

e-ISSN: 2717-7505

JOMPAC

Journal of Medicine and Palliative Care

VOLUME: 6

ISSUE: 4

YEAR: 2025

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Global trends and scientific networks in mesenchymal stem cell research in hematology: a 20-year bibliometric insight

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Cite this article as: Mandacı Şanlı N, Mandacı ED. Global trends and scientific networks in mesenchymal stem cell research in hematology: a 20-year bibliometric insight. *J Med Palliat Care*. 2025;6(4):290-297.

Received: 16.05.2025

Accepted: 20.06.2025

Published: 31.08.2025

ABSTRACT

Aims: Mesenchymal stem cells (MSCs) are multipotent stromal cells that are differentiated due to their differentiation potential and immunomodulatory activities, which is highly relevant to regenerative medicine and hematological therapies. MSCs remain one of the most actively pursued research areas in bioengineering, however, their bibliometric structure in the context of hematology is MSCs has not been thoroughly investigated. In this particular case, we set out to assess MSCs in the field of hematology by evaluating scientific output, its thematic evolution, as well as patterns of global collaboration using bibliometric techniques.

Methods: With the keyword “MSCs” in the title and restricted to the “hematology” category, a total of 1.656 publications from the years 2005 to 2024 were retrieved using Web of Science Core Collection. The data was analyzed using VOSviewer (v1.6.11) and SPSS (v25.0). Trends in annual publication activities, journal output per publication, citation rates of the most cited works, co-authored keyword networks, institutional and author cooperation networks, and and citation activity by country was examined.

Results: As noted, there was a significant increase in the publication rate from 2011-2015, followed by a decrease after this period. Over 65% of publications were contributed by two journals–Stem Cells and Development and Stem Cells. Studies that received the most citations concentrated on the immunomodulatory mechanisms of MSCs and the specific properties of tissues. University of Genoa claimed the highest citation count per article, whereas Chinese higher education institutions published the most on the topic. Core themes such as ‘differentiation,’ ‘bone marrow,’ ‘transplantation,’ and ‘exosomes’ emerged from the analysis on keyword clustering. The most noteworthy research backbone on the topic was developed collaboratively between the US and China, who both possessed strong global network intercontinental links.

Conclusion: Research on MSCs in the context of hematology showcases mature thematic development, intensive institutional collaboration, and regional collaboration clustering. The area of MSCs in hematology indicates foundational research exhaustion, but an expanding focus on exosomes and therapies that do not involve cells signals prospective, shift aimed at clinical. The work can strategically direct funding, policy, and interdisciplinary collaboration MSCs in policymaking guidance MSCs in hematology applications mean interdisciplinary MSCs guide policy.

Keywords: Mesenchymal stem cells, hematology, bibliometric analysis, scientific collaboration

INTRODUCTION

Mesenchymal stem cells (MSCs) are multipotent stromal cells capable of differentiating into a variety of mesodermal lineages, including osteoblasts, chondrocytes, and adipocytes. Originally identified in the bone marrow, MSCs have since been isolated from numerous tissues such as adipose tissue, umbilical cord, placenta, and dental pulp.^{1,2} In addition to their differentiation capacity, MSCs possess notable immunomodulatory and anti-inflammatory properties, exerting effects through paracrine signaling, cytokine secretion, and cell–cell interactions. These characteristics have positioned MSCs at the forefront of regenerative medicine and experimental cell-based therapies. Despite their therapeutic promise, the phenotypic heterogeneity and unclear molecular

identity of MSCs have led some experts to question the appropriateness of their nomenclature, proposing a shift in terminology that better reflects their functional properties.³

In the field of hematology, MSCs have emerged as biologically active components of the bone marrow microenvironment, playing essential roles in the regulation of hematopoietic stem cell (HSC) maintenance, differentiation, and niche signaling. Their immunosuppressive effects are particularly relevant in allogeneic HSC transplantation, where MSCs are used to mitigate complications such as graft-versus-host disease (GVHD). Moreover, recent studies have highlighted the potential of MSC-derived extracellular vesicles and exosomes

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as novel therapeutic tools in hematologic malignancies and inflammatory blood disorders.⁴ However, the interaction between MSCs and malignant hematopoietic cells remains a subject of debate, as evidence suggests they may exert both tumor-suppressive and tumor-promoting effects depending on the microenvironment and disease context.⁵ This dual role underscores the complexity of MSCs in hematology and the need for a deeper understanding of their mechanisms of action, therapeutic applications, and long-term safety.

MSCs hold significant potential in the treatment of hematological diseases, particularly in the fields of regenerative medicine, immunomodulation, and cell-based therapies. Despite the growing academic interest in recent years, there remains a lack of comprehensive evaluation focusing specifically on research intensity, scientific trends, and international collaboration networks within the field of hematology. This study addresses this gap by identifying the thematic concentrations of the literature, the most influential countries, institutions, and authors, thereby mapping the current state of the field. Furthermore, the bibliometric findings presented in this study serve as a strategic guide for shaping research policies, directing funding resources, and strengthening interdisciplinary collaborations.

The primary aim of this study is to analyze the scientific output related to “MSCs” within the field of hematology through bibliometric methods, thereby uncovering the structural dynamics, research trends, and collaboration networks in the field. For this purpose, 1,656 publications categorized under hematology and published between 2005 and 2024 were analyzed using the Web of Science database. The study investigates annual publication trends, the most prolific journals, highly cited articles, leading institutions, keyword usage patterns, international collaboration maps, and author network structures. Through this analysis, the study aims to provide a systematic and visual-based evaluation of the development trajectory and impact areas of mesenchymal stem cell research in the context of hematology.

METHODS

Ethics

Since this study is a bibliometric study, ethics committee approval is not required. This research employed a bibliometric design to systematically analyze publication trends, citation patterns, and collaborative networks in mesenchymal stem cell studies focused on hematology.

Data Collection

The data for this bibliometric analysis was obtained from the Web of Science (WoS) Core Collection which includes published, peer-reviewed scientific literature. The scope of the research was constrained to the “hematology” domain and “MSCs”. The search was conducted for the time frame between January 1, 2005 and December 31, 2024.

For accuracy, the search was conducted with the phrase “MSCs” in the title field only, and the subject category “hematology” was selected in the WoS Categories section. After removing duplicates and non-article entries such as

editorials, meeting abstracts, and retractions, a total of 1,656 publications were obtained and incorporated in the analysis.

Between January and March 2025, the final data collection was completed and include the following details for each eligible article:

Title of the article

Author details

Publication date

Journal name

Citation count

Affiliated institution and university details

Country of origin

Most common keywords

Data was compiled and saved into the recognized text format from the WoS database, thereafter performing two reliability assessments with independent researchers to cross check the data to ensure accuracy. Any differences were reconciled through consensus.

Performing a Bibliometric Analysis

Co-authorship networks, keyword co-occurrence maps and inter-institution collaboration patterns were constructed using VOSviewer software (version 1.6.11, Leiden University, Netherlands) for the bibliometric mapping and network visualizations as the primary focus of this analysis.

Publication trends were analyzed based on these core dimensions:

Annual active publication shifts and their peaks.

Assess productivity to learn which journals have the highest publications.

Most cited documents, authors, institutions, and countries.

Identify keywords that appear most often and their relationship among thematic clusters within the literature based on the set minimum of five occurrences.

Analyze contributing institutions and their total citation estimate.

Trace the inter-country cooperation networks in the relevant domain.

Explore co-authorship of highly active researchers.

Analyze patterns of prolific researchers and their co-authorship.

Statistical Analysis

To analyze publication output and citation backlogs for a certain publication, totals, frequencies, and percentages were summarized and described using basic descriptive statistics. All of this work was done in SPSS software version 25.0 (IBM Corp, Armonk, NY).

With VOSviewer output, the following statistics were calculated:

Total number of nodes (authors, keywords, institutions, or countries)

Their Interconnections (links) and the strength of those connections (link strength) were also calculated.

The strength of collaborative links between authors was represented by the thickness of links in network visualizations clusters, while clusters with similar themes or those located in the same geographic area were colored in identical or closely related colors. With these visualizations, the structure and the newest developments of mesenchymal stem cell research in hematology were observed and tracked over time.

RESULTS

Analysis of Annual Distribution of Publications

Figure 1 illustrates the annual distribution of publications obtained from the Web of Science database, visualizing the temporal progression of the relevant studies. According to the findings obtained from the Web of Science database, a noticeable fluctuation is observed in the annual distribution of publications on MSCs. The publication process, which began with 61 records in 2005, showed an increasing trend in the following years and reached its highest point in 2012 with 117 publications. The period between 2011 and 2015 stands out as a peak in productivity, with each year represented by more than 100 records. This indicates an intensified academic interest in MSCs during these years.

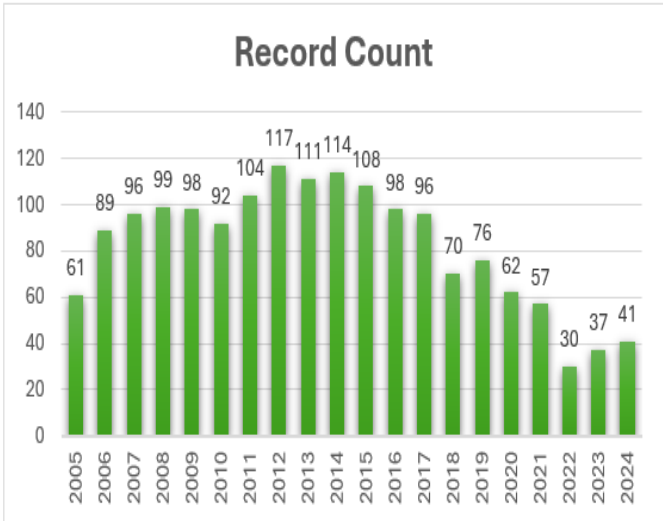


Figure 1. Annual distribution of publications

In the post-2016 period, a relative stagnation becomes apparent. In 2018, the number of publications dropped to 70, and this declining trend continued in the following years, reaching a relatively low level of 30 publications in 2022. Although a slight recovery is observed in 2023 and 2024, caution is warranted in interpreting this trend as the data from these years do not cover a full annual publication cycle. Overall, the early 2010s emerge as a peak period for research activity on this topic, whereas a decline in publication volume is observed in more recent years.

Journals with the Highest Number of Publications in the Subject Area

Table 1 presents the distribution of journals with the highest number of publications related to MSCs in the Web of Science database. These journals indicate where the literature in this field is most concentrated.

Table 1. Journals of publication, number of articles, and percentage distributions		
Publication titles	Record count	%
Stem Cells and Development	586	35.386%
Stem Cells	495	29.891%
Cytherapy	100	6.039%
Blood	48	2.899%
Experimental Hematology	39	2.355%
Circulation Research	27	1.630%
International Journal of Hematology	23	1.389%
Annals of Hematology	21	1.268%
Shock	20	1.208%
Biology of Blood and Marrow Transplantation	19	1.147%
Others	278	16.788%

Table 1 presents the academic journals with the highest number of publications on the subject of MSCs in the Web of Science database, along with the number of articles published in these journals and their percentage distributions. Out of a total of 1.656 publications, 959 are concentrated within the top ten journals. This indicates that the literature is largely clustered around a limited number of publication platforms.

In particular, stem cells and development (35.386%) and stem cells (29.891%) account for nearly two-thirds of the scientific output in this area and emerge as the primary publication venues. Combined, these two journals constitute 65.277% of all publications, highlighting their central roles in the literature. The remaining eight journals contribute between 1% and 6% individually.

All other publications outside the top ten journals represent 16.788% of the total. This proportion suggests that while research outputs are predominantly concentrated around a few high-impact journals, the literature on this topic also demonstrates a certain degree of diversity. This reflects a balanced structure in which knowledge production is both concentrated and disseminated across various journals.

Detailed Analysis of the Most Cited Studies: Authors, Article Titles, Published Journals, Years, and Citation Counts

The most highly cited scientific studies on MSCs indexed in the Web of Science database are presented in detail in Table 2, including the names of the authors, article titles, journals of publication, publication years, and total citation counts.

Table 2 presents information on the five most highly cited academic publications related to MSCs in the Web of Science

Table 2. Most cited articles on “mesenchymal stem cells”: authors, journal titles, publication years, and citation counts

No	Author(s)	Article title	Journal name	Year of publication	Citation count
1	Aggarwal S and Pittenger MF	Human mesenchymal stem cells modulate allogeneic immune cell responses	Blood	2005	3555
2	Kern S, et al.	Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue	Stem Cells	2006	2553
3	Corcione A, et al.	Human mesenchymal stem cells modulate B-cell functions	Blood	2006	1377
4	Wu YJ, et al.	Mesenchymal stem cells enhance wound healing through differentiation and angiogenesis	Stem Cells	2007	1305
5	Zappia E, et al.	Mesenchymal stem cells ameliorate experimental autoimmune encephalomyelitis inducing T-cell anergy	Blood	2005	1132

database. These studies are listed along with their authors, article titles, publishing journals, years of publication, and total citation counts.

At the top of the list is the study titled “Human MSCs modulate allogeneic immune cell responses” authored by Aggarwal and Pittenger, published in *Blood* in 2005, which has received 3.555 citations, making it the most cited publication. The second-ranked study, titled “Comparative analysis of MSCs from bone marrow, umbilical cord blood, or adipose tissue”, was authored by Kern et al. and published in *Stem Cells* in 2006. This article has received 2.553 citations. In third place is the study by Corcione et al., titled “Human MSCs modulate B-cell functions”, published in *Blood* in 2006, with a total of 1.377 citations. The fourth-ranked publication, authored by Wu et al., is titled “MSCs enhance wound healing through differentiation and angiogenesis”. It was published in *Stem Cells* in 2007 and has been cited 1.305 times. Finally, the fifth study, titled “MSCs ameliorate experimental autoimmune encephalomyelitis inducing T-cell anergy”, was written by Zappia et al. and published in *Blood* in 2005, with a total of 1.132 citations.

Statistical Evaluation of the Most Cited Institutions' Publications

The institutions to which the authors of publications on MSCs are affiliated, as well as the number of articles produced by these institutions and their total citation counts, are presented in detail in [Figure 2](#), based on data from the Web of Science database.

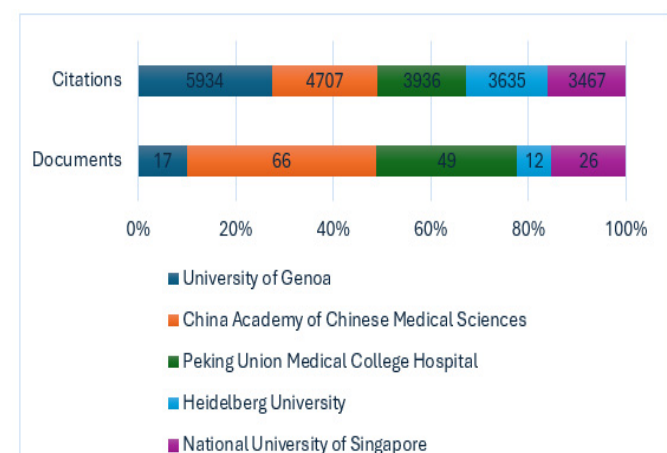


Figure 2. Most cited institutions and distribution of publications based on Web of Science data

Figure 2 illustrates the number of articles published and the total number of citations received by the most highly cited institutions related to the topic of MSCs, based on data from the Web of Science database. According to the data, the University of Genoa reached the highest citation count, with a total of 5.934 citations across 17 publications. The China Academy of Chinese Medical Sciences is the institution with the highest number of publications, producing 66 articles which collectively received 4.707 citations. Peking Union Medical College Hospital ranks third with 49 publications and 3.936 citations. Heidelberg University follows with 12 publications and 3.635 citations, while the National University of Singapore has achieved 3.467 citations from 26 publications. The figure visually demonstrates the relationship between the volume of scientific output produced by institutions and the number of citations those outputs received.

Keyword Usage Trends

The most frequently used keywords in studies related to MSCs in the Web of Science database, as well as their frequencies, are presented in **Figure 3**.

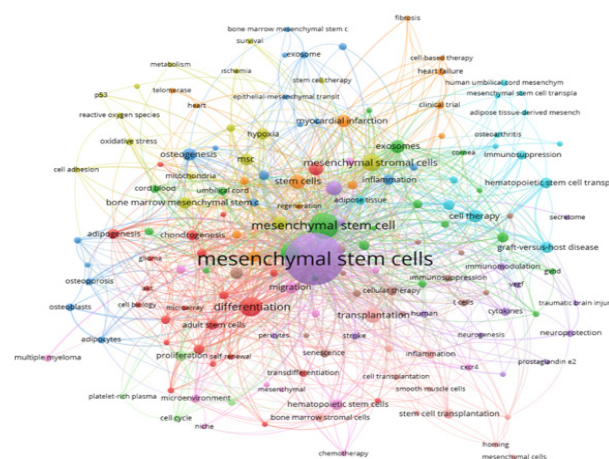


Figure 3. Frequently used keywords and their usage frequencies

The bibliometric analysis was performed using VOSviewer software, with a minimum threshold of five occurrences for keyword selection. This threshold allowed for the inclusion of only those keywords used at least five times, ensuring the analysis focused on more commonly used and scientifically significant terms. A total of 2,622 different keywords were identified, of which only 161 met the inclusion threshold and were evaluated in the analysis. This approach indicates

that the study concentrated on selected keywords and their interrelations.

The analysis revealed the most frequently used and strongly interconnected keywords in the field of mesenchymal stem cell research. A total of 1,380 keyword connections were identified, and 11 distinct clusters were detected. These findings allow for a detailed examination of the relationships between keywords within the field. Such an analysis supports a deeper understanding of the terminology used in the domain and contributes meaningfully to the identification of critical concepts for future research.

Figure 3 shows the most commonly used keywords in academic publications related to MSCs and their frequencies. According to the data, the most frequently used keyword is "MSCs", which appeared 484 times, highlighting its central importance in the literature.

The term "mesenchymal stem cell" ranked second, appearing 120 times, indicating that the singular form is also widely preferred. The keywords "differentiation" (68 times) and "bone marrow" (50 times) suggest a research focus on differentiation processes and the bone marrow origin of MSCs. Other notable but less frequently used keywords include "mesenchymal stromal cells" (frequency not specified), "transplantation" (38 times), "angiogenesis" (35 times), and "exosomes" (30 times). These terms reflect a concentration on subtopics such as tissue repair, intercellular communication mechanisms, and angiogenesis. Additionally, the term "stem cells" was used 35 times, indicating that general stem cell research still holds significant relevance in this body of literature.

These data clearly reflect the core research areas within the mesenchymal stem cell literature and the interrelationships between these areas. The frequency of keyword usage emphasizes the priorities of the research topics and the strategic importance of terminology, offering valuable insight into the structure and depth of the scientific literature.

Institutional Collaboration Analysis

The collaboration networks among institutions affiliated with the authors of publications on MSCs were analyzed using the Web of Science database. The findings of this analysis are visually presented in **Figure 4**.

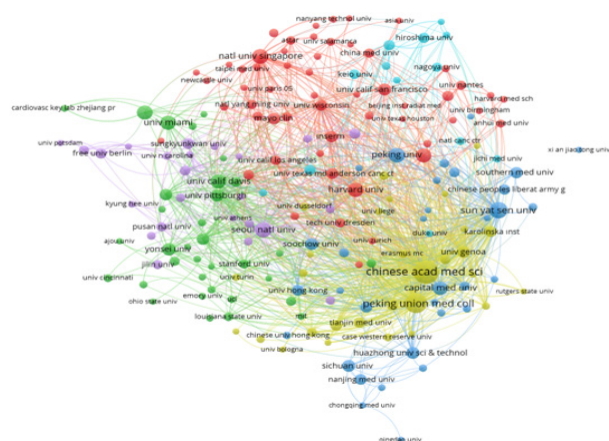


Figure 4. Institutional collaboration analysis

The collaboration analysis was conducted using VOSviewer software. In the resulting visual, colors distinguish thematically or regionally related groups, while the connections between institutions represent collaborative relationships. The thickness of these links indicates the intensity of collaboration. Such visualization provides insight into the influence of institutions within the research landscape on MSCs and helps identify strong connections and potential opportunities for collaboration.

In the map, Sun Yat-sen University, China Academy of Chinese Medical Sciences, Harvard University, and Seoul National University are positioned centrally within the collaboration network, each having 187 connections. This suggests that these institutions have wide and active collaboration networks in mesenchymal stem cell research. Stanford University follows closely with 186 connections, and the University of Wisconsin has 185 connections, making it another prominent institution in the network.

Overall, the observed connection densities and clustering patterns in the analysis indicate that research on MSCs is conducted on the basis of strong collaborations between selected institutions. This type of analysis not only allows for the assessment of existing and potential inter-institutional partnerships but also provides strategic guidance for expanding research networks and forming new academic collaborations.

Author Collaboration Analysis

Articles on MSCs indexed in the Web of Science database were analyzed to examine the collaboration networks among authors. The results of this analysis are detailed in **Figure 5**.

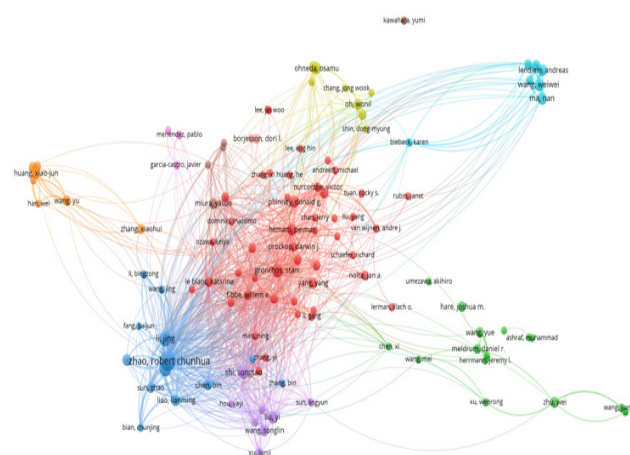


Figure 5. Author collaboration bibliometric network map (circle sizes represent key authors, and lines indicate collaboration relationships)

Figure 5 analyzes bibliographic connections among authors who have published at least five articles within a specific research area. Although a total of 10,801 authors were evaluated, only 118 authors who met the threshold were included in the analysis. The criterion of having published at least five articles was chosen to include authors who have made significant contributions to the literature and demonstrated a consistent level of research productivity. This threshold

ensures the reliability and scientific validity of the analysis by focusing on active and impactful researchers.

The figure illustrates collaboration networks and bibliographic connections among researchers in the field of MSCs. Each author is represented by a circle, the size of which indicates the magnitude of the author's contribution to the literature. Lines between circles represent collaboration strength and bibliographic linkages.

Zhao Robert Chunhua and Li Jing are located at the center of the blue cluster, indicating their significant contributions to the field. This cluster also includes Sun Zhao, Li Bingzong, and Liao Lianming, who are strongly connected through collaborative ties. In the red cluster, Prockop Darwin J., Gronthos Stan, and Phinney Donald G. occupy central positions and play a key role in the core of the field's literature. This cluster also includes prominent figures such as Le Blanc Katarina and Fibb Willem E. The yellow cluster is led by authors like Ohwada Osamu, Chang Jong Wook, and Oh Wonil, who exhibit dense internal collaboration. In the green cluster, researchers such as Hare Joshua M. and Umezawa Akihiro stand out. This group also maintains connections with other clusters, representing diverse thematic approaches in the field. The orange cluster is dominated by Huang Xiao-Jun and Han Wei, who maintain a more localized collaboration network.

In general, the different color-coded clusters represent author groups with thematic or methodological similarities. These collaboration networks contribute significantly to understanding the scientific production processes and researcher interactions in the field of MSCs.

Country-Level Citation Distribution

Citations of publications on MSCs were analyzed at the country level using the WoS database. The results of this analysis are visualized in **Figure 6**, showing the geographic distribution of citations, regional densities, and inter-country relationships.

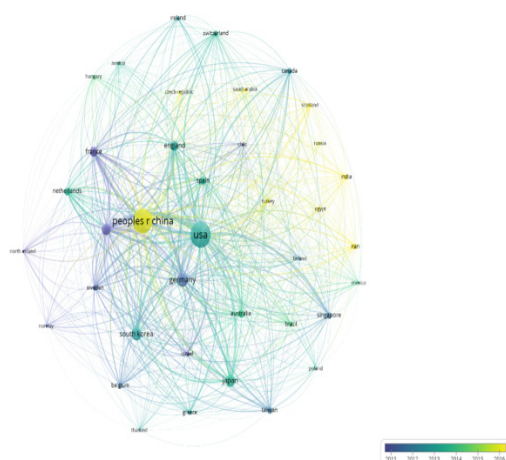


Figure 6. Country-level citation distribution analysis

Figure 6 is based on citation data from articles published in the Web of Science database and presents the distribution and academic collaboration networks among countries. The analysis considered countries that had published at least

five articles. Among 59 countries that met this criterion, 38 countries were included in the evaluation. The analysis revealed seven distinct clusters, reflecting inter-country relationships and research focus areas.

Figure 6 visualizes the geographic spread of citations and international academic collaboration networks related to MSCs. The United States (USA) stands out as the most central and dense node in the network, clearly demonstrating its leadership in this field. China (People's Republic of China), with strong connections to several other countries, also emerges as a major hub in the global scientific network.

In Europe, Germany, France, England, and the Netherlands exhibit high connection densities, indicating strong individual research productivity and mutual collaborations. These countries maintain visible roles in the international literature through their internal cooperation and ties with the United States.

In Asia, countries such as Japan, South Korea, and Singapore actively contribute to the network by establishing multiple connections, particularly with the United States and European countries.

Canada, Australia, and Brazil also appear as important actors contributing to global scientific communication through their collaborative efforts with other regions. Meanwhile, Switzerland, Spain, Israel, and Sweden are also among the countries that play prominent roles in regional and thematic collaboration networks.

In conclusion, **Figure 6** reveals that the scientific literature on MSCs is geographically widespread, with the United States, China, and leading European countries occupying central positions in international collaboration efforts.

DISCUSSION

From 2005 to 2024, this bibliometric study assesses the global research scope of MSCs in the context of hematology. The findings illustrate the evolution and productivity patterns on the literature, as well as revealing the prolific concentration of scientific output at certain countries, institutions, journals, and specific authors. These results greatly improve understanding of the development and diversification of MSC-related research over time, especially relating to hematologic conditions and their therapies.

Based on the publication trends in this study, it can be noted that MSC research in hematology showed an exceptional upsurge in productivity from 2005 to 2012, culminating in a total of 117 publications in 2012. This increase corresponds to a worldwide scientific fascination with the role of MSCs in immunomodulation, regenerative therapy, and hematopoietic support.^{1,2} The most productive period, 2011-2015, featured an unprecedented surging momentum in preclinical and translational research with more than 100 publications per year. This surge was, however, followed by a dramatic downturn where publication volume nosedived to an annual low of 30 by 2022. This decline could indicate a reframing of focus from foundational thematic MSC research to funding interests focused on clinical trials or regulation laden research, exosome-based therapies, or therapeutic approaches. Other

bibliometric analyses^{6,7} of stem cell subfields have noted similar declining patterns, which is MSC research's shift toward a more mature, reflexive, application-driven phase.

Analysis of the journals indicated that Stem Cells and Development and Stem Cells published more than 65% of total publications, sustaining their authoritative influence on the growth of MSC research. Such findings are in agreement with bibliometric patterns, suggesting a limited number of journals with substantial citations focus on specialized areas as primary sources of publication.⁸ This concentration appears to support thematic cohesion within a discipline; however, it may stifle discourse and critical debate in a multi-disciplinary context due to lack of balance.

The publications with the most citations largely stem from the mid-2000s and early 2010s, indicating enduring influence in the field. The 2005 publication by Aggarwal and Pittenger on MSC-mediated immunosuppression remains the most cited article, which verifies the significance of paracrine and anti-inflammatory functions of MSCs. Also, Kern et al.'s work on comparative MSC sources helped foster the tissue-specific differentiation potential MSCs undergo. These primary studies help answer more recent questions about therapeutic uses of MSCs such as in GVHD, bone marrow failure, and immunologic modulation of hematologic malignancies.^{4,5}

As the productivity and citation analysis indicates, a limited number of academic institutions are dominating the MSC research landscape. Taking the University of Genoa as an example, it has not been the most prolific in its publications, but it received the highest total citations, which indicates a strong impact per publication. On the other hand, China Academy of Chinese Medical Sciences topped the publication count but exhibited a relatively low citation-per-article average. These outcomes corroborate the earlier findings by Zhang et al.⁹ and Tsai et al.¹⁰ that the volume of publications does not attribute to a scientist's influence in the field. The notable presence of Asian institutions like Sun Yat-sen University and Seoul National University indicates the growing focus and expanding dominance of East Asia in the field of biomedical research, especially in cell therapy and immunology.

This type of analysis offers insights into keyword shifts within MSC research. The dominance of "MSCs," "differentiation," "bone marrow," and "immunomodulation" indicates that core biological components continue to be the focus of the research. The addition of "exosomes," "transplantation," and "angiogenesis," however, indicates that there is now more focus on the applications of acellular therapies, regenerative medicine in transplantation, and functional angiogenesis. These findings align with previous bibliometric studies on MSC research conducted in 2021 which observed increased attention on MSC-derived extracellular vesicles as a cell-free-builder for immune response and tissue engineering in hematologic malignancies.^{9,11}

The analysis of the inter-institutional collaborations shows that there are dense networks within major international research centers. Also, Harvard University, Stanford University, and National University of Singapore are important hub institutions for MSC research globally. The collaborative

link strength which is observable in these networks reflects not only the available research funding and infrastructure but the reputed translational science, clinical research, and multidisciplinary integration capabilities of the institutions involved. The clustering of the institutions into color coded thematic groups illustrates that in most cases, geographical proximity and common research interests fuel collaboration. This was also noted by Liu et al.,¹² where they noted the increasing reliance on regional consortia and intercontinental collaborations to further the stem cell research agenda.

Authorship network analysis revealed that a small set of highly productive researchers, including Zhao Robert Chunhua, Li Jing, and Prockop Darwin J., substantially shape the intellectual trajectory of the discipline. These authors, who are frequently cluster or centrality hubs, have large co-authorship networks which depict the MSC research collaboration and cumulative nature. In addition, the presence of distinct thematic clusters among authors (e.g. regenerative biology versus immunotherapy versus stromal niche research) indicates the specialization and division of labor within the discipline, as documented in other bibliometric works.^{10,13}

At the country level, the bibliometric map illustrates that the United States maintains its dominant position regarding impact and network centrality in MSC research. China is increasing its output rapidly, but tends to have a more nationally concentrated body of work. However, China's strong linkages with European and Asian countries show its increasing integration into the global MSC research community. Certain European countries like Germany, France, and the Netherlands maintain important strategic functions in collaborative networks as sponsors helping to bridge East and West through multicenter joint ventures and studies.⁷

Taken together, these findings illustrate the MSC research landscape in hematology as broad and intricate. This includes a wealth of underlying literature in the MSCs field and their hematologic applications, as well as structured flows of knowledge creation and publication globally across multiple thematic areas. MSCs therapy research collaboration in rheumatic diseases was also observed. Aside from that, sharply declining publication levels during recent years, coupled with high dependency on a few elite journals and a small number of institutions, creates additional lenses through which the MSCs field might be losing innovative potential. In addition to those, hotly contested issues like the naming MSCs, their function diversity, and long-term safety concerns pose persistent challenges to researchers and physicians alike.^{3,5}

Restoring balance requires shifting the focus to MSCs research in hematology by diving into translation difficulties, investigating more clinically relevant disease areas MSCs such as for hemoglobinopathies or marrow fibrosis, and developing MSC-centric protocols for genetic modification, clinical-grade expansion, and therapeutic application. Strategic bibliometric analyses as these provide invaluable insights into collaboration shortfalls which can be used to improve resource distribution or define global research challenges and objectives.

CONCLUSION

This bibliometric analysis shows that research on MSCs and their uses in hematology developed dynamically with a peak in scientific output in the early 2010s and a gradual decline in recent years. Leaps in scientific output are also noted in the areas of immunomodulation, hematopoietic support, and MSC-derived exosome therapies. The concentration of publications in a few high-ranking journals and institutions as well as the United States and China dominating the landscape showcases the collaborative and central character of the research. The emergence of new thematic clusters alongside strong cross-border co-authorship networks indicates potential for future advances. These conclusions strategically structure recommendations to direct future research spending, stimulate interdisciplinary MSC collaborations, and integrate MSC therapies into clinical hematology.

ETHICAL DECLARATIONS

Ethics Committee Approval

Since this study is a bibliometric study, ethics committee approval is not required.

Informed Consent

Since this study is a bibliometric study, written informed consent is not required.

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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Investigation of the effect of cannabidiol, tetrahydrocannabinol, and vancomycin combination on cariogenic bacterial retention due to microleakage under prosthetic restorations

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Cite this article as: Kuşcu S, Hayran Y, Aydın A. Investigation of the effect of cannabidiol, tetrahydrocannabinol, and vancomycin combination on cariogenic bacterial retention due to microleakage under prosthetic restorations. *J Med Palliat Care*. 2025;6(4):298-304.

Received: 21.05.2025

Accepted: 20.06.2025

Published: 31.08.2025

ABSTRACT

Aims: Oral and dental infections develop due to many different bacterial activities, and with the increasing resistance mechanism against conventional antimicrobial agents, the formation of biofilms in the microleakage under prosthetic restorations, which cause dental caries, has become a major clinical challenge to overcome. This study aims to reveal the antibiofilm effect of vancomycin (VAN) combined with cannabidiol (CBD) and tetrahydrocannabinol (THC) against biofilm formation caused by *Streptococcus mutans* (*S. mutans*) and *Staphylococcus aureus* (*S. aureus*) on dental dentin under prosthetic restorations.

Methods: Freshly extracted human teeth without caries, resorption, or fracture were collected and obtained by slicing 2 mm dentin discs. A total of 64 dentin discs were inoculated with *S. mutans* and *S. aureus* and randomly allocated into control and five experimental groups consisting of CBD, THC, CBD+VAN, THC+VAN, and CBD+THC+VAN. Antibiofilm activity and combination index were analyzed by the MTT viability test and the Chou–Talalay method, respectively. Biofilm structure was assessed by scanning electron microscopy. Analysis of variance and post hoc Tukey tests were applied for comparisons.

Results: CBD and VAN showed antimicrobial effects against *S. aureus* and *S. mutans* bacteria in unary combinations, while THC was ineffective. However, no apparent synergistic interaction was observed in the binary combinations of VAN. Interestingly, a high synergistic effect (CI<1) occurred in the triple combination against both bacterial species. When this effect in the triple combination was examined, it was seen that VAN exhibited a suitable dose reduction index (DRI>1). When these synergistic and dose reduction results are evaluated together with SEM image analysis, it can be said that the triple combination of VAN+CBD+THC probably causes the most optimum antibiofilm effect on dental caries bacteria.

Conclusion: Combining VAN with CBD and THC may offer a new approach to combat microleakage-induced bacterial retention in dental dentin under prosthetic restorations.

Keywords: Cannabidiol, tetrahydrocannabinol, vancomycin, prosthetic restorations, microleakage

INTRODUCTION

Dental caries and periodontal diseases remain significant challenges in dentistry, particularly in prosthetic treatments involving crowns and bridges. While improving functionality and aesthetics, these restorations may contribute to microleakage due to improper fit or marginal discrepancies. Microleakage provides a pathway for bacterial infiltration, leading to the formation of biofilms on the dentin surface, which can ultimately result in secondary caries and restoration failure.^{1,2}

Biofilms are structured microbial communities embedded in an extracellular matrix, adhering to surfaces such as dentin. Common cariogenic and pathogenic bacteria, including *Streptococcus mutans* (*S. mutans*) and *Staphylococcus aureus* (*S. aureus*), play critical roles in biofilm development and the

progression of dental caries. These biofilms are particularly resistant to conventional antibacterial treatments due to their protective matrix and enhanced microbial survival mechanisms.³⁻⁵

Recent advancements in dental material research have focused on incorporating bioactive compounds to mitigate biofilm formation and bacterial growth. Cannabidiol (CBD) and tetrahydrocannabinol (THC), derived from cannabis plants, have demonstrated promising antibacterial and anti-inflammatory properties.^{6,7} Vancomycin (VAN), a glycopeptide antibiotic, is widely used for its potent bactericidal activity against Gram-positive bacteria, including *S. mutans* and *S. aureus*.⁸ In clinical practice, we chose it as an antibiotic for our study because it is a preferred agent against

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resistant strains, particularly methicillin-resistant *S. aureus*, in oral and dental infections.

In this study, *S. mutans* and *S. aureus* biofilms were cultivated on dentin surfaces to model the bacterial colonization associated with microleakage in prosthetic restorations. The biofilms were then treated with CBD, THC, and VAN to evaluate their antibacterial efficacy. Cytotoxicity assays, such as the MTT assay, and morphological analyses using scanning electron microscopy (SEM) were employed to assess the effects of these compounds on bacterial viability and biofilm integrity. This research explores the potential of these bioactive agents in reducing the bacterial populations responsible for secondary caries, thereby enhancing the longevity and success of prosthetic treatments. The findings suggest that these compounds could be incorporated into oral care products such as mouthwashes, toothpaste, or dissolvable tablets, providing an innovative approach to addressing microleakage-related challenges in prosthetic dentistry.

METHODS

Ethics

This study was approved by Yozgat Bozok University Non-interventional Clinical Researches Ethics Committee (Date: 09.04.2025, Decision No: 2025-GOKAEK-257_2025.04.09_443), and all experiments were conducted in accordance with the ethical guidelines of the Helsinki Declaration.

CBD and THC Isolation

After the hemp flowers were ground in a grinder until they became a fine powder, they were left in the oven for 1 hour at 105°C for decarboxylation. The supercritical CO₂ extraction method (230 bar, 50°C, and 50 kg/h cycle conditions) was employed for extraction following this process. The extract was then mixed with ethanol in a 1:1 (m/v) ratio to remove waxy structures and placed in a -80°C freezer for 48 hours. The sample was subsequently filtered using a vacuum funnel and filter paper to separate the extracted waxes. Finally, the molecular distillation method was utilized to separate terpenes and chlorophylls. The fractions richest in CBD and THC were obtained using the molecular distillation technique at temperatures between 180°C and 200°C.

The fractions obtained were subsequently purified with flash chromatography (BUCHI Pure C815 Flash Chromatography Systems), C18 reverse phase cartridges (40 g, C18 column), and an ethanol-water mobile phase. In this context, the 210 nm band of the CBD and THC was determined, as shown in Figure 1. Purity analysis results were carried out using HPLC (2.7 µm, 4.6x150 mm, NexLeaf CBX, PDA detector, 210 nm, mobile phase acetonitrile:water (9:1)) as illustrated in Figure 2. The yield was measured as 80% and purity as 98%.

Preparation of Dentin Discs

A total of 64 permanent molars extracted for periodontal or orthodontic reasons and with intact crown integrity were used. The teeth were mechanically cleaned with a curette to prevent any external contamination, and it was ensured that there were no organic or inorganic residues on their surfaces. The cleaned teeth were stored in a 0.01% thymol solution at room temperature to preserve their biological

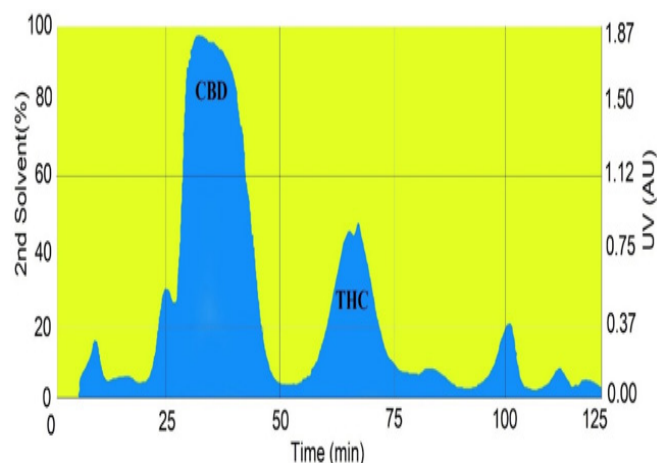


Figure 1. Flash chromatograms of CBD and THC

CBD: Cannabidiol, THC: Tetrahydrocannabinol

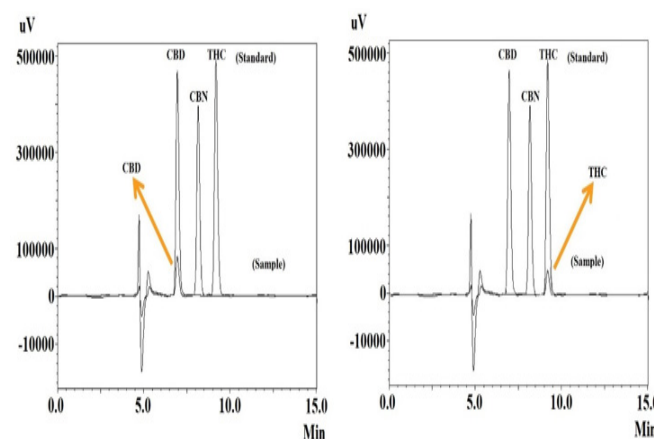


Figure 2. HPLC chromatography of CBD, THC, and standard

CBD: Cannabidiol, THC: Tetrahydrocannabinol

integrity. The teeth were embedded in polyvinyl chloride (PVC) cylinder molds of 3 cm height and 2 cm diameter using autopolymerized acrylic resin (Ortho-Jet Resin Acrylic; Lang Dental Manufacturing Co, Illinois, USA). Before completing the acrylic resin polymerization, the teeth were fixed in the molds at a height of 1 mm higher than the cemento-enamel junction. During the preparation of the samples, a large-sized, water-cooled, low-speed diamond cutting saw (Metkon Microcut 201, Htp High Tech Products, Istanbul, Turkey) was used to expose the dentin layer of the teeth. Dentin discs with a thickness of 2 mm were obtained by cutting 3 mm and 5 mm below the occlusal surface. Then, the surfaces of these dentin discs were smoothed using a circular medium-grained rotary abrasive tool (Model 902; Brasseler USA). The prepared dentin discs were marked with an acetate pen using a metal mold with a 6 mm diameter circular cavity in the middle. Following the marking process, standard samples with a diameter of 6 mm and a thickness of 2 mm were obtained by an experienced dentist using a water-cooled aerator (Bien-Air Tornado; Bien-Air Dental, Bienne, Switzerland). The accuracy of the measurements was checked with a digital caliper (Mitutoyo 500-196-30; Mitutoyo Corp., Kawasaki, Japan). In the final stage, all prepared samples were cleaned with distilled water and then treated with isopropyl alcohol

for 3 minutes to remove organic and inorganic residues on the surface altogether.

Minimum Inhibitor Concentration (MIC)

Determination

MIC values of the compounds against bacterial strains were determined on the basis of a micro-well dilution method. To determine the minimal inhibitory concentration (MIC) values, *S. aureus* (ATCC 700699) and *S. mutans* strains (ATCC 35668) in a 12-h Brain Heart Infusion broth culture were adjusted to 0.5 McFarland.⁹⁻¹¹ Each substance dissolved in dimethyl sulfoxide (DMSO) and serial twofold dilutions were made in a concentration range from 4 to 512 µg/ml in microplate wells containing nutrient broth. The growth of microorganisms was determined visually after incubation for 24 h at 35 °C. The lowest concentration at which no visible growth (turbidity) was taken as the MIC. Unary, binary, and ternary combinations of CBD, THC, and VAN were added to the wells in increasing doses and left for 24 hours of incubation. The well with no turbidity at the end of the period was selected as the MIC value.

Minimal Biofilm Inhibitory Concentration (MBIC)

Dental discs in a 24-well plate received 500 µL of a 0.5 McFarland bacterial sample and were then incubated overnight for 16 hours. At the end of the period, the dental disc samples were incubated for 72 hours for biofilm formation by changing the medium every 24 hours. After the biofilm formation, bacteria that could not adhere were gently washed with DPBS and removed from the medium. Samples were vortexed thoroughly with 500 µL of DPBS and plated in a new 24-well plate. Unary, binary, and ternary combinations of CBD, THC, and VAN were added to the wells in increasing doses and left for 24 hours of incubation. An MTT assay gives an accurate estimate of the number of viable cells. Thus, we performed an MTT assay according to AFST-EUCAST guidelines. During the experiment, one-part MTT is mixed with nine-part medium (BHI Broth for *S. mutans* and *S. aureus*) and used. First, the old medium was withdrawn. MTT solution prepared with the fresh medium was added and incubated in the dark for at least 4 hours in the incubator. Then, the MTT solution was withdrawn, and DMSO and 100 µl Sorenson's glycine buffer (glycine 0.1M, NaCl 0.1M, pH 10.5) were added to the medium and left on the mixer in the dark for 15-20 minutes. Samples were loaded onto a 96-well plate without a lid and read at 570-630 nm on a microplate reader. Unary, binary, and triple combinations were evaluated using the obtained absorbance values with the Calcsyn synergy analysis program.

Synergy Model

Synergy measurement by microplate synergy analysis was used to determine the effect of unary, binary, and triple combinations of CBD, THC, and VAN on potency compared to their activities (Table 1). The antibiofilm effects of CBD, THC, and VAN were studied for the first time on *S. aureus* and *S. mutans* dentin biofilm. The MTT cell proliferation assay for different unary, binary, and ternary drug combinations was used to evaluate the results of the *in vitro* pharmacodynamic drug interaction analysis of the selected drugs.¹² Absorbance

data (CLARIOstar microplate reader) were loaded for automated calculation of the slope of the median-effect plot (m), the dose that produces 50% effect such as IC₅₀ (Dm), and the linear correlation coefficient of the median-effect plot (r) parameters, as well as the combination index (CI) and dose reduction index (DRI) using CalcuSyn software, version 2.11, commonly used to study drug interactions described by Chou¹³ and Chou and Talalay.¹⁴

Table 1. Concentrations of substances used (µg/ml)

THC	CBD	VAN
25	25	12.5
50	50	25
100	100	50
200	200	100
400	400	200

THC: Tetrahydrocannabinol, CBD: Cannabidiol, VAN: Vancomycin

Scanning Electron Microscopy

SEM was conducted using *S. mutans* and *S. aureus* biofilms formed on the surface of dentin discs. The samples were washed twice with DPBS and fixed in 2.5% glutaraldehyde in a phosphate buffer for 16 hours and, shortly after, refixed in 2% osmium tetroxide for two hours. Then, they were dehydrated through ethanol rinses (30, 50, 90, 95, and 100%) and mounted and sputter-coated with gold. Sample surfaces were examined using SEM (Zeiss LEO 440, Cambridge, UK).

Statistical Analysis

The statistical significance of differences was determined by the one-way analysis of variance (one-way ANOVA) followed by Tukey's test. The SPSS for Windows computer program was used for statistical analyses. The results of test values were reported as mean values ±SD of three independent assays, and differences among groups were considered to be significant at $p < 0.05$.

RESULTS

Susceptibility Testing and Synergy Analysis

For the antibacterial activity studies of the test substances, the selected pathogenic Gram (+) *S. aureus* (ATCC 700699) and *S. mutans* (ATCC 35668) bacterial species were used. The plate-well technique calculated the MIC values of single molecules and combinations. Accordingly, the MIC values of the THC molecule could not be calculated since they were >512 µg/ml. CBD MIC values were measured as 8-16 µg/ml. VAN MIC value was measured as 4 µg/ml (Table 2). When we looked at the binary combinations, it was found as 4-8 µg/ml for CBD+VAN and 32 µg/ml for THC+VAN (Table 2). When we looked at the triple combinations, it was measured as 2 µg/ml (Table 2).

MTT test was performed to measure the minimal biofilm inhibitory concentration (MBIC) effects of single molecules and combinations. The ratios and effect values used for combinations are explained in Table 2, 3, 4. The activity values of the combinations were determined by the Chou-Talalay CI (mass-action law) method. After performing the MTT cell

Table 2. MIC value of unary, binary, and triple combinations of CBD, THC, and VAN

MIC (µg/ml)	THC	CBD	VAN	CBD+VAN	THC+VAN	CBD+THC+VAN	One-way ANOVA	
							F	Sig.
<i>S. aureus</i>	N.D.*	8 ^{b**}	4 ^a	4 ^a	32 ^c	2 ^a	420.46	.000
<i>S. mutans</i>	N.D.	16 ^c	4 ^{ab}	8 ^b	32 ^d	2 ^a	312.82	.000

MIC: Minimal inhibitory concentration, THC: Tetrahydrocannabinol, CBD: Cannabidiol, VAN: Vancomycin, *S. aureus*: *Staphylococcus aureus*, *S. mutans*: *Streptococcus mutans*, *N.D. Not detected
 **Values followed by the same letter in the row are not significantly different

Table 3. Combination ratios used in the study

THC 2 CBD 2 VAN 1	CBD+VAN 2/1 THC+VAN 2/1	CBD+THC+VAN 2/2/1
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THC: Tetrahydrocannabinol, CBD: Cannabidiol, VAN: Vancomycin

Table 4. Combination index method

Range of CI	Description	Range of CI	Description
<0.1	Very strong synergy	1.10-1.20	Mild antagonism
0.1-0.3	Strong synergy	1.20-1.45	Moderate antagonism
0.3-0.7	Synergy	1.45-3.3	Antagonism
0.7-0.85	Moderate synergy	3.3-10	Strong antagonism
0.85-0.90	Light synergy	10>	Very strong antagonism
0.90-1.10	Additiv		

CI: Combination index

proliferation test for each substance alone against bacteria, CompuSyn software was used to calculate the mass-action law parameters (Dm), (m), and (r) (Table 5, 6). Accordingly, the Dm values (IC₅₀) of the tested substances in *S. aureus* were found to be between 205.00, 15.00, and 4.75 µg/ml for THC, CBD, and VAN, respectively. In *S. mutans*, the Dm values (IC₅₀) of the tested substances were between 155.00, 21.00, and 3.70 µg/ml for THC, CBD, and VAN, respectively. The dose reduction index (Fa-DRI) for THC, CBD, and VAN combinations are presented in Table 7, 8, respectively. The Chou-Talalay method for drug combination is based on the median effect equation, which provides the theoretical basis for the CI, which allows the quantitative determination of drug interactions where CI <1, =1, and >1 indicate synergy, additive effect, and antagonism (Table 4). Accordingly, in *S. aureus*, the Dm values (IC₅₀) of the tested binary and triple combinations were between 4.82-35.23 and 3.34 µg/ml, respectively. In *S. mutans*, the Dm values (IC₅₀) of the tested binary and triple combinations were between 3.21-38.73 and 2.97 µg/ml, respectively.

This study evaluated the synergistic-antagonistic effects of THC, CBD, and VAN combinations with CI values for fa=0.5. Accordingly, when the binary and triple combinations tested in *S. aureus* were examined at fa=0.5, CBD+VAN (1.01) showed additive, CBD+THC+VAN (0.80) synergistic, and THC+VAN (4.33) antagonistic effects (Table 5). When the binary and triple combinations tested in *S. mutans* were examined at fa=0.5, CBD+VAN (1.03) showed additive, CBD+THC+VAN (0.90) synergistic, and THC+VAN (5.94) antagonistic effects (Table 6).

Table 5. Parameters were calculated from the median effect equation and median effect plot. 'm' is the slope, and m=1, >1 and <1 indicate hyperbolic, sigmoidal, and flat sigmoidal shape, respectively; 'Dm' denotes power; and 'r' is the linear correlation coefficient

<i>S. aureus</i>	Combination index (CI) values at			
	ED50	Dm	m	r
THC	N/A	205.00	0.63	0.92
CBD	N/A	15.00	0.90	0.92
VAN	N/A	4.75	0.72	0.93
CBD+VAN	1.01	4.82	0.87	0.94
THC+VAN	4.33	35.23	1.32	0.95
CBD+THC+VAN	0.80	3.34	0.52	0.92

S. aureus: *Staphylococcus aureus*, CI: Combination index, THC: Tetrahydrocannabinol, CBD: Cannabidiol, VAN: Vancomycin

Table 6. Parameters were calculated from the median effect equation and median effect plot. 'm' is the slope, and m=1, >1 and <1 indicate hyperbolic, sigmoidal, and flat sigmoidal shape, respectively; 'Dm' denotes power; and 'r' is the linear correlation coefficient

<i>S. mutans</i>	Combination index (CI) values at			
	ED50	Dm	m	r
THC	N/A	155.00	1.34	0.95
CBD	N/A	21.00	0.99	0.97
VAN	N/A	3.70	0.77	0.94
CBD+VAN	1.03	3.21	0.74	0.94
THC+VAN	5.94	38.73	0.84	0.94
CBD+THC+VAN	0.90	2.97	0.86	0.96

S. aureus: *Staphylococcus aureus*, CI: Combination index, THC: Tetrahydrocannabinol, CBD: Cannabidiol, VAN: Vancomycin

Table 7. Dose reduction index (DRI), DRI=1, >1 and <1 indicate no dose reduction, appropriate dose reduction, and inappropriate dose reduction for each drug in the combination, respectively

<i>S. aureus</i>	Drug alone		Dose reduction index (DRI)			
	CBD	VAN	CBD	VAN		
Fa						
0.5	15.00	4.75	1.56	0.72		
Fa						
0.5	205.00	4.75	5.39	0.19		
Fa						
0.5	205.00	15.00	4.75	49.29	3.9	1.81

S. aureus: *Staphylococcus aureus*, CBD: Cannabidiol, VAN: Vancomycin, THC: Tetrahydrocannabinol

This study also focused on the appropriate DRI of the dual and triple drug combination based on actual experimental data points. The Fa-DRI table shows the results (Table 7, 8). DRI, DRI=1, >1 and <1 indicate no dose reduction, appropriate

Table 8. Dose reduction index (DRI), DRI=1, >1 and <1 indicate no dose reduction, appropriate dose reduction, and inappropriate dose reduction for each drug in the combination, respectively

<i>S. mutans</i>	Drug alone		Dose reduction index (DRI)			
	CBD	VAN	CBD	VAN		
Fa	CBD	VAN	CBD	VAN		
0.5	21.00	3.70	2.19	0.70		
Fa	THC	VAN	THC	VAN		
0.5	155.00	3.70	3.68	0.17		
Fa	THC	CBD	VAN	THC	CBD	VAN
0.5	155.00	21.00	3.70	15.02	2.24	0.72

S. mutans: Streptococcus mutans, CBD: Cannabidiol, VAN: Vancomycin, THC: Tetrahydrocannabinol

dose reduction, and inappropriate dose reduction for each drug in the combination, respectively. Typically, the main aim of combination therapy is to achieve synergistic effects (CI<1) to reduce the dose of specific toxic drugs (DRI>1) and, consequently, to eliminate the possibility of drug resistance. Accordingly, when the Fa-DRI table was examined in detail at fa=0.5 (Table 7, 8), at 50% inhibition (fa=0.5) in *S. aureus*, none of the binary combinations showed an appropriate dose reduction (DRI<1). In contrast, the triple combinations THC/CBD/VAN (49.88/3.94/1.85) showed an appropriate dose reduction (DRI>1). At 50% inhibition (fa=0.5) in *S. mutans*, none of the binary combinations showed an appropriate dose reduction (DRI<1), while the triple combination THC/CBD/VAN (15.54/2.38/1.12) showed an appropriate dose reduction (DRI>1). These results show that the combined use of cannabinoids has the potential to be used in the near future to increase the effectiveness of the treatment of dental caries to a very high level.

SEM Analysis

When the SEM images in Figure 3 are evaluated with ImageJ software, it is understood that THC does not show antibiofilm properties alone. In the control dentin disc surface images for both *S. aureus* and *S. mutans*, it is seen that the area is covered with more bacteria. When the SEM images of CBD and THC are compared with CBD+VAN and THC+VAN for *S. mutans* and *S. aureus*, it is seen that the single combinations are less effective. When both bacterial biofilms are evaluated for CBD+THC+VAN, it is determined that the highest antibiofilm effect occurs. In accordance with the MIC and Synergy tests, when the SEM images are examined, the potency order of CBD+THC+VAN>CBD+VAN>THC+VAN>CBD>THC is revealed.

DISCUSSION

The facultative anaerobe *S. mutans* initiates dental caries, while other bacteria, such as *S. aureus*, contribute to periodontal disease. Previous studies have shown that *S. mutans* is one of the leading causes of dental caries and that acidic metabolites formed from sugar fermentation lead to dentin demineralization.^{3,15} *S. aureus*, on the other hand, is generally associated with skin and soft tissue infections, but in recent years, it has also been detected in oral infections and has been reported to trigger periodontal diseases.⁴ The pathogenicity of *S. aureus* is especially emphasized in dental root canal infections and peri-implantitis cases.¹⁶ Managing infections caused by these bacteria requires a multifaceted approach that includes mechanical cleaning and antimicrobial agents. However, the increasing prevalence of multidrug-resistant bacteria requires innovative antimicrobial strategies. VAN, a glycopeptide antibiotic, has been used to combat Gram-positive bacterial infections, including those found in the oral cavity. Although VAN is effective against various Gram-positive bacteria, its efficacy decreases with the doses used due to evolving resistance mechanisms.

The secondary metabolites of *Cannabis sativa*, CBD, and THC have demonstrated antimicrobial properties against various bacteria, including those involved in dental infections. These compounds can disrupt bacterial cell membranes and interfere with biofilm formation, but their efficacy varies depending on the bacterial species and growth conditions. Previous studies have shown that CBD is effective against *Streptococcus* and *Staphylococcus* species.¹⁷ Suppressing bacterial biofilm formation and inhibiting bacterial enzyme activity allow CBD to be evaluated as a potential agent in the fight against dental caries.¹⁸ CBD effectively reduces bioactive metabolites, especially those caused by *S. mutans*.¹⁹ Combining VAN with CBD and THC may offer a new approach to combat bacterial retention in dental dentin. The rationale for the combined use of CBD and THC with VAN is to increase antibacterial efficacy and to create the potential for synergistic effects that may reduce the risk of resistance development. Combining these drugs can exploit the antimicrobial properties of each component to disrupt bacterial cell membranes, inhibit cell wall synthesis, and interfere with biofilm formation, thereby reducing bacterial retention in dental dentin. Further research is required to elucidate the precise mechanisms of action of the combination of VAN with CBD and THC in the context of dental infections and to optimize its therapeutic potential.

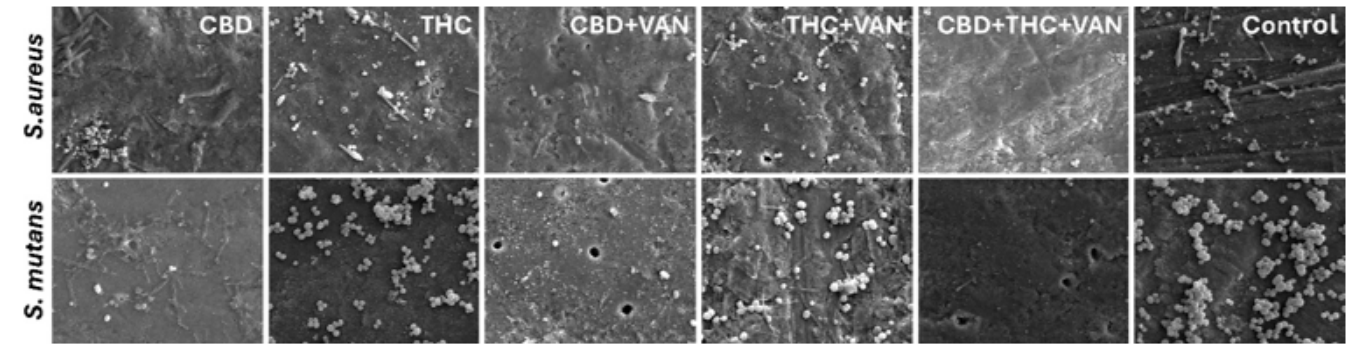


Figure 3. A scanning electron microscopic image (x25 K magnification) showing *S. mutans* and *S. aureus* biofilm formations on materials. THC: Tetrahydrocannabinol, CBD: Cannabidiol, VAN: Vancomycin, *S. aureus: Staphylococcus aureus*, *S. mutans: Streptococcus mutans*

Combination antibiotic therapies have various effects on bacterial survival, including additive, synergistic, and sometimes antagonistic effects, where combination therapy is less effective than single-drug therapies.²⁰ This is because single-drug therapies typically target a single bacterial function, whereas drug combinations are more likely to disrupt multiple bacterial processes simultaneously and produce more potent effects.²¹ Combination therapies may be effective because they treat mixed infections, enhance antimicrobial activity, avoid the need for long-term antibiotic use, and prevent the emergence of multidrug-resistant bacteria.²² One proposed theory suggests that silver nanoparticles destabilize lipopolysaccharides, increasing the permeability of the outer membrane and peptidoglycan structure, which are then recognized and captured by antibiotics, rendering resistant strains susceptible to antibiotics.²³ Here, combinations that effectively reduce the amount of VAN used prevented VAN-induced toxicity and reduced VAN resistance. This result was examined morphologically with SEM analysis, and it was shown that the findings were consistent and that the relevant combinations increased the effectiveness of VAN in the treatment of dental caries. With this study, it was added to the literature that VAN could be a safe anti-caries drug with the desired properties with an ideal combination (THC/CBD/VAN). Considering the clinical and academic importance of this study, the antibacterial activity of CBD and THC should be examined in detail, and its therapeutic potential in dentistry should be investigated. In particular, more research is needed on the pharmacokinetic profile, dose, and application methods to optimize the antibacterial activity of CBD. Future in vivo and clinical studies will more clearly demonstrate the usability of these bioactive compounds in the prevention and treatment of dental caries.

