ($p<0.0001$), particularly in boys. Also on this subject, Sybilski et al.[35] found that overweight and obesity were associated with a reduced prevalence of AR in men. However, the influence of obesity/overweight on the prevalence of sensitization to aeroallergens was not observed. The relationship between AR and obesity is not yet well characterised and further comprehensive studies are needed.

Limitations

The primary limitation of this report is that the study was carried out in a single centre, which constitutes a limitation in terms of generalisability of the results. In addition, the lack of a healthy control group and the retrospective nature of the study were other limitations however in accordance with the purpose of the study, the severity and frequency of symptoms were compared between subgroups of study population.

CONCLUSION

In conclusion, AR and obesity may have a significant impact on physical, psychological and social aspects for both children and parents. Further studies on the relationship between obesity and AR may shed light on the etiology of the diseases and lead to new management options for AR.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approval for this retrospective study was obtained from the Scientific Studies Ethics Committee of Ankara Atatürk Sanatorium Training and Research Hospital (Date: 09.10.2024, Decision No: 2024-BÇEK/151).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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The relationship between nutritional parameters and pregnancy outcomes in abortus imminens

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ABSTRACT

Aims: Abortus imminens (AI) is defined as vaginal bleeding and/or pelvic pain before the 20th week of pregnancy. It affects approximately 20% of pregnancies. The HALP score, which integrates hemoglobin, albumin, lymphocyte, and platelet levels, is a marker of inflammation and nutritional status. This study investigates the association between the HALP score and AI and its potential role in predicting pregnancy outcomes.

Methods: This retrospective study was conducted at Ankara Etlik City Hospital between September 2022 and March 2024. A total of 254 patients with AI and 260 controls were included. Data on maternal demographics and laboratory parameters, including hemoglobin, albumin, lymphocyte, and platelet levels, were collected. Statistical analyses were performed using SPSS 22.0, with significance set at $p<0.05$.

Results: The HALP score was significantly higher in the AI group than in controls ($p=0.002$). However, no significant difference in HALP scores was observed between patients who experienced pregnancy loss and those who continued their pregnancies ($p=0.350$). Preterm birth, newborn intensive care unit admission, and respiratory distress were more frequent in AI cases.

Conclusion: The HALP score is a practical and cost-effective tool for diagnosing AI. Further studies are needed to explore its clinical utility.

Keywords: Abortus imminens, HALP score, nutrition, pregnancy outcomes

INTRODUCTION

Vaginal bleeding and/or pelvic pain that occur prior to the twentieth week of pregnancy are known as abortus imminens (AI).[1,2] It occurs more frequently in the first trimester of pregnancy and complicates about one fifth of all pregnancies.[3] Although not every patient followed up for AI experiences miscarriage, these patients may experience adverse obstetric outcomes such as premature birth, fetal death in utero, bleeding before birth and low birth weight in the later weeks of pregnancy.[4] The etiology includes maternal diseases (such as diabetes mellitus, kidney and thyroid diseases), malnutrition and underweight, maternal and fetal infections, cervical insufficiency, fetal anomalies and previous surgical interventions (such as chorionic villus sampling). A history of AI in a previous pregnancy, a low socio-economic class, older maternal age, smoking and alcohol consumption also increase the risk of AI.[5-8]

There is no optimal parameter that predicts the diagnosis and course of pregnancy in AI patients. For this goal, previous research has looked at serum amyloid A, serum thiol/disulfide, serum leptin levels, and a variety of inflammatory markers, including interleukin-2 (IL-2), IL-4, interferon-γ, and IL-13. However, these parameters were not examined as part of routine laboratory tests.[3,7,9-11] The HALP score was initially established in 2015 and is based on factors like hemoglobin, albumin, lymphocytes, and platelets.[12] The presence of nutrition-related parameters such as hemoglobin and albumin and inflammation-related parameters such as platelets and lymphocytes make this score an important indicator of both inflammation and nutrition.[12-14] The HALP score has emerged as one of the most significant predictors of death and morbidity in recent years, particularly in research involving cancer patients.[15-18] Furthermore, the HALP score is a cheap assessment that is simple to compute using standard laboratory measurements.

Predicting the pregnancy's trajectory and the likelihood of an abortion in patients with AI is crucial for patient education,

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management, and postpartum care. We aimed to assess the relationship between the HALP score, an immuno-nutritional score, and AI and ascertain whether it can aid in clinical treatment procedures, given that infections, malnutrition, and underweight are some of the factors that lead to AI.

METHODS

Between September 2022 and March 2024, this study was carried out retrospectively in the Perinatology Department of Ankara Etlik City Hospital, a tertiary facility to which patients were referred from various centers. The sample was divided into 2 groups: 254 patients with AI and 260 control patients. Ankara Etlik City Hospital Scientific Researches Evaluation and Ethics Committee authorised the study protocol (Date: 25.12.2024, Decision No: AESH-BADEK-2024-1142). The Declaration of Helsinki's guidelines were followed in the conduct of this study.

AI occurs when there is vaginal bleeding, a mean gestational sac diameter of more than 25 mm, a crown-rump length (CRL) of more than 7 mm, and an ultrasound showing a fetal heartbeat.[19] Patients with an AI diagnosis between weeks 8 and 12 of pregnancy were included in the study. Age and weeks of diagnosis were matched to create a control group. The starting day of the last menstrual cycle was used to calculate the gestational age of the patients who were part of the study. In patients whose last menstruation was unknown, the week determination was calculated using the CRL at ultrasound examination during hospitalization. Exclusion criteria included chronic maternal illness, medication use, smoking, alcohol consumption, presence of congenital anomalies, multiple pregnancies, patients whose information could not be reached or who had given birth at an external center. During the study period, 342 patients with a diagnosis of AI were interned in our clinic. Thirty-three patients suffered from long-term maternal conditions: twelve had hypothyroidism, eleven had type 2 diabetes, two had type 1 diabetes, two had chronic hypertension, two had mitral and tricuspid regurgitation, one had end-stage renal disease, one had systemic lupus erythematosus, one had major depression, and one had ankylosing spondylitis. Furthermore, 6 patients had multiple pregnancies (5 twin pregnancies and 1 triplet pregnancy), while 8 patients smoked. 41 patients were excluded because they were followed up at an external center. As a result, 254 patients remained in the research after 88 patients who met the exclusion criteria were removed (**Figure 1**). Our hospital's data network was used to evaluate the patients' medical records in the past; demographic information was noted, including height, weight, mother age, and parity. Maternal venous blood was used to test hemoglobin, monocyte, white blood cell (WBC) count, lymphocyte, neutrophil, monocyte, platelet, and albumin levels at the time of diagnosis. [Hemoglobin (g/L)×albumin (g/L)×lymphocytes (/L)]/platelets (/L) was the formula used to create the HALP score.[12,13]

Obstetric complications such as spontaneous abortion and missed abortion that occurred during pregnancy follow-up of the patients were recorded and followed up accordingly. Spontaneous abortion was defined as expulsion of fetal tissue weighing less than 500 grams or before the 20th week of gestation.[20] Missed abortion is defined as a pregnancy remaining in the uterus after the death of the embryo or fetus.[21] To reduce the risk of progesterone insufficiency, patients with a diagnosis of AI who were admitted to the hospital were given 200 mg of natural micronized progesterone orally or intravaginally twice a day in our clinic. Additionally, patients with a maternal blood group that is Rhesus negative (Rh-negative) were given anti-D immunoglobulin (anti-D). The type of delivery, birth weight, sex, APGAR 1/APGAR 5 score and all neonatal morbidities were recorded.

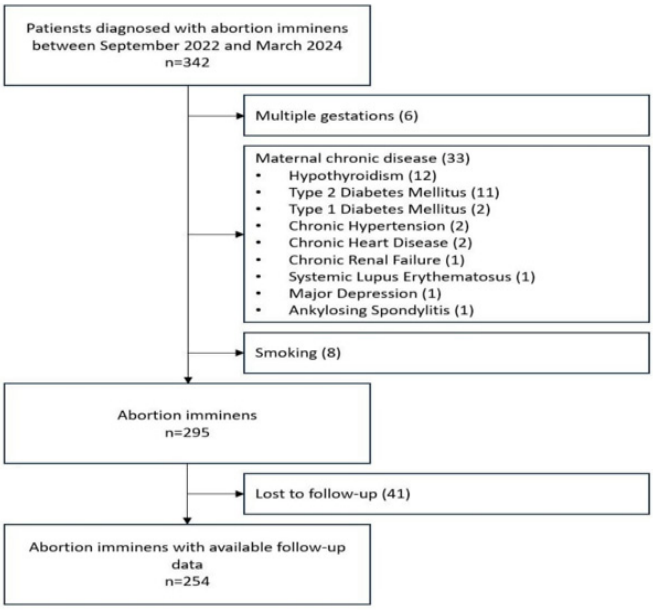

Figure 1. Flow chart

Statistical Analysis

IBM Corporation SPSS version 22.0 (IBM Corporation, Armonk, NY, USA) was used to conduct the statistical analysis. The conformance to the normal distribution was examined using the Kolmogorov-Smirnov test. For continuous variables having a normal distribution, descriptive statistics are displayed as "mean±standard deviation"; for those without, they are displayed as "median (interquartile range)". Fisher's-Exact test or the Chi-squared test were used to compare categorical variables. The Independent Sample T-test and the Mann-Whitney U test were used to compare continuous variables that were and were not regularly distributed. The best cutoff values were determined by calculating and comparing the areas under the curve (AUC) using a receiver operator characteristic (ROC) curve. For all tests, a p-value of less than 0.05 was considered statistically significant.

RESULTS

There were 260 controls and 254 patients with AI in this study. The demographic information for the two groups is displayed in **Table 1**. Both groups had comparable maternal ages, gravidities, parities, and nulliparities (p=0.574, p=0.418, p=0.379, and p=0.296, respectively). AI patients had a considerably lower body-mass index (BMI) than control patients (p<0.001). The median week of diagnosis of patients in the abortion imminens group was 9 weeks.

Table 1. Descriptive and comparative analysis of demographic data between abortus imminens and control groups

Parameter	Abortus imminens n=254 (49.4%)	Control n=260 (50.6%)	p
Age (y)	28.9±5.6	28.7±5.4	0.574[a]
Body-mass index (kg/m²)	28±5	29.6±5	<0.001[a]
Gravida	2 (2)	2 (2)	0.418[b]
Parity	1 (2)	1 (2)	0.379[b]
Nulliparous	129 (50.8%)	144 (55.4%)	0.296[c]

Values were given as mean±standard deviation, median (interquartile range), number (%). p<0.05 was considered statistically significant. a: Student t-test, b: Mann-Withney U, c: Chi-square

The laboratory results for the individuals who were part of the trial throughout the first trimester are displayed in **Table 2**. The HALP score was substantially higher in the abortion imminens group (p=0.002), standing at 37.9 (22.7) compared to 34.9 (14.5) in the control group. The AI group's hemoglobin levels were considerably greater than those of the control group (p=0.002). Patients with AI had reduced platelet and lymphocyte counts (p<0.001, p=0.007). WBC, neutrophil, monocyte, and albumin counts, among other laboratory indicators, were comparable in both groups (p=0.363, p=0.414, p=0.937, and p=0.106, respectively).

Table 2. Comparison of the patients groups' first trimester laboratory and HALP scores

	Abortus imminens n=254 (49.4%)	Control n=260 (50.6%)	p
HALP score	37.9 (22.7)	34.9 (14.5)	0.002[a]
Hemoglobin (g/dl)	12.7 (1.8)	12.4 (1.8)	0.002[a]
WBC count (10^9/L)	9.54 (3.13)	9.05 (3.11)	0.363[a]
Lymphocyte count (10^9/L)	1.93 (0.75)	2.17 (1.07)	<0.001[a]
Neutrophil count (10^9/L)	6.51 (2.89)	6.36 (2.74)	0.414[a]
Monocyte count (10^9/L)	0.59 (0.22)	0.59 (0.22)	0.937[a]
Platelet count (10^9/L)	250 (77)	271 (69)	0.007[a]
Albumin (g/L)	37.3 (3.4)	37.8 (8.8)	0.106[a]

HALP score: The hemoglobin, albumin, lymphocyte, and platelet score, WBC: White blood cell, a: Mann-Withney U test

The neonatal outcomes of the study participants are displayed in **Table 3**. 193 (76%) of the 254 patients with AI who were enrolled in the trial did not have an abortion. There were 61 patients (24%) who underwent an abortion. Of these, 41 (16.1%) were assessed as spontaneous abortions and 20 (7.9%) as missed abortions (**Figure 2**). The HALP score was 38.4 (23.2) in patients diagnosed with AI and subsequent abortion and 36.9 (25.1) in the group without abortion, and there was no significant difference between the two groups (p=0.350). In the AI patients, the results of the newborns were examined. Delivery occurred at earlier weeks and birth weight was lower compared to the control group (p<0.001 and p<0.001, respectively). In comparison to the control group, the AI group experienced significantly more preterm births, newborn intensive care unit (NICU) hospitalizations, respiratory distress syndrome (RDS), and continuous positive airway pressure (CPAP) (p=0.001, p<0.001, p<0.001, and p=0.003, respectively). Pregnancy termination way, gender, APGAR 1st min, APGAR 5th min, fetal distress, neonatal hypoglycemia, transient tachypnea of the newborn (TTN), mechanical ventilation, neonatal phototherapy, intraventricular hemorrhage, neonatal sepsis, neonatal seizures and necrotizing enterocolitis numbers were similar in both groups (p= 0.429, p= 0.606, p=0.909, p=0.544, p=0.322, p=0.492, p=0.168, p=0.055, p=0.662, p=0.426, p=0.426, p=0.426, p=0.426, respectively).

Table 3. Comparison of findings regarding newborn characteristics and labor

Parameter	Abortus imminens n=193 (42.6%)	Control n=260 (57.4%)	p
Gestational weeks at delivery	38 (2)	39 (2)	<0.001[a]
Pregnancy termination way			0.429[b]
Cesarean section	117 (60.6%)	148 (56.9%)	
Normal spontaneous vaginal birth	76 (39.4%)	112 (43.1%)	
Gender			0.606[b]
Female	94 (48.7%)	133 (51.2%)	
Male	99 (51.3%)	127 (48.8%)	
Fetal weight (gr)	2981 ± 612	3186 ± 506	<0.001[c]
1st min. APGAR	9 (1)	9 (1)	0.909[a]
5th min. APGAR	10 (1)	10 (0)	0.544[a]
Fetal distress	20 (10.4%)	20 (7.7%)	0.322[b]
Preterm birth	44 (22.8%)	30 (11.5%)	0.001[b]
Admission to neonatal intensive care unit	40 (20.7%)	23 (8.8%)	<0.001[b]
Neonatal hypoglycemia	16 (6.2%)	9 (4.7%)	0.492[b]
Transient tachypnea of the newborn	12 (6.2%)	9 (3.5%)	0.168[b]
Respiratory distress syndrome	20 (10.4%)	6 (2.3%)	<0.001[b]
Continues positive airway pressure	26 (13.5%)	14 (5.4%)	0.003[b]
Mechanical ventilation	10 (5.2%)	5 (1.9%)	0.055[b]
Phototherapy for neonates	13 (6.8%)	15 (5.8%)	0.662[b]
Intraventricular hemorrhage	1 (0.5%)	0 (0%)	0.426[d]
Neonatal sepsis	1 (0.5%)	0 (0%)	0.426[d]
Neonatal seizures	1 (0.5%)	0 (0%)	0.426[d]
Necrotizing enterocolitis	1 (0.5%)	0 (0%)	0.426[d]

[a]: Mann-Withney U test, [b]: Chi-square, [c]: Student t-test, [d]: Fisher's exact test

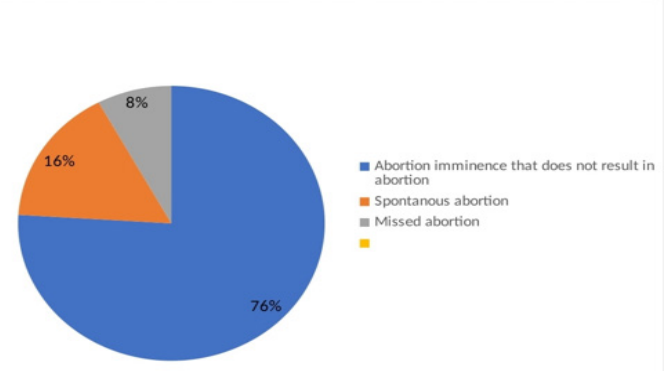

Figure 2. Outcomes of patients with abortus imminens

Table 4. Evaluation of HALP scrore in abortus imminens and control groups by ROC analysis

	LR+	Cut-off*	Sensitivity	Specificity	AUC	%95 CI	p
HALP score	1.24	>3.61	54.8%	55.9%	0.582	0.53–0.63	0.002

*Cut-off values were found according to Youden index. HALP score: The hemoglobin, albumin, lymphocyte, and platelet score, ROC: Receiver operator characteristic, LR+: Positive likelihood ratio, AUC: Area under the curve, CI: Confidence interval

The ROC analysis of the HALP score is displayed in **Table 4**. AI is diagnosed with a sensitivity of 54.8% and a specificity of 55.9% when the HALP score is greater than the cut-off value of 36.1 (AUC: 0.582, p=0.002). In **Figure 3**, the HALP score's ROC curve is displayed.

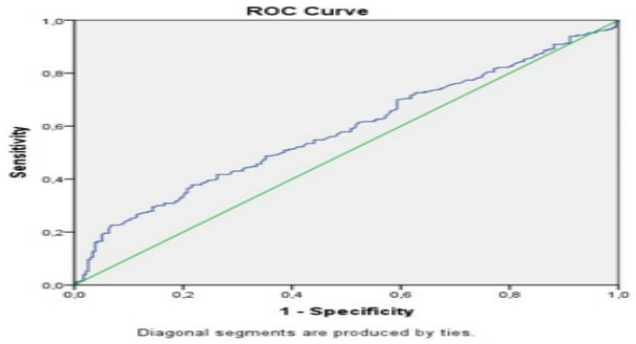

Figure 3. The ROC curve of HALP score
HALP score: The hemoglobin, albumin, lymphocyte, and platelet score, ROC: Receiver operator characteristic

DISCUSSION

This study investigated the relationship between AI diagnosis and pregnancy outcome and the HALP score. It was discovered that the AI group's HALP score was noticeably greater than the control group's. An AI is diagnosed with a sensitivity of 54.8% and a specificity of 55.9% when the HALP score is more than 36.1 (AUC: 0.582, p=0.002). In this study, the AI group had a lower gestational age and birth weight, but a greater preterm birth rate, NICU hospitalization, RDS, and CPAP. In the AI group, the HALP score no correlation with abortion rates or adverse perinatal outcomes. Additionally, this is the only study that we are aware of that looks into the relationship between AI patients and the HALP score.

Although the etiology of AI is multifactorial, one of the most emphasized causes is inflammation. Soysal et al.[20] have investigated the connection between AI and the inflammation-related systemic immune inflammatory index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio. During follow-up, it was discovered that AI patients had a considerably higher systemic immune inflammation index, which was linked to abortion.[20] Antiapolipoprotein A-1, which can be associated with inflammation, was also studied in AI patients by Vecchié et al.[22] and was found to be high in AI patients. Fetal development is influenced by the nutritional state of the mother. Negative obstetric outcomes are closely linked to malnutrition, a complicated condition marked by low protein stores, insufficient caloric intake, and a compromised immune system.[23] Hemoglobin and albumin are the parameters most commonly used in the clinic to determine the nutritional status of patients. Low albumin and anemia are associated in the literature with increased mortality and morbidity, especially in cancer patients.[12,24,25] Platelet count, lymphocyte count, hemoglobin and albumin levels are all part of the HALP score, a nutritional inflammation index that was initially established in 2015 in patients with stomach cancer.[12] Investigations on the relationship between the HALP score and the severity of the condition in patients with pre-eclampsia revealed that the HALP score increased significantly with pre-eclampsia severity.[26] The connection between AI and HALP becomes even more significant when one takes into account the roles that inflammation and diet play in the genesis of AI. The HALP score in our investigation indicated a substantial difference in AI diagnosis.

One common obstetric problem that can be linked to abortions is bleeding during the first trimester of pregnancy. Studies have shown that 14% to 50% of patients with AI who present with vaginal bleeding have had a abortions.[27,28] In our study, the number of patients who had an abortion was 61 (24%). We also compared the HALP scores between these patients and those whose pregnancies were continued. The HALP score was 38.4 (23.2) in the patients who were diagnosed with AI and subsequently had an abortion, and 36.9 (25.1) in the group who did not have an abortion, with no significant difference between the two groups. This situation may be due to the multifactorial etiology of AI as well as the patient's current intake of oral iron supplements, physiologic vascular changes in pregnancy, dehydration due to malnutrition, or changes in laboratory parameters measured from maternal blood, depending on the severity of the patient's bleeding.

In a study that compiled 14 articles, Saraswat et al.[29] assessed perinatal mortality and morbidity in AI patients. They showed that AI patients had lower APGAR ratings, a higher risk of NICU admissions, and a higher rate of preterm birth and low birth weight. Similarly, in their study, Özdemirci et al.[30] discovered that AI patients had a higher rate of low birth weight and premature birth. In our study, lower gestational age and birth weight as well as higher preterm birth, NICU admission, RDS and CPAP rates were found in the data of patients interned due to AI. However, no association was found between adverse perinatal outcomes and the HALP score. This situation can be explained by the multifactorial etiology of AI, but shows that more parameters should be evaluated together when predicting pregnancy outcomes.

Limitations

The retrospective design of our study and the limited number of patients make it difficult to evaluate the cause-effect relationship. Although chronic diseases and drug use, which would increase the effects on maternity, were not among the exclusion criteria, we may not have been able to exclude all factors that could affect hemoglobin, platelet, lymphocyte, and albumin levels. In addition, the fact that the data come from a single center limits the generalizability of the results, and the change in these parameters over time could not be taken into account. Prospective studies with a larger number

of patients could more clearly show the impact of the HALP score on assisted reproduction and obstetric outcomes.

CONCLUSION

The affordability and ease of calculation of the HALP score using routine laboratory parameters enhance its potential applicability in clinical practice. As a cost-effective and accessible tool, it may serve as a supplementary marker in evaluating patients with AI. According to our research, while the HALP score demonstrates some diagnostic value in AI, its predictive capacity for adverse pregnancy outcomes remains limited. This highlights the need for a more comprehensive approach in assessing pregnancy prognosis in AI patients.

Although the HALP score was significantly higher in the AI group compared to controls, no significant association was found between HALP levels and pregnancy loss or adverse neonatal outcomes. This suggests that while inflammation and nutritional status play a role in the pathophysiology of AI, the HALP score alone may not be sufficient to predict pregnancy trajectory.

Future research should also explore the interaction between HALP and other emerging biomarkers to develop more accurate predictive models for pregnancy outcomes in AI. Investigating HALP's potential role in different AI subgroups, such as those with recurrent pregnancy loss, autoimmune conditions, or infections, could yield valuable clinical insights. Furthermore, assessing the impact of targeted nutritional or anti-inflammatory interventions on HALP levels and pregnancy outcomes may provide evidence for novel therapeutic approaches.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ankara Etlik City Hospital Scientific Researches Evaluation and Ethics Committee authorised the study protocol (Date: 25.12.2024, Decision No: AESH-BADEK-2024-1142).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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The cerebro-placental-uterine ratio in predicting adverse perinatal outcomes in gestational diabetes: a prospective cohort study

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ABSTRACT

Aims: The primary aim of the study was to evaluate Doppler parameters focusing on fetal cerebral and placental circulation in gestational diabetes mellitus (GDM) and to investigate their relationship with maternal glycemic profiles.

Methods: A prospective cohort study was conducted involving 52 pregnant women diagnosed with GDM and 55 control participants. Doppler ultrasonography was performed between 34 and 37 weeks of gestation to evaluate key fetal hemodynamic parameters, including the umbilical artery (UA) systolic/diastolic (S/D) ratio, UA pulsatility index (PI), middle cerebral artery (MCA) S/D ratio and PI, uterine artery S/D ratio and PI, cerebro-placental ratio (CPR), and cerebro-placental uterine ratio (CPUR). Statistical analyses were performed to compare Doppler parameters between groups and to evaluate their predictive value for adverse perinatal outcomes.

Results: Both the MCA PI (p=0.019) and MCA S/D (p=0.011) differed significantly between the GDM and control groups. The median MCA PI was 1.60 in the GDM group and 1.46 in the control group. No statistically significant differences were observed in other parameters, including UA PI, CPR, or CPUR. A positive correlation was found between the CPUR and the second-hour 100-gram oral glucose tolerance test (OGTT) result (r=0.375; p=0.022). However, none of the Doppler parameters reliably predicted adverse perinatal outcomes.

Conclusion: The st udy found that fetal Doppler parameters were significantly associated only with MCA S/D and MCA PI. Perinatal outcomes were not correlated with UA, CPR, or CPUR. A positive correlation was observed between CPUR and the second-hour glucose value from the 100 g OGTT.

Keywords: Cerebroplacental-uterine ratio, cerebroplacental ratio, doppler parameters, gestational diabetes

INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most prevalent endocrinological conditions during pregnancy.[1] GDM is associated with several fetal complications, including macrosomia, birth trauma, and intrauterine growth restriction, as well as maternal complications, particularly an increased rate of operative deliveries.[2-4] Therefore, early diagnosis and close monitoring of GDM are crucial. The oral glucose tolerance test (OGTT) is still the gold standard for diagnosing GDM, despite clinicians' efforts to take preventative measures by trying to identify the condition in the first trimester.[5] Consequently, several international pregnancy organizations, including the International Association of Diabetes and Pregnancy Study Groups (IADPSG) and the World Health Organization (WHO), recommend screening pregnant women using a one- or two-step OGTT.[6]

Studies have demonstrated that Doppler ultrasound performed in pregnant women can effectively indicate adverse fetal conditions.[7] The cerebroplacental ratio (CPR), calculated by dividing the fetal middle cerebral artery (MCA) pulsatility index (PI) by the umbilical artery (UA) PI, is commonly used alongside UA Doppler evaluation to identify fetuses at risk for unfavorable perinatal outcomes.[8] It has been demonstrated that the Doppler parameter most strongly associated with placental insufficiency in intrauterine growth retardation is the cerebro-placental uterine ratio (CPUR), which is the ratio of CPR to uterine artery PI.[9] Pregnant women with GDM are believed to have higher plasma viscosity than those without the condition due to elevated blood glucose levels. This results in increased blood flow resistance and reduced flow rates, which can impair blood perfusion.[10] During pregnancy, placental villi rely on interstitial perfusion to eliminate metabolic waste products and deliver essential nutrients for

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placental growth.[11] Maternal arterial blood perfusion is the primary source of interstitial perfusion for the placental villi. Decreased placental blood perfusion due to GDM may result in inadequate fetal nutrient uptake and impair fetal development. Under unfavorable conditions in pregnant women with GDM, increased uterine and UA resistance and decreased MCA resistance are expected.

The use of color Doppler ultrasound to determine arterial hemodynamic parameters in pregnant women may serve to detect abnormal perfusion of the placenta in a timely manner and effectively predict the outcome of pregnancy. This study aimed to investigate the potential role of CPUR as a novel Doppler parameter reflecting dysregulated blood glucose levels in pregnant women with GDM. Additionally, we sought to evaluate its predictive capacity for adverse perinatal outcomes and its utility in fetal well-being assessment.

METHODS

Between April 2022 and December 2022, this prospective cohort study was conducted at the Perinatology Clinic of Etlik Zübeyde Hanım Gynecology and Obstetrics Training and Research Hospital. The study was conducted with the permission of Etlik Zübeyde Hanım Gynaecology and Obstetrics Training and Research Hospital Clinical Practice Ethics Committee (Date: 31/03/2022, Decision No: 2022/37). The study was conducted in compliance with the Declaration of Helsinki, and all patients provided their informed consent for the Doppler examination after being made aware of the research study design.

Pregnant women between 34 and 37 weeks of gestation underwent obstetric examinations. 52 pregnant women with a GDM diagnosis and 55 control pregnant women without a GDM diagnosis were involved in the study. The two-step IADPSG criteria served as the basis for the GDM diagnosis. Based on these standards, all pregnant women between 24 and 28 weeks of gestation underwent a 50-g OGTT without first undergoing a fasting blood glucose test. Unless the initial value was already diagnostic for GDM (>200 mg/dl), women whose blood glucose levels reached 140 mg/dl or above in the first hour were then given a 100-g OGTT.[13] Gestational diabetes was identified in patients who met two of the Carpenter and Coustan criteria.[14,15] At first, diet control was used to treat these people. Insulin therapy was started if, after two weeks of monitoring fasting and postprandial blood glucose levels, there was no improvement. Thus, the study covered both diet-controlled and insulin-controlled diabetes. The study excluded participants with multiple pregnancies, intrauterine growth restriction, fetal abnormalities, and other systemic disorders (such as hypertension, diabetes mellitus, and cardiovascular diseases).

The study and control groups' Doppler parameters were compared, and any discrepancies between them were investigated. Then, a subgroup analysis was performed on GDM patients, dividing them into those who were on a diet only and those who required insulin, and the groups were evaluated in terms of Doppler parameters. The ability of these measures to forecast worse perinatal outcomes in the group with gestational diabetes was evaluated as a secondary result. The occurrence of at least one poor event, such as a 5-minute APGAR score less than 7, admission to the newborn intensive care unit (NICU), umbilical cord blood pH less than 7.2, or perinatal mortality, was referred to as composite adverse perinatal outcomes (CAPO). The ratio of the MCA PI to the UA PI was used to determine the CPR. By dividing the CPR by the uterine artery PI, CPUR values were determined. At an angle of less than thirty degrees, MCA PI values were obtained from the proximal one-third of the arteries that emerged from the Circle of Willis. In the absence of fetal respiration, the UA's free loop was used to calculate the PI. At least three successive waveforms were averaged to record Doppler readings. CPR or CPUR data were recorded but not shared with the team before delivery to avoid compromising follow-up and delivery procedures. Neonatal outcomes were documented in the patient records. Pregnancy outcomes, delivery method, birth weight, and adverse perinatal outcomes were also assessed.

Statistical Analysis

All data were entered, cleaned, organized, and analyzed using IBM SPSS version 25 (IBM Corp.), USA. The Shapiro-Wilk test was used to assess the normality of data distribution. For normally distributed variables, independent Samples t-tests were performed, and data were presented as mean±standard deviation (mean±SD). For non-normally distributed variables, the median (Q1-Q3) was used, and group comparisons were conducted using the Mann-Whitney U test. The link between continuous parameters that followed the normal distribution was examined using Pearson's correlation coefficient, while values that did not were examined using Spearman's correlation coefficient. The threshold value for differentiating between the GDM and control groups was determined using the ROC analysis. A significant threshold of $p<0.050$ was established. The sample size was determined using a power analysis based on earlier research by Perez Martin et al.[16] The effect size and α-value were found to be 0.6957011 and 0.05, respectively, using the independent-samples t test; with 92 participants, the power (1-β) was computed to be 0.95. It was determined that 46 patients in each group would be sufficient to reach this power. We assume that our study's power is higher because our sample size is larger than these numbers.

RESULTS

This study included 107 pregnant women in total. There were fifty-two patients in the study group and fifty-five in the control group. The pregnant women who took part in the study had a median age of 29 (25-35). The BMI readings ranged from 27 to 35 kg/m^2, with 29 being the median. **Table 1** compares the clinical features of the two groups. Accordingly, there was no significant difference between the two groups in BMI, gestational week of examination, smoking, neonatal birth weight, cesarean section (C/S) birth rates, and APGAR scores. While the median week of birth score in the GDM group was 38, it was 39 in the control group ($p=0.020$). As anticipated, the study group's 50g OGTT readings increased statistically significantly ($p<0.001$). The groups' median values for the MCA S/D and MCA PI parameters differed statistically significantly ($p=0.011$, $p=0.019$). The control group's median MCA PI parameter value was 1.46, whereas the GDM group's was 1.60 (**Table 2**). The distributions of the other parameters

Table 1. Clinical and disease characteristics of patients and control group

	Study group n=52	Control group n=55	p
Age (years) median (Q1-Q3)	32 (27-38)	27 (25-32)	<0.001*
Gravida median (Q1-Q3)	3 (2-4)	1 (1-3)	<0.001*
Body-mass index (kg/m²) median (Q1-Q3)	32 (27-37)	29 (27-32)	0.031*
Smoking	3 (5.9%)	2 (3.6%)	0.670‡
Gestational week at examination median (Q1-Q3)	36 (34-36)	36 (35-36)	0.296*
50 g-OGTT results (mg/dl) median (Q1-Q3)	156 (147-183)	109 (94-115)	<0.001*
Weight during pregnancy (kg) median (Q1-Q3)	10 (6-12)	15 (10-18)	<0.001*
Gestational age at delivery median (Q1-Q3)	38 (37-39)	39 (38-39)	0.020*
Neonatal birthweight (grams) mean±SD	3175.06±458.38	3216.81±452.9	0.638†
Cesarean delivery (n, %)	45 (68.6%)	33 (60.0%)	0.511‡
APGAR 1. minute median (Q1-Q3)	9 (9-9)	9 (9-9)	0.771*
APGAR 5. minute median (Q1-Q3)	10 (10-10)	10 (10-10)	0.394*
Neonatal intensive care unit admission (n, %)	13 (25.5%)	8(14.5%)	0.243‡
Perinatal death	0	0	NA
CAPO	14 (26%)	9 (16%)	0.183

SD: Standard deviation, Q1-Q3: "First quartile - third quartile, OGTT: Oral glucose tolerance test, CAPO: Composite adverse perinatal outcome, *Mann-Whitney U test ; † Independent Two Sample-t test; ‡: Chi-square test

Table 2. Comparison of Doppler parameters in study groups

	Study group n=52	Control group n=55	p
Umbilical S/D median (Q1-Q3)	2.36 (2.14-2.71)	2.18 (2.09-2.66)	0.073
Umbİlical PI median (Q1-Q3)	0.86 (0.77-0.96)	0.79 (0.71-0.94)	0.139
MCA S/D median (Q1-Q3)	4.62 (3.81-6.09)	4.00 (3.27-5.00)	0.011
MCA PI median (Q1-Q3)	1.60 (1.40-1.84)	1.46 (1.22-1.69)	0.019
Uterine S/D median (Q1-Q3)	1.91 (1.69-2.50)	1.98 (1.57- 2.40)	0.676
Uterine PI median (Q1-Q3)	0.70 (0.57-1.04)	0.80 (0.50-1.02)	0.978
CPR median (Q1-Q3)	1.90 (1.54-2.19)	1.62 (1.46-2.16)	0.152
CPUR median (Q1-Q3)	2.45 (1.65-3.65)	2.32 (1.57- 3.43)	0.667

S/D: Systolic/diastolic, PI: Pulsatility index, CPR: Cerebro-placental ratio, CPUR: Cerebro-placental-uterine ratio

by group did not differ statistically significantly (p>0.050). Table 3 displays if there is a correlation between CPUR values and clinical features. The OGTT value of the second hour (100 g) and the CPUR among the parameters under study thus only showed a slight, statistically significant positive connection (r=0.342; p=0.017). The CPUR parameter and other parameters did not show any statistically significant correlation (p>0.050). The CPR parameter and other parameters did not exhibit a statistically significant connection (p>0.050). Neither CRP nor CPUR had any significant cut-off values that could be used to identify the GDM group (CRP: AUC=0.580, p=0.156; CPUR: AUC=0.524, p=0.669). Table 4 shows that neither CRP nor CPUR had any significant cut-off values to differentiate CAPO (CRP: AUC=0.521, p=0.777; CPUR: AUC=0.532, p=0.620). Other than uterine artery S/D and uterine PI (p=0.001, p=0.007), subgroup analysis between insulin users and those with diet-regulated GDM revealed no significant differences (Table 5).

Table 3. Examining the relationship between CPR and CPUR parameters and quantitative parameters

	CPR		CPUR	
	r	p	r†	p†
Birthweight (gr)	0.149†	0.126†	0.064	0.510
50 gr OGTT hour	-0.042†	0.670†	-0.045	0.647
100g OGTT (FBG)	0.071†	0.630†	-0.080	0.589
100 gr OGTT (1. hour)	0.094†	0.523†	0.023	0.876
100 gr OGTT (2. hour)	0.166†	0.260†	0.342	0.017
OGTT (3. hour)	-0.111*	0.475*	-0.132	0.395

*Pearson correlation coefficient; †Spearman's correlation coefficient, CPR: Cerebro-placental ratio, CPUR: Cerebro-placental-uterine ratio, OGTT: Oral glucose tolerance, FBG: Fasting blood glucose

DISCUSSION

This study highlights the importance of fetal Doppler parameters in predicting pregnancy outcomes in women diagnosed with GDM, providing new insights into their potential prognostic value. The only fetal Doppler parameter that was statistically different between the two groups of patients (with and without GDM) was the MCA PI. Perinatal outcomes showed no correlation with UA, CPR, CPUR. However, a positive correlation was observed between CPUR and the 100-g OGTT value.