The synergistic combination of VAN, CBD, and THC identified in this study offers promising opportunities for clinical translation, particularly in developing novel antimicrobial formulations in dentistry. Given their demonstrated antibiofilm efficacy against *S. mutans* and *S. aureus*, this combination may serve as the basis for creating effective cavity disinfectants applied before prosthetic restorations, thus reducing microleakage-related bacterial retention. Furthermore, such a formulation could be adapted into antimicrobial rinses or mouthwashes aimed at preventing biofilm formation, especially in high-risk patients with extensive restorations or compromised oral hygiene. The incorporation of this combination into surface sterilization solutions or coating materials for prosthetic components may also help reduce bacterial colonization and prolong prosthesis lifespan. In endodontic or restorative procedures, this combination might function as an intracanal or intrachamber irrigant, improving disinfection while minimizing cytotoxicity by lowering the required VAN concentration.

Limitations

This study has several limitations. First, it was conducted under in vitro conditions, which do not fully mimic the complex in vivo environment of the oral cavity, including salivary enzymes, immune components, and mechanical forces. Second, the use of mono-species biofilms may not

represent the polymicrobial structure of natural dental biofilms. In addition, the relatively small sample size and the limited number of tested combinations may restrict the generalizability of the results. Further in vivo and large-scale studies with more diverse combination groups are needed to confirm the clinical relevance of the findings.

CONCLUSION

Today, the powerful antimicrobial agents used in this study are essential in dentistry due to their favorable nature properties. They are of great interest in the clinic. Preservation of tooth integrity is vital for oral health. Therefore, reducing the microleakage-induced microbial load caused by pathogens such as *S. mutans* and *S. aureus* on dentin disc is essential. The results obtained in this study will help develop ideal powerful antimicrobial agents regarding oral hygiene and introduce them into the clinic.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by Yozgat Bozok University Non-interventional Clinical Researches Ethics Committee (Date: 09.04.2025, Decision No: 2025-GOKAEK-257_2025.04.09_443).

Informed Consent

Since the study was designed as an experimental study, written informed consent was not required.

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 association between metformin use and contrast-induced nephropathy in diabetic patients undergoing coronary angiography

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Cite this article as: Akgül A, Tunca Ç, Ayılı MD. The association between metformin use and contrast-induced nephropathy in diabetic patients undergoing coronary angiography. *J Med Palliat Care*. 2025;6(4):305-310.

Received: 11.05.2025

Accepted: 28.06.2025

Published: 31.08.2025

ABSTRACT

Aims: Contrast-induced nephropathy (CIN) is a significant cause of hospital-acquired acute kidney injury, particularly in patients with diabetes mellitus undergoing coronary angiography. Although metformin is a widely prescribed antidiabetic agent, its role in CIN prevention remains controversial. This study aimed to investigate the impact of metformin use on the development of CIN in diabetic patients undergoing coronary angiography.

Methods: This retrospective cohort study included 398 diabetic patients undergoing coronary angiography with a diagnosis of acute coronary syndrome between November 2022 and December 2024. Patients were classified into two groups based on metformin use (metformin group, n=122; non-metformin group, n=276). CIN was defined as a $\geq 25\%$ or ≥ 0.5 mg/dl increase in serum creatinine within 48 hours post-procedure. Demographic, clinical, laboratory, and procedural data were analyzed. Multivariate logistic regression was used to identify independent predictors of CIN.

Results: CIN occurred in 6.6% of patients in the metformin group and 20.3% in the non-metformin group ($p=0.001$). Metformin use was independently associated with a lower risk of CIN (OR: 0.31; 95% CI: 0.14–0.69; $p=0.004$) in the multivariate logistic regression analysis. Other independent predictors of CIN included age >65 years, chronic kidney disease, high glucose, hemoglobin, CRP, smoking, and contrast volume.

Conclusion: Metformin use does not increase the risk of CIN in diabetic patients undergoing coronary angiography. These findings support the potential renoprotective effect of metformin and question the necessity of routinely discontinuing it before contrast administration in patients with preserved renal function.

Keywords: Contrast-induced nephropathy, metformin, diabetes mellitus

INTRODUCTION

Contrast-induced nephropathy (CIN) is a serious clinical condition that accounts for approximately 11% of all hospital-acquired acute kidney injuries, primarily resulting from the use of iodinated contrast agents during coronary angiography. The in-hospital mortality rate in patients who develop CIN may reach up to 22%, and the five-year mortality rate has been reported as high as 44.6%.¹ Major risk factors for CIN include advanced age, diabetes mellitus, chronic kidney disease (CKD) (estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m²), high contrast volume, and cardiogenic shock. In elderly individuals, physiological decline in renal function increases susceptibility to contrast agents.² The nephrotoxic effects of contrast media are attributed to increased oxygen consumption in the renal medulla leading to hypoxia, along with direct tubular toxicity.³ Moreover, low hematocrit levels ($<36.8\%$) have been shown to significantly increase the risk of CIN, with a combined risk of up to 28.8% when accompanied by low eGFR.⁴

Metformin, a biguanide-class oral antidiabetic agent, has traditionally been restricted in patients with CKD due to concerns about lactic acidosis. However, recent evidence suggests that the association between metformin and lactic acidosis is weaker than previously believed. The incidence of metformin-associated lactic acidosis appears to be very rare, with no significant difference observed in lactic acidosis rates between users and non-users. For instance, the incidence was reported as 8.1 per 100,000 patient-years among metformin users compared to 9.9 among non-users.^{5,6} Furthermore, meta-analyses have demonstrated that in patients with early-stage CKD (eGFR ≥ 30 ml/min/1.73 m²), metformin reduces all-cause mortality by 29% and cardiovascular events by 24%.⁷ Its mechanisms of action include inhibition of hepatic gluconeogenesis, favorable modulation of gut microbiota, and notable anti-inflammatory effects.⁸ Recent studies have shown that metformin significantly decreases markers of renal injury and inflammation—such as BUN, creatinine, C-reactive protein (CRP), TNF- α , and IL-6—while

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improving left ventricular ejection fraction.⁹ Due to the risk of lactic acidosis associated with metformin, it was previously recommended that the drug be discontinued prior to contrast administration in patients with CKD (eGFR <60 ml/min). However, recent studies have led to guidelines being updated to indicate that metformin can be used safely in patients with an eGFR >30 ml/min.¹⁰

However, the potential effect of metformin on CIN remains insufficiently elucidated. Therefore, the present study aimed to investigate the impact of metformin use on the development of CIN in patients with type 2 diabetes mellitus undergoing coronary angiography an area with limited and conflicting evidence to date.

METHODS

The study was carried out with the permission of Ankara Etlik City Hospital Clinical Researches Ethics Committee (Date: 29.04.2025, Decision No: AEŞH-BADEK2-2025-012). Since it is a retrospective study, no consent was obtained from the patients. To ensure data confidentiality, all personal identifiers were removed and anonymized data were stored in secure, password-protected electronic databases accessible only to the study team. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

This retrospective cohort study was conducted between November 2022 and December 2024 among patients diagnosed with acute coronary syndrome (ACS) who were admitted to the emergency department of our hospital and subsequently underwent coronary angiography. The sample size was calculated based on previously reported CIN incidence rates (10–20%) and the anticipated protective effect of metformin (30–40% reduction), yielding a minimum of 380 patients with 80% power and a 5% type I error. A total of 398 patients were ultimately included in the analysis. Inclusion criteria were: age over 18 years, a diagnosis of type 2 diabetes mellitus, and an indication for coronary angiography due to ACS. All patients were on a diabetic diet and receiving insulin therapy and/or oral antidiabetic medication. However, patients using sodium-glucose cotransporter-2 inhibitors (SGLT2) were not included in the study due to its effect on the development of CIN. Exclusion criteria; known CKD (eGFR <30 ml/min/1.73 m²), acute kidney injury, active infection, history of malignancy, patients with congestive heart failure (EF<40%), patients with cardiogenic shock, autoimmune disease, severe anemia, patients using chronic antiinflammatory drugs and use of nephrotoxic drugs, known allergy to contrast media were excluded from the study to ensure study standardization. CIN was defined as an increase in serum creatinine ≥25% or an absolute rise of ≥0.5 mg/dl within 48 hours after contrast exposure.¹¹

Demographic data, clinical characteristics, and laboratory parameters were retrospectively collected from hospital records using standardized data collection forms. Laboratory values including serum creatinine, urea, electrolytes, complete blood count, liver function tests, and CRP were obtained both prior to the procedure and at 48 hours post-procedure. All laboratory analyses were performed using standard methods

in the hospital's central laboratory. eGFR was calculated using the modification of diet in renal disease (MDRD) formula. All patients received oral hydration prior to the procedure (minimum 100 ml fluid intake per hour) and intravenous isotonic fluid post-procedure (1 ml/kg/hour for at least 12 hours). Patients were monitored for at least 48 hours after coronary angiography for renal function and clinical course.

Clinically meaningful and widely accepted threshold values in the literature were selected for the dichotomization of continuous variables. CRP >10 mg/L was selected to indicate the presence of acute inflammation and its association with systemic inflammatory processes that may increase the risk of CIN. This threshold has been defined by Pearson et al.¹² as a threshold with high prognostic value in ACSs. Glucose >200 mg/dl represents uncontrolled hyperglycemia in accordance with American Diabetes Association guidelines and is clinically meaningful in assessing CIN risk. Hemoglobin <12 g/dl is consistent with the World Health Organization's definition of anemia and was selected to assess CIN risk associated with renal hypoxia. eGFR <60 ml/min/1.73 m² has been identified as an indicator of CKD according to KDIGO guidelines. Finally, contrast medium volume >300 ml has been defined in the literature as a threshold at which the risk of CIN increases significantly. The selection of these thresholds was made to ensure both clinical significance and consistency with the literature.¹¹⁻¹⁴

The 398 patients were divided into two groups based on their treatment regimen at the time of hospital admission: those who were taking metformin (n=122) and those who were not (n=276). Patients using metformin were not randomly selected. Patients in the metformin group continued the medication on the day of the procedure and thereafter. Coronary angiography was performed in all patients using the Judkins technique via either the femoral or radial artery approach. A low-osmolar, non-ionic contrast agent (iopromide, 370 mg I/ml) was used. The total volume of contrast administered was determined by the operator based on clinical and angiographic findings.

Statistical Analysis

All data analyses were conducted using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to assess the normality of continuous variables. Non-normally distributed variables were expressed as median and interquartile range (IQR), and categorical variables were presented as numbers and percentages (%). Comparisons between groups were made using the Mann-Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables, as appropriate. Laboratory parameters were also compared between patients who developed CIN and those who did not, and results were tabulated as "CIN (+) vs. CIN (-)." To identify clinical predictors of CIN, threshold values were used for several parameters: CRP >10 mg/L, hemoglobin <12 g/dl, glucose >200 mg/dl, eGFR <60 ml/min/1.73 m², age >65 years, and contrast volume >300 ml. Univariate logistic regression was initially performed, and all variables with significant associations were included in the multivariate model to identify independent predictors of CIN. Statistical significance was defined as p<0.05. p-values ≥0.01 were reported to two decimal places,

while values <0.01 were reported to three decimal places. For results with $p<0.001$, this threshold was used instead of the exact value. Of the initial 415 patients, 398 with complete data were included in the final analysis.

RESULTS

A total of 398 diabetic patients were included in the study; among them, 122 (30.7%) were on metformin therapy, while 276 (69.3%) were not. There were no statistically significant differences between the metformin and non-metformin groups in terms of age (61.5 [52.0–69.0] vs. 59.0 [52.0–66.0] years, $p=0.193$) or sex distribution (68.0% vs. 71.0% male, $p=0.631$). However, the duration of diabetes was significantly longer in the metformin group (8.5 [5.0–12.8] vs. 6.0 [3.0–9.0] years, $p=0.013$). The prevalence of hypertension and hyperlipidemia was similar between the groups, whereas smoking was significantly more frequent in the non-metformin group (33.3% vs. 55.4%, $p<0.001$). Serum glucose levels were significantly higher in patients using metformin (239.0 [175.5–297.0] vs. 127.0 [105.5–177.0] mg/dl, $p<0.001$).

There was no significant difference in hemoglobin levels ($p=0.211$); however, CRP levels were significantly higher in the metformin group (13.3 [6.6–21.2] vs. 10.1 [5.6–17.1] mg/L, $p=0.010$). Left ventricular ejection fraction, total number of stents, and contrast agent volume were comparable between the two groups (all $p>0.05$). Additionally, the use of cardiovascular medications such as aspirin (ASA), angiotensin-converting enzyme (ACE) inhibitors, statins, and beta-blockers was similar across groups—for instance, beta-blocker usage was 68.0% in the metformin group and 69.9% in the non-metformin group ($p=0.868$). These findings are summarized in [Table 1](#).

When renal function was assessed, baseline eGFR values were similar between the groups (78.0 [60.0–98.0] vs. 84.0 [66.8–102.0] ml/min/1.73 m², $p=0.069$); however, post-procedural GFR was significantly higher in the non-metformin group (80.0 [63.0–98.0] vs. 73.0 [56.0–94.0], $p=0.037$). There was no significant difference between the groups in terms of percentage change in GFR ($p=0.822$). The most striking finding was the significantly lower incidence of CIN in the metformin

Table 1. Demographic and clinical characteristics

	Metformin (+) (n=122)	Metformin (-) (n=276)	p value
Demographic and clinical characteristics			
Age (years) (median (IQR))	61.50 (52.00-69.00)	59.00 (52.00-66.00)	0.193
Duration of diabetes (years)	8.50 (5.00-12.75)	6.00 (3.00-9.00)	0.013
Sex, male, n (%)	83 (68.0%)	196 (71.0%)	0.631
Hypertension, n (%)	76 (62.3%)	159 (57.6%)	0.444
Hyperlipidemia, n (%)	54 (44.3%)	153 (55.4%)	0.051
Smoking, n (%)	41 (33.3%)	153 (55.4%)	<0.001
Medication use			
ASA, n (%)	121 (99.2%)	273 (98.9%)	1.000
ACE inhibitor, n (%)	102 (83.6%)	233 (84.4%)	0.955
Statin, n (%)	104 (85.2%)	241 (87.3%)	0.688
Beta-Blocker, n (%)	83 (68.0%)	193 (69.9%)	0.868
Laboratory and imaging findings			
CRP (mg/L)	13.3 (6.6-21.2)	10.1 (5.6-17.1)	0.01
Hemoglobin (g/dl)	13.9 (12.2-15.0)	13.9 (12.7-15.0)	0.503
Glucose (mg/dl)	239.0 (175.5-297.0)	127.0 (105.5-177.0)	<0.001
LVEF (%) (median (IQR))	47.00 (40.00-54.00)	45.00 (40.00-52.00)	0.989
Total number of stents (median (IQR))	1.00 (1.00-1.00)	1.00 (1.00-2.00)	0.638
Renal function and CIN outcomes			
Baseline eGFR (ml/min/1.73 m ²)	78.00 (60.00-98.00)	84.00 (66.75-102.00)	0.069
Post-procedural eGFR (ml/min/1.73 m ²)	73.00 (56.00-94.00)	80.00 (63.00-98.00)	0.037
eGFR change (%)	-4.00 (-8.49-1.62)	-4.05 (-8.43-1.65)	0.822
Contrast agent volume (ml)	290.0 (220.0-320.0)	280.0 (210.0-310.0)	0.095
CIN development, n (%)	8 (6.6%)	56 (20.3%)	0.001
Need for dialysis, n (%)	1 (0.8%)	4 (1.4%)	0.613
CRP (mg/L) (CIN + vs -)	16.6 (8.7-26.7)	9.5 (5.5-15.7)	<0.001
Hemoglobin (g/dl) (CIN + vs -)	13.4 (11.6-14.5)	14.0 (13.0-15.0)	<0.001
Glucose (mg/dl) (CIN (+) vs. CIN (-))	141.0 (111.0-213.0)	124.0 (103.0-157.8)	<0.001
Baseline GFR (ml/min/1.73 m ²) (CIN (+) vs. CIN (-))	71.0 (49.0-99.0)	89.0 (75.0-104.0)	<0.001

eGFR: Estimated glomerular filtration rate, HGB: Hemoglobin, CRP: C-reactive protein, LVEF: Left ventricular ejection fraction, ASA: Acetylsalicylic acid, ACE: Angiotensin-converting enzyme, IQR: Interquartile range, CIN: Contrast-induced nephropathy

group compared to the non-metformin group (6.6% vs. 20.3%, $p=0.001$). No significant difference was observed in the need for dialysis ($p=0.613$). In subgroup analyses, patients who developed CIN had significantly higher CRP levels (16.6 [8.7–26.7] vs. 9.5 [5.5–15.7] mg/L, $p<0.001$) and glucose levels (141.0 [111.0–213.0] vs. 124.0 [103.0–157.8] mg/dl, $p<0.001$). In contrast, hemoglobin levels (13.4 [11.6–14.5] vs. 14.0 [13.0–15.0] g/dl, $p<0.001$) and baseline GFR (71.0 [49.0–99.0] vs. 89.0 [75.0–104.0] ml/min/1.73 m², $p<0.001$) were significantly lower in patients who developed CIN.

In the multivariate logistic regression analysis performed to identify predictors of CIN development, metformin use was found to be independently associated with a significantly reduced risk of CIN (OR: 0.31, 95% CI: 0.14–0.69, $p=0.004$). Additional independent risk factors for CIN included age >65 years (OR: 2.43, $p<0.001$), GFR <60 ml/min/1.73 m² (OR: 2.48, $p<0.001$), glucose >200 mg/dl (OR: 1.65, $p=0.006$), hemoglobin <12 g/dl (OR: 1.92, $p<0.001$), CRP >10 mg/L (OR: 2.12, $p<0.001$), smoking (OR: 1.55, $p=0.014$), and contrast volume >300 ml (OR: 1.96, $p<0.001$). These findings and all multivariate CI and OR values resulting from univariate and multivariate statistical analyses are summarized in [Table 2](#) and illustrated in [Figure](#).

DISCUSSION

In this study, we aimed to compare the risk of CIN following coronary angiography in diabetic patients using metformin versus those not on metformin therapy. Our findings demonstrated that metformin use was associated with a significantly reduced risk of CIN. These results support the potential renoprotective effect of metformin and provide an important clinical perspective that questions the necessity of routinely discontinuing metformin prior to contrast exposure in diabetic patients.

The incidence of CIN in the metformin group was 6.6%, significantly lower than the 20.3% observed in the non-metformin group. Multivariate analysis further revealed that metformin use reduced the risk of CIN by 69% (OR: 0.31, $p=0.004$). In a randomized study by Oktay et al.,¹⁵ although the difference in CIN rates between patients continuing versus discontinuing metformin was not statistically significant (8% vs. 6%, $p=0.265$), eGFR levels were better preserved in the metformin group. Similarly, Corremans et al.¹⁶ demonstrated that metformin reduced tubular injury and inflammation.

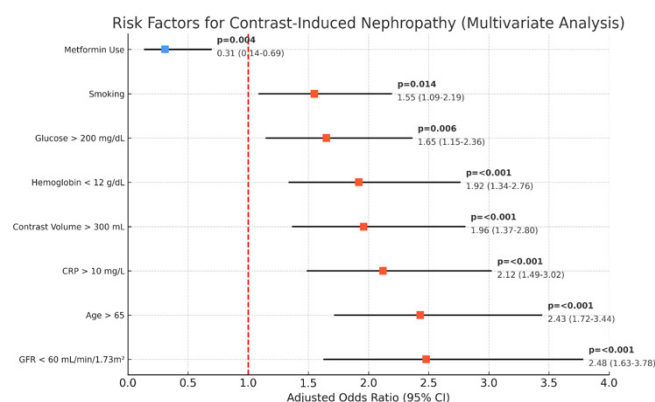


Figure. Forest plot of risk factors for contrast-induced nephropathy based on multivariate logistic regression analysis: Values to the left of reference line (OR<1) indicate protective factors, while values to the right (OR>1) indicate risk factors.

OR: Odds ratio, CI: Confidence interval, CRP: C-reactive protein, GFR: Glomerular filtration rate

Özkan and Gürdoğan¹⁷ reported a significant reduction in CIN risk with SGLT2 inhibitors (OR: 0.41), a value comparable to the protective effect observed. In our cohort, metformin use was associated with a 69% relative risk reduction in CIN (OR 0.31). This protective association is even stronger than that observed with some other agents for instance, SGLT2 inhibitors showed ~59% reduction in this study.¹⁷ González-González et al.¹⁸ showed that metformin led to an improvement in eGFR, although it had no significant effect on serum creatinine or albumin/creatinine ratio. Conversely, Yang et al.¹⁹ found no significant benefit of chronic SGLT2 inhibitor use on CIN incidence (OR: 0.92, $p=0.838$).

We observed that patients who developed CIN had significantly higher CRP levels (16.6 vs. 9.5 mg/L, $p<0.001$), and CRP >10 mg/L was associated with a 2.12-fold increased risk of CIN. This finding supports the role of inflammation in the pathogenesis of CIN and is consistent with previous reports.^{20,21} It should also be noted that CRP is higher in the group of patients using metformin, which is a cross-sectional result during ACS. This group is not healthier than the control group. Similarly, the number of patients who smoked was higher in the metformin group (55.4% vs. 33.3%), and smoking was found to be a risk factor for CIN (OR: 1.55). Although there were other risk factors affecting CIN in the metformin group, our finding that metformin reduced the risk of CIN appears to be quite significant for the results. Low hemoglobin levels (<12

Table 2. Independent risk factors for contrast-induced nephropathy based on univariate and multivariate logistic regression analyses

Risc factors	Univariate OR (95% CI)	Univariate p-value	Multivariate OR (95% CI)	Multivariate p-value
Metformin use	0.28 (0.13--0.62)	0.002	0.31 (0.14--0.69)	0.004
Age >65	3.05 (2.22--4.19)	<0.001	2.43 (1.72--3.44)	<0.001
eGFR <60 ml/min/1.73 m ²	2.76 (1.85--4.12)	<0.001	2.48 (1.63--3.78)	<0.001
Glucose >200 mg/dl	1.87 (1.34--2.61)	<0.001	1.65 (1.15--2.36)	0.006
Hgb <12 g/dl	2.18 (1.55--3.07)	<0.001	1.92 (1.34--2.76)	<0.001
CRP > 10 mg/L	2.35 (1.68--3.28)	<0.001	2.12 (1.49--3.02)	<0.001
Smoking	1.78 (1.28--2.47)	<0.001	1.55 (1.09--2.19)	0.014
Contrast volume >300 ml	2.17 (1.55--3.04)	<0.001	1.96 (1.37--2.80)	<0.001

OR: Odds ratio, CI: Confidence interval, eGFR: Estimated glomerular filtration rate, Hgb: Hemoglobin, CRP: C-reactive protein

g/dl) were also identified as an independent predictor of CIN (OR: 1.92, $p < 0.001$), in line with the findings of Abdel-Ghany et al.,²² and Su et al.,²³ who reported that low hematocrit levels increased the risk of acute kidney injury in patients with acute myocardial infarction. The contribution of anemia to CIN may be attributed to enhanced renal medullary hypoxia and exacerbation of inflammatory responses.

Baseline renal function also played a crucial role in CIN development. In our cohort, patients with eGFR < 60 ml/min/1.73 m² had a 2.48-fold higher risk of developing CIN, confirming the findings of earlier studies.²⁴⁻²⁷ These studies similarly highlighted reduced eGFR levels—particularly below 45–60 ml/min/1.73 m²—as an independent risk factor, with markedly higher CIN incidence in this population.

Moreover, classical risk factors such as high contrast volume (> 300 ml) and advanced age (> 65 years) were also significantly associated with increased CIN risk in our study. Specifically, contrast volume > 300 ml increased the risk by 1.96 times, and age > 65 years increased the risk by 2.43 times. These findings are supported by Hwang and Kim,²⁸ who showed that every 10 mL increase in contrast volume raised the CIN risk by 8%, and by Beasley et al.,²⁹ who observed a significantly higher rate of renal impairment with contrast doses ≥ 400 ml. Chang-Panesso³⁰ emphasized the higher incidence of CIN in older adults compared to younger patients, and Takura et al.³¹ demonstrated that high contrast exposure accelerated the annual decline in GFR, particularly among elderly individuals.

Limitations

This study has several limitations. First, its single-center design and relatively short follow-up duration may limit the generalizability of the results. Second, due to the observational and non-randomized design, residual confounding cannot be entirely excluded. However, the study has notable strengths, including an adequate sample size, a well-defined patient population, prospectively collected data, and adjustment for confounding variables through multivariate regression analysis. Future randomized, multicenter studies with long-term follow-up are warranted to further elucidate the renoprotective mechanisms of metformin and its effects on long-term renal outcomes in different subpopulations.

CONCLUSION

As a result, this study demonstrated that metformin use significantly reduces the risk of CIN in diabetic patients undergoing coronary angiography. The notably lower incidence of CIN in patients on metformin raises critical questions about the conventional practice of routinely withholding this drug prior to contrast procedures. Our findings suggest that metformin may exert a protective effect against contrast nephrotoxicity and support the reevaluation of current clinical guidelines. If supported by future studies, the use of metformin after coronary angiography in diabetic patients with normal or mild to moderate reduced renal function appears to be both safe and potentially beneficial in preventing CIN.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ankara Etlik City Hospital Clinical Researches Ethics Committee (Date: 29.04.2025, Decision No: AEŞH-BADEK2-2025-012).

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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Care poverty: unmet care needs in Türkiye

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Cite this article as: Danayiyen A. Care poverty: unmet care needs in Türkiye. *J Med Palliat Care*. 2025;6(4):311-317.

Received: 14.05.2025

Accepted: 04.07.2025

Published: 31.08.2025

ABSTRACT

Aims: This study examines care poverty among older adults in Türkiye by analyzing socio-demographic and health-related factors that contribute to unmet care needs in basic and instrumental activities of daily living (ADLs and IADLs).

Methods: The analysis is based on secondary data from the Turkish Statistical Institute (TUIK) for 2019 and 2022. The study focuses on disparities in both basic and instrumental activities of daily living (ADLs and IADLs) among the elderly population. Prevalence rates of unmet care needs were calculated, and socio-demographic and health-related determinants were examined. Gender differences were also analyzed, particularly with IADLs.

Results: The findings indicate that older adults with poor health, low social support, and limited access to care face a higher risk of care poverty. Based on the analysis, care poverty prevalence was found to be 14% for basic ADLs and 34.9% for IADLs. While no significant gender difference was observed in basic ADLs, women were more disadvantaged than men in instrumental ADLs.

Conclusion: This study reveals a substantial prevalence of care poverty among the elderly in Türkiye. It highlights the role of health inequalities, social vulnerability, and gender in access to care. The results provide evidence to support more inclusive and equitable long-term care policies, especially in middle-income countries experiencing population aging.

Keywords: Care poverty, unmet needs, social inequality, long-term care policies

INTRODUCTION

The aging population presents significant social, economic, and healthcare challenges globally. Rising life expectancy and declining fertility have increased the proportion of older adults, with the global population aged 60 and over expected to reach 2.1 billion by 2050.¹ In Türkiye, the elderly population surpassed 9 million in 2024, accounting for over 10.6% of the total population.² This demographic shift places growing pressure on healthcare systems, pensions, and social care infrastructures.

Long-term care (LTC) has become a critical policy issue, especially in middle-income countries like Türkiye, where formal care systems remain limited. Despite increasing demand, 90 countries still lack legal frameworks for LTC, and only 20 have regulated home care systems, leaving millions without adequate support.³ One of the most urgent issues in this context is care poverty, defined as the insufficient receipt of care, either formal (state or market-based) or informal (family or community-based), despite existing need.⁴ Unlike the narrower concept of unmet care needs, which often focuses on formal medical barriers such as staffing shortages or long waiting times,⁵ care poverty offers a broader lens. It encompasses both formal and informal care and highlights the structural mismatch between the need for care and the availability of support.

The concept of care poverty not only refers to unmet care needs but also seeks to analyze the underlying social policy shortcomings and structural inequalities that contribute to inadequate care provision. Situated within the framework of the welfare state—where access to health and social services is treated as a right—this concept underscores that the level of social protection is shaped by political decisions.⁴ Inequality manifests in the differing opportunities individuals have in accessing health, education, and public services, often stemming from imbalances in access, rights, and power.⁶ Welfare policies play a critical role in shaping individuals' capacity to meet their care needs by determining the scope, quality, and accessibility of care services. However, widespread, affordable, and high-quality care is not achieved automatically; it requires deliberate policy interventions. In the absence of publicly subsidized services, individuals are often faced with unequal choices between purchasing formal care or relying on informal support. Care poverty is used to describe these types of institutional and structural deficiencies that produce and reproduce social inequalities. Therefore, care poverty is not solely a matter of financial insufficiency; it also stems from the limited availability, accessibility, or affordability of care services—whether public, non-profit, or for-profit.⁴⁻⁶ It emerges as a multidimensional form of inequality shaped by the intersection of individual-level deprivations (such as the lack of close family members)

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and structural limitations (such as underdeveloped welfare state capacities).

In Türkiye, traditional family-based caregiving has long been dominant. However, urbanization, changing family structures, increased female labor force participation, and internal migration have weakened these patterns. While government-provided care allowances exist, they fail to fully offset the erosion of familial care capacity, especially in rural areas with poor infrastructure.⁷ Despite its policy relevance, most care poverty research has focused on high-income countries.^{4,8,9} Middle-income contexts like Türkiye remain underexplored, despite their growing elderly populations and reliance on informal care. Recent studies indicate that many older adults in Türkiye face unmet care needs in both basic and instrumental daily activities.¹⁰

This study uses nationally representative data from the 2019 and 2022 Türkiye Health Surveys to assess the prevalence and determinants of care poverty among older adults. It also explores the role of social support, assistive technologies, and access to home care services in mitigating these risks. The findings aim to inform more inclusive, equitable, and sustainable LTC strategies in Türkiye and similar settings undergoing demographic transition. In this context, the study seeks to answer the following research questions: (1) What are the socio-demographic and health-related factors associated with care poverty among older adults in Türkiye, and how do these vary across different regions and gender groups? (2) To what extent do current care structures—both formal and informal—meet the needs of older adults, and what policy interventions can be proposed to reduce care poverty in a rapidly aging, middle-income country context?

METHODS

Study Design and Participants

This study is based on the Türkiye Health Survey dataset, which is regularly conducted by the Turkish Statistical Institute (TUIK). The study population consists of survey data collected within this framework, while the sample includes older adults over 65 from the 2019 and 2022 datasets. The analysis was conducted using pre-approved official data obtained from TUIK, and the study adhered to the principles of the Helsinki Declaration.

The Türkiye Health Survey aims to address existing gaps in health indicators and provide data for a better understanding of national health and care needs. The survey covers households, excluding institutional populations such as soldiers, nursing home residents, and prisoners, as well as small settlements with low population density. In this study, the 2019 and 2022 datasets were merged to focus on older adults 65+, enhancing the representativeness of the research. Before conducting the analysis, missing observations were removed, and necessary adjustments were made.

Data Collection Tool

The study's dependent variables are: Unmet care needs in activities of daily living (ADL), unmet care needs in Instrumental Activities of Daily Living (IADL), and overall

care poverty, representing individuals experiencing unmet care needs in at least one of these domains. Measuring care needs objectively is challenging, and there is no universally accepted standard for assessing unmet care needs in the literature. The most common approach involves surveying older adults about their ability to perform essential daily activities. TUIK employs two widely recognized scales:

The activities of daily living (ADL) scale: Developed by Katz (1983), this scale assesses bathing, dressing, toileting, mobility, and eating. Responses follow the same 1–4-point rating system.¹¹

The instrumental activities of daily living (IADL) scale: Developed by Lawton and Brody (1969), this scale evaluates more complex daily tasks, including telephone use, meal preparation, household chores, managing finances, transportation, medication management, and shopping. Responses follow the same 1–4-point rating system.¹²

After completing these scales, participants were asked: "Do you regularly receive assistance for the most difficult activity?" Those who answered "yes" were further questioned: "Do you need more assistance than you currently receive?". Individuals responding "yes" to the second question were classified as experiencing care poverty, following the conceptual framework proposed by Kröger.¹⁴

Independent variables: The independent variables used in this study include: Gender (male, female), age group (65–74, 75+ years), marital status (married, not married [widowed, divorced, never married]), income level (categorized based on the national minimum wage: below, at, or above minimum wage), general health status (self-reported on a scale of 1 [very good] to 5 [very poor]), social support (individuals reporting "no close and reliable person" were classified as lacking social support), use of special equipment (yes, no), presence of a caregiver (yes, no), geographical region (seven regions based on TUIK's Level-1 Statistical Regional Classification: Marmara, Aegean, Central Anatolia, Mediterranean, Southeastern Anatolia, Eastern Anatolia, Black Sea), access to home care services (yes, no).

Statistical Analysis

Chi-square tests were used to analyze differences between independent and dependent variables. Binary Logistic Regression Analysis was conducted to identify the determinants of care poverty. First, multicollinearity analysis was performed using the variance inflation factor (VIF) values, and no multicollinearity issues were detected. Then the goodness-of-fit of logistic regression models was assessed using the Hosmer-Lemeshow Test, while model explanatory power was reported using Nagelkerke R^2 and Cox and Snell R^2 values. All analyses were performed using SPSS 25 (Statistical Package for the Social Sciences).

RESULTS

Table 1 presents the prevalence of care poverty in ADL and IADL. The study highlights variations in care poverty rates between ADLs and IADLs, reflecting differences in assistance needs.

Table 1. Prevalence of unmet care needs in ADLs and IADLs

	No care needed n (%)	Receiving adequate care n (%)	Needed more care (care poverty rate) n (%)
ADLs (basic)	4353 (77.7)	467 (8.3)	782 (14.0)
IADLs (instrumental)	2476 (44.2)	1171 (20.9)	1955 (34.9)
ADLs and IADLs total	3272 (58.4)	276 (4.9)	2054 (36.7)

ADL: Activities of daily living, IADL: Instrumental activities of daily living

This study finds that 14% of older adults in Türkiye experience care poverty in ADLs, and 34.9% in IADLs, with an overall rate of 36.7%. These findings align with Kröger's⁴ study in Finland, which reported care poverty rates of 17% for ADLs, 26% for IADLs, and 26% overall. Similarly, Simsek et al.¹⁰ found higher rates among older adults aged 80+, with 46.6% overall care poverty, including 39.3% in ADLs and 42.8% in IADLs.

Differences in prevalence rates across studies can be attributed to variations in age groups, methodology, and care system structures. Previous research has reported care poverty rates between 32.8% and 67.5%, particularly higher among the oldest adults.⁸⁻¹⁰ Given the functional differences between ADLs and IADLs, it is expected that instrumental activities involve greater unmet needs. These results confirm that IADL-related care poverty is a critical concern, reflecting broader issues in maintaining independence in later life.

Table 2 presents the analysis of care poverty in ADLs across socio-demographic and health-related variables.

The analysis shows that age, education, health status, caregiver availability, and region significantly influence care poverty in basic ADLs. Older adult aged 75+, those with poor health, and those without caregivers are at markedly higher risk ($p<0.001$). Care poverty was also more common among less educated older adults ($p<0.05$), and regional disparities were

Table 2. Unmet basic activities of daily living (ADL) needs by demographic characteristics

		Unmet ADL needs		Met ADL needs		Test*
		n	%	n	%	
Age group		543	60.4	329	70.4	$p>0.05$
	Male	239	30.6	138	29.6	
	65-74	297	38.0	244	52.2	$p<0.001$
	75 and above	485	62.0	223	47.8	
Education	Illiterate/no formal education	493	63.0	260	55.7	$p<0.05$
			33.2	180	38.5	
Gender	Female	3.7	27	5.8		
	Married	353	45.1	234	50.1	$p>0.05$
	Not married (widowed, divorced)	429	54.9	233	49.9	
Income	Low	284	36.3	146	31.3	$p>0.05$
	Middle	402	51.4	262	56.1	
	High	96	12.3	59	12.6	
General health status	Poor	567	72.5	217	46.5	$p<0.001$
	Moderate	204	26.1	212	45.4	
	Good	11	1.4	38	8.1	
Caregiver	Yes	172	26.1	27	7.1	$p<0.001$
	No	488	73.9	355	92.9	
Social support	Yes	737	94.4	441	94.4	$p>0.05$
	No	44	5.6	26	5.6	
Use of special equipment	Yes	141	21.4	25	6.5	$p<0.001$
	No	519	78.4	357	93.5	
Region of residence	Marmara	210	26.9	103	22.1	$p<0.05$
	Aegean	70	9.0	58	12.4	
	Central Anatolia	158	20.2	108	23.1	
	Mediterranean	57	7.3	47	10.1	
	Southeastern Anatolia	44	5.6	28	6.0	
	Eastern Anatolia	711	9.1	41	8.8	
	Black Sea	72	22.0	82	17.6	
Home care services	Yes	88	11.3	22	4.7	$p<0.001$
	No	694	88.7	445	95.3	

* p-values based on Chi-square tests

observed, with higher rates in Marmara, Central Anatolia, and the Black Sea regions.

While gender differences were not significant for basic ADLs, women were more disadvantaged in IADLs, consistent with Simsek et al.¹⁰ and Özbek Yazıcı et al.¹³ However, findings in the literature are mixed—Kröger¹⁴ reported no gender gap, whereas Wilkinson-Meyers et al.⁸ found women at greater risk. These discrepancies may reflect differences in dependency patterns, access to services, or cultural norms. Overall, the findings point to persistent gender inequalities in care access. Promoting gender-sensitive policies and recognizing women's caregiving labor remain essential steps in addressing care poverty in Türkiye.

The differential analysis of care poverty associated with IADL, based on socio-demographic and health-related variables, is presented in [Table 3](#).

Analysis of IADL-related care poverty shows significant associations with gender, age, education, marital status, income, health, caregiver presence, assistive equipment, and region. Women were more likely than men to experience care poverty (71.7% vs. 28.3%; $p<0.001$), and prevalence was higher among older adults aged 75+ (45.6%; $p<0.001$).

Care poverty was most common among those with low education (51.4% among illiterate older adults vs. 7.6% among high school graduates; $p<0.001$) and unmarried older adults (48.4% vs. 37.3%; $p<0.001$). It also declined with rising income ($p<0.01$) and better health status ($p<0.001$). Notably, lack of a caregiver (82.4%) and absence of assistive equipment (86.3%) were associated with drastically higher care poverty rates ($p<0.001$).

Regionally, higher rates were observed in Marmara (28.7%), Central Anatolia (20.9%), and Black Sea (21.2%) regions,

Table 3. Unmet instrumental activities of daily living (IADL) needs by demographic characteristics

		Unmet IADL needs		Met IADL needs		Test*
		n	%	n	%	
Gender	Female	1401	71.7	727	62.1	$p<0.001$
	Male	554	28.3	444	37.9	
Age group	65-74	1064	54.4	723	61.7	$p<0.001$
	75 and above	891	45.6	448	38.3	
Education	Illiterate/no formal education	1004	51.4	510	43.6	$p<0.001$
	Primary/middle school graduate or equivalent	803	41.1	538	45.9	
	High school graduate and above	148	7.6	123	10.5	
Marital status	Married	1008	51.6	734	62.7	$p<0.001$
	Not married (widowed, divorced)	947	48.4	437	37.3	
Income	Low	582	29.8	276	23.6	$p<0.01$
	Middle	1087	55.6	705	60.2	
	High	286	14.6	190	16.2	
General health status	Poor	938	48.0	351	30.0	$p<0.001$
	Moderate	844	43.2	623	53.2	
	Good	173	8.8	197	16.8	
Caregiver	Yes	230	17.6	37	5.2	$p<0.001$
	No	1079	82.4	673	94.8	
Social support	Yes	1881	96.2	1117	95.4	$p>0.05$
	No	74	3.8	54	4.6	
Use of special equipment	Yes	179	13.7	28	3.9	$p<0.001$
	No	1130	86.3	682	96.1	
Region of residence	Marmara	561	28.7	279	23.8	$p<0.001$
	Aegean	168	8.6	154	13.2	
	Central Anatolia	409	20.9	280	23.9	
	Mediterranean	164	8.4	98	8.4	
	Southeastern Anatolia	89	4.6	46	3.9	
	Eastern Anatolia	149	7.6	132	11.3	
	Black Sea	415	21.2	182	15.5	
Home care services	Yes	101	5.2	27	2.3	$p<0.001$
	No	1854	94.8	1144	97.7	

* p-values based on Chi-square tests

while Aegean, Mediterranean, and Southeastern Anatolia had significantly lower prevalence ($p<0.001$).

The logistic regression analysis presented in [Table 4](#) examines the determinants of care poverty in basic ADL, IADL, and overall care poverty encompassing both domains.

Regression models examined factors influencing care poverty across ADLs, IADLs, and combined daily activities. In the ADL model, older adults with poor health were 2.6 times more likely to experience care poverty ($OR=2.589$; $p<0.001$), while those aged 75+ had a 40% higher risk ($OR=0.601$; $p<0.01$). Use of assistive equipment ($OR=2.011$; $p<0.01$), caregiver support ($OR=3.132$; $p<0.001$), and home care services ($OR=1.916$; $p<0.05$) were also associated with higher ADL care poverty.

In the IADL model, women faced a significantly higher risk than men ($OR=0.700$; $p<0.01$), and poor health again emerged as a key determinant ($OR=1.677$; $p<0.001$). Assistive equipment ($OR=2.155$), caregiver support ($OR=2.546$), and home care ($OR=1.699$) were all significantly linked to increased IADL care poverty (all $p<0.05$).

The combined model revealed that women ($OR=1.914$; $p<0.001$), older adults aged 75+ ($OR=1.289$; $p<0.01$), and unmarried older adults ($OR=1.292$; $p<0.01$) were at greater risk. Poor health increased care poverty risk by 48% ($OR=0.483$; $p<0.001$). Notably, the use of assistive equipment ($OR=0.430$), caregiver support ($OR=0.433$), and home care services ($OR=0.455$) were associated with significantly reduced care poverty risk (all $p<0.01$).

DISCUSSION

This study examines the prevalence and determinants of care poverty among older adults in Türkiye, contributing to the global discourse on LTC inequalities and offering evidence-based recommendations for policy development in middle-

income countries facing similar demographic and structural transitions.

The findings reveal that 14% of older adults aged 65+ experience care poverty in basic daily activities (ADLs), while 34.9% face unmet needs in instrumental activities (IADLs), resulting in an overall poverty rate of 36.7%. These results highlight the growing care gap, particularly in more complex daily tasks, and underscore the limitations of both formal and informal care structures in addressing the needs of an aging population. Building on nationally representative data, this study explores the socio-demographic and health-related factors associated with care poverty among older adults, focusing on unmet needs in both basic (ADLs) and instrumental (IADLs) daily living activities. Although no significant gender difference was observed in ADL-related care poverty, women were found to be considerably more disadvantaged in IADLs. This finding is consistent with previous research by Simsek et al.¹⁰ and Özbek Yazıcı et al.,¹³ which reported higher dependency rates among older women. However, the literature remains inconclusive—while Kröger¹⁴ reported no gender-based disparity, Wilkinson-Meyers et al.⁸ identified a higher risk of care poverty among women in New Zealand. Such discrepancies may stem from gendered patterns of dependency in instrumental tasks and persistent structural barriers to accessing services. These gendered disadvantages must also be interpreted through the lens of unpaid care labor, societal expectations of caregiving roles, and higher rates of living alone among older women. Feminist gerontology emphasizes that gender is not merely a demographic variable but a structural axis that organizes access to power, resources, and support across the life course. In aging populations, especially in societies where traditional gender roles persist, women's lifelong engagement in unpaid caregiving leads to cumulative disadvantages in later life. They are not only expected to provide informal care but are

Table 4. Association of unmet ADL and IADL needs by socio-demographic characteristics—a binary logistic regression analysis

	Model 1	Model 2	Model 3
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Gender	0.996 (0.710-1.398)	0.700 (0.558-0.878)**	1.914 (1.570-2.333)***
Age group	0.601 (0.450-0.803)**	0.949 (0.774-1.163)	1.289 (1.076-1.545)**
Education	1.046 (0.807-1.355)	1.016 (0.855-1.206)	0.911 (0.782-1.061)
Marital status	1.036 (0.761-1.409)	1.174 (0.949-1.453)	0.774 (0.640-0.936)**
Income	0.991 (0.795-1.237)	1.034 (0.883-1.211)	0.950 (0.826-1.093)
General health status	2.589 (2.018-3.322)***	1.677 (1.444-1.948)***	0.483 (0.423-0.550)***
Social support	0.945 (0.516-1.731)	0.856 (0.541-1.355)	1.328 (0.891-1.978)
Use of special equipment	2.011 (1.219-3.317)**	2.155 (1.385-3.352)**	0.430 (0.291-0.635)***
Caregiver	3.132 (1.953-5.023)***	2.546 (1.732-3.744)***	0.433 (0.312-0.602)***
Region of residence	0.972 (0.914-1.033)	0.977 (0.936-1.020)	1.027 (0.989-1.066)
Home care services	1.916 (1.089-3.370)*	1.699 (1.023-2.821)*	0.455 (0.279-0.742)**
Cox and Snell R2	0.147	0.083	0.162
Nagelkerke R2	0.202	0.114	0.217
Hosmer and Lemeshow	ProbChi-Sq (8):0.792	ProbChi-Sq (8):0.537	ProbChi-Sq (8):0.656
Number of observations	1042	2019	2588

* $p<0.05$; ** $p<0.01$; *** $p<0.001$, ADL: Activities of daily living, IADL: Instrumental activities of daily living, OR: Odds ratio, CI: Confidence interval

often left without sufficient institutional support when they themselves become dependent. As highlighted by Calasanti,¹⁵ feminist gerontology urges scholars and policymakers to consider how normative caregiving expectations, combined with structural inequalities in access to care, result in the double burden faced by older women—as lifelong caregivers and later as marginalized care recipients. In the Turkish context, where the family remains the main care provider and state support is limited, these dynamics are even more pronounced, further exacerbating care poverty among aging women. Similarly, Soneghet's¹⁶ ethnographic study on home-based palliative care in Brazil demonstrates that care is not simply a physical task, but a “social arrangement” shaped by emotional exhaustion, limited material resources, and unequal social expectations. In contexts like Türkiye, where family-based care is prevalent and formal support systems remain underdeveloped, this care burden overwhelmingly falls on women, intensifying their vulnerability to care poverty and reinforcing gendered inequalities in old age.¹⁶ In line with these findings, Hernández et al.'s¹⁷ qualitative study in Mexico highlights how poor women internalize the belief that low-quality public healthcare is the only care they deserve, reinforcing a cycle of resigned acceptance and care poverty linked to both economic and gender-based marginalization. Intersectional factors—such as being older, female, widowed, and economically disadvantaged—amplify vulnerability to care poverty.^{18,19} Importantly, care poverty should not be interpreted solely as a matter of individual deprivation or familial failure. As The Polish LTC system is predominantly based on familial care, reflecting a family-oriented welfare model. Poland's experience illustrates that reliance on informal family care and fragmented governance can hinder the equitable development of LTC systems, posing significant risks as demographic shifts accelerate.²⁰

Although income was not a significant determinant in regression models, lower-income older adults reported higher IADL care poverty, supporting previous findings that financial capacity limits access to formal services. This may relate to widespread low pension incomes and the impact of inflation in Türkiye. Poor general health was the most consistent predictor of care poverty, but its effect decreased in the full model, suggesting that older adults with poor health may also receive more formal support. This underlines the importance of integrated health and social care approaches.¹⁸ The models also highlighted the mitigating effects of assistive equipment, caregiver support, and home care services. Lack of caregiver support and assistive technologies emerged as major barriers to meeting care needs. Access to home care services significantly reduced care poverty risk, especially in the full model. Although regional differences were not significant in regression models, Chi-square tests showed higher care poverty in Marmara, Central Anatolia, and the Black Sea regions. The higher prevalence in Marmara, despite being more urbanized and economically developed, may relate to internal migration patterns, higher proportions of older adults living alone, and pressure on urban care systems. In Central Anatolia and the Black Sea regions, traditional family structures are eroding while public services remain inadequate. Moreover, female labor force participation and availability of community-based

services vary significantly across regions, which may explain the unequal distribution of care burdens. A regional map or heat chart could help visualize this disparity and support policy design. This suggests the need for more regionally equitable care policies. The high prevalence in urbanized regions like Marmara highlights service access issues even in resource-rich areas.

In the Turkish context, where gender inequality remains deeply embedded in social and institutional structures, the findings reinforce the pressing need for gender-responsive care policies and the formal recognition of women's unpaid caregiving roles within the welfare system. Advancing age and marital status also emerge as critical determinants of care poverty. Individuals aged 75 and above were found to be 1.3 times more likely to experience unmet care needs, consistent with previous research by Kröger⁴ and Simsek et al.¹⁰ The elevated risk among unmarried older adults—particularly widowed women—can be attributed to the absence of spousal support, which often serves as the primary source of informal care in later life. Such patterns are not merely individual vulnerabilities but reflect broader systemic and policy-level deficits in the development of equitable and sustainable LTC systems. In middle-income countries like Türkiye, which are undergoing rapid demographic aging, these challenges demand urgent and strategic investment in care infrastructure, workforce capacity, and inclusive service models to ensure social protection for an increasingly dependent population.

Limitations

It relies on self-reported, cross-sectional survey data, which may introduce perception-based bias and limit causal inference. The dataset includes a limited number of variables and categories, restricting the depth of analysis. Future research should employ longitudinal and mixed methods approaches to better understand care poverty dynamics and older adults' lived experiences.

CONCLUSION

The cumulative disadvantages identified in this study underscore the necessity of formulating LTC strategies that are both targeted and equitable, addressing structural inequalities accumulated across the life course. Reducing care poverty among older adults requires a multifaceted approach centered on the expansion of home care services, the provision of sustained support for caregivers, and improved access to assistive technologies.

Policy priorities should include the development of gender-sensitive care infrastructure, the formal recognition of unpaid caregiving—particularly by women—and the institutionalization of a comprehensive LTC insurance scheme. Within this framework, the Turkish government's 2024 electoral commitment to establishing an elderly care insurance system represents a significant policy window. However, for such a scheme to be effective and inclusive, it must clearly define the scope of home care services, incorporate financial support mechanisms for informal caregivers, and ensure coverage for gerontechnological devices that enhance independent living.

Furthermore, policy design should account for persistently low female labor force participation and the disproportionate burden of informal care shouldered by women. To this end, integrating systematic care needs assessments into the Family Physician Program and introducing a caregiver credit (A policy tool that protects pension rights of informal caregivers by recognizing unpaid care work as contributory) mechanism under the Social Security Institution (SGK) could serve as practical and scalable solutions. These measures would not only provide formal recognition of informal caregiving but also contribute to financial security for caregivers, thereby enhancing the sustainability of the broader care system.

Finally, international experiences—such as LTC insurance models implemented in countries like Germany and South Korea—offer valuable policy templates that may be adapted to the Turkish context, provided that local demographic, cultural, and institutional factors are carefully considered in the process of implementation.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study utilized publicly available secondary data, and therefore, ethical approval and informed consent were not applicable, in accordance with national regulations.

Informed Consent

Because the study was based on secondary data obtained from TÜİK, no written informed consent form was obtained from participants.

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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Interdisciplinary consultation trends in oral and maxillofacial surgery: a 5-year retrospective review

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Cite this article as: Tepecik T, Beker RC, Baş MZ. Interdisciplinary consultation trends in oral and maxillofacial surgery: a 5-year retrospective review. *J Med Palliat Care*. 2025;6(4):318-322.

Received: 10.04.2025

Accepted: 05.07.2025

Published: 31.08.2025

ABSTRACT

Aims: This study seeks to assess the content, frequency range, and practical outcomes of consultations directed to the oral and maxillofacial surgery (OMS) clinic from several medical departments for both outpatient and inpatient care. The results of this analysis will likely emphasize the importance of managing identified conditions using a multidisciplinary approach and help guide future research in this field.

Methods: A comprehensive retrospective analysis was performed on outpatient and inpatient consultations referred to the OMS clinic from internal and surgical medical departments at İstanbul Health Sciences University Sultan 2. Abdülhamid Han Training and Research Hospital from 2017 to 2023. This study systematically analyzes patient demographics, consultation purposes, responses given, and clinical actions completed. The dataset will provide quantitative results regarding the departments that most often request consultations, the main conditions prompting these requests, and the treatments provided.

Results: Statistical data indicate that the majority of consultations directed to the OMS clinic originated from the Otolaryngology (ENT) clinic. This is followed by the emergency department, general surgery, anesthesia and reanimation department.

Conclusion: This study reveals that the majority of referrals to the OMS clinic originate from the ENT and emergency departments, primarily for temporomandibular joint disorders, sinus pathologies, and maxillofacial trauma. These results underscore the significant clinical interface between OMS and other medical specialties, highlighting the necessity for structured interdisciplinary collaboration and increased awareness regarding the scope of OMS services in hospital-based care.

Keywords: Consultation, awareness, oral and maxillofacial surgery, otolaryngology

INTRODUCTION

The department of oral and maxillofacial surgery (OMS) plays a vital role in healthcare due to its multidisciplinary nature.^{1,2} In countries like Türkiye, where medical and dental education are separate, effective collaboration between OMS and other medical fields enhances access to both preventive and therapeutic services.^{3,4} OMS specialists are trained to perform a wide range of procedures, including dentoalveolar surgery, treatment of craniofacial trauma, salivary gland disorders, and temporomandibular joint (TMJ) problems. Oral cancer is also managed effectively through multidisciplinary approaches involving plastic surgeons and microsurgical techniques. Despite this wide scope, both the public and medical professionals often underestimate the role and capabilities of OMS.^{1,4}

The need for interdisciplinary cooperation is especially evident in cases involving facial trauma, oral cancer, forensic evaluations, palliative care, medication-related osteonecrosis, and congenital anomalies.^{2,5,6} This study aims to evaluate

the current state of collaboration between OMS and related medical disciplines.

The scarcity of literature on this topic underscores the necessity for precise and comprehensive consultations. Inadequate or mistaken consultations might result in postponement of patient treatment and care, thereby compromising patient health outcomes.^{7,8} Consequently, efficient communication and collaboration between OMS and other medical disciplines is essential for achieving patient benefits from healthcare services.

This article offers a comprehensive analysis of the consultations performed in our hospital over the last five years, focusing on their frequency, content, the predominant medical departments involved, and the procedures most frequently implemented in consultation outcomes. These data will lead to the establishment of a framework for efficient collaboration between OMS and other medical disciplines.

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Several medical departments should consult OMS in certain situations. ENT clinics often refer patients with TMJ disorders and orofacial pain.⁹ Emergency departments often consult for facial trauma and infections.¹⁰ Oncology and haematology units should include OMS in cases at risk of osteonecrosis of the jaw (MRONJ).¹¹ These scenarios emphasise the interdisciplinary importance of OMS in comprehensive hospital care.

METHODS

Ethics

This study analyzed consultations made to the OMS clinic from various medical departments at Sultan 2. Abdülhamid Han Training and Research Hospital, University of Health Sciences, 2017–2023. The study was conducted in compliance with the Declaration of Helsinki and approved by the Hamidiye Scientific Researches Ethics Committee (Date: 14.03.2024, Decision No: 23/654).

Data Collection

Consultation data were obtained from the Nucleus patient database system (Monad software, Ankara, Türkiye), which contains patient referral form and electronic health records.

Inclusion Criteria

- Patients who received treatment at Sultan 2. Abdülhamid Han Hospital, University of Health Sciences, between 2017 and 2023.
- Patients who were referred to the OMS Clinic from other medical departments.
- Availability of consultation data recorded in the nucleus patient database system (Monad software, Ankara, Türkiye).

Exclusion Criteria

- Consultations referred from different branches within the field of dentistry.
- Consultations that were incomplete or incorrectly submitted.

Data Analysis

Simple percentage analysis methods were used for the remaining 503 consultations to calculate the proportion of each medical department within the total consultations. Data analysis was performed using Python programming language and Matplotlib library. The number of consultations from each department was summed and divided by the total number of consultations (Table 1). Primary complaints of patients coming from referred clinics were identified and separated (Table 2).

RESULTS

A total of 709 consultation records from departments other than dentistry were included in the study. However, 38 and 168 consultations from pediatric dentistry and general dentistry, respectively, were excluded.

The ENT department had the highest number of consultations with 315 cases, followed by the emergency department with 35 consultations and general surgery with 17 consultations.

Table 1. Number of consultations

Clinic	Number of consultations
Otolaryngology (ENT)	315
Emergency department	35
General surgery	17
Anesthesiology and reanimation	15
Internal medicine	14
Plastic and reconstructive surgery	13
Oncology	12
Infectious diseases	12
Cardiology	9
Orthopedy	7
Palliative care	6
Hematology	6
Dermatology	6
Thoracic surgery	5
Neurosurgery	5
Physical therapy and rehabilitation	4
Nephrology	3
Psychiatry	2
Cardiovascular surgery	2
Gastroenterology	2
Endocrinology	1
ENT: Ear nose throat	

Table 2. Primary reasons for consultations

Referring clinic	Primary reasons for consultations
Otolaryngology (ENT)	Temporomandibular joint pain and maxillary sinusitis complaints
Emergency department	Jaw fractures and dental abscesses
Oncology	Assessment of jaw osteonecrosis related to cancer treatments
Psychiatry	Persistent pain despite medication
Plastic surgery and palliative care	Alveolar fractures, infected cysts, and temporomandibular joint complaints
Orthopedics and neurology	Jaw fractures and temporomandibular joint pain following trauma
Cardiac surgery and cardiology	Evaluation for oral surgical procedures in patients on anticoagulant therapy
Hematology, pulmonology, infectious diseases, dermatology, internal medicine, neurosurgery, and anesthesiology	Various oral region lesions, infections, and preoperative evaluations
ENT: Ear nose throat	

Consultations were conducted regarding a range of clinical conditions and disease symptoms. Oncology patients are often evaluated for the risk of jaw osteonecrosis associated with cancer treatment. Psychiatry refers to patients with persistent pain complaints despite medication. Patients undergoing plastic surgery and palliative care sought consultations for conditions such as alveolar fractures, infected cysts, and TMJ disorders. Orthopedics and neurology consultations were requested for patients with jaw fractures and TMJ pain following trauma. ENT primarily evaluated patients presenting with TMJ pain and maxillary sinusitis. Cardiac

surgery and cardiology requested consultation for patients on anticoagulant therapy before oral surgical procedures. Other departments (hematology, pulmonology, infectious diseases, dermatology, internal medicine, neurosurgery, and anesthesiology) referred patients for various oral lesions, infections, and preoperative evaluations. The emergency department was the most frequent source of consultations for jaw fractures and abscesses.

According to the analysis results, the ENT department requested the highest number of consultations, predominantly for patients presenting with TMJ pain and maxillary sinusitis complaints. This represents the most prominent reason for consultation among all clinical conditions.

DISCUSSION

This study aimed to identify the medical specialties that most commonly refer patients to the OMS clinic, along with the rationale and frequency of these referrals. Our study is one of the few to examine the content and frequency of consultations, as indicated by data from recent literature.^{4,7}

The majority of patients referred to the OMS originating from the ENT department. ENT refers to patients with arthritis, otalgia, oral abscesses, undiagnosed oral cysts, or suspected neoplasms of the head and neck. Existing literature indicates that patients with otalgia, head and neck cancer, nasal or aural foreign bodies, and joint discomfort generally first consult or are referred to the ENT clinic.¹² A study conducted in Germany on the treatment and clinical progression of nondental orofacial pain revealed that clinicians referred patients to the ENT clinic in 59% of cases and to the OMS clinic in 54% of cases.⁹ A study in India that assessed the understanding of medical and dental practitioners concerning referrals to OMS produced analogous findings. This study indicated that dentistry students and dentists preferred sending patients with TMJ pain and disorders to the OMS clinic, while various medical departments favored the ENT clinic. Likewise, for problems associated with facial edema, abscesses, or disorders of the salivary glands, the ENT clinic was more frequently favored.¹ ENT and OMS are clinics that adopt a multidisciplinary approach. The lack of understanding regarding the abilities and treatment alternatives provided by OMS frequently leads to extended treatment duration for patients.⁵ Enhancing patient awareness will establish an optimal basis for multidisciplinary collaboration.