In perinatal practice, UA Doppler is commonly used to assess downstream circulatory impedance (i.e. flow resistance).[17] Unlike systemic arteries, the umbilical vasculature lacks innervation. Instead, vasoactive substances regulate the contractile mechanism of the UA.[18] End diastolic velocity decreases and Doppler indices rise with pregnancy issues such fetal growth retardation and preeclampsia, which are

Table 4. ROC analysis results in distinguishing study and control groups and composite adverse perinatal outcomes

	Cut-off	Sensitivity	Specificity	AUC	p	Analysis type
CPR	>1.61	75	49	0.580	0.156	GDM & control groups
CPUR	>1.15	92	20	0.524	0.669	GDM & control groups
CPR	>1.82	57	56	0.521	0.774	CAPO
CPUR	>1.49	87	25	0.532	0.270	CAPO

ROC: Receiver operator characteristic, CPR: Cerebro-placental ratio, CPUR: Cerebro-placental-uterine ratio, CAPO: Composite adverse perinatal outcome, GDM: Gestational diabetes mellitus

Table 5. Comparison of Doppler indices between DRGDM and IRGDM groups

	DRGDM (n=34)	IRGDM (n=18)	p
Umbilical S/D median (Q1-Q3)	2.38 (2.12-2.80)	2.38 (2.23-2.68)	0.939
Umbilical PI median (Q1-Q3)	0.87 (0.78-1.03)	0.88 (0.77-0.92)	0.780
MCA S/D median (Q1-Q3)	4.87 (3.74-6.13)	4.56 (4.19-5.94)	0.962
MCA PI median (Q1-Q3)	1.68 (1.44-1.90)	1.60 (1.27-1.70)	0.204
Uterine S/D median (Q1-Q3)	2.12 (1.90-2.97)	1.71 (1.47-1.90)	0.001
Uterine PI median (Q1-Q3)	0.801 (0.65-1.11)	0.63 (0.49-0.70)	0.007
CPR median (Q1-Q3)	1.94 (1.70-2.18)	1.78 (1.32-2.28)	0.519
CPUR median (Q1-Q3)	2.27 (1.49-2.91)	2.56 (1.93-4.72)	0.098

DRGDM: Diet-regulated gestational diabetes mellitus, IRGDM: Insulin- regulated gestational diabetes mellitus, S/D: Systolic/diastolic, PI: Pulsatility index, CPR: Cerebro-placental ratio, CPUR: Cerebro-placental-uterine ratio

marked by increased resistance in the fetoplacental vascular bed.[19] Doppler indices are used for fetal monitoring on the basis of this. But as the weeks of pregnancy go by, end-diastolic velocity rises, which is in line with the gradual reduction in fetoplacental blood flow impedance brought on by fetal and placental vascular and hemodynamic alterations.[20] This is demonstrated by the steady decline in PI and the systolic/diastolic (S/D) ratio over the course of pregnancy. When fetal growth restriction (FGR) and/or hypertension complicate a pregnancy, UA Doppler testing is especially helpful. For these pregnancies, Doppler ultrasonography is advised as the main monitoring method.[21,22] Doppler examination reveals the cardiovascular response of the fetus to progressive hypoxia and acidosis and helps distinguish small but structurally normal fetuses from those compromised by placental insufficiency. In general, a Doppler index for gestational age> of 95% should not be considered reassuring. Low CPR indicates redistribution of fetal blood flow (brain protective). Several thresholds for CPR have been proposed to predict an unfavorable outcome (<1, <1.05, ≤1.08).[23] In the PORTO study, which included singleton pregnancies with FGR, the rate of serious neonatal outcomes with low CPR (<1) was 18 percent (27 of 146) versus 2 percent (14 of 735).[24] However, fetuses of mothers with GDM exhibit expanded placental vasculature, increased UA diameter, and aberrant Wharton's jelly, leading to a reduction in the connective tissue component. As a result, there is a notable reduction in flow impedance in the UA and UA PI.[25] These results may support the following hypothesis: CPR as a ratio between MCA and UA PI is not predictive of perinatal outcome, which is due to the possible influence of GDM on birth. On the other hand, regular assessment of CPR or MCA in a low-risk cohort with a minimal occurrence of adverse outcomes is not advisable, as it would result in a significant number of false-negative and false-positive findings, consequently leading to an escalation of unnecessary and potentially detrimental interventions.[23] A meta-analysis has demonstrated that CPR is associated with adverse perinatal outcomes in pregnancies complicated by GDM. However, the same study emphasized that CPR should not be considered a universal screening tool for pregnancy complications.[26]

The literature suggests that Doppler indices can predict high-risk pregnancies and their fetuses that are small for their age, especially with regard to maternal hypertensive states.[27] However, there are confounding results on Doppler indices of pregnant women with GDM who fall into the high-risk category and are diagnosed and treated without placental insufficiency. Therefore, Doppler ultrasound measurements are important for an accurate understanding of the existing literature regarding prognostic accuracy and prediction of adverse perinatal outcomes due to GDM.

The optimal timing of delivery in GDM remains a matter of debate. Prolonging pregnancy beyond 38 weeks may increase the risk of shoulder dystocia, while its impact on cesarean delivery rates remains unclear.[28] WHO recommends that patients in whom GDM is the only abnormality should be delivered by 41 weeks of gestation. However, fetal well-being testing is recommended by physicians for this procedure.[29] The clinical outcomes of our investigation contribute to the evaluation of fetal well-being at term in high-risk pregnancies. This study also investigated the CPUR value for GDM among Doppler indices. Previous studies have shown that CPUR score at >40+0 weeks is predictive of adverse perinatal outcomes and invasive deliveries in low-risk pregnancies.[30] In a study evaluated along with GDM, some Doppler parameter was found to be associated with high blood glucose.[16] However, the extent to which CPUR can be used to optimize labor management needs further investigation in prospective interventional studies.

Limitations

One of limitations was although our study has a sample size higher than the minimum required to achieve a power of 0.95, further studies with larger cohorts may help to more robustly confirm the validity of our findings. However, the association between MCA PI was statistically significant even in a small cohort. The benefit is limited in patients with

GDM when it comes to making decisions about timing and mode of delivery. Further evaluation of the use of Doppler in pregnancies complicated by diabetes mellitus requires the use of standardized protocols.

CONCLUSION

This study investigated the impact of fetal Doppler parameters on pregnancy outcomes in women with GDM. The findings revealed that MCA PI was the only Doppler parameter that significantly differed between GDM and control groups. No correlation was observed between perinatal outcomes and other Doppler indices, including UA, CPR, and CPUR. However, CPUR was positively correlated with the second-hour 100-g OGTT result. While Doppler ultrasound is a valuable tool for monitoring high-risk pregnancies, its application in GDM should be approached with caution. Further research is needed to better understand the influence of GDM on fetal Doppler indices and refine clinical decision-making in this population.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of Etlik Zübeyde Hanım Gynaecology and Obstetrics Training and Research Hospital Clinical Practice Ethics Committee (Date: 31/03/2022, Decision No: 2022/37).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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High versus low dialysate sodium: a single-center small-scale prospective study

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ABSTRACT

Aims: The matter of dialysate sodium concentration has become progressively substantial in the last 50 years, when dialysis modalities have advanced quickly. In many studies, it has been established that dialysate sodium value is correlated with blood pressure alternance, hypervolemia, interdialytic weight gain (IDWG), and chronic inflammation. However, there is no clear knowledge about its direct effect on inflammation. In this study, we profited from high-sensitivity C-reactive protein (hs-CRP), which is a helpful marker, to survey the inflammation correlation with dialysate sodium (DNa).

Methods: 109 non-diabetic hemodialysis patients were enrolled in the study. All patients participating in the study were new onset, less than 6 months dialysis patients and met Kt/V of 1.4 at minimum criteria.

Results: They were divided into two groups: group 1, low dialysate sodium (137 mmol/L) and group 2, conventional dialysate sodium (140 mmol/L) and followed-up for two months. During the follow-up period, serum hs-CRP levels were measured and categorized as baseline, 1st month and second month level.

Conclusion: As a result, no statistically remarkable disparity between the groups were determined in terms of serum hs-CRP levels at baseline, 1st month, and 2nd month of the study ($p>0.05$). We did not establish any significant differences that would make it worth ignoring some symptoms symptoms such as cramps and hypotension.

Keywords: Chronic kidney disease, hemodialysis, dialysate sodium, chronic inflammation, high-sensitivity CRP

INTRODUCTION

The most critical function of the kidneys is to maintain homeostasis. They exert this by supplying acid-base, water, sodium, and other electrolyte equilibrium, and by removing toxins meanwhile. The kidneys are in charge of the generation of vital enzymes and hormones. One of the tools used to provide hemostasis is a hemodialysis device for chronic kidney end stage patients.

While preserving a relatively stable plasma concentration, the dialysis machine takes out the sodium and water assembled over the interdialytic break. The major exogenous source of sodium is dietary, and the minor source could be dialysate sodium. DNa formulas have developed over the past 50 years. Higher dialysate sodium concentrations take the lead of hemodynamic stabilization and diminish intradialytic findings but aggravate thirst and unavoidable volume expansion of course. On the contrary, lower DNa may cause less thirst and this provides more controlled weight gain but unfortunately it concludes with a greater hemodynamic instability. Observational data recommend that the correlation between dialysate sodium and consequences may vary according to serum sodium levels, sustaining the individuality of dialysate sodium.[1]

In chronic kidney disease (CKD) patients, uremia triggered chronic systemic inflammation, and this led to the 10-to 20-fold higher mortality than that in the healthy people.[2,3] Inflammation is highly common in HD patients and undesirable outcomes such as malnutrition, anemia, accelerated vascular disease occur consequently.[4,5]

Conventional factors such as diabetes, hypertension, sedentary lifestyle, lipid disorder and hyperhomocysteinemia, hyperparathyroidism, volume overload are significant causes of inflammation. In recent research, fluid overload has been related with an inflammatory reaction.[6] Takahashi's study demonstrated that monocyte IL-6 mRNA deliverance and augmentation of IL-6 levels are associated with volume overload in hemodialysis and peritoneal dialysis patients.

This can also be clarified by the hypervolemia that brighten inflammation by the translocation of endotoxins from the edematous intestinal loops; however, previous studies have argued that salt itself may incite T_H17 immunity in vivo through effects on the gut microbiota.[7] The decrease of dialysate sodium from 140 to 137 mEq/L was came along with a prominent amelioration in endothelial injury, hemodynamics, and oxidative state.[8,9]

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Therefore, in the last 50 years, dialysate sodium prescriptions have been tried to be continuously improved. However, the deficiency of randomized controlled clinical trial data in this area has embarrassed the improvement of open clinical guidelines regarding the ideal touch for dialysate sodium prescription.

It is unclear whether low sodium in dialysis fluid make better overall health and well-being for people on hemodialysis, since there is an interference of probably helpful and distorted effects, and available research studies were not designed to learn about impacts of the intervention on the heart or on overall patient health.[10]

With this intention, we conducted a prospective controlled study in our hemodialysis clinic via serum hs-CRP measurement and observed the effects of both conventional dialysate and low sodium dialysate on chronic inflammation. In this study, we aimed to determine the optimum DNa value to decrease inflammation considering current information.

METHODS

The study was conducted with the permission of the Ethics Committee of University of Health Sciences Trabzon Kanuni Training and Research Hospital (Date: 17.02.2017, Decision No: 23618724-000-2294). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this prospective controlled research, our goal is to investigate whether or not lower dialysate sodium decreases inflammatory status of the body. 109 hemodialysis patients were enrolled in University of Health Sciences Kanuni Training and Research Hospital between May-July 2017. The exclusion criteria were using of hemodiafiltration for HD, being under 18 years, having active or chronic inflammatory diseases, diabetes, hypertension and more than 3 times per week hemodialysis frequency. In addition, none of the participants were taking any medications that could play a role in sodium metabolism.

All patients were in dialysis with arteriovenous fistula less than 6 months and met Kt/V of 1.4 at minimum criteria. The ratio Kt/V (K is patient clearance, t dialysis time, V urea space) was calculated by Kt/V dialysis dose Daugirdas formula based on standard bicarbonate 4 hours dialysis session. (KtV Daugirdas=-ln ((BUNPost/BUNPre)-(0.008*hour))+((4 -(3.5*BUNPost/BUNPre))*UFVol/weight).

Pre-dialytic body temperatures were also measured in every dialysis session and temperature outside of 36.5-37.5 degrees were excluded.

The primary endpoint was determined as feeling of thirst or xerostomia, dietary sodium intake, cramping and intradialytic hypotension. Patients were randomly allocated into two groups: group 1, low dialysate sodium (137 mmol/L), and group 2, conventional dialysate sodium (140 mmol/L) and followed up for 2 months. The study groups were not blinded. After the patients were divided into two groups, serum hs-CRP levels were measured at the beginning of the study and at the 1st and 2nd month of dialysis therapy.

Statistical Analysis

The main outcome was serum hs-CRP level, which was measured with a human high-sensitivity protein Elisa Kit. Statistical analysis program was the NCSS 2007.

RESULTS

According to groups, there was no statistically important distinction between the ages (p>0.05). The rate of female cases in group 2 was higher than that of male cases (p=0.010; p<0.05) (**Table 1**).

In group 1, there was not any remarkable difference of hs-CRP level at the 1st and 2nd month compared to the beginning of the treatment (p>0.05) (**Table 2**).

In group 2, we found the similar result. Hs-CRP levels did not indicate any prominent variation during the study period. (p>0.05) (**Table 2**).

But most importantly, we could not determine any considerable difference between the groups in terms of hs-CRP (p>0.05) (**Table 3, Figure**).

During the study, intervention did not augment the episodes of cramping and intradialytic hypotension.

DISCUSSION

By affecting 10–16% of the population, CKD is a progressively widespread condition admitted as a public health priority.[11] In accordance with diverse investigations, more than 50% of patients with CKD Stage 3 or higher possess high CRP level.[12,13]

Chronic inflammation in CKD owns multiple etiologic factors such as dialysis membranes, catheters, uremic toxins, sodium, and fluid overload. Chronic and persistent inflammation is thought to contribute to atherosclerosis, osteoporosis, diabetes, cancer, and depression in CKD. Therefore, uncontrolled inflammatory response is an important preventable parameter in these patients. However, the effect of DNa on chronic inflammation remains controversial.

When dialysis began in the 1940s, Willem Kolff adjust the DNa concentration to 126.5 mEq/L.[14]

By the 1960s, most dialysis center chose to set DNa to 130 mEq/L.[15] During the 1970s and 1980s DNa concentrations were thus augmented further to optimize intradialytic BP stability. By the 1980s, DNa concentration had been 135 mEq/L generally.[16]

A decade later, DNa had increased to 140 mEq/L which is the most common concentration today.[17]

We have already known that higher DNa prescription could cause significantly higher interdialytic weight gain (IDWG). Additionally, a low dialysate sodium was recommended for better control of chronic inflammation because of its advantageous effect on IDWG and volume overload control.[18]

It is certain that low DNa decreases IDWG and might support to improve endothelial damage and inflammation implicitly. But meanwhile low DNa can also increase the incidence of hypotensive episodes and muscle cramps.[19]

Table 1. Evaluation of demographic characteristics by groups

		Groups			Test values
		Total	**Group 1 (n=56)**	**Group 2 (n=53)**	**p**
Age (year)	Min-max-(median)	24-88 (65)	24-88 (63)	31-81 (66)	t:-0.559
	Averages±SD	61.94±13.13	61.25±14.09	62.66±12,12	[a]0.577
		n (%)	**n (%)**	**n (%)**	
Gender	Female	46 (42.2)	17 (30.4)	29 (54.7)	χ^2:6.624
	Male	63 (57.8)	39 (69.6)	24 (45.3)	[b]0.010*

[a]Student-t test, [b]Pearson Chi-square test, *p<0.05

Table 2. Evaluation of hsCRP measurements by groups at the beginning ,1st and 2nd month

		Groups			Test value
		Total	**Group 1 (n=56)**	**Group 2 (n=53)**	**[c]p**
Beginning hs-CRP	Min-max (median)	0.03-13.22 (0.50)	0.03-13.22 (0.56)	0.03-6.36 (0.46)	Z:-0.467
	Averages±SD	1.11±1.85	1.25±2.22	0.96±1.36	0.641
1. month hs-CRP	Min-max (median)	0.05-11.49 (0.67)	0.05-11.49 (0.51)	0.09-5.30 (0.80)	Z:-0.785
	Averages±SD	1.30±1.82	1.41±2.24	1.18±1.24	0.432
2. month hs-CRP	Min-max (median)	0.02-10.95 (0.66)	0.06-10.95 (0.61)	0.02-10.43 (0.75)	Z:-0.840
	Averages±SD	1.43±2.04	1.40±2.13	1.47±1.96	0.401
Test value		χ^2:3.323	χ^2:0.893	χ^2:3.438	
	[d]p	0.190	0.640	0.179	
Beginning-1. month	Difference	0.20±2.13	0.17±2.56	0.23±1.57	Z:-1.012
	[c]p	0.099	0.912	0.135	0.311
Beginning-2. month	Difference	0.33±2.30	0.15±2.52	0.52±2.04	Z:-0.176
	[c]p	0.072	0.366	0.297	0.860
1.-2. month	Difference	0.13±1.92	-0.02±1.89	0.29±1.96	Z:-0.443
	[c]p	1.000	1.000	1.000	0.658

[c]Mann-Whitney U test, [d]Friedman test, *p<0.05, [c]Bonferroni Correctedi Wilcoxon signed ranks test, 00000, hs-CRP: High-sensitivity C-reactive protein

Table 3. Beginning, 1st and 2nd month of hsCRP measurement evaluation according to groups

		Groups			Test value
		Total	**Group 1 (n=56)**	**Group 2 (n=53)**	**[c]p**
Beginning hs-CRP	Normal (0-5)	103 (94.5)	52 (92.9)	51 (96.2)	χ^2: 0.594
	High (≥5.1)	6 (5.5)	4 (7.1)	2 (3.8)	[f]0.679
1st hs-CRP	Normal	104 (95.4)	52 (92.9)	52 (98.1)	χ^2:1.719
	High	5 (4.6)	4 (7.1)	1 (1.9)	[f]0.364
2nd hs-CRP	Normal	103 (94.5)	52 (92.9)	51 (96.2)	χ^2:0.594
	High	6 (5.5)	4 (7.1)	2 (3.8)	[f]0.679

[f]Fisher's Exact test, hs-CRP: High-sensitivity C-reactive protein

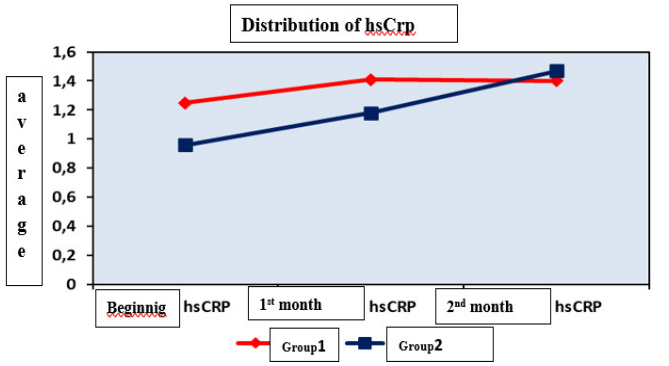

Figure. Distribution of hs-CRP
hs-CRP: High-sensitivity C-reactive protein

Mc Causland et al.[1] examined 2.272 patients from Satellite Healthcare and found that higher DNa concentrations (>140 mEq/L fixed or modeled vs. ≤140 mEq/L) were associated with greater mortality.

Hecking et al.[27] pointed that among all patients, higher DNa concentrations were not correlated with greater mortality but were associated with a lower risk of hospitalization (HR=0.97 per 2 mEq/L higher dialysate sodium, 95% CI 0.95–1.00, p=0.04). It is also reported that the risk of all-cause hospitalizations and hospitalizations due to fluid overload decreased by 3 and 6% per 2 mmol/L increase in DNa (hazard

ratio 0.97; 95% confidence interval 0.95–1.00, and hazard ratio 0.94; 95% confidence interval 0.84–1.05, respectively).[20]

In another study, it is suggested lowered dialysate sodium levels for patients treated with both angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) because of the dual blockade of the renin-angiotensin system affects sodium balance.[21]

Several observational studies have demonstrated that lower DNa is related with less thirst[22,23], lower IDWG, lower ECF volume[24], and lower BP[25,26]; however, we could not discover research for elucidating its relationship with chronic inflammation in the literature.

But these beneficials results came along with disadvantageous of intradialytic symptoms such as hypotension and cramping.

The risk of mortality has been shown to be lower in patients with a dialysate sodium prescription >140 mEq/L (HR, 0.95 per 1 mEq/L higher; 95% CI, 0.93-0.97). However, the lower mortality observed in the adjusted analyzes in patients with dialyzed serum sodium levels <137 mEq/L versus dialysate sodium prescriptions >140 mEq/L is intriguing.[27]

In the late 1990s, CRP was accepted as a strong predictor of cardiovascular decease and entire mortality in HD and PD patients. Conventional assays for CRP are not sufficient sensitive to survey lower serum values associated with the inflammatory process. Therefore, the newer hs-CRP assays were started to use to measure serum CRP below 0.1 mg/L.

Hs-CRP may be utile for prognosticating coming mortality. In hemodialysis patients with a history of coronary artery disease, higher troponin levels were associated with higher mortality than in those without coronary disease. In patients without a history of coronary artery disease, hs-CRP levels >3 mg/L were associated with significantly higher mortality.[28]

In this present study we determined that the change in the DNa value of our patients with low-dose dialysate did not detect any statistically meaningful alteration in the serum hs-CRP values of the patients compared to the conventional dialysate. CRP is chosen as an inflammatory marker because it is more practical and reliable marker than other inflammatory indicators in clinical practice due to its relative consistency in serum, ease of acquisition, and appropriateness of the international standard.

Limitations

We could not find any evidence that the DNa value may have an accurate influence on chronic inflammation in dialysis patients, independent of volume status, and a result to support low dialysate sodium hemodialysis in chronic hemodialysis patients with high exposure to chronic inflammation due to many factors, and any benefits that allow at the expense of hypotension, cramping, and thirst. The weaknesses of the study are the low number of patients, the short follow-up period, and the fact that the patients were not followed up for a sufficient period of time in terms of comorbid diseases, since only patients who had been on hemodialysis for the last 3 months were included in the study.

CONCLUSION

In the light of this study, we suggest that the preference between the low and conventional dialysate sodium should be more related to the clinical consequences which may develop during or after dialysis session than its effect on chronic inflammation.

But we need further studies with larger patient populations and longer follow-up periods on the importance of dialysate sodium value in terms of chronic inflammation before saying the last word.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Ethics Committee of University of Health Sciences Trabzon Kanuni Training and Research Hospital (Date: 17.02.2017, Decision No: 23618724-000-2294).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Perceptions of child abuse and neglect among nurses: an investigation in family health centers

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ABSTRACT

Aims: This study aims to examine the perceptions of nurses working in family health centers regarding child abuse and neglect, their involvement in reporting processes, and the challenges they encounter.

Methods: A cross-sectional descriptive study was conducted with 157 nurses working in family health centers. Data were collected through face-to-face interviews using a descriptive information form, the nurses' diagnosis of child abuse and neglect symptoms and risks scale (NCAN-RS), and the healthcare provider attitudes toward child maltreatment reporting scale (CMRS). The data were analyzed using descriptive statistics, correlation analyses, and multiple correspondence analysis.

Results: The findings revealed that 56.1% of the nurses had received prior training on child abuse and neglect, but only 37.5% found the training sufficient. A significant proportion (96.2%) had never reported a child abuse case. Awareness of child rights organizations was also limited, with only 37.6% of participants able to specify an institution. Nurses who received training, were aware of child rights organizations, and acknowledged the legal obligation to report abuse had significantly higher scores on the CMRS and NCAN-RS scales ($p<0.05$). The lack of institutional support negatively influenced reporting behaviors.

Conclusion: Although nurses play a critical role in identifying and reporting child abuse and neglect, gaps in education, institutional support, and awareness persist. Strengthening training programs, enhancing institutional support, and raising awareness about legal responsibilities may contribute to improved reporting behaviors among healthcare professionals.

Keywords: Child abuse, child neglect, nurses, mandatory reporting, primary health care

INTRODUCTION

Child abuse and neglect is a serious public health issue that affects all societies and can have lasting negative consequences for individuals. It manifests in physical, sexual, emotional, or economic forms of neglect or exploitation, all of which can harm a child's health, development, and dignity.[1,2] In 2023, 11.8% of the 217.000 children referred to security units in Turkey were victims of sexual crimes.[3] International reviews and meta-analyses indicate that 18–20% of girls and 8–10% of boys experience sexual abuse during childhood.[4,5] These statistics highlight the alarming prevalence of sexual offenses against children and underscore the need for effective measures to reduce these numbers in the coming years.

Nurses working with children play a critical role in ensuring their safety. Their responsibilities include preventing abuse, providing early intervention, and addressing the physical and psychosocial needs of victimized children.[6] Pediatric and child health nurses intervene in cases of abuse and neglect by directly engaging with children and families or referring them to child protection services.[7] As one of the primary professional groups working with children at risk of abuse and neglect, nurses represent the largest group among healthcare professionals[6] Consequently, healthcare professionals play a key role in the early detection of child abuse and neglect cases and in reporting them to the relevant authorities.[8]

This study aims to assess the knowledge levels of nurses working in family health centers regarding child abuse and neglect, their involvement in reporting processes, and the challenges they encounter. While previous studies have mainly focused on healthcare professionals in hospital settings, this research addresses nurses in primary healthcare services, filling a significant gap in literature. By examining the impact of nurses' education levels, institutional support, and awareness of legal responsibilities on reporting behaviors, this study seeks to identify barriers to reporting child abuse and propose improvements. The findings are expected to contribute to the development of training programs for healthcare professionals and the strengthening of child protection mechanisms.

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METHODS

Ethics

This study was approved by Van Yüzüncü Yıl University Non-interventional Ethics Committee (Date: 08.03.2024, Decision No: 2024/03-29). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Design

This study was conducted as a cross-sectional descriptive study.

Sample and Population

The study aimed to include all 187 nurses working in family health centers; however, it was conducted with the 157 nurses who agreed to participate. The sample was selected using a convenience sampling method, including nurses who met the inclusion criteria and voluntarily participated in the study.

Place and Time

The study was conducted through face-to-face interviews with nurses working in family health centers in a province between May 1, 2024, and October 31, 2024.

Inclusion Criteria

- Nurses working in FHCs
- Communicative nurses who accept voluntary participation in the study

Exclusion Criteria

- Nurses who did not accept voluntary participation

Data Collection Tools

Descriptive information form, and nurses' diagnosis of child abuse and neglect symptoms and risks scale and healthcare provider attitudes toward child maltreatment reporting scale were used as data collection tools. Data were collected by face-to-face interviews with nurses and self-report method.

Descriptive Information Form

To assess socio-demographic characteristics—including age, gender, educational status, marital status, number of children, employment duration, and prior education on child abuse and neglect—a 20-question form was administered. This form was developed based on a review of the literature.[7,9]

Nurses' Diagnosis of Child Abuse and Neglect Symptoms and Risks Scale (NCAN-RS)

The scale, developed by Uysal (1998), consists of 67 items and six sub-dimensions: physical symptoms, behavioral symptoms, neglect symptoms, parent characteristics, child characteristics, and familial characteristics. A higher mean score indicates a greater level of knowledge in the respective area. In Uysal's[10] study, the scale demonstrated high reliability, with a Cronbach's alpha coefficient of 0.92. In this study, the overall reliability coefficient of the scale is 0.84.

Healthcare Provider Attitudes Toward Child Maltreatment Reporting Scale (CMRS)

The Turkish validity and reliability study of the scale was conducted by Turan.[11] The scale consists of 19 items and two sub-dimensions: reporting responsibility and reporting concerns. It is evaluated using a 5-point Likert scale.[11] In the present study, the overall reliability coefficient of the scale was found to be 0.84.

Statistical Analysis

The study data were analyzed using SPSS 26 statistical software. Descriptive statistics, including mean, standard deviation, percentage, and minimum-maximum values, were calculated. Normality distribution was assessed using kurtosis and skewness values. Student's t-test was used to compare two groups when assumptions were met, while the Mann-Whitney U test was applied when assumptions were not met. For multiple group comparisons, one-way ANOVA was used, and the Kruskal-Wallis H test was applied when assumptions were violated. Pearson and Spearman correlation analyses were performed, and effect size was evaluated using eta-square (η^2). Multiple correspondence analysis (MCA) was conducted to examine relationships between categorical variables. A significance level of $p<0.05$ was considered statistically significant.

RESULTS

The majority of the nurses were between 26 and 32 years of age (54.8%), female (77.7%), and married (61.8%). More than half (56.1%) had received training on child abuse, with 72.7% of this training provided as in-service education. However, only 37.5% found the training to be sufficient. A significant proportion (96.2%) stated that they had never reported a case of child abuse. While 57.3% claimed to know the institutions responsible for children's rights, only 37.6% could name one. The percentage of those who acknowledged a legal obligation to report abuse was 29.9%, whereas 70.1% believed they had no such duty. Regarding barriers to reporting, cultural structure (29.9%) was cited as the most significant factor, followed by lack of awareness (26.8%) and insufficient education (24.8%). Among the challenges influencing reporting behavior, lack of institutional support (33.1%) and workload pressure (20.4%) were prominent. When asked about reporting in the absence of concrete evidence, 45.9% stated they would do so, while 46.5% expressed hesitation (**Table 1**).

In the study, the mean score of the CMRS scale was 72.6±7, with a minimum of 59 and a maximum of 87, and its reliability coefficient was 0.846. The sub-dimensions reporting responsibility (35.9±4.9, α=0.772) and reporting concerns (36.7±3.5, α=0.896) were identified. The total mean score of the NCAN-RS was 223.1±24.2 (α=0.843), with an average item score of 3.3±0.4. Correlation analyses revealed a strong positive correlation between CMRS and reporting responsibility (r=0.888), reporting concerns (r=0.763), and NCAN-RS (r=0.511) ($p<0.001$). Additionally, there was a moderate correlation between reporting responsibility and reporting concerns (r=0.379) and NCAN-RS (r=0.428), while

Table 1. Descriptive findings on sociodemographic characteristics and child abuse (n=157)

Variables	Categories	n	%
Age	18-25	26	16.6
	26-32	86	54.8
	33-39	28	17.8
	40 years and over	17	10.8
Marital status	Single	60	38.2
	Married	97	61.8
Gender	Female	122	77.7
	Male	35	22.3
Number of children	One	36	22.9
	Two or more	35	22.3
	No child	86	54.8
Years of working in the profession	1-5	60	38.2
	6-10	47	29.9
	11-15	29	18.5
	16 years or more	21	13.4
Previous training on child abuse and neglect	Yes	88	56.1
	No	69	43.9
Place of training	In-service trainings	64	72.7
	Environment*	18	20.5
	School, social media-TV	6	6.8
Adequacy of the training received	Sufficient	33	37.5
	Not sufficient	26	29.5
	Partially	29	33.0
Previous reporting of child abuse and/or neglect	Yes	6	3.8
	No	151	96.2
Being aware of institutions and organizations related to children's rights	Yes	90	57.3
	No	67	42.7
Specifying institutions and organizations for children's rights	At least one institution specified	59	37.6
	Did not specify any institution	98	62.4
Reason for not being aware of institutions and organizations for children's rights	Lack of training	27	40.3
	Lack of awareness	40	59.7
Status of reporting child abuse by law	Obligation to notify	47	29.9
	No obligation to notify	110	70.1
The reason why the recorded data on abuse and neglect incidents is lower than the estimated rate	Cultural structure	47	29.9
	Lack of awareness	42	26.8
	Lack of training	39	24.8
	All	29	18.5
Does the lack of support from the organizational (hospital) culture prevent reporting possible abuse?	Yes	52	33.1
	No	105	66.9
Do you think that child abuse cases can be solved without the involvement of child services?	Yes	14	8.9
	No	143	91.1
Do workload pressures discourage reporting child abuse?	Yes	32	20.4
	No	125	79.6
Should cases of child abuse and neglect be reported even if the evidence is uncertain?	Yes	72	45.9
	No	12	7.6
	Hesitating	73	46.5

a strong correlation was observed between reporting concerns and NCAN-RS (p<0.001, **Table 2**).

In the study, no significant differences were found between age, gender, marital status, number of children, years of professional experience, or place of education and the CMRS and NCAN-RS scores (p>0.05). However, individuals who received training had higher scale scores, with a large effect observed in reporting responsibility and CMRS (η^2=0.16-0.19), and a moderate effect observed in the other scales (p<0.05). Additionally, those who were aware of child rights institutions had higher scores (p<0.05). The scores of those who accepted the legal obligation to report were significantly higher (η^2=0.20-0.23). Lack of corporate culture support negatively affected reporting behavior (η^2=0.08-0.09). Furthermore, the scores of those who stated they would report abuse even in the absence of concrete evidence were the highest (η^2=0.09-0.27, **Table 3**).

Multiple correspondence analysis was conducted for the variables "receiving training on child abuse and neglect before", "being aware of institutions and organizations for children's rights", "specifying institutions and organizations for children's rights", "reporting child abuse by law", "lack of support from the hospital culture preventing reporting possible abuse", and "reporting child abuse and neglect cases even if evidence is uncertain", which were found to be correlated with both CMRS and NCAN-RS (**Table 4**).

According to the results of the Multiple Correspondence Analysis, a two-dimensional model was created. The first dimension includes variables A, B, C, F, G, and H, while the second dimension includes variables D and E. The eigenvalue of the first dimension was 3.056, explaining 44.7% of the total variance, while the eigenvalue of the second dimension was 1.375, explaining 16.4% of the total variance. Together, these two dimensions explain 61.1% of the total variance. In the first dimension, the variables "previous training on child abuse and neglect" (0.651), "reporting child abuse by law" (0.58), and "reporting child abuse even if evidence is uncertain" (0.472) were found to have high discriminative power. In the second dimension, the variables "being aware of institutions and organizations for children's rights" (0.517) and "specifying institutions and organizations for children's rights" (0.492) also had high discriminative power. These findings suggest that the first dimension represents awareness and reporting behaviors related to child abuse and neglect, while the second dimension highlights the level of awareness of children's rights and knowledge of relevant institutions (**Table 4**).

Variables A, B, C, F, G, and H tend to cluster around the first dimension (on the X-axis), while variables D and E cluster around the second dimension (on the Y-axis). In the first dimension, the variables with high discriminative power are "receiving training on child abuse and neglect before (C)" (0.651), "reporting child abuse by law (F)" (0.58), and "reporting child abuse and neglect cases even if evidence is uncertain (H)" (0.472). In the second dimension, the variables with high discriminative power are "being aware of institutions and organizations for children's rights" (0.517) and "specifying institutions and organizations for children's rights" (0.492). These variables reflect the participants' awareness of public institutions and organizations addressing child abuse (**Figure 1**).

Figure 2 illustrates the multiple fit analysis, visualized according to the categories that represent the sub-dimensions of the variables. Fields 2 and 3 correspond to the categories of the variables associated with the first dimension, while Fields 1 and 4 correspond to those related to the second dimension. Participants who scored above the average on the CMRS and NCAN-RS scales are located in Field 2 (X=+1, Y=+1). This group includes individuals who have received training on child abuse and neglect, those who are aware of the legal obligation to report child abuse, those who believe that hospital culture does not hinder reporting behavior, and those who would report child abuse even in the absence of definitive evidence. Conversely, participants who scored below the average on the CMRS and NCAN-RS scales are positioned in Field 3 (X=-1, Y=-1). This group consists of individuals who have not received training, those who believe there is no legal obligation to report child abuse, those who perceive a lack of hospital support as a barrier to reporting, and those who are hesitant to report suspected child abuse. Participants who are aware of institutions and organizations advocating for children's rights and can identify them are situated in Field 4 (X=+1, Y=-1), whereas those who lack such awareness and cannot specify these institutions are placed in Field 1 (X=-1, Y=+1). This analysis effectively highlights the relationship between participants' scale scores and the distribution of the variables.

DISCUSSION

In this study, CMRS results indicated that healthcare professionals' awareness levels were generally moderate. Metinyurt et al.[12] reported that while healthcare professionals exhibited higher awareness in recognizing behavioral symptoms of child neglect and abuse, they had deficiencies

Table 2. Results of the scales and correlation between scales

	$\bar{X}$±SD	Min-max	Median (mode)	(α)	Reporting responsibility*	Concerns related to reporting*	NCAN-RS
CMRS	72.6±7	59-87	72(77)	0.846	r:0.888**	r:0.763**	r:0.511**
Reporting responsibility*	35.9±4.9	22-46	36(35)	0.772		r:0.379**	r:0.428**
Concerns related to reporting*	36.7±3.5	29-44	37(36)	0.896			r:0.425**
NCAN-RS	223.1±24.2	160-261	226(260)	0.843			
NCAN-RS (Mean)	3.3±0.4	2.4-3.9	3.4(3.9)				

$\bar{X}$±SD: Mean±standard deviation, Min-max: Smallest-Greatest value, Median (mode): Most repeated value, α: Cronbach's alpha reliability coefficient, r: Pearson correlation coefficient (parametric correlation) *CMRS sub-dimensions, **p<0.001

Table 3. Results related to the comparison of the scale and its sub-dimensions according to independent variables

	Reporting responsibility		Concerns related to reporting		CMRS		NCAN-RS	
	$\bar{X}$±SD	Statistics	$\bar{X}$±SD	Statistics	$\bar{X}$±SD	Statistics	$\bar{X}$±SD	Statistics
Age								
18-25	35.2±3.7	F:1.318	36.6±3.3	F:0.04	71.8±5.8	F:0.74	3.3±0.4	F:1.061
26-32	36.4±4.8	p:0.271	36.8±3.5	p:0.989	73.2±7	p:0.53	3.4±0.3	p:0.367
33-39	34.5±5.2		36.7±3.3		71.2±6.6		3.2±0.4	
40 years and over	36.4±6		36.6±4.2		73.1±9.2		3.3±0.4	
Marital status								
Single	35.9±4.4	KW:0.3	36.8±3.7	KW:2.12	72.7±6.4	KW:1.03	3.4±0.3	KW:0.26
Married	35.8±5.1	p:0.861	36.6±3.3	p:0.346	72.4±7.2	p:0.597	3.3±0.4	p:0.877
Divorced	37.7±7.8		40±4		77.7±11		3.3±0.2	
Gender								
Female	35.8±5	t:-0.31	36.9±3.4	t:0.722	72.6±7.2	t:0.142	3.3±0.4	t:-0.702
Male	36.1±4.3	p:0.757	36.4±3.7	p:0.472	72.5±6.4	p:0.887	3.4±0.3	p:0.484
Number of children								
One	36.9±4.4	KW:1.49	37.1±3	KW:1.01	74±6.2	KW:1.91	3.4±0.3	KW:0.14
Two or more	35.6±6.2	p:0.475	37±3.9	p:0.601	72.5±8.5	p:0.383	3.3±0.4	p:0.929
No child	35.6±4.4		36.5±3.5		72.1±6.6		3.3±0.4	
Years of working in the profession								
1-5	36±4.3	F:0.469	36.8±3.7	F:0.76	72.8±6.7	F:0.817	3.4±0.4	F:0.649
6-10	35.8±4.6	p:0.704	36.5±3.2	p:0.518	72.3±6.6	p:0.487	3.3±0.3	p:0.585
11-15	36.5±5.5		37.4±3.2		73.9±7		3.4±0.4	
16 years or more	34.9±6		36±3.8		70.9±8.4		3.3±0.5	
Previous training on child abuse and neglect								
Yes	37.6±4.6	t:5.478	37.7±3.4	t:3.997	75.3±6.6	t:5.99	3.4±0.3	t:3.685
No	33.7±4.4	p:0.000*	35.6±3.2	p:0.000*	69.2±5.8	p:0.000*	3.2±0.4	p:0.000*
		r:-.387* η^2:0.16		r:-.300* η^2:0.09		r:-.418* η^2:0.19		r:-.235* η^2:0.08
Place of training								
School	37.3±3.7	F:0.781	37.3±3.3	F:0.407	74.6±6.2	F:0.219	3.5±0.3	F:0.591
Media-Environment	39.8±3.7	p:0.461	36.8±4.1	p:0.667	76.7±3.6	p:0.804	3.5±0.3	p:0.556
In-service trainings	37.5±4.8		37.9±3.4		75.3±7		3.4±0.3	
Adequacy of the training received								
Sufficient	35.2±4.4	KW:1.13	35.9±3.9	KW:4.80	71.1±7.2	KW:2.61	3.3±0.4	KW:1.50
Not sufficient	36±4.8	p:0.568	37.6±3	p:0.09	73.6±6.4	p:0.271	3.4±0.3	p:0.472
Partially	36.2±6.1		36.9±2.9		73.1±7.6		3.3±0.4	
Previous reporting of child abuse and/or neglect								
Yes	38.7±5.9	U:325.5	38±3.5	U:365	76.7±9	U:325	3.6±0.2	U:207.5
No	35.7±4.8	p:0.25	36.7±3.5	p:0.429	72.4±6.9	p:0.249	3.3±0.4	p:0.025*
								r:-.180* η^2:0.03
Being aware of institutions and organizations related to children's rights								
Yes	36.6±4.8	t:2.374	37.2±3.5	t:2.015	73.9±7.2	t:2.68	3.4±0.3	t:2.092
No	34.8±4.7	p:0.019*	36.1±3.4	p:0.046*	70.9±6.4	p:0.008*	3.3±0.4	p:0.038*
		r:-.148 η^2:0.03		r:-.155 η^2:0.02		r:-.172* η^2:0.04		r:-.149 η^2:0.02
Specifying institutions and organizations for children's rights								
At least one institution specified	37.5±4.9	t:3.364	37.7±3.3	t:2.866	75.2±7	t:3.829	3.4±0.3	t:0.762
Did not specify any institution	34.9±4.6	p:0.001	36.1±3.4	p:0.005	71±6.5	p:0.000	3.3±0.4	p:0.815
		r:-.241* η^2:0.16		r:-.228* η^2:0.09		r:-.267* η^2:0.19		

Table continued...

Table 3. Results related to the comparison of the scale and its sub-dimensions according to independent variables (continued)								
Reason for not being aware of institutions and organizations for children's rights								
Lack of training	36.3±4.6	t:-0.02	37.1±3.3	t:0.168	73.4±6.7	t:0.07	3.3±0.3	t:-1.792
Lack of awareness	36.3±5.2	p:0.984	37±3.4	p:0.867	73.3±6.7	p:0.945	3.4±0.3	p:0.078
Status of reporting child abuse by law								
Obligation to notify	39.1±4.3	t:6.151	38.6±3.2	t:4.645	77.7±6.4	t:6.877	3.5±0.2	t:4.016
No obligation to notify	34.5±4.4	p:0.000*	36±3.3	p:0.000*	70.4±6	p:0.000*	3.3±0.4	p:0.000*
		r:-.432* η^2:0.20		r:-.343* η^2:0.12		r:-.453* η^2:0.23		r:-.293* η^2:0.09
The reason why the recorded data on abuse and neglect incidents is lower than the estimated rate								
Lack of Training	35.9±5.2	F:1.162	36.4±3.5	F:0.781	72.3±6.9	F:0.929	3.3±0.4	F:1.248
Lack of Awareness	35.9±5.1	p:0.326	37.4±3.5	p:0.506	73.3±7.1	p:0.428	3.4±0.4	p:0.295
Cultural Structure	35±4		36.4±3.4		71.4±6.3		3.3±0.3	
All	37.1±5.3		36.8±3.6		73.9±7.9		3.4±0.4	
Does the lack of support from the organizational (hospital) culture prevent reporting possible abuse?								
Yes	33.9±4.7	t:-3.682	35.7±3.4	t:-2.729	69.6±6.1	t:-3.984	3.3±0.4	t:-1.416
No	36.8±4.7	p:0.000*	37.3±3.4	p:0.007*	74.1±6.9	p:0.000*	3.4±0.3	p:0.159
		r:.251* η^2:0.08		r:.204* η^2:0.07		r:.283* η^2:0.09		
Do you think that child abuse cases can be solved without the involvement of child services?								
Yes	36.1±5.4	U:983	35.3±4.2	U:716	71.4±7.8	U:886.5	3.3±0.5	U:953.5
No	35.8±4.8	p:0.912	36.9±3.4	p:0.078	72.7±6.9	p:0.485	3.3±0.4	p:0.773
Do workload pressures discourage reporting child abuse?								
Yes	36.7±5.2	t:1.037	37.4±3.7	t:1.209	74.1±6.9	t:1.329	3.3±0.4	t:0.239
No	35.7±4.8	p:0.301	36.6±3.4	p:0.228	72.2±7	p:0.186	3.3±0.4	p:0.811
Should cases of child abuse and neglect be reported even if the evidence is uncertain?								
Yes (A)	38.2±4.7	F:19.263	38.2±3.1	F:15.795	76.4±6.6	F:27.888	3.4±0.3	F:7.786
No (B)	32.8±3.6	p:0.000*	33.9±2.9	p:0.000*	66.8±5	p:0.000*	3.1±0.4	p:0.001*
Hesitating (C)	34.1±4.2	A>B.C**	35.8±3.3	A>B.C**	69.8±5.5	A>B.C**	3.3±0.4	A>B**
		r:-.386* η^2:0.20		r:-.325* η^2:0.17		r:-.430* η^2:0.27		r:-.207* η^2:0.09

F: ANOVA, KW: Kruskal Wallis H test, r: Spearman's rho (nonparametric correlation), t: Independent sample t test, U: Mann-Whitney U test, **Post Hoc analysis for multiple comparisons, η2: Eta squared effect size, *p<0.05

Table 4. Central coordinates, dimensions and variance explained by the categories of variables					
Variables	**Categories**	**X**	**Y**	**1**	**2**
A. CMRS*	Below average	-0.558	-0.432	**0.341**	0.204
	Above average	0.61	0.472		
B. NCAN-RS*	Below average	-0.345	-0.243	**0.109**	0.054
	Above average	0.315	0.222		
C. Previous training on child abuse and neglect	Received training	0.743	0.139	**0.651**	0.023
	Not received training	-0.877	-0.164		
D. Being aware of institutions and organizations related to children's rights	Yes	0.476	-0.621	0.304	**0.517**
	No	-0.639	0.834		
E. Specifying institutions and organizations for children's rights	At least one institution specified	0.719	-0.904	0.311	**0.492**
	Did not specify any institution	-0.433	0.544		
F. Status of reporting child abuse by law	Obligation to notify	1.165	0.326	**0.58**	0.045
	No obligation to notify	-0.498	-0.139		
G. Does the lack of support from the organizational (hospital) culture prevent reporting possible abuse?	Yes	-0.846	-0.105	**0.288**	0.004
	No	0.34	0.042		
H. Should cases of child abuse and neglect be reported even if the evidence is uncertain?	Yes	0.633	0.166	**0.472**	0.036
	No	-1.077	-0.412		
	Hesitating	-0.66	-0.147		
	Self-value			3.056	1.375
	Variance Explained %			44.7	16.4

* The CMRS and NCAN-RS scales were included in the analysis by transforming them into two categories, below average and above average, according to the mean. X: X (horizontal) axis, Y: Y (vertical) axis, 1: First dimension, 2: Second dimension

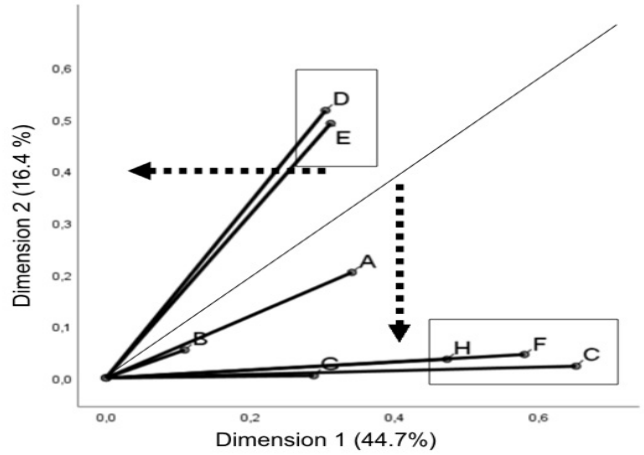

Figure 1. Graph on separation criteria

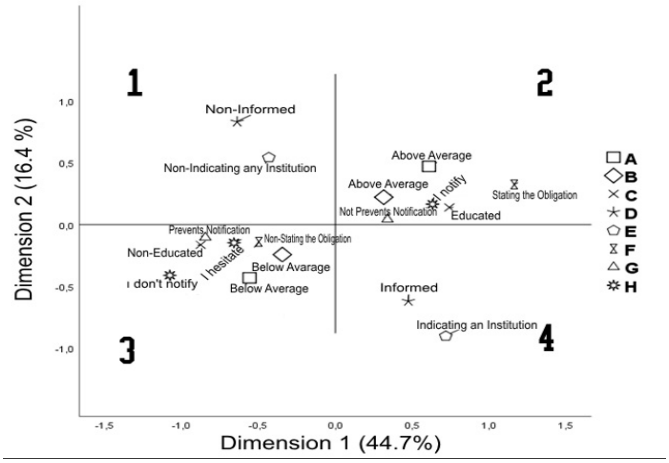

Figure 2. Multiple fit analysis graph

A: CMRS, B: NCAN-RS, C: Previous training on child abuse and neglect, D: Being aware of institutions and organisations for children's rights, E: Specifying institutions and organizations for children's rights, F: Reporting child abuse by law, G: Lack of support from the hospital culture prevents reporting possible abuse, H: Reporting cases of child abuse and neglect even if evidence is uncertain

in identifying characteristics of children vulnerable to abuse. Similarly, Üstündağ[13] found that overall awareness levels were moderate, but awareness of emotional abuse remained relatively low. These findings suggest that awareness levels regarding child neglect and abuse may vary depending on individual characteristics and professional fields. The significant positive relationship observed between CMRS scores and reporting responsibility, concerns about reporting, and general reporting tendencies highlights the role of awareness and perceived responsibility in reporting behaviors. This finding further suggests that personal perceptions and concerns significantly influence individuals' decisions to report child abuse cases.

Mandatory child abuse reporting laws have been established to facilitate early detection of abuse, protect children, and ensure timely interventions.[14] However, the scope of these laws and the reporting obligations they impose vary across countries. In many nations, reporting cases of child abuse and neglect is a legal requirement.[8] Similarly, in Turkey, healthcare professionals and other public officials are legally obligated to report such cases to the relevant authorities.[1,2] In this study, participants who were aware of the legal obligation to report child abuse had higher scale scores, suggesting that awareness of legal responsibility plays a crucial role in increasing the tendency to report such cases.[9]

Nurses, who interact directly with children, are considered among the most suitable clinical guides for training programs aimed at preventing sexual abuse.[15] Research suggests that child abuse can be prevented through awareness-raising training programs, which play a critical role in early intervention, recognizing risk factors, and implementing protective measures.[16-18] In this study, participants who had received training on child abuse and neglect had higher scale scores, highlighting that such training not only increases awareness but also enhances reporting behaviors.

Previous research indicates that a lack of knowledge about child abuse and neglect, fear of retaliation or personal harm after reporting, concerns about income loss, social pressure, and fear of legal consequences negatively impact individuals' willingness to report such cases.[19,20] Additionally, many individuals are unaware of the existence of reporting mechanisms and the authorities responsible for handling these situations.[21] These factors may hinder individuals from recognizing and engaging with institutions dedicated to children's rights. In this study, participants who were aware of institutions related to children's rights had higher scale scores, suggesting that awareness levels directly influence reporting behaviors. Therefore, training programs to address knowledge gaps and initiatives to raise awareness about children's rights may encourage individuals to fulfill their reporting responsibilities.

Pre-hospital care providers transport a significant number of pediatric patients to emergency departments each year, making their role crucial in the healthcare system.[22] However, due to limited training in child abuse and neglect, they often feel inadequate in recognizing and managing suspected cases.[23,24] Although mandatory reporting laws have evolved over time, training for these professionals has not been updated at the same pace, and curriculum development as well as clinical support have remained insufficient.[25] Additionally, research indicates that nurses may avoid involvement in child abuse cases and reporting due to fears of misjudgment that could result in legal consequences.[26] In this study, participants who stated that they would report abuse even in the absence of conclusive evidence had higher scale scores than other groups, suggesting a stronger tendency to fulfill reporting responsibilities. A lack of training and inadequate clinical support may contribute to healthcare professionals' hesitancy in reporting child abuse. Therefore, updating training programs and strengthening institutional support mechanisms are essential to enhance pre-hospital care providers effectiveness in recognizing and reporting abuse cases.

Studies have identified various factors that influence healthcare professionals' tendency to report child abuse and neglect, highlighting the critical role of organizational structure, welfare services, community resources, and professional relationships in this process.[9,27,28] In this study, it was found that a lack of support from the institutional culture negatively impacted both reporting responsibility and awareness. Insufficient institutional support not only increases individual

hesitations but also limits healthcare professionals' knowledge of their legal obligation to report, ultimately weakening their reporting behaviors. Consistent with previous research,[1,9,13] this finding suggests that effective reporting of child abuse requires not only individual awareness and legal regulations but also a well-structured organizational framework, clear reporting protocols, and strong professional support systems.

Limitations

This study has several limitations. First, it was conducted only with nurses working in family health centers in a specific region, limiting the generalizability of the findings to the broader nursing population. Second, the study employed a cross-sectional design, preventing the assessment of changes in nurses' knowledge and attitudes over time. Third, data were collected through self-reports, which may introduce the risk of social desirability bias. Future research should explore this topic with larger sample sizes and longitudinal study designs to gain deeper insights.

CONCLUSION

This study evaluates the knowledge levels, participation in reporting processes, and challenges faced by nurses working in family health centres regarding child abuse and neglect. The findings suggest that increasing nurses' awareness and education on child abuse and neglect positively influences reporting behaviours. Nurses who received training, were knowledgeable about children's rights, and were aware of the legal obligation to report abuse demonstrated a higher tendency to report cases. However, factors such as a lack of institutional support and inadequate training negatively impacted the reporting process. Therefore, developing comprehensive training programs, strengthening institutional support mechanisms, and increasing awareness of legal responsibilities are essential to improving healthcare professionals' reporting behaviours.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by Van Yüzüncü Yıl University Non-interventional Ethics Committee (Date: 08.03.2024, Decision No: 2024/03-29).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Relationship between phase angle, nutritional status, and blood biochemical parameters in hemodialysis patients: an example study in Edirne city center*

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ABSTRACT

Aims: Phase angle (PA) is recommended as a noninvasive and objective index to make an assessment of hemodialysis patients' nutritional conditions. This study aimed to investigate the relationship of PA with nutritional status and blood biochemical parameters in patients on hemodialysis.

Methods: A descriptive and cross-sectional research design was employed. The study was conducted with 100 hemodialysis patients (mean±SD: 62.79±11.73 years) between February and July 2024. Data collection tools included a questionnaire about patients' descriptive characteristics, a 24-hour food record form, the Global Leadership Initiative on Malnutrition (GLIM) criteria, the Malnutrition Universal Screening Tool (MUST), the 7-point Subjective Global Assessment (7p-SGA) scale, and the Nutritional Risk Screening-2002 (NRS-2002) scale.

Results: Patients with or at risk of malnutrition, identified using GLIM, MUST, and 7p-SGA criteria, had significantly lower mean PA, than patients without malnutrition risk (p=0.001, p=0.008, p=0.004, respectively). According to NRS-2002 criteria, participants who were at risk of malnutrition and needed starting a nutrition plan had significantly lower mean PA than those requiring weekly NRS-2002 assessments (p=0.017). The association of PA with lean body-mass (r=0.257, p=0.010), muscle mass (r=0.264, p=0.008), TSF thickness (r=0.259, p=0.009) and albumin (r=0.313, p=0.002) was positive, weak or very weak, and statistically meaningful.

Conclusion: Hemodialysis patients with or at risk of malnutrition had lower PA values according to various assessment tools. This suggests that PA may function as a possible indicator for identifying nutritional deficiencies in hemodialysis patients without delay.

Keywords: Phase angle, nutritional status, biochemical parameters

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INTRODUCTION

Chronic renal failure (CRF) is a public health concern that is increasingly common worldwide, has links to above average levels of morbidity and mortality risks, and impacts quality of life adversely.[1] Protein energy wasting (PEW) in hemodialysis patients is defined as the loss of somatic and circulating body protein along with energy reserves and is a common complication.[2,3] Therefore, nutrition has critical importance in terms of the survival rates of patients. For this reason, studying hemodialysis patients' nutrition and detecting malnutrition are of critical significance to reduce mortality and morbidity.[4] Parameters indicating body composition, such as body-mass index (BMI), lean body-mass (kg), muscle percentage, total fat mass (kg), total fat percentage, and triceps skinfold (TSF) thickness and biochemical parameters, such as albumin, total protein, and C-reactive protein (CRP), are utilized to reveal nutritional status as objective indicators.[5]

In addition, the nutritional status assessment and screening tools, such as the Global Leadership Initiative on Malnutrition (GLIM) criteria, the Malnutrition Universal Screening Tool (MUST), the Nutritional Risk Screening-2002 (NRS-2002), and the 7-point Subjective Global Assessment (7p-SGA) scale, which are used to evaluate individuals, BMI, unintentional body weight loss, decreased muscle mass, changes in food intake, and functional capacity, provide an international standard for defining malnutrition.[6-8]

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Phase angle (PA), measured with BIA, has recently become a focus of interest as a noninvasive assessment method and an objective indicator of nutritional status.[3]

The BIA-measured PA reflects the body's resistance and response to an external current. PA is the most clinically relevant impedance parameter and an index of cell membrane integrity and viability. PA is a direct measure of BIA and therefore is not affected by assumptions that may involve body composition or hydration assessments. A lower PA level indicates reduced cell integrity or cell death, while a higher value indicates a large amount of intact cell membrane. Furthermore, PA has recently been utilized to assess the advancement of disease and predict clinical outcomes in many clinical situations.[3] Therefore, it has been shown as a reliable marker for the early detection of malnutrition in many clinical areas. A decrease in PA indicates a deterioration in nutritional status.[4]

Some studies have shown that PA values are lower in individuals with malnutrition and PEW, there is a link between these lower values and elevated malnutrition and PEW risk, and that PA functions as an independent predictor of these conditions.[7,9]

A review of the literature indicated that there was no study on the examination of the PA by using more than one nutritional screening tool. In the present study, four screening tools, namely GLIM, 7p-SGA, NRS-2002, and MUST, were used to investigate whether PA produced parallel results with these tools. In addition, the relationship between PA and anthropometric measurements, handgrip strength, biochemical parameters, energy, and nutritional indicators such as protein intake was evaluated. In this way, our study aimed to make a significant contribution to the literature by showing the usability of PA in nutritional status assessments with a broader perspective. As a result, we aimed to examine the association of PA with nutritional status and blood biochemical parameters in hemodialysis patients.

METHODS

Ethics

The study was approved by the Ethics Committee of Trakya University Faculty of Medicine (Date: 13.11.2023, Decision No: 17/37). Afterwards, to initiate the study in the specified hospitals, the necessary institutional approvals were taken (Trakya University Directorate of Health Research and Application Center [No: E-79056779-600-577279, approved on 5 January 2024] and Edirne Governorship Provincial Health Directorate [No: E-98308410-806.01-234001145, approved on 12 January 2024]). At the outset, individuals signed an informed consent form explaining the objective of the research. The Declaration of Helsinki was followed in the present research.

Study Design and Participants

This descriptive, cross-sectional study was conducted between February and July 2024 at the Trakya University Hospital Hemodialysis Unit, Edirne Sultan Murat I Hospital Dialysis Unit, and Private Diyamar Dialysis Center. The study included patients who could understand and speak Turkish, were aged ≥20 years, had CRF, were on standard four-hour three-days-a-week fashion hemodialysis treatment for six months or longer, gained ≤4 kg between two hemodialysis sessions, and had diabetes, hyperlipidemia, or hypertension or several of them. Patients who used antihypertensive drugs before hemodialysis, had amputations or physical or mental disabilities, received parenteral nutrition support during the study, were hospitalized for surgical or medical treatment within the last month, had active infection or rheumatic disease, had cancer, had endocrine diseases, such as liver disease, thyroid, parathyroid, or adrenal gland diseases, had neurological and psychiatric disorders, had chronic inflammation such as active hepatitis or HIV (+), had a history of ischemic heart disease, were scheduled for transplantation, had recently undergone transplantation and were on dialysis again, were pregnant or breastfeeding, or smoked or consumed alcohol were excluded from the study.

G*power 3.1.9 software was utilized to estimate sample size. According to the correlation analysis with a statistical power of 80% and a significance level of α=0.05 performed on G*power 3.1.9 software, the smallest sample size required to achieve an effect size of d=0.30 was calculated as 84, and the study was completed with 100 people.[10]

Measurements

The researchers gathered study data. A questionnaire form about the sociodemographic characteristics, dietary habits, body composition, and biochemical parameters, a 2-day 24-hour food consumption record form (non-dialysis day-dialysis day), the GLIM criteria, the MUST, the Subjective global assessment-7 point scale (SGA-7P), and the nutritional risk screening scale - 2002 (NRS-2002) were applied to the patients.

Before the study was initiated, a patient group of 15 was evaluated to ensure the consistency and accuracy of measurements. Anthropometric measurements of each patient were taken three times, and the averages of these measurements were included in the evaluation. In addition, the responses of the individuals to the nutritional status screening and assessment tools were collected with three different repeated measurements. All measurements were performed by a single expert who had education in the field to ensure the consistency and accuracy of measurements and to eliminate bias.

The descriptive characteristics form: This form consists of questions about gender, age, marital status, duration of kidney disease, and presence of accompanying diseases.

Anthropometric measurements and body composition: Patients' height values were measured with a stadiometer (Holtain, England), with the head in the Frankfort plane and the feet adjacent. The individuals' BMI (kg/m^2), lean body mass (kg), muscle mass (kg), body weight (kg), body fat mass (kg), and body fat percentage (%) measurements were taken using the Tanita MC-780 MA model bioelectrical impedance analyzer. BIA measurements were taken from the dry weights of the patients one hour after the hemodialysis session. Individuals' BMI values were evaluated with reference to the World Health Organization (WHO) categorization: <18.5 kg/

m^2, underweight; 18.5–24.9 kg/m^2, normal weight; 25-29.9 kg/m^2, overweight; and ≥30.0 kg/m^2, obese.[11]

The TSF thickness measurements of the patients were made in the sitting position by using a Holtain skinfold caliper. The skin and subcutaneous fat tissues were measured at the midpoint between the elbow and shoulder on the back of the arm by gently holding and compressing it with the thumb and index finger, and the value was recorded in millimeters.[8]

The PA measurements of the patients were made using a Tanita MC-780 MA model bioelectrical impedance analyzer. PA is the arctangent value calculated from the resistance and reactance obtained from the BIA and represents cellularity, cell membrane integrity, and cell function. The higher the PA value is, the better the patient's nutritional status is.[12]

The patients' hand grip strength (HGS) measurements were performed using a hand dynamometer (Camry) before dialysis (after at least five minutes of rest). First, patients sat on a chair and held their arms at a right angle (90°). The measurement was started with the arm with the least fistula or the dominant arm and then moved on to the second arm. A one-minute interval was left between each measurement. The evaluation was based on the mean value of three readings from the dominant hand.[13]

Biochemical parameters: The data regarding the blood biochemical parameters of the patients measured within the last month, such as total protein (g/dl), serum albumin (g/dl), CRP (mg/l) were obtained from medical records.

24-hour food consumption record: The 24-hour food consumption records of the patients were taken two times, one on the dialysis treatment day and the other on the day when there was no dialysis session. Participants delivered an account of everything they ate or drank during a certain period, which the researcher recorded on the relevant form. The mean energy consumption for these two days was calculated eventually. The energy and protein values taken with the daily diet were analyzed on the "computer-assisted nutrition information system (BeBis) full version 9".[14]

The Global Leadership Initiative on Malnutrition (GLIM): The leaders of the prominent clinical nutrition societies (ESPEN, ASPEN, Latin American Federation of Nutritional Therapy, Clinical Nutrition, and Metabolism (FELANPE), and Asian Parenteral and Enteral Nutrition Association (PENSA)] designed the GLIM diagnostic criteria by consensus. The aim of establishing the GLIM criteria was to provide global standardization in the diagnosis of malnutrition and to prevent delays in diagnosis and treatment.

GLIM criteria adopt a two-step approach to diagnosing malnutrition. In the first step, the nutritional risk is determined using a validated screening tool. In the second step, a comprehensive assessment is performed to diagnose malnutrition and grade its severity. The GLIM criteria include three phenotypic (unintentional weight loss, low BMI, and decreased muscle mass) and two etiological criteria (reduced nutrient intake or digestion and inflammation/disease burden). The diagnosis of malnutrition requires the presence of at least one phenotypic and one etiological criterion. The degree of malnutrition is then determined according to the phenotypic criteria and classified as moderate or severe.[15]

The Malnutrition Universal Screening Tool (MUST): The MUST was developed by the British Association for Parenteral and Enteral Nutrition (BAPEN) in 2003. It can be applied in the community, hospitals, and all other care settings to detect malnutrition, risk for malnutrition, and obesity in adults.[16]

The MUST consists of five steps and three sections used to question BMI, unintentional loss of body weight (in the last three to six months), and acute disorders. Each section is scored between 0 and 2: 0 points for a BMI value of >20 kg/m^2, 1 point for BMI value of 18.5-20 kg/m^2, and 2 points for a BMI value of <18.5 kg/m^2. If the weight loss is <5%, the score is 0; if it is 5-10%, the score is 1, and if it is > 10%, the score is 2 points. If there is no acute illness and the possibility of not being able to take food for the next >5 days, the score is 0 points, or 2 points otherwise. At the end of the evaluation, those who score 0 are classified as low risk, those who score 1 are classified as medium risk, and those who score ≥ 2 are classified as "high risk." A care plan is created according to the risk level.[16]

The 7-point Subjective Global Assessment (7p-SGA) scale: Churchill developed the subjective global assessment as a seven-point tool (SGA-7P).[17] Eminsoy et al.[18] studied the Turkish reliability and validity of this measure. Scoring with SGA-7P is done according to a standard protocol. Patients are evaluated by questioning their weight loss, food intake, gastrointestinal problems, muscle loss, and functional capacity in the last six months using a standard form. Scores are interpreted as follows: 7-6, well-nourishment; 5-3, mild to moderate malnourishment; and 2-1 malnourishment. Patients' malnutrition status is evaluated based on this classification.[18]

The Nutritional Risk Screening-2002 (NRS-2002): NRS-2002 was developed by an ESPEN study group led by Kondrup[19] in 2003, and it was adapted to Turkish by Başak Bolayır.[20] It was developed to screen nutritional risk in inpatients and to classify those likely to get the benefits of nutritional support.[20] During the application of this tool, individuals are first given a preliminary screening test. In this test, they are asked about their BMI value, loss of weight in the past three months, decrease in food consumption in the past week, and whether their condition is severe. "Yes" response to any of these items triggers the main screening section, or the preliminary screening is repeated at certain intervals if all items are answered "no." In the main screening section of the scale, nutritional status irregularity is evaluated according to the percentage of weight loss as none (0 points), mild (1 point), moderate (2 points), and severe (3 points). Disease severity is evaluated similarly to nutritional irregularity as none (0 points), mild (1 point), moderate (2 points), and severe (3 points). At the end of the test, the scores obtained from the main screening section are summed, and if the individual is over seventy years old, an extra 1 point is added due to age to calculate the total score. It is concluded that the individual has a risk of nutrition and it is necessary to start a nutritional care scheme in cases where the score is ≥3. The screening test

should be done again at a certain frequency in cases where the score is <3.[19,20]

Statistical Analysis

Descriptive tests, such as number (n), percentage (%), mean, standard deviation (±sd), minimum (min.), and maximum (max.) values, were utilized in analyses. Kolmogorov-Smirnov test was utilized to test normality. In the comparison of the means of two independent groups, Student's t-test was applied in parametric distributions, and the Mann-Whitney-U test was employed in nonparametric distributions. Kruskal-Wallis H test was utilized in nonparametric distributions to make three-or more-group comparisons. Dunn's test, one of the post hoc tests, was employed to examine the source of significant differences obtained from comparisons of three or more groups, and the results were presented by performing Bonferroni correction. The relationship between two numerical variables was examined with Pearson's correlation analysis in parametric distributions and with Spearman's correlation analysis in nonparametric distributions. Data were analyzed on Statistical Package for the Social Sciences 26.0 (SPSS 26.0) software. Significance was set at $p<0.05$. Daily dietary energy and protein values were analyzed using the 'computer-supported nutrition information system' (BeBis) full version 9".[14]

RESULTS

Table 1 shows factual characteristics of the individuals. As seen in the table, average age was 62.79±11.73 years, 57.0% were male, and 93.0% were married. The average duration of participants' kidney disease was 10.37±12.65 years. Findings showed that 81.0% of the adults had an accompanying disease, with the most prevalent ones being hypertension (69.1%), diabetes (30.9%), and cardiovascular disorders (CVD) (16.0%) (Table 1).

Table 1. Distribution of participants' descriptive characteristics

Variables	n	%
Gender		
Female	43	43.0
Male	57	57.0
Age (mean±SD: 62.79±11.73, min.:33, max.: 89)		
Marital status		
Married	93	93.0
Single	7	7.0
Duration of the kidney disease (mean±SD: 10.37±12.65, min.: 1, max.: 72)		
Presence of accompanying diseases		
Yes	81	81.0
No	19	19.0
Accompanying diseases* (n=81)		
Hypertension	56	69.1
Diabetes mellitus	25	30.9
Cardiovascular diseases	13	16.0
Gastrointestinal diseases	18	22.2
Respiratory diseases	7	8.6
Hypothyroidism	4	4.9
Cancer	5	6.2

*Multiple options were marked, SD: Standard deviation

Table 2 shows the distribution of participants' body composition and biochemical parameters by gender. BMI was 25.82±5.50 kg/m² in females and 24.65±5.20 kg/ m² in males in average. The BMI classification of the participants was as follows: underweight, 10.0%; normal weight, 48.0%; overweight, 22.0%; obese, 20.0% (not shown in the table). The mean PA value was 5.17±1.18° in females and 5.58°±1.02° in males (Table 2).

Table 3 shows the comparison of participants' PA values according to the GLIM, MUST, 7p-SGA, and NRS-2002 criteria. According to the GLIM criteria, malnutrition was determined at stage 1 (moderate malnutrition) in 15.0% of the participants and stage 2 (severe malnutrition) in 11.0%. According to the MUST criteria, 9.0% of the participants were found to have a moderate risk and 21.0% a high risk. According to the 7p-SGA criteria, 10.0% of the participants were determined to have mild and moderate malnutrition. According to the NRS-2002 criteria, 16.0% of the participants had a nutritional risk, and therefore a nutritional plan needed to be initiated (Table 3).

The GLIM criteria and the PA yielded a statistically significant difference ($p=0.000$). When the source of the difference was examined, it was found that those with stage 1 malnutrition had statistically significantly lower mean PA values than those who were not at risk of malnutrition ($p=0.001$). The MUST criteria and the PA yielded a statistically significant difference ($p=0.004$). According to the source of this difference, those at high risk had statistically significantly lower PA values than those at low risk ($p=0.008$). According to the SGA-7P criteria, the mean PA values of those with mild and moderate malnutrition were statistically significantly lower than the mean values of those who were well-nourished ($p=0.004$). The mean PA values of the participants who had a nutritional risk according to the NRS-2002 criteria and who needed a nutritional plan were statistically significantly lower than the values of those who required weekly NRS-2002 evaluation ($p=0.017$) (Table 3).

The relationship between certain parameters and PA values is shown in Table 4. A positive weak or very weak statistically significant relationship was observed between PA and lean body mass ($r=0.257$, $p=0.010$), muscle mass ($r=0.264$, $p=0.008$), TSF thickness ($r=0.259$, $p=0.009$), and albumin ($r=0.313$, $p=0.002$) (Table 4).

DISCUSSION

The relationship of PA with nutritional status and blood biochemical parameters in patients receiving hemodialysis was investigated in the present research. The main findings revealed that PA was lower in individuals with or at risk of malnutrition and showed significant relationships with certain indicators of nutritional status.