Most patients referred by the ENT clinic exhibit unexplained abscesses or swelling in the facial area, bone loss, and probable cancer concerns. The management of oral cancer requires a comprehensive strategy. The etiology and medical treatment are often addressed by working together with ENT and OMS clinics.² A study conducted in Australia reported that patients were referred to both ENT and OMS specialists in a mixed manner for the management of maxillofacial oncology and pathology. This overlap likely reflects the traditional approach in Australia, where head and neck oncology is primarily managed by ENT-led multidisciplinary teams. However, recent findings suggest that these teams are increasingly incorporating OMS specialists, indicating a growing awareness of their role in comprehensive oncologic care.¹³

Following the ENT clinic, the emergency department accounted for the majority of patient referrals to our clinic. Most of these patients were referred for urgent diagnosis and management of maxillofacial fractures. It is thought that the absence of a permanent plastic surgery unit in our hospital has increased the frequency of referral of trauma patients to our clinic. Keeping the airway open, ensuring that the patient is breathing properly, controlling bleeding, avoiding shock, and ensuring that no other serious traumas, including spinal cord injuries or internal organ damage, are the key goals of emergency clinic evaluations for trauma patients.¹⁰

Following the resolution of these principal issues, a thorough evaluation of the characteristics of oral and facial injuries should be performed. A comprehensive medical history encompassing the timing and mechanism of the injury, any prior injuries, and the patient's medical history must be obtained. Document complaints included pain, limited mobility, or dental sensitivity to temperature variations.¹⁴ Optimal treatment outcomes should be attained through the prompt involvement of a multidisciplinary trauma team. An experienced maxillofacial surgeon should be included in the team for optimal case management.¹⁵ Although the majority of patients who report to the ER with craniofacial trauma do not exhibit fractures, concussions frequently accompany trauma. This was based on data gathered from recent research in the field. The management of patients in emergency situations typically fails to consider this particular component. The delicate nature of the injury and the dependence on patient history for diagnosis are likely to blame this mistake. Furthermore, cognitive and clinical symptoms frequently improve over time patients are tested, which is another reason for the occurrence of oversight. It is recommended that patients in such circumstances be referred for OMS as well as neurosurgical services through the utilization of a multidisciplinary approach. Evaluation of probable fractures and dentoalveolar injuries should be performed by the OMS team. Additionally, consultation with a neurosurgeon is required to rule out brain damage and examine the possibility of traumatic brain injuries.¹⁶

Patients who present to the emergency clinic for the treatment of abscesses in the craniofacial region are another primary explanation for their presentations. Non-dental deep neck abscesses can be caused by a variety of factors, including, but not limited to, peritonsillar or retropharyngeal abscesses, sialadenitis, epiglottitis, cervical lymphadenitis, intravenous drug usage in the jugular vein, and trauma. In addition, iatrogenic causes, including infections of surgical wounds and subsequent infections that result from trauma-induced injuries, can also be a contributing factor.¹⁷ The head and neck region is significantly affected by multiple problems that can arise from these abscesses and have the potential to be life-threatening. Several problems are included in this category. In addition to being expandable across tissue planes, odontogenic (tooth-supported) and non-odontogenic abscesses have the potential to grow into deep areas of the neck and sternum.¹⁸ Evaluation of the airway is the major reason for consultation with an ENT performed in the emergency room. Nevertheless, in many instances, substantial thoracotomy

and lateral/anterior cervicotomy are required to drain all purulent contents. A multidisciplinary strategy that includes an ENT surgeon, maxillofacial surgeon, thoracic surgeon, and infectious disease specialist is believed to be the most effective method for treating the complicated consequences of head and neck pathology.¹⁹ The reason why abscess patients with dental origin are referred to our clinic is that patients who apply to the emergency room due to abscesses and infections in the maxillofacial region that are not of dental origin are referred to the ENT clinic more frequently. In the management of infections in the maxillofacial region, we often work together with the ENT clinic.

Associated with medication osteonecrosis of the jaw, also known as MRONJ, is a disorder that is traditionally considered uncommon; nonetheless, it is frequently seen in OMS units. Despite this, it is difficult to collect precise data regarding the incidence (and more importantly, the prevalence). Generally, it is anticipated that the risk of MRONJ affects less than one percent of individuals who are at risk. This risk is affected by a number of factors, such as the reason for drug use, the type of medicine, the amount of dental-alveolar surgery performed, and the existence of comorbidities in the patient.⁶ Bisphosphonates and anti-angiogenic pharmaceuticals are used by a significant number of patients in cancer, physical therapy, and orthopedic clinics. These medications can expose patients to the risk of developing MRONJ. Both inadequate appraisal of the stages of the disease and insufficient recognition of the MRONJ criteria in clinical practice are factors that contribute to the advancement of the disease. A study conducted in the United Kingdom found that just seven percent of patients were referred to a maxillofacial surgery clinic when they were in the second stage of MRONJ.¹¹ For the early diagnosis and treatment of patients taking drugs that are associated with an increased risk of MRONJ, it is essential to establish a multidisciplinary treatment approach that involves the maxillofacial surgery clinic.²⁰ The majority of patients who were referred to our clinic from these departments were brought here because of oral wounds that were not healing, osteomyelitis, jaw pain, or necrosis. This situation shows that there is not enough sensitivity in the community and among clinics about the risk of MRONJ.

CONCLUSION

Most referrals to the OMS clinic came from the ENT and emergency departments, mainly for TMJ disorders, sinus pathologies, trauma, and MRONJ. These findings underline the need for greater awareness of OMS services and stronger interdisciplinary collaboration to improve patient care.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approved by the Hamidiye Scientific Researches Ethics Committee (Date: 14.03.2024, Decision No: 23/654).

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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Monocyte-to-HDL ratio as an inflammatory marker: does it reflect blood pressure patterns?

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Cite this article as: Astan R, Dayanan R. Monocyte-to-HDL ratio as an inflammatory marker: does it reflect blood pressure patterns? *J Med Palliat Care*. 2025;6(4):323-327.

Received: 14.06.2025

Accepted: 06.07.2025

Published: 31.08.2025

ABSTRACT

Aims: The monocyte-to-high-density lipoprotein cholesterol ratio (MHR) has emerged as a novel inflammatory marker associated with cardiovascular risk. Both hypertension (HT) and non-dipping blood pressure patterns are known to contribute to increased cardiovascular morbidity and mortality. However, the potential association between MHR and circadian blood pressure variations remains unclear. To investigate the relationship between MHR and dipper pattern status, as assessed by 24-hour ambulatory blood pressure monitoring (ABPM), in individuals with and without HT.

Methods: A total of 160 adults (mean age 52.7 ± 12.1 years; 41.9% male) who underwent ABPM were included in the study. Participants were divided into four subgroups based on their hypertensive status and dipping pattern: normotensive dipper, normotensive non-dipper, hypertensive dipper, and hypertensive non-dipper. MHR values were compared among these groups. Due to the non-normal distribution of MHR, statistical analyses were performed using non-parametric methods.

Results: No statistically significant difference in MHR was observed between hypertensive and normotensive participants ($p=0.319$) or among the four subgroups ($p=0.436$). Similarly, there was no significant association between MHR and the dipper pattern across all participants ($p=0.714$).

Conclusion: MHR does not appear to be associated with hypertensive status or circadian blood pressure variation patterns. Further studies with larger cohorts and longitudinal designs are needed to clarify the potential role of MHR in blood pressure physiology.

Keywords: Monocyte to HDL cholesterol ratio, ambulatory blood pressure monitoring, hypertension, dipper pattern, non-dipper pattern

INTRODUCTION

Hypertension (HT) is one of the leading causes of cardiovascular morbidity and mortality worldwide.¹ Twenty-four-hour ambulatory blood pressure monitoring (ABPM), which takes into account the circadian rhythm of blood pressure, provides more precise information compared to conventional office measurements.^{2,3} A physiological nocturnal decline in blood pressure of approximately 10–20% is expected, a pattern known as the dipper pattern, which is considered to play a protective role against cardiovascular diseases.^{4,5} In contrast, insufficient nocturnal blood pressure reduction referred to as the non-dipper pattern is considered an independent risk factor for predicting cardiovascular events.^{4,6,7}

In recent years, the role of inflammation in the pathophysiology of HT has been increasingly investigated.^{8–10} Monocytes are immune cells that contribute to chronic inflammation, whereas HDL cholesterol has anti-inflammatory and antioxidant properties that provide protection against atherosclerosis.^{11,12}

The ratio of these two parameters, known as the monocyte-to-HDL cholesterol ratio (MHR), has been proposed as a novel biomarker of systemic inflammation, and its prognostic value has been explored in various cardio-metabolic conditions such as HT, coronary artery disease, stroke, and obstructive sleep apnea.^{13–19}

However, the relationship between MHR and HT subtypes (dipper vs. non-dipper) remains unclear in the current literature. This study aimed to investigate the distribution of MHR in hypertensive and normotensive individuals, as well as its association with dipper and non-dipper blood pressure patterns.

METHODS

Ethics

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Scientific Researches Ethics Committee of

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Batman Training and Research Hospital (Date: 21.06.2023, Decision No: 352). As this was a retrospective study utilizing anonymized patient data collected during routine clinical care, the requirement for informed consent was waived by the ethics committee.

Study Design and Participants

This retrospective cross-sectional study was conducted on 160 individuals aged 18 years and older who underwent 24-hour ABPM due to suspected HT. Based on antihypertensive medication use and medical history, participants were classified into two groups: hypertensive and normotensive. Furthermore, both hypertensive and normotensive individuals were subdivided into four groups according to whether their systolic blood pressure decreased by $\geq 10\%$ during sleep, resulting in dipper and non-dipper classifications.

Individuals were excluded from the study if they had secondary HT, a known history of cardiovascular disease (such as coronary artery disease, heart failure, or stroke), a diagnosis of diabetes mellitus or an HbA1c level of $\geq 6.5\%$, chronic kidney disease with an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m², active infection or systemic inflammatory disease, a history of malignancy or autoimmune disorders, were using anti-inflammatory, lipid-lowering, or immunosuppressive medications, or if their ABPM or laboratory data were incomplete.

Data Collection

Demographic data, body-mass index (BMI), biochemical parameters (total cholesterol, LDL, triglycerides, ALT, glomerular filtration rate, etc.), and complete blood count results of the participants were obtained from the electronic medical record system. MHR was calculated by dividing the peripheral blood monocyte count by the HDL cholesterol level.

Ambulatory Blood Pressure Measurements

Blood pressure measurements were obtained using a 24-hour ABPM device (Rozinn RZ250 ABP recorder, SN R 02157/0807, Glendale, NY, USA) in accordance with standard protocols. Mean daytime and nighttime values were recorded, and participants were classified as dipper or non-dipper based on these measurements.^{3,5}

Statistical Analysis

The data analysis was performed with SPSS Statistics (IBM Corporation, Somers, NY software, version 22). The normality of the distribution of continuous variables was determined using the Kolmogorov-Smirnov test. The continuous variables were expressed as mean and standard deviation or as median and interquartile range, depending on the normality of their distribution. Categorical variables are interpreted by frequency tables. Categorical variables were described as frequencies and percentages. Categorical features and relationships between groups were assessed using an appropriate Chi-square test. Variables that were not normally distributed were compared using the Kruskal-Wallis test. When binary comparisons were required, Mann-Whitney U test was used. The statistically significant two tailed p-value was considered as <0.05 .

RESULTS

A total of 160 participants (67 males [41.9%] and 93 females [58.1%]) who underwent 24-hour ABPM were included in the study. The mean age was 52.7 ± 12.1 years. Based on ABPM results, 55 individuals (34.4%) exhibited a dipper blood pressure pattern (22 normotensive, 33 hypertensive), while 105 individuals (65.6%) demonstrated a non-dipper pattern (31 normotensive, 74 hypertensive).

The baseline clinical and biochemical characteristics of the study population are summarized in [Table 1](#). The median MHR for all participants was 11.45 (IQR: 8.2–16.0).

Table 1. Baseline characteristics of patients

Variables*	Results (n=160)
Sex-male (%)	67 (41.9)
Age, years	52.7±12.1
Body-mass index, kg/m ²	27.1 (25.8-27.8)
Glomerular filtration rate, ml/min	98.0 (86-110)
Alanine transaminase, IU/L	18 (14-26)
White blood cell count, 10 ³ /mm ³	7.7 (6.8-9.0)
Absolute neutrophil count, 10 ³ /mm ³	4.5 (3.7-5.4)
Absolute lymphocyte count, 10 ³ /mm ³	2.4 (1.9-2.8)
Total cholesterol, mg/dl	183.8±33.1
Low-density lipoprotein, mg/dl	106.8±28.1
Triglyceride, mg/dl	154 (103-195)
Monocyte-HDL ratio	11.45 (8.2-16.0)
Hypertension, yes, n (%)	85 (78.6)
Systolic BP, mmHg	
Awake	129.2±14.8
Asleep	121.1±16.0
24h	127.3±14.4
Diastolic BP, mmHg	
Awake	82.2±11.2
Asleep	75.2±11.4
24h	80.6±10.8
Sleep time relative BP decline, mmHg	
Systolic	8.1±9.9
Diastolic	7.0±8.5

*Continuous variables were expressed as means±standard deviation, or medians (interquartile ranges) and categorical variables as numbers with percentages for the description of baseline characteristics. HDL: High-density lipoprotein, BP: Blood pressure

Participants were first categorized based on the presence or absence of HT. The median MHR was not significantly different between hypertensive and normotensive individuals ($p=0.319$).

To evaluate whether circadian blood pressure variation was associated with MHR, all participants were further stratified into four subgroups:

- Normotensive dipper (n=22)
- Normotensive non-dipper (n=31)
- Hypertensive dipper (n=32)
- Hypertensive non-dipper (n=53)

The results of the monocyte/HDL ratio according to the blood pressure and dipper pattern of the patients are shown in [Table 2](#).

Table 2. The results of the monocyte/HDL ratio according to the blood pressure and dipper pattern of the patients

	Normotensive* (n=53)		Hypertensive* (n=85)		p value
	Dipper (n=22)	Non-dipper (n=31)	Dipper (n=32)	Non-dipper (n=53)	
Monocyte-HDL ratio	9.2 (7.9-12.9)	10.5 (8.1-14.6)	12.1 (7.4-17.2)	11.9 (8.2-17.0)	0.436

*Median (interquartile range), HDL: High-density lipoprotein

There was no statistically significant difference in MHR among these four subgroups ($p=0.436$). Median (IQR) MHR values were as follows:

- Normotensive dipper: 9.2 (7.9–12.9)
- Normotensive non-dipper: 10.5 (8.1–14.6)
- Hypertensive dipper: 12.1 (7.4–17.2)
- Hypertensive non-dipper: 11.9 (8.2–17.0)

Among hypertensive individuals, MHR did not differ significantly between dipper and non-dipper subgroups ($p=0.845$). Similarly, in the normotensive group, no significant difference in MHR was found between dipper and non-dipper participants ($p=0.432$).

When participants were grouped solely by dipping status regardless of hypertensive status, MHR was again not significantly different between dipper and non-dipper individuals ($p=0.714$). These findings are illustrated in [Figure 1, 2](#).

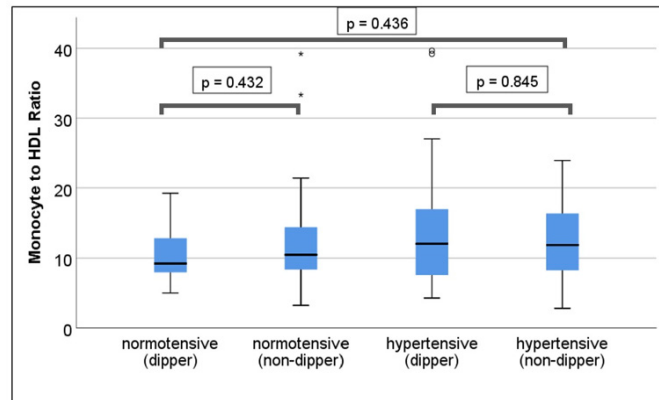


Figure 1. Comparison of the results of the monocyte/HDL ratio according to the blood pressure and dipper pattern of the patients
HDL: High-density lipoprotein

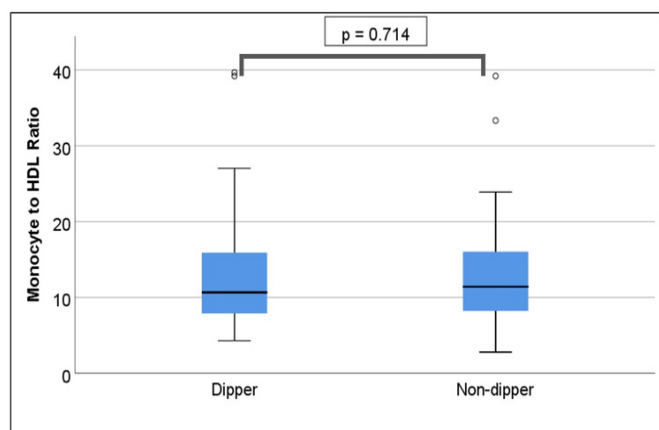


Figure 2. Comparison of monocyte/HDL ratio results according to dipper pattern of all participants
HDL: High-density lipoprotein

DISCUSSION

In this study, we evaluated the relationship between the MHR and circadian BP patterns in a cohort of normotensive and hypertensive individuals assessed via 24-hour ABPM. Contrary to expectations based on the known pro-inflammatory milieu associated with HT and its sub-types, our findings indicate that MHR is not significantly associated with hypertensive status or with dipper/non-dipper BP patterns.

The pathophysiological link between inflammation and HT is well established, and this relationship has been supported by several recent studies. Furthermore, a number of studies have revealed that, patients with NDHT have higher levels of inflammatory markers compared with those with DHT.^{20,21} Monocytes playing a crucial role in vascular endothelial dysfunction, atherosclerotic progression, and BP regulation through cytokine production and reactive oxygen species.^{9,22} Conversely, HDL possesses anti-inflammatory, antioxidant, and vasodilatory properties.^{11,23} As a result, MHR has been proposed as a composite index reflecting the balance between pro- and anti-inflammatory forces and has shown promise as a prognostic marker in cardiovascular disease, heart failure, and stroke.^{8,14,15,18,19,24–27}

However, the lack of a significant association between MHR and circadian BP patterns in our study may be attributed to several factors. First, although inflammation plays a role in the pathogenesis of HT, not all sub-types of HT particularly those characterized solely by altered circadian rhythm (i.e., non-dipping status) may share the same inflammatory burden. Additionally, previous studies linking MHR to cardiovascular risk have typically focused on populations with overt disease (e.g., coronary artery disease, diabetes mellitus, or chronic kidney disease), in which inflammatory markers are generally more pronounced.^{8,14,15,18,27}

One of the strengths of this study is the use of 24-hour ABPM, which provides superior diagnostic and prognostic insights compared to clinic-based BP measurements by capturing nocturnal BP patterns and overall BP variability.²⁸ Furthermore, the exclusion of patients with confounding systemic inflammatory or metabolic conditions (e.g., diabetes, secondary HT, cardiovascular disease) ensured a relatively "clean" population for exploring subtle associations.

However, the study is not without limitations. First, its cross-sectional design precludes causal inference and may overlook temporal relationships between inflammatory status and BP alterations. Second, although the sample size is reasonable, it may still be underpowered to detect intra group differences, particularly when stratifying participants into four subgroups. Third, MHR is a static marker derived from a

single blood sample; longitudinal measurements or additional inflammatory biomarkers (e.g., CRP, IL-6, TNF- α) could have provided a more nuanced picture of systemic inflammation. Another limitation is the potential influence of unmeasured confounders such as sleep quality or physical activity levels.

Although MHR is a practical and cost-effective inflammatory marker, our findings suggest its limited utility in classifying hypertensive patients based on circadian BP profiles. Nonetheless, its prognostic value in other contexts such as cardiovascular event prediction or metabolic syndrome assessment remains well supported.^{14,18,25} Future studies should employ prospective longitudinal designs with larger cohorts and include a broader panel of inflammatory and oxidative stress biomarkers. Incorporating imaging-based assessments of subclinical atherosclerosis or endothelial dysfunction (e.g., carotid intima media thickness, flow-mediated dilation) may also help contextualize MHR in relation to target organ damage.

Finally, in light of the growing interest in personalized medicine, stratifying patients not only by hypertensive phenotype but also by inflammatory endo-type may inform more tailored therapeutic strategies in the future.

CONCLUSION

In this study, we investigated the relationship between the MHR and circadian blood pressure patterns among normotensive and hypertensive individuals assessed via 24-hour ABPM. Our findings indicate that MHR does not differ significantly based on hypertensive status or dipper/non-dipper blood pressure profiles. These results suggest that MHR, although a recognized marker of systemic inflammation and cardiovascular risk in other contexts, may have limited value in differentiating individuals based on their blood pressure dipping patterns.

Given the established role of inflammation in the pathophysiology of HT and cardiovascular disease, further longitudinal studies with larger cohorts and more comprehensive inflammatory profiling are warranted to fully elucidate the potential role of MHR in blood pressure regulation and its utility in cardiovascular risk stratification.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval was obtained from the Scientific Researches Ethics Committee of Batman Training and Research Hospital (Date: 21.06.2023, Decision No: 352).

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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Bone-modifying agents and survival in patients treated with immune checkpoint inhibitors

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Cite this article as: Baş O, Güner İ, Tokatlı M, et al. Bone-modifying agents and survival in patients treated with immune checkpoint inhibitors. *J Med Palliat Care*. 2025;6(4):328-331.

Received: 04.03.2025

Accepted: 07.07.2025

Published: 31.08.2025

ABSTRACT

Aims: Management of bone metastasis is crucial for cancer patients. The objective of this study was to assess the correlation between survival outcomes and bone-modifying agents (BMAs) in patients treated with immune checkpoint inhibitors (ICIs).

Methods: This study was conducted in individuals who received at least 3 doses of ICIs between January 2018 and December 2023 and had bone metastases at initiation of ICIs. We retrospectively collected data on each patient from their medical records, including information on cancer, the specific immunotherapy treatment, and the BMAs they were receiving.

Results: 142 patients were included. The median follow-up was 36 [interquartile range (IQR)=18-50] months and the median follow-up from the initiation of BMAs to the last control was 14 months (IQR=5-29). After adjustment for age, gender, Eastern Cooperative Oncology Group (ECOG) score and number of prior treatment lines in the multivariate analyses, patients who did not use BMAs had decreased overall survival (OS) (HR: 2.30, 95%CI: 1.03-2.45; p=0.036). In addition, BMAs use was associated with long-term benefit defined as having a survival of equal to or longer than 24 months (HR: 2.85, 95%CI 1.13-7.21; p=0.027).

Conclusion: It was found that using BMAs could be an independent predictor of OS in patients treated with ICI and who had bone metastasis. This finding may lead clinicians to start BMAs as soon as possible after bone metastases are detected.

Keywords: Immune checkpoint inhibitors, denosumab, zoledronic acid, survival, long-term benefit

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have become a crucial part of cancer treatment and have shown efficacy in several types of tumors, including renal cell carcinoma (RCC),¹ melanoma,² non-small cell lung cancer (NSCLC),³ head and neck squamous cell carcinoma (HNSCC),⁴ and urothelial cancer.⁵ Nivolumab, pembrolizumab, and atezolizumab have significantly improved cancer treatment outcomes,⁶ whether administered as monotherapy or combined with other chemotherapies or bone-modifying agents (BMAs) such as zoledronic acid or denosumab.⁷

Bone metastases and skeletal-related events (SREs) are important problems in cancer patients.^{8,9} SREs have physical effects such as reduced mobility and weakness; emotional effects such as fear of fracture and disability; and social effects that limit patients' relationships and daily activities. All of this demonstrates that there is a strong relationship between SREs and patients' quality of life (QoL). In addition, SREs are even associated with mortality.^{10,11} In prostate cancer, the relationship between QoL and SREs is very well defined in

patients treated with hormonal agents and/or chemotherapy.¹² Similar to prostate cancer, the importance of SREs for patients with breast cancer has been demonstrated.¹³

The relationship between the use of BMA and survival in patients treated with ICIs is not very well defined. Therefore, this study aimed to demonstrate a relationship between using BMAs and survival in patients treated with ICIs.

METHODS

Ethics

We conducted a retrospective study of patients with advanced cancer who received at least 3 doses of ICI in Hacettepe University Oncology Hospital between January 2018 and December 2023. Among them, patients with bone metastasis were included. The protocol was approved by the Hacettepe University Health Sciences Researches Ethics Committee (Date: 05.03.2024, Decision No: 2024/05-21 SBA 24/332). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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Data Collection

We retrospectively collected comprehensive data on each patient from their medical records, including information on their age, gender, medical history, other health conditions they had, type of cancer, the specific immunotherapy treatment they were receiving, and Eastern Cooperative Oncology Group (ECOG) score. This information was collected before any immunotherapy treatment was administered.

Statistical Analysis

The data analyses were performed using the SPSS Version 23. All data are expressed as either median (IQR) for continuous variables or the number of patients (percentage) for categorical variables. Groups were compared using the chi-square test for categorical variables and Mann-Whitney U test or Kruskal-Wallis test for quantitative variables. The overall survival (OS) time was defined as the period from treatment initiation to the last follow-up and/or death. Progression-free survival (PFS) time was defined as the period between treatment initiation and disease progression and/or death. Survival analyses were conducted using Kaplan-Meier analyses, and comparisons of survival times between prognostic subgroups were done using the log-rank test. The significant predictors of OS were evaluated by multivariate analysis using Cox's proportional hazards model. Multivariable logistic regression analyses were performed to determine clinically relevant factors associated with long-term benefit. Variables showing associations at a significance level of $\alpha=0.25$ in univariable analysis were selected for inclusion in the multivariable model. Covariates were also selected according to the results of previous research. A type-1 error level of $<5\%$ was used to infer statistical significance.

RESULTS

Baseline Characteristics

142 patients were included in this study. Demographic and clinicopathologic factors are presented in [Table 1](#). Median age was 60 [interquartile range (IQR) = 50-67] years, 79 (55.6%) patients were men. NSCLC (26.1%), malign melanoma (19%), and RCC (15.5%) were the most common diagnoses. 110 (77.5%) patients received ICIs as a second or later line treatment.

Association of BMAs with Patient Outcomes

The median follow-up was 36 (IQR=18-50) months and the median follow-up of the initiation of BMA to the last control was 14 months (IQR=5-29). The time from diagnosis of bone metastasis to initiation of BMAs was 14 weeks (IQR=1-29). After adjustment for age, gender, ECOG score, and number of prior lines in the multivariate analyses, patients who did not use BMAs had decreased OS (HR: 2.30, 95% CI: 1.03-2.45; $p=0.036$) ([Table 2, Figure](#)). Moreover, BMAs use was associated with long-term benefit, which is defined as having a survival of equal to or longer than 24 months after ICI initiation (HR: 2.85, 95%CI 1.13-7.21; $p=0.027$) ([Table 3](#)).

DISCUSSION

This study showed an important relationship between using BMAs and survival in patients treated with ICIs. It is demonstrated that BMA use was an independent indicator

Table 1. Baseline characteristics of patients with bone metastasis (n=142)

Characteristic	
Median age (IQR)	60 (IQR=50-67)
Gender	
Male	79 (55.6%)
Female	63 (44.4%)
ECOG	
0-1	84 (59.2%)
≥ 2	50 (35.2%)
Not reported	8 (5.6%)
Median ICI doses (IQR)	8 (IQR=5-15)
Diagnosis	
NSCLC	37 (26.1%)
Malign melanoma	27 (19.0%)
Renal cell carcinoma	22 (15.5%)
Breast cancer	10 (7.0%)
Head and neck cancer	11 (7.7%)
Others*	35 (24.7%)
Number of prior lines	
0	32 (22.5%)
1	54 (38.0%)
≥ 2	56 (39.4%)
Types of ICIs	
Nivolumab	114 (80.2%)
Pembrolizumab	11 (7.7%)
Atezolizumab	15 (10.6%)
Nivolumab+Ipilimumab	2 (1.4%)
Type of bone-modifying agent	
Zoledronic acid	54 (38.0%)
Denosumab	6 (4.2%)
None	82 (57.7%)
Median BMA doses (IQR)	8 (3-16)

IQR: Interquartile range, ECOG: Eastern Cooperative Oncology Group, ICI: Immune checkpoint inhibitor, NSCLC: Non-small cell lung cancer, BMA: Bone modifying agent, *Thyroid cancer, thymic carcinoma, small cell lung cancer, sarcoma, pancreas cancer, gastric cancer, mesothelioma, bladder cancer, endometrium cancer

Table 2. Cox-regression analysis of covariates associated with overall survival

	Overall survival	
	Univariate analysis p value	Multivariate analysis p value (HR, 95 %CI)
Gender		
Male	0.001	<0.001
Female		(HR=2.34 95% CI 1.5-3.66)
Age (years)	0.001	<0.001
		(HR=1.03 95% CI 1.01-1.04)
Bone-modifying agent		
Yes	0.016	0.036
No		(HR: 1.60 95% CI 1.03-2.45)
ECOG score		
0-1	0.028	<0.001
≥ 2		(HR:2.30 95% CI:1.46-3.62)
Number of prior lines		
0	0.551	(-)
1		
≥ 2		

ECOG: Eastern Cooperative Oncology Group

of better OS when adjusted for age, gender, ECOG score, and number of prior treatment lines. Also, there was an association between using BMAs and long-term benefit from ICIs.

The presence of bone metastases can form an immunosuppressive microenvironment, which may decrease the response to ICIs.¹⁴ BMAs such as zoledronic acid and denosumab are mainly used to treat patients with bone metastasis by inhibiting osteoclast-mediated bone resorption,

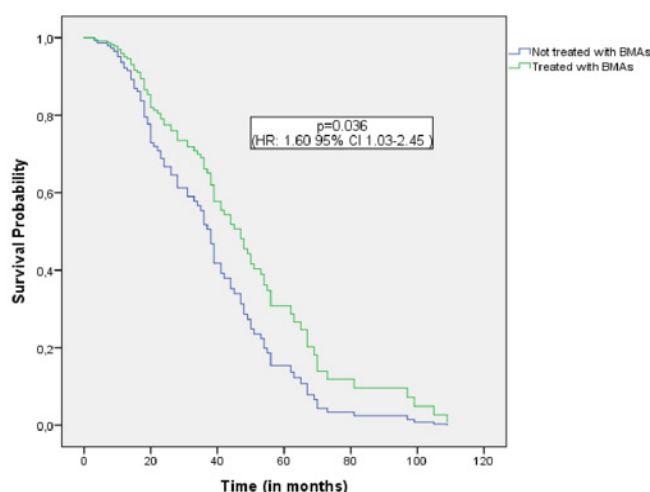


Figure. Cox regression analysis curve of patients treated with ICIs. Patients who received BMAs had a statistically significant better overall survival than patients who did not receive BMA: Bone modifying agent

Table 3. Logistic regression analysis of covariates associated with the development of long-term benefit

	Long-term benefit	
	Univariate analysis p value	Multivariate analysis p value
Gender		
Male		
Female	0.300	(-)
Age (years)	<0.001	<0.001
Bone-modifying agent		
Yes		
No	0.017	0.027
ECOG score		
0-1		
≥2	0.001	0.003
Number of prior lines		
0		
1		
≥2	0.50	(-)

ECOG: Eastern Cooperative Oncology Group

which helps correct the immunosuppression. Moreover, BMAs may have an antitumor effect itself against cancer cells.¹⁵⁻¹⁷ As demonstrated by Zheng et al.¹⁸ and Sun et al.,¹⁹ patients diagnosed with NSCLC who had bone metastasis treated with ICIs and zoledronic acid exhibited superior outcomes in comparison to those treated with ICIs only. In a parallel study, Tamiya et al.²⁰ demonstrated that BMAs may have a positive clinical impact on patients with bone metastasis, particularly those diagnosed with gastrointestinal cancer and NSCLC. All this information supports our findings that BMAs may improve survival outcomes in all cancer patients treated with ICIs.

Studies have shown that BMAs+ICIs in the treatment of HCC can improve QoL and PFS.²¹ The synergistic effect of BMAs+ICIs has been demonstrated in NSCLC and melanoma.²² Similarly, Levee et al.²³ demonstrated the potential for a synergistic anti-tumour effect to be achieved by the addition of BMAs to pembrolizumab in patients diagnosed with breast cancer. A trial conducted in Italy demonstrated

that the combination of ICIs and BMAs (zoledronic acid or denosumab) results in superior survival outcomes when compared with the use of ICIs alone.²⁴ The use of BMAs+ICIs in other cancers is not well understood. In our study, we included all types of solid cancers. Nevertheless, the number of patients is limited, and the presentation of certain cancer types is ineffective. Therefore, further randomized controlled trials are needed to define the relationship between BMAs and survival outcomes.

ICIs are now approved as first-line treatment either alone or in combination with chemotherapy or even another immunotherapy. However, in most low-middle income countries (LMICs), ICIs are not available as first-line treatment for most cancers, such as lung cancer, melanoma, and RCC. In our study, only 22.5% of patients received ICIs as a first-line treatment. While this seems to be a confounding factor for survival outcomes, our results represent real life, which is valuable for LMICs. However, this issue limits the applicability of our results to countries with access to immunotherapy in the earlier lines. Also in our study, denosumab was underrepresented, which may be a confounding factor. However, a meta-analysis involving more than 7,000 patients demonstrated that, while denosumab was associated with superior QoL, there was no difference in OS.²⁵

Limitations

Our study has several limitations. Our study is retrospective, single-center, and the number of patients is relatively small. Our patient population included different cancers and different immunotherapies. Therefore, the results should be interpreted with caution. Despite these limitations, we have shown that the use of BMAs is important for improving survival outcomes. In addition, there is an association between the long-term benefit of ICIs and BMAs.

CONCLUSION

As a result, we have demonstrated that there is a significant association between the use of BMAs and survival in ICI-treated patients with bone metastases. This finding may lead clinicians to start BMAs as soon as possible after bone metastases are detected. Randomized controlled trials are necessary to demonstrate the association between BMAs and survival outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval

The protocol was approved by the Hacettepe University Health Sciences Researches Ethics Committee (Date: 05.03.2024, Decision No: 2024/05-21 SBA 24/332).

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.

Acknowledgement

The authors would like to thank all of the study participants, physicians, and nurses for their assistance with the study data collection.

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Assessment of vaccination rates and attitudes toward pneumococcal, influenza, and COVID-19 vaccines among asthmatic patients and adults aged 65 years and older without asthma

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Cite this article as: Özsoy M, Bilgin G, Arslan İ, Altaş Baştuğ Ö, Cesur S. Assessment of vaccination rates and attitudes toward pneumococcal, influenza, and COVID-19 vaccines among asthmatic patients and adults aged 65 years and older without asthma. *J Med Palliat Care*. 2025;6(4):332-338.

Received: 12.05.2025

Accepted: 09.07.2025

Published: 31.08.2025

ABSTRACT

Aims: The aim of this study is to evaluate the vaccination rates and attitudes toward pneumococcal, influenza, and COVID-19 vaccines in asthmatic patients and individuals aged 65 years and older without asthma.

Methods: The study was planned as a prospective observational study between September 15, 2023, and November 15, 2023. The study included a total of 220 outpatient patients, comprising asthma-diagnosed patients who visited the Pulmonology and Family Medicine outpatient clinics at Ankara Training and Research Hospital, Health Sciences University, and 65-year-old adults without asthma. An informed consent form was completed by asthma patients and individuals aged 65 years and older without asthma who agreed to participate in the study. A questionnaire consisting of 15 questions was administered to these participants. A p-value of ≤ 0.05 was considered statistically significant.

Results: Of the asthma patients who participated in the study, 75 (59.1%) were female and 35 (37.6%) were male. The mean age of the asthma patients was 48.93 ± 11.03 . Of the outpatient patients aged 65 years and older without asthma who participated in the study, 52 (40.9%) were female and 58 (62.4%) were male. The mean age was 72.08 ± 4.97 . Patients aged 65 years and older with asthma were excluded from the study. The average age of the 65-year-old and older outpatient patients without asthma who participated in the survey was statistically significantly higher than that of the asthma patient group. The influenza vaccination rate among asthma patients who participated in the survey was 30.3%, the pneumococcal vaccination rate was 27.4%, and the rate of COVID-19 vaccination was 83.6%. Among the 65-year-old and older outpatient patients without asthma who participated in the survey, the influenza vaccination rate was 69.7%, the pneumococcal vaccination rate was 72.6%, and the COVID-19 vaccination rate was 99%. There was a statistically significant difference between asthmatic patients and outpatient patients aged 65 years and older in terms of influenza and pneumococcal vaccination rates.

Conclusion: Vaccination rates for influenza and pneumococcal vaccines were found to be very low among asthmatic patients and outpatients over the age of 65 without asthma, while COVID-19 vaccination rates were found to be high in both groups. We believe that providing adequate information to family physicians and other healthcare providers who examine asthma patients and individuals aged 65 and older about the benefits and potential side effects of influenza vaccines, as well as publishing news articles in the media highlighting the importance of vaccination for high-risk individuals, could help increase vaccination rates.

Keywords: Asthma, pneumococcal vaccine, influenza vaccine, COVID vaccine, attitude toward vaccines

INTRODUCTION

The most effective, cheapest, and easiest way to prevent infectious diseases is to get vaccinated against the microorganisms that cause them.¹ Influenza, pneumococcal, and COVID-19 infections are major causes of mortality and morbidity in asthmatic patients and individuals aged 65 and older, and vaccination is available to protect against all three of these pathogens.

Asthmatic patients and individuals aged 65 years and older without asthma are at risk for influenza, pneumococcal, and COVID-19 infections, and these three infectious diseases are significant causes of mortality and morbidity in these patients.²⁻⁶ Influenza, pneumococcal, and COVID-19 infections are among the causes of pneumonia in asthmatic patients and individuals aged 65 and older, and vaccination

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provides protection against these infectious agents. To date, no serious side effects have been reported with influenza and pneumococcal vaccines.⁷⁻¹⁰ However, rare serious side effects such as cardiovascular complications, thrombosis, and thrombocytopenia have been reported with COVID-19 vaccines.¹²

Influenza and pneumococcal infections are important causes of mortality and morbidity in asthma patients and elderly patients.¹³

The main risk factors that increase the development of infection and mortality in the COVID-19 outbreak are advanced age, especially concomitant hypertension, cardiovascular disease, diabetes mellitus, chronic lung disease, malignancies, especially hematologic, immunosuppressive treatment or disease, organ transplantation, chronic renal failure, obesity and smoking.¹⁴

The aim of this study was to determine the rates of pneumococcal, influenza and COVID-19 vaccination, attitudes towards vaccination and the factors affecting their attitudes in asthmatic patients and individuals over 65 years of age, who are in the risk group for pneumococcal, influenza and COVID-19 infections and all three infections can result in mortality and morbidity.

METHODS

For the study, ethical approval was obtained from the Ethics Committee of the Health Sciences University, Ankara Training and Research Hospital, Clinical Researches Ethics Committee (Date: 10.08.2023, Decision No: 1322), and informed consent forms were obtained from the patients. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was planned as a prospective observational study between September 15, 2023, and November 30, 2023. The study included a total of 220 outpatient patients, comprising asthma patients diagnosed at the Department of Pulmonology and Family Medicine outpatient clinics of Ankara Training and Research Hospital, Health Sciences University, and 65-year-old adults without asthma. An informed consent form was completed by asthma patients, and a 15-question questionnaire was administered to individuals aged 65 years and older without asthma who agreed to participate in the study. The questionnaire form has been attached to the document ([Supplementary Table 1](#))

Asthma patients aged 18 years and older and under 65 years were included in the study, while outpatient clinic patients without asthma aged 65 years and older and under 90 years were also included.

Statistical Analysis

All data analysis was performed using IBM SPSS 25.0 software. Numerical parameters were tested for normality using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Numerical parameters were presented as mean and standard deviation, while categorical parameters were reported as frequency and percentage. For the comparison of numerical parameters between the two groups, Student's t-test or one-way ANOVA

tests were used for those following a normal distribution, and Mann-Whitney U or Kruskal-Wallis tests were used for those not following a normal distribution. The chi-square test was used for the comparison of categorical parameters. A p-value of <0.05 was considered statistically significant.

RESULTS

Of the asthma patients who participated in the study, 75 (59.1%) were female and 35 (37.6%) were male. The mean age of the asthma patients was 48.93 ± 11.03 . Of the outpatient patients aged 65 years and older without asthma who participated in the study, 52 (40.9%) were female and 58 (62.4%) were male. The mean age was 72.08 ± 4.97 . Patients aged 65 years and older with asthma were excluded from the study ([Table 1](#)).

The average age of the 65-year-old and older outpatient patients without asthma who participated in the survey was statistically significantly higher than that of the asthma patient group ($p < 0.001$).

The influenza vaccination rate among asthma patients who participated in the survey was 30.3% ($n=23$), and the pneumococcal vaccination rate was 27.4% ($n=17$). and the rate of COVID-19 vaccination was 83.6% ($n=92$). Among the 65-year-old and older outpatient patients without asthma who participated in the survey, the influenza vaccination rate was 69.7% ($n=53$), the pneumococcal vaccination rate was 72.6% ($n=45$), and the COVID-19 vaccination rate was 99% ($n=98$). There was a statistically significant difference in influenza and pneumococcal vaccination rates between asthmatic patients and outpatient patients aged 65 years and older ($p < 0.001$). Influenza and pneumococcal vaccination rates were higher in outpatient patients aged 65 years and older without asthma than in asthmatic patients. There was no statistically significant difference in COVID-19 vaccination rates ($p: 0.089$).

The most common reasons for asthmatic patients not getting the influenza vaccine were, in order of frequency, perceiving the vaccine as ineffective ($n=36$) and fear of side effects ($n=30$). The reasons for not getting the influenza vaccine among individuals aged 65 and older without asthma were, in order of frequency, believing the vaccine is ineffective ($n=30$) and fear of side effects ($n=17$). The reasons for not getting the pneumococcal vaccine among asthmatic patients were, in order of frequency, believing the vaccine is ineffective ($n=36$) and fear of side effects ($n=32$). The reasons for not getting the pneumococcal vaccine among individuals aged 65 and older without asthma were, in order of frequency, believing the vaccine to be ineffective ($n=30$) and fear of side effects ($n=20$). The majority of asthmatic patients and non-asthmatic outpatients aged 65 and older did not respond to the question about their reasons for not getting the COVID-19 vaccine. The most common responses to the question about who recommended the influenza, pneumococcal, and COVID-19 vaccines among asthmatic patients were the media and other physicians. Similarly, among outpatients aged 65 years and older without asthma, the most common responses to the question of who recommended the influenza, pneumococcal, and COVID-19 vaccines were the media and other physicians, respectively. There was no statistically significant difference

Supplementary Table 1. Sociodemographic characteristics, underlying diseases and survey questions

1. Age:	
2. Gender	☐ Female ☐ Male
3. Smoking	☐ Yes ☐ No
4. Smoking duration -Month:...Year:...	
5. Underlying disease (diabetes, hypertension, heart failure, chronic kidney disease, immunosuppression, COPD (chronic bronchitis or emphysema), chronic liver disease, other diseases, etc.) ☐ Yes ☐ No	
6. Diabetes mellitus	☐ Yes ☐ No
7. Hypertension	☐ Yes ☐ No
8. Heart failure	☐ Yes ☐ No
9. Chronic kidney disease	☐ Yes ☐ No
10. Immuno suppression	☐ Yes ☐ No
11. Chronic obstructive pulmonary disease	☐ Yes ☐ No
12. Chronic liver disease	☐ Yes ☐ No
13. Other diseases ☐ Yes ☐ No	Disease name:.....(Please specify)
Questionnaire questions	
1. Do you believe the flu vaccine protects against the flu? ☐ Yes ☐ No	
2. Do you believe that the pneumococcal vaccine protects against pneumonia? ☐ Yes ☐ No	
3. Do you believe the COVID-19 vaccine protects against COVID-19 disease? ☐ Yes ☐ No	
4. Who recommended the flu vaccine? ☐ Family physician ☐ Doctor ☐ Nurse ☐ Pharmacist ☐ Other (Please specify)	
5. Who recommended the pneumonia vaccine? ☐ Family physician ☐ Doctor ☐ Nurse ☐ Pharmacist ☐ Other (specify)	
6. Who recommended the COVID-19 vaccine? ☐ Family physician ☐ Doctor ☐ Nurse ☐ Pharmacist ☐ Other (Please specify)	
7. Did you get a flu vaccine this year? ☐ Yes ☐ No	
8. Did you get a pneumococcal vaccine this year? ☐ Yes ☐ No	
9. Did you get a COVID-19 vaccine this year? ☐ Yes ☐ No	
10. What is your reason for not getting the flu vaccine?	
☐ I didn't know I had to get vaccinated	
☐ Not recommended by my doctor	
☐ I don't think it will be useful	
☐ Because I think the time has passed	
☐ Because I am afraid of side effects	
☐ Because I cannot provide	
☐ Because I didn't know it was free	
☐ Due to negative news about vaccination in the media	
☐ Fear of injection	
11. Reasons for not getting the pneumococcal vaccine	
☐ I didn't know I had to get vaccinated	
☐ Not recommended by my doctor	
☐ I don't think it will be useful	
☐ Because I think the time has passed	
☐ Because I am afraid of side effects	
☐ Because I cannot provide	
☐ Because I didn't know it was free	
☐ Due to negative news about vaccination in the media	
☐ Fear of injection	
12. Reasons for not getting the COVID-19 vaccine	
☐ I didn't know I had to get vaccinated	
☐ Not recommended by my doctor	
☐ I don't think it will be useful	
☐ Because I think the time has passed	
☐ Because I am afraid of side effects	
☐ Because I cannot provide	
☐ Because I didn't know it was free	
☐ Due to negative news about vaccination in the media	
☐ Fear of injection	
13. Indication for vaccination if vaccinated against influenza (If there is more than one indication, all will be marked)	
☐ Over 65 years of age ☐ Asthma ☐ COPD ☐ Heart failure ☐ Chronic kidney disease ☐ Immuno suppression ☐ Chronic liver disease ☐ Other conditions (Please specify)...	
14. Indication if pneumococcal vaccine (If there is more than one indication, all will be marked)	
☐ Being over 65 years of age ☐ Asthma ☐ COPD ☐ Heart failure ☐ Chronic kidney disease ☐ Immuno suppression ☐ Chronic liver disease ☐ Splenectomy ☐ Other conditions (Please specify)....	
15. Indication if vaccinated against COVID-19 (If there is more than one indication, all will be marked)	
☐ Being over 65 years of age ☐ Asthma ☐ COPD ☐ Heart failure ☐ Chronic kidney disease ☐ Immunosuppression ☐ Chronic liver disease ☐ Other conditions (Please specify)...	

Table 1. Patients' gender, education levels, and status of influenza, pneumococcal, and COVID-19 vaccination

		Asthma patients	Patients aged 65 and over	p
		Number (%)	Number (%)	
Gender	Female	75 (59.1)	52 (40.9)	0.002
	Male	35 (37.6)	58 (62.4)	
Education	Uneducated	12 (24)	38 (76.0)	<0.001
	Literate	7 (63.6)	4 (36.4)	
	Elementary school	39 (48.1)	42 (51.9)	
	Middle school	14 (73.7)	5 (26.3)	
Belief in the effectiveness of the flu vaccine	High school	31 (79.5)	8 (20.5)	0.418
	University	7 (35.0)	13 (65.0)	
	Yes	50 (47.2)	56 (52.8)	
	No	60 (52.6)	54 (47.4)	
Belief in the effectiveness of the pneumonia vaccine	Yes	50 (51)	48 (49)	0.786
	No	60 (49.2)	62 (50.8)	
Belief in the protection provided by the COVID-19 vaccine	Yes	98 (50)	98 (50)	1
	No	12 (50)	12 (50)	
Flu vaccination status in the last 5 years	Yes	23 (30.3)	53 (69.7)	<0.001
	No	87 (60.4)	57 (39.6)	
Pneumonia vaccination status in the last 5 years	Yes	17 (27.4)	45 (72.6)	<0.001
	No	93 (58.9)	65 (41.1)	
COVID-19 infection status	Yes	62 (42.5)	84 (57.5)	0.002
	No	48 (64.9)	26 (35.1)	
COVID-19 vaccination status and number of doses	No	18 (60)	12 (40)	0.086
	Once	0 (0)	1 (100)	
	Twice	41 (61.2)	26 (38.8)	
	Three times	33 (44.6)	41 (55.4)	
	Four times	12 (35.3)	22 (64.7)	
	Five times	6 (42.9)	8 (57.1)	

COVID-19: Coronavirus disease 2019

between the asthmatic patient group and the patient group over 65 years of age.

The responses to survey questions regarding who recommended influenza, pneumococcal, and COVID-19 vaccines and the reasons for not getting vaccinated among asthmatic patients and 65-year-old and older outpatient patients group are presented in [Table 2](#).

DISCUSSION

Asthmatic patients and individuals over 65 years of age are at risk for pneumococcal, influenza and COVID-19 infections. Vaccination rates against these three infectious agents are low in both asthmatic patients and people over 65 years of age.¹⁵

Although vaccines are available free of charge for individuals in the risk group, vaccination rates are not at the desired levels even among healthcare personnel.^{1,16-18}

Although vaccination practices vary according to age and underlying risk factors, they are highly effective, safe, and much less costly than treating the disease in preventing mortality and morbidity associated with infectious diseases.^{19,20}

In our study, influenza and pneumococcal vaccination rates among outpatients aged 65 years and older were found to be statistically significantly higher than those among patients with asthma, while no difference were found between the two groups in terms of COVID-19 vaccination. Ekinici et al.²⁰ examined the influenza vaccination rates among adults with chronic diseases and reported that there were no differences in vaccination rates according to gender, but vaccination rates increased with age, particularly in the 65-74 age group, which had higher vaccination rates than the 45-54 age group. Similarly, in our study, influenza, pneumococcal, and COVID-19 vaccination rates were higher in individuals aged 65 years and older with an average age of 72.08±4.9 compared to asthmatic patients with an average age of 48.9±11.03. In terms of education level, the number of uneducated individuals among those aged 65 and older was statistically significantly higher than among asthmatic patients. It has been reported that vaccination behavior with influenza vaccine is not affected by age and gender, but the rate of vaccination increases with increasing educational level. It has been reported that the reason for this may be that increasing educational level provides a higher awareness about the vaccine and leads to regular vaccination.²¹ Unlike this study,

Table 2. Responses to survey questions regarding who recommended influenza, pneumococcal, and COVID-19 vaccines to asthmatic patients and non-asthmatic outpatients aged 65 years and older group, and the reasons for not getting vaccinated

		Asthma patients	Patients aged 65 and over
		Number (%)	Number (%)
Who recommends the flu vaccine?	Family doctor	23 (54.8)	19 (45.2)
	Another department doctor	34 (51.5)	32 (48.5)
	Nurse	1 (100)	0 (0)
	Pharmacist	14 (42.4)	19 (57.5)
	Media	38 (48.7)	40 (51.3)
Who recommends the pneumococcal vaccine?	Family doctor	23 (54.8)	19 (45.2)
	Another department doctor	34 (51.5)	32 (48.5)
	Nurse	1 (100)	0 (0)
	Pharmacist	14 (42.4)	19 (57.5)
	Media	38 (48.7)	40 (51.3)
Who recommends the COVID-19 vaccine?	Family doctor	23 (54.8)	19 (45.2)
	Another department doctor	34 (51.5)	32 (48.5)
	Nurse	1 (100)	0 (0)
	Pharmacist	14 (42.4)	19 (57.5)
	Media	38 (48.7)	40 (51.3)
Reason for not getting the flu shot	Non-response	20 (28.2)	51 (71.8)
	Not knowing	0 (0)	7 (100)
	Seeing it as useless	36 (54.5)	30 (45.5)
	Wasting time	7 (77.8)	2 (22.2)
	Fear of side effects	30 (63.8)	17 (36.2)
	Unable to obtain	1 (100)	0 (0)
	Thinking it is not free	16 (84.2)	3 (15.8)
Reason for not getting the pneumonia vaccine	Non-response	15 (25.9)	43 (74.1)
	Not knowing	1 (8.3)	11 (91.7)
	Seeing it as useless	36 (54.5)	30 (45.5)
	Wasting time	8 (80)	2 (20)
	Fear of side effects	32 (61.5)	20 (38.5)
	Unable to obtain	2 (100)	0 (0)
	Thinking it is not free	16 (80)	4 (20)
Reason for not getting the COVID-19 vaccine	Non-response	92 (48.7)	97 (51.3)
	Seeing it as useless	8 (40)	12 (60)
	Wasting time	3 (100)	0 (0)
	Fear of side effects	7 (87.5)	1 (12.5)

COVID-19: Coronavirus disease 2019

the vaccination rate in our study was higher in patients aged 65 and over with a lower education level.

Sözener et al.¹³ reported in a questionnaire study conducted in asthmatic patients and a control group that asthma patients' knowledge about influenza vaccine and influenza was inadequate and their belief in the protective effect of the vaccine was low contrary to expectations. In the study, one fifth of the patients stated that they did not believe in the protective effect of the vaccine. The authors reported that informing health care professionals as well as patients about influenza through various activities is very important in terms of preventive medicine.

Özışık et al.²² conducted a prospective, observational questionnaire study on 155 patients hospitalized in an acute

care unit and found that although 145 (93.5%) of the patients had an indication for both pneumococcal and influenza vaccines, only 17.2% of the patients with an indication for pneumococcal vaccine received the vaccine and only 29.7% of the patients with an indication for influenza vaccine received the vaccine. In the study, it was reported that patients received influenza and pneumococcal vaccines in line with the recommendations of physicians other than family physicians and the most common reason for not receiving vaccination was inadequate information about vaccination.

In our study, the most common reasons for not receiving the influenza vaccine among asthmatic groups and aged 65 years and older in outpatient groups were perceived ineffectiveness of the vaccine and fear of side effects, respectively. The reasons

for not receiving pneumococcal vaccination among asthmatic groups and aged 65 years and older outpatients groups were also determined to be, in order of frequency, perceiving the vaccine as ineffective and fear of side effects. The majority of asthmatic groups and aged 65 years and older outpatients groups did not respond to the question about the reason for not getting the COVID-19 vaccine. The answers to the question about who recommended the influenza, pneumococcal, and COVID-19 vaccines among asthmatic groups and aged 65 years and older outpatients groups were, in order of frequency: the media and other physicians. Similar to the study by Özişik et al.,²² vaccines were recommended by physicians apart from family physicians in our study. Among those who were vaccinated, news reports in the media were the most common reason for vaccination, followed by recommendations from physicians apart from family physicians. Recommending the vaccine to patients in the risk group by family physicians or other physicians can increase vaccination rates.

Despite the importance of vaccination in adult asthmatic patients and those in risk groups being demonstrated in many studies, adult vaccination remains well below target levels. The individual's satisfaction with their condition, the burden of vaccination on the individual, lack of trust in vaccines, and consideration of various vaccine-related factors (individual and social risk-benefit ratio) are the main factors affecting vaccination.¹⁹

The influenza vaccine has been reported to be 60% effective in healthy individuals under the age of 65, 50-60% effective in preventing hospitalization in the elderly, and 80% effective in preventing mortality.^{20,22,23}

According to the national vaccination guidelines in Türkiye, influenza and pneumococcal vaccines are recommended for individuals aged 65 and older and for those having underlying risk factors (e.g., COPD, asthma, diabetes, chronic kidney disease, heart failure, HIV infection, etc.).^{19,23} The costs of these vaccines are covered free of charge by the social security institution.¹⁹

Çiftci et al.²¹ evaluated the pneumococcal vaccination rate, the effect of pneumococcal vaccination on hospitalization rates, and patients' attitudes toward pneumococcal vaccination in a survey of 1,251 patients (671 women, 580 men) who visited an outpatient clinic for chest diseases.

The study found that only 9.9% of the 766 patients who were eligible for pneumococcal vaccination had received the vaccine and that the vaccination rate increased with age. The study found that pneumococcal vaccination rates were significantly higher among individuals aged 65 years and older, as well as among patients with chronic lung disease, heart disease, and diabetes. In the study, the main reasons for not getting the pneumococcal vaccine were that it was not necessary or that people were unaware of its necessity. Those who got the vaccine reported that they obtained information about it mainly from their physicians. In the multiple regression analysis, obtaining information from a physician, being 65 years of age or older, and having chronic lung disease were reported as the most important factors influencing vaccination behavior. In our study, similarly, influenza,

pneumococcal, and COVID-19 vaccination rates were high among individuals aged 65 years and older. Among those who were vaccinated, the primary reason for vaccination was news reports, followed by recommendations from a physician apart from their family physician. Our study differs from others in that it examined vaccination rates for three different vaccines (influenza, pneumococcal, and COVID-19) and patients' attitudes toward these vaccines.

In a study conducted in the United States, the reasons for not getting vaccinated included the doctor's failure to recommend vaccination and misconceptions such as "vaccination is not necessary for healthy people".²³

Çiftci et al.²¹ reported that the reason for not receiving the pneumococcal vaccine among patients in the risk group was not negative perceptions about the vaccine, but rather a lack of information about it. The study reported that physicians were the most important source of information about the vaccine for patients and recommending it could increase vaccination rates.

Many studies have investigated the relationship between patients' educational level and vaccination rates.^{20,21} Hatipoğlu et al.²⁴ and Akman et al.²⁵ reported higher pneumococcal vaccination rates among patients with higher educational levels in their studies.

Hatipoğlu et al.²⁴ conducted a survey of 97 participants, including 67 (69%) HIV-negative patients aged 65 and older and 30 (31%) HIV-positive patients, and found that the influenza and pneumococcal vaccination rates among all patients were 30% and 29%, respectively. It was found that both influenza and pneumococcal vaccination rates were higher in HIV-positive patients than in HIV-negative patients aged 65 years and older. The most common reason for not receiving influenza and pneumococcal vaccines was that the vaccine was not recommended by the physician.

Today, social media and the press are important sources of medical information for the public. In our study, asthma patients and outpatients aged 65 and older who participated in the survey indicated that news reports in the press were the primary reason for getting vaccinated, highlighting the importance of the press and media in encouraging vaccination among individuals in high-risk groups. It has been reported that social media use can increase vaccination rates and compliance with vaccinations.²⁶

Furthermore, it has been reported that initiatives carried out through social media can eliminate barriers to vaccination among adults, particularly in relation to COVID-19 vaccinations.^{27,28}

CONCLUSION

In summary, while recommending vaccination, physicians should take into account the age factor as well as comorbidities such as asthma, COPD and other indications for vaccination in young patients. We are of the opinion that Chest Diseases specialists who follow asthmatic patients should explain the importance of vaccination against influenza, pneumococcal and COVID-19 infections to the patients, and that increasing

health literacy in the society may increase the positive approach towards vaccines and vaccination rates.

ETHICAL DECLARATIONS

Ethics Committee Approval

For the study, ethical approval was obtained from the Ethics Committee of the Health Sciences University, Ankara Training and Research Hospital, Clinical Researches Ethics Committee (Date: 10.08.2023, Decision No: 1322).

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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Exploring psychosocial coping among older women following a breast cancer diagnosis

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Cite this article as: Gümüş Demir Z. Exploring psychosocial coping among older women following a breast cancer diagnosis. *J Med Palliat Care*. 2025;6(4):339-346.

Received: 30.04.2025

Accepted: 10.07.2025

Published: 31.08.2025

ABSTRACT

Aims: This research investigates how women aged 60 and above, diagnosed with breast cancer within the last five years, perceive and navigate the psychosocial challenges brought on by their illness.

Methods: The study included 25 women who met the age and diagnosis criteria. Data was collected through in-person, semi-structured interviews. A thematic analysis approach was applied to identify patterns in how participants coped with emotional strain, accessed support systems, and made sense of their condition. The study was conducted in accordance with the COREQ (Consolidated Criteria for Reporting Qualitative Research) to ensure methodological rigor.

Results: Participants described optimism, emotional support from others, and spiritual beliefs as central to their psychological adjustment. Conversely, issues related to altered body image, social withdrawal, and uncertainty about treatment were reported as key stressors.

Conclusion: The findings point to the essential role of psychosocial coping in adapting to a cancer diagnosis later in life. They highlight the need for early, individualized support interventions particularly those that address body image concerns and strengthen social networks to help older patients better manage the psychological impact of the disease.