In the current study, the mean PA value was found to be 5.17±1.18° in female and 5.58±1.02° in male patients on hemodialysis treatment. These values varied in the relevant literature.[7,21] These differences may have been due to confounding factors affecting the PA, characteristics of the study population (e.g., age, gender, ethnicity, nutritional status, presence of comorbidities), and the variety of BIA devices used.[22,23]

According to previous studies, PA is a valuable indicator reflecting hemodialysis nutritional status.[3,7] It is also thought

Table 2. Distribution of participants' body composition and biochemical parameters by gender

	Female (n=43)		Male (n=57)	
	Mean±SD	Min.-max.	Mean±SD	Min.-max.
BMI (kg/m²)	25.82±5.50	15.6-38.5	24.65±5.20	16.3-41.9
Lean body mass (kg)	45.34±7.90	28.7-69.0	58.73±7.88	43.8-77.9
Body fat mass (kg)	19.36±9.02	5.70-37.60	14.07±9.22	1.70-42.10
TSF thickness (mm)	27.78±6.01	15-39	27.45±5.90	10-37
PA (°)	5.17±1.18	1.8-7.7	5.58±1.02	3.4-7.8
HGS (kg)	16.91±6.83	2.8-30.0	28.90±12.22	7.8-49.7
Total protein (g/dl)	6.78±0.55	5.30-8.40	6.65±0.52	5.80-8.20
Albumin (g/dl)	3.82±0.34	2.90-4.60	3.92±0.36	3.00-4.70
CRP (mg/L)	14.33±23.81	0.30-122.00	11.23±13.65	0.30-59.60
Daily protein intake (g/kg/day)	0.67±0.37	0.14-1.98	0.80±0.41	0.23-2.16
Daily energy intake (kcal/kg/day)	17.63±8.76	5.40-47.25	20.67±8.93	5.80-54.89

*BMI: Body-mass index, TSF: Triceps skinfold, PA: Phase angle, HGS: Hand grip strength, CRP, C-reactive protein, SD: Standard deviation, Min: Minimum, Max: Maximum

Table 3. Comparison of participants' PA values according to GLIM, MUST, SGA-7P, and NRS-2002 criteria

	n	%	Phase angle	
			Mean±SD	p-value
GLIM#				
Not at risk[a]	74	74.0	5.64±1.08	0.000***
Stage 1 malnutrition (moderate malnutrition)[b]	15	15.0	4.57±0.84	
Stage 2 malnutrition (severe malnutrition)	11	11.0	4.95±0.92	
MUST#				
Low risk (routine clinical care)[c]	70	70.0	5.64±1.10	**0.004****
Moderate risk (monitoring)	9	9.0	4.94±0.87	
High risk (treatment)[d]	21	21.0	4.83±0.95	
7p-SGA#				
Well-nourishment	90	90.0	5.51±1.09	**0.004****
Mild to moderate malnutrition	10	10.0	4.48±0.77	
NRS-2002##				
NRS assessment weekly	84	84.0	5.50±1.08	**0.017***
Nutritional risk; nutrition plan should be started	16	16.0	4.88±1.13	

Kruskal-Wallis H test; ## Mann-Whitney U test; Post Hoc Dunn's test. Phase angle: b<a, d<c; *p<0.05, **p<0.01, ***p<0.001. PA: Phase angle, GLIM: Global Leadership Initiative on Malnutrition, MUST: Malnutrition Universal Screening Tool, 7p-SGA: 7-point Subjective Global Assessment, NRS-2002: Nutritional Risk Screening Scale-2002, SD: Standard deviation

Table 4. Correlation between participants' certain parameters and PA values

Parameters	Phase angle (PA)	
	r	p
BMI (kg/m²)[1]	0.158	0.116
Lean body mass (kg)[2]	0.257	**0.010***
Muscle mass (kg)[2]	0.264	**0.008****
Body fat mass (kg)[1]	0.076	0.225
Body fat percentage (%)[2]	0.159	0.114
TSF thickness (mm)[2]	0.259	**0.009****
HGS (kg)[1]	0.164	0.103
Total protein(g/dl)[1]	0.055	0.587
Albumin(g/dl)[1]	0.313	**0.002****
CRP (mg/L)[1]	-0.095	0.345
Mean daily protein intake (g/kg/day)[1]	0.038	0.705
Mean daily energy intake (kcal/kg/day)[2]	0.126	0.210

*BMI: Body-mass index, TSF: Triceps skinfold, PA: Phase angle; HGS: Hand grip strength, CRP: C-reactive protein,[1]Spearman's correlation analysis; [2]Pearson's correlation analysis; r: Correlation coefficient; *p<0.05, **p<0.01, ***p<0.001.

that fluid and electrolyte imbalances in hemodialysis patients may affect BIA readings, leading to a false diagnosis of malnutrition, whereas PA calculations involving normalization of reactance by resistance may be less affected by excess fluid. Therefore, it has been suggested that PA has the potential to be a screening norm for diagnosing malnutrition in this patient group.[7] Composite or non-composite nutritional indices have been used in previous studies to examine the connection of PA with nutritional condition in hemodialysis patients.[3,21] However, it has been suggested that the lack of a standard definition of malnutrition and the use of different indices to assess nutritional status may affect the variability of PA and nutritional condition associations.[24] In this context, in the present study, we examined the relationship between PA and malnutrition assessment criteria, such as GLIM, MUST, NRS-2002, and SGA-7P, as well as the relationship of PA with other indicators, such as body composition, anthropometric measurements, biochemical parameters, dietary intake, and HGS, which is a functional measurement.

In the present study, the mean PA values of individuals determined to be at risk of malnutrition or malnourished based on the NRS-2002, the GLIM, and SGA-7P criteria were lower than the values of those not at risk or not malnourished. In addition, individuals in the high-risk group evaluated with MUST had lower mean PA values than those in the low-risk group. These findings were consistent with previous studies in the literature. Some studies have shown that PA values are lower in individuals with malnutrition and PEW, these lower values are associated with increased malnutrition and PEW risk, and that PA is an independent predictor for these conditions.[7,9] It is known that PA has a positive relationship with lean body mass and a negative one with extracellular/intracellular fluid ratio. Malnutrition is characterized by the premature transfer of fluids from the intracellular to the extracellular space, an increase in the extracellular/intracellular fluid ratio, and a concomitant decrease in body cell mass, with these changes emerging as a decrease in the PA.[25] This provides a potential explanation for why the PA may be an indicator of malnutrition.

In the present study, PA was identified to have a positive correlation with muscle percentage and lean body-mass in hemodialysis patients. It also had a significant positive relationship with TSF thickness, an indicator of body fat mass. However, the positive relationships between PA and fat mass and fat percentage assessed by BIA did not reach statistical significance. In the literature, the relationships between PA and muscle percentage and lean body mass were similar to the findings of our study.[23,26] Muscle cells conduct electricity well as they have high levels of electrolyte and fluid content, while showing above average reactance because of the capacitive properties of their cell membranes. These properties cause reactance to increase and resistance to decrease with increasing muscle mass, which is reflected as a higher PA value.[27] On the other hand, body fat mass, which is a poor conductor of electricity due to its low water content and leads to higher resistance, might be expected to cause a decrease in PA. However, the direction and strength of the relationships between PA and body fat mass appear to depend on population characteristics (age, sex, health status, etc.).[28] Taken together, these findings suggest that PA may reflect nutritional status through lean body mass rather than body fat mass.

A positive relationship was found between PA and albumin in the present study. Most previous studies also showed results consistent with these findings.[3,21] A decrease in albumin levels is considered an important indicator of malnutrition and may contribute to changes in PA. However, it should be kept in mind that low albumin levels may reflect not only nutritional status but also factors such as inflammation and fluid overload, which may also affect PA.[29] Consistent with previous studies, no significant relationship was found between PA and CRP.[9,21,25]

The association between BMI and PA was not meaningful in this study. Similar results were shown in previous study.[26] This suggests that BMI may be an inadequate indicator of cell health due to its limited ability to distinguish between lean body mass and body fat mass.[30] However, contrary to our study, some studies indicated a positive relationship between PA and BMI.[3,7,9] It has been suggested that increasing BMI may an increase the number of fat or muscle cells and that this increase in cellular mass may affect the reactance associated with the amount of cell membrane, resulting in higher PA values.[9]

To our surprise, the findings of this study revealed that PA did not have a significant correlation with dietary energy and protein intake. These results were consistent with the results of a previous study, in which it was claimed that daily dietary intake variances might have weakened these relationships. It was seen that PA was less successful in revealing dietary energy and protein intake, but it could still detect PEW.[31]

Many previous studies have shown a positive relationship between HGS an indicator of muscle strength, and PA.[3,23] However, despite the positive correlation between muscle percentage and PA, the association of HGS with PA was not meaningful in the present study. This suggests that increases in body muscle mass and therefore PA do not always increase in parallel with muscle strength. In fact, similar results were shown in a previous study involving peritoneal dialysis patients. The authors stated that muscle strength was affected not only by body muscle percentage but also by a number of factors, such as electrolyte imbalances, anemia, heart diseases, neurological problems, and mental status. They also emphasized that the annual decline rates between muscle strength and body muscle percentage were different and that the relationship between HGS and PA was the result of a complex and multifactorial interaction.[27]

Limitations

This study has several limitations that should be noted. First, despite including all institutions/centers providing dialysis services in the Edirne province of Turkiye, it had a relatively small sample size. This limits the generalizability of the findings to larger hemodialysis patient populations. Multicenter studies with larger sample sizes are needed to ensure the generalizability of our findings to larger patient populations. Additionally, the exclusion of patients with clinical factors that were likely to have an impact on nutritional status was intended to reduce the potential impact of these factors on the results. However, this may limit the applicability of the study findings to larger hemodialysis populations. In future studies, doing subgroup analyses by including larger and more heterogeneous patient groups to overcome the limiting effects of the exclusion criteria and controlling the effects of clinical factors may increase the generalizability of the findings. Second, the cross-sectional design of our study limits the determination of causal relationships between PA and the indicators of nutritional status. Longitudinal studies are needed to better understand these relationships. Finally, confounding factors that may affect PA (e.g., age, gender, ethnicity, nutrition, and presence of comorbidities) may have influenced our results. In future studies, careful control and statistical modeling of such factors will increase the validity of the results.

CONCLUSION

This study revealed that PA may be an important biomarker in the assessment of nutritional status in hemodialysis patients. The results showed that patients classified as malnourished or at risk of malnutrition according to various assessment tools (GLIM, MUST, NRS-2002, and SGA-7P) had lower PA values. This suggests that PA may serve as a potential indicator for the early detection of nutritional deficiencies in this patient population. In addition, PA was found to be associated with some indicators related to albumin and body composition. However, the fact that it did not show a significant relationship with other biochemical and functional nutritional parameters suggests that PA focuses on aspects different from traditional measures in the assessment of nutritional status and can be used as a complementary tool. In conclusion, PA may serve as a valuable biomarker in determining nutritional status-related risks and supporting nutritional management in hemodialysis patients. It is recommended that future studies with larger samples take into account the effects of confounding factors,

the effect of PA on clinical outcomes be further examined, the potential use of this measure be expanded, and its importance in clinical practice be increased.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Ethics Committee of Trakya University Faculty of Medicine (Date: 13.11.2023, Decision No: 17/37).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Comparison of iron, vitamin B12, and vitamin D levels in healthy children and children with speech and language disorders

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ABSTRACT

Aims: This study investigated the relationship between speech and language disorders in children and their levels of vitamin D (25(OH)D3), vitamin B12, and iron.

Methods: A total of 163 children participated in the study. Among 111 children diagnosed with speech and language disorders, the distribution included stuttering (n=12), articulation disorder (n=55), developmental language disorder (n=36), fluency disorder (n=4), atypical autism (n=3), and rapid speech disorder (n=1). Additionally, 52 healthy children were included as a control group. The levels of iron, vitamin B12, and vitamin D were recorded for both groups.

Results: Average levels in the study group were as follows: vitamin D at 24.88±14.788 ng/ml, vitamin B12 at 267.43±174.523 pg/ml, and iron at 74.19±34.479 µg/dl. Iron levels were significantly lower in children with speech disorders compared to those in the control group (z=1.986, p=0.049). However, no significant differences were found among the various subgroups of speech disorders in terms of iron, vitamin B12, or vitamin D levels. A positive correlation was observed between vitamin D and vitamin B12 levels within the speech disorder group (p<0.05).

Conclusion: This study suggests a potential link between lower iron levels and speech disorders, though further research is required to validate these findings in children with speech and language disorders.

Keywords: Speech sound disorder, stuttering, vitamin D, B12, iron

INTRODUCTION

Speech and language are essential aspects of daily life and serve as key tools for interpersonal communication. Language consists of two primary components: receptive language and expressive language.[1] There is a broad consensus that language development is a complex process.[2,3] The prevalence of speech disorders among children is estimated to be between 1% and 12% in preschool and school-age groups.[4]

Vitamin B12 is a crucial nutrient impacting various systems, including the central nervous system, where it plays an important role in neural metabolism. As a water-soluble vitamin, B12 is involved in the metabolism of every cell in the human body.[5] Vitamin B12 deficiency in infants has been associated with brain atrophy and demyelination, potentially affecting neural conduction velocities due to impaired myelination.[6] This slowing of transmission in the visual and auditory systems can hinder learning abilities.[7] Consequently, delayed myelination in infancy may lead to delays in cognitive skill acquisition, while brain atrophy may cause regression of these skills.

While vitamin D deficiency has long been linked to rickets, chronic vitamin D inadequacy is now also associated with a range of non-skeletal health outcomes. Epidemiological studies suggest possible links between low vitamin D levels and conditions such as diabetes, cancer, and certain autoimmune diseases. Experimental studies have shown that vitamin D has effects beyond bone health, including anti-proliferative, pro-differentiative, pro-apoptotic, and immunomodulatory functions.[8-10]

To our knowledge, no studies have investigated iron, vitamin D, and vitamin B12 levels simultaneously in children with speech and language disorders. This study aims to explore whether there is a connection between speech disorders and deficiencies in iron, vitamin D, and vitamin B12.

METHODS

Ethics committee approval was obtained from Kırşehir Ahi Evran University Faculty of Medicine Clinical Researches Ethics Committee (Date: 21/02/2023, Decision No: 2023-04/29). The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Our study was conducted by retrospectively reviewing the medical records of 163 pediatric patients who presented to the outpatient clinic with complaints of speech disorders between January 2021 and January 2023. Patients with chronic

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diseases, those taking vitamin supplements, and those with neurological or psychiatric conditions, hearing impairments, or anatomical abnormalities were excluded from the study. All children with speech disorders were assessed and treated by a certified speech and language therapist.

For children aged 2 to 8, articulation and phonological skills were evaluated using the Turkish pronunciation and phonology test (SST), administered by a speech and language therapist.[11] Receptive and expressive language skills were assessed with the Turkish early language development test (TEDIL), which comprises two parallel sets, Forms A and B. Each form includes subtests for receptive and expressive language that provide insights into morphological, semantic, and syntactic development. TEDIL results also allow for comparison with peers, offering a standardized score and an equivalent age range.[12] Additional information about each child's development was obtained from their family. Speech samples were collected by recording the child's natural speech patterns through video or casual conversation. These samples were analyzed to assess fluency and stuttering frequency.

All laboratory data were sourced from tests conducted in our hospital's biochemistry lab, and iron, vitamin B12, and vitamin D levels were recorded from patient files. Serum 25-OH vitamin D levels were categorized as follows: levels below 20 ng/ml indicated deficiency, levels between 20-30 ng/ml indicated insufficiency, and levels above 150 ng/ml indicated toxicity.[13] A serum vitamin B12 level below 200 pg/ml was considered deficient.[14]

Statistical Analysis

Data were analyzed using the IBM SPSS Statistics software (Version 25.0, IBM Corp., 2017, Armonk, NY, USA). Descriptive statistics were presented as mean±standard deviation, median (minimum-maximum), percentage, and frequency values. Normality and homogeneity of variances were assessed using the Shapiro-Wilk and Levene's tests, respectively.

For comparisons between two groups, the Independent Samples t-test (Student's t-test) was used if parametric assumptions were met; otherwise, the Mann-Whitney U test was applied. For comparisons among three or more groups, One-Way Analysis Of Variance (ANOVA) followed by Tukey's HSD test was employed if assumptions were met, while the Kruskal-Wallis test and Bonferroni-Dunn test were used when non-parametric methods were required.

The relationships between continuous variables were assessed using the Pearson Correlation Coefficient when parametric assumptions were satisfied; otherwise, the Spearman Correlation Coefficient was used. The cutoff value for iron levels was determined via ROC analysis. Statistical significance was set at $p<0.05$ and $p<0.01$.

RESULTS

A total of 163 children, comprising 111 patients and 52 controls, were included in this study. The average age of the children was 6.41±3.32 years. Among the group, the mean vitamin D level was 24.88±14.79 ng/ml, the mean B12 level was 267.43±174.52 pg/ml, and the mean iron level was 74.19±34.48 µg/dl. Gender distribution was 44.8% female and 55.2% male.

Speech disorders were present in 68.1% of the children, while 31.9% had no speech disorders. Of the 111 children with speech disorders, 3.6% were diagnosed with fluency disorder, 2.7% with atypical autism, 32.4% with developmental language disorder, 10.8% with stuttering, and 49.5% with speech sound disorders (**Table 1**).

Table 1. Distribution of the children participating in the research by demographic characteristics

		Mean	SD
Age		6.41	3.321
D vitamin		24.88	14.788
B12		267.43	174.523
		n	**%**
Gender	Female	73	44.8
	Male	90	55.2
Speech disorder	Yes	111	68.1
	No	52	31.9
Diagnosis	Fluency disorder	4	3.6
	Atypical autism	3	2.7
	Developmental language disorder	36	32.4
	Stuttering	12	10.8
	Rapid speech disorder	1	0.9
	Articulation disorders	55	49.5

SD: Standart deviation

Since the distributions of B12 and iron values did not follow a normal distribution, the Mann-Whitney U test was used for analysis. Results showed a statistically significant difference in mean B12 levels based on the presence of a speech disorder ($z=3.117$, $p=0.011$), with children in the speech disorder group having higher mean B12 levels than those without speech disorders. Additionally, iron levels demonstrated a statistically significant difference based on the presence of a speech disorder ($z=1.986$, $p=0.049$) (**Table 2**), with lower iron levels observed in the group with speech disorders.

Table 2. Mann-Whitney U test results for speech disorder status

	Speech disorder	n	Mean	SD	z	p
B12	Yes	72	267.43	174.523	3.117	0.001
	No	52	249.12	87.99		
Iron	Yes	67	74.19	34.479	1.986	0.049
	No	52	86.88	34.704		

SD: Standart deviation

In the speech disorder group, iron levels were further evaluated with a ROC curve analysis, which identified a cutoff value of 44 µg/dl for iron, with 25.4% sensitivity and 92.31% specificity. This result may serve as a diagnostic criterion distinguishing between patient and control groups (**Figure**).

When evaluating the subgroups of speech disorders (fluency disorder, atypical autism, developmental language disorder, stuttering, and speech sound disorders) using the Kruskal-

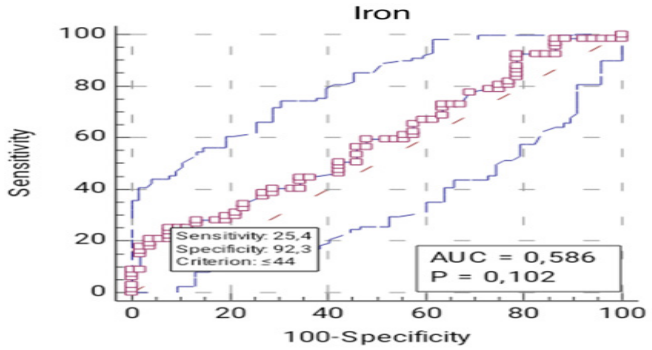

Figure. ROC Curve for iron in children with speech disorders
ROC: Receiver operating characteristic, AUC: Area under the curve

Wallis test, mean levels of vitamin D, vitamin B12, and iron showed no statistically significant differences across diagnostic subgroups (**Table 3**).

Finally, correlation analysis of vitamin D, B12, and iron levels indicated a positive correlation between vitamin D and vitamin B12 in the speech disorder group ($p<0.05$) (**Table 4**).

DISCUSSION

Language and speech are among the most complex human skills. There is a strong correlation between language development and early cognitive development.[15] Although the exact impact of cognitive abilities on language acquisition is not fully understood, language development typically progresses alongside cognitive development, with both functions interacting throughout the language learning process.[15] Experimental studies have indicated that active vitamin D may influence brain and neuron development through its neuroprotective and antioxidant effects.[16] Additionally, one experimental study found a correlation between low serum vitamin D levels and cognitive dysfunction, though this relationship remains inconclusive.[17-19]

According to Sagiroglu's research, no significant difference in vitamin D levels was found between children with articulation disorders and those who stutter compared to a control group.

Table 4. Correlations between vitamin D, B12, and iron variables

Speech disorder			Vitamin D	Vitamin B12
Yes	B12	r	0.319	-
		p	0.001	-
	Iron	r	-0.147	-0.112
		p	0.386	0.417
No	Iron	r	-	-0.052
		p	-	0.718

However, children with functional language development disorders had lower vitamin D levels compared to healthy children.[20] This study also reported that speech and language disorders were more common in males, particularly among those with functional language development disorders. Golding et al.[21] found that children of mothers with low vitamin B12 levels were more likely to have speech disorders. Another observational study showed that maternal B12 intake from food or supplements during the second trimester was associated with better receptive language skills in children at age 3, though this association was not observed at age 7.[22,23] In a study by Dror and Allen[24], including 48 cases, children with vitamin B12 deficiency exhibited clinical and radiological signs of demyelination, such as apathy, cerebral atrophy, and hypotonia. While neurological symptoms improved rapidly with vitamin B12 treatment, delays in cognitive and language development persisted in these children over the long term.

In contrast to previous studies, our study found that children in the speech disorder group had higher B12 levels than those in the healthy group. This may be due to prior vitamin B12 supplementation among children presenting with speech disorders. Additionally, a positive correlation was found between B12 and vitamin D levels within the speech disorder group, suggesting that both should be considered together when evaluating children with speech disorders.

A study by Lozoff et al.[25] found that children with iron deficiency anemia had poorer motor and cognitive functions

Table 3. Kruskal-Wallis test results regarding the subgroup diagnosis of children with speech disorder

	Diagnosis	n	Mean	SD	Test İst.	p
D vitamin	Fluency disorder	18.50	3.536	2.500	0.983	0.429
	Atypical autism	28.00	.	.		
	Developmental language disorder	22.91	8.792	2.651		
	Stuttering	18.57	5.442	2.057		
	Speech sound disorder	29.50	18.724	4.187		
B12	Fluency disorder	3	259.00	151.321	0.383	0.820
	Atypical autism	1	293.00	.		
	Developmental language disorder	23	293.11	104.530		
	Stuttering	9	261.86	117.675		
	Speech sound disorder	35	250.81	127.794		
Iron	Fluency disorder	87.50	10.607	7.500	1.422	0.245
	Atypical autism	.	.	.		
	Developmental language disorder	64.37	36.726	8.426		
	Stuttering	67.40	36.643	11.588		
	Speech sound disorder	82.23	31.738	5.365		

SD: Standard deviation

than children without anemia. Another study observed that language skills, environmental sound perception, and motor development were lower in children with chronic iron deficiency compared to those without iron deficiency.[26] In our study, children with speech disorders had significantly lower iron levels than the healthy group. The ROC curve analysis revealed that an iron threshold of 44 µg/dl distinguished between the patient and control groups with 25.4% sensitivity and 92.31% specificity. This threshold may serve as an important criterion for treatment planning and follow-up in the patient group.

In a study by Yasin et al.[27] the most common cause of language and speech delays in children was found to be developmental language disorders. Similarly, our study identified developmental language disorders as the most frequent cause.

Limitations

This study had a limited sample size, with 163 participants, which may impact the generalizability of the findings. Conducting studies with larger sample sizes would yield more reliable and comprehensive results. Additionally, the research was conducted in a single pediatric clinic, which may limit the diversity of the sample. Addressing these limitations in future studies and following the recommendations provided could enhance our understanding of the roles of iron, vitamin B12, and vitamin D in children with speech disorders, ultimately improving diagnostic capabilities and clinical practice.

CONCLUSION

Language and speech disorders appear to be common within society. When evaluating children with speech disorders, it is crucial to monitor iron, vitamin D, and vitamin B12 levels to enhance treatment success and prevent potential future complications. Further clinical studies are essential to establish stronger, evidence-based conclusions on this topic.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethics committee approval was obtained from Kırşehir Ahi Evran University Faculty of Medicine Clinical Researches Ethics Committee (Date: 21/02/2023, Decision No: 2023-04/29).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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HLA-B27 positivity and associated factors in spondyloarthritis patients from Turkiye: a single-center study

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ABSTRACT

Aims: Spondyloarthropathies (SpA) constitute a category of multisystemic inflammatory seronegative arthritis. A genetic correlation exists between SpA and the human leukocyte antigen (HLA)-B27 gene. HLA-B27 positive is observed in roughly 90% of patients with ankylosing spondylitis. This study seeks to ascertain the prevalence of HLA-B27 positivity and its associated factors in SpA patients within the Turkish population, while also comparing the demographic, clinical, and radiological characteristics between HLA-B27 positive and negative groups, their utilization of bDMARDs, and the baseline and post-treatment disease activity metrics.

Methods: The study comprised 300 patients having accessible HLA-B27 findings. SpA patients were classified into two groups according to their HLA-B27 status: positive and negative. Demographic parameters, HLA-B27 results, disease activity scores, and the existence of radiographic abnormalities were documented in both groups.

Results: Of the 300 patients involved in the study, 224 (74.7%) tested positive for HLA-B27. The median age of all patients was 45 years, with HLA-B27 positive individuals being younger. The median age for symptom start was 35 years, while the median age for diagnosis was 39 years. Analysis of the radiographic features based on ASAS criteria indicated that the radiographic axial SpA group comprised the largest proportion of patients at 69.2%, followed by non-radiographic axial SpA at 23.4%, and peripheral SpA at 7.4%. Upon comparison of the two groups, the seropositive cohort exhibited a markedly elevated prevalence of familial history. Hypertension was the predominant comorbidity in both the HLA-B27 positive and negative cohorts. The prevalence of smokers was markedly greater in the HLA-B27 positive cohort. The frequencies of radiographic sacroiliitis, syndesmophytes, bamboo spine, and hip involvement were elevated in the positive group when compared. Uveitis exhibited greater prevalence in the positive cohort. Upon comparison of the two groups, the post-treatment reductions in BASDAI, BASFI, VAS Pain, ESR, and CRP levels were more pronounced in the positive group than in the negative group. In comparing the HLA-B27 positive and negative cohorts, no significant disparities were observed in the frequency of single or multiple treatment modifications. Nevertheless, the alteration of bDMARD treatment was less common in the HLA-B27 positive cohort than in the negative cohort.

Conclusion: HLA-B27-positive patients were younger, mostly male, experienced an earlier onset of disease, and demonstrated a more active disease progression. The treatment response was superior in the positive group relative to the negative group.

Keywords: HLA-B27, spondyloarthropathies, seropositive, seronegative

INTRODUCTION

Spondyloarthropathies (SpA) constitute a category of multisystemic inflammatory seronegative arthritis marked by inflammation of the vertebrae, peripheral joints, and periarticular tissues. The SpA group comprises ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis, and enteropathic arthritis.[1] A genetic correlation exists between SpA and the human leukocyte antigen (HLA)-B27 gene. HLA-B27 is a molecule encoded at the B locus of the major histocompatibility complex located on the short arm of chromosome 6. HLA-B27 positive is identified in around 90% of patients with AS.[2] The prevalence of HLA-B27 positive differs by race and ethnicity. HLA-B27 positive is observed in 90–95% of patients with AS in Northern European countries, with the highest prevalence documented among Native Americans.[3] A research in Turkey identified HLA-B27 positive in 70% of patients with AS.[4] The pathophysiology of AS and the precise function of HLA-B27 in disease progression remain inadequately elucidated.[5] Evidence indicates that HLA-B27 positive in AS patients may correlate with early illness onset, prompt diagnosis, familial predisposition, heightened

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incidence of acute anterior uveitis, increased frequency of advanced-stage sacroiliitis, prolonged disease duration, and accelerated disease progression.[6]

This study seeks to ascertain the prevalence of HLA-B27 positivity and its associated factors in SpA patients within the Turkish population, while also comparing the demographic, clinical, and radiological characteristics of HLA-B27 positive and negative groups, their utilization of bDMARDs, and the baseline and post-treatment disease activity parameters.

METHODS

Ethics

Our study adhered to the 2013 modification of the Helsinki Declaration, and ethical approval was obtained from the Institutional Review Board of Health Sciences University Ankara Atatürk Sanatorium Training and Research Hospital (Date: 11.12.2024, Decision No: 2024-BÇEK/180).

Patient Selection

From December 1, 2023, to November 1, 2024, the records of SpA patients scheduled to receive or currently undergoing bDMARD medication were examined in the automation system. The study comprised 300 biologically naive participants with accessible HLA-B27 findings. This study was a single-center, retrospective, descriptive analysis. According to ASAS criteria, the SpA patient cohort was composed of individuals diagnosed with radiographic axial SpA (rAxSpA), non-radiographic axial SpA (nrAxSpA), and peripheral SpA (pSpA).

Study Parameters

The SpA patients involved in the study were classified into two groups according to their HLA-B27 status: positive and negative. The following variables were recorded in both groups: demographic characteristics, age at diagnosis, age at symptom onset, diagnostic delay, disease duration, family history of rheumatologic diseases, comorbidities, smoking status, peripheral joint involvement, extra-articular manifestations, HLA-B27 results, baseline (when the first biological treatment was started) and post-treatment (on the date of last biological treatment) erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, and disease activity scores (BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, VAS: Visual Analogue Scale, VAS Pain, VAS Fatigue, VAS Global), as well as the number of bDMARD switches during follow-up. Furthermore, the presence of radiographic sacroiliitis, syndesmophytes in the lumbar, thoracic, and cervical vertebrae, bamboo spine, hip involvement, and sacroiliitis findings on magnetic resonance imaging (MRI) were documented. The prevalence and distribution of radiographic axial spondyloarthritis, non-radiographic axial spondyloarthritis, and peripheral spondyloarthritis were examined in accordance with ASAS criteria.

Statistical Analysis

The data analysis was conducted utilizing SPSS Statistics for Windows, Version 23.0 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). The adherence of numerical variables to a normal distribution was assessed using both visual approaches (histograms and probability plots) and analytical techniques (Kolmogorov-Smirnov and Shapiro-Wilk tests). Continuous variables were represented as mean±SD in descriptive analyses, while categorical variables were represented as frequencies and percentages. In independent groups, categorical data and rates were compared using eligibility criteria, employing Chi-square or Fisher testing. The independent samples t-test analyzed the means of two independent groups for normally distributed variables. p values less than 0.05 were deemed statistically significant. The Mann-Whitney U test was employed to compare the medians of non-normally distributed data from separate groups. $p<0.05$ was deemed statistically significant.

RESULTS

Demographic Attributes and Axial, Articular, and Extra-Articular Observations of SpA

Of the 300 patients participating in the study, 224 (74.7%) tested positive for HLA-B27. Among the patients, 155 (51.7%) were male, with females predominating in the HLA-B27 negative group, while men predominated in the positive group [125 (55.8%) vs. 30 (39.5%), p=0.01]. The median age of all patients was 45 years (range 20–68), with HLA-B27 positive patients being younger [44 years (range 20–59) compared to 46 years (range 27–68), p=0.01]. The median age at symptom onset was 35 (10–49) years, the median age at diagnosis was 39 (19–53) years, the median diagnostic delay was 4 (0–21) years, and the median disease duration was 5 (0–20) years. The median (min-max) duration of biological treatment is 10 (6-11) months. The median (min-max) age at symptom onset was significantly younger in the positive group, with values of 34.5 (10–47) compared to 36 (16–49), p=0.03. Similarly, the median (min-max) age at diagnosis was also significantly younger in the positive group, recorded at 38.5 (19–53) against 41 (20–53), p=0.01. The median (min-max) diagnostic delay [4 (0–21) years vs. 4 (0–18) years, p=0.68] and median (min-max) illness duration [5 (0–19) years vs. 6 (0–20) years, p=0.5] were comparable between the groups.

Analysis of the radiographic features based on ASAS criteria indicated that the radiographic axial SpA group comprised the largest proportion of patients at 69.2%, followed by non-radiographic axial SpA at 23.4%, and peripheral SpA at 7.4%. A comparison between the HLA-B27 positive and negative cohorts indicated that radiographic axial SpA and peripheral SpA were markedly more prevalent in the positive cohort, while non-radiographic axial SpA was more common in the negative cohort (**Table 1**).

An assessment of the radiographic findings from the sacroiliac, hip, lumbar, thoracic, and cervical radiographs, together with sacroiliac MRI results, indicated that 69.3% of patients exhibited radiographic sacroiliitis, whereas 91.7% demonstrated sacroiliitis on MRI. **Table 1** presents the percentages of individuals exhibiting radiographic syndesmophytes, bamboo spine, hip involvement, and peripheral arthritis. The HLA-B27 positive group exhibited substantially higher rates of radiographic syndesmophyte, bamboo spine, hip involvement, and radiographic sacroiliitis

Table 1. Comparison of radiographic findings between HLA-B27 negative and positive groups

		HLA-B27			
		All patients n (%) 300 (100)	**Positive n (%) 224 (74.7)**	**Negative n (%) 76 (25.3)**	**p value**
SpA disease groups (according to ASAS)	Radiographic axial SpA, n (%)	208 (69.3)	163 (72.8)	45 (59.2)	0.02
	Non-radiographic axial SpA, n (%)	70 (23.3)	39 (17.4)	31 (40.8)	0.000
	Peripheral Spa, n (%)	22 (7.3)	22 (9.8)	0 (0)	0.005
Radiographic sacroiliitis, n (%)		208 (69.3)	163 (72.8)	45 (59.2)	0.02
Sacroiliitis on MRI, n (%)		275 (91.7)	202 (90.2)	73 (96.1)	0.1
Radiographic syndesmophyte, n (%)		72 (24)	60 (26.8)	12 (15.8)	0.05
Radiographic bamboo spine, n (%)		17 (5.7)	16 (7.1)	1 (1.3)	0.05
Radiographic hip involvement, n (%)		29 (9.7)	27 (12.1)	2 (2.6)	0.01
Peripheral arthritis, n (%)		88 (29.3)	73 (32.6)	15 (19.7)	0.03

SpA: Spondyloarthropathies, MRI: Magnetic resonance imaging, HLA-B27: Human leukocyte antigen B27

positivity when compared to the other groups. No substantial variation was noted in the incidence of sacroiliitis on MRI between the two cohorts (Table 1).

Concerning articular and extra-articular manifestations, uveitis was identified in 57 (19%) patients, psoriasis in 77 (25.7%), inflammatory bowel disease in 19 (6.3%), dactylitis in 15 (5%), and enthesitis in 69 (23%). A comparative analysis revealed that uveitis was significantly more prevalent in the positive group [49 (21.9%) vs. 8 (10.5%), p=0.02], while no significant differences were observed in the prevalence of psoriasis [60 (26.8%) vs. 17 (22.4%), p=0.44], inflammatory bowel disease [16 (7.1%) vs. 3 (3.9%), p=0.32], dactylitis [12 (5.4%) vs. 3 (3.9%), p=0.62], and enthesitis [54 (24.1%) vs. 15 (19.7%), p=0.43].

SpA Familial History and HLA-B27

In the family history of 122 patients (40.7%), there was a documented history of rheumatologic disease. Upon comparison of the two groups, the seropositive cohort exhibited a markedly elevated prevalence of familial history [99 (44.2%) vs. 23 (30.3%), p=0.03].

Comorbid Conditions

No significant differences in comorbidities were observed between the HLA-B27 positive and negative groups for asthma/COPD [40 (17.9%) vs. 9 (11.8%), p=0.22], hyperlipidemia [36 (16.1%) vs. 15 (19.7%), p=0.46], cardiovascular disease [32 (14.3%) vs. 10 (13.2%), p=0.8], or chronic kidney disease [14 (6.3%) vs. 3 (3.9%), p=0.45]. The positive group had a considerably greater prevalence of hypertension [78 (34.8%) vs. 16 (21.1%), p=0.02] and diabetes [46 (20.5%) vs. 6 (7.9%), p=0.01]. Hypertension was the predominant comorbidity in both the HLA-B27 positive and negative cohorts. The prevalence of smokers was markedly greater in the HLA-B27 positive cohort [74 (33%) compared to 14 (18.4%), p=0.01].

Baseline and Post-Treatment Disease Activity and Function with Biologic Disease-Modifying Antirheumatic Drugs (bDMARDs)

Table 2 summarizes the mean baseline and post-treatment disease activity levels (BASDAI, BASFI, VAS Global, VAS Fatigue, VAS Pain) along with the mean ESR and CRP data for all patients. Upon comparison of baseline disease activity between groups, the HLA-B27 positive cohort exhibited elevated BASDAI, BASFI, VAS Pain, and VAS Fatigue scores, whereas no significant difference was observed in VAS Global ratings. The baseline levels of ESR and CRP were elevated in the HLA-B27 positive cohort. Upon comparison of post-treatment disease activity metrics between groups, BASDAI, BASFI, and VAS Pain scores were markedly elevated in the HLA-B27 negative cohort. Nonetheless, disease activity metrics diminished in both cohorts following treatment. Upon comparison of the two groups, the post-treatment reductions in BASDAI, BASFI, VAS Pain, ESR, and CRP levels were more pronounced in the positive group than in the negative group (Table 2).

bDMARD Therapeutics and Results

Upon evaluating all SpA patients about their bDMARD selections throughout follow-up, Adalimumab emerged as the most commonly preferred drug, accounting for 111 individuals (37%). Subsequently, Certolizumab accounted for 84 cases (28%), Etanercept for 79 cases (26.3%), Golimumab for 43 cases (14.3%), Secukinumab for 38 cases (12.7%), and Infliximab for 15 cases (5%). In a cohort of HLA-B27+patients, Adalimumab was administered to 85 individuals (37.9%), Etanercept to 66 (29.5%), Certolizumab to 65 (29%), Secukinumab to 16 (21.1%), Golimumab to 33 (14.7%), and Infliximab to 12 (5.4%). Among HLA-B27 negative individuals, Adalimumab was selected by 26 (34.2%), Etanercept by 66 (29.5%), Certolizumab by 19 (25%), Golimumab by 10 (13.2%), Secukinumab by 22 (9.8%), and Infliximab by 12 (5.4%) people. In the comparison of groups, Secukinumab was more commonly favored in the negative group [16 (21.1%) vs. 22 (9.8%), p=0.01]. No statistically significant differences were seen between the two groups regarding additional bDMARDs.

In the assessment of bDMARD therapy alterations, 248 (82.7%) patients maintained their treatment, 34 (11.3%) underwent one treatment modification, and 18 (6%) experienced several treatment modifications. No significant differences were seen between the HLA-B27 positive and negative groups regarding the rate of single treatment modifications [27 (12.1%) vs. 7 (9.2%), p=0.49] or multiple treatment changes [16 (7.1%) vs. 2 (2.6%), p=0.15]. Nonetheless, the alteration of bDMARD

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Table 2. Comparison of change of disease activity parameters after treatment between HLA-B27 negative and positive groups

		HLA-B27			
		All patients	**Positive**	**Negative**	**p value**
Baseline sedimentation, mm/h		20 (2-110)	20.5 (2-110)	19 (2-60)	0.03
Baseline CRP, mg/dl		17 (1-76.9)	17.7 (1-75.1)	10.9 (1-76)	0.000
Recent Sedimentation, mm/h		4 (1-66)	4 (1-66)	5 (1-26)	0.02
Recent CRP, mg/dl		4 (0.9-25)	5 (0.9-25)	2 (1-20)	0.000
Baseline disease activity	BASDAI, (0-10)	7.5 (4.5-9.8)	7.5 (5-9.8)	7.2 (4.5-9.2)	0.02
	BASFI, (0-10)	7.5 (4.5-9.8)	7.7 (4.5-9.8)	7.2 (5.4-9.8)	0.05
	VAS global, (0-100)	76 (45-100)	77 (45-99)	75 (45-100)	0.88
	VAS pain, (0-100)	81 (45-100)	82.5 (45-100)	75 (45-98)	0.01
	VAS fatigue, (0-100)	65 (20-96)	66 (20-96)	62 (30-95)	0.01
After treatment disease activity	BASDAI, (0-10)	3.8 (2.2-6.5)	3.7 (2.2-5.8)	4 (2.5-6.5)	0.003
	BASFI, (0-10)	3.7 (1-7.9)	3.5 (1-7.9)	4.3 (1-7.8)	0.05
	VAS global, (0-100)	35 (5-89)	35 (8-89)	35 (5-75)	0.19
	VAS pain, (0-100)	45 (10-90)	45 (10-90)	54 (30-88)	0.02
	VAS fatigue, (0-100)	35 (5-80)	35 (5-80)	25.5 (5-78)	0.01
BASDAI change		-34 (-71.-6)	-37 (-71.-9)	-29 (-57.-6)	0.000
BASFI change		-33 (-80.-10)	-35 (-80.-10)	-30 (-60.-12)	0.000
VAS global change		-32 (-86.2)	-30 (-86.2)	-37 (-80.-9)	0.03
VAS pain change		-25 (-78.-5)	-27 (-78.-5)	-20 (-41.-5)	0.000
VAS fatigue change		-25 (-90.10)	-25 (-90.10)	-26 (-85.-5)	0.94
CRP change, mg/dl		-11 (-75.9)	-12 (-70. 9)	-6 (-75.1)	0.001
Sedimentation change, mm/h		-14 (-94.1)	-16.5 (-94.1)	-11 (-51.-1)	0.002

HLA-B27: Human leukocyte antigen B27, CRP: C-reactive protein, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, VAS: Visual Analogue Scale. All values are given as median (minimum-maximum).

treatment was less common in the HLA-B27 positive cohort compared to the negative cohort [181 (80.8%) vs. 67 (88.2%), p=0.14].

DISCUSSION

74.7% of the patients in our study were identified as HLA-B27 positive. Patients who tested positive for HLA-B27 were younger, and there was a notable male predominance in this cohort. This group exhibited an earlier start of symptoms and diagnosis, although the diagnostic delay was comparable across the groups. Upon comparison of the rates of radiographic sacroiliitis, syndesmophytes, bamboo spine, and hip involvement, the positive group exhibited a higher prevalence of these conditions. However, no distinction was observed between the two groups in terms of the frequency of MRI-detected sacroiliitis. Radiographic axial spondyloarthritis and peripheral spondyloarthritis were more prevalent in the positive group, while non-radiographic axial spondyloarthritis was more common in the negative group. Uveitis was more common in the positive group, however no differences were observed between the groups regarding psoriasis, inflammatory bowel disease, dactylitis, or enthesitis. There was a family history of rheumatologic disease in 40.7% of the patients, with a higher prevalence in the positive group. Moreover, diabetes, hypertension, and smoking were more prevalent in the positive group. Upon comparison of the two groups, the mean baseline values of BASDAI, BASFI, VAS Fatigue, VAS Pain, ESR, and CRP were elevated in the positive group relative to the negative group. Nonetheless, the post-treatment decrease in BASDAI, BASFI, VAS Pain, ESR, and CRP values was more pronounced in the positive group. No significant differences were seen in bDMARD treatment adjustments between HLA-B27 positive and negative groups concerning single or multiple medication alterations. Nevertheless, there were fewer therapy adjustments in the HLA-B27 positive cohort than in the negative cohort.

Despite the fact that the mechanism of HLA-B27 positivity in the pathogenesis of SpA is not completely understood, genetic predisposition is a well-established fact. In the journal Nature on March 9, 1973, Caffrey and James[7] first demonstrated the significant association between AS and HLA-B27. Schlosstein[8] subsequently corroborated this assertion. In addition, HLA-B27 has been identified as being associated with SpA in forms other than AS. It has been noted that homozygous individuals who are positive for HLA-B27 have a greater susceptibility to AS than heterozygous individuals. In Finland, this rate was 11%, whereas in Korea, it was 29.8%, compared to 0.87%.[9] The degree of HLA-B27 positivity is contingent upon one's ethnicity and race. Günal[4] and Alamanos[10] experienced lower positivity rates than other populations in an HLA-B27 analysis of Greek and Turkish populations, which are geographically similar. Our study established the HLA-B27 positive rate at 74.7%.

Although it is believed that AS is 2 to 5 times more prevalent in men, recent research suggests that the male-to-female ratio has been declining.[11] In two studies that focused on patients with predominantly HLA-B27-negative AS[12] and those that

included the full range of axial SpA[13], it was discovered that HLA-B27-positive patients were more likely to be male than their negative counterparts. In contrast, three additional investigations failed to detect any distinction.[10,14,15] Male dominance was observed among HLA-B27-positive patients in our investigation.

According to Feldtkeller et al.[11], the average age of AS onset was 25.1±8.5 years. This was reported as 23.5±8.9 years in a population-based study conducted in Turkey.[4] The literature presents contradictory findings concerning the age of disease onset in HLA-B27-positive versus negative patients. The tiny sample sizes of the studies can be a contributing factor to the inconsistencies.[16] In a comprehensive study that included 1080 AS patients, it was noted that HLA-B27-positive patients exhibited disease onset an average of three years earlier than their negative counterparts.[11] In contrast to a large study conducted in China that did not disclose a difference[12], subsequent studies have demonstrated a 5 to 9-year difference in the age at which the disease onset occurred between the two patient groups.[9,15] In a prospective, multicenter French cohort (DESIR) that included 708 patients with early axial SpA, HLA-B27-positive patients exhibited a younger disease onset.[13] In this SpA cohort, patients who were HLA-B27-positive experienced a shorter diagnostic delay than those who were negative. HLA-B27-negative AS patients are diagnosed at a later stage and experience prolonged diagnostic delays, as indicated by a multitude of studies in the literature.[5,11,13] HLA-B27-positive patients exhibited a younger age at symptom onset and diagnosis in our study, while the diagnostic delay periods were comparable.

Khan[16] conducted the initial comparison of the clinical characteristics of AS patients who were HLA-B27-positive and those who were negative in 1977. Consequently, numerous studies have assessed the prevalence of musculoskeletal manifestations of AS, such as hip arthritis, enthesitis, dactylitis, and peripheral arthritis. The majority of studies have emphasized that HLA-B27-positive AS patients have a substantially higher prevalence of these features than their negative counterparts. However, two studies did not find a significant difference.[14,17] It is widely acknowledged that hip arthritis is a reliable indicator of severe disease in AS.[18] In the positive group of our cohort, hip involvement was more prevalent. The literature has not generally shown a significant relationship between the occurrence of peripheral arthritis and HLA-B27 status, in contrast to our study.[6] In the DESIR cohort[13] and a Brazilian AS cohort[14], a substantially higher prevalence of enthesitis was observed in HLA-B27-positive AS patients; however, this finding was not reported in other studies.[9,12,15] There was no distinction in the frequency of enthesitis between the two groups in our investigation. Consistent with our research, two studies that documented dactylitis prevalence found no significant difference between HLA-B27-positive and negative AS patients.[12,13]

The prevalence of uveitis in our sample was markedly elevated in the HLA-B27-positive group, corroborating findings in the literature.[19,20] The initial report indicating that acute anterior uveitis is more prevalent in HLA-B27-positive AS patients compared to their negative counterparts was published in 1977.[16] HLA-B27-associated uveitis is alarming due to its high incidence, effect on relatively young individuals, frequently recurring inflammatory episodes, and potential for vision-threatening ocular consequences.[21] Acute anterior uveitis is the predominant kind, comprising almost 90% of all instances. Fifty percent of all acute anterior uveitis cases are positive for HLA-B27. About 50% of patients with HLA-B27-positive acute anterior uveitis acquire SpA during follow-up, whereas approximately 25% of those diagnosed with SpA suffer acute anterior uveitis.[22]

Research demonstrates that HLA-B27 is a significant genetic marker for psoriatic arthritis (PsA); nevertheless, the elevated prevalence of HLA-B27 among PsA patients (<20%) does not extend to psoriasis. Individuals with psoriasis demonstrate a prevalence of HLA-B27 positive comparable to that of the healthy population (4.5% versus 7.2%). Literature indicates a marginally reduced HLA-B27 prevalence in people with concurrent psoriasis compared to those without (80% vs. 90.5%).[23] Likewise, a separate study involving patients with AS[16] and another encompassing the entire axial SpA spectrum indicated a greater frequency of psoriasis among HLA-B27-negative patients.[13] Our investigation revealed no significant difference in psoriasis prevalence between the HLA-B27-positive and negative groups.

The prevalence of HLA-B27 in IBD patients has not risen relative to the general population.[24] Numerous research have indicated that IBD is more commonly found in HLA-B27-negative individuals. The incidence of IBD is approximated at 1% among HLA-B27-positive AS patients and 9% among HLA-B27-negative individuals.[14] A comprehensive assessment of 908 HLA-B27-positive and 90 HLA-B27-negative patients indicated IBD prevalences of 9% and 20%, respectively ($p<0.001$).[17] among the DESIR cohort examining early axial spondyloarthritis patients, a markedly elevated frequency of inflammatory bowel disease was seen among HLA-B27-negative individuals.[13] Our analysis revealed no significant difference in IBD prevalence between the HLA-B27-positive and negative groups.

In the axial SpA DESIR cohort, inflammatory and structural lesions in the spine or sacroiliac joints, identified using radiography and MRI, were more common in HLA-B27-positive individuals than in those who were negative.[13] A cross-sectional study in Belgium with 619 AS patients indicated a trend of increased HLA-B27 positive among those with spinal syndesmophytes (89%) and complete ankylosis (87%).[25] Conversely, a separate cross-sectional investigation of 398 patients identified no correlation between HLA-B27 positive and radiographic severity.[26] Our investigation revealed that the prevalence of radiographic sacroiliitis, syndesmophytes, and bamboo spine was greater in the HLA-B27-positive cohort.

The incidence of familial AS is elevated among persons possessing the HLA-B27 allele. Zhang et al.[27] conducted a study revealing that a family history was more prevalent among HLA-B27-positive people. Approximately 20% of HLA-B27-positive relatives of AS patients are reported to develop the condition, but only 1.3% of HLA-B27-positive persons in the general population have been diagnosed with the disease.[28] In

our study, 40.7% of HLA-B27-positive individuals exhibited a familial history of rheumatologic disease.

Although there is a prevalent belief that HLA-B27 correlates with disease severity in AS, its influence on structural development in the spine or sacroiliac joints remains unproven. Published cohort studies have indicated comparable BASDAI[29] and BASFI[9,15,29] scores in both HLA-B27-positive and negative individuals. The DESIR cohort indicated marginally inferior BASDAI and BASFI scores in the HLA-B27-negative patient demographic.[13] Our investigation revealed that, at baseline, disease activity indicators such as BASDAI, BASFI, VAS Fatigue, VAS Pain, ESR, and CRP levels were elevated in HLA-B27-positive patients compared to their negative counterparts. Post-treatment, the disease activity indicators, together with the mean ESR and CRP values, diminished in both cohorts. In the comparison of the two groups, the post-treatment decrease in BASDAI, BASFI, VAS Pain, ESR, and CRP values was more pronounced in the positive group than in the negative group.

No substantial difference was observed between single and multiple medication changes when comparing HLA-B27-positive and negative groups in our cohort for b-DMARD therapy modifications. A greater number of HLA-B27-positive individuals necessitated fewer modifications to b-DMARD treatment than the negative group. Two studies examining the impact of HLA-B27 on disease activity and treatment response in AS patients concluded that HLA-B27 status, whether positive or negative, did not affect treatment regimen decisions or alterations.[1,30] Treatment selection in clinical practice is determined by the patient's clinical presentation. The primary drawback of our study is its single-center, retrospective design.

CONCLUSION

In conclusion, HLA-B27 positive in the Turkish population was observed to be lower than in other ethnic groups. Patients who tested positive for HLA-B27 were younger, mostly male, experienced an earlier onset of disease, and demonstrated a more active disease progression. The treatment response was superior in the positive group relative to the negative group. Due to the strong correlation between HLA-B27 positive and uveitis, this aspect should be taken into account while formulating treatment plans. Moreover, the heightened incidence of rheumatologic disorders among the relatives of HLA-B27-positive individuals warrants attention.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval was obtained from the Institutional Review Board of Health Sciences University Ankara Atatürk Sanatorium Training and Research Hospital (Date: 11.12.2024, Decision No: 2024-BÇEK/180).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Evaluation of pulmonary hydatid cysts in children: 5-year data from a single center

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ABSTRACT

Aims: The aim of this study was to evaluate the demographic characteristics, clinical symptoms, complications, and treatment options of patients with pulmonary hydatid cysts.

Methods: A retrospective chart review of all pediatric patients (age <18 years) diagnosed with pulmonary hydatid cysts between January 1, 2019 and June 30, 2024 was performed. Patients were divided into two groups: patients with ruptured cyst and patients with unruptured cyst. All data were compared between the two groups.

Results: A total of 44 patients with a mean age of 116.01±44.41 months were included in the study. The most common symptom was cough (n=38, 86.4%), followed by chest pain (n=22, 50%). The most common complication was cyst rupture (n=10, 22.7%), and followed by pleural effusion (n=9, 20.5%). Forty-two (95.5%) patients underwent surgery and 14 (31.8%) patients required admission to the intensive care unit admission after surgery. Hemoptysis, cyst diameter, intensive care unit admission, length of stay, and recurrence were significantly more associated with cyst rupture.

Conclusion: Pulmonary hydatid cysts should be considered in the differential diagnosis of children presenting with lower respiratory tract symptoms such as fever, cough, hemoptysis, and chest pain, especially in regions where echinococcosis is endemic. Pulmonary hydatid cysts can lead to life-threatening complications such as bronchial rupture. Hemoptysis and larger cyst diameter are associated with bronchial rupture.

Keywords: Childhood, cystic echinococcosis, pulmonary hydatid cyst, rupture

INTRODUCTION

Cystic echinococcosis, or hydatid disease, is a zoonosis caused by the larval stage of the cestode *Echinococcus granulosus*.[1] The life cycle of *Echinococcus granulosus* typically involves dogs as the definitive host and ruminants (e.g., sheep, goats) as intermediate hosts. Humans serve as incidental intermediate hosts by acquiring infection through ingestion of food contaminated with dog-laid eggs.[2,3] It is endemic in South America, East Africa, Australia and Mediterranean countries and still poses a health problem especially in the eastern and southeastern parts of Turkiye.[4,5]

In contrast to adults, the lung is the most common localizing organ in children. Hydatid cysts may rarely occur in organs other than the lung and liver, such as the spleen, kidney, brain, and soft tissues.[6] Hydatid cysts grow more rapidly in the lung than in the liver. This is due to the elastic structure of the lung and the negative intrathoracic pressure.[7] Rupture is the main complication of cysts and may be related to the presence of symptoms, and to morbidity and mortality. The diameter and the location of the cyst has been proposed as risk factors for cyst rupture. Pulmonary hydatid cysts (PHCs) are more likely to rupture than hepatic hydatid cysts.[8] In children, PHCs often cause respiratory symptoms such as cough, hemoptysis, chest pain, shortness of breath, and fever.[1]

The aim of this study was to evaluate the epidemiologic characteristics, clinical symptoms, complications, and treatment options of patients with PHCs.

METHODS

Ethical approval was obtained from the Institutional Ethics Committee of Necmettin Erbakan University Faculty of Medicine (Date: 18.10.2024, Decision No: 2024/5260). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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A retrospective chart review of all pediatric patients (age <18 years) diagnosed with PHC at Necmettin Erbakan University Faculty of Medicine, Pediatric Pulmonology Clinic between January 1, 2019 and June 30, 2024 was performed. Patients with (1) compatible histopathologic findings, (2) positive serology with compatible clinical presentation, or (3) a clinical presentation, epidemiology, and imaging compatible with PHC were included in the study. Patient demographics, presenting symptoms, clinical findings, computed tomography (CT) findings (cyst location, diameter), treatment modalities (surgical, medical), complications, length of hospital stay, history of recurrence and intensive care unit (ICU) admission were recorded.

Statistical analyses

The Kolmogorov-Smirnov test was used to determine the normality of the distribution. Continuous data were presented as mean±standard deviation for variables with a normal distribution and as median and interquartile range (IQR) for variables with a non-normal distribution. Categorical data were presented as frequencies and percentages. The patients were divided into two groups as patients with ruptured cyst and patients with unruptured cyst. Student's t-test was used to compare two groups of continuous data and chi-squared test was used to compare categorical data. MedCalc statistical software (MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org), version 20.110 was used for all analyses. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 44 patients diagnosed with PHC were included in the study. The mean age was 116.01±44.41 months. Twenty-four (54.5%) patients were male and 20 (45.5%) were female. Twenty-eight (63.6%) patients were from rural areas and 16 (36.4%) were from urban areas.

Two (4.5%) patients were asymptomatic. The most common symptom was cough (n=38, 86.4%), followed by chest pain (n=22, 50%). There were 8 (18.2%) patients who had two cysts. The most common lung involvement was found in right lower lobe with 13 (29.5%) patients. Twenty (45.5%) patients had liver involvement and 3 (6.8%) patients had other organ involvement. The most common complication was cyst rupture (n=10, 22.7%), and followed by pleural effusion (n=9, 20.5%). All of the patients received albendazole as a first-line treatment. Forty-two (95.5%) patients underwent surgery and 14 (31.8%) patients required admission to the ICU admission after surgery. **Table 1** summarizes the detailed clinical findings of the patients.

When comparing patients with a ruptured cyst to patients without a ruptured cyst, hemoptysis was significantly more common in patients with a ruptured cyst. In addition, cyst diameter, ICU admission, length of stay, and recurrence were significantly more associated with cyst rupture. **Table 2** summarizes the comparison of patients with and without cyst rupture.

Table 1. Clinical characteristics of the study population

Symptoms, n (%)	
Asymptomatic	2 (4.5)
Cough	38 (86.4)
Weakness	12 (27.3)
Sputum	20 (45.5)
Chest pain	22 (50)
Fever	19 (43.2)
Hemoptysis	3 (6.8)
Abdominal pain	5 (11.4)
Nausea-vomiting	2 (4.5)
Dyspnea	6 (13.6)
Night sweats	2 (4.5)
Weight loss	3 (6.8)
Anaphylaxis	1 (2.3)
Localization, n (%)	
Right	
Upper lobe	5 (11.4)
Middle lobe	5 (11.4)
Lower lobe	13 (29.5)
Left	
Upper lobe	7 (15.9)
Middle lobe	3 (6.8)
Lower lobe	11 (25)
Hepato-pulmonary involvement	20 (45.5)
Spleen	3 (6.8)
Patients with two cysts, n (%)	8 (18.2)
Diameter of the cyst, mm, mean±SD	64.02±29.02
Complications, n (%)	
Rupture	10 (22.7)
Bronchus	7 (15.9)
Parenchyma	3 (6.8)
Pleural effusion	9 (20.5)
Atelectasis	6 (13.6)
Pneumothorax	1 (2.3)
Surgery, n (%)	42 (95.5)
Intensive care unit admission, n (%)	14 (1.8)
Length of stay in hospital, days, mean±SD	7.68 ± 4.27
Recurrence, n (%)	6 (13.5)

SD: Standard deviation

DISCUSSION

This infection is more common in areas where livestock markets are common. Humans become infected through food contaminated with eggs in the feces of the primary host. In the gastrointestinal tract, the larvae penetrate the intestinal mucosa and travel via the porto-caval anastomosis to the liver or via the general circulation to the lungs or other organs.[9] While it is an endemic disease in South America, East Africa, Australia, and Mediterranean countries, it is also a growing thoracic pathology in non-endemic countries due to increased global travel and immigration.[5,10] In a study conducted in Istanbul, which is an industrialized city, Arinc et al.[4] reported that 54.1% of pulmonary HC patients came from rural areas, and this finding shows the effect of increased migration and travel. Our hospital is located in an Anatolian city where livestock markets are common and an important source of livelihood even in the city center, and our results showed that 63.6% of the admissions were from rural areas. Although most of the patients from rural areas, rupture was more common in urban patients even no statistical difference.

Once cysts enter the body and mature in the resident organ, they may remain latent for a long time and symptoms may not appear until they reach a certain size or complications arise. Only 10-19% of patients are reported to be asymptomatic. The most common symptoms reported are cough, chest pain, and sputum production.[11] In this study, only 2 (4.5%) patients

Table 2. Comparison of patients with ruptured and unruptured cysts

	Ruptured cyst (n=10)	Unruptured cyst (n=34)	p value
Age, months, mean±SD			
Gender, n (%)			
Male	3 (30)	21 (61.8)	0.147
Female	7 (70)	13 (38.2)	
Sociogeographic status, n (%)			
Rural areas	5 (50)	23 (67.6)	0.456
Urban areas	5 (50)	11 (32.4)	
Symptoms, n (%)			
Cough	10 (100)	28 (82.4)	0.310
Weakness	1 (10)	11 (32.4)	0.241
Sputum	7 (70)	13 (38.2)	0.147
Chest pain	6 (60)	16 (47.1)	0.472
Fever	4 (40)	15 (44.1)	0.817
Hemoptysis	3 (30)	0 (0)	**0.009**
Abdominal pain	0 (0)	5 (14.7)	0.198
Nausea-vomiting	1 (10)	1 (2.9)	0.346
Dyspnea	2 (20)	4 (11.8)	0.505
Night sweats	1 (10)	1 (2.9)	0.346
Weight loss	1 (10)	2 (5.9)	0.548
Anaphylaxis	1 (10)	0 (0)	0.227
Localization, n (%)			0.481
Right	4 (40)	19 (55.9)	
Upper lobe	0 (0)	5 (14.7)	
Middle lobe	1 (10)	4 (11.8)	
Lower lobe	3 (30)	10 (29.4)	
Left	6 (60)	15 (44.1)	
Upper lobe	2 (20)	5 (14.7)	
Middle lobe	1 (10)	2 (5.9)	
Lower lobe	3 (30)	8 (23.5)	
Hepato-pulmonary involvement	2 (20)	18 (52.9) 20 (45.5)	0.083
Spleen	0 (0)	3 (8.8)	0.331
Diameter of the cyst, mm, mean±SD	84.40±30.77	58.02±26.00	0.010
Intensive care unit admission, n (%)	8 (80)	6 (17.6)	0.001
Length of stay in hospital, days, mean±SD	10.40±4.47	6.88±3.92	0.020
Recurrence, n (%)	4 (40)	2 (5.9)	0.018

SD: Standard deviation

were asymptomatic and had uncomplicated PHC, which is lower then the literature. Among the symptomatic 42 (95.5%) patients, the most common symptoms were cough and chest pain, as expected.

While hydatid cysts are more common in the liver in adults, they are more common in the lungs in children.[12] PHCs grow more rapidly and are more likely to become symptomatic due to the compressibility of lung tissue, high vascularity, and low negative pressure.[6,13] Faster growth leads to more complications. While there are some studies reporting that the rupture rate increases with increasing cyst size, there are also studies reporting the opposite situation.[14-18] Previous studies have reported rupture rates ranging from 21.1% to 53.1%.[18,19] In this study, there were 10 (22.7%) patients who experienced cyst rupture, which is consistent with the literature. All 3 patients with hemoptysis were in the ruptured group. The mean diameter of the cysts was higher in the ruptured group than in the unruptured group with a statistical difference. In addition, the length of stay, ICU admission, and recurrence were more common in ruptured cysts, as expected. Although there was no statistical difference, the left-sided cysts were more likely to be rupture. This may be due to the lower compressibility of the lung tissue on the left side compared to the right side as a result of the left-located heart.

Conventional surgery is the main treatment for PHC. The goal of this surgery is to remove all parasitic material and repair the bronchial fistulas while preserving as much lung tissue as possible, especially in children. Kocaman et al.[20] reported that 93.2% of their patients underwent surgery. In this study, 42 (95.5%) patients underwent surgery, which is consistent with the literature. One patient with anaphylaxis underwent emergency surgery. Two patients did not require surgery and were treated with albendazole alone.

Limitations

The major limitations of our study were the retrospective collection of data from a single center and the small number of patients. Cystic echinococcosis, especially PHC, is difficult to diagnose and requires a high index of suspicion, especially in children and centers from non-endemic regions. Furthermore, due to the retrospective nature of the study, we were unable to assess and evaluate the surgical data and its impact on recurrence.

CONCLUSION

In conclusion, hydatid cysts are still a health problem, especially in urban areas. PHC can be life-threatening, leading to anaphylaxis and bronchial rupture. PHC should be considered in the differential diagnosis of children presenting with lower respiratory tract symptoms such as fever, cough, hemoptysis, and chest pain, especially in regions where echinococcosis is endemic.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval was obtained from the Institutional Ethics Committee of Necmettin Erbakan University Faculty of Medicine (Date: 18.10.2024, Decision No:h 2024/5260).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

ANATOLIAN CURRENT MEDICAL

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Can levels of serum uric acid and HDL cholesterol effectively predict the presence of fatty liver in children with obesity?

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ABSTRACT

Aims: Our study aimed to evaluate the relationship between biochemical parameters such as high uric acid and low HDL levels and metabolic dysfunction-associated steatohepatitis (MDAS) in children with obesity.

Methods: The records of 81 obese children with a body mass index above two standard deviations for their age who underwent fasting lipids, liver enzymes, uric acid level, oral glucose tolerance tests (OGTT), and abdominal ultrasounds to assess fatty liver were reviewed retrospectively. The findings from physical examinations and results from laboratory and imaging tests were documented. The relationship between laboratory data and MDAS was examined.

Results: The study included 81 children, 27 males and 54 females. Fifty-six out of the total participants, accounting for 69.2%, were diagnosed with steatohepatitis. the MDAS and non-MDAS subjects' SUA levels were 6.34±1.36 mg/dl and 5.26±1.09 mg/dl, respectively. HDL levels were significantly lower in MDAS children than in non-MDAS children (39.90±7.89 vs. 45.23±7.32, p=.005,). Moreover, the MDAS and non-MDAS subjects' SUA levels were 6.34±1.36 mg/dl and 5.26±1.09 mg/dl, respectively. There was a statistical difference between the two groups (p<.001,).To assess the diagnostic performance of each marker and predictive model, we conducted a receiver operating characteristics (ROC) analysis. As individual predictors, SUA (AUC=0.729 [95% CI, 0.619–0.822], cut-off >6.89, sensitivity=37.5, specificity=100) and HDL (AUC=0.699 [95% CI, 0.587–0.796], cut-off ≤39.2, sensitivity=51.8, specificity=84) showed similar diagnostic performance in discriminating MDAS from non-MDAS patients.

Conclusion: Elevated SUA levels with low HDL levels may significantly predict MDAS.

Keywords: Uric acid, HDL, obesity, children, fatty liver

INTRODUCTION

Obesity is a significant factor in several endocrine diseases, including insulin resistance (IR), type 2 diabetes (T2D), hypertension, hyperuricemia, and metabolic syndrome. This significantly strains patients, families, and the public health system. Many cross-sectional studies have shown that obesity, as diagnosed by body-mass index (BMI), often leads to hyperuricemia.[1] Recent studies have found that hyperuricemia not only leads to gouty arthritis and nephropathy but may also be associated with IR, T2D, and cardiovascular morbid events.[1-3]

Metabolic dysfunction-associated steatohepatitis (MDAS) can be seen as a hepatic manifestation of metabolic syndrome in children and adolescents. The incidence of MDAS is increasing parallel to the increase in obesity, hyperlipidemia, and T2D mellitus. Uric acid is a product of purine metabolism due to protein catabolism. Its increased levels are associated with high consumption of purines (animal protein, meat, and seafood) and fructose (fruit, processed foods). High serum uric acid (SUA) levels play an essential role in the pathophysiology of arterial hypertension, renal failure, congestive heart failure, and T2D, and some studies have shown that it directly induces fat accumulation in hepatocytes.[3] In a large prospective cohort study of 2832 individuals in China, the authors found that high SUA levels were an independent risk factor for MDAS.[4] A large-scale population-based study in Western countries also found that hyperuricemia was significantly associated with MDAS.[5] In contrast, a recent cross-sectional study in children and adolescents in Brazil showed that SUA levels were associated with metabolic syndrome and puberty but not with MDAS.[6]

Our study aimed to evaluate SUA, HDL, and other laboratory parameters that may be associated with MDAS in obese children.

METHODS

The study was approved by the local ethics committee of Selçuk University Faculty of Medicine (Date: 08.10.2024, Decision No: 2024/509). All procedures were carried out in

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accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study analyzed the records of patients who visited the endocrinology clinic with concerns about excessive weight from November 2020 to May 2022. Eighty-one children aged ten years and over, with a BMI standard deviation score (BMI-SDS) ≥2, who underwent abdominal ultrasound to evaluate liver steatosis and who also underwent fasting lipids [included total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglycerides (TGs)]; fasting glucose, fasting insulin, SUA, and OGTT tests in our hospital were included in the study.

The patient's records documented height, weight, all anthropometric measurements, age, gender, laboratory, and clinical findings. The presence of acanthosis nigricans was evaluated in patients whose physical examinations were performed by a single pediatric endocrinologist. Pubertal status was assessed according to Tanner staging.[7]

The relationship between the presence and degree of MDAS in the patient's abdominal USG and SUA and other laboratory levels was evaluated. All subjects were divided into two groups (with or without MDAS) based on hepatic ultrasound examination results.

Statistical Analysis

All data processing and statistical analyses were performed using R language version 4.2.1. (www.r-project.org). A two-sided p-value<.05 was considered statistically significant. Patient characteristics were reported as mean±standard deviation (SD) or median with quartiles [1st quartile–3rd quartile] for numerical variables and frequency (n) with percentage (%) for categorical variables. Before statistical analyses, the Shapiro-Wilk normality test was used to check the conformity of the distributions of continuous variables to the normal distribution. In addition, Levene's test was used to assess the homogeneity of variances when comparing continuous variables between groups. Comparisons (univariate analysis) between groups were analyzed by student's t-test, Welch's t-test, Mann-Whitney U test for numerical data, and Chi-square test with Yates continuity correction for categorical data. The variables found to be significant in the univariate analysis were included in the multiple analysis. A multiple logistic regression analysis was performed to examine.

Logistic regression analysis with a stepwise backward elimination approach was used for model development. The predictive accuracy of the models was compared using receiver operating characteristic (ROC) curves. Multiple models considered covariates with a p-value of 0.10 or less significant.

In multiple models, sex was included as a covariate.

The odds ratio (OR) and 95% confidence interval (CI) of the risk factors.

RESULTS

The study included 81 children, 27 males and 54 females. Fifty-six out of the total participants, accounting for 69.2%, were diagnosed with steatohepatitis. The mean age of the whole cohort was 14.09±2.24 years; it was 13.93±2.36 years in the non-MDAS group and 14.17±2.20 years in the MDAS group. Based on the records of pubertal examination, only seven patients (7.4%) were found to be in the prepubertal period.

Compared with the non-MDAS children, MDAS children were more likely to be male and overweight and had higher biochemical indices, including serum levels of insulin, AST, ALT, and GGT (**Figure 1 A-E and H**). In addition, HDL levels were significantly lower in MDAS children than in non-MDAS children (39.90±7.89 vs. 45.23±7.32, p=.005, **Figure 1-G**). Moreover, the MDAS and non-MDAS subjects' SUA levels were 6.34±1.36 mg/dl and 5.26±1.09 mg/dl, respectively. There was a statistical difference between the two groups (p<.001, **Figure 1-F**). The clinical and biochemical characteristics of the study population are summarized in **Table**.

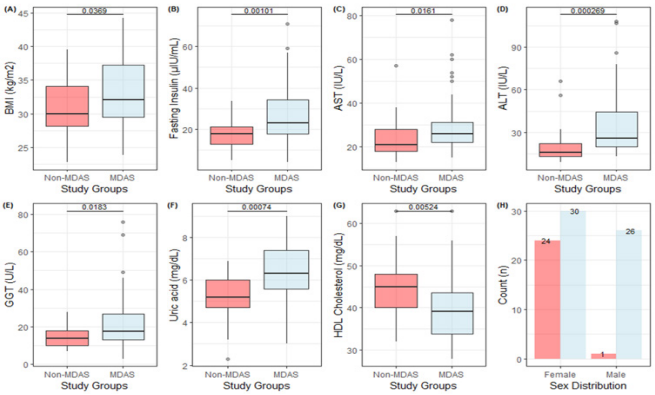

Figure 1. Boxplots compare (**A**) BMI, (**B**) fasting insulin, (**C**) AST, (**D**) ALT, (**E**) GGT, (**F**) uric acid, and (**G**) HDL cholesterol for children with MDAS and non-MDAS groups. The boxplots represent the data distribution; the horizontal line indicates the median. The sample's first and third quartiles are the box's lower and upper hinges. (H) The bar plot shows the sex distribution of the study groups
BMI: Body-mass index, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transferase, HDL: High-density lipoprotein, MDAS: Metabolic dysfunction-associated steatohepatitis

Multiple logistic regression analyses of sex, BMI, ALT, AST, GGT, SUA, and HDL parameters identified only sex, uric acid, and HDL as significant independent predictors of MDAS.