Keywords: Older women, breast cancer, coping strategies, psychosocial adaptation

INTRODUCTION

Cancer is a growing global public health concern, particularly in the context of an aging population.¹ Among malignancies affecting elderly women, breast cancer is one of the most common and is known to significantly impact individuals' quality of life across physical, emotional, and social domains.^{2,3} Women over the age of 60 who are diagnosed with breast cancer must navigate both biomedical and psychosocial challenges during the diagnosis and treatment process.⁴ The psychosocial coping strategies employed by patients play a crucial role in their ability to adapt to treatment and the broader cancer experience.⁵

Psychosocial coping strategies encompass the cognitive and behavioral mechanisms individuals use to manage highly stressful life events such as cancer.⁶ Studies have shown that women diagnosed with breast cancer often turn to active coping, seek social support, rely on religious beliefs, and adopt emotional regulation strategies during their adaptation process.^{7,8} However, elderly individuals face additional difficulties in this context, including physical limitations, social isolation, increased dependency, and cognitive decline.⁹⁻¹¹ These factors may impair psychosocial adjustment, particularly in older women whose sense of independence has diminished.¹² For elderly breast cancer patients, the

effectiveness of social support systems is one of the strongest predictors of psychological well-being.^{13,14} Evidence suggests that individuals with strong social networks are more likely to develop adaptive coping strategies and show better adherence to treatment.^{15,16} Furthermore, psychoeducation programs have been reported to reduce stress levels and improve quality of life.¹⁷⁻¹⁹ However, research specifically focusing on the effectiveness of psychosocial interventions in elderly women with breast cancer remains limited.¹² Although research specifically focusing on the effectiveness of psychosocial interventions in elderly women with breast cancer remains limited, existing studies have predominantly centered on younger patient populations, and qualitative data concerning the experiences of older women are scarce. This gap hinders a comprehensive understanding of the unique psychosocial challenges faced by elderly women and complicates the development of targeted intervention strategies.

This study analyzes the psychosocial difficulties and coping strategies of women aged 60 and above who have been diagnosed with breast cancer within the past five years. It aims to explore how these women navigate the challenges associated with cancer through the theoretical lenses of stress-coping theory and social support theory. According to the model

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proposed by Lazarus and Folkman,²⁰ individuals employ either problem-focused coping strategies (which involve directly addressing the problem) or emotion-focused coping strategies (which focus on managing emotional responses). Problem-focused coping includes seeking treatment options, pursuing social support, and making lifestyle changes.²⁰⁻²² Emotion-focused coping involves acceptance, religious engagement, and avoidance behaviors.^{7,23} Due to physical and social constraints, elderly individuals tend to rely more heavily on emotion-focused coping mechanisms.^{10,12} Spiritual coping, body image perception, and social isolation can interact and collectively shape an individual's overall psychological resilience. For instance, challenges related to body image may lead to social withdrawal, while spiritual beliefs can offer emotional strength that acts as a buffer against such withdrawal.

Older women with a breast cancer diagnosis often experience additional burdens such as functional decline, long-term treatment demands, cognitive impairments, and social isolation.^{1,8} Those with limited social support are at greater risk for experiencing psychological distress.^{14,15} While religious and spiritual coping strategies can promote emotional resilience, they may also contribute to passivity in medical decision-making.^{18,21,24} Given the scarcity of qualitative studies in this field, the present study seeks to fill this gap by shedding light on the mechanisms of coping and the role of support systems in this population. Specifically, the research examines how elderly women diagnosed with breast cancer construct both emotion- and problem-focused coping mechanisms, identifies the factors that influence these processes, and explores the contribution of social and spiritual resources. Ultimately, the aim is to enhance our understanding of the psychosocial experiences of elderly breast cancer patients and to support the development of more responsive healthcare and support systems.

METHODS

Ethics

The research adhered to the COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist for qualitative studies and received approval from the Üsküdar University Non-interventional Researches Ethics Committee (Date: 31.12.2024, Decision No: 61351342/020-726).²⁶ All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Research Design

This study, grounded in a phenomenological approach, investigates participants' perceptions of their illness experience, the coping strategies they adopted, and the support mechanisms they utilized. Thematic analysis was employed to identify core themes emerging from the data.²⁵ Participation was voluntary, and written informed consent was obtained from all participants. Data confidentiality was ensured through anonymization and encryption; all personal information was strictly protected and used solely for research purposes.

Participants and Sampling

The study included a total of 25 women aged 60 and older who had received a breast cancer diagnosis within the preceding five years. A combination of purposive and snowball sampling techniques was used to recruit participants. To be eligible, individuals needed to be at least 60 years old and have a confirmed diagnosis of breast cancer. Women with notable cognitive impairments or serious physical health conditions that could interfere with participation were not included.

The initial pool of participants was formed through professional and academic networks of the researcher. Subsequent participants were identified through referrals from individuals already enrolled in the study. As detailed in Table 1, the sample reflected a range of backgrounds and life circumstances, capturing the heterogeneity among older women living with breast cancer. The participants were between 61 and 78 years of age. While most were married, there was also significant representation from women who were widowed or single. Educational attainment varied, encompassing levels from primary education to university degrees. At the time of data collection, treatment status varied as well: some participants were still receiving active care, while others had already completed their treatment journey.

Table 1. Participant demographics and treatment details					
Participant	Age	Marital status	Education level	Diagnosis year	Treatment status
K1	67	Married	University	4	Continues
K2	61	Single	University	5	Completed
K3	70	Single	Middle school	5	Completed
K4	62	Single	Middle school	4	Completed
K5	66	Married	High school	1	Continues
K6	65	Married	High school	3	Continues
K7	68	Married	Middle school	5	Completed
K8	66	Single	High school	2	Continues
K9	78	Married	Middle school	4	Completed
K10	69	Married	Middle school	4	Continues
K11	68	Married	Primary school	5	Completed
K14	72	Married	High school	3	Continues
K15	66	Married	University	3	Continues
K16	68	Single	Middle school	4	Completed
K17	62	Married	High school	2	Continues
K12	77	Widow	University	2	Continues
K13	66	Married	Primary school	4	Completed
K18	78	Widow	High school	1	Continues
K19	74	Widow	Middle school	2	Completed
K20	63	Single	Primary school	1	Continues
K21	69	Married	University	4	Completed
K22	75	Single	High school	5	Continues
K23	68	Married	Primary school	4	Completed
K24	65	Widow	High school	3	Completed
K25	71	Single	University	2	Continues

Differences in age, marital status, education level, and treatment experiences among participants offered a valuable lens for examining how psychosocial coping strategies may vary across demographic subgroups. This heterogeneity within the sample provided an opportunity to explore, in greater depth, the unique psychological and social challenges encountered by older women diagnosed with breast cancer, as well as the coping responses they adopted. Recognizing such variation is critical to the design of tailored psychosocial interventions that reflect the specific needs, preferences, and life contexts of this population.

Data Collection

Data were gathered through semi-structured interviews guided by a pre-formulated question set developed specifically for this study. The interview guide was created by the researcher based on the study's objectives and informed by a review of relevant academic literature and comparable qualitative research. Before formal data collection began, the guide underwent a pilot phase to assess clarity and relevance, after which necessary modifications were made.

Interviews were conducted in person, either at participants' homes or workplaces, depending on their preferences and comfort. To create a safe and relaxed atmosphere, the scheduling and location of interviews were adapted to accommodate individual circumstances. All interviews were conducted privately, one-on-one, with no third parties present. Each session was held only once per participant, lasted approximately 30 minutes, and was audio recorded. The recordings were later transcribed verbatim for analysis.

The interviews were carried out by a researcher with clinical and academic experience in geropsychology. Importantly, the researcher had no prior personal or professional relationship with any of the participants before the study commenced. To maintain objectivity, leading questions were avoided, and neutrality was preserved throughout the data collection process. Participants were informed about the purpose of the study and the reasons for its implementation. To safeguard confidentiality, all audio recordings were anonymized, and the collected data were used exclusively for research purposes.

Data Analyses

Thematic analysis, as outlined by Braun and Clarke,²⁵ was utilized for data analysis. The data collection process was concluded once recurring patterns began to emerge during interviews and no new information surfaced, indicating that data saturation had been reached. The coding process involved identifying overarching themes that reflected participants' coping strategies, sources of support, and the challenges they encountered.

Analysis began with the transcription of audio-recorded interviews, followed by repeated readings to facilitate preliminary interpretation. Meaningful statements were identified, and initial codes were generated. These codes were then grouped into broader thematic categories, with relationships among themes carefully assessed and refined.

To ensure a detailed and interpretative approach, data coding was carried out manually without the use of software. All themes were derived inductively from the raw data rather than

being pre-defined. Saturation was considered achieved when themes and sub-themes were consistently repeated across participants' accounts, at which point further recruitment was discontinued. The findings were presented in a manner consistent with the data and were supported with direct quotations from participants. To enhance the trustworthiness of the analysis, the coding process was cross-checked by two independent researchers. The results were interpreted within the context of relevant literature and aligned with the study's overall objectives. During the classification of some themes, overlapping statements caused difficulty in defining category boundaries. This was overcome through cross-coding by two independent researchers.

Emerging Themes

Data derived from the interviews were organized into two primary thematic categories: (A) psychosocial coping mechanisms employed by older women following a breast cancer diagnosis, and (B) the core challenges they encountered while navigating this experience.

A. Psychosocial coping mechanisms: In the aftermath of diagnosis, participants described adopting a variety of strategies to manage the emotional and interpersonal difficulties they faced. Among the most common approaches were efforts to maintain a positive outlook, draw strength from close relationships, engage in spiritual practices, and seek professional mental health support.

Positive outlook and hope: A prevailing theme across many accounts was the conscious effort to remain hopeful and emotionally grounded during treatment. Participants frequently described how cultivating a positive mindset helped them process their diagnosis and stay committed to managing the disease.

Support from family and social circles: Emotional strength was often bolstered by meaningful connections with spouses, children, extended family, and health professionals. These relationships provided essential comfort and helped reduce feelings of isolation.

Spiritual and religious beliefs: For many, spiritual beliefs served as a vital resource. Prayer and faith-based practices were said to offer inner peace and a way to find meaning in the illness, positioning spiritual coping as a central pillar in psychological resilience.

Access to professional help: Several participants emphasized the benefits of psychological counseling or therapy in dealing with fear, uncertainty, and emotional stress. These services were seen as key tools in navigating the psychological weight of cancer.

B. Key challenges during the coping journey: Despite their efforts to adapt, participants also reported experiencing a range of emotional and social difficulties throughout their cancer journey. The most salient challenges included:

Processing the diagnosis emotionally: The moment of diagnosis was described as shocking and emotionally overwhelming. Feelings of disbelief, fear, and denial were common initial responses. Although many participants eventually came to accept their condition, doing so was often described as emotionally exhausting.

Dealing with altered body image: The physical consequences of treatment—such as hair loss or surgical scarring—significantly impacted how participants perceived themselves.

These changes were linked to decreased self-esteem and, in some cases, withdrawal from social interactions.

Diminishing social support and loneliness: While initial support from friends and family was often strong, some participants reported that it waned over time. This gradual decline left several women feeling alone and emotionally unsupported during later stages of their treatment or recovery.

Coping with daily life adjustments and uncertainty: Required changes in lifestyle including modified diets, new exercise habits, and ongoing medical appointments disrupted routines and contributed to stress. Added to this was the constant uncertainty about disease progression, which many described as a source of chronic anxiety.

These findings suggest that the needs of elderly women coping with breast cancer are multifaceted and extend well beyond

physical care. To support long-term well-being, psychosocial interventions must be holistic and adaptable, offering not only emotional and practical support but also personalized solutions that reflect the lived realities of aging individuals facing a serious health condition.

Excerpts from Patient Testimonials

To gain a deeper understanding of participants' experiences throughout the breast cancer journey, selected quotations from the interviews have been included. These direct statements provide clearer insights into the coping strategies employed and the challenges encountered by the patients. [Table 2](#) presents participant excerpts aligned with the thematic categories related to psychosocial coping mechanisms and the difficulties faced during the process.

Table 2. Excerpts from patient testimonials

Themes	Quotations
	Psychosocial coping strategies
Positive perspective and hope	"All my life I have always tried to think positively. When I got the diagnosis, I knew I couldn't change what was happening, but I could control how I reacted, so I approached my treatment seriously but tried to keep my spirits up." "... I said to myself, 'OK, this has happened to me, but it's not going to happen by crying' I thought I should focus on the solution. Otherwise, I wouldn't be able to get out of bed." "...My son and daughter-in-law have always been with me. They never left me alone during the treatment process. Their support gave me great strength." (K1)
	"I was shocked when I first heard it, but I thought there was no point in worrying. I focused on what I could do, not on what I could not change." (P5)
	"After chemotherapy, my stomach was terrible, I couldn't eat, but I pushed myself by saying 'I have to be strong'." (P13)
	"When my hair falls out, I learnt to look in the mirror and say, 'I am still me'." (P20)
	"There were difficult times, but giving up was not an option for me. I knew that keeping a positive perspective would help me." "...I had difficult days during the treatment, but I always said, 'This too shall pass'. Holding on to that thought kept me going." (P10)
Social and familial support	"I don't give up! Who is cancer? It cannot easily defeat a stubborn person like me!" (P19)
	"Every morning when I woke up, I looked in the mirror and said to myself, 'Come on, we will fight today too'. I had to be strong." (P12)
	"My husband was my biggest supporter. He did everything to keep my morale high and believed that we would get through this process together." (P6)
	"I survived this process thanks to my children. Their presence gave me hope and motivation." (P13)
	"My sister came with me to every appointment. Sometimes she would laugh and say, 'I attend the appointments to believe that you are sick'." (P4)
Spiritual beliefs and religious resources	"My husband held my hand every time I went through chemotherapy and made jokes so that I would not cry. Laughing with him gave me strength." (P15)
	"My neighbors cooked and brought such good food... It was as if I was a child and entrusted to them. How nice to have such friends!" (P23)
	"When my son said 'Mum, you are strong, you will win this war', my eyes filled with tears. It was such a beautiful feeling..." (P5)
	"My daughter combed my hair after every chemotherapy, she held the hair that fell out with my hand, but she did not cry. She supported me and I supported her." (P22)
	"I learnt to trust, my beliefs gave me strength in this process. After all, whatever happens will happen, I tried to move forward patiently." (P1)
Spiritual beliefs and religious resources	"My son used to tell me, 'Mum, you need to be strong', but I found strength in my faith." (P5)
	"We come from God; we will return to God. But I do not intend to leave yet! I still have to raise my grandchildren." (P7)
	"I felt more peaceful when I prayed every night. It was something that comforted me, my prayers supported me a lot in this process." (P9)
	"When I learnt about my illness, I felt a great fear, but then I said, 'There is a reason for this, God will show me a way.' (P13)
	"I did not neglect my prayers, I continued to pray as much as I could. Sometimes I was exhausted, but I needed it to rest my soul." (P17)
	"I prayed every time I went through chemotherapy. I felt peace inside, you know?" (P18)
	"Reading the Qur'an relaxed me during this process. I felt stronger and calmer." (P21)
	"Everything about my illness was uncertain, but thanks to my faith, I did not lose hope for the future." (P14)
	"I think that this disease is a test given to me. I try to increase my patience." (P22)
	"I was very scared when I first received chemotherapy, but as I prayed, I felt relieved." (P16)
	"I took refuge in God, there was nothing else to do. After a certain point, surrendering is good for people." (P25)
	"I always thought that this was not the end. If I was not a person of faith, I would not have stayed so strong." (P4)

The table continues

Table 2. Excerpts from patient testimonials (The table continues)

Use of professional support and therapy	"Having regular sessions with my psychiatrist really helped me. Talking to someone who understood my fears made a big difference." (P3)
	"Receiving therapy gave me great strength. I was hesitant at first, but then I realized how good it was for me." (P6)
	Receiving psychological support helped me to manage my anxieties ... "Sharing my worries in therapy gave me great relief." "...My doctor said, 'Talk, tell, don't keep it to yourself'. I did what he said, it really worked." (K14)
	"Going to a psychologist seemed ridiculous at first, but after the first session I realized that it is essential to talk to an expert in this process" (P3)
	"My nurse was so sincere... Before every chemotherapy, she would say 'Today is a good day, we will get through it together.'" (P8)
	"My doctor said, 'We will manage this process together'. That feeling of trust was very good for me." (P17)
Psychological difficulties after diagnosis	
Acceptance of the diagnosis	"When the doctor told me I had cancer, I was completely lost. At first, I couldn't understand the situation, but soon I realized that denial wouldn't work. I thought about it for days and said to myself, 'This is my reality, and I need to fight'." (P2)
	"At first, I felt like my world had collapsed, but I got used to it in time. Uncertainty scared me, but I adapted in." (P4)
	"Accepting the disease was the most difficult stage. At first I ignored it, then I was scared, but finally I decided to fight." (P16)
Physical change and problems in body perception	"When my hair fell out, I realized for the first time that I was really sick. I couldn't look in the mirror." (P2)
	"I felt an emptiness in my chest after the operation. I feel like I am an incomplete person now." (P6)
	"My body has changed, I have changed, but no one around me understands this." (P13)
	"I couldn't get out of bed on the days I received chemotherapy. Nausea, dizziness, weakness... You feel like you are finished." (P5)
	"Radiotherapy ruined my skin. I became unable to touch it, I could not sleep because of the pain." (P12)
	"After the operation, I was constantly infected. Constant pain, constant fatigue... It feels like it will never end." (P24)
Lack of social support feeling of loneliness	"When I got the diagnosis, everyone was with me, but in time I became lonely. People seem to be supportive, but after a while they forget." (P8)
	"My friends do not approach me like they used to. They are uneasy even while talking, as if I have become a different person." (P17)
	"I had to quit my job. I used to be a working, productive person. Now I am always at home, which makes me even more depressed." (P10) "I hesitate to go out, people look at me with pity. These looks hurt me more." (P23)
Forced changes in lifestyle and future anxiety	"I used to eat and drink whatever I wanted. Now I eat thinking about every bite. This is very annoying." (P4)
	"The doctor said 'Do sports' but I have no energy. This recommendation is too much for someone who has not done sports all my life." (P12)
	"I have to eat healthy food all the time, but sometimes I want to give up everything and be like before." (P22)
	"Going to the hospital has become my daily routine. Every test brings a new worry." (P9)
	"One test ends and another begins. It is as if I am in a never-ending cycle." (P15)
	"Now I plan my life according to doctor's appointments. I never thought I would have such a life before." (P19)

DISCUSSION

This study explores the psychosocial coping strategies and challenges experienced by elderly individuals diagnosed with breast cancer. The findings reveal that patients frequently relied on optimism, social support, religious beliefs, and professional psychological assistance to navigate the illness. However, challenges such as accepting the diagnosis, adjusting to changes in body image, experiencing social isolation, and adapting to lifestyle modifications were found to negatively affect psychological well-being.

Optimism and psychological resilience emerged as key components in facilitating adjustment to a breast cancer diagnosis. Participants with a positive outlook often interpreted the disease as a challenge rather than a threat, which contributed to improved psychological adaptation.^{15,23,26} Prior research supports the notion that optimism enhances mental health and treatment adherence. Nonetheless, maintaining a positive mindset can be difficult for some patients without psychological support, highlighting the need to expand access to counseling and educational programs.^{2,5,23,27}

Social connections were consistently described as a major source of emotional strength for participants. Those with

robust support networks—especially from family, friends, or caregiving professionals—reported fewer symptoms of depression and anxiety, and they appeared better equipped to manage the psychological toll of the illness.^{14,16} However, several participants mentioned that this support diminished over time, which contributed to a growing sense of loneliness. These insights underscore the need for cancer care systems to build enduring, reliable support structures that can accompany patients beyond the initial treatment period.^{28,29}

Religious and spiritual resources were another commonly cited form of coping. Many participants shared that prayer and faith offered not only emotional comfort but also a sense of control during a period of great uncertainty. These practices helped them make meaning of their experience and manage distress. However, the impact of spiritual coping varied across individuals. Some derived significant peace from their beliefs, while others did not find such strategies helpful—pointing to the importance of providing flexible, personalized psychosocial support in clinical care.^{7,8,30}

Coming to terms with the diagnosis emerged as one of the most emotionally taxing aspects of the cancer journey. For many, the early response was marked by fear, denial, and

worry. With time and adequate psychosocial support, several participants reported gradual acceptance. Yet some continued to experience prolonged emotional distress and had difficulty coping in the absence of professional intervention. This highlights the value of integrating early-stage psychological counseling into cancer care, starting at the point of diagnosis.^{11,31,32}

Alterations in body image due to treatment were also cited as a significant emotional challenge. Changes such as hair loss or visible scarring from surgery had a direct impact on how participants viewed themselves. These shifts in self-image often contributed to reduced confidence and, in some cases, social withdrawal. Although prior studies have established the importance of body image in psychological well-being, supportive interventions that address this issue remain scarce. Developing focused psychological support around body image concerns is therefore a key recommendation.³³⁻³⁵

Furthermore, the day-to-day adjustments required by treatment such as modifying diet, incorporating physical activity, and attending frequent medical appointments added layers of stress for many participants. These disruptions to routine life were compounded by anxiety about the future, particularly the uncertainty surrounding disease progression.^{36,37} Studies have shown that enforced lifestyle changes can contribute to a diminished sense of control and increased emotional strain. In response, healthcare systems should aim to provide not only clinical care but also structured support that helps patients manage ambiguity with greater confidence.³⁸⁻⁴⁰

Taken together, these findings point to the importance of psychosocial care that is not only comprehensive but also responsive to the nuanced needs of older women coping with breast cancer. Targeted interventions such as psychoeducation, peer-based support groups, and access to integrated mental health services can make a substantial difference in managing emotional burden and fostering adaptive coping.⁴¹⁻⁴³ However, these supports should be tailored to the unique preferences and challenges of older patients. For some, individual counseling may prove more effective than group-based interventions, and care models should remain flexible to accommodate such variation. The study findings clearly indicate that the first six months following diagnosis represent the most vulnerable period in terms of psychosocial adjustment, highlighting the importance of developing intervention programs specifically tailored to this critical phase.

Limitations

This study has several limitations. The findings may not be generalizable to populations in different cultural or socioeconomic contexts, highlighting the need for multi-center studies to gain broader insights. Due to its cross-sectional design, the study was unable to capture long-term changes in coping strategies, suggesting the importance of conducting longitudinal research. The psychological impact of body image changes was not analyzed in depth across patients who underwent mastectomy versus breast-conserving surgery, indicating a need for more comparative investigations. Additionally, pre-existing psychiatric

conditions were not assessed, which limits understanding of individual differences in psychological responses. The study also did not evaluate the effectiveness of specific psychosocial interventions, underscoring the need for future experimental studies in this area.

CONCLUSION

This study examined the psychosocial coping strategies employed by elderly women diagnosed with breast cancer, highlighting the core challenges they face and the mechanisms they use to adapt. Optimism, social support, spiritual beliefs, and professional psychological assistance emerged as the primary coping resources. However, accepting the diagnosis, concerns related to body image, social isolation, treatment uncertainty, and lifestyle modifications were identified as major psychological stressors.

The initial six months following a breast cancer diagnosis emerged as a highly sensitive and transitional phase, marked by increased emotional and physical strain. This period appeared to be particularly critical for psychosocial adjustment, requiring more intensive and tailored support. Participants with limited social networks often struggled more profoundly with long-term adaptation, while those who turned to spiritual beliefs seemed to demonstrate greater emotional resilience. Changes in body image such as hair loss or surgical alterations had a noticeable impact on women's self-esteem and, in some cases, led to social withdrawal. Although many participants expressed a desire to find meaning in their experience, existing support structures often fell short in addressing these deeper psychological and existential needs.

In light of these findings, it becomes clear that psychosocial interventions must extend beyond one-on-one therapy. Structured support systems that include targeted responses to body image concerns should be integrated into care models. The first six months post-diagnosis should be seen as a window of opportunity to implement personalized interventions that enhance emotional regulation and psychological well-being. A combination of individual and group-based psychoeducational sessions may offer valuable support during this period. Moreover, lifestyle adjustment programs incorporating guidance on nutrition, physical activity, and regular medical monitoring should be embedded within a holistic and coordinated care plan. Such long-term, multifaceted strategies are essential for meeting the evolving psychosocial needs of elderly women facing breast cancer and for building a more responsive and sustainable support system.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Üsküdar University Non-interventional Researches Ethics Committee (Date: 31.12.2024, Decision No: 61351342/020-726).

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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Early and late complications and predictors of port removal in cancer patients with totally implantable venous access devices (TIVADs): a single-center retrospective study

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Cite this article as: Türkmen U, Tekin KA, Çelikten AE, Yiğit G. Early and late complications and predictors of port removal in cancer patients with totally implantable venous access devices (TIVADs): a single-center retrospective study. *J Med Palliat Care*. 2025;6(4):347-354.

Received: 12.06.2025

Accepted: 10.07.2025

Published: 31.08.2025

ABSTRACT

Aims: Totally implantable venous access devices (TIVADs), placed subcutaneously, are widely used in cancer patients for the administration of long-term intravenous therapies. However, these systems may be associated with early and late complications that can necessitate device removal. This study aimed to evaluate the incidence and clinical characteristics of complications related to port catheter implantation in oncology patients, and to identify risk factors associated with port removal.

Methods: In this retrospective, single-center study, 313 adult cancer patients who underwent subcutaneous port catheter implantation between January 2022 and July 2024 were included. All procedures were performed under local anesthesia using a dual-incision technique with ultrasound and fluoroscopy guidance. Patients were monitored for early (<30 days) and late (≥30 days) complications. Factors associated with port removal were analyzed using univariate and multivariate logistic regression models.

Results: The mean age of the patients was 62.45±7.75 years, with the most common malignancies being colorectal (45.0%), gastric (25.9%), and pancreatic cancers (8.9%). Early complications were observed in 3.2% of patients, while late complications occurred in 25.6%. The most frequent complications included infection (8.3%), catheter dysfunction (4.8%), and venous thrombosis (3.8%). Port removal was required in 66 patients (21.1%), most commonly due to local infection (6.1%), occlusion (4.8%), skin erosion (5.4%), and catheter-related bloodstream infection (CRBSI) (2.2%). Univariate analysis revealed significant associations between port removal and low body-mass index, metastasis, chemotherapy, and several complications (p<0.05). In multivariate analysis, metastatic disease was identified as an independent risk factor (OR: 10.14; p<0.001), while advanced age was inversely associated with port removal (OR: 0.95; p=0.021).

Conclusion: Complications related to TIVADs are common and may frequently lead to port removal, especially in metastatic cancer patients. Infection and mechanical dysfunction are the leading causes of removal. Careful follow-up and individualized preventive strategies in high-risk patients may improve long-term port functionality.

Keywords: Cancer patients, complications, port removal, totally implantable venous access device, venous port catheter

INTRODUCTION

In the treatment of cancer patients, the long-term intravenous administration of agents such as chemotherapy, antibiotics, blood products, and nutritional solutions is often required. This necessity has led to the widespread use of methods that ensure reliable vascular access while minimizing the risk of complications. Totally implantable venous access devices (TIVADs) were developed for this purpose and have become an integral part of oncologic treatment practice in recent years.¹⁻²

Despite their advantages, TIVADs are associated with early and late complications such as infection, venous thrombosis,

catheter dysfunction, and skin erosion. These complications may disrupt port function, interfere with treatment continuity, and in some cases require complete device removal. The reported rates of port-related complications vary widely in the literature, depending on factors such as insertion technique, venous access route, clinical characteristics of the patient population, and follow-up duration.³⁻⁵

Complication and port removal rates also show wide variation across studies. While complication rates have been reported between 2% and 26%, port removal rates typically range from 1.2% to 10.8%.⁵⁻⁹ In contrast, a study focusing solely on breast

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cancer patients reported a notably high port removal rate of 30.2%.¹⁰ These discrepancies may stem from differences in patient selection, duration of port use, and criteria for removal. Moreover, an imaging-based review highlighted the broad clinical and radiological spectrum of port-related complications, emphasizing the importance of early diagnosis, another potential contributor to the variability in reported rates.¹¹

In recent years, alternative surgical approaches to TIVAD implantation have emerged, particularly with respect to anatomical site selection and incision technique. Among breast cancer patients, upper arm port placement has gained popularity, and a single-incision technique described by Song et al.¹² has been shown to provide shorter procedure times and better cosmetic outcomes.

Most existing studies focus on isolated cancer subgroups, and data regarding heterogeneous oncologic populations reflective of real-world practice remain limited. Additionally, many studies do not classify the clinical relevance of complications in detail, nor do they sufficiently explore the factors influencing decisions for port removal. To address this gap, the present retrospective study analyzes early and late complications following TIVAD implantation in 313 cancer patients with various tumor types and evaluates the clinical predictors of port removal, with reference to findings reported in the literature.

METHODS

Ethics

This study was designed as a retrospective, single-center, observational clinical investigation. Approved by the Researches Ethics Committee of Hitit University Faculty of Medicine (Date: 14.08.2024, Decision No: 2024/67) and conducted in accordance with the principles of the Declaration of Helsinki. Data from patients who underwent port catheter implantation between January 2022 and July 2024 were reviewed.

Patient data were retrospectively collected from hospital records and electronic medical databases. Informed consent forms were obtained from all patients prior to the procedure.

Patient Selection

The study included adult patients aged 18 years or older who underwent subcutaneous venous port catheter implantation for the administration of systemic therapy related to malignancy. All procedures were performed under local anesthesia using a dual-incision technique, guided by ultrasonography and fluoroscopy, and conducted by the same surgical team. Only patients who had at least one documented use of the port after implantation were included in the analysis.

Exclusion Criteria

- Patients who were followed up at another center after port implantation
- Patients with incomplete follow-up data or who never used the implanted port

- Patients with active infection, sepsis, or increased bleeding risk due to anticoagulation at the time of the procedure
- Patients who underwent port implantation using a different technique (e.g., single incision, upper extremity placement)

Procedural Technique

Port catheter implantations were performed under sterile conditions and local anesthesia, with Doppler ultrasound guidance. One incision was made for venous puncture, typically the internal jugular vein or, if anatomically favorable, the subclavian vein, and a second incision was created in the pectoral region to form the port pocket. The catheter was tunneled subcutaneously to connect with the port chamber. Under fluoroscopic guidance, the catheter tip was advanced to the cavoatrial junction and its position was confirmed. Following implantation, port function was tested with saline and heparinized saline. All patients underwent post-procedural chest radiography, and were discharged with a 10-day course of oral prophylactic antibiotics.

Follow-up and Clinical Monitoring

After port implantation, all patients were regularly followed for early (<30 days) and late (≥30 days) complications. In patients with suspected infection, blood cultures and catheter tip cultures were obtained. For other catheter-related complications (e.g., thrombosis or malposition), additional imaging modalities such as venous Doppler ultrasonography or CT angiography were used when necessary.

Definitions and Classification of Complications

Complications related to the venous port catheter system were categorized into early and late complications according to widely accepted criteria in the literature:

Early complications: Defined as complications occurring within the first 30 days following implantation. These included:

- Pneumothorax
- Catheter malposition
- Pocket infection
- Wound complications
- Technical failure or malfunction at initial use

Late complications: Defined as complications occurring after 30 days, typically associated with long-term use. These included:

- Catheter-related bloodstream infections (CRBSI)
- Venous thrombosis (clinically evident and/or confirmed by Doppler USG)
- Catheter occlusion/dysfunction
- Catheter migration or fracture
- Skin erosion or port chamber rotation
- Extravasation
- Any complication requiring port system removal

Definitions

CRBSI: Presence of clinical signs of infection along with isolation of the same microorganism from both blood culture and catheter tip culture, or infection not attributable to another source.

Local infections: Defined as cases limited to redness, tenderness, or purulent discharge around the port site, without systemic signs of infection. These patients were initially managed conservatively, with port removal reserved for refractory or progressive cases.

Venous thrombosis: Confirmed thrombus detected by Doppler USG or CT venography in patients with symptoms such as pain, edema, or catheter dysfunction on the port side.

Catheter dysfunction: Inadequate filling, poor infusion flow, or inability to achieve blood return through the catheter.

Skin erosion: Breakdown of overlying skin exposing the port chamber or rendering it superficial.

Extravasation: Leakage of cytotoxic agents outside the vein causing damage to surrounding tissue.

Statistical Analysis

The data analyses were performed using SPSS version 23.0 (IBM Inc., Chicago, IL, USA). The distribution of continuous variables was assessed using visual methods (histograms, Q-Q plots) and analytical tests (Kolmogorov–Smirnov test). Continuous variables that did not follow a normal distribution were presented as median (minimum–maximum) or as mean±standard deviation. The Mann–Whitney U test was used for comparisons between groups.

Categorical variables were expressed as frequencies and percentages (%). Relationships between categorical variables were analyzed using the Chi-square test, and Fisher's exact test was used when more than 20% of the expected cell counts were below 5. All tests were two-tailed.

To identify factors associated with port removal, univariate analyses were initially conducted. Variables with a p-value <0.05 and those deemed clinically relevant were included in a binary logistic regression model. In the multivariate analysis, independent effects of variables were reported as odds ratios (OR) with 95% confidence intervals (CI) and corresponding p-values.

A p-value <0.05 was considered statistically significant for all analyses.

RESULTS

A total of 313 cancer patients who underwent subcutaneous venous port implantation were included in this study. Demographic and clinical characteristics are summarized in [Table 1](#). The mean age of the patients was 62.45 ± 7.75 years, and the mean body-mass index (BMI) was 26.31±2.07 kg/m². Among the patients, 32.3% were female, 15.3% had diabetes mellitus (DM), 41.2% had hypertension, 7.3% had chronic obstructive pulmonary disease (COPD), and 1.9% had chronic kidney disease (CKD). The most common malignancies were colorectal cancer (45.0%), gastric cancer (25.9%), and pancreatic cancer (8.9%). The proportion of patients receiving

ongoing chemotherapy was 30.0%, and metastatic disease was present in 51.4% of the cases.

Table 1. Baseline demographic and clinical characteristics of the patients (n=313)

Variables		n=313
Age		62.45±7.75
BMI (kg/m²)		26.31±2.07
Sex (female)		101 (32.3%)
DM		48 (15.3%)
Hypertension		129 (41.2%)
COPD		23 (7.3%)
CKD		6 (1.9%)
Cancer type	Lung	6 (1.9%)
	Breast	13 (4.2%)
	Endometrium	2 (0.6%)
	Ovary	2 (0.6%)
	Prostate	9 (2.9%)
	Esophagus	8 (2.6%)
	Stomach	81 (25.9%)
	Hepatobiliary	15 (4.8%)
	Pancreas	28 (8.9%)
	Colo-rectal	141 (45.0%)
	Hodgkin lymphoma	3 (1.0%)
	Multiple myeloma	5 (1.6%)
Receiving chemotherapy		94 (30.0%)
Presence of metastasis		161 (51.4%)
BMI: Body-mass index, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, CKD: Chronic kidney disease		

BMI: Body-mass index, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, CKD: Chronic kidney disease

[Table 2](#) presents data on complications encountered during the operative and postoperative periods. Ports were implanted on the right side in 83.7% of cases, and the most commonly used venous access route was the internal jugular vein (IJV) (97.1%). Early complications (<30 days) occurred in 10 patients (3.2%), while late complications (≥30 days) were observed in 80 patients (25.6%). The most frequent complications were infection (8.3%), venous thrombosis (3.8%), and catheter occlusion/dysfunction (4.8%).

Pneumothorax was detected in only 2 patients (0.6%), both of whom required tube thoracostomy. [Figure 1](#) shows a chest radiograph demonstrating pneumothorax after port implantation. Catheter malposition, defined as incorrect positioning of the catheter tip and rotation of the port chamber, was observed in only 1 patient (0.3%), and the port system was removed in that case ([Figure 2](#)).

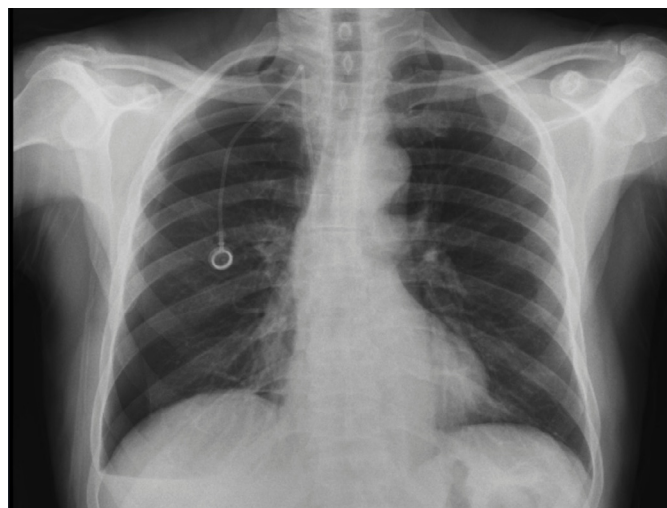
Infection developed in 26 patients (8.3%), of which 7 (2.2%) were diagnosed as CRBSI and 19 (6.1%) as local infections. Microbiologically, *Staphylococcus aureus* was isolated in 13 patients (5 CRBSI, 8 local), and coagulase-negative staphylococci (CoNS) were identified in 13 patients (2 CRBSI, 11 local infections).

Catheter occlusion or dysfunction was observed in 15 patients, all of whom underwent port removal. Venous thrombosis occurred in 12 patients, but only 6 of these required port

Table 2. Operative and postoperative data of the patients (n=313)

Variables	n=313
Port insertion side (right)	262 (83.7%)
Venous access route (IJV)	304 (97.1%)
Early complication (<30 days)	10 (3.2%)
Late complication (≥30 days)	80 (25.6%)
Pneumothorax	2 (0.6%)
Venous thrombosis	12 (3.8%)
Infection (overall)	26 (8.3%)
CRBSI	7 (2.2%)
Local infection	19 (6.1%)
Infection microorganism	
<i>Staphylococcus aureus</i>	13 (4.2%)
CoNS	13 (4.2%)
Port removal required	66 (21.1%)
Catheter occlusion/dysfunction	15 (4.8%)
Catheter malposition	1 (0.3%)
Skin erosion	17 (5.4%)
Extravasation	1 (0.3%)
Venous thrombosis	6 (1.9%)
Local infection	19 (6.1%)
CRBSI	7 (2.2%)

IJV: Internal jugular vein, CRBSI: Catheter-related bloodstream infection, CoNS: Coagulase-negative *Staphylococci*

**Figure 1.** Posteroanterior chest radiograph demonstrating pneumothorax following port implantation. The lung contour is visible, separated from the right lateral thoracic wall, indicating the presence of a pneumothorax

removal due to symptomatic or extensive thrombosis; the remaining 6 patients were managed conservatively with anticoagulation therapy.

In total, port removal was performed in 66 patients (21.1%). The reasons for port removal were as follows:

- Catheter occlusion/dysfunction: 15 (4.8%)
- Catheter malposition: 1 (0.3%)
- Skin erosion: 17 (5.4%)
- Extravasation: 1 (0.3%)

**Figure 2.** Chest radiograph of a patient showing catheter tip malposition and rotation of the port reservoir

- Venous thrombosis: 6 (1.9%)
- Local infection: 19 (6.1%)
- CRBSI: 7 (2.2%)

Univariate Analysis Findings

Comparisons between patients who underwent port removal and those who did not are presented in [Table 3](#). Univariate analyses revealed statistically significant associations between port removal and the following variables ($p < 0.05$):

Table 3. Univariable comparison of demographic and clinical variables between patients with and without port removal

Variable	Port removed (n=66)	Not removed (n=247)	p-value
Age (years)	59.80±7.17	63.29±7.73	0.023 ^a
BMI (kg/m ²)	25.11±1.86	26.66±2.02	<0.001 ^a
Sex (female)	23 (34.8%)	78 (31.6%)	0.648 ^b
Diabetes mellitus	8 (12.1%)	40 (16.2%)	0.48 ^b
Hypertension	23 (34.8%)	106 (42.9%)	0.265 ^b
COPD	4 (6.1%)	19 (7.7%)	0.783 ^c
CKD	0 (0.0%)	6 (2.4%)	0.349 ^c
Presence of metastasis	53 (80.3%)	108 (43.7%)	<0.001 ^b
Receiving chemotherapy	31 (47.0%)	63 (25.5%)	0.001 ^b
CRBSI	7 (10.6%)	0 (0.0%)	<0.001 ^c
Venous thrombosis	6 (9.1%)	6 (2.4%)	0.03 ^c
Catheter occlusion/dysfunction	15 (22.7%)	3 (1.2%)	<0.001 ^c
Malposition	1 (1.5%)	0 (0.0%)	0.208 ^c
Skin erosion	17 (25.8%)	0 (0.0%)	<0.001 ^c
Extravasation	1 (1.5%)	0 (0.0%)	0.208 ^c
Infection (any)	26 (39.4%)	0 (0.0%)	<0.001 ^c

Data are presented as mean±standard deviation for continuous variables and number (percentage) for categorical variables. a: Mann-Whitney U, b: Chi-square, c: Fisher's exact. BMI: Body-mass index, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, CRBSI: Catheter-related bloodstream infection

- Lower BMI
- Presence of metastasis
- Receiving chemotherapy
- Presence of infection

- Venous thrombosis
- Catheter occlusion/dysfunction
- Skin erosion
- CRBSI
- Positive microbiological culture results

In contrast, no significant relationship was found between port removal and variables such as sex, DM, hypertension, COPD, CKD, side of port placement, or the venous access route used ($p>0.05$). Although local infections were more frequent, most cases were successfully managed with conservative treatment, allowing preservation of the port system. Therefore, local infections did not show a statistically significant association with port removal ($p>0.05$). In contrast, systemic infections such as CRBSI were more decisive in the decision to remove the port.

Multivariate Logistic Regression Findings

Among the variables that showed statistical significance in the univariate analysis, direct complication-related factors leading to port removal were excluded from the multivariate model. Instead, the multivariate logistic regression analysis was performed using only demographic and clinical predictors. Based on this approach, two independent risk factors for port removal were identified: the presence of metastasis significantly increased the risk of port removal (OR: 10.14; $p<0.001$), whereas older age was inversely associated with port removal (OR: 0.95; $p=0.02$) (Table 4). Receiving chemotherapy approached statistical significance ($p=0.054$), while BMI was not found to be an independent risk factor ($p=0.35$).

Table 4. Multivariate logistic regression analysis of factors associated with port removal

Variable	OR	95% CI	p-value
Age	0.951	0.912–0.991	0.021
Presence of metastasis	10.14	3.55–29.01	<0.001
Receiving chemotherapy	1.97	0.98–3.95	0.054
BMI	0.90	0.71–1.18	0.35

OR: Odds ratio, CI: Confidence interval, BMI: Body-mass index. Variables with $p<0.05$ in univariate analysis were included in the model

These findings suggest that while certain complications (such as infection, thrombosis, or occlusion) are direct causes of port removal, clinical features like metastatic disease and advanced age may serve as indirect but important predictive factors for port discontinuation.

DISCUSSION

TIVADs are widely used in oncology patients to facilitate chemotherapy, parenteral nutrition, and long-term intravenous therapy. Although these systems enhance patient comfort, they are associated with a range of potential complications, including infection, venous thrombosis, catheter dysfunction, and skin erosion. The incidence of such complications may vary depending on factors such as implantation technique, patient characteristics, duration of use, and the structural properties of the port system employed.

In our retrospective study, early (<30 days) and late (≥ 30 days) complications, as well as clinical factors associated with port removal, were thoroughly investigated in 313 oncology patients who underwent subcutaneous venous port catheter implantation. The overall complication rate was 28.8%, with the most common late complications being infection (8.3%), catheter dysfunction (4.8%), and venous thrombosis (3.8%). Port explantation was required in 66 patients (21.1%), mostly due to infection, mechanical occlusion, skin erosion, and thrombosis. These findings underscore the significant impact of TIVAD-related complications on both clinical outcomes and continuity of oncologic treatment.

In our cohort, TIVAD-related infections occurred in 8.3% of patients, with 2.2% classified as CRBSIs and 6.1% as localized infections. These rates are higher than those reported in some large-scale studies, but comparable to others. For example, in a prospective study, the overall port-related infection rate was reported at 2.8%, with only 1.7% resulting in port removal.¹³ Similarly, in the study by Walser,¹ CRBSI rates ranged between 0.3–1.4 per 1000 catheter days, and pocket infections were reported at a rate of 2–3%. In contrast, our study found a notably higher local infection rate of 6.1%, nearly double that reported in these series. Furthermore, infections remain one of the most concerning late complications in oncology patients receiving TIVADs. Wang et al.¹⁴ developed and validated a nomogram to predict post-insertion infection risk based on clinical variables such as diabetes, chemotherapy regimen, leukocyte count, and serum albumin levels. While our study did not include individualized risk prediction, our infection rates are consistent with the literature and support the continued safe use of TIVADs in oncologic practice.

When examining the microbiological distribution of infections in our study, the most frequently isolated pathogens were CoNS and *Staphylococcus aureus*, each detected in 13 cases (4.2%). This distribution aligns with the common pathogens reported in the review by Lebeaux et al.,¹⁵ which noted that CoNS infections typically respond to antibiotic therapy, whereas infections caused by *S. aureus* or *Candida* species often necessitate port removal. Furthermore, antibiotic lock therapy has been reported to achieve up to a 75% success rate in managing CoNS-related infections. However, in our series, the majority of patients with CoNS infections ultimately required port removal. This may be attributed to the fact that antibiotic lock therapy is not routinely implemented in our institutional protocol, or possibly due to the presence of advanced biofilm formation that reduced the efficacy of systemic antibiotics.

In the systematic review by Ruesch et al.,³ the infection rate associated with catheters inserted via the IJV was reported to be 6.3%, which may partially explain the 8.3% overall infection rate observed in our study, where the IJV was utilized in 97.1% of cases. Additionally, some studies have reported infection rates ranging between 2.8% and 3.0%.^{7,8} This discrepancy may be attributed to the high prevalence of metastatic disease in our patient population (51.4%), their immunocompromised status, and the possibility of longer catheter dwell times.

In the guideline-level review by Vescia et al.,² infection rates in TIVAD systems were reported to range between 3% and 12%, while the incidence of CRBSIs was defined as 0.2–1.4 per 1,000 catheter-days. In our study, the CRBSI rate was 2.2% on a per-case basis. Although this rate cannot be directly compared due to the absence of catheter-day data, it should still be considered within acceptable limits. However, the relatively high incidence of port pocket infections highlights the need for close monitoring, especially in patients with thin subcutaneous tissue or those receiving immunosuppressive therapy.

The impact of the insertion side on complication rates has been increasingly recognized in recent literature. In a 2024 retrospective comparative study of female breast cancer patients, O'Mahony et al.¹⁶ demonstrated that catheter tip migration from the supine to erect position was significantly more pronounced in right-sided ports. Importantly, in left-sided ports, zone migration was statistically associated with an increased risk of complications ($p=0.023$). Although our study did not directly assess catheter tip position changes, the lower rate of complications observed in right-sided ports may be partly explained by the positional instability highlighted in O'Mahony's study.¹⁶

In conclusion, although the overall infection rates observed in our study were consistent with the ranges reported in the literature, the relatively high rate of local infections is noteworthy. This finding suggests a need to reassess post-insertion care protocols, particularly regarding standardized skin care and port site hygiene. Moreover, as emphasized in the study by Lebeaux et al.,¹⁵ therapeutic strategies for *S. aureus* and CoNS infections should be tailored according to the specific pathogen involved.

In our study, catheter-related venous thrombosis was observed in 3.8% of patients, and port removal was required in only half of these cases (1.9%). This rate aligns with the broad range of thrombosis incidences reported in previous studies. Particularly, in ports inserted via the IJV, the incidence of thrombosis has been reported to range between 2% and 6%.^{1,3} In some series, the thrombosis rate was considerably higher for the jugular route (12.8%) compared to the subclavian (6.5%) and cephalic (9.2%) veins.⁴ The high prevalence of IJV usage in our study (97.1%) may partially explain the observed thrombosis rate. Similarly, Liu et al.¹⁷ reported a 6.1% incidence of TIVAD-related thrombosis in a large cohort of 1,586 breast cancer patients, identifying left-sided IJV access, larger-diameter catheters (particularly 8F), and prolonged indwelling duration as independent risk factors. Although their study focused exclusively on breast cancer patients, the clinical relevance of catheter size, laterality, and duration shares meaningful parallels with our findings. Nevertheless, the fact that most thrombosis cases in our cohort were managed conservatively without necessitating port removal helped keep the explantation rate limited.

The rate of catheter dysfunction or occlusion in our cohort was 4.8%, and all such cases required port removal. This figure is consistent with those reported in the literature, which generally range between 2% and 5%.^{1,2} However, some studies focusing on single-incision port placements have

reported lower rates, as low as 1.2% or even 0.1%.^{6,8} Variations in dysfunction rates may be attributed to differences in implantation technique, tunnel length, catheter material, intensity of use, and maintenance protocols. Our findings indicate that this complication often necessitates invasive intervention. Moreover, an umbrella review by Elliott et al.¹⁸ emphasized that catheter occlusions remain a frequent and serious issue, with rates as high as 14–36%, and highlighted the role of standardized flushing and locking protocols in prevention. This underscores the need for further protocol development to reduce dysfunction-related port removals.

Skin erosion complications were observed at a relatively high rate of 5.4% in our series, and all cases resulted in port removal. In contrast, lower rates have been reported in the studies by Nakamura et al.⁷ (1.5%), El-Balat et al.¹⁰ (0.7%), and Biffi et al.¹³ (0.3%). This discrepancy may be attributed to several factors, including the thickness of the subcutaneous tissue at the port pocket site, patients' cachectic or metastatic status, nutritional deficiencies, and immunosuppression. Additionally, reduced skin elasticity in elderly or systemically compromised patients may facilitate the development of this complication.

Furthermore, in the study by Song et al.,¹² the single-incision technique used for TIVAD placement in the upper arm was associated with shorter procedure times and better cosmetic outcomes, while maintaining comparable complication rates. Differences in implantation site (chest vs. upper arm) and surgical technique may play a decisive role in the frequency of complications such as infection and skin erosion. These findings suggest that the surgical approach not only affects cosmetic outcomes but also has a direct impact on clinical results and patient satisfaction.

In our study, a total of 66 patients (21.1%) required removal of the port system. This rate exceeds the 1.2% to 10.8% range reported in many previous studies.⁵⁻⁹ However, some series involving only breast cancer patients have reported port removal rates as high as 30.2%.¹⁰ This discrepancy may be explained by differences in patient populations, particularly the proportion of metastatic cases, overall systemic conditions, and the clinical protocols followed. In our study, complications that did not resolve despite conservative treatment also played a decisive role in the decision to remove the port.

The relatively higher complication rates observed in our study compared to some other series can be attributed to the broader and more clinically representative patient population. Many studies in the literature focus solely on specific oncological subgroups; for example, Hong et al.⁹ examined head and neck malignancies, El-Balat et al.¹⁰ studied only breast cancer patients, and Song et al.¹⁹ evaluated patients with right-sided breast cancer. In contrast, our study included a wide range of tumor types, including colorectal, gastric, pancreatic, pulmonary, and hematologic malignancies, with 51.4% of patients being in the metastatic stage. This scenario likely reflects the coexistence of multiple factors that may predispose to complications, such as immunosuppression, malnutrition, poor skin integrity, and limited mobility.

These findings demonstrate that complications associated with TIVADs are not solely dependent on technical proficiency;

rather, factors such as patient selection, procedural practices, follow-up protocols, and individualized care strategies play a critical role in outcomes.

In our study, univariate analysis identified several variables significantly associated with port removal, including advanced age, presence of metastatic disease, current chemotherapy, BMI, and complications such as CRBSI, catheter dysfunction, thrombosis, and skin erosion. However, since these complications were direct causes of port explantation, only demographic and clinical variables were included in the multivariate logistic regression model. In this analysis, metastatic disease [OR: 10.14, 95% CI: 3.55–29.01; $p < 0.001$] emerged as the strongest independent predictor of port removal. Conversely, advanced age [OR: 0.95, 95% CI: 0.91–0.99; $p = 0.021$] was inversely associated with port explantation, while ongoing chemotherapy showed a borderline association ($p = 0.054$).

Metastatic disease is typically accompanied by increased risk factors such as malnutrition, immunosuppression, and poor skin and tissue integrity, all of which predispose patients to complications like infection, skin erosion, and thrombosis. Indeed, the impact of metastasis on port removal has been indirectly reported in studies by El-Balat et al.¹⁰ and Lebeaux et al.¹⁵ Our data confirm this trend, indicating a stronger inclination toward port removal—rather than preservation—when complications arise in metastatic patients.

Interestingly, advanced age was inversely associated with port removal in our multivariate model. Although counterintuitive at first glance, this may reflect a clinical preference for conservative management in older patients due to their overall condition and treatment plans, even when complications occur. Additionally, the tendency to avoid aggressive interventions in elderly individuals may lead to a higher rate of port retention, even in the face of infection or mechanical issues. In the study by Walser et al.,¹ older individuals were reported to have higher complication rates, though how this influenced port removal decisions was not clearly addressed. Therefore, the relationship between age and port removal should be interpreted cautiously in the clinical context.

In the study by Song et al.,¹² infection risk was linked to systemic conditions such as diabetes, hypertension, and hyperlipidemia. In contrast, our findings highlight metastatic disease and advanced age as key clinical predictors of port-related complications requiring removal. This discrepancy suggests that patient risk profiles may vary depending on the study population and surgical techniques employed.

In conclusion, metastatic disease appears to be a significant risk factor for reduced long-term TIVAD sustainability. In these patients, a thorough risk assessment should be performed before implantation, and close monitoring for infection, skin integrity, and port function is essential postoperatively. Advanced age was inversely associated with port removal, possibly due to the preference for less aggressive or conservative management in elderly patients. Thus, even when complications occur in older individuals, the clinical

tendency may favor port preservation. For both patient groups, the implementation of preventive strategies, including antibiotic prophylaxis, skin care education, and regular port function monitoring, may enhance port longevity and reduce the need for explantation.

Limitations

This study has several limitations. First, due to its retrospective design, data collection was based on patient files and hospital records, which may result in missing or inaccurately documented clinical details. Second, the study was conducted at a single center, with all port implantations performed using the same surgical technique and primarily by the same team. Therefore, the generalizability of the findings to other centers may be limited. Third, since data regarding the duration of catheter use were not collected, complication rates per 1000 catheter-days could not be calculated. Additionally, variability in follow-up durations among patients may have influenced the observed frequency of late complications. Fourth, decisions regarding port explantation were based on individualized clinical judgment, which may have introduced subjectivity, for example, a more conservative approach might have been preferred for elderly patients, potentially affecting the interpretation of explantation rates. Finally, some important clinical variables such as patients' performance status, nutritional condition, chemotherapy regimens, and comorbid systemic diseases could not be included in the model. Thus, future prospective, multicenter studies with longer follow-up periods are needed.

CONCLUSION

Subcutaneous venous port catheters are indispensable tools for meeting the long-term intravenous treatment needs of oncology patients; however, they carry significant risks of complications such as infection, thrombosis, catheter dysfunction, and skin erosion. In this study, early and late complications related to TIVADs were comprehensively evaluated in a heterogeneous patient population characterized by a wide range of tumor types and a high proportion of metastatic disease. Notably, infections and mechanical issues were shown to be closely associated with port removal.

Multivariate analysis revealed that metastatic disease is an independent risk factor significantly increasing the likelihood of port explantation. Conversely, older age was inversely associated with explantation, possibly reflecting a clinical tendency toward less aggressive intervention and more conservative management in this age group. These findings indicate that successful port use is influenced not only by technical expertise but also by patient profile and clinical decision-making processes.

In conclusion, careful risk assessment should be conducted prior to port placement in patients with metastatic disease or of advanced age. Post-implantation, close monitoring of infection, skin integrity, and port function is essential. Individualized preventive measures, such as antibiotic prophylaxis, skin care education, and regular port function assessments, may help reduce complication rates and improve the long-term sustainability of the port system.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approved by the Researches Ethics Committee of Hitit University Faculty of Medicine (Date: 14.08.2024, Decision No: 2024/67).

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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The relationship between the frequency and severity of postpartum diastasis recti abdominis with the density of striae gravidarum

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Cite this article as: Kalkan B, Alptekin O, Dal ÇN. The relationship between the frequency and severity of postpartum diastasis recti abdominis with the density of striae gravidarum. *J Med Palliat Care*. 2025;6(4):355-360.

Received: 28.06.2025

Accepted: 14.07.2025

Published: 31.08.2025

ABSTRACT

Aims: This study aims to evaluate how the presence and severity of striae gravidarum (SG) affect the frequency and severity of postpartum diastasis recti abdominis (none/mild/severe).

Methods: This study included 107 patients who underwent caesarean section for various indications and were examined for diastasis recti during postpartum outpatient clinic visits. SG was scored according to the Davey scoring system and interrectal distances were measured by ultrasonography during postpartum outpatient clinic visits and evaluated for diastasis recti at postpartum weeks 3-6.

Results: Patients who scored 0 points according to the Davey score, indicating the absence of striae, were excluded from the study. Patients in the mild and severe groups were then compared in terms of DRG 1 and DRG 2. It was observed that the groups were homogeneously distributed. A significant difference ($p < 0.001$) was found in terms of the supra-umbilic interrectal distance (DRG 1) between the mild striae group (Davey score 1-2) and the severe striae group (score ≥ 3). When evaluated in terms of subumbilical interrectal distance (DRG 2), a significant difference was observed between the groups ($p = 0.003$). The findings indicate that increasing striae density correlates with greater interrectal distance, placing patients at higher risk of diastasis recti.

Conclusion: The SG score can be utilized as a predictive tool to determine the likelihood of diastasis recti occurring during pregnancy. Furthermore, this study could contribute to understanding the pathogenesis of both SG and diastasis recti by examining collagen and fascia tissue samples in larger patient populations.

Keywords: Striae gravidarum, diastasis recti, postpartum diastasis recti abdominis, postpartum complications, striae gravidarum severity

INTRODUCTION

Striae gravidarum (SG) is a common, misshapen skin change that affects 55% to 90% of women. It may occur during pregnancy, particularly in the anterior abdominal wall and flank areas.¹ The condition is characterized by the thinning of the epidermis, the loss of dermal papillae and rete ridges, as well as a decrease in the levels of collagen, fibronectin and fibrils that form the extracellular matrix. SG initially manifests as flat, pink to red bands, designated as "Striae Rubra" or "Immature Striae." Subsequent to this, it undergoes a process of swelling, elongation, and widening, acquiring a purple-red coloration. Over time, the scars gradually fade and become hypopigmented (striae alba or striae matures). Eventually, these striae appear as wound-like, wrinkled, white, and atrophic scars parallel to skin tension lines.^{2,3}

Dysfunctional fibroblasts are unable to provide the necessary support tissue to respond appropriately to mechanical stretch. Fibrillary collagen types I and III are the primary components

of the interstitial matrix. These collagens are essential for maintaining tissue stability and functionality. Collagen, a component of the abdominal fascia and aponeurosis, including the linea alba, plays an important structural role in providing support and resistance to the abdominal wall against intra-abdominal pressure.⁴

Although the literature offers various descriptions of diastasis recti abdominis (DRA), it can be defined as the separation of the rectus abdominis muscles along the midline of the abdominal wall, accompanied by gap formation. The diagnosis of DRA is based on the presence of at least a 2.5 cm opening at any level of the linea alba, or the presence of sufficient space for two fingers to enter in one or more regions located just above the umbilicus, 3 and 5 cm above the umbilicus, and 3 cm below the umbilicus. It is a common occurrence for the muscles to separate during pregnancy. A re-examination must therefore be performed after the puerperium period to

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confirm the diagnosis. In light of the quantity and quality of collagen density and the support and resistance functions of fibroblasts in the abdominal wall, it is important to consider that disruptions in this mechanism may play a role in the formation of diastasis recti. In a study, it was observed that both type I and type III collagen were present in lower quantities in women with DRA than in women with a normal abdominal wall.^{5,6}

The common mechanism involving dysfunctional fibroblasts may be responsible for the histopathogenesis of both SG and DRA. Based on this scientific reality, the evaluation of how the presence of SG affects the frequency and severity of postpartum DRA, in proportion to its severity (none/mild/severe), constitutes the primary objective for this study.

METHODS

The study was conducted with the permission of the Clinical Researches Ethics Committee of Erzincan Binali Yildirim University (Date: 22.03.2021, Decision No: 05/20). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study encompasses cases admitted to the gynecology and obstetrics service between March 2021 and March 2022, who underwent a cesarean section for various reasons, and who underwent a diastasis recti examination during postnatal outpatient clinic visits. Pregnancies beyond 34 weeks who were between the ages of 18-35, who gave birth by cesarean section, and who had a cesarean section at most 3 times were included in the study; Women who had a history of non-cesarean abdominopelvic surgery, who had more than four cesarean sections, who had a known muscle or skin disease, who received corticosteroid treatment for any reason, who had multiple pregnancy or polyhydramnios, who had a history of gestational diabetes or who gave birth to a macrosomic baby were excluded from the study. Pregnant women who were hospitalized for delivery were evaluated using the Davey scoring system in terms of pregnancy-related striae density. This evaluation was conducted without any specific sequence, solely by a gynecologist and obstetrician. The Davey scoring system is as follows: The abdomen is divided into four quadrants using the midline and a line drawn horizontally from the umbilicus as a reference. In each quadrant, a score is assigned based on the number of striae present. A score of 0 is given for no striae, 1 for moderate striae (1-3), and 2 for numerous striae (4 or more). The total line score is calculated by summing the scores for all four quadrants. Patients with no stretch marks are classified as belonging to the "no stretch marks" group. Patients with a total striae score of 1 or 2 are classified as belonging to the "mild striae" group, while patients with a score between 3 and 8 are classified as belonging to the "severe striae" group. During abdominal skin examinations, all colors of stripes, including reddish, bright, and silvery stripes, are included. Women who met the specified criteria during pregnancy and whose data were recorded with the Davey scoring system were invited to the hospital to undergo evaluation by a physical medicine and rehabilitation (PMR) specialist at the PMR outpatient clinic between three and six months postpartum. The evaluation process involved a

physical examination method to determine the presence and severity of DRA. Among those evaluated, DRA was defined as significant as follows: A minimum of a 2.5 cm gap is present at any level of the linea alba, or one or more cases are observed just above the umbilicus, at 3 and 5 cm above the umbilicus, and at 3 cm below the umbilicus. "There should be sufficient space in the area for two fingers to fit.

The study included patients of various ages, occupations (high physical activity, low physical activity, housewife), smoking status, presence of chronic disease, number of births, weight gained during pregnancy, week of birth, baby birth weight, family history of SG (yes/no), number of deliveries by caesarean section, breastfeeding status, and other relevant information. The status of milk pumping (yes/no), history of abdominal and/or pelvic floor exercises (yes/no), height, weight (at the time of birth and at the postpartum third to sixth month control), and body-mass index (BMI) information were recorded. Finally, among those with DRG, IRD (inter rectal distance) was measured and recorded via ultrasonography within 3 days by a different gynecologist and obstetrician, who was unaware of the study details, to avoid bias.

Statistical Analysis

Normality of the numerical data was examined by the Shapiro-Wilk test. Since quantitative variables did not meet the normality assumption, minimum, maximum, median value and 1st and 3rd quartile values were given in their descriptive statistics. Differences in measurement results between independent groups were analyzed using the Mann-Whitney U test, as normality assumptions were not met. Additionally, Spearman's correlation analysis was used to understand the relationship structure between the measurement results. SPSS (version 26.0, SPSS Inc., Chicago) software was used for statistical analysis of the data. Significance levels were adjusted according to asymptotic 2-sided tests. $p < 0.05$ was considered statistically significant.

RESULTS

Upon examination of the data from 107 patients included in the study, it was found that while the age of the patients ranged between 19 and 44 years, the average age was 28.76 ± 5.57 years. Additionally, the BMI of the patients was found to be between 17 kg/m^2 and 41 kg/m^2 , with an average of 27.25 ± 4.29 . The number of caesarean sections ranged between 1 and 4, with a mean value of 1.83 ± 0.82 , and the number of births (parity) ranged between 1 and 7, with a mean value of 2.17 ± 0.99 . These findings are consistent with the expected relationship between the number of cesarean sections and age. The gestational age at birth ranged from 35 to 41 weeks, with an average of 38.09 ± 1.27 weeks. The average birth weight was 3040.37 ± 450.56 grams, with a range of 2000 to 4030 grams. It is anticipated that the infant's birth weight will increase with the gestational age. One patient was diagnosed with gestational diabetes mellitus and another with hypothyroidism. Only 4 (3.7%) of the 107 patients were smokers, and their smoking was below 10 cigarettes per day. 10 of the 107 patients (9.25%) reported high physical activity levels, while the remaining 97 (90.65%) patients indicated that their occupations required

low physical activity. None of the patients reported a history of exercise for the pelvic floor muscles ([Table 1](#)).

Table 1. Demographic and clinical characteristics of the study population (n=107)

Descriptive statistics		
	Mean	SD
Number of C/S	1.83	0.82
Age	28.76	5.57
Parity	2.17	0.99
Weight	76.94	11.94
Gestational age	38.09	1.27
Birth weight	3040.37	450.56
BMI	27.25	4.29
DRG1	12.69	4.24
DRG2	12.61	5.08
Davey total	4.96	2.29

C/S: Caesarean sections, BMI: Body-mass index, DRG1: Supraumbilical interrectal distance, DRG2: Infraumbilical interrectal distance, SD: Standard deviation

When Spearman's correlation analysis was performed, there was a strong significant relationship ($p<0.001$) ($\rho=0.479$) between age and parity. There was a strong correlation ($p<0.001$) ($\rho=0.403$) between the age of the patients and the increase in the number of cesarean sections, which is an expected situation. There was a strong correlation ($p<0.001$) ($\rho=0.733$) between the number of births and the increase in the number of cesarean sections, which is a predicted situation in the study. A significant and strong correlation was found between the increase in the number of deliveries and the sub-umbilical interrectal distance (DRG2) ($p=0.009$) ($\rho=0.252$). A correlation was also found between the mother's weight and the baby's birth weight ($p=0.015$) ($\rho=0.236$). There was no correlation between the mother's weight and interrectal distances, but a strong significant

correlation was found for all four Davey scores and the sum of Davey scores ($p=0.002$) ($\rho=0.294$). This may be explained by the fact that obesity alone causes striae. The strong correlation ($p<0.001$) ($\rho=0.375$) between birth week and infant birth weight is a legitimate finding since the birth weight of the baby is expected to increase as the week progresses. The negative correlation ($p=0.044$) ($\rho=-0.195$) between height and number of cesarean sections may be explained by the decrease in cephalopelvic discordance as height increases. Again, a significant correlation was found between height and Davey 1 score ($p=0.039$) ($\rho=0.200$). No significant correlation was found between BMI and interrectal distances, but a strong significant correlation was found for Davey scores ($p=0.033$) ($\rho=0.211$). This may be explained by the relationship between obesity and striae formation.

When the main objective of the study was evaluated in terms of interrectal distances and Davey scores, a strong significant correlation was found for the interrectal distance above the umbilicus and below the umbilicus ($p<0.001$) ($\rho=0.518$). Similarly, when the relationship between infraumbilical interrectal distance and Davey scores was analyzed, a strong significant relationship was found between all four Davey scores and total Davey scores ($p<0.001$) ($\rho=0.349$). Similarly, when the relationship between infraumbilical interrectal distance and Davey scores was analyzed, a strong significant relationship was found between all four Davey scores and total Davey scores ($p=0.002$) ($\rho=0.301$) ([Table 2, 3](#)).

When the supra-umbilicus interrectal distance (DRG 1) and sub-umbilicus diastasis recti (DRG 2) distances were analyzed in terms of total score according to the Davey scoring system, the number of patients with DRG 1 measurement was 12 mm and DRG 2 measurement was 9 mm. In patients with Davey score 1 or 2 (mild striae) ($n=25$), DRG 1 measurements ranged between 6 and 19 mm. DRG 2 measurements ranged between 6 and 24 mm. In patients with a Davey score of 3 or more,

Table 2. Correlation matrix of demographic and clinical variables

Variables		Age	Parity	Weight	BWeek	BW	C/S	Height	PW	BMI
Parity	rho	.479**								
	p	.000								
Weight	rho	-.035	.088							
	p	.721	.367							
BWeek	rho	-.089	-.088	.178						
	p	.361	.366	.067						
BW	rho	.170	.041	.236*	.375**					
	p	.079	.674	.015	.000					
C/S	rho	.403**	.733**	.170	-.156	.016				
	p	.000	.000	.080	.109	.867				
Height	rho	-.162	-.189	.338**	.051	.134	-.195*			
	p	.095	.051	.000	.602	.170	.044			
PW	rho	-.037	.108	.961**	.195*	.226*	.168	.313**		
	p	.703	.266	.000	.044	.019	.084	.001		
BMI	rho	.027	.156	.867**	.185	.167	.190	-.038	.911**	
	p	.784	.115	.000	.061	.093	.055	.700	.000	

BWeek: Birth week, C/S: Number of cesarean sections, BW: Baby weight, PW: Postpartum weight, BMI: Body-mass index, DRG1: Supraumbilical interrectal distance, DRG2: Infraumbilical interrectal distance

Table 3. Correlations between Davey scores and interrectal distances

Variables		Age	Parity	Weight	BWeek	BW	C/S	Height	PW	BMI	DRG1	DRG2	Davey1	Davey2	Davey3	Davey4
DRG1	rho	.079	.131	.075	-.102	-.002	.044	.074	.047	.086						
	P	.418	.177	.441	.297	.987	.652	.447	.628	.389						
DRG2	rho	.037	.252**	.128	-.101	-.099	.122	.130	.076	.096	.518**					
	P	.703	.009	.189	.299	.308	.211	.181	.435	.337	.000					
Davey1	rho	.025	.010	.283**	-.001	.025	.043	.200*	.214*	.211*	.554**	.487**				
	P	.797	.917	.003	.995	.796	.664	.039	.027	.033	.000	.000				
Davey2	rho	.015	-.009	.225*	-.006	-.108	.054	.090	.168	.196*	.451**	.509**	.862**			
	P	.874	.926	.020	.954	.270	.578	.357	.085	.048	.000	.000	.000			
Davey3	rho	-.086	.066	.345**	-.047	.114	.052	.038	.302**	.316**	.331**	.359**	.439**	.470**		
	P	.376	.497	.000	.628	.242	.593	.696	.002	.001	.001	.000	.000	.000		
Davey4	rho	-.067	.102	.310**	-.071	.044	.097	.028	.263**	.288**	.274**	.382**	.415**	.476**	.894**	
	P	.496	.297	.001	.465	.650	.322	.773	.006	.003	.004	.000	.000	.000	.000	
Davey score	rho	-.073	.034	.294**	.035	.055	.116	.083	.228*	.211*	.349**	.301**	.631**	.602**	.685**	.614**
	P	.456	.725	.002	.724	.574	.235	.396	.018	.033	.000	.002	.000	.000	.000	.000

BWeek: Birth week, C/S: Number of caesarean sections, BW: Baby weight, PW: Postpartum weight, BMI: Body-mass index, DRG1: Supraumbilical interrectal distance, DRG2: Intraumbilical interrectal distance

DRG 1 measurements ranged between 6 and 23 mm. When analyzed in terms of DRG 2, measurements ranged between 4 and 26 mm (Table 4).

Table 4. Relationship between Davey scores and interrectal distances

	DRG1	DRG2
	Median [Q1–Q3]	Median [Q1–Q3]
Davey scores		
Mild	9 [8–11]	9 [7–11]
Severe	14 [10–16]	12 [9–16]
*p	<.001	.003

Q1: Percentile 25, Q2: Percentile 75, Min: Minimum, Max: Maximum, *p shows the results of Mann-Whitney U analysis, DRG1: Supraumbilical interrectal distance, DRG2: Intraumbilical interrectal distance

Patients in the mild and severe groups were then compared in terms of DRG 1 and DRG 2. It was found that the groups did not conform to normal distribution and there was a significant difference ($p < 0.001$) between the mild striae group with Davey score 1-2 and the severe striae group with score 3 and above in terms of supra-umbilicus interrectal distance (DRG 1). When evaluated in terms of sub-umbilicus interrectal distance (DRG2), it was observed that the groups did not comply with the normal distribution and there was a significant difference between them ($p = 0.003$). These data suggest that as the striae density increases, the intrarectal distance will also increase and put patients at higher risk of diastasis recti.

DISCUSSION

This study shows that the frequency of SG in pregnant women, whether mild or severe according to the Davey scoring system, can give an idea in predicting diastasis recti. Although the pregnant woman's BMI was effective in the development of striae, the number of previous cesarean sections, gestational week and baby birth weight did not have any significance in terms of striae density and diastasis recti.

A study investigating the relationship between type 1 and type 3 collagen density and the development of abdominal hernias revealed that low collagen levels were associated with an increased risk of hernia development. Furthermore, the incidence of diastasis recti was found to be higher in patients with low collagen levels.⁷ Furthermore, studies have demonstrated that type 1 and 3 collagen levels are diminished in obese patients.⁸ Although our study did not include histological data on collagen types and amounts, the visual appearance of striae density, which is a result of collagen deficiency, was shown to be associated with diastasis recti. In this study, the higher striae density observed in patients with higher BMIs aligns with the findings of the study conducted by Szczyński et al.⁸ A number of studies have indicated that the development of diastasis recti is more prevalent in patients with low collagen levels, and that these patients are more susceptible to hernia formation.⁹⁻¹²

Pregnancy represents one of the most significant factors influencing the development of diastasis recti.¹³ In this study, all patients who had given birth were examined for diastasis recti, indicating that all patients had experienced at least one pregnancy. Nevertheless, there was no discernible correlation between the rise in the number of pregnancies and the interrectal distance. In the study conducted by RM Blotta et al.,⁷ it was asserted that pregnancy alone does not result in permanent diastasis recti.

In a study conducted by Doğan and colleagues,¹⁴ it was proposed that there is a correlation between the formation of adhesions and SG density in patients with a high density of SG. Fibroblast activity is responsible for collagen production. Since the problems arising in this mechanism may play a role in the formation of striae, they may be related to defects in the anterior abdominal wall such as decreased adhesion development and diastasis recti.^{15,16} It has been shown that in the case of normally functioning fibroblasts, both striae

formation and peritoneal adhesions will be less.¹⁷ A study by Kapadia et al.¹⁸ demonstrated a correlation between connective tissue collagen and skin elasticity. The study also revealed a potential link between perineal tears and a deficiency in collagen synthesis.

Despite the prevalence of research indicating a correlation between high infant birth weight and increased maternal weight and the formation of SG, findings from Farahnik et al.¹⁹ and Chang et al.¹ challenge this assumption. Their studies revealed no significant relationship between infant birth weight and maternal striae formation. In this study, although there was a relationship between maternal BMI and striae density, there was no relationship between baby birth weight and striae score. The lack of a relationship between infant birth weight and the study may be attributed to the exclusion of macrosomic babies and pregnancies with polyhydramnios. Studies conducted by Wierrani et al.²⁰ demonstrated that the application of vitamin C, hyaluronic acid, and various vitamins to areas with striae led to an increase in fibroblast activity and collagen production in those areas. The results of this study indicate that it is important to consider the possibility of diastasis recti developing in patients with high SG scores due to defective fibroblast activity and low collagen levels.

Limitations

The use of only the Davey score and ultrasonographic measurements is among the limitations of this research. It is clear that more objective results can be obtained if samples are taken during the operation and histopathologic examinations are performed and added to the study.

CONCLUSION

The SG score can be utilized as a predictor of the likelihood of diastasis recti occurring during pregnancy, with the potential to inform clinical decision-making regarding the need for surgical intervention. Furthermore, this study may contribute to the understanding of the pathogenesis of striae gravidarum and diastasis recti, particularly when supported by future collagen studies conducted in larger patient cohorts and fascia tissue samples.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Clinical Researches Ethics Committee of Erzincan Binali Yildirim University (Date: 22.03.2021, Decision No: 05/20).

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 impact of age and sex on clinical symptoms in low and intermediate-low risk pulmonary embolism

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Cite this article as: Arı E, Arı M. The impact of age and sex on clinical symptoms in low and intermediate-low risk pulmonary embolism. *J Med Palliat Care*. 2025;6(4):361-366.

Received: 25.06.2025

Accepted: 17.07.2025

Published: 31.08.2025

ABSTRACT

Aims: The diagnostic process of pulmonary thromboembolism (PTE) can be complex due to its wide spectrum of clinical presentations. The type and frequency of symptoms vary not only with the embolism risk category but also in relation to individual demographic factors such as age and sex. This study aims to evaluate the influence of demographic variables on clinical presentation by investigating the distribution of symptoms according to age and sex in patients with acute PTE classified as low or intermediate-low risk.

Methods: This retrospective, cross-sectional study was conducted at the Emergency Department of Dışkapı Yıldırım Beyazıt Training and Research Hospital between February 1, 2020, and February 1, 2021. A total of 329 patients aged 18 years and older who were classified as low or intermediate-low risk according to the 2019 European Society of Cardiology guidelines were included in the study. The patients' demographic characteristics and clinical symptoms were retrospectively analyzed. Symptom distributions were compared across different age and sex groups.

Results: The most frequently reported symptoms among patients were dyspnea (79.3%) and chest pain (53.7%). Leg pain and/or swelling were significantly more common in younger male patients (26%, $p=0.001$), while presyncope was more frequently observed in older female patients (27.3%, $p=0.001$). Hemoptysis was found to be significantly less common in older female patients compared to other groups (8.2%, $p=0.012$).

Conclusion: The symptom profile in PTE varies significantly based on patients' demographic characteristics. Our study suggests that recognizing these differences during the diagnostic process may help facilitate clinical management by preventing diagnostic delays, particularly in patient groups presenting with atypical symptoms.

Keywords: Gender, pulmonary embolism, symptoms, age

INTRODUCTION

Pulmonary thromboembolism (PTE) is a serious cardiopulmonary emergency characterized by a wide range of clinical manifestations, often posing diagnostic challenges.¹ The presentation and severity of symptoms vary depending not only on the size and location of the embolus but also on individual patient characteristics such as age, sex, and cardiopulmonary reserve. This heterogeneity necessitates the evaluation of symptoms in the context of demographic factors to enable early diagnosis and the development of appropriate treatment strategies.² PTE may present along a broad clinical spectrum, ranging from an asymptomatic course to hemodynamic instability or sudden death. In the literature, the most commonly reported clinical symptoms are dyspnea and pleuritic chest pain, while syncope is recognized as a key indicator of right ventricular dysfunction.³ Additionally, although rare, hoarseness due to Ortner's syndrome-caused by compression of the recurrent laryngeal nerve by a dilated

pulmonary artery has also been reported.⁴ The influence of age on the clinical manifestations of PTE is well established, with older patients tending to present with more atypical symptoms. Moreover, due to hormonal and anatomical differences, sex is considered to play a significant role in symptomatology.⁵ While estrogen and related neurohormonal mechanisms are known to influence the pathophysiology of thromboembolic events, the specific impact of these factors on the clinical presentation of PTE remains insufficiently explored.

PTE often presents with common symptoms such as dyspnea and chest pain, which may mimic other conditions seen in the emergency department, thereby complicating the diagnostic process.⁶ It is well recognized that the clinical course and symptomatology of PTE can vary depending on the embolism risk level. Therefore, the evaluation of demographic factors such as age and sex is of critical importance in PTE patients.

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Considering these demographic variables plays a key role in facilitating early diagnosis and planning effective treatment strategies. In this study, patients classified as high risk with hemodynamic instability were excluded, allowing for the analysis to focus solely on those in the intermediate-low and low risk groups. This approach aimed to enable a more consistent assessment of clinical findings within a homogeneous patient population and to more clearly elucidate the relationship between symptoms and demographic variables.

METHODS

Ethics

The study was approved by the Clinical Researches Ethics Committee of Ankara Etlik City Hospital (Date: 06.03.2024, Decision No: AEŞH-BADEK-2024-058). Throughout the study, the ethical principles outlined in the Declaration of Helsinki were strictly followed, and patient rights were fully respected.

This retrospective, cross-sectional, and observational study was conducted at the Emergency Department of Dışkapı Yıldırım Beyazıt Training and Research Hospital between February 1, 2020, and February 1, 2021. The study population consisted of patients aged 18 years and older who presented to the emergency department during the specified period and were diagnosed with acute PTE. The diagnosis of acute PTE was established based on clinical findings, laboratory tests, and radiological evaluations, with computed tomography pulmonary angiography-the gold standard diagnostic modality-being utilized for confirmation. The diagnostic criteria were assessed in accordance with current international guidelines.

Risk Stratification of Pulmonary Embolism

The risk levels of the patients included in the study were classified according to the criteria outlined in the 2019 European Society of Cardiology (ESC) Guidelines on Pulmonary Embolism.⁷ This classification considered hemodynamic stability, clinical findings, laboratory results, and imaging parameters. The high-risk group comprised patients exhibiting signs of hemodynamic instability, such as hypotension, shock, or cardiac arrest. The intermediate-high risk group included hemodynamically stable patients with clinical and laboratory indicators suggesting elevated risk. In this study, only patients categorized as low or intermediate-low risk were included. This approach was adopted to ensure a more homogeneous patient population and to minimize the confounding clinical impact of hemodynamic instability.

Patient data were retrospectively collected through the hospital's electronic medical record system. The variables included in the analysis comprised demographic characteristics (age and sex) as well as comorbid conditions (such as hypertension, diabetes mellitus, and malignancy). Additionally, symptoms reported by patients at the time of emergency department presentation-such as dyspnea, chest pain, syncope, and hemoptysis-were systematically recorded. Vital signs measured upon admission (blood pressure, heart rate, respiratory rate, and oxygen saturation) and physical examination findings were also evaluated.

Furthermore, patients' clinical course, treatment processes, and hospitalization status were monitored throughout their follow-up.

Sample Size Determination

The sample size for this study was calculated using the G*power 3.1.9.7 statistical power analysis software. A power analysis was conducted for the Chi-square test, which was planned for group comparisons to detect significant differences. An effect size (w) of 0.3 (moderate), an alpha error probability of 0.05, and a statistical power of 80% (0.80) were assumed. Considering the study aimed to evaluate four age-sex subgroups (young males, elderly males, young females, elderly females), it was estimated that each subgroup should include at least 130 patients, indicating a minimum total sample size of 520 patients.

However, our final cohort comprised 329 patients who met the predefined inclusion and exclusion criteria. The main reason for not reaching the target sample size was a marked decrease in the number of emergency department admissions during the study period, which coincided with the coronavirus disease 2019 (COVID-19) pandemic. Despite this limitation, the available sample size was deemed sufficient to perform meaningful and reliable analyses, considering the retrospective nature of the data and the study objectives. This issue has been acknowledged as a limitation and was taken into account when interpreting the results.

Inclusion Criteria

- Age 18 years or older
- Diagnosis of acute PTE following presentation to the emergency department
- Classified as intermediate-low or low risk according to the 2019 ESC guidelines
- Availability of complete clinical and radiological data

Exclusion Criteria

- Patients diagnosed with intermediate-high or high-risk PTE
- Cases with chronic PTE identified at the time of diagnosis
- Asymptomatic patients or those diagnosed incidentally
- Individuals under the age of 18
- Pregnant patients
- Patients with incomplete or missing clinical data
- Patients with a current diagnosis of COVID-19 infection or a documented history of previous COVID-19 infection

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as counts and percentages for categorical variables, and as mean $\pm$ standard deviation or median (minimum-maximum) for continuous variables, depending on the normality of distribution. The Kolmogorov-Smirnov test was used to assess the normality of data distribution. For

comparisons between groups, the independent samples t-test was used for normally distributed continuous variables, while the Mann–Whitney U test was applied for non-normally distributed variables. Differences between categorical variables were evaluated using the Chi-square test. When a significant difference was observed in multiple group comparisons, the Bonferroni correction was applied to adjust for multiple testing. Correlation analysis was performed to assess the relationships between symptoms and mortality. A p-value of <0.05 was considered statistically significant; after Bonferroni correction, the threshold for significance was set at $p<0.0125$.

RESULTS

A total of 520 patients were initially planned to be included in the study, and 456 patients were ultimately recruited. Of these, 7 patients were excluded due to chronic PTE, 18 patients were excluded as they were asymptomatic or incidentally detected, 48 patients were excluded due to being in the high or moderate-to-high risk group, 28 patients were excluded because of incomplete medical records, and 26 patients were excluded due to active or prior COVID-19 infection. As a result, 329 patients were included in the final analysis. The patient recruitment and selection process is summarized in the patient inclusion and exclusion flowchart (Figure).

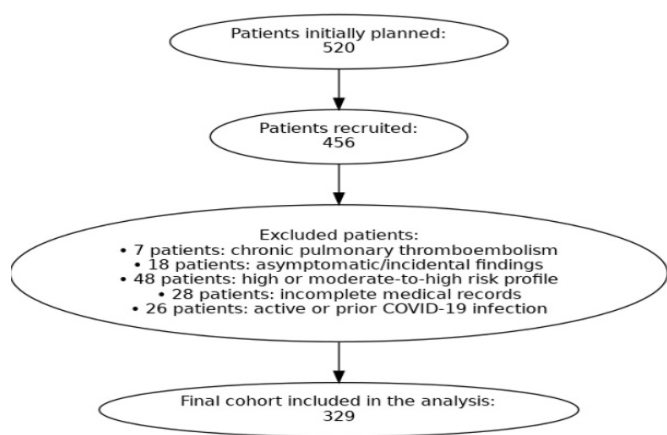


Figure. Patient inclusion and exclusion flowchart

The final study cohort consisted of 329 patients, of whom 190 (57.7%) were female and 139 (42.3%) were male. The mean age of the patients was 66 ± 16.5 years. Acquired risk factors were present in 52.2% of the cases ($n=172$), with immobilization being the most common, observed in 23.4% ($n=77$) of patients. Additionally, 51.1% ($n=169$) of patients had at least one comorbid condition. Among comorbidities, hypertension was the most frequently reported diagnosis (31.3%, $n=103$), followed by diabetes mellitus (14.3%, $n=47$).

Regarding presenting symptoms in the emergency department, 94.8% ($n=312$) of patients reported at least one symptom. The most common symptom was dyspnea, present in 262 patients (79.6%), followed by chest pain (63.5%, $n=209$) and cough (19.4%, $n=64$).

Detailed demographic and clinical characteristics of the study population are presented in Table 1.

Table 1. Demographic and clinical characteristics of the patients

	All patients n (%) 329 (100%)
Age, years (mean $\pm$ SD)	66 $\pm$ 16.5
Gender	
Female	190 (57.8%)
Male	139 (42.2%)
Acquired risk factor	172 (52.2%)
Immobilization	77 (23.4%)
Comorbidity	169 (51.1%)
Hypertension	103 (31.3%)
Diabetes mellitus	47 (14.3%)
Symptoms	312 (94.8%)
Shortness of breath	262 (79.6%)
Chest pain	209 (63.5%)
Cough	64 (19.4%)

SD: Standard deviation

In this study, the age groups were defined by using the median age within each sex category as a reference point, and patients were subsequently classified into “young” and “elderly” subgroups. Based on this method, the mean age for male patients was 50 ± 12.2 years in the young group and 78 ± 6.2 years in the elderly group. Among female patients, the mean age was 53 ± 11.5 years for the young subgroup and 79 ± 6.6 years for the elderly subgroup. Statistical analyses demonstrated that this age stratification was significantly associated with sex ($p<0.001$). Accordingly, the age classification considering sex-specific distributions was deemed an appropriate approach for evaluating clinical findings in the context of both age and sex. The distribution of ages by sex is presented in Table 2.

Table 2. Age distribution of patients by sex

	Young men n:77 (23.4%)	Old men n:62 (18.9%)	Young women n:80 (24.3%)	Old women n:110 (33.4%)	p value
Age (mean $\pm$ SD)	50 $\pm$ 12.2	78 $\pm$ 6.2	53 $\pm$ 11.5	79 $\pm$ 6.6	<0.001

SD: Standard deviation

The 329 patients included in the study were categorized into four groups based on sex and median age: younger males, older males, younger females, and older females. Symptom distributions were then analyzed across these subgroups. Although dyspnea and chest pain were the most commonly reported symptoms in all groups, the distribution of certain symptoms showed statistically significant differences according to age and sex.

Presentation with leg pain or swelling was significantly more frequent in younger male patients (26%, $p=0.001$). This symptom was observed in only 4.8% of older males, 13.8% of younger females, and 7.3% of older females. Presyncope was notably more common in the older female group, with 27.3% of patients presenting with this symptom. In comparison, the rates were 10.4% in younger males, 14.5% in older males, and 7.5% in younger females ($p=0.001$).

On the other hand, hemoptysis was significantly less frequent in older female patients (8.2%, $p=0.012$), while it was reported in 25% of younger females, 22.1% of younger males, and 19.4% of older males. Other symptoms such as dyspnea, chest pain, cough, and palpitations did not show statistically significant differences between groups ($p>0.05$).

A detailed breakdown of symptom distribution by patient subgroup is provided in [Table 3](#).

DISCUSSION

In this study, the distribution of symptoms according to age and sex was evaluated in cases of acute PTE classified as intermediate-low and low risk. The findings indicate that the clinical presentation of PTE is influenced not only by embolic burden and localization but also significantly by demographic factors. The most frequently reported symptoms were dyspnea (79.3%) and chest pain (53.7%), which are largely consistent with the prevalence rates reported in large cohort studies such as PIOPED-II.⁸ The frequency of chest pain similarly aligns with current observational data.

Moreover, hormonal and physiological differences associated with sex may particularly influence the clinical symptom profile in patients with intermediate-low and low-risk PTE. In women, estrogen is known to play a pivotal role in modulating vascular tone, the coagulation system, and endothelial function. In addition to its prothrombotic effects, postmenopausal hormonal changes have been shown to impact cardiopulmonary reserve capacity and autonomic nervous system responses. These physiological alterations may contribute to the higher prevalence of symptoms such as presyncope-linked to impaired hemodynamic adaptation-among older female patients.

The age at which PTE is diagnosed shows significant variation by sex. In general, PTE tends to occur at younger ages in male patients, a finding that is often attributed to certain risk factors more commonly observed in men.⁹ In contrast, PTE is typically diagnosed at older ages in women, which is thought to be influenced by hormonal changes and physiological alterations associated with the postmenopausal period.¹⁰ These demographic differences highlight the importance of age and sex as key determinants in the diagnosis of PTE and underscore the need for individualized approaches in risk assessment and clinical management.

In our study, a statistically significant difference in the mean age at diagnosis was also observed between male and female patients. Male patients were diagnosed with PTE at a younger age compared to females, who were diagnosed later in life. These findings are consistent with the current literature and emphasize the importance of considering sex- and age-specific risk factors and symptom profiles in clinical evaluation. Additionally, to classify patients by age and sex, “young” and “elderly” subgroups were created by using the median age within each sex group as a reference. This approach allowed for a more accurate analysis of clinical symptoms and risk factors by accounting for sex-specific age distributions. In our study, significant differences were observed between these age groups, supporting a clearer understanding of the impact of demographic variables on PTE presentation.

The analysis of symptoms based on age and sex revealed distinct clinical variations among different patient subgroups. Notably, the higher frequency of leg pain and swelling in younger male patients suggests an increased risk of deep vein thrombosis (DVT) within this group. The existing literature supports this observation, indicating that the lifetime risk of venous thromboembolism is higher in men compared to women.¹¹ In our study, ultrasonographic evaluations also showed a higher rate of DVT detection among younger male patients compared to other age and sex groups; however, this difference did not reach statistical significance. In a retrospective study conducted among Chinese patients with DVT, it was reported that age and sex influence the incidence of DVT, with a higher risk observed particularly in males and age-related triggers varying accordingly.¹² These findings support the notion that DVT may occur more frequently and present with more pronounced symptoms in male patients.

Although our study included only intermediate-low and low-risk PTE cases, the significantly higher prevalence of presyncope in the older female group (27.3%) suggests that early hemodynamic alterations and right ventricular strain may manifest more prominently in this population. Age-related reductions in right ventricular functional reserve, decreased vascular compliance, and changes in autonomic regulatory mechanisms may contribute to the development of presyncope-like symptoms even in the absence of overt hemodynamic instability.¹³ Moreover, the literature highlights that presyncope may serve as an early indicator of potentially serious cardiovascular conditions, underscoring the need for

Table 3. Comparison of symptoms in acute pulmonary embolism according to age and sex					
	Young men n:77 (23.4%)	Old men n:62 (18.9%)	Young women n:80 (24.3%)	Old women n:110 (33.4%)	p value*
Dyspnea	56 (72.7%)	54 (87%)	65 (81.3%)	87 (79.1%)	0.208
Chest pain	51 (66.2%)	41 (66.1%)	55 (68.8%)	62 (56.4%)	0.295
Cough	19 (24.7%)	12 (19.4%)	11 (13.8%)	22 (20.8%)	0.388
Hemoptysis	17 (22.1%)	12 (19.4%)	20 (25%)	9 (8.2%)	0.012**
Palpitation	7 (9.1%)	6 (9.7%)	6 (7.5%)	16 (14.5%)	0.415
Leg pain/swelling	20 (26%)	3 (4.8%)	11 (13.8%)	8 (7.3%)	0.001**
Presyncope	8 (10.4%)	9 (14.5%)	6 (7.5%)	30 (27.3%)	0.001**

*Chi-square test was applied. **With Bonferonni correction, $p<0.0125$ was considered significant.

careful monitoring and management of such patients in the emergency department setting.¹⁴ In this context, for patients with PE presenting with presyncope, particularly elderly women, it is crucial to accurately assess the risk of possible complications and ensure appropriate clinical follow-up. This observation suggests that hemodynamic instability in elderly female patients may manifest with earlier clinical signs.

The lower frequency of hemoptysis observed in older female patients compared to other groups may suggest a reduced risk of pulmonary infarction in this population. Pulmonary infarction is typically associated with distal arterial occlusion and insufficient collateral circulation. According to the literature, aging may promote the development of collateral pulmonary vessels, which could reduce the incidence of infarction and, consequently, the occurrence of hemoptysis.¹⁵ Additionally, it has been reported that reduced alveolar tissue elasticity and changes in capillary membrane permeability in elderly individuals are among the factors that may limit the development of hemoptysis. Furthermore, in a study by Pribish et al.,¹⁶ it was noted that the incidence of hemoptysis was lower in females compared to males, and this difference was suggested to be attributable to physiological variations related to age and sex.

Limitations

This study has several limitations. First, it was conducted retrospectively at a single center, which may pose a risk of incomplete records and information bias, potentially affecting the accuracy of patient data. The evaluation of symptoms relied on patient self-reports and clinical documentation, which may have limited the ability to fully capture the diversity of subjective symptoms. Additionally, the relatively small study population and lack of representation from different ethnic groups may restrict the generalizability of the findings. Moreover, since the data collection period overlapped with the COVID-19 pandemic, there was a noticeable decline in patient admissions, and patients with an active or prior COVID-19 infection were excluded. These factors further limited the sample size and study scope and may affect the generalizability of the results.

CONCLUSION

This study demonstrated that symptom presentation in patients with intermediate-low and low-risk PTE can vary by age and sex. Notably, DVT-related symptoms were more frequently observed in younger males, while presyncope was more prominent among older female patients. Furthermore, the significantly lower rate of hemoptysis in older women suggests that age-related physiological changes may play a role in reducing the risk of pulmonary infarction in this population.

Recognizing these differences in symptom profiles may improve diagnostic accuracy, particularly in patients presenting with atypical symptoms, and facilitate more effective clinical management. Age- and sex-sensitive clinical assessment strategies may contribute substantially to the early diagnosis and treatment of PTE.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Clinical Researches Ethics Committee of Ankara Etlik City Hospital (Date: 06.03.2024, Decision No: AEŞH-BADEK-2024-058).

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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Quality and content analysis of hip arthroscopy videos on YouTube™

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Cite this article as: Ateş O, Karıksız M. Quality and content analysis of hip arthroscopy videos on YouTube™. *J Med Palliat Care*. 2025;6(4):367-370.

Received: 18.06.2025

Accepted: 30.07.2025

Published: 31.08.2025

ABSTRACT

Aims: We have planned a study aimed at analyzing the content and quality of videos related to hip arthroscopy on YouTube. YouTube™ is indeed one of the most popular platforms for video content on the Internet, offering a vast array of videos on various topics ranging from entertainment to educational resources. The platform hosts a substantial amount of orthopedic video content that is not subject to any screening or editorial review process. The quality of videos on hip arthroscopy has not been assessed before. This study aimed to evaluate the quality and comprehensiveness of YouTube™ videos on the topic of hip arthroscopy.

Methods: The videos were evaluated by one orthopedic surgeon using the Journal of the American Medical Association (JAMA) criteria, the DISCERN tool for consumer health information quality and the Global Quality Score (GQS). This evaluation aimed to determine the accuracy of these assessment methods.

Results: Among the first 50 videos evaluated, 20 (40%) were uploaded by doctors, 10 (20%) by physiotherapists, 8 (16%) by individual patients sharing their experiences, 3 (6%) by clinics, 4 (8%) by health channels, and 5 (10%) by hospitals. The average number of views was 1.150 (range: 1-18.553), the average video length was 12 minutes and 10 seconds (range: 24 seconds to 1 hour and 10 minutes), the average number of likes was 102.46 (range: 1-3,546), and the average number of dislikes was 8 (range: 0-98). The average DISCERN score was 32.46 (range: 14-68), the average VPI was 40.36 (range: 0-460), the average GQS was 2.24 (range: 1-4), and the average JAMA score was 2.41 (range: 1-3).

Conclusion: The quality of information about hip arthroscopy on YouTube is generally low and offers limited educational value. Therefore, healthcare providers should caution their patients about relying on these sources and provide more reliable educational alternatives.

Keywords: Hip arthroscopy, video quality, video analysis, YouTube

INTRODUCTION

Today, the easiest, cheapest and fastest way to access information is using the internet. As in other fields, many people refer to online resources to get an idea before medical applications. Video sharing sites and online search sites have become quite popular in this respect.¹

YouTube has emerged as one of the most prominent platforms for video content, catering to a diverse audience with interests spanning from entertainment to education. More than 400 videos are uploaded on YouTube per minute and more than hundred million hours of videos are watched every day.² YouTube hosts a vast collection of medical education videos.³ Many patients turn to the platform to utilize its extensive video archive as they seek information about their health conditions.⁴

In wide video in pain, there is a significant amount of content related to orthopedic procedures, including hip arthroscopy.⁵ However, unlike traditional medical literature, the content

on YouTube is not subjected to any formal screening or editorial review process, raising concerns about its quality and reliability.

Patients with hip joint disorders also frequently search for their diseases on video sharing sites. Hip arthroscopy is a relatively new and very popular topic in orthopedic surgery. Hip arthroscopy is a minimally invasive surgery that employs an arthroscope to both diagnose and address issues within the hip joint. Conditions such as impingement, labral tear, bone spurs, synovitis and loose fragments can be treated with hip arthroscopy.⁶

Despite the growing presence of hip arthroscopy videos on YouTube, there has been no comprehensive assessment of their quality and educational value. Given the potential influence of these videos on patient knowledge and decision-making, it is crucial to evaluate their accuracy and comprehensiveness.

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This study aims to fill this gap by systematically analyzing the quality of YouTube videos on hip arthroscopy, utilizing established evaluation tools such as the Journal of the American Medical Association (JAMA) criteria, the DISCERN tool for consumer health information quality, the Global Quality Score (GQS), and the hip score. By doing so, we seek to provide insights into the current state of online educational resources for hip arthroscopy and offer recommendations for healthcare providers and patients alike.

METHODS

Our study was designed as a cross-sectional study and no ethics committee approval was obtained because no animal or human material was used and none of the similar studies in the literature required ethics committee approval. In accordance with the World Medical Association Declaration of Helsinki, we did not apply to any medical ethics committee for the approval of this study because all of the videos used in the study were obtained from a public social media site and did not contain human or animal subjects.

This study aimed to evaluate the quality and comprehensiveness of YouTube™ videos on the topic of hip arthroscopy. A systematic search was conducted on June 1, 2024, using the keyword "Hip arthroscopy" on YouTube, which yielded 28 million results. From these, the first 50 videos were selected for detailed analysis.

The inclusion criteria for the videos were: content related to hip arthroscopy, available in English, and accessible to the public without any restrictions. One orthopedic surgeon evaluated the selected videos using the following assessment tools: JAMA: This tool assesses video quality based on authorship, attribution, disclosure, and currency. By assigning 1 point for the presence of each criterion, the total JAMA benchmark score was calculated. DISCERN: This tool evaluates the quality of consumer health information, focusing on reliability and treatment options.⁸ DISCERN consists of 16 questions (graded 1-5) and three parts: reliability (questions 1-8), quality information on treatment choices (questions 9-15), and overall score (question 16). The DISCERN manual contains detailed information for each question, as well as instructions and examples to make the evaluation easy. According to this tool, considering the total average scores, websites were divided into 5 groups as follows: score between 16 and 26 is very poor, score between 27 and 38 is poor, score between 39 and 50 is fair, score between 51 and 62 is good, and score higher than 63 is excellent. GQS: This score rates the overall quality and flow of the video, considering its educational value to the general public.^{9,10} The video power index (VPI) is a metric used to measure the popularity of YouTube videos. It is calculated by multiplying the like ratio by the view ratio and then dividing the result by 1000.¹¹

For each video, the following data was collected: Upload source (doctor, physiotherapist, patient, clinic, health channel, hospital). Number of views, video length, number of dislikes and likes. Scores based on the JAMA criteria, DISCERN, GQS, and hip score.

Descriptive statistics were used to summarize the data, standard deviation, including mean and range where applicable. The scores from the various assessment tools were analyzed to determine the overall quality and comprehensiveness of the videos.

By using these established criteria and tools, this study aimed to provide a thorough evaluation of the quality and educational value of hip arthroscopy videos available on YouTube™.

RESULTS

A total of 50 videos were included in the analysis. The average number of views per video was 1.150, with a range from 1 to 18.553. The average duration of the videos was 12 minutes and 10 seconds, ranging from 24 seconds to 1 hour and 10 minutes. The videos received an average of 102.46 likes (range: 1-3.546) and 8 dislikes (range: 0-98) (Table 1).

Table 1. Demographic and quality scores of YouTube video analysis		
Metric	Average value	Range
Number of views	1150	1- 18.553
Video length	12m 10s	24s-1h 10m
Number of likes	102.46	1-3.546
Number of dislikes	8	0-98
DISCERN score	32.46	14-68
VPI	40.36	0-460
GQS	2.24	1-4
JAMA score	2.41	1-3
VPI: Video power index, GQS: Global Quality Score, JAMA: Journal of the American Medical Association		

The distribution of video upload sources was as follows: 20 (40%) by doctors, 10 (20%) by physiotherapists, 8 (16%) by individual patients, 3 (6%) by clinics, 4 (8%) by health channels, and 5 (10%) by hospitals (Figure).

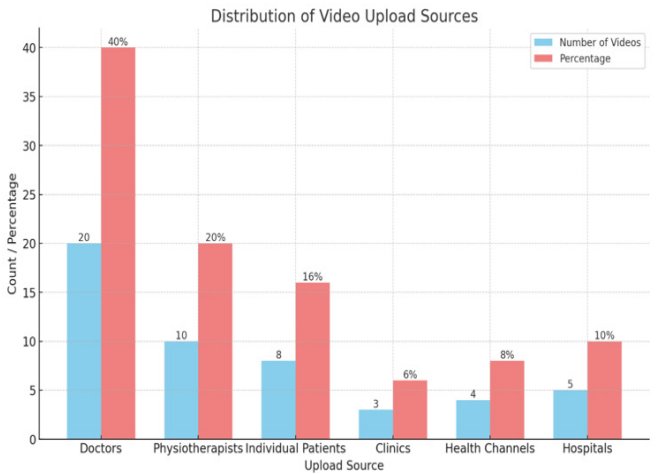


Figure. Analysis results of videos by upload source type

Quality assessment scores were calculated using several standardized tools. The DISCERN score, which evaluates the quality of consumer health information, had an average of 32.46, with scores ranging from 14 to 68. The VPI, measuring video popularity, averaged 40.36, with a range from 0 to 460.

The GQS, assessing overall video quality, averaged 2.24, with scores between 1 and 4. Finally, the JAMA score, evaluating the reliability and quality of medical information, averaged 2.41, ranging from 1 to 3 (Table 1). The average DISCERN score was 32.46 (range: 14-68), the average VPI was 40.36 (range: 0-460), the average GQS was 2.24 (range: 1-4), and the average JAMA score was 2.41 (range: 1-3). There was a statistically significant relationship observed between the video length, likes, VPI, and the JAMA, GQS, and DISCERN scores ($p < .05$). Here, it shows inverse correlation with rho values (Table 2).

Table 2. Correlation between video metrics and quality assessment scores

Feature	JAMA (rho; p)	DISCERN (rho; p)	GQS (rho; p)
VPI	-0.70; <.01	-0.78; <.01	-0.73; <.01
Likes	-0.68; <.01	-0.80; <.01	-0.76; <.01
Duration	-0.80; <.01	-0.84; <.01	-0.74; <.01

VPI: Video power index, GQS: Global Quality Score, JAMA: Journal of the American Medical Association, Rho: Spearman's rho, p: p value

DISCUSSION

The Internet serves as a resource where patients can cross-reference information given by their clinicians and gather additional, new, or sometimes conflicting data.⁴ Patients regard the Internet as an important source of health information, which has influenced the dynamics between patients and healthcare providers.⁴ Several studies have been carried out to evaluate the quality of YouTube videos related to orthopedic diseases.³ The findings of this study highlight a significant issue regarding the quality of hip arthroscopy videos available on YouTube. Despite the platform's popularity and its extensive array of video content, the educational value and reliability of the information presented in these videos are generally low.⁵ This is particularly concerning given the high volume of search results and the potential influence these videos can have on patients seeking medical information online. Some studies have shown that low-quality content obtained from YouTube negatively affects the doctor-patient relationship.¹¹⁻¹³

Among the first 50 videos evaluated, the majority were uploaded by doctors (40%) and physiotherapists (20%), followed by individual patients (16%), clinics (6%), health channels (8%), and hospitals (10%). While one might expect higher quality content from professional sources such as doctors and hospitals, the results indicate that even these videos often fall short of delivering comprehensive and accurate information. While it is often noted that clinicians are the primary uploaders of videos in various studies, there are also reports indicating that clinicians contribute fewer videos, similar to what our data suggests.¹⁴ Despite the generally high-quality content of clinician-uploaded videos, literature indicates that these videos tend to have lower viewership because they may not be easily understood by patients.¹⁵ Additionally, some studies highlight that videos uploaded by clinicians can be lacking in both content and quality.¹⁶

The average DISCERN score of 32.46 out of a possible 80 points underscores the inadequacy of the consumer health

information provided in these videos. This score suggests that many videos lack essential details about treatment options and the reliability of the information presented. Similarly, the average GQS of 2.24 out of 5 indicates that the overall educational quality and flow of the videos are suboptimal. The relatively low JAMA scores, averaging 2.41 out of 4, further emphasize the deficiencies in authorship, attribution, disclosure, and currency of the videos. These scores reflect a need for greater transparency and adherence to quality standards in the creation and dissemination of online medical content. In our study, the average JAMA, the average GQS and the average DISCERN score were consistent with findings reported in the literature.¹¹⁻¹⁶ Higher quality videos were associated with higher DISCERN and JAMA scores.

While the number of publications on hip arthroscopy in our country has begun to increase in recent years, it remains quite low.¹⁷ In addition to these publications, there has also been an increase in the number of informative videos. MacLeod et al.¹⁸ also noted the low quality of these publications in their systematic review. While this low quality is to be expected in a relatively new treatment like hip arthroscopy, the same situation exists in publications covering meniscal injuries.¹⁹ Therefore, the main problem with surgically informative YouTube videos remains the lack of quality.

The high variability in video length, views, likes, and dislikes suggests that there is no consistent standard for producing hip arthroscopy videos on YouTube. This inconsistency may contribute to the overall low quality of information available, as viewers are left to navigate a wide range of content without clear indicators of reliability.

This is particularly worrisome considering the wide audience reach of YouTube. The average view count we observed indicates that a substantial number of individuals are potentially exposed to inaccurate information about hip arthroscopy. This can lead to unrealistic expectations, poor treatment decisions, and unnecessary anxiety for patients.

Given these findings, it is imperative for healthcare providers to guide their patients towards more reliable and comprehensive educational resources. Providers should also consider creating and sharing high-quality videos that adhere to established guidelines for medical information. This would not only improve the quality of online health information but also help patients make more informed decisions about their care.

Limitations

This study has some limitations. First, the data is collected from YouTube and may not be generalizable to other platforms. Second, the study relies on the accuracy of the self-reported information in the video descriptions. Third, the scoring instruments used have limitations. For example, the JAMA criteria may not be fully applicable to all videos, and the hip score is a specific metric designed for a particular surgical procedure.

Despite these limitations, this study will provide valuable insights into the quality and content of hip arthroscopy videos on YouTube.

CONCLUSION

While YouTube offers a convenient platform for disseminating information about hip arthroscopy, the current state of video content is insufficient for educational purposes. Efforts must be made to improve the quality and reliability of these videos to ensure that patients receive accurate and valuable health information.

ETHICAL DECLARATIONS

Ethics Committee Approval

Our study was designed as a cross-sectional study and no ethics committee approval was obtained because no animal or human material was used and none of the similar studies in the literature required ethics committee approval.

Informed Consent

Since all of the videos used in the study were obtained from a public social media site, informed consent is not required.

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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Prognostic significance of inflammatory biomarkers in predicting mortality among geriatric patients with sepsis in the intensive care unit

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Cite this article as: Bulun Yediyıldız M, Taşkın K, Durmuş İ, Fidan R. Prognostic significance of inflammatory biomarkers in predicting mortality among geriatric patients with sepsis in the intensive care unit. *J Med Palliat Care*. 2025;6(4):371-376.

Received: 04.06.2025

Accepted: 31.07.2025

Published: 31.08.2025

ABSTRACT

Aims: This study aims to investigate the prognostic significance of inflammatory biomarkers including the C-reactive protein (CRP)/albumin ratio, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and procalcitonin (PCT) in predicting mortality among geriatric patients with sepsis in the intensive care unit (ICU).

Methods: This retrospective study analyzed the medical records of 239 patients aged 65 years and older who were hospitalized with sepsis in the ICU between May and October 2023. Demographic characteristics, APACHE II scores, laboratory biomarkers (CRP, PCT, complete blood count), length of ICU stay and mortality outcomes were collected. Univariate and multivariate logistic regression analyses were used to determine predictors of mortality.

Results: The overall mortality rate was 66.9%. CRP, CRP/albumin ratio, mean platelet volume (MPV), red blood cell distribution width (RDW), lactate and APACHE II scores were significantly higher ($p < 0.05$). In multivariate analysis only the CRP/albumin ratio and APACHE II score remained independent predictors of mortality. The CRP/albumin ratio showed moderate discriminatory power (AUC: 0.632) at a cutoff value of 6.20, with a sensitivity of 48.8% and a specificity of 73.4%.

Conclusion: The CRP/albumin ratio and APACHE II score were independently associated with mortality in elderly septic patients. These accessible and cost-effective parameters may aid in early risk stratification and guide clinical decision-making in the ICU setting.

Keywords: Sepsis, APACHE II, elderly, inflammatory, intensive care units, mortality

INTRODUCTION

Sepsis is a life-threatening condition characterized by a dysregulated host response to infection, frequently leading to organ dysfunction and high mortality rates particularly in elderly populations.¹ Due to immunosenescence and the prevalence of comorbidities, geriatric patients are especially vulnerable to rapid clinical deterioration and adverse outcomes when sepsis occurs.^{2,3}

Accurate and early prediction of mortality in septic patients remains a critical challenge in intensive care practice. While clinical scoring systems such as the APACHE II are widely used for assessing severity and prognosis, recent studies suggest that various hematological and biochemical parameters may also serve as valuable prognostic markers. Inflammatory biomarkers and total blood count have gained increasing attention due to their accessibility, cost-effectiveness and potential to reflect systemic inflammatory burden.⁴⁻⁸ Consequently, researchers have increasingly

focused on accessible, cost-effective laboratory biomarkers that can provide additional prognostic value.^{5,9}

Given the unique immunological profile of older adults, it is important to assess the predictive performance of these markers specifically within geriatric cohorts. This study aims to evaluate the relationship between inflammatory biomarkers and mortality in elderly sepsis patients admitted to the intensive care unit (ICU) and determine whether these markers, alongside APACHE II can support early risk stratification. By integrating these biomarkers with clinical scoring systems such as APACHE II, we sought to identify reliable predictors that could enhance early risk stratification and guide clinical decision-making in the intensive care setting.

METHODS

This retrospective study was conducted at Tuzla State Hospital with the approval of the Scientific Researches

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Ethics Committee of Kartal Koşuyolu Training and Research Hospital (Date: 04.03.2025, Decision No: 2025/03/1062). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Electronic medical records of patients aged 65 years and older who were diagnosed with sepsis and admitted to the Tuzla State Hospital intensive care unit between May and October 2023 were analyzed. The diagnosis of sepsis was made in accordance with the sepsis-3 criteria, which stipulate that the condition is to be identified in cases where there is suspected or documented infection and a sequential organ failure assessment (SOFA) score of at least two.

Collected data included demographics, APACHE II scores, laboratory parameters (total blood count, C-reactive protein (CRP), procalcitonin (PCT), albumin) obtained within the first 2 hours of ICU admission, ICU length of stay and mortality status. Patients were excluded if they were younger than 65, had missing data, hematological malignancies were transferred from other ICUs or were receiving immunosuppressive therapy.

Statistical Analysis

The data analyses were performed using IBM SPSS Statistics 28.0. Continuous variables were assessed using Kolmogorov-Smirnov and Shapiro-Wilk tests. Comparisons used independent samples t-tests or Mann-Whitney U tests depending on distribution. The patients were grouped as survivors and non-survivors for comparative analyses of clinical and laboratory parameters. Chi-square tests analyzed

categorical variables. ROC analysis determined cutoff values, both univariate and multivariate logistic regression analyses assessed predictors of mortality. A p-value <0.05 indicated statistical significance.

RESULTS

A total of 239 patients (aged 65–95) were included. Of the patients included in the study, 46.9% were female and 53.1% were male. Overall mortality was 66.9%. No significant differences were found between survivors and non-survivors regarding age, gender, white blood cells (WBC), neutrophils, lymphocytes, platelet-to-lymphocyte ratio (PLR) or platelets ($p>0.05$) ([Table 1](#)).

However albumin levels were significantly lower in the non-survivors group. Conversely, neutrophil-to-lymphocyte ratio (NLR), mean platelet volume (MPV), red blood cell distribution width (RDW), CRP, CRP/albumin ratio, PCT, lactate, APACHE II score and length of stay in ICU were significantly higher ($p<0.05$) ([Table 1](#), [Figure 1](#)).

In the univariate analysis, NLR and PCT values were not statistically significant predictors of mortality ($p>0.05$). However, MPV, RDW, CRP, albumin, CRP/albumin ratio, lactate, APACHE II score and length of stay demonstrated significant predictive value in distinguishing between survivors and non-survivors ($p<0.05$) ([Table 2](#)). In the multivariate analysis, only the CRP/albumin ratio and APACHE II score remained as independent predictors of mortality ($p<0.05$). The CRP/albumin ratio showed a

Table 1. Distribution of laboratory and clinical variables according to mortality status

		Mortality (-) (n:79)		Mortality (+) (n:160)		p-value
		Mean±SD/n %	Median	Mean±SD/n %	Median	
Age		79.9±8.9	81.0	81.0±7.9	81.0	0.356 m
Gender	Female	41 51.9%		86 53.8%		0.787 X ²
	Male	38 48.1%		74 46.3%		
WBC		12.7±5.6	11.8	14.9±9.2	13.1	0.098 m
Neutrophil		10.8±5.3	10.0	13.0±8.7	11.4	0.070 m
Lymphocyte		1.16±1.04	0.98	1.12±1.47	0.80	0.075 m
NLR		15.5±20.6	10.4	18.9±18.7	13.2	0.034 m
PLR		315.5±292.1	237.6	338.5±313.5	272.4	0.547 m
Platelet		244.6±115.7	240.0	222.0±123.9	210.0	0.112 m
MPV		10.7±2.1	10.7	11.6±1.5	11.6	0.001 m
RDW		51.8±8.8	51.4	54.3±9.3	52.3	0.042 m
CRP		135.6±95.4	128.0	169.2±110.0	149.9	0.024 m
Albumin		28.7±4.5	29.0	25.3±6.0	25.0	0.000 t
CRP/albumin		4.9±3.5	4.0	7.6±6.1	6.0	0.001 m
PCT		7.3±17.3	1.0	12.1±21.7	2.5	0.001 m
Lactate		2.2±1.6	1.9	3.4±3.0	2.6	0.000 m
APACHE II score		26.6±7.1	25.0	50.6±8.7	52.0	0.000 m
Length of stay in ICU		12.1±15.8	5.0	16.8±16.5	12.0	0.005 m

t: Independent samples t test, m: Mann-whitney u test, X²: Chi-square test. Units: WBC: Neutrophil, Lymphocyte, Platelet (×10⁹/L), MPV (fL), RDW (%), CRP (mg/L), Albumin (g/L); PCT (ng/mL), Lactate (mmol/L), Length of stay in ICU (days). SD: Standard deviation, WBC: White blood cells, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MPV: Mean platelet volume, RDW: Red blood cell distribution width, CRP: C-reactive protein, PCT: Procalcitonin, ICU: Intensive care unit

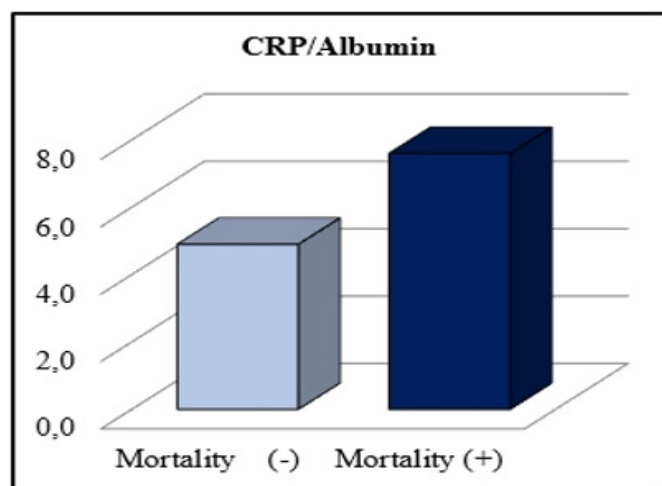


Figure 1. Comparison of CRP/albumin ratio between survivor and non-survivor groups
CRP: C-reactive protein

statistically significant predictive performance with an area under the receiver operating characteristic curve (AUC) of 0.632 (95% CI: 0.560–0.704) (Table 2).

At the cut off value of 6.20 for the CRP/albumin ratio, the AUC was 0.611 (95% CI: 0.536–0.685), indicating statistical significance ($p=0.005$). At this threshold, sensitivity was 48.8%, positive predictive value (PPV) was 78.8%, specificity was 73.4%, and negative predictive value (NPV) was 41.4% (Table 3, Figure 2).

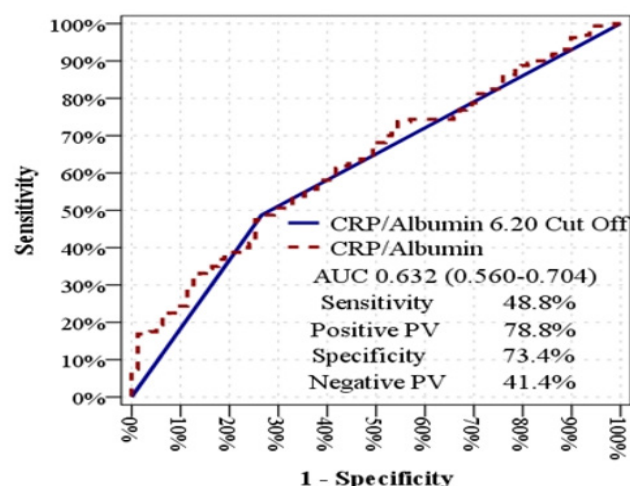


Figure 2. Receiver operating characteristic (ROC) curve for CRP/albumin ratio in predicting mortality
CRP: C-reactive protein, AUC: Area under the curve, PV: Predictive value

ROC analysis was performed for the APACHE II score, yielding an AUC of 0.979, indicating excellent discriminative ability in predicting ICU mortality among geriatric sepsis patients. With a cutoff value of 37, the APACHE II score showed significant ability to distinguish between survivors and non-survivors (AUC: 0.934). At this threshold, the APACHE II score demonstrated the following predictive values for mortality: sensitivity 95.6%, specificity, 91.1%, PPV 95.6% and NPV was 91.1% (Table 4).