To assess the diagnostic performance of each marker and predictive model, we conducted a ROC analysis (**Figure 2**). As individual predictors, SUA (AUC=0.729 [95% CI, 0.619–0.822], cut-off >6.89, sensitivity=37.5, specificity=100) and HDL (AUC=0.699 [95% CI, 0.587–0.796], cut-off ≤39.2, sensitivity=51.8, specificity=84) showed similar diagnostic performance in discriminating MDAS from non-MDAS patients (DeLong's test Z=0.403, p=.687). The predictive model, including sex as a confounding variable, had a superior diagnostic performance for the diagnosis of MDAS compared to SUA (DeLong's test Z=2.200, p=.028) and HDL (DeLong's test Z=2.465, p=.014) with an AUC of 0.833 [95% CI, 0.733–0.906].

DISCUSSION

MDAS is a complex disease that has become the most common chronic liver condition in both children and adults globally. Over the past few decades, the prevalence of MDAS has more than doubled.[8] With the rising obesity rates, these numbers are expected to increase even more.[9] In a meta-

Table. The clinical and biochemical characteristics of the study population

	Non-MDAS(n=25)	MDAS (n=56)	p-value
Age (months)	167.16±28.33	170.11±26.46	.652[1]
Sex (male/female)	1 (4%)/24 (96%)	26 (46.4%)/30 (53.6%)	<.001[2]
Weight (kg)	76.68±16.13	89.96±19.64	.004[1]
Weight SD	2.94±0.99	3.37±1.20	.128[1]
Height (cm)	156.98±10.60	162.96±11.75	.032[1]
Height SD	0.17±1.00	0.65±1.57	.099[3]
BMI (kg/m²)	30.82±4.48	33.31±5.05	.037[1]
BMI SD	2.68±0.65	2.90±0.69	.175[1]
Pubertal status	23 (92%)	52 (92.9%)	>.999[4]
Acanthosis nigricans	19 (76%)	41 (73.2%)	>.999[2]
Stria	12 (48%)	27 (48.2%)	>.999[2]
FBS (mg/dl)	86.68±10.94	88.04±12.70	.645[1]
Fasting insulin (µIU/ml)	18 (13–21.4)	23.2 (18–34.25)	.001[5]
PBS (mg/dl)	110 (90–125)	106 (89.25–125)	.595[5]
Post-prandial insulin (µIU/ml)	65.4 (54–87)	71.5 (44.15–117.25)	.775[5]
HbA1c (%)	5.50±0.54	5.68±0.73	.287[1]
AST (IU/L)	21 (18–28)	26 (22–31.25)	.016[5]
ALT (IU/L)	16 (13–22)	26 (20–44.5)	<.001[5]
GGT (U/L)	14 (10–18)	17.5 (13–27)	.018[5]
Uric acid (mg/dl)	5.26±1.09	6.34±1.36	<.001[1]
TSH (mIU/L)	1.8 (1.47–2.7)	2.6 (1.9–3.2)	.051[5]
fT4 (ng/dl)	1.04±0.22	1.09±0.20	.293[1]
Vitamin B-12 (pg/ml)	255 (183–302)	270.5 (217–374.5)	.269[5]
25 (OH) vitamin D (ng/ml)	12.4 (8.7–15)	12.25 (7.72–16.7)	.935[5]
TG (mg/dl)	116 (87–154)	120.5 (90.75–168.25)	.529[5]
Total cholesterol (mg/dl)	157.16±31.70	159.02±34.61	.820[1]
LDL cholesterol (mg/dl)	91.04±24.47	92.63±29.31	.814[1]
HDL cholesterol (mg/dl)	45.23±7.32	39.90±7.89	.005[1]
Haemoglobin (g/dl)	13.7 (13–14.2)	13.8 (13.05–14.45)	.649[5]
PTH (pg/ml)	51 (43–67)	53 (35.38–72)	.963[5]

[1] student's t-test; [2] Chi-square test with Yates continuity correction; [3] Welch's t-test; [4] Fisher's exact test; [5] Mann-Whitney U test.
Data were presented as mean±standard deviation or median with quartiles [1st quartile–3rd quartile], as appropriate for numerical data; categorical variables were also described as count (n) and percentage (%).
MDAS: Metabolic dysfunction-associated steatohepatitis, BMI: Body-mass index, FBG: Fasting blood sugar, PBS: Postprandial blood sugar (OGTT 2nd hour blood sugar), AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transferase, TSH: Thyroid stimulating hormone, fT4; Free thyroxine, TG; Triglyceride, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, PTH: Parathyroid hormone, SD: Standard deviation

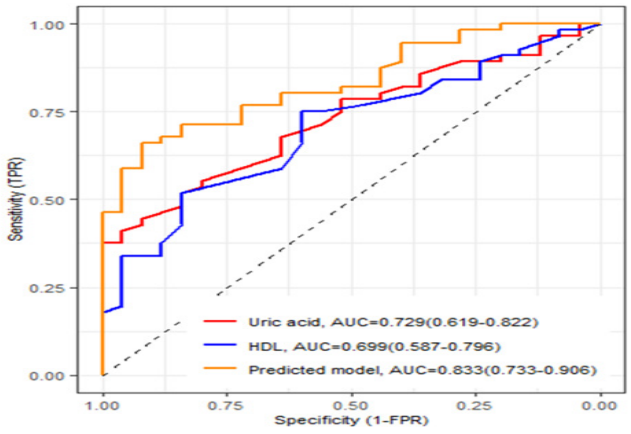

Figure 2. Receiver operating characteristics (ROC) curve of SUA, HDL, and the predictive model combining SUA and HDL, and adjusting for sex as a confounding variable to identify MDAS
HDL: High-density lipoprotein, MDAS: Metabolic dysfunction-associated steatohepatitis, SUA: High serum uric acid

analysis conducted by Anderson et al.[10], MDAS in children with obesity was estimated to be 34.2% (95% CI: 27.8–41.2%), compared to 7.6% (95% CI: 5.5–10.3%) in the general pediatric population. Our study found MDAS in 69.2% (56 participants) of the 81 children examined for obesity.

Dietary factors such as high fructose intake, consumption of high-glycemic index foods, and sugar-sweetened beverages play a crucial role in developing MDAS.[11] The fructose component of sugar and high-fructose corn syrup contributes to the formation of fatty liver by promoting the creation of new fat and inhibiting the breakdown of fatty acids.[12] The effects mentioned are linked to fructokinase's metabolism of fructose. This process leads to the conversion of nucleotides and the formation of uric acid. It also causes a decrease in adenosine triphosphate (ATP), which results in prooxidative and pro-inflammatory effects that worsen the formation of

fat in the liver.[13,14] A meta-analysis of 11 studies from various countries, including China, Korea, Japan, India, and the United States, found a significant association between SUA and MDAS. The risk of MDAS was almost doubled in the highest SUA group compared to the lowest group.[15] Similarly, this study found that patients with MDAS had higher SUA values than those without.

In the literature, some studies suggest that high SUA has a more significant impact on causing fatty liver in females than males. However, studies indicate that the predictive value of SUA levels is higher in males or similar in both genders.[4,15-17] In this study, the estimated model, including Gender as a confounding variable, had a superior diagnostic performance in men compared to SUA and HDL for MDAS diagnosis. The different results may stem from variations in sample sizes, populations, definitions of hyperuricemia, lifestyles, and dietary habits.

HDL is the primary vehicle for transporting cholesterol from peripheral cells to the liver for disposal and catabolism. However, during this intricate metabolic process, molecules other than lipids (such as hormones, vitamins, proteins, and miRNAs) are also known to be incorporated into HDL particles and transported to distant organs. This process may play a role in maintaining cardiovascular health.[18] Although the mechanism is unclear, a relationship between MDAS and low HDL levels has been described.[19] A large Mendelian randomization study found low HDL levels associated with MDAS.[20] Multiple sex-adjusted logistic regression analyses performed in this study showed that a higher risk of having MDAS was associated with higher SUA levels and lower HDL levels.

While liver biopsy remains the gold standard for diagnosing and staging MDAS, ultrasonography is the most widely used screening tool for hepatic steatosis in clinical practice.[21,22] New scoring systems have improved the reliability of ultrasonography in this disease.[23,24] The sensitivity of liver ultrasonography may vary depending on hepatic fat content. However, as previously mentioned, liver ultrasonography offers several advantages, including its noninvasiveness. It has also been reported that when performed correctly, it can detect liver fat content as low as 5% or more.[25] Fatty liver screening of obese children included in the study was performed using ultrasonography.

Limitations

Our study has some limitations. First, as mentioned above, our cross-sectional study design cannot establish causality between uric acid and MDAS. Instead, such data should be viewed as hypothesis-generating. Secondly, the fatty liver condition was assessed using ultrasound. Third, more direct and accurate visceral adiposity and IR measurements were unavailable in this study. Fourthly, this study focused exclusively on obese children and compared them based on the presence of DAS. A healthy control group was not included in the evaluation. Finally, we did not account for lifestyle or dietary factors, such as meat and fructose intake, which may contribute to increased uric acid levels and MDAS. Healthy lifestyle changes should be the primary approach, not just lowering uric acid levels.

CONCLUSION

As a result, pediatric MDAS is likely to continue progressing as a hidden epidemic in the coming years. To avoid a diagnosis of exclusion, reaching an international consensus on terminology and improving diagnostic methods is essential. We think that easily accessible and cost-effective methods such as SUA and HDL are practical parameters for MDAS prediction.

In addition, further studies are needed to better understand the relationship between SUA and MDAS and evaluate whether specific dietary or pharmacological strategies to reduce serum uric acid levels may benefit MDAS.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the local ethics committee of Selçuk University Faculty of Medicine (Date: 08.10.2024, Decision No: 2024/509).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Assessment of frailty status in non-geriatric peritoneal dialysis and hemodialysis patients

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ABSTRACT

Aims: The aim of this study was to evaluate and compare frailty status in non-geriatric hemodialysis (HD) and peritoneal dialysis (PD) patients and to assess whether there is a difference between frail and non-frail patients in HD and PD patients.

Methods: 28 PD and 28 HD patients were included in this cross-sectional study. The Edmonton Frailty Scale (EFS) was used to assess frailty status, including questions on cognition, general health status, addiction, social support, medication, nutrition, depression and sphincter continence, and a physical test assessing standing and walking.

Results: The mean age was 51.3+9.6 years and 24 (43%) of the individuals were female. There was no difference between HD and PD patients in terms of EFS score. Twelve (43%) of HD patients and 10 (36%) of PD patients were found to be frail (p=0.784). There was a positive correlation between age and EFS score in both HD and PD patients (r=0.896, p<0.001, r=0.661, p<0.001, respectively). In HD patients, there was a correlation between the EFS score and HbA1c (r=0.570, p=0.002). In HD patients, frail patients were older, had lower creatinine values and higher HbA1c levels (p<0.001, p=0.008, and p=0.006, respectively), while in PD patients, frail patients were older (p<0.001).

Conclusion: There was no difference in frailty between HD and PD patients. It should be noted that frailty is common in non-geriatric dialysis patients. Measuring frailty may help clinicians to identify vulnerable patients and intervene early to mitigate adverse outcomes.

Keywords: Frailty, hemodialysis, peritoneal dialysis, non-geriatric frailty

INTRODUCTION

Frailty is defined as a medical syndrome characterized by decreased strength, resilience, and reduced physiological function, which increases an individual's susceptibility to adverse health outcomes such as dependency or mortality. It has multiple causes and contributing factors.[1] Although it is commonly associated with advanced age, certain conditions that involve processes similar to aging—such as sarcopenia, oxidative stress, chronic inflammation, and hormonal imbalances—can also lead to frailty at younger ages.[2]

Chronic kidney disease (CKD) is a public health problem that can progress to end-stage renal disease (ESRD) requiring renal replacement therapies such as kidney transplantation, hemodialysis (HD) and peritoneal dialysis (PD). Cellular aging, loss of telomeric structures, mitochondrial dysfunction, and impaired DNA repair capacity play a crucial role in the development of frailty during the aging process.[3] These processes occur prematurely in the CKD population, ultimately leading to conditions such as sarcopenia, vascular dysfunction, and progressive organ damage.[4] Additionally, factors such as anorexia caused by uremic toxins, sarcopenia, losses occurring through dialysate and urine, catabolic effects, chronic low-grade inflammation, anabolic hormone deficiency or resistance, physical inactivity, cognitive decline, and comorbidities contribute to frailty in patients with CKD and ESRD.[5] Studies have shown that CKD increases the likelihood of frailty compared to individuals without renal dysfunction and those with other chronic conditions such as diabetes, cancer, and rheumatoid arthritis.[6] In ESRD patients receiving dialysis treatment, it has been revealed that there is a higher rate of frailty than both individuals without renal dysfunction and CKD patients.[7] Furthermore, frailty is associated with a higher risk of mortality in the ESRD population regardless of age.[8]

The Edmonton Frail Scale (EFS) is an easily applicable, multidimensional tool that assesses various aspects of frailty, including cognitive status, level of dependency, social support, physiological factors, and psychological well-being.[9] It has been previously used in several studies to evaluate frailty in patients with CKD and ESRD.[10] A study conducted on HD patients demonstrated that frailty, as determined by EFS, was

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associated with an increased risk of mortality, emergency department visits, and hospitalizations.[11]

In this study, it was aimed to evaluate and compare the frailty status in non-geriatric HD and PD patients, and to evaluate whether there is a difference between frail and non-frail patients in HD and PD patients by using the EFS, which assesses different frailty dimensions.

METHODS

Written informed consent was obtained from all participants after a full explanation of the study's procedures and objectives. This study Malatya Turgut Özal University Approved by the Non-interventional Clinical Researches Ethics Committee (Date: 10.07.2024, Decision No: 45). The study was conducted in accordance with the principles of the Declaration of Helsinki. Data were collected between 15 July and 15 August 2024. Individuals receiving dialysis treatment for less than 3 months, individuals with a history of hospitalisation for any reason other than vascular access problem in the last 3 months, individuals with active infection, individuals with severe visual or hearing problems, individuals with neurological or psychiatric conditions preventing proper test administration, amputees and individuals with active malignancy were excluded.

The study was conducted in the HD and PD unit of the nephrology clinic in a training and research hospital, where 112 HD patients and 43 PD patients were followed up. The flow chart illustrating the study population selection is shown in **Figure**. The study included 28 PD and 28 HD patients who were older than 18 years and younger than 65 years, who agreed to participate in the study, who had the capacity to understand the tests and sign the informed consent form, who had been receiving HD or PD for more than three months.

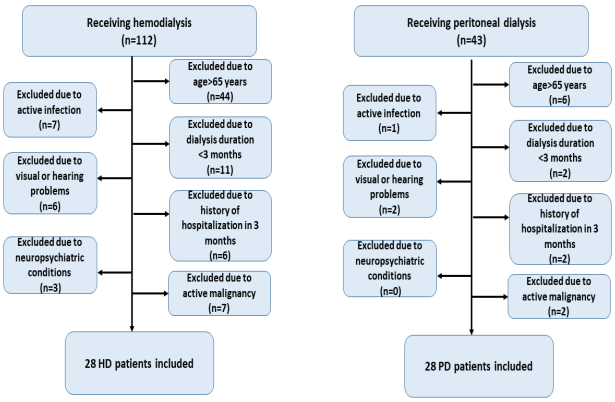

Figure. Flow chart illustrating the study population selection

The EFS, a frailty assessment tool consisting of 11 items distributed across nine domains, was used to evaluate frailty status. The scale was first developed by Rolfson et al.[9] in 2006, and its Turkish version was validated by Aygör et al.[12] in 2014. **Table 1** presents the EFS. The EFS includes questions on cognition (clock drawing test), general health status, dependency, social support, medication, nutrition, depression and sphincter continence, and a physical test including standing and walking. Each item in the EFS can be scored between 0 and 2. The total score varies between 0 and 17. Scores between 0-5 correspond to non-frail, 6-7 to sensitive, 8-9 to mildly frail, 10-11 to moderately frail and 12-17 to severely frail.

In HD patients, the physical test involving walking and the clock drawing test assessing cognitive function were conducted before the midweek dialysis session. After the patients were connected to the dialysis machine, the remaining nine items of the EFS were administered, and their responses were recorded. EFS assessment of HD patients was not performed in the post-weekend session to avoid the effects of prolonged uremia. In a previous study evaluating frailty in HD patients with EFS, physical assessments were performed before the dialysis session, while other assessments were performed during the dialysis session.[13] Similarly, in our study, we performed physical assessments before the dialysis session and other assessments during the dialysis session. For PD patients, the frailty assessment was performed during routine follow-ups, ensuring that the evaluation took place when the abdominal cavity was empty.

During data collection, demographic variables recorded included age, sex, body-mass index (BMI; kg/m^2), presence of diabetes mellitus (DM), dialysis duration (months), and marital status. Hemoglobin, serum albumin, urea, creatinine, sodium, potassium, calcium, phosphorus, intact parathyroid hormone (iPTH) and HbA1c were recorded as laboratory parameters. DM was defined based on self-reported history, medical records indicating a DM diagnosis, or a fasting glucose level of ≥126 mg/dl.

Statistical Analysis

Data analyses in this study were performed using SPSS version 20. The normality of numerical data was assessed using the Kolmogorov-Smirnov test. Parametric data were presented as mean±standard deviation (SD), non-parametric data as median (interquartile range, IQR), and categorical variables as frequency (percentage). For comparisons between two independent groups, Student's t-test was used for parametric data, while Mann-Whitney U test was applied for non-parametric data. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, as appropriate. Correlation analysis was conducted to assess relationships between numerical variables. p-value <0.05 was considered statistically significant.

RESULTS

A total of 56 individuals were included in the study, with 28 receiving HD and 28 receiving PD. The mean age of the participants was 51.3±9.6 years, and 24 (43%) were female. Among the HD patients, 14 (50%) were receiving HD via an arteriovenous fistula, while 27 PD patients were receiving continuous ambulatory PD. No significant difference was found between HD and PD patients regarding total EFS scores. Frailty was identified in 12 (43%) HD patients and 10 (35%) PD patients (p=0.784). A summary of the demographic characteristics, frailty status, and laboratory parameters of HD and PD patients is presented in **Table 2**. The results of the correlation analysis for HD and PD patients are shown in **Table 3**. Comparisons between frail and non-frail patients within the HD and PD groups are detailed in **Table 4**.

Table 1. Edmonton frail scale[9]

Frailty domain	Item	0 points	1 point	2 points
Cognition	Please imagine that this pre-drawn circle is a clock. I would like you to place the numbers in the correct positions then place the hands to indicate a time of 'ten after eleven'	No errors	Minor spacing errors	Other errors
General health status	In the past year, how many times have you been admitted to a hospital?	0	1-2	>2
	In general, how would you describe your health?	Excellent, very good, good	Fair	Poor
Functional independence	How many of the following activities do you need assistance with? - Meal preparation - Shopping - Transportation - Telephone - Housekeeping - Laundry - Managing money - Taking medications	0-1	2-4	5-8
Social support	When you need help, can you count on someone who is willing and able to meet your needs?	Always	Sometimes	Never
Medication use	Do you use five or more different prescription medications on a regular basis?	No	Yes	-
	At times, do you forget to take your prescription medications?	No	Yes	-
Nutrition	Have you recently lost weight such that your clothing has become looser?	No	Yes	-
Mood	Do you often feel sad or depressed?	No	Yes	-
Continence	Do you have a problem with losing control of urine when you don't want to?	No	Yes	-
Functional performance	I would like you to sit in this chair with your back and arms resting. Then, when I say 'GO', please stand up and walk at a safe and comfortable pace to the mark on the floor (approximately 3 m away), return to the chair and sit down'	0-10 sec	11-20 sec	One of >20 s patient unwilling, or requires assistance
Total score	Final score is the sum of column totals			

Table 2. Comparison of patients' demographic characteristics, frailty status, and laboratory parameters

Variable	Hemodialysis (n=28)	Peritoneal dialysis (n=28)	p-value
Age mean±SD	51.3±9.6	51.3±9.6	0.989
Female, n (%)	12 (43)	12 (43)	1.000
Married, n (%)	26 (93)	27 (96)	1.000
Dialysis duration, months, mean±SD	67±46	34±18	0.001
Body-mass index, kg/m², mean±SD	25.1±6.1	23.8±4.0	0.252
Diabetes mellitus, n (%)	6 (21)	4 (14)	0.729
Total EFS score (median [IQR])	5 [0-10]	2 [0-10]	0.344
Non-frail (0-5), n (%)	14 (50)	17 (61)	0.561
Vulnerable (6-7), n (%)	2 (7)	1 (4)	1.000
Frail (8-17), n (%)	12 (43)	10 (35)	0.784
Mild frailty (8-9), n (%)	5 (18)	0 (0)	0.051
Moderate frailty (10-11), n (%)	2 (7)	7 (25)	0.143
Severe frailty (12-17), n (%)	5 (18)	3 (11)	0.700
Laboratory parameters			
Urea (mg/dl), mean±SD	119±26	119±35	0.930
Serum creatinine (mg/dl), mean±SD	9.1±3.1	8.9±2.5	0.787
Sodium (mEq/L), mean±SD	136±3	134±4	0.044
Potassium (mEq/L), mean±SD	5.2±0.6	4.4±0.8	<0.001
Calcium (mg/dl), mean±SD	9.0±0.8	8.6±0.6	0.044
Phosphorus (mg/dl), mean±SD	5.2±1.2	4.8±1.4	0.296
Hemoglobin (g/dl), mean±SD	10.7±1.8	10.6±1.5	0.857
Albumin (g/dl), mean±SD	3.7±0.3	3.2±0.5	<0.001
HbA1c (%), median [IQR]	5.2 [4.7-6.7]	5.1 [4.7-5.9]	0.572
Intact parathormone (pg/ml), median [IQR]	349 [168-733]	213 [152-334]	0.057

SD: Standard deviation, EFS: Edmonton frail scale; IQR: Interquartile range

Table 3. Correlation analysis results in hemodialysis and peritoneal dialysis patients

Hemodialysis							
	EFS total score	**Age**	**Dialysis duration**	**Body-mass index**	**Albumin**	**Hba1c**	**iPTH**
EFS total score	r	.896	-.313	.167	-.251	.570	-.290
	p	<0.001	.105	.397	.197	.002	.135
Age	r		-.259	.224	-.183	.446	-.292
	p		.183	.262	.352	.017	.132
Dialysis duration	r			-.282	-.532	-.221	.337
	p			.146	.004	.257	.079
Body-mass index	r				.121	-.166	-.240
	p				.538	.379	.218
Albumin	r					-.075	.068
	p					.703	.731
HbA1c	r						-.190
	p						.333
Peritoneal dialysis							
	EFS total score	**Age**	**Dialysis duration**	**Body-mass index**	**Albumin**	**Hba1c**	**iPTH**
EFS total score	r	.661	.119	-.002	-.216	.283	-.182
	p	<0.001	.547	.993	.270	.145	.355
Age	r		-.315	-.028	-.364	.469	-.599
	p		.103	.889	.057	.012	.001
Dialysis duration	r			.003	.030	-.228	.731
	p			.987	.878	.243	<0.001
Body mass index	r				-.098	-.204	-.112
	p				.621	.298	.570
Albumin	r					-.006	.036
	p					.975	.854
HbA1c	r						-.301
	p						.120

EFS: Edmonton frail scale, iPTH: Intact parathormone

DISCUSSION

In this study, no significant difference in frailty status was found between HD and PD patients who were not in the geriatric age group. We observed that frailty increased with age in both patient groups. Among HD patients, those classified as frail were older, had lower creatinine levels, and higher HbA1c levels. In PD patients, we found that frail patients were older.

Frailty is commonly observed in both young and elderly patients with ESRD. Studies conducted with different age groups and using various frailty assessment tools have reported that the prevalence of frailty ranges from 6% to 82% in HD patients and 27% to 76% in PD patients.[14] In one study focusing on HD patients, the prevalence of frailty was found to be 71% in elderly patients and 47% in younger patients.[15] Another study evaluating frailty in HD patients under the age of 65 using the EFS reported a frailty prevalence of 51%.[13] In our study, the prevalence of frailty among HD patients under 65 years old was 43%, as determined by EFS. A study by Chao et al.[16] also reported an EFS-based frailty prevalence of 43% in HD patients. In a study evaluating frailty in PD patients with a different scale, the prevalence of frailty was reported to be 34%.[17] In our study, the prevalence of frailty in PD patients was 36%. The prevalence of frailty in dialysis patients found in our study is consistent with the findings in the literature. A prospective study conducted on HD patients demonstrated that frailty, as measured by EFS, was associated with an increased risk of hospitalization, emergency department admission, and mortality.[11] Another study including both HD and PD patients also found that frailty was linked to higher mortality and hospitalization rates.[18] Given its high prevalence in dialysis patients and its association with adverse health outcomes, recognizing and detecting frailty at an early stage is of critical importance.

To the best of our knowledge, no previous study in the literature has compared frailty status between HD and PD patients using the EFS. In our study, no significant difference in frailty status was found between HD and PD patients, with 43% of HD patients and 36% of PD patients classified as frail. A study that assessed frailty using the frailty phenotype scale reported a frailty prevalence of 46% in HD patients and 34% in PD patients, with no significant difference between the two groups.[17] Similarly, another study including both HD and PD patients found that dialysis modality did not influence frailty status.[18] However, a study using the modified Fried frailty index indicated that HD patients were more likely to

Table 4. Comparison of frail and non-frail patients in hemodialysis and peritoneal dialysis

	Hemodialysis		
	Frail (n=12)	**Non-frail (n=16)**	**p-value**
Age, mean±SD	59.8±5.1	44.9±6.8	<0.001
Female, n (%)	4 (33)	8 (50)	0.620
Married, n (%)	11 (92)	15 (94)	1.000
Dialysis duration, months, mean±SD	50±28	81±53	0.080
Body-mass index (kg/m²), mean±SD	26.2±7.7	24.3±4.7	0.418
Diabetes mellitus, n (%)	3 (25)	3 (19)	1.000
Laboratory parameters			
Urea (mg/dl), mean±SD	112±14	124±32	0.253
Creatinine (mg/dl), mean±SD	7.4±1.9	10.4±3.2	0.008
Sodium (mEq/L), mean±SD	136±3	136±3	0.680
Potassium (mEq/L), mean±SD	5.2±0.5	5.2±0.6	0.952
Calcium (mg/dl), mean±SD	9.0±0.8	9.0±0.9	0.933
Phosphorus (mg/dl), mean±SD	5.1±1.3	5.2±1.1	0.833
Hemoglobin (g/dl), mean±SD	10.5±1.0	10.8±2.3	0.683
Albumin (g/dl), mean±SD	3.6±0.2	3.8±0.4	0.220
HbA1c (%) median [IQR]	6.2 [5.2-7.1]	4.8 [4.5-5.2]	0.006
Intact parathormone (pg/ml) median [IQR]	245 [126-574]	417 [232-859]	0.059
	Peritoneal dialysis		
	Frail (n=10)	**Non-frail (n=18)**	**p-value**
Age, mean±SD	59.3±5.7	46.9±8.5	<0.001
Female, n (%)	5 (50)	7 (39)	0.864
Married, n (%)	10 (100)	17 (94)	1.000
Dialysis duration, months, mean±SD	37±13	32±21	0.491
Body-mass index (kg/m²), mean±SD	21.8±3.0	21.8±4.7	0.914
Diabetes mellitus, n (%)	3 (33)	1 (6)	0.116
Laboratory parameters			
Urea (mg/dl), mean±SD	122±38	118±35	0.772
Creatinine (mg/dl), mean±SD	8.6±2.7	9.1±2.5	0.620
Sodium (mEq/L), mean±SD	133±6	134±3	0.494
Potassium (mEq/L), mean±SD	4.0±0.6	4.6±0.8	0.085
Calcium (mg/dl), mean±SD	8.7±0.5	8.6±0.7	0.560
Phosphorus (mg/dl), mean±SD	4.5±0.8	5.0±1.6	0.399
Hemoglobin (g/dl), mean±SD	10.2±1.5	10.8±1.5	0.309
Albumin (g/dl), mean±SD	3.0±0.3	3.3±0.6	0.179
HbA1c (%), median [IQR]	5.3 [4.9-6.6]	5.0 [4.7-5.7]	0.175
Intact parathormone (pg/ml), median [IQR]	271 [128-366]	213 [164-306]	0.759

SD: Standard deviation, IQR: Interquartile range

be frail compared to PD patients.[19] Due to the small number of patients included in our study, comprehensive studies with more patients comparing frailty status in HD and PD patients are needed.

A study comparing frail and non-frail HD patients based on the EFS found results similar to ours, showing that frail patients were older and had lower creatinine levels.[11] It has been shown that each year of life increases the probability of frailty by 3% in dialysis patients.[20] In our study, a positive correlation between age and frailty was observed in both patient groups. A study including both HD and PD patients also found that frailty increased with age, while higher creatinine levels were associated with lower frailty.[18] The relationship between serum creatinine and frailty in HD patients may be explained by muscle mass loss due to sarcopenia.[21,22] Sarcopenia is more prevalent in HD patients than in PD patients.[23] In our study, the absence of a significant difference in creatinine levels between frail and non-frail PD patients may be attributed to the lower prevalence of sarcopenia in PD patients. Furthermore, we found that frail HD patients had higher HbA1c levels. A meta-analysis evaluating factors associated with frailty in HD patients concluded that the presence of DM was linked to frailty.[24] However, in our study, no significant difference was found between frail and non-frail patients

in terms of DM prevalence, which may be due to the small number of diabetic patients in our sample. The relationship between HbA1c levels and frailty in dialysis patients has not been extensively studied. However, a study conducted in elderly patients demonstrated that higher HbA1c levels were associated with an increased risk of frailty.[25] Further research is needed to evaluate the potential link between HbA1c levels and frailty in dialysis patients. We also showed that, although not statistically significant, frail patients tend to have lower iPTH in HD patients. A study in HD patients showed that frail patients had lower iPTH levels.[26] The lower iPTH levels in frail patients in HD patients may be related to the tendency to adynamic bone disease. On the other hand, another study found no difference in iPTH levels between frail and non-frail patients in HD patients.[11] More comprehensive studies with more patients focusing on the relationship between frailty, iPTH and mineral bone disorders in HD patients may contribute to the literature.

Limitations

Our study has several limitations. The first is the small number of patients. Second, the study was conducted at a single center. Third, frailty was assessed cross-sectionally at a single time point, and no prospective follow-up was conducted. Strength of our study is that, to the best of our knowledge, it is the first study to compare frailty status between HD and PD patients using the EFS.

CONCLUSION

In our study, no significant difference in frailty status was found between HD and PD patients. It is important to recognize that frailty is prevalent among non-geriatric dialysis patients. Assessing frailty can assist clinicians in identifying vulnerable patients and enabling early interventions to mitigate adverse outcomes. This is particularly crucial for ESRD patients, who are at high risk for morbidity and poor clinical outcomes. Due to the small number of patients included in the study, larger-scale studies with a greater number of patients are needed to improve the generalizability of our findings.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study Malatya Turgut Özal University Approved by the Non-interventional Clinical Researches Ethics Committee (Date: 10.07.2024, Decision No: 45).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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The academic influence of thyroid imaging: a bibliometric perspective in radiology

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ABSTRACT

Aims: Thyroid imaging is an essential component of diagnosing and managing thyroid diseases, including thyroid nodules and thyroid cancer. Various imaging modalities such as ultrasonography (US), Doppler US, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET/CT) are widely utilized for accurate evaluation and risk stratification. Despite the increasing research activity in thyroid imaging, a comprehensive bibliometric analysis focusing solely on radiology publications has not been conducted. This study aims to perform a bibliometric analysis of thyroid imaging research within the field of radiology, identifying publication trends, highly cited works, leading institutions, collaborative networks, and emerging research areas.

Methods: A systematic bibliometric analysis was conducted using data from the Web of Science (WoS) Core Collection. The search was restricted to radiology-related publications on thyroid imaging between January 2005 and December 2024. VOSviewer (version 1.6.11) was used to map citation networks, keyword co-occurrence, and institutional collaborations. Statistical analyses were performed using SPSS to examine publication growth, citation trends, and thematic clusters.

Results: A total of 4.007 articles were identified. The number of publications has steadily increased over the years, with the highest number of publications recorded in 2024 (317 articles). US remains the dominant imaging technique in thyroid imaging research, whereas PET/CT and MRI are gaining prominence in specific clinical applications. The European Journal of Nuclear Medicine and Molecular Imaging, Clinical Nuclear Medicine, and the Journal of Nuclear Medicine were the most influential journals. Mayo Clinic, Yonsei University, and Duke University emerged as the leading institutions in the field. Keyword analysis revealed major research themes related to thyroid nodules, malignancy risk assessment, ultrasound-guided interventions, and advanced imaging techniques.

Conclusion: The field of thyroid imaging has expanded significantly, with a clear dominance of US in research and clinical applications. However, the increasing role of PET/CT, MRI, and AI-driven imaging technologies indicates a shift towards advanced diagnostic methods. Future research should integrate artificial intelligence (AI) and radiomics into thyroid imaging to enhance diagnostic precision and clinical utility. The findings from this bibliometric analysis provide valuable insights into research trends, influential contributors, and future directions in thyroid imaging within radiology.

Keywords: Thyroid imaging, ultrasonography, thyroid nodules, bibliometric analysis, medical imaging trends

INTRODUCTION

Imaging of the thyroid gland is significant in the evaluation of most thyroid diseases, including the more complex ones like thyroid nodules and thyroid cancer. Diagnostic imaging techniques such as ultrasonography (US), Doppler US, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET/CT) have been used extensively to improve diagnostic efficacy and to assist clinical decision making.[1] Among these, US remains the primary modality, as it enables in vivo, real-time imaging of the thyroid gland using a non-invasive procedure and has a high diagnostic yield.[2] The implementation of the standardized Thyroid Imaging Reporting and Data System (TI-RADS) and ultrasound-guided fine-needle aspiration (FNA) has further strengthened the role of imaging in classification and assessment of the cancer risk of thyroid nodules.[3,4]

With the advancement of medical fields, the Su, Gao, and Xu triad notes in their article from 2021 that has cited bibliometric analysis as one of the top trending tools that helps in assessing scientific retrieval, its impact, and collaborations around the globe. Many bibliometric investigations have covered different components of thyroid imaging like thyroid ultrasound, thyroid nodules with FNA, and thyroid cancer including its imaging and management codes.[5-7] All these works have been

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performed efficiently; however, most research strives towards certain sub-division, which makes it possible to claim that in-depth bibliometric analysis of thyroid imaging research relevant to radiology does not exist.

Thyroid imaging has become an integral part of the diagnosis, evaluation and follow-up of thyroid diseases and its continuously changing technological aspects are transforming the clinical management. Ultrasound remains the most important and standard method of imaging, especially in the evaluation of thyroid nodules and structural abnormalities, while PET/CT and MRI are used more frequently in selected areas of practice. With the growing interest around the world concerning the field of thyroid imaging, there is a need to perform a bibliometric analysis to examine the research volume, patterns of publications, and the major contributors in this developing area.

This study aims to conduct a comprehensive bibliometric analysis of thyroid imaging research within the radiology field. It will assess publication patterns, citation impact, influential studies, research collaborations, and emerging themes. By mapping the scientific landscape, this analysis seeks to identify key contributors and trends that shape the field of thyroid imaging.

This research is significant as it quantifies academic contributions to thyroid imaging, offering insights for researchers, radiologists, and policymakers. The findings can help identify influential studies, leading institutions, and future research directions. Moreover, this study aims to facilitate clinical applications, technological advancements, and interdisciplinary collaborations in thyroid imaging.

METHODS

Ethical approval was not obtained, as the study is a bibliometric analysis; however, institutional information is available.

This digital analysis was performed with data received from the WoS database Core Collection, where scientists globally publish for peer review. The primary focus of researches was “thyroid imaging” focusing on thyroid’s and thyroid’s disorders published across various platforms from January 2005 to December 2024.

A comprehensive search strategy was implemented using WoS’s advanced search, with the primary keyword being "thyroid imaging" appearing in the title. Additional keywords and search queries were structured using Boolean operators to refine the results. The initial search yielded a broad dataset, which was then filtered using specific inclusion and exclusion criteria. Only articles that could be classified under “radiology” in WoS were selected to narrow the focus.

After applying the classification filter, a total of 4.007 articles were obtained. To further refine the dataset, a secondary screening was performed based on predefined inclusion and exclusion criteria: (1) inclusion of articles that focused primarily on imaging techniques used for thyroid evaluation, (2) exclusion of conference abstracts, letters, editorials, and non-English articles. The filtering process involved analyzing article titles, abstracts, and other MESH-recognizable tags and keywords to ensure relevancy. To be more selective, the process was consolidated to peer-reviewed studies only so that all duplicates and non-contributing papers were omitted. The selection procedure was verified with two independent researchers who checked for discrepancies and resolved them through discussion.