Table 2. Logistic regression analysis of inflammatory and clinical parameters associated with mortality

	Univariate model			Multivariate model		
	OR	%95 CI	p-value	OR	%95 GA	p-value
NLR	1.011	0.994-1.029	0.211			
MPV	1.392	1.158-1.674	0.000			
RDW	1.033	1.000-1.066	0.049			
CRP	1.003	1.000-1.006	0.023			
Albumin	0.893	0.847-0.941	0.000			
CRP/albumin	1.124	1.051-1.203	0.001	1.207	1.054-1.381	0.006
PCT	1.014	0.998-1.031	0.092			
Lactate	1.382	1.148-1.662	0.001			
APACHE II score	1.401	1.274-1.540	0.000	1.431	1.288-1.590	0.000
Length of stay in ICU	1.020	1.001-1.040	0.041			

OR: Odds ratio, CI: Confidence interval, NLR: Neutrophile-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MPV: Mean platelet volume, RDW: Red blood cell distribution width, CRP: C-reactive protein, PCT: Procalcitonin, ICU: Intensive care unit. Logistic regression was performed using the Forward LR method

Table 3. Association between CRP/albumin ratio and mortality outcomes: ROC curve findings

		AUC	95% confidence interval	p-value
CRP/albumin		0.632	0.560-0.704	0.001
CRP/albumin 6.20 cut-off		0.611	0.536-0.685	0.005
		Mortality (-)	Mortality (+)	%
CRP/albumin	<6.20	58	82	Sensitivity
	≥6.20	21	78	Positive predictive value (PPV)
				Specificity
				Negative predictive value

CRP: C-reactive protein, ROC: Receiver operating characteristic curve, AUC: Area under the curve

Table 4. Association between APACHE II and mortality outcomes: ROC curve findings

		AUC		95% confidence interval	p-value
APACHE II score		0.979		0.965-0.994	0.000
APACHE II score 37 cut-off		0.934		0.893-0.975	0.000
		Mortality (-)	Mortality (+)		%
APACHE II score	<37	72	7	Sensitivity	95.6%
	≥37	7	153	Positive predictive value (PPV)	95.6%
				Specifity	91.1%
				Negative predictive value	91.1%

ROC: Receiver operating characteristic curve, AUC: Area under the curve

DISCUSSION

This study evaluated the prognostic significance of various inflammatory biomarkers, including the CRP/albumin ratio, NLR, PLR and other parameters in predicting mortality among geriatric patients diagnosed with sepsis in the ICU. The findings highlight the clinical relevance of these markers, particularly the CRP/albumin ratio and APACHE II score, in risk stratification for this vulnerable population.

The CRP/albumin ratio, which reflects both systemic inflammation and nutritional status, has been investigated as a standalone indicator of prognosis in critically ill populations.^{10,11} Our results demonstrated that CRP/albumin ratio was significantly higher in non-survivors and remained an independent predictor of mortality in multivariate analysis. This finding is consistent with previous studies suggesting that this ratio is a valuable marker in critical illness.¹²⁻¹⁴ However, in a study CRP/albumin ratio found higher in non survivor group but has no effect on mortality.¹⁵

The CRP/albumin ratio had moderate discriminatory ability (AUC: 0.632) in our cohort, aligning with results from a study who reported an AUC of 0.665 in elderly ICU patients.¹³ In other studies CRP/albumin ratio has outperformed CRP or albumin alone in predicting mortality in ICU patients, with AUC values ranging from 0.612 to 0.807 depending on the clinical setting.¹⁶ At the determined cutoff value of 6.20 for the CRP/albumin ratio, the sensitivity was relatively low (48.8%), while the specificity was moderate (73.4%), and the PPV was high (78.8%). These findings suggest that although the CRP/albumin ratio may not be sufficiently sensitive to detect all patients at risk of mortality, it is more effective in correctly identifying those who are likely to experience poor outcomes. The relatively low NPV (41.4%) further supports this interpretation, indicating that a low ratio does not reliably exclude mortality risk. This pattern is consistent with previous studies where CRP/albumin demonstrated moderate-to-high specificity but limited sensitivity.^{16,17} As such, while the CRP/albumin ratio can serve as a useful tool for confirming high-risk status in elderly septic patients, it should be interpreted in conjunction with other clinical and laboratory findings to guide decision-making effectively.

Neutrophils and lymphocytes make up the majority of circulating leukocytes, and their relative proportion can change significantly in response to systemic stress and inflammation. The NLR is a simple, cost-effective and readily

available parameter derived from routine complete blood counts, commonly used as a surrogate marker of the balance between innate and adaptive immune responses. In our study, although NLR was elevated in non-survivors in univariate analysis, it did not retain significance in multivariate regression, possibly due to confounding by stronger predictors or immunosenescence in elderly populations. Similar findings were reported by in a study which observed elevated NLR levels among non-survivors in septic elderly patients but noted only modest discriminatory performance.¹⁸ In contrast, other studies have identified NLR as an independent predictor of mortality in critically ill patients with stronger associations in broader ICU cohorts.¹³ The lack of significance in our multivariate model may be due to the inclusion of more robust predictors such as the CRP/albumin ratio and APACHE II score, which may overshadow the effect of NLR. Another possible explanation is that the immune response in geriatric patients may be blunted or atypical due to immunosenescence, reducing the dynamic range of NLR values and limiting their prognostic utility in this age group.

The PLR is another derived inflammatory index, calculated by dividing the platelet count by the lymphocyte count. It has been proposed as a marker of both thrombotic and inflammatory activity, with higher values linked to adverse outcomes in various critical illnesses. However, in our study, PLR did not differ significantly between survivors and non-survivors. This result is consistent with the findings of Sargin,¹⁵ who also reported no significant association between PLR and sepsis-related mortality in elderly patients. The relatively poor performance of PLR in our cohort may reflect its lower sensitivity to the specific pathophysiological processes of sepsis or a diminished inflammatory response in the elderly. It is possible that PLR is more reflective of localized inflammatory processes rather than systemic derangements.

Some studies have reported conflicting results regarding the prognostic utility of NLR and PLR. For example, Yeşilkaya et al.¹¹ found both markers to be significantly associated with ICU mortality in septic patients, including in multivariate models. The discrepancy with our findings may stem from differences in patient demographics, inclusion criteria or timing of biomarker measurements. Notably, our study population was exclusively geriatric and composed entirely of patients with confirmed sepsis, whereas other studies included mixed age groups and broader ICU diagnoses. This diagnostic homogeneity, while a strength in some respects, may limit

the variability necessary to observe significant effects from markers like NLR or PLR.

PCT, while significantly elevated in non-survivors in univariate analysis, failed to remain significant in multivariate analysis—mirroring findings by Rout et al.¹⁹ This might reflect its limited prognostic utility when systemic inflammation is already widespread. Although PCT is useful for detecting bacterial infection, its role in predicting mortality appears limited in elderly ICU patients, possibly due to altered biomarker kinetics or immune response. In our cohort, the high prevalence of comorbidities and immunosenescence likely contributed to this outcome by dampening the systemic inflammatory response or altering biomarker kinetics.

Markers such as RDW, MPV, lactate and hypoalbuminemia also correlated with poor outcomes, highlighting their potential use in mortality prediction. These biomarkers are closely associated with systemic inflammation, impaired tissue perfusion and altered erythropoiesis, all of which are characteristic of severe sepsis and septic shock.²⁰ Additionally, hypoalbuminemia in non-survivors suggests a link between catabolic status and poor outcomes in the elderly.¹² While many studies have confirmed the association between these markers and mortality, other investigations have reported that their predictive performance can vary depending on timing of measurement, underlying comorbidities and sepsis severity.^{14,16} However, variability in their predictive value across studies suggests they should complement—not replace—clinical scoring systems like APACHE II.

The APACHE II score emerged as one of the strongest independent predictors of mortality, reaffirming its established role in ICU risk assessment. Our findings also confirm the APACHE II score's strong predictive value for ICU mortality in geriatric sepsis patients. It combines physiological variables, age and comorbidities into a single score. Prior studies have consistently validated its prognostic accuracy in sepsis and elderly populations.²¹ When combined with objective biomarkers like CRP/albumin, it may enhance early risk detection and guide clinical decision-making.

When used alongside laboratory biomarkers such as the CRP/albumin ratio, prognostic precision may be further enhanced. Combining clinical scoring systems with objective inflammatory markers allows for a more nuanced evaluation of both systemic physiology and immune response, which may be especially useful in elderly patients whose presentations are often atypical or confounded by comorbidities.¹⁹ This complementary approach can help clinicians prioritize resource allocation and make timely therapeutic decisions in the ICU setting.

In summary, the results of our study support the integration of simple and accessible inflammatory markers—particularly the CRP/albumin ratio—into clinical decision-making protocols for elderly septic patients. While composite indices such as NLR and PLR offer some utility, their predictive strength appears inferior to that of combined inflammatory-nutritional markers like the CRP/albumin ratio. Given the

aging global population and the high vulnerability of elderly individuals to sepsis, further large-scale prospective studies are warranted to validate these findings and to determine standardized cutoff values that can be reliably applied across diverse clinical settings.

Limitations

Limitations include its retrospective single-center design, reliance on baseline biomarker values and exclusion of immunosuppressed patients. The data regarding comorbidities were available; however, the data were too heterogeneous for standardized analysis. The status of mechanical ventilation and the requirements for oxygen support were not documented. Additionally, only baseline values of biomarkers were considered; serial measurements might provide deeper insight into their dynamic prognostic value. Finally, we excluded patients with immunosuppressive conditions, which could limit the applicability of our results to broader ICU populations. Moreover, potential confounding factors such as unrecorded comorbidities, medication use or variations in sepsis management protocols may have influenced biomarker levels and outcomes. In addition, although the dataset contained the hematological parameters necessary to calculate emerging indices such as the pan-immune-inflammation value (PIV) and systemic immune-inflammation index (SII), these markers were not evaluated due to the predefined focus of the study. Future multicenter, prospective studies with larger and more diverse cohorts are necessary to confirm and extend our findings.

CONCLUSION

Our study suggests that combining the CRP/albumin ratio with APACHE II may be used together to aid early mortality risk assessment in geriatric sepsis patients. These tools are simple, cost-effective and accessible in most ICU settings. Prospective multicenter trials are needed to validate their routine use.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approval has been obtained from the Scientific Researches Ethics Committee of Kartal Koşuyolu Training and Research Hospital (Date: 04.03.2025, Decision No: 2025/03/1062).

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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Outcomes and predictors of malignancy in radiologically non-adenomatous adrenal lesions: a retrospective study

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Cite this article as: Çatak M, Koca B. Outcomes and predictors of malignancy in radiologically non-adenomatous adrenal lesions: a retrospective study. *J Med Palliat Care*. 2025;6(4):377-382.

Received: 17.07.2025

Accepted: 02.08.2025

Published: 31.08.2025

ABSTRACT

Aims: To compare the clinical, radiological, functional, and pathological characteristics of radiologically diagnosed adrenal adenomas versus non-adenomatous lesions and to identify predictors of malignancy and clinical significance among the non-adenomatous group.

Methods: This retrospective study included 63 adult patients who underwent adrenalectomy between January 2015 and December 2024. Patients were classified based on preoperative computed tomography (CT) and/or magnetic resonance imaging (MRI) reports as having either radiologically suspected adrenal adenoma or non-adenomatous lesions. Clinical features, comorbidities, hormonal function, imaging characteristics, and histopathological outcomes were compared between the two groups. Logistic regression analysis was performed within the non-adenomatous group to identify independent predictors of malignancy and clinical relevance. ROC curve analysis was used to assess the diagnostic utility of tumor size.

Results: Of the 63 patients, 29 (46.0%) were classified as adrenal adenomas and 34 (54.0%) as non-adenomatous lesions. Tumor size was significantly smaller in the adenoma group (mean 27.1 ± 6.8 mm vs. 48.5 ± 13.7 mm, $p < 0.001$). Functional tumors were more prevalent in the adenoma group (93.1% vs. 41.2%, $p < 0.001$). Malignancy (adrenocortical carcinoma and metastasis) was observed exclusively in the non-adenomatous group. Within this group, functional lesions were independently associated with malignancy ($p = 0.019$, OR=8.95). ROC analysis showed moderate diagnostic value of tumor size for predicting malignancy (AUC=0.648, 95% CI: 0.372–0.924). Histopathological confirmation showed perfect concordance in the adenoma group (positive predictive value 100%). The adenoma group had higher rates of hypertension ($p = 0.013$) and coronary artery disease ($p = 0.012$).

Conclusion: Radiologically non-adenomatous adrenal lesions are more likely to be malignant than radiologically diagnosed adenomas. Tumor size and functional status can aid in malignancy prediction within this subgroup. Radiologic classification offers high specificity, particularly for adenomas, and may guide preoperative risk stratification.

Keywords: Adrenalectomy, adrenal adenoma, non-adenomatous adrenal lesion, malignancy risk, histopathology

INTRODUCTION

The widespread use and improved accessibility of cross-sectional imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) have led to a marked increase in the detection of adrenal lesions.¹ While many of these lesions are incidentally discovered, a substantial proportion are identified in patients presenting with clinical symptoms or biochemical evidence suggestive of adrenal dysfunction.² Regardless of the context in which they are found, adrenal masses require a systematic evaluation to determine their hormonal activity and potential for malignancy.³

International guidelines emphasize that the cornerstone of adrenal mass assessment involves determining both the functional status of the lesion and its radiologic characteristics.⁴

Functioning tumors such as pheochromocytoma, cortisol-secreting adenomas, and aldosterone-producing adenomas often necessitate surgical removal due to their associated clinical syndromes.^{4,5} Meanwhile, the distinction between benign and malignant lesions—particularly in radiologically indeterminate or non-adenomatous-appearing masses—relies heavily on imaging features, such as size, attenuation values, contrast washout behavior, and morphological patterns.⁶

Although lipid-rich adrenal adenomas can be reliably diagnosed based on imaging findings alone, radiologically non-adenomatous lesions present a diagnostic challenge.^{7,8} These lesions may represent lipid-poor adenomas, pheochromocytomas, adrenocortical carcinomas (ACC), or metastatic deposits.⁸ Consequently, such lesions often prompt

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surgical intervention for definitive diagnosis and treatment planning. Nevertheless, the predictive accuracy of radiologic interpretations—especially in the preoperative setting—remains an area of ongoing investigation.^{7,8}

In this retrospective study, we aimed to compare the clinical, radiologic, functional, and histopathological features of adrenal masses that were preoperatively classified as either adenomatous or non-adenomatous based on imaging reports. We also sought to identify preoperative predictors of malignancy and clinical relevance specifically within the radiologically non-adenomatous group. By analyzing the concordance between imaging-based classification and final pathological outcomes, we aimed to provide insight into the reliability of radiologic assessments in guiding adrenal surgery.

METHODS

This retrospective study included patients who underwent adrenalectomy at Tokat Gaziosmanpaşa University Hospital between January 2015 and December 2024. The study protocol was approved by the Tokat Gaziosmanpaşa University Non-interventional Scientific Researches Ethics Committee (Date: 10.06.2025, Decision No: 24-MOBAEK-211). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 88 patients who underwent adrenal surgery were initially assessed. Of these, 8 patients were excluded due to missing preoperative radiologic imaging (CT or MRI), 15 patients were excluded because no adrenal lesion was detected on preoperative imaging performed during radical nephrectomy, and 2 patients were excluded as surgery was performed for trauma-related indications. After exclusions, 63 patients were included in the final analysis.

Radiologic classification of adrenal lesions was based on original CT and/or MRI reports issued at the time of diagnosis. These reports were prepared by expert radiologists specialized in abdominal imaging. No additional re-evaluation or reinterpretation of the imaging studies was performed retrospectively. Based on the radiologic interpretation, adrenal lesions were classified into two groups:

Adenoma group: Lesions radiologically interpreted as consistent with adrenal adenoma, typically characterized by smooth borders, homogeneous texture, unenhanced CT attenuation values ≤ 10 Hounsfield units (HU), and/or absolute or relative washout compatible with benign adenoma.

Non-adenomatous group: Lesions with radiologic features inconsistent with adenoma, such as irregular margins, heterogeneous structure, higher HU values, or atypical washout behavior.

Patients were grouped based on this radiologic classification. Clinical, laboratory, radiologic, and postoperative histopathological data were retrospectively collected and compared between the two groups.

All patients underwent standardized endocrine evaluation prior to surgery. A 1 mg overnight dexamethasone suppression test was performed (1 mg dexamethasone orally

at 23:00, followed by serum cortisol measurement at 08:00 the next morning). In addition, 24-hour urinary metanephrine and normetanephrine, plasma aldosterone and renin levels, and DHEA-S levels were evaluated. Serum cortisol (including post-DST), DHEA-S, and plasma aldosterone/renin were measured using electrochemiluminescence or chemiluminescent immunoassay methods. Urinary metanephrine and normetanephrine were analyzed via HPLC with electrochemical detection.

Data on incidental versus symptomatic presentation were also recorded. For CT-based evaluations, unenhanced HU values and washout characteristics were documented where available.

Postoperative histopathological findings were compared with preoperative radiologic interpretations to assess diagnostic concordance. Histopathological classification was based on final surgical pathology reports. Additionally, among patients with radiologically non-adenomatous lesions, predictors of malignancy were analyzed using logistic regression modeling and ROC curve analysis.

For the purpose of malignancy analysis, only patients in the radiologically defined non-adenomatous group were evaluated. In this group, ACC and metastatic adrenal lesions were considered malignant, while other histopathological diagnoses such as pheochromocytoma, adrenal cysts, and ganglioneuroma were classified as non-malignant. Additionally, to assess clinical significance beyond malignancy, a separate subgroup analysis was performed within the non-adenomatous cohort. In this analysis, lesions were considered clinically significant if they were histopathologically confirmed as pheochromocytoma, ACC, or adrenal metastasis. These entities were selected because of their established impact on perioperative management, need for specific surgical precautions, and implications for long-term follow-up and oncologic treatment. Lesions such as adrenal cysts, ganglioneuroma, or incidental lipid-poor adenomas were excluded from this category due to their typically benign nature and limited clinical consequences.

Statistical Analysis

All data analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corporation, Armonk, NY, USA). The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR), depending on data distribution. Categorical variables were presented as frequencies and percentages. For comparison between radiologically defined adenoma and non-adenoma groups, the independent samples t-test or Mann–Whitney U test was used for continuous variables, and the chi-square test or Fisher's exact test for categorical variables, as appropriate.

Logistic regression analysis was performed within the radiologically non-adenomatous group to identify independent predictors of malignancy and clinically significant lesions. Variables with $p < 0.25$ in univariate analysis were included in multivariate models. The Hosmer–Lemeshow goodness-

of-fit test was used to assess model calibration. In addition, receiver operating characteristic (ROC) curve analysis was conducted to evaluate the discriminatory ability of tumor size in predicting malignancy, and the area under the curve (AUC) was reported with 95% confidence intervals. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 63 patients with adrenal lesions who underwent adrenalectomy were included in the study. Based on preoperative radiological interpretation (CT and/or MRI), 29 patients (46.0%) were classified as having adrenal adenomas, while 34 patients (54.0%) were considered to have non-adenomatous lesions.

Comparison of Clinical and Radiologic Features Between Adenoma and Non-Adenoma Groups

There was no statistically significant difference in age between the adenoma and non-adenoma groups (mean age: 51.4 ± 13.2 vs. 50.6 ± 12.9 years, respectively; $p=0.785$). However, tumor size was significantly smaller in the adenoma group (27.1 ± 6.8 mm) compared to the non-adenoma group (48.5 ± 13.7 mm; $p<0.001$).

Sex distribution differed significantly, with a higher proportion of females in the adenoma group (86.2%) compared to the non-adenoma group (58.8%) ($p=0.016$). Functional lesions were significantly more common in the adenoma group (93.1%) than in the non-adenoma group (41.2%) ($p<0.001$).

Regarding lesion laterality, adenomas were predominantly located on the left side (69.0%), while non-adenomatous lesions more frequently involved the right adrenal gland (58.8%). This difference was statistically significant ($p=0.027$). No significant difference was observed in terms of incidental versus symptomatic presentation between the groups ($p=0.211$) (Table 1).

Table 1. Comparison of radiologically diagnosed adenoma and non-adenoma groups

Parameter	Adenoma group (n=29)	Non-adenoma group (n=34)	p-value
Number of patients	29	34	
Age (mean $\pm$ SD)	51.4 ± 13.2	50.6 ± 12.9	0.785
Sex-female	25/29 (86.2%)	20/34 (58.8%)	0.016
Tumor size (mm, mean $\pm$ SD)	27.1 ± 6.8	48.5 ± 13.7	<0.001
Functional lesion	27 (93.1%)	14 /34(41.2%)	<0.001
Incidental presentation	14 (48.3%)	17 (53.1%)	0.211
HT	21 (72.4%)	13 (40.6%)	0.013
DM	11 (37.9%)	8 (25.0%)	0.276
CAD	9 (31.0%)	2 (6.3%)	0.012
Malignancy	0 (0%)	7 (20.6%)	<0.001

SD: Standard deviation, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease

Clinical Relevance and Postoperative Pathology

All 29 patients radiologically diagnosed with adenoma were confirmed to have adenomas on histopathological

examination (positive predictive value: 100%). In contrast, among the 34 non-adenoma cases, final pathology revealed diverse diagnoses: pheochromocytoma (n=11, 32.4%), adrenocortical carcinoma (n=4, 11.8%), adrenal metastasis (n=3, 8.8%), adrenal cyst (n=3, 8.8%), ganglioneuroma (n=1, 2.9%), and adenoma (n=12, 35.3%) (Table 2).

Table 2. Histopathological diagnoses in the non-adenomatous group

Pathological diagnosis	n	% within non-adenomatous group
Pheochromocytoma	11	32.4%
ACC	4	11.8%
Metastasis	3	8.8%
Adrenal cyst	3	8.8%
Ganglioneuroma	1	2.9%
Adenoma	12	35.3%

ACC: Adrenocortical carcinoma

All malignant and metastatic lesions were exclusively observed in the non-adenoma group, highlighting the importance of radiologic suspicion ($p<0.001$)

Among patients radiologically diagnosed with adrenal adenoma, 44.8% (n=13) had primary aldosteronism (PA), 41.4% (n=12) had Cushing's syndrome (subclinical or clinical), and 13.8% (n=4) were non-functioning adenomas.

Comorbidities

There was no significant difference in the prevalence of diabetes mellitus between the two groups (37.9% vs. 25.0%; $p=0.276$). However, hypertension was significantly more common in the adenoma group (72.4%) than in the non-adenoma group (40.6%) ($p=0.013$). Similarly, coronary artery disease (CAD) was more frequently observed in the adenoma group (31.0% vs. 6.3%; $p=0.012$) (Table 1).

Predictors of Malignancy in the Non-Adenoma Group

To identify independent predictors of malignancy (ACC or metastasis) among radiologically non-adenomatous lesions, binary logistic regression was performed including age, sex, tumor size, localization, and functional status. Left-sided localization was found to be a significant independent predictor of malignancy (OR: 19.5; 95% CI: 1.18–321.2; $p=0.038$). Tumor size demonstrated a borderline association (OR: 1.044; 95% CI: 0.996–1.094; $p=0.075$), while age, sex, and hormonal functionality were not significant. The model showed good fit (Hosmer–Lemeshow test: $p=0.591$) (Table 3a).

Table 3a. Binary logistic regression analysis for predicting malignancy (non-adenoma group)

Variable	p value	Exp (B)	95% CI lower	95% CI upper
Age	0.259	1.056	0.961	1.161
Sex	0.479	2.264	0.236	21.748
Tumor size	0.075	1.044	0.996	1.094
Localization (left)	0.038	19.487	1.182	321.224
Functionality	0.509	0.38	0.021	6.734

Exp (B): Odds ratio, CI: Confidence interval, Bolded variables indicate statistical significance at $p<0.05$.

ROC curve analysis was conducted to assess the performance of tumor size in predicting malignancy among non-adenomatous lesions. The AUC was 0.648 (95% CI: 0.372–0.924), indicating modest discriminatory ability, though not statistically significant ($p=0.233$). The optimal cut-off value was 44.0 mm, with 71.4% sensitivity and 63.0% specificity.

Predictors of Clinically Significant Lesions in the Non-Adenoma Group

In a separate analysis targeting clinically significant lesions (pheochromocytoma, ACC, or metastasis), functional activity was identified as a statistically significant predictor (OR: 8.95; 95% CI: 1.43–56.15; $p=0.019$), suggesting that hormonally active lesions are significantly more likely to be clinically relevant in non-adenoma group (Table 3b).

Table 3b. Binary logistic regression analysis for clinically significant lesions in radiologically non-adenomatous group				
Variable	Sig.	Exp (B)	95% CI lower	95% CI upper
Age	0.79	0.991	0.929	1.058
Sex	0.335	2.346	0.415	13.26
Size	0.575	1.01	0.977	1.043
Localization	0.407	2.073	0.37	11.605
Functionality	0.019	8.948	1.426	56.147
Exp (B): Odds ratio. CI: Confidence interval. Binary logistic regression was performed to identify independent predictors of clinically significant lesions (pheochromocytoma, ACC, or metastasis) among patients with radiologically non-adenomatous adrenal masses. A p-value <0.05 was considered statistically significant.				

DISCUSSION

In this retrospective surgical cohort, we compared the clinical, radiologic, hormonal, and histopathological features of radiologically diagnosed adrenal adenomas versus non-adenomatous lesions. One of the most striking findings of our study was that all 29 radiologically diagnosed adrenal adenomas were histopathologically confirmed, yielding a positive predictive value (PPV) of 100%. This exceptional concordance highlights the high specificity of imaging-based diagnosis in adrenal adenomas and supports the reliability of non-invasive imaging in guiding clinical decision-making. This high diagnostic accuracy reinforces the reliability of radiologic features—such as smooth contours, low unenhanced CT attenuation values, and typical washout characteristics—in identifying benign adrenal adenomas. In contrast, the radiologically non-adenomatous group exhibited a markedly heterogeneous pathology spectrum, including all malignant and metastatic cases. Furthermore, this group was characterized by significantly larger tumor sizes, a right-sided predominance, and lower rates of hormonal functionality. Notably, left-sided localization emerged as an independent predictor of malignancy, and functional activity was strongly associated with clinically significant lesions such as pheochromocytoma, ACC, or metastasis. These findings highlight the importance of careful preoperative evaluation of radiologically atypical adrenal masses and support the role of combined radiological and functional assessment in surgical decision-making.

All 29 lesions radiologically interpreted as adenomas were confirmed as such histopathologically, yielding a PPV of 100%. This underscores the reliability of radiologic hallmarks—such as low unenhanced attenuation (≤ 10 HU), homogeneous appearance, smooth borders, and classic washout behavior—in the diagnosis of benign adenomas.⁹ Prior research by Lanoix et al.⁷ demonstrated that the presence of microscopic or macroscopic fat within a lesion is highly specific for adenoma. Their CT/MRI-based model also incorporated lesion diameter, calcifications, and hemorrhage, achieving an AUC of 0.91 for adenoma prediction.⁷

In contrast, the radiologically non-adenomatous group in our study exhibited a diverse histopathological spectrum, including pheochromocytoma, ACC, metastases, and rare entities such as ganglioneuroma. Notably, all malignant and metastatic lesions were exclusively detected in this group, reinforcing the clinical importance of radiologic suspicion in malignancy prediction.¹⁰ Similar findings have been reported Albano et al.¹² and Torresan et al.,¹¹ who demonstrated that non-adenoma imaging features—such as irregular margins, high attenuation, heterogeneity, and lack of typical washout—were significantly associated with malignancy risk and poor diagnostic confidence using conventional imaging modalities. These results underscore the challenges posed by radiologically indeterminate lesions and highlight the potential value of advanced imaging markers or radiomics-based approaches in improving preoperative risk stratification.

Within the radiologically non-adenomatous group, our regression analysis identified left-sided localization as an independent predictor of malignancy, despite the majority of non-adenomatous lesions in our cohort being right-sided. This apparent discrepancy may suggest that while non-adenomatous lesions are more frequently right-sided in clinical practice, those located on the left may carry a disproportionately higher malignancy risk. Anatomical and vascular differences between the adrenal glands—such as the longer left adrenal vein, asymmetric lymphatic drainage, or proximity to the aorta—might contribute to differences in tumor behavior and dissemination potential.¹³ However, large-scale registry studies have not demonstrated significant survival differences between left- and right-sided adrenal malignancies.¹⁴ This highlights the need for further investigation in future studies with surgically confirmed cohorts, where radiologic suspicion and operative pathology are tightly correlated. Our findings thus raise the hypothesis that radiologically suspicious left-sided lesions may warrant closer scrutiny, even though they appear less frequent.

ROC analysis in our study showed that tumor size had only moderate discriminatory ability for malignancy prediction (AUC=0.648), with a proposed cut-off of 44 mm offering 71.4% sensitivity and 63.0% specificity. While tumor size alone may not be sufficient for a definitive diagnosis, it remains a valuable adjunct when combined with imaging morphology and functional evaluation. The lack of statistical significance in our ROC analysis may, in part, be attributed to the limited number of malignant cases ($n=7$), which likely reduced the

power to detect a significant discriminatory threshold. Prior studies have consistently demonstrated that increasing tumor size is associated with a higher risk of malignancy.¹⁵ In a retrospective single-center study including 131 adrenalectomy cases, all patients with ACC had tumors larger than 50 mm, and the risk of both ACC and pheochromocytoma increased proportionally with tumor size, yielding an AUC of 0.883 for ACC prediction based solely on lesion diameter.¹⁶ However, these risks diminished considerably when lipid-rich adenomas (HU<40) were considered, underscoring the necessity of integrating radiologic characteristics with size in risk assessment.

Furthermore, longitudinal imaging data have also highlighted that tumor growth dynamics; including absolute growth, percentage growth, and growth rate are significant predictors of malignancy. In a large retrospective cohort with surgical histopathology confirmation, all three growth parameters were independently associated with malignant potential, with an absolute growth threshold of 0.8 cm providing optimal sensitivity and specificity (72% and 81.1%, respectively).¹⁷ Notably, some malignant lesions demonstrated minimal or no growth over time, indicating that static imaging features should also be incorporated into malignancy risk models. Therefore, while size and growth provide essential clues, their interpretation should be contextualized alongside imaging density, morphology, and hormonal functionality for informed surgical decision-making.

Importantly, all clinically significant lesions—including ACC, metastases, and pheochromocytoma—were exclusively observed in the radiologically non-adenomatous group, confirming the clinical value of radiological suspicion in predicting higher-risk pathology. Similar observations were reported where non-adenomatous imaging features—such as irregular margins, high attenuation, and lesion heterogeneity—were strongly associated with clinically relevant adrenal tumors.^{16,18} The presence of hormonal functionality in these radiologically suspicious lesions was also found to be independently associated with clinical significance. This suggests that when radiologically non-adenomatous features are accompanied by functional activity, the risk of clinically important disease is substantially increased—even in the absence of overt malignancy.

Another critical implication of our findings is the potential to avoid unnecessary surgeries. Given the 100% PPV of radiologically defined adenomas and their exclusively benign pathology, resection may not be required in many cases. This supports recent guideline recommendations that discourage routine biochemical testing for pheochromocytoma in lesions with imaging characteristics typical of adenoma, thereby minimizing overdiagnosis and overtreatment.³ Similarly, a large cohort study by Imga et al.¹⁹ demonstrated that most adrenal incidentalomas were nonfunctioning and benign, with tumor size serving as a helpful indicator for distinguishing between functional and nonfunctional lesions. Their findings further emphasize the importance of imaging-based evaluation in identifying patients who do not require surgical intervention.

In terms of comorbidities, we observed no significant difference in the prevalence of diabetes mellitus between groups. However, hypertension and CAD were significantly more common in the adenoma group. These associations likely reflect the higher prevalence of functional adrenal disorders—such as PA and subclinical Cushing syndrome (SCS)—within this group, which are well-established contributors to cardiometabolic risk. In our cohort, the number of patients with PA was notably high, which may help explain the significant differences observed in hypertension and CAD prevalence. These findings are consistent with prior studies showing that excess aldosterone and cortisol secretion contribute to endothelial dysfunction, myocardial fibrosis, and increased cardiovascular events in affected individuals.²⁰⁻²²

In summary, our study reinforces the high specificity of radiological diagnosis for adrenal adenomas and highlights the greater clinical relevance and malignancy risk associated with radiologically non-adenomatous lesions. Radiologic classification—when combined with lesion size and functional assessment—can provide a robust framework for individualized preoperative decision-making.

Limitations

This study has several limitations that should be considered when interpreting the results. First, the retrospective, single-center design may introduce selection bias and limits the generalizability of our findings. Second, despite standardized imaging protocols, variability in CT and MRI interpretation could not be fully eliminated, although all reports were generated by experienced radiologists. Third, Although multivariate analysis identified left-sided localization as a predictor of malignancy, the small number of malignant cases (n=7) limits the statistical power of this finding. The wide confidence intervals observed in the model reflect this limitation. Therefore, our results should be interpreted cautiously and validated in larger, multicenter studies. Lastly, while our focus was on preoperative radiologic classification, we did not include advanced imaging techniques such as chemical shift MRI or PET/CT, which may further improve diagnostic accuracy in future studies.

CONCLUSION

Radiologically non-adenomatous adrenal lesions are associated with a significantly higher likelihood of malignancy and clinical relevance compared to radiologically diagnosed adenomas. Tumor functionality and lesion localization may aid in predicting malignancy among this subgroup. Importantly, radiologic features consistent with adenoma demonstrated perfect concordance with postoperative pathology, reinforcing the high specificity of imaging-based diagnosis. These findings support current recommendations discouraging unnecessary biochemical testing and surgical intervention for radiologically typical adrenal adenomas. A radiologic-first approach, when integrated with clinical and hormonal data, may optimize preoperative risk stratification and help avoid overtreatment in patients with incidentally discovered adrenal lesions.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study protocol was approved by the Tokat Gaziosmanpaşa University Non-interventional Scientific Researches Ethics Committee (Date: 10.06.2025, Decision No: 24-MOBAEK-211).

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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A prospective randomized study comparing vaginal dinoprostone plus oxytocin versus oxytocin alone for labor induction in nulliparous women with unripe cervix

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Cite this article as: Ağar E, Davas Nİ. A prospective randomized study comparing vaginal dinoprostone plus oxytocin versus oxytocin alone for labor induction in nulliparous women with unripe cervix. *J Med Palliat Care*. 2025;6(4):383-387.

Received: 15.07.2025

Accepted: 04.08.2025

Published: 31.08.2025

ABSTRACT

Aims: To compare the effectiveness and outcomes of two medications (oxytocin and dinoprostone) used for cervical ripening and labor induction.

Methods: Term nulliparous pregnant women with Bishop score <4 who received labor induction indication were divided into two groups. The first group received vaginal dinoprostone followed by oxytocin. The second group received only oxytocin only. Labor onset times, delivery duration, Bishop scores, contraction frequencies every 10 minutes, cesarean rates, and Apgar scores of newborns were compared between the two groups.

Results: Although there was no statistically significant difference in terms of active labor onset time between the dinoprostone and oxytocin groups, a significant difference was observed regarding the time to delivery. (dinoprostone: 873.5±219.12 minutes; oxytocin: 637.4±339.3 minutes; p=0.0001). A significant difference was also found between the two groups in terms of mean Bishop scores at 2, 4, 6, 8, and 10 hours. (p=0.0001, p=0.0001, p=0.008, p=0.033, respectively). Similarly, there was a significant difference between the two groups regarding contraction frequency per 10 minutes in the first 2 hours of induction. (dinoprostone: 0.22±0.42/10 minutes; oxytocin: 0.72±0.88/10 minutes; p=0.0001) No statistically significant difference was found between the two groups in terms of cesarean rates. However, it was determined that the oxytocin group had a 2.06 times higher probability of undergoing cesarean section compared to the other group. OR:2.06 (0.83-5.10, 95% CI). The mean 1st minute Apgar score of babies in the dinoprostone group was 6.49±0.19 and the 5th minute Apgar score mean was 9.10±0.11. The mean 1st minute Apgar score of babies in the oxytocin group was 6.80±0.17 and the 5th minute Apgar score mean was 8.80±0.15, with no statistical significance detected between the two groups (p>0.05).

Conclusion: Dinoprostone can be preferred as a method to reduce cesarean rates; however, oxytocin may be preferred in clinics with high patient density due to its faster effect and quicker completion of delivery.

Keywords: Cervical ripening, labor induction, oxytocin, dinoprostone

INTRODUCTION

Cervical ripening and labor induction are frequently utilized obstetric interventions in cases where spontaneous labor has not commenced or needs to be initiated early due to medical reasons. Labor induction is performed in approximately 20% of term pregnancies, with 25-50% of these applications being conducted due to post-term pregnancy.^{1,2} Timely initiated induction has critical importance in terms of reducing maternal and fetal morbidity and mortality.³

The choice of labor induction method depends mostly on the cervical ripeness status, and this condition is usually evaluated clinically with the Bishop score. In cases with Bishop score <4, induction failure and cesarean rates increase.^{4,5} Therefore,

cervical ripening before labor induction is an important step in patients with an unripe cervix. One of the most commonly used agents for this purpose is dinoprostone, which is a prostaglandin E₂ analog. Oxytocin, on the other hand, has also been widely used for many years to initiate and advance labor.⁶

In the literature, there are numerous studies comparing the effectiveness of dinoprostone and oxytocin in labor induction. However, there is no clear consensus on which agent is superior, especially in nulliparous pregnant women with an unripe cervix.^{7,8} In clinical practice, agent selection depends not only on effectiveness but also varies according to various

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factors such as induction duration, time to delivery, cesarean rates, fetal outcomes, and patient load of the healthcare institution.

The aim of this study is to comparatively evaluate the differences between dinoprostone followed by oxytocin application and oxytocin infusion alone in term nulliparous pregnant women with an unripe cervix (Bishop score <4) in terms of induction success, labor duration, cesarean rate, and neonatal outcomes.

METHODS

Ethics

This prospective, randomized, and controlled study was conducted between May 2005 and May 2006 at the 2nd Department of Obstetrics and Gynecology of Şişli Etfal Training and Research Hospital. Ethical approval was not required for this thesis study in accordance with national regulations in effect at the time of data collection (2005–2006). Institutional approval was obtained. The dataset originates from a completed medical thesis archived under thesis number 659197 at the ULAKBİM National Thesis Center. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study population consisted of term nulliparous pregnant women with an indication for labor induction and an unripe cervix (Bishop score <4). Inclusion criteria included post-term pregnancy, preeclampsia, oligohydramnios, and gestational diabetes mellitus. In contrast, patients with conditions such as multiple pregnancy, placenta previa, breech presentation, cephalopelvic disproportion, and premature rupture of membranes were excluded from the study.

A total of 100 nulliparous pregnant women who met the eligibility criteria and gave consent to participate in the study were randomized into two equal groups. The randomization was based on the protocol number assigned to each patient by the hospital's registration system at admission. Patients with an odd protocol number were assigned to the dinoprostone+oxytocin group, and those with an even protocol number were assigned to the oxytocin group. Group 1 (n=50) received oxytocin infusion following vaginal dinoprostone application, while group 2 (n=50) was followed with only intravenous oxytocin infusion.

Intervention Protocols and Monitoring

For patients in group 1, a 10 mg intravaginal pessary with a hydrogel matrix structure that releases 0.3 mg dinoprostone per hour was placed in the posterior fornix. This pessary was equipped with a 15 cm long string for easy removal when necessary. The application was performed as a single dose, and patients were not allowed to mobilize for the first hour after application, and continuous cardiotocographic (CTG) monitoring was provided. For patients in both groups, oxytocin was prepared as a 1% solution in 0.9% NaCl. The infusion was started at 4 mU/min and was titrated by increasing by 2 mU/min every 30 minutes until regular uterine contractions were achieved. Induction was continued

without exceeding the recommended maximum dose and was maintained until delivery occurred.

Throughout the study, vaginal examinations were performed by the same obstetrician to reduce subjective differences in evaluation. Amniotomy was performed in both groups when patients entered the active phase of the first stage of labor. The bishop score was recorded through vaginal examination at the beginning of induction and then at specific hourly intervals (2nd, 4th, 6th, 8th, 10th, 12th, 14th, 16th, 18th, 20th, and 22nd hours). Uterine contraction frequency was evaluated and recorded from CTG at 10-minute intervals. All patients were monitored with CTG from the beginning of induction until delivery. The 1st and 5th minute Apgar scores of newborns after delivery were also recorded as important parameters.

Statistical Analysis

Quantitative data were presented as mean±standard deviation ($X \pm SD$). The independent sample t-test was used for comparisons between groups, the Chi-square (χ^2) test for categorical variables, and the McNemar test when necessary. Statistical analyses were performed using SPSS v.13.0 software, and $p < 0.05$ was considered statistically significant.

RESULTS

The mean age, body-mass index, and gestational week (in days) of all patients included in the study are presented in [Table 1](#). There was no statistically significant difference between patients in the two groups in terms of age, body mass index, and gestational week (all p values >0.05).

Table 1. Demographic data

Clinical information	Dinoprostone+oxytocin	Oxytocin	t	p
Age	26.42±4.7	24.86±4.27	1.73	0.085
BMI	24.76±1.39	25.22±1.34	-1.64	0.102
Gestational day	288.02±7.3	286.84±8.03	0.77	0.444

BMI: Body-mass index

The distribution of patients in the oxytocin and dinoprostone+oxytocin groups according to labor induction indications is presented in [Table 2](#).

Table 2. Labor induction indications

Indication	Dinoprostone+oxytocin		Oxytocin	
Postterm pregnancy	35	70.0%	34	68.0%
Oligohydramnios	5	10.0%	3	6.0%
Diabetes mellitus	2	4.0%	6	12.0%
Preeclampsia	8	16.0%	7	14.0%
Total	50		50	

The majority of labor induction indications in patients in both groups consisted of postterm pregnancies.

The mean labor onset and time to delivery of patients in both groups are presented in [Table 3](#). While no statistically significant difference was found in terms of labor onset times in the dinoprostone+oxytocin group ($p=0.148$), a significant

difference was detected in terms of time to delivery. The mean delivery time in the dinoprostone+oxytocin group was 873.5 ± 219.12 minutes, while it was found to be 637.4 ± 339.3 minutes in the oxytocin group ($p=0.0001$).

Table 3. Labor onset and time to delivery

	Dinoprostone+oxytocin (min)	Oxytocin (min)	t	p
Labor onset	357.8 ± 169.67	301.2 ± 215.74	1.46	0.148
Time to delivery	873.5 ± 219.12	637.4 ± 339.3	4.13	0.0001
Min: Minimum				

The Bishop scores of the dinoprostone+oxytocin and oxytocin groups during labor monitoring are presented in Figure 1.

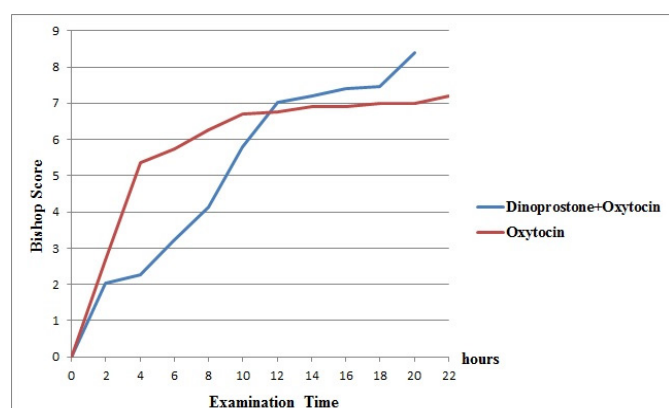


Figure 1. Bishop scores over time

Especially in the early hours of induction (2nd, 4th, 6th, 8th, and 10th hours), it was observed that the Bishop score increased faster in the oxytocin group compared to the dinoprostone+oxytocin group, and this difference was statistically significant ($p=0.0001$, $p=0.0001$, $p=0.008$, $p=0.033$, respectively). At the 12th, 14th, and 16th hours, no significant difference was found between the groups in terms of the Bishop scores ($p>0.05$).

The mean number of contractions per 10 minutes observed on cardiotocography in patients in both groups during labor monitoring is presented in Figure 2.

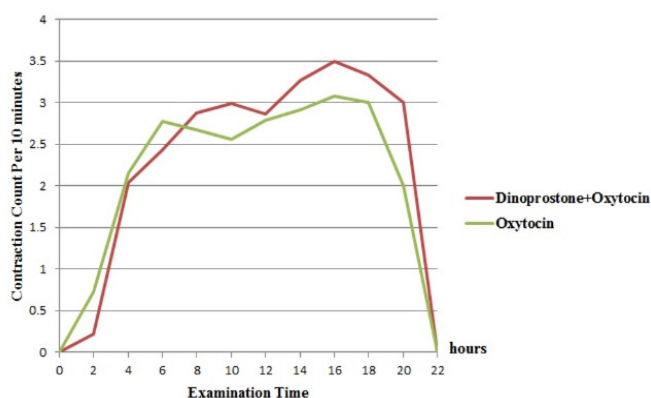


Figure 2. Contraction monitoring during labor (number of contractions per 10 minutes)

In the first two hours of induction (0-2 hours), a significant difference was found between the two groups in terms of the number of contractions per 10 minutes on cardiotocography

(dinoprostone+oxytocin: $0.22 \pm 0.42/10$ minutes; oxytocin: $0.72 \pm 0.88/10$ minutes; $p=0.0001$). No significant difference was observed between the groups in the subsequent hours.

In the dinoprostone+oxytocin group, the pessary was removed in 27 patients because 12 hours had passed, in 10 patients because active labor had started, in 10 patients because fetal distress occurred, and in 3 patients due to transient maternal reactions such as nausea, vomiting, hypotension, and tachycardia. In 2 patients in the Oxytocin group, induction was considered unsuccessful because the first stage of labor did not begin within 12 hours; these patients underwent cesarean section after their systemic and obstetric examinations were re-evaluated and induction was attempted again the next day.

The percentages (%) of patients who delivered according to time intervals are presented in Figure 3.

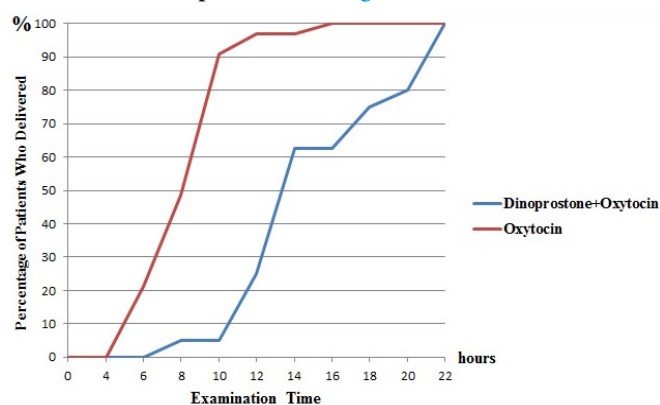


Figure 3. Percentage of patients who delivered

While 7 patients (21.2%) in the Oxytocin group delivered at the 6th hour and 16 patients (48.5%) at the 8th hour, in the dinoprostone+oxytocin group, no delivery had occurred at the 6th hour, and only 2 patients (5%) delivered at the 8th hour.

Cesarean delivery occurred in 20% ($n=10$) of the dinoprostone+oxytocin group and in 34% ($n=17$) of the oxytocin group.

The total cesarean rates are presented in Table 4.

Table 4. Cesarean rates

	Dinoprostone+oxytocin		Oxytocin	
Cesarean section	10	20.0%	17	34%
Vaginal delivery	40	80.0%	33	66%
$p=0.177$ (Chi-square test)				

While all cesarean sections in the dinoprostone+oxytocin group were performed due to fetal distress ($n=10$), 15 of the cesarean sections in the oxytocin group were due to fetal distress and 2 were performed as a result of repeated unsuccessful inductions. Although there was no statistically significant difference between the two groups in terms of cesarean rates ($p=0.177$), it was determined that the oxytocin group had a 2.06 times higher probability of undergoing cesarean section than the dinoprostone group (OR: 2.06; 95% CI: 0.83-5.10).

No statistically significant difference was found between the groups in terms of 1st and 5th minute Apgar scores of newborns (all *p* values >0.05). The mean 1st minute Apgar score of newborns in the dinoprostone+oxytocin group was found to be 6.49 ± 0.19 and the 5th minute Apgar score was 9.10 ± 0.11 . The mean 1st minute Apgar score of newborns in the oxytocin group was recorded as 6.80 ± 0.17 and the 5th minute Apgar score was 8.80 ± 0.15 .

No serious maternal systemic side effects were observed in either patient group throughout the study. Additionally, no maternal, fetal, or neonatal mortality was encountered.

DISCUSSION

In this randomized controlled study, we compared the effectiveness and outcomes of dinoprostone followed by oxytocin application versus oxytocin application alone in pregnant women with an unripe cervix (Bishop <4) who had an indication for cervical ripening and labor induction.

In the meta-analysis conducted by Alfircvic et al.,⁷ oxytocin was shown to have a lower effect on achieving delivery within 24 hours compared to vaginal dinoprostone. In our study, we also observed that delivery did not occur within 24 hours in 2 patients in the oxytocin group, while all patients in the dinoprostone group delivered within 24 hours.

In the Cochrane database study by Kelly et al.,⁸ it is reported that the use of vaginal prostaglandin for labor induction in term pregnancy increases vaginal delivery rates. In our study, we found that vaginal dinoprostone pessary increased the vaginal delivery rate (Table 4).

In the study conducted by Kulhan and colleagues,⁹ it was stated that regular contractions were achieved earlier in the oxytocin group, the desired contraction frequency was reached in 6-8 hours in the dinoprostone group, while this duration was 2-3 hours in the oxytocin group. In our study, when we examined the contraction frequency every 10 minutes with cardiotocography after starting induction, a significant difference in favor of oxytocin was observed in the first two hours of induction. No significant difference was observed between the groups in the following hours (Figure 2).

According to the Cochrane analysis conducted by Kelly and colleagues,⁸ it was stated that the risk of cesarean section increased 1.44 times in the oxytocin group compared to the vaginal dinoprostone group OR: 1.44 (1.12-1.86). In our study, the risk of cesarean section in patients in the oxytocin group increased 2.06 times compared to the dinoprostone group [OR: 2.06 (0.83-5.10)] and is consistent with the literature.

In a similar study conducted with the same induction protocol,¹⁰ the mean delivery time in the oxytocin group was 8.3 hours (498 minutes), while in our study, the mean delivery time in the oxytocin group was longer at 10.62 hours (637.4 minutes). This difference may be due to the inclusion of patients who underwent cesarean section in the statistical calculations in our study.

In the same study,¹⁰ the mean Bishop score in the oxytocin group was found to be 7.5, while in our study, the mean Bishop score was found to be 6.2. This difference may similarly be due to the inclusion of patients who underwent cesarean section in the statistical calculations.

In the study conducted by Aghideh et al.,¹¹ they applied labor induction with oxytocin, misoprostol, dinoprostone, and balloon catheter methods, and stated that no significant difference was observed between these four groups in terms of Apgar scores of babies who delivered vaginally. Keskin and colleagues¹² showed that there was no significant difference between the two groups in terms of fetal blood gas parameters in term pregnancies that underwent labor induction with oxytocin and dinoprostone. Consistent with these studies, our study results also showed no significant difference between the Apgar scores of babies in the two groups.

Limitations

This study was conducted as a single-center study. Therefore, the generalizability of the findings to different clinical conditions or patient groups may be limited. The inclusion of only term nulliparous pregnant women in the study restricts the applicability of the results to multiparous or preterm pregnancies.

The relatively small number of participants may have prevented reaching statistical significance in some subgroups, particularly regarding cesarean rates. This situation can be considered as a factor that limits the statistical power of the study.

CONCLUSION

We examined the effects of oxytocin and dinoprostone used for labor induction on labor duration, time to delivery, Bishop score, cesarean rates, and Apgar scores of newborns. Both agents can be used for labor induction. Dinoprostone can be preferred as a method to reduce cesarean rates; however, oxytocin may be preferred in clinics with high patient load due to its faster effect and quicker completion of delivery. The choice of method will depend on the clinician's experience, hospital conditions, and the patient's condition.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval was not required for this study in accordance with national regulations in effect at the time of data collection (2005–2006). The dataset originates from a completed medical thesis archived under thesis number 659197 at the ULAKBİM National Thesis Center.

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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Comparison of pulsed radiofrequency and steroid injection in the treatment of carpal tunnel syndrome guided by USG imaging

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Cite this article as: Boğa Z, Saraç ME. Comparison of pulsed radiofrequency and steroid injection in the treatment of carpal tunnel syndrome guided by USG imaging. *J Med Palliat Care*. 2025;6(4):388-395.

Received: 21.07.2025

Accepted: 04.08.2025

Published: 31.08.2025

ABSTRACT

Aims: The research evaluated the effectiveness between ultrasonography-guided pulsed radiofrequency treatment and steroid injection therapy for carpal tunnel syndrome.

Methods: The research included 60 patients who received carpal tunnel syndrome diagnoses. The patients received their treatment based on two distinct approaches which formed separate groups: 30 patients who underwent ultrasonography-guided injection of 40 mg methylprednisolone acetate and 30 patients who underwent ultrasonography-guided application of pulsed radiofrequency targeting the median nerve at 42°C for 120 seconds. Visual Analog Scale (VAS) score, Boston Carpal Tunnel Scale and physical examination findings were evaluated before treatment, at 1, 3 and 6 months. All patients underwent EMG before the procedure and at 6 months.

Results: At baseline, no significant variations were observed across groups regarding demographic characteristics as well as clinical parameters. At the third month, the VAS score decreased to 2.9 ± 1.5 in the RF group while it was still 3.8 ± 2.1 in the steroid group ($p=0.048$). Functional scores of the Boston scale were 1.6 ± 0.7 in the pulsed radiofrequency group and 2.0 ± 0.8 in the steroid group ($p=0.037$). In the electrophysiologic evaluation at the sixth month, motor distal latency was 3.9 ± 0.7 ms in the RF group versus 4.3 ± 0.8 ms in the steroid group ($p=0.041$). The rate of more than 50% improvement in VAS score was 80% in the RF group compared to 60% in the steroid group.

Conclusion: Pulsed radiofrequency therapy delivers superior long-term results than steroid injection does. As a minimally invasive method, it should be evaluated before surgery.

Keywords: Carpal tunnel syndrome, median nerve, pulsed radiofrequency treatment, corticosteroid injection, ultrasonography

INTRODUCTION

Carpal tunnel syndrome (CTS) represents the most frequently encountered compression neuropathy of the upper limb and the most prevalent peripheral nerve entrapment syndrome globally, comprising nearly 90% of all nerve entrapment conditions.¹ Its prevalence in the general population ranges from 3-26%, occurring in 7-16% of the adult population.^{1,2} The disease is particularly associated with a threefold increased risk in women, reaching up to 6% in women over 40 years of age.^{2,3} CTS develops due to median nerve entrapment within the carpal canal, manifesting with clinical features including pain, paresthesia, sensory deficits, reduced manual skills and muscle weakness.^{3,4} It stands out as an important occupational health problem with its increasing prevalence, especially in occupations requiring repetitive wrist movements, and creates an annual economic burden of 2.7-4.8 billion dollars in the USA.⁵ Ultrasound-guided minimally invasive treatment approaches stand out as an innovative approach

in the treatment of CTS by mechanically releasing adhesions around the nerve and reducing inflammation.⁶

Although there are several studies in the literature on conservative treatment of CTS and minimally invasive approaches, there are not enough standardized studies directly comparing the efficacy of different treatment modalities.^{2,6} Especially in studies comparing ultrasound-guided pulsed radiofrequency with steroid injection, data on optimal dosages, long-term effects, and efficacy for CTS cases of different severity are limited.^{3,6} Furthermore, additional studies are required on the standardization of therapeutic manual techniques and comparison of procedures.^{3,7} This highlights the need for comprehensive comparative studies to determine the most optimal minimally invasive approach for managing CTS and to develop standardized protocols in clinical practice.

METHODS

Ethics

This study has been approved by the Scientific Researches Ethics Committee of Adana City Training and Research Hospital (Date: 08.05.2025, Decision No: 516). Personal data were anonymized and coded and analyzed for maintaining patient privacy. Information security was ensured on encrypted computers and databases accessible only to the study team. The research was performed following the Declaration of Helsinki principles and Good Clinical Practice standards.

Study Population and Sample

This retrospective comparative study was conducted in patients with confirmed CTS diagnosis who were admitted to our clinic between June 1, 2024 and October 1, 2024. The CONSORT flow diagram in Figure 1 shows the process of patient enrollment and allocation and follow-up and analysis. After the six-month follow-up period of the last enrolled patient was completed in April 2025, the data screening process was completed between May 15, 2025 and May 30, 2025.

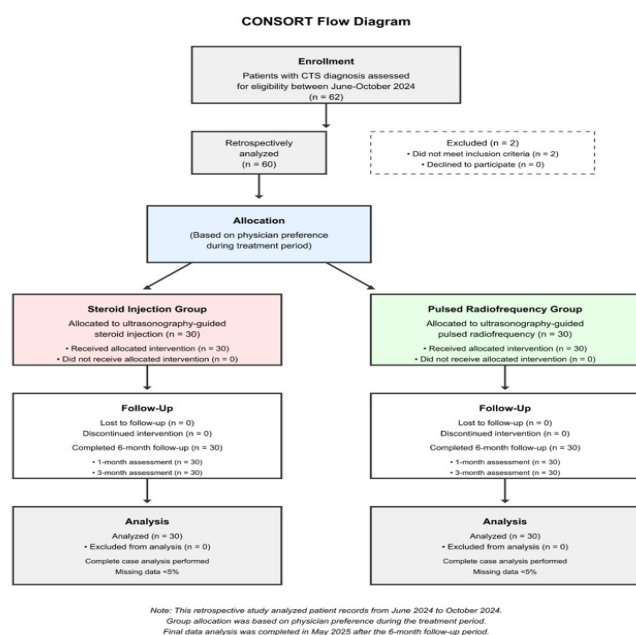


Figure 1. CONSORT flow diagram: Retrospective study flowchart showing patient enrollment, allocation, and analysis.
CTS: Carpal tunnel syndrome

Power analysis was conducted to identify a 1.5 point variance in Visual Analog Scale (VAS) scores between groups at 80% statistical power with 5% alpha error level, and a minimum of 28 patients were required for each group. The main outcome measure for sample size calculation was the VAS pain score at 3 months post-treatment, with an effect size of 0.75 based on previous literature. While a total of 56 patients were required for both groups, a total of 62 patients were targeted considering a 10% probability of missing data. However, since 60 eligible patients meeting the appropriate inclusion requirements were identified during the research period, this study was finalized with 60 participants. The decrease from

62 to 60 patients (3.2% reduction) did not significantly affect the statistical power, which remained above 78%.

The inclusion criteria were as follows: age between 18 to 65 years, clinical plus electrophysiologic diagnosis of CTS, refractory to conservative treatment or first time diagnosis. All patients received electrophysiological confirmation of CTS diagnosis before enrollment with mild to moderate severity according to the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) criteria.⁸

Exclusion criteria were defined as pregnancy or breastfeeding, history of other hand surgery or trauma, bleeding disorder, infection, dermatologic disorder, uncontrolled systemic diseases, inappropriate anatomical variations and patients who could not complete the follow-up period. The established criteria served to maintain uniformity in the study participants while reducing potential confounding elements that might impact treatment results.

The severity of CTS was evenly distributed between groups since 40% of patients in the steroid group had mild CTS and 36.7% in the RF group had mild CTS while 60% in the steroid group and 63.3% in the RF group had moderate CTS with no significant difference ($p=0.793$). The VAS score between 0-10 was operationally defined as VAS for pain intensity assessment, not sleep quality. The Boston Carpal Tunnel Scale was operationally defined as validated scales assessing functional status and symptom severity.

The study did not receive registration in a clinical trial registry because it analyzed routine clinical practice data retrospectively. We support the practice of prospective registration for all studies including retrospective analyses of clinical practice data.

Study Procedures

Data collection was performed by retrospective review of patient files and all data were recorded using standardized forms. According to the follow-up protocol, patients were evaluated at baseline, first month, 3rd month and sixth month visits and VAS score, Boston Carpal Tunnel Scale and physical examination findings were recorded at each control. EMG was routinely performed in all patients before the procedure as part of the diagnostic workup to confirm CTS diagnosis and determine severity and at 6-month follow-up to assess treatment efficacy objectively. Within the scope of the laboratory protocol, electromyography evaluations were performed by an experienced technician in the electrophysiology unit of the hospital using standard techniques and motor distal latency, sensory distal latency, nerve conduction velocity and amplitude values were measured in millisecond (ms), meter/second (m/s) and millivolt (mV) units. Ultrasonography evaluations were performed with the device available in the outpatient clinic and median nerve thickness was measured in millimeters (mm). In terms of reliability and validity of the data collection tools, test-retest reliability for the VAS for pain has been reported in the literature as $r=0.94$ and Cronbach's alpha value for the Boston Carpal Tunnel Questionnaire has been reported as 0.91.^{9,10}

Response Protocol

The 60 patients enrolled in the study were retrospectively allocated to two groups; 30 patients underwent ultrasonography-guided steroid injection and 30 patients underwent ultrasonography-guided pulsed radiofrequency application. Group assignment was based on physician preference during the treatment period. The non-randomized allocation method creates selection bias which we discuss as a limitation in our discussion section. In both groups, the procedures were initiated by first applying local anesthesia with 2 ml of 2% prilocaine (Priloc). The median nerve was visualized between the proximal and distal lines at the wrist level using a linear ultrasonography probe.

In the pulsed radiofrequency group, a 45-degree angle was entered between palmaris longus and flexor carpi radialis tendons or between palmaris longus and flexor carpi ulnaris tendons. After determining median nerve localization within the carpal tunnel under ultrasonographic guidance, a 22G needle was advanced around that nerve. Intraneural placement was excluded and the needle was positioned circumferentially without direct contact with the nerve. Pulsed radiofrequency was applied at 42°C using 2 Hz frequency with 20 ms pulse duration in two 120-second cycles (**Figure 2B**). In the steroid group, the median nerve circumference was localized at a 45-degree angle between the proximal and distal lines using the same ultrasonographic approach. 40 mg methylprednisolone acetate was injected around the nerve with a 22 gauge needle. Intraneural injection was excluded and care was taken to administer the drug into the space around the nerve (**Figure 2A**). **Figure 2C** shows the ultrasonographic visualization of the median nerve and surrounding anatomical structures during the procedures. Both procedures were performed by an experienced physician in an outpatient clinic under sterile conditions and lasted an average of 15-20 minutes. After the procedure, the patients were kept under observation for 30 minutes for the development of complications and were discharged after confirmation that there was no problem.

Statistical Analysis

The data analysis was conducted with SPSS version 23.0 software (IBM Corporation, Armonk, New York, United States). The conformity of data to normal distribution was assessed using Shapiro-Wilk test and $p > 0.05$ was considered as normally distributed. Chi-square and Fisher's exact tests were utilized to compare categorical variables. Mann-Whitney U test was employed for between-group comparisons of non-normally distributed continuous data and Wilcoxon signed-rank test was utilized for within-group comparisons. For normally distributed data that met sphericity assumptions (Mauchly's test $p > 0.05$), analysis of variance for repeated measures was applied for repeated measures analysis. For non-normally distributed repeated measures data, Friedman test was used followed by post-hoc Wilcoxon signed-rank tests.

To address multiple comparisons, Bonferroni correction was applied for the primary outcomes (VAS score, Boston functional score, and Boston symptom severity score), with adjusted significance level set at $p < 0.017$ ($0.05/3$). Missing data

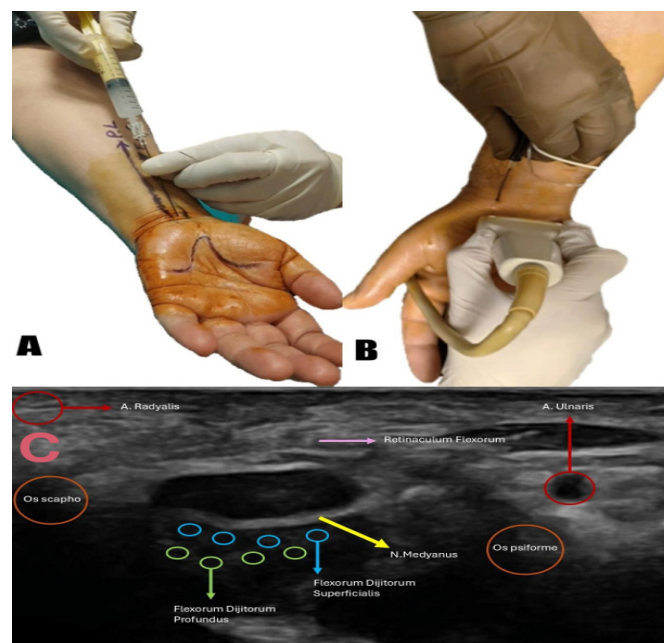


Figure 2. Ultrasound-guided carpal tunnel procedures: (A) Steroid injection technique, (B) Pulsed radiofrequency needle placement, (C) Ultrasonographic anatomy of the carpal tunnel showing median nerve (N. medyanus) and surrounding structures

A.: Artery, Os: Bone

management was performed with complete case analysis and the rate of missing data remained below 5%. Additionally, multivariable linear regression analysis was performed to adjust for potential confounders including age, gender, BMI, symptom duration, and baseline severity. Propensity score analysis was considered but not performed due to the small sample size and balanced baseline characteristics between groups. Subgroup analyses were performed according to age and gender factors. p values were calculated with two-tailed tests and reported as two-digit for $p \geq 0.01$ and three-digit for $p < 0.01$. Statistical significance was set at $p < 0.05$ for secondary outcomes and $p < 0.017$ for primary outcomes after Bonferroni correction. Data are expressed as mean (SD) values.

RESULTS

When demographic data from 60 participants enrolled in our research were analyzed, it was observed that both treatment groups had similar characteristics. While mean age in the steroid group was 52.4 years, the RF group averaged 51.8 years with no statistically significant difference between groups ($p = 0.782$). When gender distribution was analyzed, female patients were significantly superior. The proportion of female patients was 73.3% in the steroid group and 80% in the pulsed radiofrequency group. Body-mass index values were close to each other in both groups and averaged around 28 kg/m². The dominant hand was affected in more than half of participants. No significant difference was found between groups regarding symptom duration before treatment; mean symptom duration was around 15 months in both groups (**Table 1**).

In the detailed clinical evaluation performed in the pre-treatment period, it was found that the baseline characteristics of the groups were homogeneously distributed. VAS scores indicating pain intensity were around 7 points in both groups, indicating that the patients experienced moderate

Table 1. Demographic and clinical characteristics of patients

Feature	Steroid group (n=30)	RF group (n=30)	p value	Statistics test
Age (years)	52.4±8.7	51.8±9.2	0.782	Mann-Whitney U
Gender			0.598	Chi-square test
- Female, n (%)	22 (73.3)	24 (80.0)		
- Male, n (%)	8 (26.7)	6 (20.0)		
BMI (kg/m ²)	28.3±4.2	27.9±3.8	0.693	Mann-Whitney U
Dominant hand involvement, n (%)	18 (60.0)	17 (56.7)	0.793	Chi-square test
Symptom duration (months)	14.6±8.3	15.2±7.9	0.756	Mann-Whitney U

RF: Radiofrequency, BMI: Body-mass index

to severe pain. No statistically significant differences were observed between groups in either functional or symptom severity subscales of the Boston Carpal Tunnel Scale. Among the physical examination findings, Tinel's test positivity rate was 86.7% in the steroid group and 90% in the pulsed radiofrequency group. Phalen test positivity rates were similarly above 80% in both groups. In ultrasonographic evaluation, median nerve thickness measurements did not differ between the groups with a mean of 12.7 mm (Table 2).

Changes in clinical parameters in the post-treatment follow-up revealed remarkable findings. At the first month follow-up, it was observed that both treatment methods were effective, but no significant differences were found between groups. By third month, superiority for the pulsed radiofrequency group became evident. VAS scores decreased to an average of 2.9 points in the pulsed radiofrequency group and remained at 3.8 points for the steroid cohort, and this difference achieved statistical significance. A comparable trend was noted in functional scores of Boston Carpal Tunnel Scale; the scores decreased to 1.6 points in the pulsed radiofrequency group and remained at 2.0 points in the steroid group. Symptom severity scores also improved significantly in favor of the pulsed radiofrequency group (Figure 3).

The physical examination results showed better outcomes for both groups as time progressed. The Tinel's test showed a significant reduction in positivity from 90% before treatment to 30% for the RF group versus 46.7% for the steroid cohort during third month. The improvement continued into the sixth month when the pulsed radiofrequency group reached 20% positivity and the steroid group reached 43.3% positivity showing a statistically significant between-group difference ($p=0.048$). The Phalen test showed similar decreases in positivity rates where the pulsed radiofrequency group reached

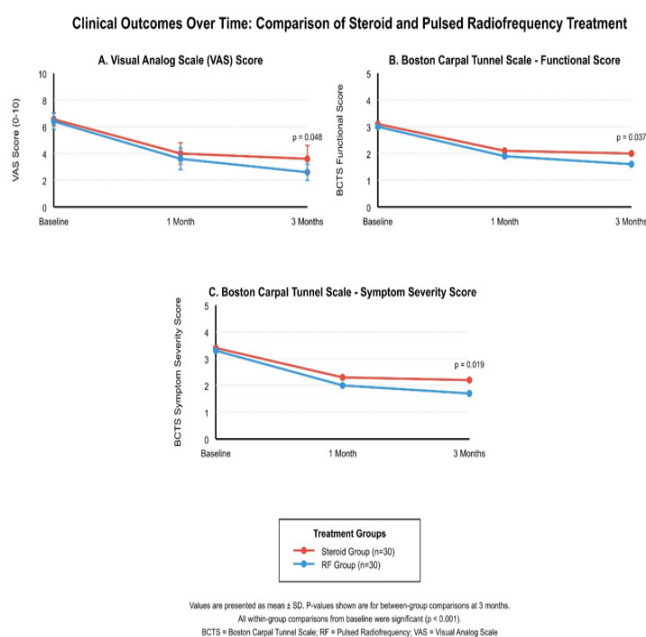


Figure 3. Clinical outcomes over time following ultrasound-guided steroid injection versus pulsed radiofrequency treatment for carpal tunnel syndrome: Comparison of (A) Visual Analog Scale (VAS) scores for pain intensity (0-10 scale), (B) Boston Carpal Tunnel Scale (BCTS) functional scores, and (C) BCTS symptom severity scores between steroid injection group (red line, n=30) and pulsed radiofrequency (RF) group (blue line, n=30) at baseline, 1 month, and 3 months post-treatment. Data are presented as mean±standard deviation. p-values indicate between-group comparisons at 3 months (Mann-Whitney U test). All within-group comparisons from baseline were statistically significant ($p<0.001$, repeated measures ANOVA).

20% at the third month but the steroid group maintained 40%. The sixth-month measurements showed a decrease to 13.3% in the pulsed radiofrequency group while the steroid group maintained 36.7% positivity with a significant group difference ($p=0.026$). The median nerve thickness measured through ultrasonography remained at 12.6-12.8 mm in both

Table 2. Pretreatment clinical evaluation parameters

Parameter	Steroid group (n=30)	RF group (n=30)	p value	Statistics test
VAS score (0-10)	7.2±1.4	7.0±1.6	0.584	Mann-Whitney U
Boston Carpal Tunnel Scale				
- Functional score	3.1±0.8	3.0±0.9	0.642	Mann-Whitney U
- Symptom severity score	3.4±0.7	3.3±0.8	0.573	Mann-Whitney U
Tinel's test positive, n (%)	26 (86.7)	27 (90.0)	0.692	Chi-square test
Phalen test positive, n (%)	24 (80.0)	25 (83.3)	0.740	Chi-square test
USG median nerve thickness (mm)	12.8±2.1	12.6±2.3	0.721	Mann-Whitney U

RF: Radiofrequency, VAS: Visual Analog Scale, USG: Ultrasonography

groups before treatment and decreased after treatment. The median nerve thickness reached 9.8 mm for the RF group versus 10.8 mm for the steroid cohort during third month with a statistically significant between-group difference ($p=0.041$). The sixth-month measurements showed increased differences between groups with 9.2 mm for the RF group versus 10.5 mm for the steroid cohort ($p=0.018$). These tests and USG measurements showed significant improvements throughout all follow-up periods according to intra-group comparisons (Table 3).

The most evident sign of real improvement was through electrophysiologic evaluations. The electromyography tests conducted at the sixth month follow-up revealed that patients who received pulsed radiofrequency treatment achieved better results than those who received steroids. The motor distal latency values in the pulsed radiofrequency group decreased to 3.9 mss but the steroid group maintained values at 4.3 mss. The sensory distal latency measurements showed identical patterns between groups where the pulsed radiofrequency group had 3.2 milliseconds and the steroid group had 3.6 mss. The nerve conduction velocity showed better improvement in the patients who received pulsed radiofrequency treatment.

The motor nerve conduction velocity reached 51.2 m/s in the pulsed radiofrequency group but stayed at 47.8 m/s in the steroid group. The electrophysiologic improvements showed that pulsed radiofrequency treatment generated more sustained and effective nerve function benefits (Table 4).

The safety profiles of both treatment methods showed acceptable side effect results. The pulsed radiofrequency group experienced pain elevation in 23.3% of cases but the steroid group experienced this side effect in 10% of patients. The pulsed radiofrequency group reported numbness in 13.3% of patients but the steroid group reported this side effect in 6.7% of patients. The pulsed radiofrequency group experienced one infection as a serious complication while the steroid group had one patient develop a minimal hematoma. The total complication rates between the two groups showed a 40% rate in the pulsed radiofrequency group and a 20% rate in the steroid group but the difference failed to achieve statistical significance (Table 5).

The superiority of the pulsed radiofrequency group was clearly evident in the parameters evaluating treatment success. Patients achieving 50% or more reduction in VAS

Table 3. Physical examination findings follow-up

Parameter	Group	Before treatment	Month 1	Month 3	Month 6	p value (1 st month)	p value (3 rd month)	p value (6 th month)	p value (1 st month)	p value (3 rd month)	p value (6 th month)
Tinel test positive, n (%)	Steroid	26 (86.7)	15 (50.0)	14 (46.7)	13 (43.3)	<0.001	<0.001	<0.001	0.417	0.175	0.048
	RF	27 (90.0)	12 (40.0)	9 (30.0)	6 (20.0)	<0.001	<0.001	<0.001			
Phalen test positive, n (%)	Steroid	24 (80.0)	11 (36.7)	12 (40.0)	11 (36.7)	<0.001	<0.001	<0.001	0.390	0.079	0.026
	RF	25 (83.3)	8 (26.7)	6 (20.0)	4 (13.3)	<0.001	<0.001	<0.001			
USG median nerve thickness (mm)*	Steroid	12.8±2.1	11.2±1.8	10.8±1.6	10.5±1.5	<0.001	<0.001	<0.001	0.216	0.041	0.018
	RF	12.6±2.3	10.7±1.7	9.8±1.4	9.2±1.3	<0.001	<0.001	<0.001			

RF: Radiofrequency, USG: Ultrasonography, *Comparison with pretreatment (Wilcoxon test), **Comparison between groups (Chi-square test), ***Comparison between groups (Mann-Whitney U test)

Table 4. Electrophysiologic evaluation

EMG parameter	Steroid group		RF group		p value*	p value**
	Before treatment	Month 6	Before treatment	Month 6		
Motor distal latency (ms)	4.8±0.9	4.3±0.8	4.7±1.1	3.9±0.7	0.003	0.041
Sensory distal latency (ms)	3.9±0.7	3.6±0.6	3.8±0.8	3.2±0.5	0.012	0.009
Motor nerve conduction velocity (m/s)	45.2±6.3	47.8±5.9	44.8±5.9	51.2±6.1	0.025	0.026
Sensory nerve conduction velocity (m/s)	42.1±7.2	44.7±6.8	41.8±6.8	48.3±7.2	0.031	0.041
Motor action potential amplitude (mV)	6.8±2.1	7.4±2.0	6.9±2.3	8.2±2.1	0.089	0.164

EMG: Electromyography, RF: Radiofrequency, *6th month comparison with pretreatment (Wilcoxon test), **6th month comparison between groups (Mann-Whitney U)

Table 5. Complications and side effects

Complication	Steroid group (n=30)	RF group (n=30)	p value	Statistics test
Temporary increase in pain, n (%)	3 (10.0)	7 (23.3)	0.165	Fisher's exact test
Transient numbness, n (%)	2 (6.7)	4 (13.3)	0.389	Fisher's exact test
Infection, n (%)	0 (0.0)	1 (3.3)	0.314	Fisher's exact test
Bleeding/hematoma, n (%)	1 (3.3)	0 (0.0)	0.314	Fisher's exact test
Total complications, n (%)	6 (20.0)	12 (40.0)	0.084	Chi-square test

RF: Radiofrequency

scores reached 80% for the pulsed radiofrequency cohort, while it remained at 60% in the steroid group. The proportion of patients with clinically significant improvement in the Boston Carpal Tunnel Scale was 86.7% for the RF group versus 66.7% for the steroid cohort. In terms of patient satisfaction, the pulsed radiofrequency group achieved more successful results; 90% of the patients rated the treatment outcome as good or excellent, while this rate remained at 73.3% in the steroid group. When the electromyographic recovery rate, which is the most objective criterion, was analyzed, 73.3% recovery was found in the pulsed radiofrequency group, while this rate remained at 50% for the steroid cohort with this difference achieving statistical significance (Figure 4).

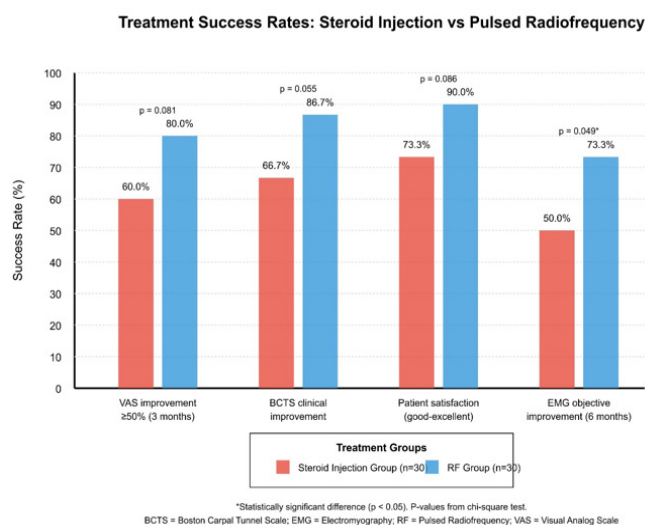


Figure 4. Comparison of treatment success rates between ultrasound-guided steroid injection and pulsed radiofrequency for carpal tunnel syndrome: Bar graph showing percentage of patients achieving predefined success criteria in steroid injection (red bars) versus pulsed radiofrequency (RF, blue bars) groups (n=30 each). Success criteria evaluated include: $\geq 50\%$ reduction in Visual Analog Scale (VAS) pain scores at 3 months, clinically meaningful improvement in Boston Carpal Tunnel Scale (BCTS), patient satisfaction rated as good-excellent, and objective improvement in electromyography (EMG) findings at 6 months. *Statistically significant difference ($p < 0.05$). p-values derived from Chi-square test.

DISCUSSION

This study aimed to evaluate the efficacy of ultrasound-guided pulsed radiofrequency therapy and corticosteroid injection for managing CTS. Our research showed that both treatment approaches delivered equivalent early benefits yet pulsed radiofrequency therapy produced superior long-term results. The study's observational nature requires us to understand these results in relation to our research while acknowledging that the retrospective design prevents us from establishing cause-and-effect relationships. The treatment modalities showed equivalent early benefits but pulsed radiofrequency therapy was associated with more enduring and effective results during long-term follow-up. The observed difference became most apparent during the third month and electrophysiological tests at the sixth month suggested these findings. The choice between minimally invasive treatments should consider long-term efficacy based on these preliminary observations.

The demographic characteristics determined in our study are largely consistent with the CTS literature. The mean age

in both treatment groups was around 51-52 years, which is different from the age ranges reported in the literature. The mean age of 34.21 ± 7.685 years reported by Ullah et al.¹² and 31.8 years reported by Hulkkonen et al.¹³ are significantly lower than our findings. This difference may be explained by the selection of our study population from the older age group and the chronic course of the disease. In terms of female gender dominance, our findings are consistent with the literature; the prevalence of female patients, 73.3% in the steroid group and 80.0% in the RF group, is similar to the 80.8% found by Ullah and colleagues¹² and the 77% observed by Mathew and colleagues.¹⁴ Our BMI values were found to be in the range of $27\text{--}28 \text{ kg/m}^2$ in both groups, which is similar to the $28.0 \pm 6.4\%$ and $27.5 \pm 6.4\%$ reported by Mathew et al.¹⁴ 0 ± 6.4 and $27.9 \pm 4.5 \text{ kg/m}^2$. In addition, in parallel with the finding of Nowak et al.¹⁵ that the prevalence of CTS in obese patients was 50.8%, the BMI values of our study group were in the overweight category, which is consistent with the literature in terms of the risk factors of the disease.

Our first month results show that both treatment modalities are effective in the short term and are consistent with the findings in the literature. Significant improvement was observed in VAS scores in both groups and the values measured as 3.8 ± 1.6 in the RF group and 4.2 ± 1.8 in the steroid group reflect a similar improvement pattern with the decrease in the NRS score (from 6.00 to 3.50) reported by Krzywdzak et al.¹⁶ our Boston Carpal Tunnel Scale functional scores were found as 1.9 ± 0.8 for the RF cohort versus 2.1 ± 0.9 for the steroid cohort, indicating a more modest improvement, in contrast to the dramatic decrease in the BKTS-FSS score (from 17.16 ± 5.71 to 7.07 ± 7.75) reported by Krzywdzak et al.¹⁶ at 4 weeks. Our symptom severity scores of 2.0 ± 0.7 for the RF cohort and 2.3 ± 0.8 is consistent with the significant improvement reported by Hofer et al.¹⁷ in the steroid group, but shows a more limited improvement than the significant decrease in the BKTS-SSS score (from 33.53 ± 3.29 to 10.33 ± 10.06) reported by Krzywdzak et al.¹⁶ Our finding that pulsed radiofrequency and steroid injection showed similar efficacy in the early period, as reported in the narrative review by Gupta et al.¹⁸ The differences between the groups, which did not reach statistical significance, are in line with the similarity in early period efficacy highlighted in the systematic review by Chan et al.¹⁹

Our third and sixth month results suggest that pulsed radiofrequency therapy may be associated with better outcomes than steroid injection in the long term, findings that are consistent with the long-term efficacy patterns in the literature. The decrease in VAS scores to 2.9 ± 1.5 in the RF group and 3.8 ± 2.1 in the steroid group at the third month with a significant between-group difference ($p = 0.048$) are consistent with the high failure rates (41.8%) seen in steroid injection in the long-term follow-up of Ly-Pen et al.²⁰ Significant differences in BKTS functional and symptom severity scores in favor of the RF cohort ($p = 0.037$ and $p = 0.019$, respectively) coincides with Gonu et al.²¹ who reported improvement in symptoms in only 61% of steroid-injected patients at 6-month follow-up. In our six-month electrophysiologic findings, motor distal latency measured $3.9 \pm 0.7 \text{ ms}$ and sensory distal

latency measured 3.2 ± 0.5 ms for the RF cohort, while these values were 4.3 ± 0.8 ms and 3.6 ± 0.6 ms in the steroid group, respectively. The significant differences in motor and sensory conduction velocities in favor of the RF cohort ($p=0.026$ and $p=0.041$, respectively) show a parallel pattern with the findings of Chakk et al.²² that pulsed radiofrequency ablation may provide more permanent electrophysiological changes compared to electric field ablation.

The complication profiles and success rates found in our study were found to be at acceptable levels when compared with minimally invasive CTS treatment methods in the literature. Although our total complication rates of 40.0% for the RF cohort versus 20.0% for the steroid cohort were higher than the surgical complication rates reported by Carmo²³ (9.55% granulomatous reaction, 3.82% palmar ecchymosis), this difference seems to be due to mild complications such as transient increased pain. The fact that Kamel et al.²⁴ reported no serious complications after minimally invasive ultrasonography-guided median nerve decompression is consistent with absence of major complications in our study. Our VAS score improvement rates of 50% or more were 80.0% for the RF cohort compared to 60.0% for the steroid cohort, and although these values are lower than the 92% symptom resolution rate reported by Carmo,²³ they are satisfactory for non-invasive approaches. Our rates of clinically significant improvement in BCTS were 86.7% for the RF cohort versus 66.7% for the steroid cohort, showing a similar pattern to the significant improvement reported by Alimohammadi et al.²⁵ in BCTQ scores after surgery. In terms of patient satisfaction, our rates of 90.0% for the RF cohort compared to 73.3% for the steroid cohort were close to the 77% very satisfied patient rate reported by Carmo²³ and suggests potential superiority of RF treatment from the patient perspective. The fact that our rate of objective improvement in EMG was statistically superior for the RF cohort (73.3%) compared to the steroid cohort (50.0%) emphasizes this importance of objective evaluation in parallel with the finding of Mertz et al.²⁶ that electrophysiological measurements were used in 49.5% of studies.

Limitations

Multiple essential limitations from the retrospective study design need to be taken into account when interpreting our research results. The physician preference-based patient allocation system together with the absence of randomization created significant selection bias which could have affected our research findings. The non-random assignment process might produce systematic variations between groups which surpass the recorded baseline characteristics. The retrospective study design prevents us from establishing cause-and-effect relationships so we can only document the relationships between treatment approaches and results. The observed outcomes could have been influenced by unmeasured patient characteristics together with physician expertise and patient preferences and socioeconomic variables and other confounding factors. Our statistical adjustments do not rule out the possibility of remaining confounding effects. The restricted sample size reduces the ability to generalize our results while the six-month follow-up duration prevents

us from evaluating outcomes after this period. The lack of extended follow-up information prevents us from understanding how the observed differences will change or remain stable or grow throughout time. The strengths of our study include standardized assessment tools and regular follow-up protocols and the evaluation of both subjective and objective parameters. The observational findings need validation through well-designed prospective randomized controlled trials before any definitive conclusions can be drawn regarding the superiority of one treatment over another.

CONCLUSION

Based on our retrospective analysis, pulsed radiofrequency therapy under ultrasonography guidance for managing CTS appears to be associated with more effective as well as durable results in the long term compared to steroid injection. Although both methods demonstrated similar improvement in the early period, pulsed radiofrequency therapy showed a trend toward significant superiority especially after the third month, with these differences supported by electrophysiologic parameters. The observational findings need careful interpretation because the study design is retrospective and there was no randomization and potential unmeasured confounding factors. Prospective randomized controlled trials are needed to confirm these preliminary observations and to determine if a true causal relationship exists. As a minimally invasive approach, pulsed radiofrequency therapy may offer an effective therapeutic option to consider before surgery for patients with treatment-resistant conservative management, though optimal patient selection criteria and standardized treatment protocols remain to be established through future research.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study has been approved by the Scientific Researches Ethics Committee of Adana City Training and Research Hospital (Date: 08.05.2025, Decision No: 516).

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.

Acknowledgment

We thank Prof. Dr. Yurdal Gezeran for his contributions.

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Does the time since diagnosis affect the quality of life in patients with haematological malignancies at early and late period?

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Cite this article as: Balık B, Mutlu YG, Sevindik ÖG. Does the time since diagnosis affect the quality of life in patients with haematological malignancies at early and late period? *J Med Palliat Care*. 2025;6(4):396-402.

Received: 18.06.2025

Accepted: 08.08.2025

Published: 31.08.2025

ABSTRACT

Aims: We aimed to determine the quality of life, social support levels and factors affecting patients who were diagnosed with hematological malignancy and received therapy, regarding the certain time points after diagnosis. Turkish version of the EORTC-QLQ-C30 scale is a tool with valid and reliable indicators in assessing the quality of life of patients with hematological cancer. It makes it essential to support our patients throughout the therapy and even after the end of treatment, both medically and socially with experts in the field.

Methods: Turkish version of the EORTC QLQ-C30 v.3.0 was used to assess QoL measures. A total of 89 patients were included and were grouped according to the demographics, diagnostic sub-groups and time elapsed from diagnosis.

Results: The scales resulted to be similar across gender and diagnostic groups. When the groups were compared, it was found that the scores in the physical function and role function scales were higher and the scores in the fatigue, loss of appetite, constipation, and diarrhoea scales were lower in younger patients. Constipation was higher in the first 6 months, and no significant difference was observed between groups regarding the remaining QoL measures, interestingly this was also available for a comparison between 1 year period and more.

Conclusion: The time from diagnosis had no apparent impact on QoL measures in our patient group. It makes it essential to support our patients throughout the therapy and even after the end of treatment, both medically and socially with experts in the field.

Keywords: Quality of life, malignancy, haematological, time effect

INTRODUCTION

The World Health Organization (WHO) defines the quality of life as "perceiving one's own life in a culture and value system according to one's own goals, expectations, standards and interests". Studies show that having an acute and/or chronic illness can significantly reduce the quality of life.¹ The name of the "cancer" disease, the fear given by the name, anxiety for the future, the stress caused by what may be experienced during the disease process and the undesirable effects related to the treatment significantly affect the quality of life of the patients and their relatives. Despite all these negativities and side effects due to treatment, it is important to improve and maintain the quality of life of patients during and after treatment.² People are now concerned not only with the length of life, but also with its quality.

On December 15, 2020, the International Agency for Research on Cancer (IARC), a subsidiary of the WHO, published latest estimates of the global cancer burden, named the World Cancer Statistics. According to the GLOBOCAN 2020 database, which can be accessed online as part of the IARC Global Cancer Observatory, the number of new cancer

cases for 2020 in our country was reported as 233.834 and the number of cancer-related deaths was 126.335. Among all malignancies, leukemias were 10th, non-hodgkin lymphomas 11th, myeloma 18th, Hodgkin lymphoma 23rd commonest one. Hematological malignancies negatively affect the quality of life (HRQoL) and well-being of patients, and living with these diseases trigger physical, emotional, cognitive, social functioning, and financial problems.³⁻⁵

However, few studies, worldwide, have addressed the health-related quality of life (HRQoL) of patients with hematological malignancies.⁶ In this study, we aimed to determine the quality of life, social support levels and factors affecting patients who were diagnosed with hematological malignancy and received therapy with time since diagnosis.

METHODS

EORTC QLQ-C30 Quality of Life Version 3.0 Turkish Scale, which was previously validated in Turkish, was used in this current study. Permission to use the scale was obtained from our institution and EORTC, itself. This study was

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performed in line with the principles of the Declaration of Helsinki. Approval has been granted by the İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 27.01.2021, Decision No: E-10840098-772.02-2618). Informed consent was obtained from all individual participants included in the study.

A total of 89 hematological cancer patients who were admitted to our hospital between January 2021 and February 2021 were included. The data obtained from the scale were evaluated by demographic characteristics, diagnosis, and time from the diagnosis of the patients.

This prospective study employed a consecutive sampling method to include participants meeting predefined inclusion criteria. A prior power analysis was conducted to ensure adequate statistical power, with the study designed to achieve 80% power to detect clinically relevant differences. Data collection involved standardized, validated instruments administered at multiple time points to assess outcomes longitudinally. All procedures adhered to relevant ethical standards, and rigorous data quality control measures were implemented throughout the study.

Statistical Analysis

The data were evaluated in the SPSS 23.0 package program, and the mean, percentage distributions, correlation, t test, Mann-Whitney U test, Kruskal-Wallis test were used in statistical analysis. In line with the results, the factors affecting the quality of life of the patients were tried to be determined and improvements were made in the necessary care principles.

EORTC QLQ-C30 quality of life scale: The EORTC QLQ-C30 version 3.0 quality of life scale is a globally used scale which was developed by EORTC in cancer patients. In our country, content validity and reliability study were conducted by Beser and Oz,² Cronbach alpha coefficient (r) was reported as 0.9014. The scale consists of three sub-dimensions: general health score (general well-being), functional scale and symptom scale, and includes 30 questions for the past week. Functional scale includes physical, role, cognitive, emotional, and social functions. The symptom scale consists of the weakness, pain, nausea-vomiting, dyspnoea, insomnia, loss of appetite, constipation, diarrhoea, and financial difficulties. The first 28 of the 30 items in the scale is a four-point Likert-type scale and the items are scored as none: 1, a little: 2, quite: 3, much: 4. In the 29th question of the scale, the patient is asked to evaluate his health with the scale from 1 to 7 (1: very poor and 7: excellent) and the general quality of life in question 30. The 29th and 30th questions in the scale are questions that form the field of general well-being. Higher functional scale score, general health scale scores and a low symptom scale score indicates a better quality of life.⁷ Measurement invariance of the EORTC QLQ-C30 was approved in a large sample of patients with hematological malignancies by Sommer et al,⁸ and they also confirmed that this questionnaire is a valid and robust measurement tool in patients with hematological malignancies, also for comparisons across groups and time.

Other study covariates included patient socio-demographic characteristics (gender and age) and clinical history (time

since diagnosis and cancer type). We categorized the following variables: patient age (<55 years; ≥ 55); cancer type (leukemias, lymphomas, plasma cell diseases (PCD), myelodysplastic syndrome/ myeloproliferative neoplasies (mds/mpn), and others); time from diagnosis (<6 months; ≥ 6 months, >1years; ≥ 1 years)

RESULTS

Demographic Parameters

A total of 89 patients, 37 (42%) female and 52 (59%) male, were included in the study. Median age was 55 (17- 85) years. The patients were divided into two groups according to their age as over 55 years old (43 patients, 48.3%) and below (46 patients, 51.7%). According to their diagnosis, patients were categorized into 5 different groups as leukemias (25 patients, 28.1%), lymphomas (31 patients, 34.8%), PCD (25 patients, 28.1%), mds/mpn (6 patients, 6.7%) and others (2 patients, 2.2%). Regarding the time difference between the completion of QLQ questionnaire and the time of diagnosis, patients were divided into groups as the ones the difference is less than 6 months or more (46 patients, 51.7% vs. 43 patients, 48.3%), and less than 12 months or more (62 patients, 69.7% vs. 27 patients, 30.3%).

Results of the EORTC QLQ-C30 Quality of Life Scale for Each Group

EORTC QLQ-C30 quality of life scale general health status subscale mean score of the patients was found to be 55.8 ± 27.39 . It was determined that the patients got the highest score from the cognitive function (77.52 ± 23.17) and the lowest score from the physical function (59.02 ± 28.61) in the functional scale section. In the symptom scale section, the highest mean score was observed in the fatigue item (50.43 ± 31.11), while the three most common symptoms were determined as fatigue, insomnia, and pain, respectively.

When the averages of the functional status subgroups were evaluated, it was found to be as cognitive function 77.52 ± 23.17 , physical function 59.02 ± 28.61 , role function 66.29 ± 35.70 , social function 60.86 ± 34.55 , emotional function 71.44 ± 27.46 .

Within the symptom's subgroup, the mean score for economic difficulties was 39.70 ± 36.19 , the mean score for fatigue was 50.43 ± 31.11 , the average pain score was 36.14 ± 32.58 , and insomnia points was 39.70 ± 37.56 , the mean constipation score was 24.71 ± 32.77 , the mean score of anorexia was 32.95 ± 35.70 , the mean score for nausea and vomiting was 15.91 ± 26.34 , the average score for respiratory distress was 20.22 ± 29.99 , diarrhoea average score was 17.97 ± 28.45 (Table 1).

The quality-of-life measures were not statistically different between disease categories (Table 2).

The scales were also resulted to be similar across gender groups (Table 3).

When the age groups were compared, it was found statistically significant that the scores in the physical function and role function scales were higher and the scores in the fatigue, loss of appetite, constipation and diarrhoea scales were found to be lower in the group under 55 years old (Table 4).

Table 1. Evaluation of the quality of life of all patients

Evaluation of the all patients	Mean±SD	Median/IQR
1. General health status	55.80±27.39	58.33/41.67
2. Physical function	59.02±28.61	60/40
3. Role function	66.29±35.70	66.66/66.67
4. Emotional function	71.44±27.46	83.33/37.5
5. Cognitive function	77.52±23.17	83.33/33.33
6. Social function	60.86±34.55	66.66/66.67
7. Fatigue	50.43±31.11	55.55/55.56
8. Nausea-vomiting	15.91±26.34	0/25
9. Pain	36.14±32.58	33.33/66.67
10. Dyspnea	20.22±29.99	0/33.33
11. Insomnia	39.70±37.56	33.33/66.67
12. Loss of appetite	32.95±35.70	33.33/66.67
13. Constipation	24.71±32.77	0/33.33
14. Diarrhea	17.97±28.45	0/33.33
15. Financial problems	39.70±36.19	33.33/66.67

SD: Standard deviation, IQR: Interquartile range

The general health status point average of the group participating in the study was 58.3 (41.67) and the functional status average is 65.16 (2.78±100), symptom status mean was 30.86 (0±80.2).

When we evaluated the results of the survey based on the averages of general health status, functional status, and

symptom status, we found that the average of symptom status was low in the group under 55 years of age (p value: 0.003) (Table 5).

When the patients were compared with the time from diagnosis as <6 months and ≥6 months, it was observed that the complaint of constipation was higher in the first 6 months (Table 6). There was not any other dissimilarity. Considering the first 12 months and after, there was no significant difference between the two groups (Table 7).

DISCUSSION

The only goal in cancer treatment is not to eliminate the disease, but to increase the quality of life by reducing post-treatment morbidity. Quality of life includes all situations and factors affecting the individual.

Bikmaz et al,⁹ in their study including leukemia patients, found the mean overall health score of EORTC QLQ-C30 as 59.76 at a similarly moderate level. In our study, the general health status point average was 58.3 (IQR; 41.67). The general health status of the patients was found to be moderate. This finding is also aligned with Abdu et al.,¹¹ who observed similar HRQoL scores in adults with hematological cancers. Fatigue, insomnia, and pain were the most commonly reported symptoms in our cohort, corroborating earlier studies.^{3,10,11,15}

The functional health status of the patients was found to be 67.8 (IQR; 32.91), which should be graded as a moderate level also. It was determined that the patients obtained the

Table 2. Effects of disease diagnosis on quality of life

Diagnosis	Leukemias		Lymphomas		PCD		Mds-mpn		Others		P
	Mean±SD	Median/IQR	Mean±SD	Median/IQR	Mean±SD	Median/IQR	Mean±SD	Median/IQR	Mean±SD	Median/IQR	
1. General health status	53±28.96	50/41.67	57.53±26.9	66.67/33.33	57.33±30.08	58.33/41.67	51.39±19.31	50/27.08	58.33±11.79	58.33/-	0.84
2. Physical function	53.6±31.53	53.33/60	69.68±20.86	73.33/26.67	52.27±31.84	53.33/53.33	51.11±24.46	60/36.67	70±42.43	70/-	0.17
3. Role function	62.67±34.79	66.67/66.67	70.97±35.22	100/66.67	64±36.54	66.67/66.67	58.33±46.84	66.67/87.5	91.67±11.79	91.67/-	0.72
4. Emotional function	76.67±26.68	91.67/41.67	68.82±31.91	83.33/41.67	70±26.02	75/33.33	68.44±17.21	70.83/35.42	70.83±5.89	70.83/-	0.58
5. Cognitive function	79.33±24.19	83.33/33.33	78.49±21.6	83.33/33.33	75.33±27.69	83.33/41.67	72.22±8.61	66.67/16.67	83.33±0	83.33/-	0.71
6. Social function	58.67±36.36	66.67/66.67	65.05±34.79	66.67/66.67	56±35.97	66.67/58.33	58.33±22.97	58.33/50	91.67±11.79	91.67/-	0.57
7. Fatigue	53.33±34.25	55.56/61.11	46.59±31.87	44.44/55.56	48.89±29.4	44.44/50	59.26±19.46	61.11/30.56	66.67±47.14	66.67/-	0.78
8. Nausea-vomiting	18.67±29.39	0/33.33	18.28±31.14	0/16.67	9.33±15.28	0/16.67	11.11±17.21	0/33.33	41.67±35.36	41.67/-	0.43
9. Pain	32.67±34.85	16.67/66.67	33.87±33.47	33.33/66.67	36.67±28.46	33.33/33.33	50±33.33	33.33/58.33	66.67±47.14	66.67/-	0.5
10. Dyspnea	26.67±37.27	0/33.33	17.20±28.38	0/33.33	16±25.68	0/33.33	27.78±25.09	33.33/41.67	16.67±23.57	16.67/-	0.67
11. Insomnia	41.33±38.83	33.33/83.33	35.48±38.43	0/66.67	42.67±37.91	33.33/66.67	44.44±40.37	50/75	33.33±0	33.33/-	0.93
12. Loss of appetite	34.64±41.37	33.33/83.33	36.56±34.81	33.33/66.67	25.33±30.85	0/50	33.33±42.16	16.67/75	50±23.57	50/-	0.67
13. Constipation	28±34.26	0/66.67	16.13±32.05	0/33.33	26.67±28.87	33.33/33.33	44.44±40.37	50/75	33.33±47.14	33.33/-	0.19
14. Diarrhea	12±18.95	0/33.33	17.20±30.88	0/33.33	22.67±31.51	0/33.33	33.33±36.51	33.33/50	0±0	0/-	0.32
15. Financial problems	38.67±38.10	33.33/66.67	31.18±35.42	33.33/66.67	52±34.8	33.33/50	27.78±25.09	33.33/41.67	66.67±47.14	66.67/-	0.16

PCD: Plasma cell diseases, Mds/mpn: Myelodysplastic syndrome/myeloproliferative neoplasies, SD: Standard deviation, IQR: Interquartile range

Table 3. The effect of gender on quality of life

Gender	Female		Male		P
	Mean±SD	Median/IQR	Mean±SD	Median/IQR	
1. General health status	52.70±29.99	58.33 / 33.33	58.01±25.46	58.33/33.33	0.315
2. Physical function	51.71±30.57	60 /53.33	64.23±26.21	66.67/40	0.061
3. Role function	64.41±37.51	66.67/66.67	67.63±34.68	75/62.5	0.725
4. Emotional function	65.09±32.50	83.33/45.83	75.96±22.49	83.33/37.5	0.140
5. Cognitive function	72.52±25.52	83.33/33.33	81.09±20.88	83.33/33.33	0.090
6. Social function	54.50±38.22	66.67/75	65.38±31.28	66.67/66.67	0.212
7. Fatigue	55.56±30.2	55.56/44.44	46.79±31.53	38.89/52.78	0.204
8. Nausea-vomiting	15.77±26.34	0/25	16.03±26.6	0/29.17	0.932
9. Pain	42.79±31.8	50/50	31.41±32.62	16.67/50	0.078
10. Dyspnea	20.72±28.71	0/33.33	19.87±3.14	0/33.33	0.693
11. Insomnia	37.84±34.39	33.33/66.67	41.03±39.94	33.33/66.67	0.849
12. Loss of appetite	32.43±38.08	33.33/66.67	33.33±34.30	33.33/66.67	0.727
13. Constipation	22.52±33.38	0/33.33	26.28±32.56	0/33.33	0.456
14. Diarrhea	23.42±33.21	0/33.33	14.10±24.11	0/33.33	0.211
15. Financial problems	45.05±37.03	33.33/66.67	35.90±35.45	33.33/66.67	0.240

SD: Standard deviation, IQR: Interquartile range

Table 4. The effect of age groups on quality of life

Age	<55 years		≥55 years		P
	Mean±SD	Median/IQR	Mean±SD	Median/IQR	
1. General health status	58.7±27.33	62.5/35.42	52.71±27.44	50/41.67	0.27
2. Physical function	67.97±24.73	73.33/40	49.46±29.64	53.33/53.33	0.003*
3. Role function	73.91±33.27	91.67/50	58.14±36.8	66.67/66.67	0.041*
4. Emotional function	72.28±28.87	83.33/35.42	70.54±26.19	83.33/41.67	0.445
5. Cognitive function	79.71±22.75	83.33/33.33	75.19±23.67	83.33/33.33	0.283
6. Social function	60.51±34.49	66.67/66.67	61.24±35.02	66.67/66.67	0.907
7. Fatigue	41.79±32.13	33.33/44.44	59.69±27.43	66.67/44.44	0.006*
8. Nausea-vomiting	14.86±28.38	0/16.67	17.05±24.26	0/33.33	0.161
9. Pain	34.78±33.49	33.33/66.67	37.6±31.93	33.33/50	0.616
10. Dyspnea	17.39±28.75	0/33.33	23.26±31.32	0/33.33	0.281
11. Insomnia	33.33±34.89	33.33/66.67	46.51±35.74	33.33/33.33	0.061
12. Loss of appetite	22.46±32.24	0/33.33	44.19±36.17	33.33/66.67	0.002*
13. Constipation	14.49±28.68	0/33.33	35.66±33.65	33.33/66.67	0.001*
14. Diarrhea	10.87±23.36	0/8.33	25.58±31.57	33.33/33.33	0.007*
15. Financial problems	41.3±38.61	33.33/66.67	37.98±33.79	33.33/66.67	0.784

SD: Standard deviation, IQR: Interquartile range, * p<0.05

highest score from “cognitive function” and the lowest score from “physical function” on functional scales. In symptom scales, the highest mean score was seen in “fatigue item”, while the three most common symptoms were “fatigue”, “insomnia” and “pain”, respectively. It is desirable for the patients to have high scores in cognitive and emotional function, and this is thought to support the patient positively. According to the responses obtained from the questionnaire, the lower occupational functions of the patients can be due to the inability to spare time for efforts and disease-related treatment processes. In addition, it can be said that feeling weak and tired due to the side effects of the disease and treatment negatively affects their occupational functions.³

Experiencing more intense symptoms of fatigue, anorexia and insomnia are usually related to nausea and vomiting, changes in blood values and disease process due to the disease and treatment.^{9,10} Inability to fully cover the expenses of intensive treatment by their social insurance or the long bureaucratic processes (preparation of drug reports, etc.), and the decrease in their income levels because of the vacancy on work during the treatment and follow-up period may lead to financial difficulties.³

No statistically significant differences in quality of life were observed across diagnostic subgroups, supporting Efficace et al.⁶ and Immanuel,¹² who concluded that the type of

Table 5. Comparisons of all groups' scales

		General health status			Functional status			Symptom status		
		Mean±SD	Median/ IQR	p	Mean±SD	Median/ IQR	p	Mean±SD	Median/ IQR	p
Gender	Female	52.7±29.99	58.33/33.34	0.315	60.16±22.82	61.39/31.94	0.080	32.90±18.45	32.72/19.14	0.358
	Male	58.01±25.46	58.33/33.33		68.72±18.87	73.75/25.69		29.42±20.49	28.09/28.09	
Age groups	<55 years	58.70±27.33	62.50/33.33	0.270	68.85±20.26	74.03/25	0.104	25.70±20.08	26.85/27.78	0.003
	≥55 years	52.71±27.44	50/41.67		61.21±21.12	61.39/31.39		36.39±17.76	37.04/33.33	
Diagnosis	Leukemias	53±28.96	50/41.67	0.843	63.99±21.01	67.22/28.06	0.617	31.78±23.91	30.25/35.19	0.696
	Lymphomas	57.53±26.90	66.67/33.33		68.42±19.14	73.61/27.5		28.06±18.94	28.40/29.63	
	PCD	57.33±30.80	58.33/25		62.49±25.21	64.72/42.78		31.14±16.14	32.72/24.69	
	Mds-mpn	51.39±19.31	50/16.66		60.14±11.30	61.94/15.84		36.83±17.75	39.20/29.01	
Time from diagnosis	<6 months	58.51±21.19	58.33/16.67	0.404	65.34±19.13	67.22/31.95	0.987	32.02±20.18	32.72/27.78	0.605
	≥6 months	52.91±32.78	50/50		64.96±22.90	68.06/38.33		29.63±19.20	28.40/29.01	
Time from diagnosis	<1 years	57.26±25.41	58.33/33.33	0.501	65.80±20.13	67.50/32.78	0.708	31.29±20.36	32.41/29.63	0.775
	≥1 years	52.47±31.76	50/50		63.69±22.95	68.06/32.23		29.88±18.18	27.78/30.25	

SD: Standard deviation, IQR: Interquartile range, PCD: Plasma cell diseases, Mds/mpn: Myelodysplastic syndrome/myeloproliferative neoplasias

Table 6. The effect of time from diagnosis (<6 months/≥6 months) on quality of life

Time from diagnosis	<6 months		≥6 months		P
	Mean±SD	Median/IQR	Mean±SD	Median/IQR	
1. General health status	58.51±21.19	58.33/20.83	52.91±32.78	50/50	0.404
2. Physical function	57.83±28.08	60/46.67	60.31±29.46	66.67/33.33	0.604
3. Role function	65.94±36.84	83.33/66.67	66.67±34.88	66.67/50	0.928
4. Emotional function	68.48±27.10	75/41.67	74.61±27.81	83.33/25	0.194
5. Cognitive function	78.26±21.33	83.33/33.33	76.74±25.23	83.33/33.33	0.997
6. Social function	63.04±34.05	66.67/66.67	58.53±35.33	66.67/66.67	0.547
7. Fatigue	54.11±32.34	55.56/58.33	46.51±29.62	44.44/44.44	0.279
8. Nausea-vomiting	18.48±26.11	0/33.33	13.18±26.62	0/16.67	0.178
9. Pain	3804±32.14	33.33/66.67	34.11±33.32	33.33/50	0.522
10. Dyspnea	19.57±28.61	0/33.33	20.93±31.73	0/33.33	0.985
11. Insomnia	36.96±37.99	33.33/66.67	42.64±37.32	33.33/66.67	0.446
12. Loss of appetite	32.61±37.51	33.33/66.67	33.33±34.12	33.33/66.67	0.747
13. Constipation	31.88±36.49	33.33/66.67	17.05±26.60	0/33.33	0.049*
14. Diarrhea	14.49±22.94	0/33.33	21.71±33.24	0/33.33	0.477
15. Financial problems	42.03±36.13	33.33/66.67	37.21±36.52	33.33/66.67	0.497

SD: Standard deviation, IQR: Interquartile range, * p<0.05

hematological malignancy is not a major determinant of long-term QoL outcomes.

Younger patients (<55 years) demonstrated significantly better physical and role functioning scores and a lower symptom burden, including fatigue, appetite loss, constipation, and diarrhea. These results align with Immanuel et al.,¹² who found better HRQoL in younger hematologic cancer patients, attributed to greater resilience and fewer comorbidities. This is further supported by the work of Macía et al.¹³ and Caldiroli et al.¹⁴ who highlight resilience and coping as key mediators of quality of life in cancer patients.

Although gender differences were not statistically significant, men tended to report slightly better physical functioning scores (p=0.06), a trend also noted in recent studies

emphasizing the potential impact of physical capacity and social roles on perceived QoL.^{11,15}

Regarding time since diagnosis, most QoL parameters did not show significant variation, except for constipation, which was more prevalent during the early months. This contrasts with longitudinal findings by Ehooman et al.,¹⁵ who reported dynamic HRQoL changes over long-term follow-up in hematologic cancer survivors. The discrepancy may be due to the cross-sectional design and shorter follow-up in our study.

Recent evidence, including Abdu et al.¹¹ and Caldiroli et al.¹⁴ underscores the importance of resilience as a mediator of quality of life and the need for structured survivorship care to address delayed psychosocial and functional impairments in hematologic cancer survivors.

Table 7. The effect of time from diagnosis (<1 year/≥1 year) on quality of life

Time from diagnosis	<1 year		≥1 year		P
	Mean±SD	Median/IQR	Mean±SD	Median/IQR	
1. General health status	57.26±25.41	58.33/33.33	52.47±31.76	50/50	0.501
2. Physical function	59.03±27.66	60/40	59.01±31.25	66.67/40	0.823
3. Role function	65.59±36.45	75/66.67	67.90±34.57	66.67/50	0.834
4. Emotional function	70.70±27.28	79.17/41.67	73.15±28.34	83.33/25	0.655
5. Cognitive function	79.30±22.11	83.33/33.33	73.46±25.43	83.33/33.33	0.278
6. Social function	62.90±34.33	66.67/66.67	56.17±35.25	66.67/50	0.373
7. Fatigue	52.33±31.9	55.56/55.56	46.09±29.35	44.44/44.44	0.391
8. Nausea-vomiting	18.28±27.78	0/33.33	10.49±22.24	0/16.67	0.124
9. Pain	36.29±31.58	33.33/66.67	35.80±35.42	33.33/66.67	0.827
10. Dyspnea	22.04±30.14	0/33.33	16.05±29.77	0/33.33	0.223
11. Insomnia	36.56±37.55	33.33/66.67	46.91±37.28	33.33/66.67	0.204
12. Loss of appetite	33.33±36.71	33.33/66.67	32.10±33.95	33.33/66.67	0.992
13. Constipation	27.42±33.89	0/41.67	18.52±29.72	0/33.33	0.211
14. Diarrhea	18.28±28.10	0/33.33	17.28±29.77	0/33.33	0.707
15. Financial problems	37.10±35.76	33.33/66.67	45.68±37.15	0/66.67	0.302

SD: Standard deviation, IQR: Interquartile range

Overall, our findings indicate that age and resilience are more consistent predictors of quality of life than disease subtype or time elapsed since diagnosis, at least within the first year post-diagnosis.

Strengths of our study should be listed as including a wide variety of subtypes of malignancies, comparison among time from diagnosis, a single institution design, a seemingly population having a comparable socio-economic and socio-cultural status and use of a valid and robust measurement tool which allows for comparisons across groups and time in patients with hematological malignancies.

Limitations

One of the most important limitations of the study is the small sample size and the other is a lack of disease specific questionnaires which was not a valid concern of this study according to purposes and aims.

CONCLUSION

In this study, the mean score of general health status (55.80±27.39), one of the subdimensions of the QoL scale, was found to be moderate. The most common symptoms experienced by patients were fatigue, insomnia, and pain. These symptoms negatively impacted their quality of life.

The Turkish version of the EORTC QLQ-C30 Scale proved to be a valid and reliable tool for evaluating the quality of life in patients with hematological malignancies.

Importantly, our findings indicate that the time from diagnosis had no apparent impact on most QoL dimensions, but younger age was associated with significantly better functional status and fewer symptoms.

It is therefore essential to support patients not only during therapy but also after the end of treatment, both medically

and socially, with a multidisciplinary and individualized approach.

We will aim to establish an interdisciplinary survivorship support group to address the long-term needs of patients with hematologic cancers.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approval has been granted by the İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 27.01.2021, Decision No: E-10840098-772.02-2618).

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 prevalence of styloid process elongation in Southeastern Anatolia

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Cite this article as: Polat ME, Durmuş Hİ, Dönmez G. The prevalence of styloid process elongation in Southeastern Anatolia. *J Med Palliat Care*. 2025;6(4):403-408.

Received: 22.07.2025

Accepted: 12.08.2025

Published: 31.08.2025

ABSTRACT

Aims: Styloid process is a cylindrical bony projection extending from the inferior part of the temporal bone. A styloid process measuring more than 30 mm in length is defined as elongated styloid process (ESP) and may lead to symptoms associated with Eagle syndrome, such as throat pain, dysphagia, and neurological discomfort. Although the exact etiology of styloid process elongation is not fully understood, proposed causes include congenital elongation, calcification of the stylohyoid ligament, and osseous proliferation at the ligament's attachment sites. This study is designed to determine the prevalence of styloid process elongation in patients attending the Faculty of Dentistry at Harran University and to analyze the findings in relation to global epidemiological data.

Methods: This retrospective study was conducted using archived panoramic radiographs of 1.107 patients (534 males, 573 females) treated at the Harran University, Department of Oral and Maxillofacial Surgery between January 2023 and December 2023. The length of the styloid process was measured from the tympanic plate to its tip. Elongation was recorded for measurements exceeding 30 mm. The data were analyzed using the Pearson's Chi-square test for categorical variables. A p-value of <0.05 was considered statistically significant.

Results: The prevalence of ESP in the studied population was found to be 8.8%, with no statistically significant difference between males (44.3%) and females (55.7%) ($p=0.420$). Additionally, no significant association was identified between ESP and age groups ($p=0.451$). The longest measured styloid process was 42 mm, while the shortest was 14 mm. The average length was 22 mm in males and 21 mm in females, with no significant difference observed between sexes. Among patients diagnosed with ESP, 66% had no systemic disease; the most common comorbidities were hypertension and diabetes mellitus.

Conclusion: The prevalence of ESP in the Southeastern Anatolian population was determined to be 8.8%, which is consistent with findings reported in other populations. No significant association was found between ESP and either gender or age groups. Considering the variability in prevalence across different regions, further advanced studies utilizing CBCT and CT imaging techniques are necessary to improve diagnostic accuracy and assess potential clinical implications.

Keywords: Elongated styloid process, Eagle syndrome, prevalence, panoramic radiography, anatomical variation

INTRODUCTION

The styloid process is a slender, cylindrical projection of bone that arises from the inferior portion of the temporal bone, anterior to the stylomastoid foramen.¹ It originates embryologically from Reichert's cartilage, which derives from the second pharyngeal arch.³ The ossification of this structure begins during the third trimester of gestation and continues into early postnatal life. Anatomically, the styloid process is located laterally in the neck, positioned between the internal carotid artery and internal jugular vein. Several cranial nerves including the glossopharyngeal, facial, hypoglossal, vagus, and accessory nerves course in close proximity to it.⁴ The styloid process is the origin for two important ligaments the stylohyoid and stylomandibular ligaments. These connect to the hyoid bone and the ramus of the mandible,

respectively.^{5,6} They play a role in the movement of the throat and jaw. The stylohyoid ligament helps elevate the hyoid bone, while the stylomandibular ligament restricts the movement of the mandible, preventing excessive opening and forward movement.⁷ A condition called styloid process elongation occurs when the length of the process exceeds 30 mm from its base at the temporal bone to its tip.^{2,6,8} The precise cause of elongation is still not completely understood, but factors such as congenital elongation, calcification of the stylohyoid ligament, and bone growth at the ligament attachment site have been suggested.^{2,9} As shown in [Table 1](#), research across various populations presents differing findings.

The evaluation of styloid process elongation is commonly performed using panoramic imaging. Due to its cost-

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Table 1. Findings of previous studies on elongated styloid process (ESP>30 mm)				
Study	Year	Demographic population	Participants	ESP prevalence (%)
Al Zarea et al. ²	2017	Saudi Arabian	198	44.0%
Vieira et al. ³	2015	Brazilian	736	43.89%
Kaufman et al. ⁸	1970	American	484	28.0%
Gossman & Tarsitano ³³	1977	American	4200	4.0%
Monsour & Young ³⁴	1986	Australian	1200	21.1%
Ferrario et al. ³⁵	1990	Italian	286	84.4%
Radfar et al. ³⁶	2008	Iranian	1000	22.0%
Gökçe et al. ³²	2008	Turkish	698	7.7%
Asrani et al. ²⁷	2010	Indian	500	19.4%
Nalçacı et al. ²⁴	2006	Turkish	189	27.0%
Bagga et al. ³⁷	2012	Indian	2706	52.1%
Chabikuli et al. ³⁸	2016	South African	147	69.0%
Rai et al. ³⁹	2017	West Indian	987	27.3%
Gracco et al. ⁴⁰	2017	Italian	600	31.0%
ESP: Elongated styloid process				

effectiveness and accessibility, panoramic radiography is preferred as the initial radiological diagnostic tool.¹⁰⁻¹⁴ Enlargement of the styloid process plays a role in the pathogenesis of Eagle syndrome, a condition characterized by different symptoms such as earache, headache, and tinnitus. This syndrome commonly presents with dysphagia and cervical discomfort resulting from the extended styloid process. It is reported to occur in approximately 4% to 10.3% of individuals exhibiting an elongated styloid process (ESP).⁶ Although several studies have been conducted on the Turkish population, there is a lack of data specific to the Southeastern Anatolia region. In this context, the present study was undertaken to address this gap. The primary aim of the study is to retrospectively evaluate patients treated at the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Harran University, in order to determine the prevalence of ESP in the Southeastern Anatolia region and to analyze its relationship with systemic diseases. Furthermore, the study aims to compare the prevalence of ESP in this population with data from various demographic regions worldwide.

METHODS

This study was conducted using archived radiographic images obtained from the Easydent radiography software of patients treated at the Department of Oral and Maxillofacial Surgery, Harran University, between January 2023 and December 2023. Ethical approval for the study was obtained from the Clinical Researches Ethics Committee of Harran University (Date: 30.12.2024, Decision No: 51). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. A total of 1.618 patients were randomly selected; after excluding 511 patients who did not meet the criteria, 1.107 patients remained in the study, comprising 534 males and 573 females. Patients were categorized based on age and gender, and records of systemic diseases were reviewed

and included in the analysis. The measurement of the styloid process was calculated from the point where it separates from the lower part of the tympanic plate to the tip of the process. The right and left styloid processes were calculated independently of each other. Parameters exceeding 30 mm were recorded as elongation (Figure).



Figure. Measurement method of the styloid process on panoramic radiograph

Radiological images of patients admitted to our clinic within the specified dates were examined without considering differences in age or gender. The evaluation proceeded according to the order of patient registration. Patients who did not have available radiological images in our clinic, whose radiographs were deemed inconclusive for evaluation, or who were under the age of 18 were excluded, and the next patient in the registration sequence was included instead. A total of 221 patients were excluded due to the absence of radiological images, 103 due to radiographs being inconclusive for evaluation, and 187 due to being under the age of 18.

The magnification ratio in panoramic radiography may vary depending on factors such as the type of device, the focal-film distance, patient positioning, and technical parameters used. Therefore, standardizing the magnification ratio is crucial to ensure accurate measurements in research. In modern digital panoramic units, calibration can be performed via imaging software by entering a known reference length to verify measurement accuracy. In this study, calibration was carried out using the manufacturer's specifications of the radiographic device. Additionally, all patient images were obtained using the same device, under identical technical settings, and with proper patient positioning, allowing for reliable relative comparisons.