For each of the selected publications, more information was captured, including title, authors, year of publication, journal name, publication’s impact factor, affiliated country, institution, citation count, and some of the keywords. The data extraction process was systematically performed and validated by two independent researchers to ensure consistency and accuracy.

VOSviewer (version 1.6.11, Leiden University, Netherlands) was used for bibliometric mapping and visual analyses. This software could then be employed to study citation networks, keyword relationships, and collaboration patterns. The study attempted to cover the following aspects in detail:

Trends in the number of publications each year.

Breakdown of publications by the journals in which they were published.

Citation activity of major articles.

Networks of co-occurring keywords to find theme clusters.

Network of participants on institutional and country levels that show global collaborations in research of thyroid imaging.

Statistical Analysis

Statistical methods were applied that provide basic features of research citation patterns distribution and journal impact estimators. SPSS was used for estimating the shifts in published volumes and citation numbers alongside the passage of time. Descriptive and inferential statistics were conducted to analyze trends in publication outputs, citation distributions, and the relative impact of different research themes. Mapping the top 150 keyword allows for finding dominant emerging trends and thematic clusters in thyroid imaging. Additionally, statistical significance testing was performed to assess variations across different time periods and research domains.

Collaboration between institutions and countries was studied to determine the integration and concentration of the research activities. The mapping of intra-institutional and interstate scientific collaborations reflects the life of the networking and collaborative activity in thyroid imaging research.

The entire data collection and analysis procedure is depicted in **Figure 1**.

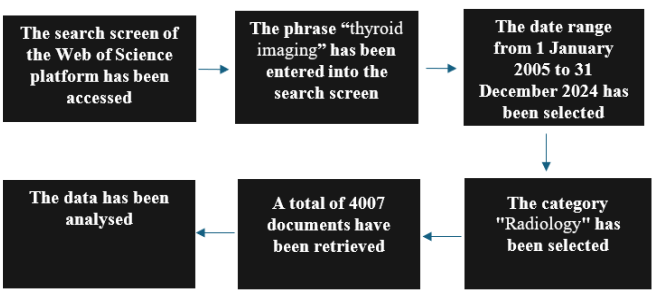

Figure 1. Data collection and analysis procedure

RESULT

Analysis of the Distribution of Articles by Year

The analysis based on Web of Science data presents the distribution of studies on "thyroid imaging" published between 2005 and 2024 (**Figure 2**).

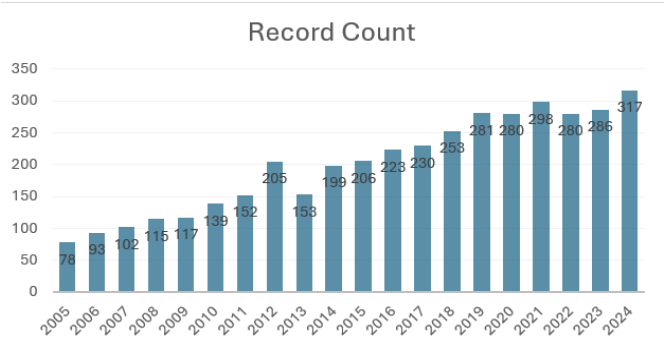

Figure 2. Distribution of articles by year

In the initial years, the number of publications was relatively low. In 2005, 78 studies were published, and a gradual increase was observed until 2010. By 2010, the number of published articles reached 139, and in 2012, a significant increase was noted, reaching 205 articles.

From 2015 onward, a continuous upward trend in publication numbers was observed, reaching 253 articles in 2018 and 281 in 2019. Although there was a slight decline in 2020 (280 articles), the number rose again in 2021, with 298 publications recorded, one of the highest figures in the dataset. In 2022 and 2023, the numbers were 280 and 286 articles, respectively.

The highest number of publications was recorded in 2024, with 317 articles published. This trend suggests that "thyroid imaging" has been gaining increasing academic attention, particularly in recent years, due to advancements in imaging technologies and their widespread use in clinical applications, driving accelerated scientific research in the field.

Leading Academic Journals Publishing on Thyroid Imaging

The distribution of journals that have published the most articles on "thyroid imaging" in the Web of Science database is presented in **Table 1**.

Table 1. Journals in which articles were published, number of publications, and publication rates

Publication titles	Record count	% of 4.007
European Journal of Nuclear Medicine and Molecular Imaging	272	6.78%
Clinical Nuclear Medicine	260	6.48%
Journal of Nuclear Medicine	198	4.94%
Nuclear Medicine Communications	125	3.12%
Journal of Ultrasound in Medicine	102	2.54%
American Journal of Roentgenology	100	2.49%
European Radiology	94	2.34%
Ultrasound in Medicine and Biology	89	2.22%
European Journal of Radiology	88	2.19%
Medical Physics	66	1.64%

According to the analysis, the European Journal of Nuclear Medicine and Molecular Imaging ranked first, publishing 272 articles (6.78%), making it a leading academic platform in the field of thyroid imaging. This indicates that researchers in this area frequently prefer this journal for disseminating their findings.

Clinical Nuclear Medicine ranked second with 260 articles (6.48%), followed by the Journal of Nuclear Medicine with 198 articles (4.94%). These findings highlight that nuclear medicine and molecular imaging journals serve as primary sources for thyroid imaging research.

Other notable journals contributing significantly to the field include:

- Nuclear Medicine Communications (125 articles, 3.12%)
- Journal of Ultrasound in Medicine (102 articles, 2.54%)
- American Journal of Roentgenology (100 articles, 2.49%)
- European Radiology (94 articles, 2.34%)
- Ultrasound in Medicine and Biology (89 articles, 2.22%)
- European Journal of Radiology (88 articles, 2.19%)

Additionally, Medical Physics, which published 66 articles (1.64%), highlights the growing significance of physical modeling and imaging technologies in thyroid imaging research.

Analysis of the Most Cited Studies: Authors, Article Titles, Publishing Journals, Years, and Citation Counts

Table 2 presents a detailed analysis of the most cited studies in the field of thyroid imaging, including author details, journal names, publication years, and citation counts.

The most cited article was published by Tessler et al. (2017) in the Journal of the American College of Radiology, discussing the ACR TI-RADS system and its standardized approach to thyroid nodule assessment. With 1.463 citations, this study has significantly influenced clinical practice by providing a systematic evaluation method for thyroid nodules.

Another highly cited study by Kratochwil et al. (2019) was published in the Journal of Nuclear Medicine, focusing on 68Ga-FAPI PET/CT and its application across various types of cancer. This study, with 971 citations, highlights the effectiveness of next-generation PET/CT techniques in imaging malignancies, including thyroid cancer.

Similarly, the study by Fletcher et al. (2008) received 841 citations, providing recommendations on the use of 18F-FDG PET in oncology. This study sheds light on the role of PET in thyroid imaging processes, emphasizing its relevance in oncological applications.

US-based research on thyroid nodules has also received significant academic attention. The retrospective multicenter study by Moon et al. (2008), which has 821 citations, explored the differentiation of benign and malignant thyroid nodules using ultrasound. Additionally, Kwak et al. (2011) published a study that received 800 citations, evaluating the effectiveness

Table 2. Author information, published journals, publication years, and citation counts of the most cited articles on "thyroid imaging"

No	Author(s)	Article title	Journal name	Publication year	Citation count
1	Tessler FN, et al.	ACR thyroid imaging, reporting and data system (TI-RADS): white paper of the ACR TI-RADS committee	Journal of the American College of Radiology	2017	1463
2	Kratochwil C, et al.	^{68}Ga-FAPI PET/CT: tracer uptake in 28 different kinds of cancer	Journal of Nuclear Medicine	2019	971
3	Fletcher JW, et al.	Recommendations on the use of ^{18}F-FDG PET in oncology	Journal of Nuclear Medicine	2008	841
4	Moon WJ, et al.	Benign and malignant thyroid nodules: US differentiation-multicenter retrospective study	Radiology	2008	821
5	Kwak JY et al.	Thyroid imaging reporting and data system for US features of nodules: a step in establishing better stratification of cancer risk	Radiology	2011	800

of TI-RADS in malignancy risk stratification, further reinforcing the importance of standardized ultrasound reporting systems.

Statistical Evaluation of the Most Cited Institutions in Thyroid Imaging Research

The Web of Science database was used to analyze the institutions affiliated with authors of thyroid imaging research, the number of articles published by these institutions, and the citations received by these publications. **Table 3** presents a detailed breakdown of the most cited institutions, the number of their publications, and their citation counts.

Table 3. Distribution of the most cited institutions and number of publications according to Web of science data

Organization	Documents	Citations
Mayo Clinic	53	4559
Yonsei University	60	4417
Duke University	50	4288
Washington University	34	4134
Johns Hopkins University	44	3709

According to the data, Mayo Clinic stands out as the most influential institution in this field, with 53 publications receiving 4.559 citations. This indicates that Mayo Clinic's research in thyroid imaging has had a significant impact on the literature and has become a key reference for further studies.

Similarly, Yonsei University has published 60 articles, accumulating 4.417 citations, demonstrating its strong research output and academic influence in this domain. Duke University ranks third, with 50 publications and 4.288 citations, highlighting its substantial contributions to thyroid imaging research.

Washington University and Johns Hopkins University also hold prominent positions, with 34 publications receiving 4.134 citations and 44 publications receiving 3.709 citations, respectively. Despite publishing fewer articles than some other institutions, these universities have achieved high citation counts, indicating that their research is widely recognized and frequently referenced within the academic community.

Overall, the most cited institutions are among the world's leading medical schools and research centers, reflecting their substantial contributions to thyroid imaging techniques. These findings suggest that thyroid imaging research is largely driven by prestigious academic institutions that set the direction for advancements in this field.

Relational Distribution of Keywords in Scientific Literature

The most frequently used keywords in "thyroid imaging" research within the Web of Science database, along with their occurrence frequencies, are presented in **Figure 3**.

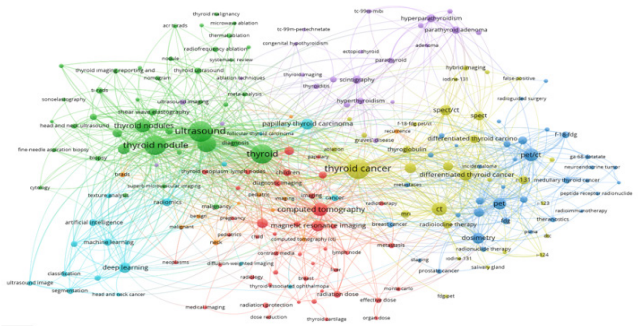

Figure 3. Most frequently used keywords and their usage distribution

Bibliometric analysis was conducted using VOSviewer software, with a minimum threshold of 10 occurrences for keyword selection. This threshold ensures that only keywords used at least 10 times were included in the analysis, allowing the study to focus on more widely used and scientifically meaningful terms. Although 6.339 different keywords were identified in the dataset, only 200 met this threshold and were considered in the evaluation. This method ensures that the analysis is concentrated on established keywords and their interrelationships.

The analysis results reveal the most frequently used keywords and their strongest associations within the research field. A total of 2.867 connections were identified among the keywords, which were grouped into seven distinct clusters. These findings allow for a detailed examination of keyword relationships within the field, enhancing the understanding of terminology and identifying critical concepts for future research.

Figure 3 visualizes the most commonly used keywords and their interconnections in academic publications on thyroid imaging. The terms "thyroid cancer" (142 connections) and "thyroid" (137 connections) have the strongest links,

indicating that research in this field is predominantly focused on the diagnosis and evaluation of thyroid cancer.

The widespread use of "ultrasound" (123 connections) and "US" (106 connections) confirms that ultrasound remains the primary imaging modality for diagnosing thyroid diseases. Similarly, the frequent occurrence of "thyroid nodule" (113 connections) highlights the significance of nodule classification and malignancy risk assessment in thyroid imaging research.

Additionally, the keyword "CT" (90 connections) underscores the role of advanced imaging techniques, particularly in cases where malignancy is suspected. These findings provide a clear picture of the fundamental concepts and terminology shaping the scientific discourse in thyroid imaging.

Analysis of Institutional Collaborations in Thyroid Imaging Research

The institutions publishing research on thyroid imaging and their collaboration networks were analyzed, and the results are visually represented in **Figure 4**.

Figure 4. Bibliometric network visualization of inter-institutional collaboration

In the VOSviewer analysis, colors represent thematic or regional groups, while connections indicate collaborations between institutions. The thickness of these connections reflects the intensity of collaboration. This visualization highlights leading institutions in the field of thyroid imaging and helps identify strong academic networks and potential collaboration opportunities.

The analysis identified University of Ulsan and Mayo Clinic as the most collaborative institutions, with 30 connections each. This indicates that these two institutions have established extensive academic networks and contributed significantly to joint research publications in thyroid imaging.

Other highly collaborative institutions include:

- Sungkyunkwan University (24 connections)
- Shanghai Jiao Tong University (18 connections)
- Universität Duisburg-Essen (15 connections)

These institutions have formed strong research partnerships with specific groups and hold significant positions in the global academic network. Notably, the strong collaborations between Asian and European institutions suggest that the field of thyroid imaging research has a well-established international collaboration network.

These findings indicate that research collaborations in thyroid imaging are concentrated around specific academic hubs and play a crucial role in scientific productivity in this field.

Analysis of Author Collaborations in Thyroid Imaging Research

Thyroid imaging articles indexed in the Web of Science database were analyzed to evaluate author collaboration networks. The results are detailed in **Figure 5**.

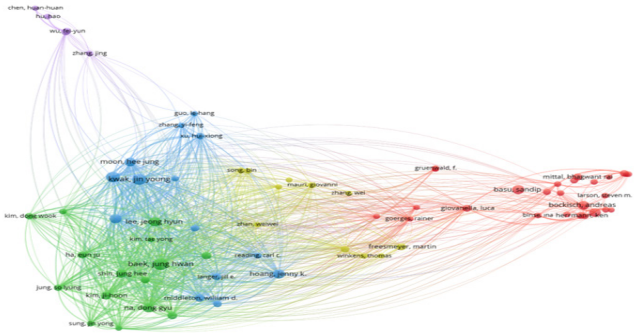

Figure 5. Bibliometric network map of author collaboration (the size of the circles represents the main authors, while the lines between the circles indicate collaboration relationships.)

Figure 5 presents the bibliographic connections among authors who have published at least 10 articles in this research area. A total of 71 authors were evaluated, but only those meeting the threshold were included in the final analysis.

Setting a minimum publication threshold of 10 articles ensures that only highly productive and influential researchers are considered. This approach enhances the reliability and academic significance of the analysis by focusing on active and impactful contributors in thyroid imaging research.

The figure visualizes collaboration networks among thyroid imaging researchers. Each author is represented by a circle, where the size of the circle reflects their contribution to the literature. The lines connecting the circles indicate collaboration strength and bibliographic linkages. The visualization was generated using VOSviewer, with different colors representing distinct research groups and thematic collaborations.

- Blue cluster: Researchers such as Kwak Jin Young and Moon Hee Jung are centrally positioned, forming strong collaboration networks. This cluster is primarily focused on ultrasound and nodule evaluation.
- Green cluster: Researchers like Baek Jung Hwan, Na Dong Gyu, and Kim Tae Yong have wide collaboration networks, mainly contributing to studies on thyroid nodule evaluation and malignancy classification.
- Red cluster: Authors such as Bockisch Andreas, Mittal Bhagwant Rai, and Giovanella Luca lead this group, which is strongly associated with nuclear medicine and PET/CT-based thyroid imaging.
- Yellow cluster: Includes authors like Giovanni Mauri and Zhang Wei, who focus primarily on thyroid biopsy techniques and interventional imaging.

- Purple cluster: Comprises Wu Fei-Yun and Zhang Jing, representing a smaller network focused on regional or specific subfields.

Overall, collaboration networks in thyroid imaging research are structured around regional and methodological similarities, reflecting the interdisciplinary nature of the field and the core dynamics of research collaborations.

Country-Based Citation Distribution

The citation distribution of thyroid imaging articles across countries was analyzed using the Web of Science (WoS) database. The results are visually represented in **Figure 6**, illustrating the geographical spread of citations, regional research density, and international academic collaborations.

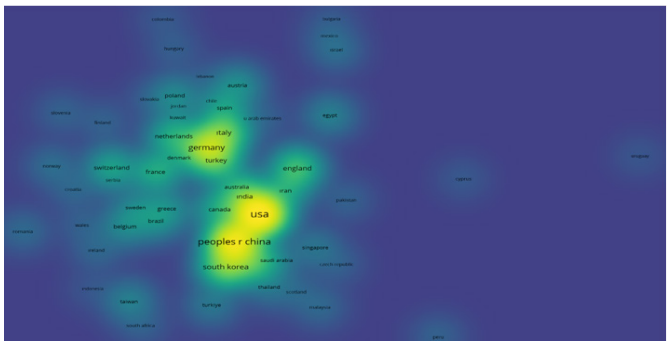

Figure 6. Analysis of citation distribution by country

Figure 6 presents the country-level distribution of citations and the global academic collaboration network based on articles indexed in Web of Science. The analysis considered countries with at least five published articles, and among the 90 eligible countries, 58 were included in the final evaluation.

The United States and China emerged as the countries with the highest citation intensity, indicating that research groups in these nations have made significant contributions to thyroid imaging and hold widespread influence in the academic community.

Other high-impact countries include:

- South Korea, Germany, and the United Kingdom, which exhibit strong scientific output in thyroid imaging research.
- Germany, Italy, France, and the Netherlands demonstrate strong regional collaborations within Europe.
- Turkey and Iran contribute to the citation network by engaging in regional academic collaborations.

Overall, Figure 6 reflects the global distribution of academic impact in thyroid imaging, providing insights into international collaborations and potential research opportunities within the field.

DISCUSSION

This bibliometric analysis provides an update on the imaging of the thyroid within the category of radiology by presenting collaborative networks, research trends, and influential studies. After performing the analysis, we compare the results from our study in contrast to previously conducted bibliometric studies on thyroid US and thyroid imaging related research and realize important differences and similarities are present which tell this field's life cycle and its current status.

There are several past studies that have conducted the bibliometric imaging trends analysis for US and thyroid cancer research. As an example of this approach, Su et al.[5] conducted an analysis on the publication records of thyroid US studies and noted the increasing assertiveness of ultrasound-validated studies in this specialty. To follow, similarly to Tang et al.[8] who performed a bibliometric analysis of ultrasound-guided ablation of thyroid nodules, there is an explosive increase of interest in interventional ultrasound studies. These studies, which claim that ultrasound is the foremost imaging technique utilized in thyroid imaging, are also supported by our analysis as the publications we reviewed contained the terms u "thyroid ultrasound," "thyroid nodule," and "US."

Zhang et al.[9] conducted a bibliometric analysis of publications to track the advancements in the diagnostics and therapeutics of thyroid nodules through imaging. Although they considered a wider scope which included other endocrine studies, our study is focused on thyroid imaging within radiology, which provides us the opportunity to analyze the imaging modalities used and the trends in publication and citations for this specific area. Our results prove that thyroid nodules remain a topic of interest for many high impact publications that seek to evaluate graduate's imaging techniques for malignancy risk assessment.

Wu et al.[7] looked at bibliometric data for research on thyroid cancer and reported that the past two decades have shown a dramatic increase in research productivity in the field. Emphasis is placed on diagnostic imaging in the form of PET/CT and MRI as important tools for thyroid cancer detection and staging. A contrasting view was reached that while there are some specific cases where PET/CT and MRI are applicable, ultrasound is the foremost imaging technique for thyroid patients for radiology research. These differences stem from the concern of thyroid diseases as a cross-scientific field ie. radiology oncology and endocrinology, which is why our study differed from Wu and Zhou's.

Liu et al.[6] conducted a bibliometric study on the role of FNA in the diagnosis of thyroid nodules, detailing its important diagnostic feature within the research scope of FNA. Our findings complement this by demonstrating that other landmark studies in thyroid imaging utilize FNA along with ultrasound which further emphasizes the role of ultrasound guided procedures in thyroid disease diagnosis. It is consistent with prior literature advocating the dual application of imaging and biopsy techniques for greater diagnostic precision.

In most bibliometric studies, the scope of focus was peripheral. In contrast, our study focuses on the specialty area of thyroid imaging as a separate branch of radiology which makes it possible to analyze the publication activity, the principal stakeholders, and the degree of inter-institutional collaboration in more detail. This focus on only radiology journals sets this work apart from more advanced studies that concentrate on endocrinology, oncology, and other related subjects making the analysis useful for practicing radiologists and imaging scientists.

But there is a caveat to this study as is in many other bibliometric works which is, selectivity of the databases.[10,11] Web of Science is excellent for baseline bibliometric analyses but other databases like Scopus or PubMed have much more to offer. Subsequent work that uses multiple databases may shed much needed light on how thyroid imaging is studied around the world.

Our research shows that the thyroid imaging domain has evolved continuously with a big growth in publications in the last ten years.[12] The increasing use of US indicates its being the primary method of imaging the thyroid. However, growing interest in PET/CT and MRI suggests that advanced imaging services may be offered in the future for thyroid diseases.

Further studies should be directed towards the application of artificial intelligence (AI) in the thyroid imaging, as automatic diagnostic devices are being developed for medical imaging. Moreover, extending bibliometric studies to evaluate the association of new imaging markers and radiomics with thyroid diseases would mark a new era in research in this specialty.

Limitations
The investigation was limited to the Web of Science database which, though sturdy, does not include all relevant resources published in Scopus, PubMed or Google Scholar. There is also the issue that citation count does not always match research quality, as some newer studies have not been cited much but are promising in terms of their impact.

CONCLUSION
This study identified the most influential publications and authors in the field of thyroid imaging within radiology, providing a comprehensive overview of research trends. The findings confirm that ultrasound remains the primary imaging modality for thyroid evaluation, while PET/CT and MRI are gaining importance in specific clinical scenarios. Unlike previous bibliometric analyses, this study explores radiology citation networks in greater detail, highlighting key research clusters and publication patterns.

The increasing number of radiology publications in recent years reflects growing academic interest, driven by technological advancements and evolving clinical needs. Future research should focus on integrating AI and radiomics into thyroid imaging to enhance diagnostic accuracy and clinical decision-making. As imaging technologies continue to advance, interdisciplinary collaboration will play a crucial role in shaping the future of thyroid imaging research.

ETHICAL DECLARATIONS
Ethics Committee Approval
Since the study was a bibliometric analysis, ethical approval was not obtained.

Informed Consent
Since the study was a bibliometric analysis, informed consent was not obtained.

Referee Evaluation Process
Externally peer-reviewed.

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

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

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Correlation between triglyceride-glucose index and length of intensive care unit stay in sepsis

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ABSTRACT

Aims: The aim of this study is to retrospectively evaluate the impact of the triglyceride-glucose (TyG) index on mortality and length of stay in septic patients in a tertiary intensive care unit.

Methods: This retrospective, descriptive cohort study diagnosed with sepsis. The study involved 208 patients. The primary aim was to assess the prognostic value of TyG for predicting mortality at 28 days following hospital admission in these patients. In addition, the study evaluated ICU all-cause mortality as a primary endpoint, with secondary endpoints encompassing the length of ICU stay.

Results: The prognostic value of the TyG in predicting mortality among sepsis patients was assessed using ROC curve analysis. The analysis yielded an area under the curve (AUC) of 0.798 (95% confidence interval: 0.729–0.867, p<0.001), indicating good discriminatory ability. An optimal cut-off value of 9.10 was identified, which provided a sensitivity of 82% and a specificity of 75% for mortality prediction. In the multivariate model, HbA1c and TyG index also retained their independent associations with mortality (HbA1c: OR: 1.65, 95% CI: 1.25–2.18, p=0.002; TyG index: OR: 2.20, 95% CI: 1.40–3.40, p=0.001) and prolonged ICU stay (HbA1c: OR: 1.35, 95% CI: 1.05–1.75, p = 0.020; TyG index: OR: 1.75, 95% CI: 1.15–2.68, p=0.010). The TyG index, an indicator of insulin resistance, demonstrated a strong association with prolonged ICU stay (OR: 1.80, 95% CI: 1.20–2.70, p=0.004). These results support the potential utility of the TyG index as a valuable biomarker for risk stratification in sepsis patients.

Conclusion: Our study reveals that the TyG index holds potential as a biomarker for forecasting mortality and extended ICU stays in sepsis patients. Given its simplicity and cost-effectiveness, the TyG index could potentially be incorporated into clinical practice to guide management decisions in sepsis.

Keywords: Triglyceride-glucose index, sepsis, insulin resistance, mortality

INTRODUCTION

Sepsis, characterized by an overwhelming response to infection, is a critical condition that ranks among the leading causes of multi-organ failure and mortality in intensive care units (ICUs).[1] Consequently, numerous studies have been conducted on different scoring systems and risk factors to improve the prognosis of sepsis. Many of these scoring systems require extensive clinical and laboratory data, which can be impractical for routine use. In contrast, the triglyceride-glucose (TyG) index is derived from fasting blood glucose (FBG) and triglyceride levels, appears to be a simple and easily accessible scoring system.[2]

One of the less understood but increasingly recognized aspects of sepsis is its impact on metabolic regulation, particularly the development of insulin resistance (IR). IR is a complex metabolic disturbance commonly observed in sepsis, characterized by impaired glucose uptake and utilization by peripheral tissues despite normal or elevated insulin levels. IR in sepsis has been associated with increased mortality and poorer outcomes. IR is defined as a reduction in the sensitivity of peripheral tissues to insulin.[3] During sepsis, uncontrolled release of cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) interferes with insulin signaling pathways, resulting in decreased insulin sensitivity in target tissues. Additionally, the septic state induces an increase in stress hormones, which exacerbate IR through their anti-insulin effects. Sepsis-induced oxidative stress damages mitochondrial function, contributing to IR. Furthermore, sepsis affects insulin signaling pathways by reducing the translocation of glucose transporter 4 (GLUT4) to the cell membrane, thereby limiting glucose uptake.[3]

IR in the intensive care setting has been associated with hyperglycemia, increased risk of organ failure, prolonged hospital stays, and higher mortality rates in previous studies.[4]

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Moderate-quality evidence suggests that the TyG index has a positive correlation with nephropathy, ischemic stroke risk[5] and both the severity and prognosis of coronary artery disease.[6] Although previous studies[7,8] have emphasized the prognostic potential of TyG index in sepsis patients, there is still a lack of research investigating its influence on overall survival duration in this population or assessing whether a nonlinear relationship exists between the TyG index and short-term mortality risk in sepsis.

The objective of this study is to retrospectively assess the impact of the TyG index on mortality and length of stay among septic patients in a tertiary intensive care unit.

METHODS

Ethics

The study protocol was approved by the Clinical Researches Ethics Committee of Karatay University (Date: 01.11.2024, Decision No: 2024-025). This study is a retrospective cohort analysis conducted among patients admitted to the ICU. Due to the retrospective design and the use of previously collected, anonymized data, the requirement for obtaining individual informed consent was waived in accordance with institutional guidelines. The study was conducted in accordance with the 1975 Declaration of Helsinki, as revised in 2013.

Study Population

This retrospective, descriptive, observational study was conducted in the tertiary care ICUs 1, 2, and 3 at Konya City Hospital, which collectively provide a total of 45 ICU beds. The study period extended from January 1, 2022, to September 30, 2024. We included adult patients (aged ≥18 years) admitted to the ICU with sepsis, as defined by the sepsis 3.0 criteria and a sequential organ failure assessment (SOFA) score of ≥2 at admission.[9] To minimize confounding, patients without documented FBG and triglyceride (TG) measurements within the first 24 hours of ICU admission were excluded. Additionally, individuals using triglyceride-lowering medications (e.g., fenofibrate) were not included. After applying these criteria, our final study cohort comprised 208 patients.

Data Collection

Patient data, including demographic information (age, gender, height, weight, and body-mass index) and clinical parameters (APACHE II and SOFA scores), were extracted from the hospital's electronic information system by trained personnel. In addition, laboratory values and vital signs recorded at the time of ICU admission were collected. The TyG index, a surrogate marker for IR, was calculated using the formula: ln [fasting triglyceride (mg/dl)×fasting glucose (mg/dl)]/2.[10] Data collection was performed following standardized protocols to ensure accuracy and consistency, and the study was approved by the institutional review board prior to data extraction.

Primary and Secondary Outcomes

The primary outcome of this study was all-cause mortality in the ICU. Secondary outcomes included long-term follow-up mortality and ICU length of stay.

Statistical Analysis

Continuous data are expressed as either mean±standard deviation (SD) or median with interquartile range (IQR), while categorical data are provided as counts and percentages. Group comparisons for continuous variables were performed using the Student's t-test, and categorical variables were compared using either Pearson's Chi-square or Fisher's exact test.

The distribution normality of the TyG index was initially assessed, after which a multifactorial linear regression was employed to evaluate its association with ICU length of stay. To further investigate the relationship between the TyG index and ICU mortality, multivariate logistic regression analyses were conducted, with odds ratios (ORs) and 95% confidence intervals (CIs) calculated to quantify these associations. The optimal cutoff value was determined using the receiver operating characteristic (ROC) curve.

All statistical analyses were conducted using R software (version 4.0.4; R Foundation for Statistical Computing, Vienna, Austria) and SPSS (IBM SPSS Statistics, Version 24.0; Armonk, NY, USA). Statistical significance was determined by a two-sided P-value of less than 0.05.

RESULTS

Table 1 summarizes the baseline characteristics of the 208 sepsis patients included in the study. The overall median age was 78 years (IQR: 67–90), with no significant difference between survivors (median 77 years, IQR: 65–87) and non-survivors (median 80 years, IQR: 74–91; p=0.160). Similarly, the proportion of male patients was comparable between survivors (53.8%) and non-survivors (53.8%; p=0.270). Notably, survivors exhibited a significantly higher median body-mass index (22.5 kg/m^2, IQR: 21.3–23.7) compared to non-survivors (21.0 kg/m^2, IQR: 20.0–22.4; p<0.002).

Analysis of sepsis severity revealed that non-survivors had a higher prevalence of severe sepsis (39.3% vs. 21.0%; p<0.010) and septic shock (18.0% vs. 8.4%; p<0.009) than survivors. While most comorbid conditions were similarly distributed between the two groups, cancer was significantly more common among non-survivors (21.3% vs. 5.0%; p=0.002). Regarding the site of infection, lower respiratory tract infections were significantly more frequent in survivors (79.8%) compared to non-survivors (61.8%; p<0.001), whereas the rates of genitourinary, hepatobiliary, and gastrointestinal infections were similar across groups.

Furthermore, mortality prediction scores were significantly higher in non-survivors, with a median SOFA score of 5 (IQR: 3–8) versus 2 (IQR: 1–4) in survivors (p<0.001) and a median APACHE II score of 28 (IQR: 20–33) compared to 18 (IQR: 14–22) in survivors (p<0.001). Consistent with the increased severity of illness, non-survivors also experienced

Table 1. General characteristics of the survivor and the non-survivor groups

Variable	Total (n: 208)	Survivors (n: 119)	Non-survivors (n: 89)	p-value
Age, year	78 (67–90)	77 (65–87)	80 (74–91)	0.160
Male, n (%)	108 (52.0)	64 (53.8)	64 (53.8)	0.270
BMI, kg/m^2	23.1 (22.1–25.0)	22.5 (21.3–23.7)	21.0 (20.0–22.4)	0.002
Sepsis severity, n (%)				
Severe sepsis	60 (28.8)	25 (21.0)	35 (39.3)	0.010
Septic shock	26 (12.5)	10 (8.4)	16 (18.0)	0.009
Co-morbidity, n (%)				
Hypertension	160 (76.9)	92 (77.3)	68 (76.4)	0.245
Diabetes mellitus	135 (64.9)	80 (67.2)	55 (61.8)	0.460
Cerebrovascular disease	65 (31.3)	38 (31.9)	27 (30.3)	0.330
Cancer	25 (12.0)	6 (5.0)	19 (21.3)	0.002
COPD	120 (57.7)	68 (57.1)	52 (58.4)	0.170
Chronic kidney disease	15 (7.2)	9 (7.6)	6 (6.7)	0.240
Congestive heart failure	98 (47.1)	57 (47.9)	41 (46.1)	0.440
Dementia	42 (20.2)	25 (21.0)	17 (19.1)	0.280
Site of infection, n (%)				
Lower respiratory	150 (72.1)	95 (79.8)	55 (61.8)	<0.001
Genitourinary	90 (43.3)	60 (50.4)	30 (33.7)	0.160
Hepatobiliary	30 (14.4)	20 (16.8)	10 (11.2)	0.280
Gastrointestinal	35 (16.8)	25 (21.0)	10 (11.2)	0.120
Mortality prediction model				
SOFA score	3 (2–5)	2 (1–4)	5 (3–8)	<0.001
APACHE II score	20 (15–26)	18 (14–22)	28 (20–33)	<0.001
Charlson's comorbidity index	3 (2–5)	2 (2–4)	4 (3–6)	<0.001
LOS in ICU (day)	13 (6–20)	12 (7–18)	19 (13–28)	<0.001

Data are presented as median (IQR) and categorical variables were presented as quantity and frequency (%); Mann–Whitney U and χ^2 tests were used for comparisons ($p<0.05$ considered significant); abbreviations: BMI: Body-mass index, COPD: Chronic obstructive pulmonary disease, ICU: Intensive care unit, LOS: Length of stay, APACHE II: Acute physiology and chronic health evaluation II, SOFA: Sequential organ failure assessment, IQR: Interquartile range

a significantly longer ICU stay (median 19 days, IQR: 13–28) than survivors (median 12 days, IQR: 7–18; p<0.001).

Table 2 presents the laboratory parameters stratified by outcome. There was no significant difference in hemoglobin levels between survivors (12.0 [10.8–13.4] g/dl) and non-survivors (12.3 [9.7–12.6] g/dl; p=0.085). Similarly, platelet counts were comparable between survivors (225 [170–360]×10^3 cells/mm^3) and non-survivors (220 [165–350]×10^3 cells/mm^3; p=0.600). Notably, serum albumin levels were significantly lower in non-survivors (3.0 [2.7–3.7] g/dl) compared to survivors (3.6 [3.2–4.0] g/dl; p<0.001). C-reactive protein levels were elevated in non-survivors (112 [80–290] g/dl) relative to survivors (108 [75–210] g/dl; p<0.002), and FBG was also higher among non-survivors (115 [100–140] mg/dl vs. 108 [93–130] mg/dl; p=0.010). Glycated hemoglobin (HbA1c) was significantly greater in the non-survivor group (8.8 [6.9–10.5] %) compared with survivors (6.3 [6.0–6.8] %; p<0.001). Although total cholesterol levels tended to be higher in non-survivors (148.20 [46.81] mg/dl) than in survivors (142.27 [42.62] mg/dl), the difference was not statistically significant (p=0.134). In contrast, triglyceride levels were significantly increased in non-survivors (148.06±77.29 mg/dl) compared to survivors (106.24±28.30 mg/dl; p<0.001). LDL-C values did not differ significantly between groups (77.50 [34.56] mg/dl in non-survivors vs. 77.49 [34.35] mg/dl in survivors; p=0.902), while HDL-C was markedly lower in non-survivors (35.52 [13.01] mg/dl) than in survivors (39.83 [14.44] mg/dl; p<0.001). Finally, the TyG index was significantly elevated in non-survivors (9.43±0.71) relative to survivors (9.11±0.59; p<0.001).

The univariate and multivariate logistic regression analyses for mortality and prolonged ICU stay are presented in **Table 3**.

In the univariate analysis, lower albumin levels were significantly associated with both mortality (OR: 0.45, 95% CI: 0.30–0.67, p<0.001) and prolonged ICU stay (OR: 0.60, 95% CI: 0.40–0.90, p=0.015). Similarly, higher HbA1c levels were correlated with increased mortality risk (OR: 1.80, 95% CI: 1.40–2.30, p<0.001) and prolonged ICU stay (OR: 1.40, 95% CI: 1.10–1.80, p=0.008). The TyG index, an indicator of IR, demonstrated a strong association with mortality (OR: 2.50, 95% CI: 1.60–3.90, p<0.001) and prolonged ICU stay (OR: 1.80, 95% CI: 1.20–2.70, p=0.004). Furthermore, elevated triglyceride levels were identified as a significant predictor of mortality (OR: 1.02, 95% CI: 1.01–1.03, p<0.001) and prolonged ICU stay (OR: 1.01, 95% CI: 1.00–1.02, p=0.030), with each 10 mg/dL increase in triglycerides contributing to a higher risk. Conversely, higher HDL-C levels exhibited a protective effect against mortality (OR: 0.95, 95% CI: 0.92–0.98, p=0.002) and prolonged ICU stay (OR: 0.97,

Table 2. The laboratory data of the survivor and the non-survivor groups

Variable	Total (n: 208)	Survivors (n: 119)	Non-survivors (n: 89)	p-value
Laboratory parameter				
Hemoglobin, g/dl	12.1 (10.8–13.5)	12.0 (10.8–13.4)	12.3 (9.7–12.6)	0.085
Platelet count, x1000 cells/mm^3	230 (170–345)	225 (170–360)	220 (165–350)	0.600
Albumin, g/dl	3.7 (3.3–4.1)	3.6 (3.2–4.0)	3.0 (2.7–3.7)	<0.001
C-reactive protein, g/dl	105 (70–225)	108 (75–210	112 (80–290)	<0.002
FBG (mg/dl)	110 (95–135)	108 (93–130)	115 (100–140)	0.010
HbA1c	7.2 (6.0–8.1)	6.3 (6.0–6.8)	8.8 (6.9–10.5)	<0.001
T-chol (mg/dl)	143.20 (43.73)	142.27 (42.62)	148.20 (46.81)	0.134
TG (mg/dl)	186.48±123.39	106.24±28.30	148.06±77.29	<0.001
LDL-C (mg/dl)	78.39 (33.25)	77.49 (34.35)	77.50 (34.56)	0.902
HDL-C (mg/dl)	46.47 (16.64)	39.83 (14.44)	35.52 (13.01)	<0.001
TyG index	9.21±0.66	9.11±0.59	9.43±0.71	<0.001

Data are presented as median (IQR) or mean±SD as indicated; comparisons between groups were performed using appropriate statistical tests with p<0.05 considered significant. FBG: Fasting blood glucose, HbA1c: Hemoglobin A1c, T-chol: Total cholesterol, TG: Triglycerides, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TyG index: Triglyceride glucose index

Table 3. Univariable and multivariable logistic regression analysis for mortality and prolonged ICU stay

Variable	Mortality		Prolonged ICU Stay	
	Univariable OR (95% CI)	**p-value**	**Univariable OR (95% CI)**	**p-value**
Albumin (g/dl)	0.45 (0.30–0.67)	<0.001	0.60 (0.40–0.90)	0.015
HbA1c (%)	1.80 (1.40–2.30)	<0.001	1.40 (1.10–1.80)	0.008
TG (mg/dl)*	1.02 (1.01–1.03)	<0.001	1.01 (1.00–1.02)	0.030
TyG index	2.50 (1.60–3.90)	<0.001	1.80 (1.20–2.70)	0.004
HDL-C (mg/dl)	0.95 (0.92–0.98)	0.002	0.97 (0.94–1.00)	0.045
APACHE II	1.12 (1.08–1.16)	<0.001	1.09 (1.05–1.13)	<0.001
SOFA scores	1.14 (1.09–1.19)	<0.001	1.10 (1.05–1.15)	<0.001
Diabetes	1.45 (1.10–1.90)	0.015	1.40 (1.05–1.88)	0.020
	Multivariable OR (95% CI)	**p-value**	**Multivariable OR (95% CI)**	**p-value**
Albumin (g/dl)	0.50 (0.33–0.75)	0.001	0.65 (0.43–0.98)	0.040
HbA1c (%)	1.65 (1.25–2.18)	0.002	1.35 (1.05–1.75)	0.020
TG (mg/dl)*	1.015 (1.005–1.025)	0.004	1.012 (1.002–1.022)	0.022
TyG index	2.20 (1.40–3.40)	0.001	1.75 (1.15–2.68)	0.010
HDL-C (mg/dl)	0.96 (0.93–0.99)	0.005	0.98 (0.95–1.01)	0.080
APACHE II	1.10 (1.06–1.14)	<0.001	1.08 (1.04–1.12)	0.002
SOFA scores	1.12 (1.07–1.17)	<0.001	1.08 (1.04–1.13)	0.002
Diabetes	1.15 (0.90–1.50)	0.210	1.10(0.88–1.40)	0.325

*OR for TG represents the odds ratio per 10 mg/dl increase. *Data are presented as odds ratios (OR) with 95% confidence intervals (CI). In these models, mortality and prolonged ICU stay (defined as ICU stay>median duration) served as dependent variables. Variables with p<0.05 in univariable analysis were included in the multivariable models. ICU: Intensive care unit, HbA1c: Hemoglobin A1c, TG: Triglycerides, TyG index: Triglyceride glucose index, HDL-C: High-density lipoprotein cholesterol, APACHE II: Acute physiology and chronic health evaluation II

95% CI: 0.94–1.00, p=0.045). Each one-unit increase in the APACHE II score was significantly associated with a higher risk of mortality (OR=1.12; 95% CI: 1.08–1.16; p<0.001) and prolonged ICU stay (OR=1.09; 95% CI: 1.05–1.13; p=0.001). Each one-unit increase in the SOFA score was significantly associated with a higher risk of mortality (OR=1.14; 95% CI: 1.09–1.19; p<0.001) and prolonged ICU stay (OR=1.10; 95% CI: 1.05–1.15; p=0.001).

In the multivariate model, which adjusted for potential confounders, albumin remained a significant independent predictor for both mortality (OR: 0.50, 95% CI: 0.33–0.75, p=0.001) and prolonged ICU stay (OR: 0.65, 95% CI: 0.43–0.98, p=0.040). HbA1c and TyG index also retained their independent associations with mortality (HbA1c: OR: 1.65, 95% CI: 1.25–2.18, p=0.002; TyG index: OR: 2.20, 95% CI: 1.40–3.40, p=0.001) and prolonged ICU stay (HbA1c: OR: 1.35, 95% CI: 1.05–1.75, p = 0.020; TyG index: OR: 1.75, 95% CI: 1.15–2.68, p=0.010). Triglyceride levels remained an independent predictor of mortality (OR: 1.015, 95% CI: 1.005–1.025, p=0.004) and prolonged ICU stay (OR: 1.012, 95% CI: 1.002–1.022, p=0.022). HDL-C levels remained protective against mortality (OR: 0.96, 95% CI: 0.93–0.99, p=0.005), although its association with prolonged ICU stay was not statistically significant in the multivariate model (p=0.080). In the adjusted model, each one-unit increment in the APACHE II score was significantly associated with increased mortality (OR=1.10; 95% CI: 1.06–1.14; p<0.001) and prolonged ICU stay (OR=1.08; 95% CI: 1.04–1.12; p=0.002). In the multivariable

model, each one-unit increment in the SOFA score was significantly associated with increased mortality (OR=1.12; 95% CI: 1.07–1.17; p<0.001) and prolonged ICU stay (OR=1.08; 95% CI: 1.04–1.13; p=0.002).

In the univariable analysis, diabetes was significantly associated with both increased mortality (OR: 1.45, 95% CI: 1.10–1.90, p=0.015) and prolonged ICU stay (OR: 1.40, 95% CI: 1.05–1.88, p=0.020). However, after adjusting for potential confounders in the multivariable logistic regression model, diabetes was no longer a significant independent predictor of mortality (OR: 1.15, 95% CI: 0.90–1.50, p=0.210) or prolonged ICU stay (OR: 1.10, 95% CI: 0.88–1.40, p=0.325). These findings suggest that while diabetes may influence sepsis outcomes through metabolic dysregulation, its effect appears to be mediated by other clinical and biochemical factors included in the model.

In an additional subgroup analysis, patients with TyG levels below 8.0-values potentially reflecting malnutrition, severe illness, or insufficient metabolic reserves-were specifically examined. After adjustment for potential confounders, these patients demonstrated a statistically significant increased risk of mortality (OR: 2.10, 95% CI: 1.25–3.26, p=0.007) as well as a higher likelihood of prolonged ICU stay (OR: 1.90, 95% CI: 1.10–3.14, p=0.023) compared to patients with higher TyG levels.

The ROC curve analysis (**Figure**) was performed to assess the prognostic value of the TyG in predicting mortality among sepsis patients. To further evaluate the prognostic performance of the TyG index, we compared its predictive capability with established severity scores, including APACHE II and SOFA scores. The TyG index demonstrated a good discriminatory ability for predicting mortality in sepsis patients, with an AUC of 0.798, a sensitivity of 82%, and a specificity of 75%. The positive predictive value (PPV) was calculated as 63.8%, indicating that approximately two-thirds of patients classified as high-risk based on the TyG index (≥9.10) experienced mortality. The negative predictive value (NPV) was 88.6%, suggesting that the TyG index effectively identifies patients with a lower likelihood of mortality.

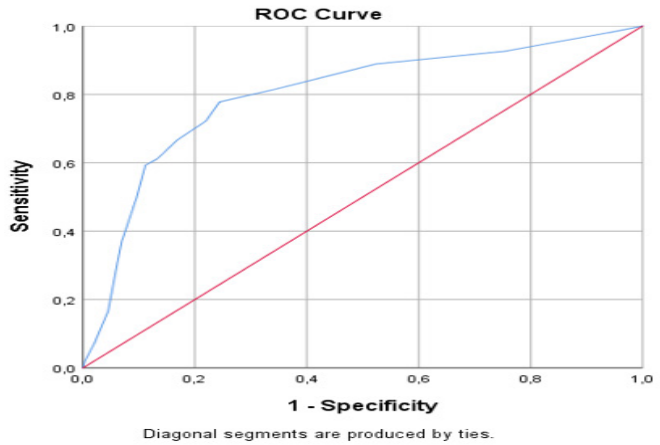

Figure. ROC curve for TyG index in mortality prediction
AUC of 0.798 (95% confidence interval: 0.729–0.867, p<0.001) (PPV: 63.8% , NPV: 88.6%) ROC: Receiver operating characteristic, TyG: Triglyceride-glucose, AUC: Area under the curve, PPV: Positive predictive value, NPV: Negative predictive value

When compared to other prognostic scores, the APACHE II score exhibited the highest predictive accuracy (AUC: 0.90), with slightly superior PPV (72%) and NPV (92%) values. The SOFA score (AUC: 0.88) also demonstrated comparable predictive power, with a PPV of 70% and NPV of 91% (**Table 4**).

Table 4. Compare the TyG index with severity scores

Score	AUC	Sensitivity	Specificity	PPV	NPV
TyG index (cut-off: 9.10)	0.798	82%	75%	63.8%	88.6%
APACHE II	0.90	85%	78%	72%	92%
SOFA score	0.88	80%	77%	70%	91%

TyG: Triglyceride–glucose index, APACHE II: Acute physiology and chronic health evaluation II, SOFA: Sequential organ failure assessment, AUC: Area under the curve, PPV: Positive predictive value, NPV: Negative predictive value

DISCUSSION

The provided study presents a comprehensive analysis of a study investigating the prognostic significance of the TyG index in predicting mortality and prolonged ICU stay among patients with sepsis. This research contributes valuable insights to the field of critical care medicine and offers potential improvements in patient management strategies. The study demonstrated a robust discriminative capability of the TyG index, with an area under the curve (AUC) of 0.798 (95% CI: 0.729–0.867, p<0.001). This high AUC value indicates that the TyG index is a reliable predictor of outcomes in sepsis patients. An optimal threshold value of 9.10 was established, exhibiting 82% sensitivity and 75% specificity. These metrics suggest that the TyG index can effectively identify patients at higher risk of adverse outcomes, allowing for more targeted interventions and resource allocation.

The TyG index's role as a predictor of ICU outcomes in septic patients has been supported by several studies. Elevated TyG levels are consistently associated with longer ICU LOS and increased mortality rates, underscoring its potential as a prognostic marker.[11,12]

The relationship between IR and sepsis is multifaceted and involves several interconnected pathophysiological mechanisms. First, IR has been closely linked to impairments in the fibrinolytic system, endothelial dysfunction, blood-brain barrier disruption, and oxidative stress, all of which contribute to the exacerbation of sepsis-related infections and the suppression of the host immune response.[13-16] Second, IR plays a crucial role in metabolic dysregulation, which further intensifies infection due to the heightened release of cytokines and inflammatory mediators. Lastly, IR, in conjunction with hyperglycemia and hyperlipidemia, has been associated with the development of cardiovascular and cerebrovascular diseases, as well as organ dysfunction. These conditions not only aggravate infection severity but also lead to cellular acidosis and oxidative stress, ultimately compromising the host immune defense.[17]

The current results are consistent with previous literature, which has underscored the importance of metabolic dysregulation and IR in the pathophysiology of sepsis.[18,19]

Several studies have identified the TyG index as a cost-effective and reliable surrogate marker for IR, and its elevation has been linked to adverse outcomes in critically ill patients.[3,4] Our findings further support these observations by demonstrating that even after adjusting for potential confounders, the TyG index remains an independent predictor of poor outcomes in sepsis.

An optimal cut-off value of 9.10 was identified based on the ROC curve which provided a sensitivity of 82% and a specificity of 75% for mortality prediction. This value is consistent with previous studies, such as the study by Zhang et al.[20] which identified a cut-off value of 9.0 in non-diabetic critically ill patients with sepsis, and the study by Lou et al.[21] which reported a cut-off value of 8.9. In line with our study results, these findings underscore the potential of the TyG index as a valuable biomarker for risk stratification in sepsis patients. Further studies with larger cohorts are needed to validate these findings.

The logistic regression analyses reveal several noteworthy associations between the evaluated biomarkers, severity scores, and clinical outcomes. In both univariable and multivariable models, lower albumin levels were significantly associated with increased odds of mortality and prolonged ICU stay, suggesting that hypoalbuminemia may serve as a robust indicator of adverse outcomes in critically ill patients. Similarly, elevated HbA1c levels emerged as a significant risk factor; patients with higher HbA1c values experienced markedly increased odds of both mortality and extended ICU admission, highlighting the potential impact of chronic glycemic control on acute critical illness prognosis. Interestingly, while the protective effect of higher HDL-C levels was noted, its association with prolonged ICU stay did not remain statistically significant in the multivariate analysis, suggesting that further investigation is warranted.

Additionally, our findings indicate that higher triglyceride (TG) levels and an elevated TyG index are independently associated with worse clinical outcomes. Notably, the TyG index, which integrates fasting glucose and TG levels as a surrogate marker for IR, demonstrated one of the strongest associations with both mortality (univariable OR: 2.50; multivariable OR: 2.20) and prolonged ICU stay (univariable OR: 1.80; multivariable OR: 1.75). Our findings suggest that the TyG index may serve as a valuable prognostic tool in clinical practice.

Moreover, established severity scoring systems, namely the APACHE II and SOFA scores, consistently exhibited significant associations with both outcomes. Each one-unit increase in APACHE II and SOFA scores was positively correlated with approximately a 10–12% and 12–14% elevating the likelihood of mortality, respectively, as well as significant increases in the odds of prolonged ICU stay. The consistency of these findings across univariable and multivariable analyses reinforces the independent prognostic value of these scores in critically ill patients. Similar to our study, in a study by Zhang et al.[13], incorporating the TyG index into SOFA and APACHE II models improved their predictive accuracy for mortality and LOS in septic patients. This synergy likely reflects the complementary nature of metabolic and organ function parameters in determining patient outcomes.

Traditional scoring systems like SOFA and APACHE assess organ dysfunction and physiological derangements but lack direct measures of metabolic health. The TyG index bridges this gap by providing a metabolic perspective, which is particularly relevant in sepsis-associated conditions like acute kidney injury and cardiovascular dysfunction.[13,22] Future studies should explore the integration of the TyG index into composite scoring models to enhance predictive capabilities.

Overall, these data underscore the importance of integrating both metabolic markers, such as the TyG index, and traditional severity scores in risk stratification models. The strong and independent associations observed suggest that these parameters could be pivotal in guiding clinical decision-making and tailoring therapeutic interventions in the ICU setting.

Recent meta-analyses and reviews have consistently underscored the prognostic value of the TyG index across various clinical conditions. Yang et al.[22] demonstrated that a higher TyG index is significantly associated with increased risks of ischemic stroke (OR: 1.37; 95% CI: 1.22–1.54), stroke recurrence (OR: 1.50; 95% CI: 1.19–1.89), and mortality (OR: 1.40; 95% CI: 1.14–1.71), reinforcing its utility in risk stratification. Similarly, Li-Yin et al.[5] conducted an umbrella review of 29 meta-analyses and found that a high TyG index is significantly linked with increased risks of contrast-induced nephropathy, stroke, and coronary artery disease severity. Moreover, Nayak et al.[23] provided comprehensive evidence showing that elevated TyG levels are associated with adverse outcomes across kidney disease, diabetes, metabolic disorders, cerebrovascular, and cardiovascular conditions. Together, these findings support the TyG index as a robust and cost-effective biomarker for predicting adverse clinical outcomes, aligning with our study's results on sepsis risk stratification and underscoring its potential for broader clinical application.

It is important to acknowledge that some studies have reported contrasting results regarding the prognostic value of metabolic markers in sepsis. Variations in patient populations, sample sizes, and study designs may contribute to these discrepancies. Such conflicting findings emphasize the need for further multicentric and large-scale research to consolidate the role of the TyG index and related metabolic parameters in sepsis prognosis.

Contrasting evidence exists regarding the specificity of the TyG index in critical illness. Some studies highlight its sensitivity to confounders such as pre-existing metabolic disorders, medications, and nutritional status, which may limit its reliability in heterogeneous ICU populations.[24] Furthermore, its prognostic value may vary across subgroups, such as diabetic versus non-diabetic patients, necessitating tailored interpretations.

In the additional subgroup analysis, patients with TyG levels below 8.0-values that may reflect malnutrition, severe illness, or insufficient metabolic reserves-were specifically evaluated. After adjusting for potential confounders, these patients exhibited a significantly increased risk of mortality (OR: 2.10,

95% CI: 1.25–3.26, p=0.007) as well as a higher likelihood of prolonged ICU stay (OR: 1.90, 95% CI: 1.10–3.14, p=0.023). These findings suggest that very low TyG levels may serve as an indicator of adverse clinical outcomes in sepsis.

Notably, given the potential influence of underlying malnutrition and severe clinical conditions in this patient group, more aggressive and targeted interventions may be warranted. This aspect of our study aligns with existing literature on the prognostic value of metabolic biomarkers and may provide insight into new approaches for managing critically ill patients.[25] However, the limited sample size in the subgroup analysis necessitates caution in interpreting the generalizability of these findings. Future studies with larger cohorts are needed to further explore these associations and refine clinical applications.

Our results indicate that the TyG index is a promising, cost-effective biomarker for risk stratification in sepsis patients, as it is derived from routine laboratory tests. Its incorporation into clinical practice could facilitate the early identification of high-risk individuals, thereby enabling timely, intensive monitoring and targeted therapeutic interventions such as tailored nutritional support and metabolic management. Moreover, when used in conjunction with existing prognostic scoring systems, the TyG index has the potential to enhance predictive accuracy and optimize resource allocation in the ICU.

Limitations

This sudy had several limitations. First, being retrospective and including a single center may introduce a selection bias and limit the generalizability of the findings. Additionally, reliance on previously recorded data in a retrospective study may be prone to information bias, as not all relevant clinical variables may have been consistently documented. The relatively small sample size, may have limited the statistical power of our study. This point could impact the robustness of our findings and their generalizability to larger and more diverse patient populations. The lack of longitudinal data on dynamic changes in the TyG index over the course of ICU stay is another limitation, as such changes could provide additional prognostic information. Despite these limitations, the study's strengths lie in its comprehensive analysis, which integrated robust laboratory data with clinical outcomes using ROC curve analysis and multivariate logistic regression, thereby providing a nuanced evaluation of the TyG index's predictive utility.

CONCLUSION

In summary, our research indicates that the TyG index serves as a promising biomarker for forecasting mortality and extended ICU stays in sepsis patients. Given its simplicity and cost-effectiveness, the TyG index could potentially be incorporated into clinical practice to guide management decisions in sepsis. Future prospective, multicenter studies are required to confirm these findings and to further investigate the underlying mechanisms that connect metabolic dysfunction to adverse outcomes in sepsis.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study protocol was approved by the Clinical Researches Ethics Committee of Karatay University (Date: 01.11.2024, Decision No: 2024-025).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Review

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The increase in *Aspergillus* infections during and after the COVID-19 pandemic

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ABSTRACT

This paper aims to identify the correlation between *Aspergillus* infections and the COVID-19 pandemic. The literature review used PubMed, EBSCO, Proquest Central at Kırıkkale University, Google, and Google Scholar. Between 2024 and 1980, the keywords "*Aspergillus*," "aspergillosis," "invasive pulmonary aspergillosis," "IPA," "COVID-19-associated pulmonary aspergillosis," "CAPA," and "COVID-19" were searched. An association between COVID-19 pneumonia and invasive pulmonary aspergillosis (IPA), a complication seen in patients with severe respiratory syndromes, has been recently demonstrated, and the clinical features of COVID-19-associated pulmonary aspergillosis (CAPA) have been detailed. Due to diagnostic delays and the quick deterioration of respiratory diseases, infections caused by the *Aspergillus* genus are frequently recognized after the fact, which is a sad reality. From direct angioinvasion to hypersensitivity reactions, *Aspergillus* may inflict various human diseases. Invasive *Aspergillus* infections are sporadic in immunocompetent people and nearly always affect those immunosuppressed due to lung illness, immunosuppressive medication, or immunodeficiency. *Aspergillus fumigatus (A. fumigatus)* was found in most COVID-19 patients, and CAPA was also detected in several of these individuals. Also, patients with severe respiratory illnesses, like influenza and MERS-CoV, have been found to have multiple instances of IPA as super-infections. The function of antifungal prophylaxis in CAPA is unknown even though *A. fumigatus* was detected before the start of CAPA. On the other hand, voriconazole medication may be effective if begun right after.

Keywords: Aspergillus, invasive pulmonary aspergillosis, COVID-19 associated pulmonary aspergillosis, COVID-19, *Aspergillus fumigatus*

INTRODUCTION

Recently, there was an association between COVID-19 pneumonia and invasive pulmonary aspergillosis (IPA), a complication seen in patients with severe respiratory syndromes. The clinical features of COVID-19-associated pulmonary aspergillosis (CAPA) have been detailed. Diagnostic delays and the quick deterioration of respiratory problems typically result in the late diagnosis of *Aspergillus* genus infections.[1]

Due to the immune-compromising properties of SARS-CoV-2 and medications such as tocilizumab and dexamethasone, some researchers were concerned that COVID-19 patients could have a fungal superinfection.[2-6] The reported cumulative rates of CAPA range from 0.7 to 7.7 percent in COVID-19 patients[7,8], 2.5 to 39.1 percent in COVID-19 intensive care unit patients[9,10], and 3.2 to 29.6 percent in COVID-19 patients requiring mechanical ventilation.[7,11]

Aspergillus infections and the COVID-19 pandemic are the foci of this research.

METHODS

The literature review utilized Google, Google Scholar, PubMed, EBSCO, and Proquest Central at Kırıkkale University. From 2024 to 1980, we searched for "*Aspergillus*," "aspergillosis," "IPA," "COVID-19-associated pulmonary aspergillosis," "CAPA," and "COVID-19."

ASPERGILLOSIS

The fungus *Aspergillus* is present in all organic materials. There are more than a hundred species of *Aspergillus*, but only

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two—*Fumigatus fumigatus* and *Aspergillus niger (A. niger)*—cause severe sickness in humans. *Aspergillus flavus (A. flavus)* and *Aspergillus clavatus* are less common. Fungal spores can infect humans through the air we breathe.[12]

From direct angioinvasion to hypersensitivity reactions, *Aspergillus* may inflict various human diseases. The following four primary syndromes[12] are caused by *Aspergillus*, which primarily affects the lungs:

- Aspergillosis of the airways and lungs (ABPA)
- *Aspergillus* chronic pneumonia with necrotizing microorganisms (CNPA)
- Aspergilloma
- Aspergillosis with metastasis

Endophthalmitis, endocarditis, and abscesses in the myocardium, kidneys, liver, spleen, soft tissue, central nervous system (CNS), and bone can result from *Aspergillus* hematogenously disseminating beyond the lung in patients with severely impaired immune systems. Regarding fungal endocarditis, Candida species is the most common culprit, followed closely by *Aspergillus*. In cardiac surgery, wound infections and endocarditis caused by *Aspergillus* can arise.[12]

ABPA, a hypersensitivity reaction to A fumigatus colonization of the tracheobronchial tree, co-occurs with asthma and cystic fibrosis (CF). Both ABPA and allergic fungal sinusitis are possible. Two uncommon hypersensitivity lung illnesses induced by *Aspergillus* species are broncho-centric granulomatosis and malt worker's lung.[12]

A mycetoma, or fungus ball, occurs in the lung parenchyma when an aspergilloma grows in an existing hollow. Cavitary disease can have several underlying causes, such as CF, sarcoidosis, emphysematous bullae, treated tuberculosis, or another necrotizing infection. Although the fungus ball can move inside the cavity, it will not penetrate the cavity wall. The risk of hemoptysis, however, is twelve.

Patients with immunosuppression, whether from drinking, long-term corticosteroid treatment, underlying lung disease, or any other cause, are more likely to experience CNPA, a subacute process. The gradual cavitary pulmonary infiltration that CNPA causes is sometimes not noticed for weeks or months due to how rare it is.[12]

Rapidly progressing and frequently deadly invasive aspergillosis affects immunocompromised individuals, such as those who are profoundly neutropenic, have undergone bone marrow or solid organ transplants, have advanced AIDS[13] or chronic granulomatous disease, and so on. In this infectious process, blood vessel invasion causes multifocal infiltrates, which can be cavitary, wedge-shaped, and based on the pleura. The CNS is a potential target for dissemination.[12]

Pathophysiology

Aspergillus causes colonization, hypersensitivity reactions, persistent necrotizing infections, and potentially fatal, quickly progressing angioinvasion. Invasive *Aspergillus* infections are sporadic in immunocompetent people and nearly always occur in immunosuppressed patients due to underlying pulmonary illness, immunosuppressive medication therapy, or immunodeficiency.[12]

Aspergillus hyphae stand out histologically compared to other fungi due to the many septae that branch at 45° angles. Tissue stained with silver allows one to see the hyphae more clearly. Even though other *Aspergillus* species have been found in nature, the one most commonly infecting humans is *Aspergillus fumigatus (A. fumigatus)*. The occurrence of *A. flavus* and *A. niger* is reduced. This disparity in frequency is likely associated with the fact that *A. fumigatus* can thrive at average human body temperature, in contrast to the majority of *Aspergillus* species.[12]

The respiratory system's mucous membrane and ciliary activity are the first lines of protection against inhaled spores in humans. The fungus is engulfed and destroyed by macrophages and neutrophils. However, poisonous compounds produced by numerous *Aspergillus* species prevent macrophage and neutrophil phagocytosis. Additionally, corticosteroids hinder the activity of neutrophils and macrophages.[12]

Neutrophil malfunction or reduced numbers can be caused by underlying immunosuppression, such as HIV illness, chronic granulomatous disease, or pharmaceutical immunosuppression. Vascular invasion is more common in immunocompromised people and can cause lung infarction, bleeding, and necrosis. In people with CNPA, granulomas form, and alveoli consolidate. Hyphae can be seen inside the granulomata.[12]

Risk Factors

Several factors can increase the likelihood of invasive aspergillosis following a bone marrow transplant. These include central venous catheters, prolonged neutropenia, graft-versus-host disease, high-dose corticosteroid therapy, disruption of standard mucosal barriers, and transplants from unrelated or unmatched donors.[12,13]

People on long-term corticosteroid treatment for severe sickness or chronic obstructive pulmonary disease (COPD) are at increased risk of developing an invasive *Aspergillus* infection, even if they do not have a history of cancer or chemotherapy and are likely not immunocompetent.[14]

About a quarter of intubated patients with severe coronavirus disease 2019 (COVID-19) had pulmonary aspergillosis, which is associated with a higher risk of death within 30 days.[15-19] The incidence of CAPA among intensive care unit patients was reported to be between 4% and 35% in a report from April 2021.[20] The question of whether CAPA is a separate entity is still up for debate, according to a March 2021 comparative investigation. However, the high mortality rate (60-70%) among the presumed ICU cases provides support for this theory.[21]

COMPLICATIONS OF COVID-19

Some of the many complications that can arise from contracting COVID-19 include pneumonia, acute respiratory distress syndrome, heart damage, arrhythmia, septic shock, dysfunction of the liver and kidneys, and failure of multiple organs.[22]

Severe symptoms requiring intensive care are experienced by around 5% of COVID-19 patients and 20% of those hospitalized. Acute liver injury (19%), pneumonia (75%), acute respiratory distress syndrome (15%), acute kidney injury (9%), and AKI (9%). More and more cases of cardiac damage, such as myocarditis, dysrhythmias, abrupt heart failure, and troponin increase, have been documented. Thrombotic coagulopathy, which can lead to venous and arterial thromboembolic events, affects 10% to 25% of COVID-19 hospitalized patients. Impaired consciousness and stroke are examples of neurologic symptoms.[22] Up to 40% of patients in the intensive care unit die.[23]

Long COVID

More and more patients have suffered long-term, post-infection consequences as the COVID-19 epidemic has progressed. Although the majority of patients make a full recovery, a small percentage may experience side effects such as exhaustion, shortness of breath, coughing, anxiety, depression, trouble concentrating (often known as "brain fog"), issues with the digestive system, disturbed sleep, pain in the joints, and chest discomfort that worsens weeks or months after the initial sickness has passed. Researchers are conducting long-term investigations to learn more about these problems.[24]

The medical word for what is usually referred to as long COVID or "long haulers" is post-acute sequelae of SARS-CoV-2 infection (PASC). In their recommendations on the clinical spectrum of COVID-19, the National Institutes of Health address issues such as long-lasting symptoms or organ failure following acute infection.[25]

Future Public Health Implications

According to Datta et al.[26], who evaluated the topic, the public health consequences of extended COVID need to be investigated. Late inflammatory and virologic consequences may manifest, similar to other illnesses such as Lyme disease, syphilis, and Ebola. To know what this disease is all about, we need to look at evidence beyond acute infection and post-acute hyperinflammatory sickness.[26]

The capacity of SARS-CoV-2 to infiltrate endothelial cells through the surface-expressed angiotensin-converting enzyme-2 (ACE-2) causes thrombotic symptoms in severe COVID-19. Microthrombotic consequences, such as deep vein thrombosis (DVT), peripheral edema (PE), and stroke, might result from immunothrombosis, which is itself caused by endothelial inflammation, complement activation, thrombin production, platelet, and leukocyte recruitment, and the start of innate and adaptive immunological responses.[27]

Immunosuppressive treatments may cause an increase in *Aspergillus* infections. It should be kept in mind and if necessary, *Aspergillus* treatments should be given to the patients.[28]

INVASIVE PULMONARY ASPERGILLOSIS (IPA) AND COVID-19-ASSOCIATED PULMONARY ASPERGILLOSIS (CAPA)

Patients with severe respiratory syndromes often experience interstitial pneumonia (IPA), which is caused by the *Aspergillus* species and is associated with significant fatality rates.[18,29] Several risk factors can lead to IPA, the most common of which is lung epithelial injury and long-term corticosteroid treatment.[26] Multiple reports have reported IPA as super-infections in patients with severe respiratory illnesses, such as influenza and MERS-CoV.[18,30]

In reality, postmortem diagnosis is often made in patients with COVID-related pulmonary aspergillosis. Unfortunately, due to their essential concerns, we could not routinely obtain samples from the patient's lower respiratory tract. The likelihood of defining an *Aspergillus* fungal colonization and the promptness of an accurate diagnosis of pulmonary aspergillosis were both negatively affected by this discomfort. The patient's respiratory condition quickly deteriorated due to these delays and other risk factors, such as significant lung injury and protracted therapy with corticosteroids.[30] The patient has a history of diabetes, which increases the risk of fungal angioinvasion due to changes in blood artery structure. Agar gel immunodiffusion was used to identify Aspergillus-specific antibodies in serum to clarify the eventuality of a prior chronic *Aspergillus* infection. Based on the negative result, it is highly probable that the patient contracted an illness while intubating in a healthcare facility. Most recent findings indicate that *Aspergillus* spp. in immunocompetent hosts is acknowledged as a possible source of VAP.[31,32]

Although *Aspergillus niger* can cause severe lung disease, it is more commonly mentioned as the source of otomycosis and cutaneous infections rather than invasive aspergillosis.[33] Research into agricultural regions of southern Italy for the existence of triazole-resistant *Aspergillus* isolates also found other species of the fungus. Even though these species aren't as dangerous as *A. fumigatus*, which can cause invasive illness in susceptible people, they are often found isolated in Sicily.[34] The patient's respiratory status was so bad that he died even though the fungal etiology was determined, and voriconazole was given quickly. Therefore, including immunocompetent hosts, instances with severe respiratory syndromes should be evaluated for IPA as a potential consequence.[35,36]

According to Salmanton-García et al.[2], patients were expected to face the possibility of fungal superinfection due to the significant immunomodulation and lymphocyte depletion brought about by COVID-19 and the following use of medications targeting the immune system. From March 2020 to August 2020, 186 individuals worldwide with coronavirus disease-associated pulmonary aspergillosis (CAPA) were surveyed. A total of 182 patients were admitted to the ICU; among them, 175 required mechanical ventilation, and 180 had acute respiratory distress syndrome. On average, CAPA was detected ten days after the diagnosis of coronavirus illness.

Of the patient cultures tested, 80.3% included *A. fumigatus*, with four strains exhibiting resistance to azoles. A majority of patients (52.7%) were given voriconazole. Overall, 52.2% of patients passed away, with 33.0% of those fatalities being linked to CAPA. According to our findings, the cumulative incidence of CAPA in the intensive care unit ranged from 1.0% to 39.1%.

According to the study by Salmanton-García et al.[2], 26.9% of COVID-19 patients had positive results for *Aspergillus* in their BAL cultures, while 33.9% had positive results for galactomannan. In 35.4% of IAPA[36] and 35.4% of CAPA, cultures were taken from non-bronchial aspirates (such as sputum, bronchial aspirate, non-bronchial lymph node, or tracheal aspirate).

A patient diagnosed with CAPA and prescribed voriconazole was reported by Kitayama et al.[37] in their study. Radiological results and BDG levels both improved after treatment. Specifically, tocilizumab was likely pivotal in bringing about the illness in this instance. Despite the lack of solid evidence supporting antifungal prophylaxis medication for CAPA, this case demonstrates that the presence of *Aspergillus* in airway specimens before the start of the disease may indicate a high risk of developing CAPA. It should be taken into consideration when planning antifungal prophylaxis.

December 2020 saw the publication of consensus criteria for the identification of CAPA by the ECMM and the International society for human and animal mycology. These criteria classified patients as having probable, proved, or potential CAPA.[38] In 77.6% (149/192) of CAPA patients, the diagnosis was made by lower respiratory tract culture, with bronchoalveolar lavage fluid (BALF) being the primary source, according to a systematic study of CAPA.[39] Two fungal biomarkers documented in CAPA diagnosis are galactomannan antigen (GM) and BDG. Using a threshold value of 0.5 for serum and 1.0 for BALF, about 18.2% (35/192) of CAPA patients tested positive for GM in blood, and 45.3% (87/192) tested positive in BALF. Only 10.4% (20/192) of CAPA patients were positive for other BDG blood indicators. Overall, 48.4% (93/192) of patients diagnosed with CAPA died, with mortality rates varying among hospitals, according to the same analysis. Since there is a lack of reliable diagnostic tests, individuals thought to have IPA should begin antifungal therapy without delay to manage the disease better.[40]

The first defense against CAPA is voriconazole or isavuconazole.[38] Although the ideal number of weeks of antifungal treatment for CAPA is unclear, a group of experts has recommended 6-12 weeks.[38] From an infection control standpoint, BALF could not be explored; nevertheless, GM in serum was opposing, BDG was positive, CT revealed a new consolidation with a cavity, and *Aspergillus* was discovered in sputum culture. As a result, Kitayama et al.[37] promptly began treating patients with voriconazole after making a potential CAPA diagnosis using the ECMM criteria; this led to a positive outcome.

Furthermore, even though A. It still needs to be made clear what function antifungal prophylaxis plays in CAPA since fumigatus was discovered before the start of the disease. Antifungal prophylaxis decreases the likelihood of developing CAPA. Still, it does not enhance the outcome, according to Hatzl et al.[41] Since the article by Kitayama et al.[37] notes that COVID-19 patients with CAPA had bad outcomes, we cannot conclude that antifungal prophylaxis is effective in preventing CAPA. A multicenter randomized trial is necessary to establish the importance of antifungal prophylaxis in severe COVID-19 since their data is a single-center, non-randomized observational analysis.

Limitation of this review, the is a narrative review, it is not systematic review.

CONCLUSION

Although *A. fumigatus* was discovered before the pandemic, the function of antifungal prophylaxis in CAPA must be clarified. On the other hand, voriconazole medication may be effective if begun right after diagnosis.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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