Participant Criteria

- **Age range:** Adult individuals (>18 years) were included in the study.
- **Gender:** Both male and female participants were eligible, or a specific population could be targeted.
- **Presence of symptoms:** Participants could be either symptomatic (e.g., exhibiting signs of Eagle syndrome) or asymptomatic.

- History of prior surgery: Individuals with no history of trauma or surgical procedures in the head and neck region were preferred.

Imaging Criteria

- **Radiological method:** Panoramic radiography was the preferred method for measurements.
- **Styloid process measurement method:** A length greater than 30 mm was considered elongated.
- **Styloid process morphology:** All morphological types normal, elongated, segmented, or pseudoarthrotic were included in the study without distinction.

Inclusion Criteria

- Patients with adequate image quality
- Cases with sufficient clinical information for diagnostic evaluation
- Patients presenting anatomical variations relevant to the objectives of the study
- Patients over the age of 18

Exclusion Criteria

- Fractures, surgical interventions, or congenital anomalies that could directly affect the styloid process
- Radiographic images with distortion or insufficient quality for measurement
- Systemic diseases affecting bone metabolism (e.g., advanced osteoporosis, Paget's disease)
- Patients with a history of pregnancy in their anamnesis

Statistical Analysis

The data analysis included frequency analysis to summarize the demographic data of the participants. Pearson's Chi-square test of independence was conducted to evaluate relationships between categorical variables, with all expected cell counts exceeding 5 (Howell, 2011). Categorical data were presented as frequency (n) and percentage. A p-value of less than 0.05 was considered statistically significant. Data analysis was carried out using IBM SPSS Statistics version 27 (IBM Corp., Released 2020).

RESULTS

In 2023, radiographic images of patients who applied to the Department of Oral and Maxillofacial Surgery at Harran University Faculty of Dentistry were collected. A total of 1,107 patients, including 534 males and 573 females, aged between 18 and 74 years, were included in the study. Panoramic radiographs were used to measure the elongation of the styloid process, and evaluations were conducted by two independent observers at different times. Styloid process elongation was detected in 97 radiographic images (43 males and 54 females). The percentages were calculated based on age and gender groups to derive meaningful statistical outcomes. The average prevalence of ESP was calculated as 8.8%. Among all included patients, the length of the styloid process ranged from 14 mm

to 42 mm. The mean length was 22 mm in males and 21 mm in females. No statistically significant difference in length was observed between genders.

A Chi-square goodness-of-fit test was conducted to evaluate whether systemic comorbidities were evenly distributed among individuals with ESP. The results revealed a statistically significant deviation from an equal distribution, $\chi^2(9)=312.7$, $p<0.001$. The majority of ESP cases had no systemic disease (66%), while specific conditions such as hypertension and type 2 diabetes were more frequently observed than others. This suggests a non-random pattern in the distribution of systemic diseases among individuals with ESP, warranting further investigation into potential underlying mechanisms.

Table 2 presents the distribution of the participants' characteristics. Of the participants, 28.9% were in the 18–29, 22.9% in the 30–39, 15.8% in the 40–49, 15.7% in the 50–59, and 16.6% were aged 60 and above. Regarding gender, 51.8% of the participants were female and 48.2% were male. Regarding the presence of ESP, 8.8% of the participants were found to have ESP, while 91.2% did not exhibit this condition.

Table 2. Demographic characteristics of the participants

Variable	n	%
Age		
18-29	320	28.9
30-39	254	22.9
40-49	175	15.8
50-59	174	15.7
60 and above	184	16.6
Gender		
Male	534	48.2
Female	573	51.8
ESP (p/a)		
Present (n=97)	97	8.8
Absent (n=1010)	1010	91.2
ESP: Elongated styloid process		

Table 3 presents the distribution of patients with ESP according to gender and age groups. Among the patients with ESP, 44.3% were male and 55.7% were female. When age groups were examined, 20.6% of the patients were in the 18–29 age range, 17.5% in the 30–39 range, 15.5% in the 40–49 range, 21.6% in the 50–59 range, and 24.7% were aged 60 and above.

Table 3. Distribution of patients with ESP by gender and age groups

Age group	Total (n)	Male (n)	Male (%)	Female (n)	Female (%)
18-29	20	10	50.0	10	50.0
30-39	17	4	23.5	13	76.5
40-49	15	7	46.7	8	53.3
50-59	21	10	47.6	11	52.4
60 and above	24	12	50.0	12	50.0
Total	97	43	44.3	54	55.7
ESP: Elongated styloid process					

Evaluating the gender distribution within each age group: in the 18–29 age group, the male-to-female ratio was equal at 50% each. In the 30–39 group, the proportion of females was higher at 76.5% compared to males at 23.5%. The distribution in the 40–49 group was more balanced, with 46.7% males and 53.3% females. In the 50–59 group, 47.6% were male and 52.4% were female. In the 60 and above group, the gender distribution was equal, with both males and females comprising 50%.

Table 4 presents the results of the relationship between ESP status and gender groups among the participants. While 8.8% of the participants had ESP, 91.2% did not. Among those with ESP, 44.3% were male and 55.7% were female. In the group without ESP, 48.6% were male and 51.4% were female. The analysis of the relationship between gender and ESP status ($\chi^2=0.650$, $p=0.420$) showed when looking at the statistics, there are no acceptable differences ($p>0.05$).

Table 4. Gender distribution of participants according to ESP

Variable/group	Gender		Test statistic	p
	Male (n=534)	Female (n=573)		
ESP (p/a)				
Present (n=97)	43 (44.3%)	54 (55.7%)	0.650	0.420*
Absent (n=1010)	491 (48.6%)	519 (51.4%)		
ESP: Elongated styloid process, n: Number of observations,				

ESP: Elongated styloid process, n: Number of observations,

Table 5 presents the results of the relationship between gender and age groups among participants with ESP. When examining the relationship between gender and age groups ($\chi^2=3.679$, $p=0.451$), no statistically significant association was found ($p>0.05$).

Table 5. Distribution of patients with ESP according to gender and age groups

Variable/group	Gender		Test statistic	p
	Male (n=43)	Female (n=54)		
Age				
18-29 (n=20)	10 (50%)	10 (50%)		
30-39 (n=17)	4 (23.5%)	13 (76.5%)		
40-49 (n=15)	7 (46.7%)	8 (53.3%)	3.679	0.451 ^k
50-59 (n=21)	10 (47.6%)	11 (52.4%)		
60 and above (n=24)	12 (50%)	12 (50%)		

ESP: Elongated styloid process, k: Pearson Chi-square independence test

Table 6 presents the distribution of systemic comorbidities among participants with ESP. Among individuals diagnosed with ESP, 66% had no accompanying systemic disease. The most commonly observed systemic conditions were hypertension and diabetes mellitus. Additionally, a smaller proportion of participants presented with asthma, combinations of hypertension and diabetes, and a history of cardiovascular operations. The percentage of observed systemic diseases is indicated in **Table 6**. Other systemic conditions such as anticoagulant use, thyroid dysfunctions, and history of radiotherapy and chemotherapy were observed with lower prevalence rates, each accounting for 1.0% of

cases. These findings suggest that ESP may frequently occur independently of systemic diseases; however, the presence of certain cardiometabolic conditions highlights the need for further investigation into potential associations.

Table 6. Systemic disease association in participants with ESP

Variable	n	%
Anticoagulant	1	1.0
Asthma	2	2.1
Asthma+type 2 diabetes	1	1.0
Type 1 diabetes	2	2.1
Type 1 diabetes+anticoagulant	1	1.0
Type 2 diabetes	5	5.2
Type 2 diabetes+cardiovascular surgery	1	1.0
Hypertension	8	8.2
Hypertension+type 1 diabetes	1	1.0
Hypertension+type 2 diabetes	4	4.2
Hyperthyroidism	1	1.0
Hypotension	1	1.0
Hypotension+asthma	1	1.0
Hypotension+chemotherapy+radiotherapy+bisphosphonate	1	1.0
Cardiovascular surgery	2	2.1
Radiotherapy+chemotherapy	1	1.0
No systemic disease	64	66.0

ESP: Elongated styloid process

DISCUSSION

The styloid complex consists of three main components: the styloid process of the temporal bone, the stylohyoid ligament, and the lesser cornu of the hyoid bone. The styloid process itself is a narrow, tapering bony projection extending from the temporal bone. Its length generally varies from a few millimeters to an average of approximately 2.5 cm. The proximal segment of the styloid process is delineated by the tympanic plate.^{15,16} Elongation is defined when the styloid process exceeds 30 mm in length. However, a limited number of studies suggest that elongation should be considered when the length surpasses 45 mm.¹⁷ Elongation of the styloid process may lead to symptoms such as throat pain and dysphagia, commonly associated with Eagle syndrome.¹⁸

Although panoramic radiography is widely used due to its accessibility and cost-effectiveness, it has certain limitations compared to computed tomography (CT). Panoramic images represent three-dimensional structures in two dimensions, which can lead to distortion, magnification errors, and overlapping of anatomical features. These factors may adversely affect the accuracy of measurements, especially in complex anatomical regions such as the styloid process. CT imaging, on the other hand, provides higher spatial resolution and three-dimensional visualization, allowing for more precise assessment of the length, angulation, and morphological variations of the styloid process. Therefore, measurement errors inherent to panoramic radiography should be acknowledged, and the results interpreted with

caution. Nonetheless, panoramic radiography is preferred due to its routine use by dental practitioners and its ability to provide a comprehensive view of the maxillofacial complex. This technique also allows for accurate measurement of the full length of the styloid process.^{19,20} Additionally, panoramic radiographs offer advantages such as cost-effectiveness, lower radiation dose compared to CT, and ease of interpretation.²¹ The diagnosis of styloid process elongation has been confirmed through panoramic radiographic imaging in numerous studies, including those by Koshy et al.,¹ Abuhaimed et al.,⁵ Assiri et al.,⁶ and Erol et al.²²

Due to the potential for anatomical superimposition and variability in magnification rates, caution must be exercised when performing absolute measurements and relative comparisons using such imaging modalities. Accurate interpretation of these imaging techniques requires a thorough understanding of both the anatomical structures and possible anatomical variations or abnormalities that may affect this region. Measurements should be repeated by different observers to ensure reliability.³ In this study, two independent observers evaluated the images.

The length of the styloid process can be influenced by developmental processes, hormonal effects, and hereditary factors.^{3,23} Studies investigating the relationship between gender and styloid process length have yielded conflicting results. Some studies report no significant association between gender and elongation, which aligns with our findings.^{24,25} However, other studies have indicated a significant correlation between gender and styloid process elongation.^{19,26} In our study, although the number of panoramic radiographs differed between male and female participants, the percentage results revealed no statistically significant difference.

In our study, no statistically significant difference was found in the prevalence of ESP among different age groups in patients with radiographically confirmed elongation. According to More and Asrani,²⁷ an increase in calcification length has been reported with advancing age. Similarly, Anbiaee and Javadzadeh,²⁸ and Al-Khateeb et al.,²⁹ stated that the length of the styloid process is associated with increasing age. These researchers suggested that this condition may be related to age-related degeneration of the connective tissue complex and continued accumulation of calcium salts. However, in line with our findings, studies by Basekim et al.,³⁰ Gözil et al.,³¹ and Gökçe et al.³² did not identify a significant difference between age groups.

In previous studies, the prevalence of ESP has been reported to vary widely, ranging from 1.4% to 83.6%. In our study, the prevalence of styloid process elongation was found to be 8.8%. When compared with the results of previous studies, this rate is considered moderate and may be explained by geographic and genetic factors. The wide variability in the reported prevalence of ESP across different regions can be attributed to differences in diagnostic and imaging interpretation criteria, geographical location, and specific characteristics of local populations.^{1,2,11,15} Additionally, the imaging modality chosen for measurement may influence the reported outcomes.

Our study provides important data by revealing the prevalence of styloid process elongation in the Southeastern Anatolia region and evaluating its association with systemic diseases. A review of the literature shows that similar studies have been conducted in Türkiye by researchers such as Gökçe et al.,³² Nalçacı et al.,²⁴ and Erol et al.²² The findings suggest that the length of the styloid process should be considered in the evaluation of patients presenting with head and neck pain. Although assessments made using panoramic radiography provide clinically relevant information, confirmatory studies utilizing three-dimensional imaging modalities are warranted.

Limitations

This study has several limitations. The retrospective design restricts control over the data collection process. Additionally, the absence of symptomatic data prevented the evaluation of correlations between radiological findings and clinical symptoms. Therefore, the relationship between styloid process elongation and patient symptoms could not be thoroughly investigated. Future prospective studies incorporating detailed clinical assessments are necessary to better understand the clinical significance of radiographic findings.

For future research, it is recommended to conduct prospective studies utilizing CT or cone-beam computed tomography (CBCT) imaging alongside comprehensive clinical symptom assessments. Such an approach would provide three-dimensional anatomical detail and enable more accurate correlation between styloid process elongation and patient symptoms. This integrated evaluation could enhance understanding of the clinical relevance of radiographic findings and improve diagnostic accuracy.

CONCLUSION

As a result, the prevalence of ESP was found to be 8.8%, which is consistent with previous studies conducted in Türkiye and in different demographic populations. Variations in the reported prevalence of ESP across studies may result from differences in radiographic interpretation criteria and population-specific characteristics. The data in our study were obtained from panoramic radiographs within a Turkish population.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval for the study was obtained from the Clinical Researches Ethics Committee of Harran University (Date: 30.12.2024, Decision No: 51).

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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Finite element analysis of various implant configurations using zygomatic and pterygoid implants in the rehabilitation of the atrophic maxilla

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Cite this article as: Tapçı O, Ayrancı F, Toğaç E. Finite element analysis of various implant configurations using zygomatic and pterygoid implants in the rehabilitation of the atrophic maxilla. *J Med Palliat Care*. 2025;6(4):409-415.

Received: 28.07.2025

Accepted: 13.08.2025

Published: 31.08.2025

ABSTRACT

Aims: This study aimed to evaluate the biomechanical behavior of different implant-supported rehabilitation concepts involving zygomatic and pterygoid implants in the atrophic maxilla using finite element stress analysis (FESA).

Methods: A 3D finite element model of an atrophic maxilla was generated from CT data and restored using three different implant configurations, including zygomatic and pterygoid implants. Linear static FESA was performed under vertical loading (150 N) in both anterior (tooth 11) and posterior (tooth 16) regions. Von Mises and principal stress values were calculated for implants, abutments, prosthetic substructure, and cortical and cancellous bone.

Results: Under anterior loading, the highest von Mises stress on implants and abutments was observed in model III (56.07 MPa), while model II (27.937 MPa) showed the lowest. Under posterior loading, the highest stress on implants was recorded in model II (80.475 MPa), and the lowest in model III (31.123 MPa). Stress distribution in bone tissues varied across models, with model I generally showing the highest principal stress under posterior loading, and model III the lowest. The results highlighted that different implant configurations lead to significant variations in stress patterns.

Conclusion: Among the evaluated configurations, model II provided superior biomechanical performance, suggesting that the implant combination in this model may offer a more favorable stress distribution in the prosthetic rehabilitation of the atrophic maxilla. These findings underscore the importance of implant design and placement strategy, which can be optimized using FESA prior to clinical application.

Keywords: Atrophic maxilla, zygomatic implants, pterygoid implants, finite element analysis, biomechanical stress, implant-supported prosthesis

INTRODUCTION

Centrally located in the midfacial region, the maxilla is a structurally and functionally crucial bone that provides essential support for the viscerocranium, contributes significantly to both facial esthetics and oral functionality, and plays a pivotal role in maintaining the structural and aesthetic integrity of the face.^{1,2} Trauma, pathological conditions, congenital anomalies, or prolonged edentulism following tooth loss inevitably result in significant esthetic and functional deterioration of the maxilla. Traditional prosthetic and surgical approaches may be insufficient in the prosthetic rehabilitation of severely atrophic jaws. Moreover, bone augmentation methods such as bone grafting, guided bone regeneration, sinus floor elevation, and distraction osteogenesis entail disadvantages such as prolonged treatment, increased cost, and patient morbidity.^{3,4} Single-stage surgical approaches using zygomatic and pterygoid implants have emerged as viable alternatives in the prosthetic rehabilitation

of the atrophic maxilla. The zygoma is a crucial structure in terms of defining the width and projection of the midface and contributes significantly to the shape and volume of the orbit. It serves as an attachment point for the masseter, temporalis, and zygomaticus major and minor muscles. In addition, it articulates with the skull at the zygomaticofrontal suture, zygomaticosphenoid suture, and zygomatic arch, and with the maxilla at the zygomaticomaxillary buttress and inferior orbital rim.⁵

Zygomatic dental implants were first introduced by Brånemark in 1988, primarily for the rehabilitation of patients with maxillofacial defects resulting from tumor resection, trauma, or congenital anomalies. Their clinical indications gradually expanded to include the management of severely atrophic maxillae, offering a viable alternative to conventional grafting procedures, such as sinus floor elevation and appositional grafting via Le Fort I osteotomy, which typically require two-

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stage surgeries and are associated with a heightened risk of postoperative complications.⁶

The placement of dental implants in the posterior maxillary region has been the subject of significant debate due to the typical presence of low-density trabecular bone and thin cortical bone in this area. These characteristics have been shown to increase the risk of implant failure.⁷ In order to address this challenge, pterygoid dental implants were introduced by Tulasne in 1992.

A comprehensive understanding of the biomechanics of dental implants is essential for selecting the most appropriate treatment strategy. Assessing the stress-related mechanical behavior of both the maxilla and the implant system plays a critical role in treatment planning. However, conducting such evaluations through in vivo studies remains inherently difficult due to ethical, technical, and practical limitations. As an alternative, virtual and biomechanical modeling offers a more practical and reproducible framework for biomechanical analysis. Finite element analysis (FEA) stands out among these approaches as a non-invasive and highly versatile method that enables repeated simulations, precise control of experimental variables, and the creation of models in diverse geometries and configurations. Furthermore, FEA facilitates the acquisition of highly accurate quantitative data and has been extensively employed in the evaluation of dental implants, owing to its strong correlation with both in vitro biomechanical testing and in vivo observations. This study investigates the biomechanical effectiveness of different rehabilitation concepts involving zygomatic and pterygoid implants in the atrophic maxilla using finite element stress analysis (FESA).

METHODS

Ethics

The study was conducted with the permission of the Ethics Committee of Ordu University Non-interventional Scientific Researches (Date: 26.02.2025, Decision No: 60). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This study was conducted in collaboration between the Ordu University Dentistry Faculty, Türkiye, and Ay Tasarım Ltd. Şti., and was supported by the Ordu University Scientific Research Projects Coordination Unit under project number B-2430.

The Construction of the 3D Finite Element Model

An atrophic maxilla model was created using data from the Visible Human Project. Computed tomography (CT) images from a 59-year-old woman were reconstructed with a 0.2 mm slice thickness, exported in DICOM 3.0 format, and converted into a 3D model using 3D-Doctor software. Bone tissues were segmented using an interactive segmentation method, and 3D models were generated via the “3D Complex Render” method. The anatomical structures obtained were prepared for analysis using Blender and Fusion 360 software. Zygomatic and pterygoid implants (J Dental Care) and their compatible multi-unit abutments were scanned and digitized

in STL format. Zygomatic implants 3.9 mm in diameter and 42.5 mm in length were placed in the regions of teeth 12 and 22, and implants 3.9 mm in diameter and 40 mm in length and in the regions of teeth 15 and 25. The pterygoid implants were 4 mm in diameter and 20 mm in length. Zygomatic implants were placed at a 45° angle and pterygoid implants at a 30° angle. The metal substructure (Cr-Co alloy) and the prosthetic superstructure (PMMA) were modeled in Fusion 360 software. The mechanical properties of the models were defined in Fusion 360. The materials’ elastic moduli and Poisson’s ratios were based on literature values. All models were assumed to be isotropic, homogeneous, and linearly elastic. Maximum mesh density was implemented to achieve the most realistic results (Table 1). All experimental groups and the corresponding number of nodes and elements for each model are summarized in Table 2. The types of dental implants and their respective placements employed for the restoration of the atrophic maxilla are illustrated in Figure 1.

Table 1. Isotropic material properties of titanium and cr-co alloy, cancellous and cortical bone, PMMA		
	Young modulus (MPa)	Poisson's ratio
Titanium alloy	110.000	0.33
Cr-Co alloy	220.000	0.30
Cortical bone	13.700	0.30
Cancellous bone	1.370	0.30
PMMA	2.700	0.35
PMMA: Prosthetic superstructure		

Table 2. Models and the number of nodes-elements on each model			
Models		Number of nodes	Number of elements
Model I	Zygomatic implants were placed in regions 12, 22, 15, and 25 (Quad Zygoma configuration).	243562	1159984
Model II	Zygomatic implants were inserted in regions 12 and 22, while pterygoid implants were placed in regions 17 and 27.	175341	800890
Model III	Zygomatic implants were inserted in regions 15 and 25, and pterygoid implants were placed in regions 17 and 27.	200591	958601

Loading and Boundary Conditions

For chewing simulation, spherical food bolus models were placed in the anterior (tooth 11) and posterior (tooth 16) regions, and a vertical force of 150 N was applied to each model (Figure 2). Bone models were fixed from distant surfaces of the analysis region to define boundary conditions.

Analysis Method

Linear static FEA was applied to all models. Von Mises stress and principal stress values (σ_1 , σ_3) were evaluated. The Von Mises values indicated stress accumulation and the risk of deformation in metal structures, while principal stress values were particularly used to assess the strength of brittle materials.

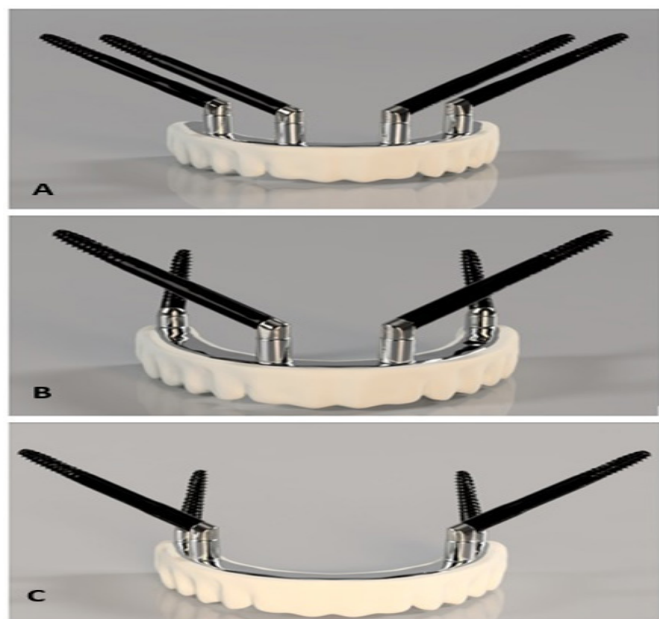


Figure 1. The types of dental implants and their respective placements
A: Zygomatic implants were placed in regions 12, 22, 15, and 25 (Quad Zygoma configuration) (model I).
B: Zygomatic implants were inserted in regions 12 and 22, while pterygoid implants were placed in regions 17 and 27 (model II)
C: Zygomatic implants were inserted in regions 15 and 25, and pterygoid implants were placed in regions 17 and 27 (model III)

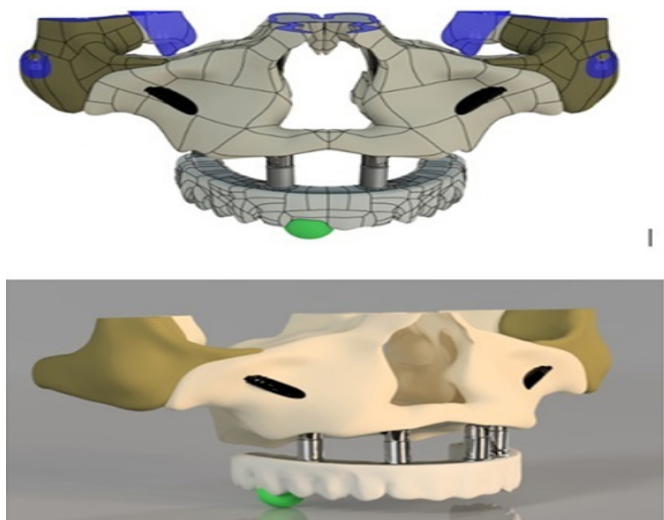


Figure 2. Spherical food bolus model positioned in the anterior and posterior regions

RESULTS

Von Mises Stress Analysis Values

Under anterior loading conditions, model III exhibited the highest von Mises stress values on the implants, and model II the lowest. Conversely, under posterior loading, the greatest stress was observed in model II, and the lowest in model III. Under anterior loading, the highest von Mises stress on the abutments was observed in model III, and the lowest in model II. Under posterior loading, model I exhibited the highest stress values, and model III the lowest. Under anterior loading conditions, model III exhibited the highest von Mises stress within the prosthetic metal substructure, and model II the lowest. In contrast, under posterior loading, the highest stress

was identified in model I, and the lowest in model III (Table 3, Figure 3).

Table 3. Von mises stress values

		Anterior loading	Posterior loading
Implants	Model I	20.032	67.704
	Model II	27.937	80.475
	Model III	56.07	31.123
Abutments	Model I	32.569	66.626
	Model II	27.399	38.922
	Model III	42.358	22.143
Prosthetic metal substructure	Model I	20.708	56.947
	Model II	16.952	38.914
	Model III	60.07	17.696

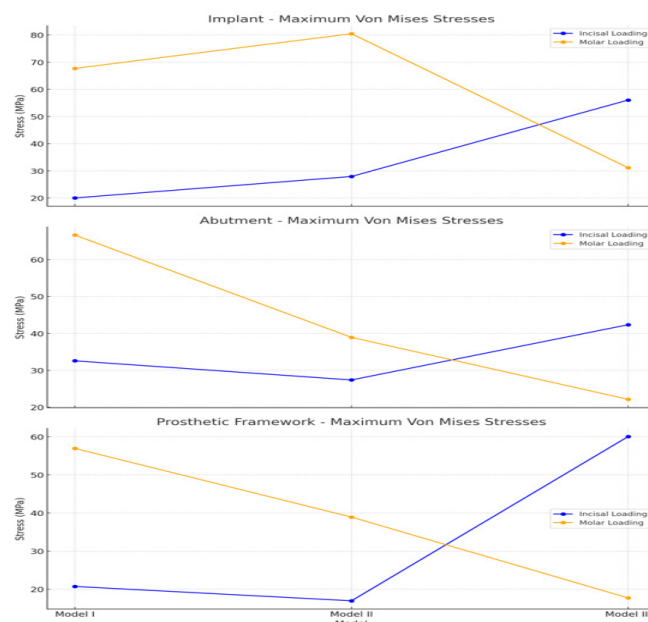


Figure 3. Distribution of maximum stresses in implants, abutments, and prosthetic frameworks under anterior (incisal) and posterior (molar) loading

Principal Stress Values

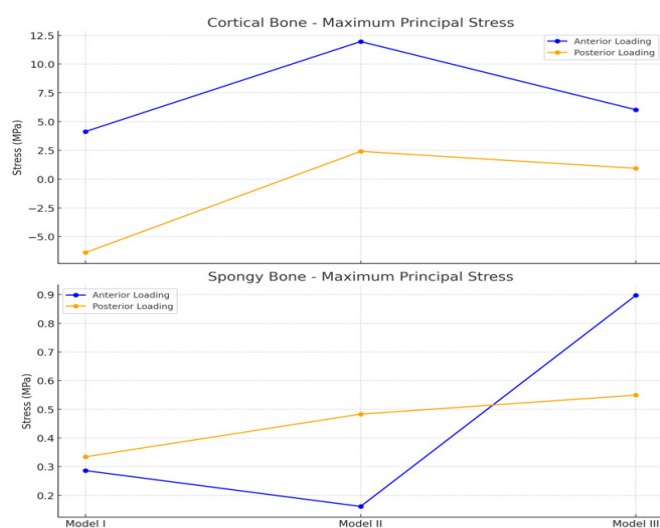
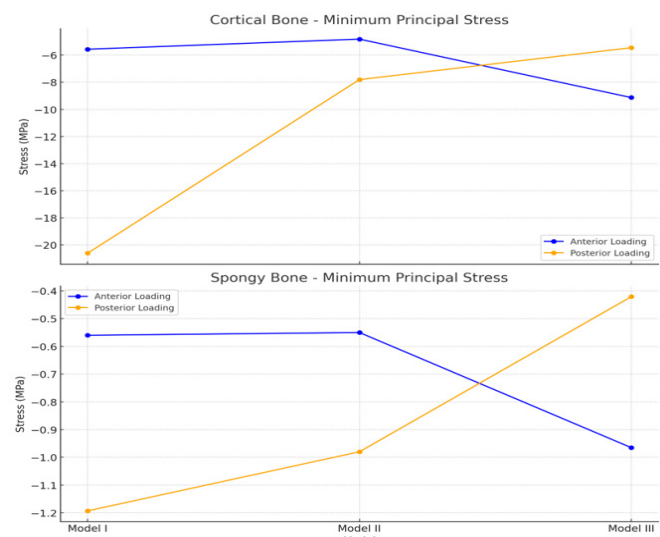
During anterior loading, the highest maximum principal stress in the cortical component of the alveolar bone occurred in model II, and the lowest in model I. During anterior loading, the highest minimum principal stress was in model III, and the lowest in model II. During posterior loading, the highest maximum principal stress was in model I, and the lowest in model III. The highest minimum principal stress during posterior loading was also in model I, and the lowest in model III. During anterior loading, the highest maximum principal stress in the cancellous bone was identified in model III, and the lowest in model II. The highest minimum principal stress during anterior loading was in model III, and the lowest in model II. During posterior loading, the highest maximum principal stress was in model III, and the lowest in model I. Finally, the highest minimum principal stress during posterior loading was in model I, and the lowest in model III (Table 4, 5, Figure 4, 5).

Table 4. Maximum principal stress values

		Anterior loading	Posterior loading
Cortical component	Model I	4.133	-6.39
	Model II	11.957	2.409
	Model III	6.03	0.936
Cancellous component	Model I	0.286	0.334
	Model II	0.161	0.483
	Model III	0.897	0.549

Table 5. Minimum principal stress values

		Anterior loading	Posterior loading
Cortical component	Model I	-5.563	-20.616
	Model II	-4.817	-7.805
	Model III	-9.13	-5.451
Cancellous component	Model I	-0.56	-1.193
	Model II	-0.55	-0.98
	Model III	-0.965	-0.421

**Figure 4.** Distribution of maximum principal stress values in cortical and spongy bone under anterior (incisal) and posterior (molar) loading**Figure 5.** Distribution of minimum principal stress values in cortical and spongy bone under anterior (incisal) and posterior (molar) loading

DISCUSSION

Since the exact replication of clinical trials is often impractical, FESA has emerged as a valuable computational tool in implantology.⁸ In this method, it is common practice to assume that the models are isotropic, homogeneous, and linearly elastic.⁹ In the present study, modeling was conducted based on these assumptions, resulting in a numerically accurate simulation consisting of approximately 900.000 elements and 200.000 nodes, which aligns closely with similar studies in the literature.^{10,11}

There are no universally standardized values for the elastic modulus and Poisson's ratio of materials commonly used in FESA, such as implants, abutments, metal frameworks, cortical bone, cancellous bone, and PMMA. Consequently, values reported in previous studies have been frequently adopted. In the present study, the mechanical properties of the materials were determined by referencing well-established data from the literature.¹²⁻¹⁵

Helkimo et al.¹⁶ reported maximum bite forces of 382 N in males and 216 N in females in the molar region, and of 176 N and 108 N, respectively, in the incisal region. Similarly, Haraldson and Carlsson¹⁷ documented an average bite force of 144.4 N in patients with implant-supported prostheses. The 150 N anterior and posterior loading values used in the present study fall within these physiological limits.

In order to more accurately simulate functional occlusal forces, loading was applied using spherical food bolus models placed in the anterior and posterior regions, rather than through conventional vertical or oblique vector forces. This method, as also described by Ayali et al.¹⁸ and Dayan and Geckili,¹⁹ allowed for a more physiologically relevant and realistic stress distribution.

Forty to sixty percent resorption of the alveolar ridge height and width occurs following tooth extraction, particularly within the first 2–3 years. The most pronounced decrease in alveolar height typically takes place during the first three months, which can significantly hinder optimal implant placement.²⁰ In natural dentition, mechanical stimulation of the periodontal ligament plays a crucial role in preserving alveolar bone volume. Its absence after tooth loss leads to accelerated bone resorption. Mechanical and/or structural support of the alveolar walls is therefore recommended to mitigate further deterioration.²⁰

Socket preservation techniques using synthetic grafts, xenografts, allografts, and platelet-rich fibrin have demonstrated favorable outcomes in mitigating post-extraction alveolar bone resorption.²¹ However, the reduction in bone volume and quality following edentulism presents significant challenges for conventional implant placement.²²

An atrophic maxilla not only impairs oral function, but also contributes to psychosocial distress and a reduced quality of life.²³ In order to address these deficiencies, bone augmentation procedures, including grafting and advanced surgical techniques such as Le Fort I osteotomy, may be necessary to achieve a sufficient bone volume for successful prosthetic

rehabilitation.²⁴ However, these approaches typically involve multiple surgical stages and prolonged treatment, which may compromise patient comfort and increase overall morbidity. An alternative, zygomatic implants, which can be placed in a single-stage surgical procedure, eliminate the need for advanced grafting techniques and offer significant advantages in the rehabilitation of atrophic maxillae.²⁵ Zygomatic implants provide significant advantages in elderly patients or those with limited mobility due to the shorter treatment duration involved and fewer clinical appointments required. Treatment is completed in a shorter time compared to graft-based implant procedures, providing practical benefits for patients. However, varying results regarding long-term implant survival have been reported. The main disadvantage of zygomatic implants is the greater risk of complications due to their proximity to anatomical structures. It is therefore recommended that surgery be performed by experienced specialists. The use of patient-specific, bone-supported titanium guides has also been described for the minimization of complications.

A systematic review and meta-analysis by Moraschini et al.²⁶ focused on studies involving zygomatic and conventional implants with at least five years of follow-up. No statistically significant difference was determined in terms of long-term implant success. Additionally, the most common biological complication associated with zygomatic implants was sinusitis, a condition particularly common with the intrasinus technique.

Multicenter randomized controlled trials by Esposito et al.²⁷ and Davo et al.²⁸ demonstrated that patients treated with zygomatic implants exhibited significantly shorter prosthetic treatment times, together with higher success rates and implant survival, compared to conventional grafting procedures.

These findings indicate that zygomatic implants represent a reliable and effective alternative for both short- and long-term prosthetic rehabilitation in patients with severely atrophic maxillae. Despite their association with a higher risk of complications, zygomatic implants have consistently yielded superior clinical outcomes in cases characterized by extensive maxillary bone loss.

In addition to zygomatic implants, pterygoid implants have also emerged as a promising option for the prosthetic rehabilitation of the atrophic posterior maxilla.²⁹ In a retrospective study by Curi et al.,²⁹ three-year follow-up revealed 99% implant survival and 97.7% prosthesis survival, with an average bone loss of 1.21 mm around the implant. Similarly, a systematic review and meta-analysis by Araujo et al.³⁰ reported a high survival rate of 94.87% for pterygoid implants, although the retrospective nature of the studies considered limited the level of evidence. In addition to long-term survival rates, recent studies have also evaluated short-term clinical outcomes and patient-reported satisfaction with pterygoid implants. In a retrospective study evaluating short-term clinical outcomes and patient satisfaction, Wu et al.³¹ reported survival rates of 96.5% for anterior implants and 97.8% for pterygoid implants. No significant differences were observed in clinical parameters between the implant

types, and patient satisfaction levels were high for prostheses supported by both configurations. Similarly, in a prospective cohort study, Signorini et al.³² reported 100% implant survival and success rates, with no implant loss or complications observed after a one-year follow-up period.

Supporting these findings, D'Amario et al.³³ emphasized that pterygoid implants represent a viable treatment option for patients with posterior maxillary atrophy, although they cautioned that the surgical complexity of this technique necessitates careful interpretation of clinical outcomes. Similarly, Cea-Arestin et al.³⁴ reported a 98.3% success rate in their evaluation of 178 pterygoid implants, further reinforcing the clinical reliability of this approach.

From a biomechanical perspective, Wilkerson et al.³⁵ demonstrated that pterygoid implants contribute to reduced stress and strain in the surrounding bone during atrophic maxilla rehabilitation. In line with these findings, the present study aimed to evaluate the biomechanical effectiveness of combining pterygoid and zygomatic implants as an alternative to the use of four zygomatic implants. This configuration is hypothesized to reduce stress on the bone, eliminate the posterior cantilever effect, and potentially minimize prosthetic and biological complications.

In order to evaluate that hypothesis, this study investigated the biomechanical behavior of various implant configurations under simulated functional loading. The model incorporating zygomatic implants in positions 12–22 and pterygoid implants in 17–27 demonstrated the most balanced stress distribution in both anterior and posterior loading scenarios. This configuration exhibited a biomechanical performance comparable to, and even potentially more favorable than, the traditional Quad Zygoma concept.

CONCLUSION

Within the constraints of our FEA, the combined use of zygomatic and pterygoid implants demonstrated a favorable biomechanical profile for the rehabilitation of the atrophic maxilla. By re-establishing posterior support, this configuration reduces the posterior cantilever arm and occlusal loads more evenly across the arch, which may help limit peak stresses at the bone–implant interface and within the prosthetic framework. Clinically, this translates into a viable alternative to concepts that rely solely on zygomatic anchorage or extended cantilevers, particularly in cases with severe posterior maxillary resorption and limited residual bone height. The approach is compatible with immediate or early loading protocols when cross-arch splinting is achievable, and it may simplify prosthetic design by allowing shorter posterior spans. Because computational models necessarily simplify biological reality (e.g., assumptions of linear-elastic, isotropic materials, static loading conditions, and ideal osseointegration), prospective clinical studies are warranted to validate these findings. Well-designed multicenter cohorts or randomized comparisons against alternative full-arch strategies (e.g., Quad Zygoma or posterior cantilever designs) should report standardized endpoints including implant and prosthesis survival, marginal bone level changes, biomechanical/biologic complication rates, sinus-related

events, masticatory function, patient-reported outcomes, and cost-effectiveness.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Ethics Committee of Ordu University Non-interventional Scientific Researches (Date: 26.02.2025, Decision No: 60).

Informed Consent

In this study, no biological material was used, no personal data are available. Therefore, informed consent is not required.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

This study was conducted in collaboration between the Ordu University Dentistry Faculty, Türkiye, and Ay Tasarım Ltd. Şti., and was supported by the Ordu University Scientific Research Projects Coordination Unit under project number B-2430.

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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Partners' personality traits and anger styles as mediators in the relationship between borderline personality traits and sexual self-schema

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Cite this article as: Güler K, Demir V. Partners' personality traits and anger styles as mediators in the relationship between borderline personality traits and sexual self-schema. *J Med Palliat Care*. 2025;6(4):416-421.

Received: 02.07.2025

Accepted: 15.08.2025

Published: 31.08.2025

ABSTRACT

Aims: This study aims to examine the mediating role of anger styles and personality traits in the relationship between borderline personality traits and sexual self-schemas exhibited by individuals.

Methods: In this study, 402 participants aged 18 and older (249 women and 153 men) completed the socio-demographic information form, the borderline personality scale, the sexual self-schema scale, and the state-trait anger expression inventory. The research employed the relational screening model. Statistical analyses were conducted using IBM SPSS 27 software.

Results: According to the findings of the study, borderline personality traits were found to be negatively associated with loving/compassionate, sensual/stimulating, and direct/straightforward sexual self-schemas. There is a significant negative correlation between all sexual self-schemas and trait anger, including anger-in and anger-out behaviors. Similarly, a significant negative correlation was found between sexual self-schemas and borderline personality traits. On the other hand, there was a negative correlation between neuroticism, one of the five-factor personality traits, and sexual self-schemas, and a positive correlation between neuroticism and borderline personality traits. Furthermore, mediation analyses suggested that anger styles may function as a possible mechanism in the relationship between borderline personality traits and sexual self-schemas. Neuroticism was also identified as a potential mechanism in this relationship.

Conclusion: Based on the findings from this study, borderline personality traits appear to be associated with lower levels of loving/compassionate, sensual/stimulating, and direct/straightforward sexual self-schemas. Anger styles and neuroticism, one of the five-factor personality traits, were also found to be potential mechanisms explaining this relationship.

Keywords: Borderline personality traits, sexual self-schema, five-factor personality inventory, trait anger, anger-in, anger-out

INTRODUCTION

Borderline personality disorder (BPD) is considered one of the most complex and challenging psychopathologies in the psychology literature, characterized by pervasive patterns of instability in emotions, self-image, and interpersonal relationships. Among the most distinguishing features of BPD are impulsivity and intense emotional outbursts. Individuals with BPD have difficulty maintaining emotional stability, exhibit impulsive behaviors, and engage in unstable relationships.¹ This condition leads to severe disruptions in self-perception and relationships with others, which can significantly affect sexual self-schemas.² Sexual self-schemas encompass individuals' beliefs, attitudes, and perceptions about their sexuality. In this context, the personality traits of partners and anger management styles play a key role in shaping the sexual self-schemas of individuals with BPD.³

Research on BPD shows that personality traits have a significant impact on interpersonal dynamics and emotional control. High levels of neuroticism are often associated with ineffective emotional regulation techniques, such as rumination and suppression, which can exaggerate BPD symptoms and negatively affect relationships.⁴ However, traits like neuroticism and extraversion are associated with more flexible regulation techniques like reappraisal, which can improve overall well-being and relationship satisfaction.⁵ These dynamics can lead to disruptions in the romantic and sexual self-schemas of individuals with BPD. Studies have also shown that individuals with BPD frequently experience deceptive bodily ownership sensations, feeling as though they are under the control of a body that is not their self-control.⁶ Distortions in body image can significantly affect

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overall psychological functioning, leading to instability in sexual identity and severe problems in relationships. Researchers have specifically linked dissociative symptoms to sexual dysfunctions. In conjunction with sexual trauma, these symptoms can negatively affect sexual identity and behaviors.⁷ BPD not only affects an individual's inner world, but also profoundly influences their relationships with partners. The personality traits and anger management styles of partners play a significant role in shaping the sexual self-perception and overall mental health of individuals with BPD.⁸ Severe conflict and emotional dysregulation may result from maladaptive expressions of anger, such as outbursts or denial, further clouding the individual's perception of their sexual and romantic identity. These findings may contribute to developing therapeutic interventions aimed at improving the quality of life for individuals with BPD.

In conclusion, the complex interactions between personality traits, anger management styles, and sexual self-schemas in individuals with BPD are critical for understanding the challenges these individuals face in both their emotional world and relationships. To create more effective therapeutic interventions, it is necessary to study and understand these connections and interactions in greater detail. Therefore, the data obtained from this study is expected to guide and support future research in the relevant literature.

METHODS

Ethics

The study was conducted with the permission of the İstanbul Doğuş University Ethics Committee (Date 26.01.2024, Decision No: 2023/86). Informed consent was obtained from all patients for the procedure. All procedures were carried out following ethical rules and the principles of the Declaration of Helsinki.

This study aims to examine the mediating role of an individual's personality traits and anger styles in the relationship between borderline personality traits and sexual self-schema. The study employed a relational screening model and obtained the sample through a convenience sampling method. While the study population consists of individuals aged 18 and above living in İstanbul, the sample consists of 402 participants, including 249 women and 153 men (Table 1). A total of 13 individuals with a prior psychiatric diagnosis were excluded from the initial pool, resulting in a final sample of 402 participants. The research used the socio-demographic information form, borderline personality scale (Turkish BPQ), sexual self-schema scale, and state-trait anger expression inventory (STAXI).

Data Collection Tools

Sociodemographic information form: These questions were prepared to interpret the participants' information and presented to the sample. The questions in the form related to the participant's age, gender, educational status, and marital status. The form also inquired whether participants had received a prior psychiatric diagnosis to exclude those with such a diagnosis.

Table 1. Distribution of demographic information of participants

		n	%
Gender	Woman	249	61.9
	Man	153	38.1
Age	18-25	64	15.9
	26-40	255	63.4
	41-55	83	20.6
Marital status	Single	143	35.6
	Married	259	64.4
Educational status	High-school graduate	43	10.7
	Undergraduate/associate degree	267	66.4
	Master's degree/doctoral degree	92	22.9
	Total	402	100.0

Borderline personality scale (Turkish BPQ): The BPQ, an 80-item self-assessment scale developed by Poreh and others⁹ based on the DSM-IV criteria for BPD, consists of 9 subscales: impulsivity, affective instability, abandonment, relationships, self-image, suicide and self-mutilation, emptiness, intense anger, and quasi-psychotic states.¹⁰ Participants marked "true" or "false" for each item, and the internal consistency (Cronbach's α) of the Turkish BPQ was found to be 0.94.⁹ The Turkish version has been validated and reliable, making it useful for identifying BPD diagnostic criteria.⁹

Sexual self-schema scale (SSSS): Originally based on the SSSS for women¹¹ and the SSSS for men,¹² these scales were later combined by Hill¹³ into a common SSSS for both men and women. The Turkish validation and reliability study showed that the scale had internal consistency and could be used in Turkish measurements.¹⁴

State-trait anger expression inventory (STAXI): Spielberger et al.¹⁵ developed the trait anger and anger expression styles scale with an internal consistency coefficient of 0.73. The scale divides anger into "trait" and "state" components. The Turkish validation and reliability study adapted the scale, which consists of four subscales: trait anger, anger-in, anger-out, and anger control.¹⁶ The trait anger and anger expression styles scale consists of 34 items, rated on a 4-point Likert-type scale.¹⁷

Statistical Analysis

All data analyses were conducted using IBM SPSS 27 software in this study. Pearson Correlation analysis was used to examine the level and direction of relationships between the scales. Model 4 was identified using Process Macro 4.2 to evaluate the indirect effect of the mediator variable. All statistical analyses were performed within a 95% confidence interval, with the significance level set at $p < .05$.

The reliability levels of the scales were assessed using Cronbach's Alpha coefficients, and it was found that these coefficients were above 0.60 (Table 1). This finding indicates that the scales are reliable.¹⁸ Subsequently, skewness and kurtosis coefficients were examined to check the normal distribution of the scales, and it was determined that all scales had coefficients within the ± 2 range. This suggests that the scales meet the assumption of normal distribution¹⁹ (Table 2).

Table 2. Descriptive statistics, Skewness, Kurtosis, and Cronbach's Alpha Coefficients for the sexual self-schema scale, trait anger and anger expression scale, five-factor personality inventory, and borderline personality scale

	n	Min	Max	$\bar{M}$	SD	Skewness	Kurtosis	(α)
SSSS _{Loving/compassionate}	402	11	61	26.06	12.02	-0.23	0.75	0.92
SSSS _{Sensual/stimulating}	402	12	66	37.70	13.42	-0.61	-0.21	0.89
SSSS _{Direct/straightforward}	402	10	56	27.51	10.11	-0.44	0.17	0.84
STAXI _{Trait anger}	402	10	40	24.96	7.31	-0.58	0.10	0.88
STAXI _{Anger in}	402	8	32	19.51	5.41	-0.49	-0.04	0.78
STAXI _{Anger out}	402	8	32	18.60	5.89	-0.64	0.23	0.86
STAX _{Anger control}	402	8	32	21.69	5.41	-0.67	-0.17	0.80
FFM _{Extraversion}	402	1	5	2.70	0.90	-1.08	0.15	0.82
FFM _{Agreeableness}	402	1	4	2.86	0.72	-0.67	-0.57	0.73
FFM _{Conscientiousness}	402	1	5	3.09	0.83	-0.87	-0.28	0.79
FFM _{Neuroticism}	402	1	4	2.37	0.79	-0.55	0.16	0.73
FFM _{Openness}	402	1	5	2.98	0.69	-0.21	-0.08	0.70
Borderline personality scale	402	0	67	23.27	15.40	-0.33	0.67	0.95
Impulsivity	402	0	9	2.41	2.24	-0.14	0.91	0.77
Affective instability	402	0	10	3.65	2.63	-0.86	0.46	0.77
Abandonment	402	0	9	3.09	2.19	-0.63	0.52	0.70
Relationships	402	0	8	2.43	2.27	-0.49	0.80	0.78
Self-image	402	0	9	2.33	2.16	-0.22	0.87	0.76
Suicide and self-mutilation	402	0	7	2.07	1.91	-0.44	0.77	0.72
Emptiness	402	0	10	2.99	2.34	-0.10	0.81	0.73
Intense anger	402	0	9	2.26	2.11	-0.27	0.78	0.70
Quasi-psychotic states	402	0	7	2.03	1.92	-0.12	1.01	0.78

Min: Minimum, Max: Maximum, SD: Standard deviation, SSSS: Sexual self-schema scale, STAXI: State-trait anger expression inventory

RESULTS

As a result of the correlation analysis, sexual self-schemas were compared with trait anger, anger styles, and borderline personality traits. A positive correlation was found between the loving/compassionate subdimension of the SSSS and the variable of extraversion ($r=.11$, $p<0.05$). Negative correlations were found between this subdimension and the variables of trait anger ($r=-.12$, $p<0.05$), anger-in ($r=-.22$, $p<0.01$), anger-out ($r=-.12$, $p<0.05$), neuroticism ($r=-.22$, $p<0.01$), Turkish BPQ ($r=-.29$, $p<0.01$), impulsivity ($r=-.27$, $p<0.01$), affective instability ($r=-.21$, $p<0.01$), abandonment ($r=-.20$, $p<0.01$), relationships ($r=-.24$, $p<0.01$), self-image ($r=-.17$, $p<0.01$), suicide and self-mutilation ($r=-.25$, $p<0.01$), emptiness ($r=-.24$, $p<0.01$), intense anger ($r=-.26$, $p<0.01$), and quasi-psychotic states ($r=-.22$, $p<0.01$) (Table 3).

Positive correlations were found between the subdimension of sensual/stimulating from the sexual self-schema and the variables of extraversion ($r=.12$, $p<0.05$) and conscientiousness ($r=.13$, $p<0.05$). Negative correlations were found with the variables of trait anger ($r=-.14$, $p<0.01$), anger-in ($r=-.24$, $p<0.01$), anger-out ($r=-.11$, $p<0.05$), neuroticism ($r=-.27$, $p<0.01$), Turkish BPQ ($r=-.39$, $p<0.01$), impulsivity ($r=-.32$, $p<0.01$), affective instability ($r=-.31$, $p<0.01$), abandonment ($r=-.32$, $p<0.01$), relationships ($r=-.24$, $p<0.01$), self-image ($r=-.28$, $p<0.01$), suicide and self-mutilation ($r=-.29$, $p<0.01$), emptiness ($r=-.33$, $p<0.01$), intense anger ($r=-.36$, $p<0.01$), and quasi-psychotic states ($r=-.27$, $p<0.01$) (Table 3).

For the direct/straightforward subdimension of the sexual self-schema, negative correlations were found with the variables of trait anger ($r=-.12$, $p<0.01$), anger-in ($r=-.22$, $p<0.01$), anger-out ($r=-.11$, $p<0.05$), neuroticism ($r=-.19$, $p<0.01$), Turkish BPQ ($r=-.33$, $p<0.01$), impulsivity ($r=-.29$, $p<0.01$), affective instability ($r=-.27$, $p<0.01$), abandonment ($r=-.26$, $p<0.01$), relationships ($r=-.22$, $p<0.01$), self-image ($r=-.23$, $p<0.01$), suicide and self-mutilation ($r=-.24$, $p<0.01$), emptiness ($r=-.27$, $p<0.01$), intense anger ($r=-.29$, $p<0.01$), and quasi-psychotic states ($r=-.26$, $p<0.01$) (Table 3).

Positive correlations were found between trait anger and the variables of the borderline suicide and self-mutilation ($r=.23$, $p<0.01$), emptiness ($r=.12$, $p<0.05$), and intense anger ($r=.17$, $p<0.01$) (Table 3).

Additionally, positive correlations were found between anger-in and the variables of the Turkish BPQ ($r=.27$, $p<0.01$), impulsivity ($r=.19$, $p<0.01$), affective instability ($r=.21$, $p<0.01$), abandonment ($r=.20$, $p<0.01$), relationships ($r=.25$, $p<0.01$), self-image ($r=.21$, $p<0.01$), suicide and self-mutilation ($r=.22$, $p<0.01$), emptiness ($r=.19$, $p<0.01$), intense anger ($r=.27$, $p<0.01$), and quasi-psychotic states ($r=.17$, $p<0.01$) (Table 3).

A negative correlation was found between anger-out and conscientiousness ($r=-.10$, $p<0.05$), while positive correlations were found between anger-out and the variables of the Turkish BPQ ($r=.20$, $p<0.01$), impulsivity ($r=.13$, $p<0.01$), affective instability ($r=.12$, $p<0.05$), relationships ($r=.23$,

Table 3. Examination of the relationship between sexual self schema, trait anger-anger styles, personality traits, borderline personality traits

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1-SSSS Loving/compassionate	1																					
2-SSSS Sensual/stimulating	.67**	1																				
3-SSSS Direct/straightforward	.60**	.79**	1																			
4-STAXI _{Trait} anger	-.12*	-.14**	-.12*	1																		
5-STAXI _{Anger in}	-.22**	-.24**	-.22**	.56**	1																	
6-STAXI _{Anger out}	-.12*	-.11*	-.11*	.79**	.61**	1																
7-STAXI _{Anger control}	.05	-.04	-.04	-.36**	-.28**	-.36**	1															
8-FFM _{Extra-version}	.11*	.12*	.06	-.04	.02	-.06	.00	1														
9-FFM _{Agreeableness}	.00	.07	.00	-.03	.00	-.09	-.01	.53**	1													
10-FFM _{Conscientiousness}	.04	.13*	.05	-.06	-.04	-.10*	-.03	.55**	.73**	1												
11-FFM _{Neuroticism}	-.22**	-.27**	-.19**	-.04	-.05	-.01	-.02	-.51**	-.36**	-.32**	1											
12-FFM _{Openness}	.03	.09	.07	-.08	-.02	-.09	-.05	.52**	.43**	.43**	-.30**	1										
13-Borderline personality scale	-.29**	-.39**	-.33**	.16**	.27**	.20**	-.02	-.15**	-.10*	-.11*	.21**	-.11*	1									
14-Impulsivity	-.27**	-.32**	-.29**	.11*	.19**	.13**	-.03	-.12*	-.09	-.09	.15**	-.09	.79**	1								
15-Affective instability	-.21**	-.31**	-.27**	.09	.21**	.12*	-.01	-.16**	-.09	-.07	.23**	-.10*	.78**	.58**	1							
16-Abandonment	-.20**	-.32**	-.26**	.09	.20**	.09	.00	-.16**	-.04	-.10*	.21**	-.15**	.78**	.57**	.61**	1						
17-Relationships	-.24**	-.24**	-.22**	.20**	.25**	.23**	.00	-.10*	-.07	-.09	.12*	-.07	.82**	.56**	.56**	.58**	1					
18-Self-image	-.17**	-.28**	-.23**	.06	.21**	.10*	.06	-.13**	-.07	-.10	.16**	-.11*	.79**	.55**	.54**	.61**	.67**	1				
19-Suicide and self-mutilation	-.25**	-.29**	-.24**	.23**	.22**	.26**	-.03	-.14**	-.10*	-.09	.15**	-.11*	.75**	.56**	.54**	.51**	.71**	.50**	1			
20-Emptiness	-.24**	-.33**	-.27**	.12*	.19**	.17**	-.02	-.13**	-.15**	-.12*	.16**	-.10	.83**	.61**	.52**	.58**	.66**	.61**	.61**	1		
21-Intense anger	-.26**	-.36**	-.29**	.17**	.27**	.18**	-.04	-.09	-.05	-.08	.17**	-.03	.81**	.63**	.56**	.56**	.56**	.59**	.50**	.66**	1	
22-Quasi-psychotic states	-.22**	-.27**	-.26**	.10	.17**	.16**	-.07	-.03	-.05	.00	.07	.01	.65**	.43**	.43**	.38**	.44**	.43**	.38**	.56**	.60**	1

SSSS: Sexual self-schema scale, STAXI: State-trait anger expression inventory

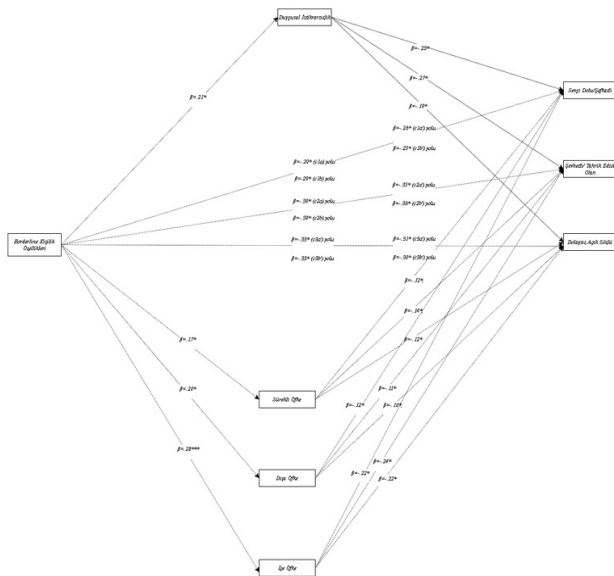
$p < 0.01$), self-image ($r = .10$, $p < 0.05$), suicide and self-mutilation ($r = .26$, $p < 0.01$), emptiness ($r = .17$, $p < 0.01$), intense anger ($r = .18$, $p < 0.01$), and quasi-psychotic states ($r = .16$, $p < 0.01$) (Table 3).

A negative correlation was found between extraversion and Turkish BPQ ($r = -.15$, $p < 0.01$), impulsivity ($r = -.12$, $p < 0.05$), affective instability ($r = -.16$, $p < 0.01$), abandonment ($r = -.16$, $p < 0.01$), relationships ($r = -.10$, $p < 0.05$), self-image ($r = -.13$, $p < 0.01$), suicide and self-mutilation ($r = -.14$, $p < 0.01$), and emptiness ($r = -.13$, $p < 0.01$). A negative correlation was also found between agreeableness and Turkish BPQ ($r = -.10$, $p < 0.05$), suicide and self-mutilation ($r = -.10$, $p < 0.05$), and emptiness ($r = -.15$, $p < 0.01$); and between conscientiousness and Turkish BPQ ($r = -.11$, $p < 0.05$), abandonment ($r = -.10$, $p < 0.05$), and emptiness ($r = -.12$, $p < 0.05$). A positive correlation was observed between neuroticism and Turkish BPQ ($r = .21$, $p < 0.01$), impulsivity ($r = .15$, $p < 0.01$), affective instability ($r = .23$, $p < 0.01$), abandonment ($r = .21$, $p < 0.01$), relationships ($r = .12$, $p < 0.05$), self-image ($r = .16$, $p < 0.01$), suicide and self-mutilation ($r = .15$, $p < 0.01$), emptiness ($r = .16$, $p < 0.01$), and intense anger ($r = .17$, $p < 0.01$). A negative correlation was found

between openness to experience and Turkish BPQ ($r = -.11$, $p < 0.05$), affective instability ($r = -.10$, $p < 0.05$), abandonment ($r = -.15$, $p < 0.01$), self-image ($r = -.11$, $p < 0.05$), and suicide and self-mutilation ($r = -.11$, $p < 0.05$) (Table 3).

It was determined that borderline personality traits significantly predicted the loving/compassionate sexual self-schema ($\beta = -.29$, $p < .05$). When neuroticism was included as a mediator in the relationship, a decrease was observed in the beta value of borderline personality traits as the independent variable ($\beta = -.26$, $p < .05$), and it was concluded that the mediator variable was statistically significant ($\beta = -.03$, 95% CI). When anger styles were included as a mediator, a decrease was observed in the beta value of borderline personality traits ($\beta = -.25$, $p < .05$), and the mediator variable was found to be statistically significant ($\beta = -.04$, 95% CI) (Figure).

It was determined that borderline personality traits significantly predicted the sensual/stimulating sexual self-schema ($\beta = -.39$, $p < .05$). When neuroticism was included as a mediator, a decrease was observed in the beta value of borderline personality traits ($\beta = -.35$, $p < .05$), and the mediator



* $p < .05$ Test used: Process Macro 4.2

Figure. The mediating role of partners' personality traits and anger styles in the relationship between borderline personality organization and sexual self-schema

variable was found to be statistically significant ($\beta = -.04$, 95% CI). When anger styles were included as a mediator, a decrease was observed in the beta value of borderline personality traits ($\beta = -.36$, $p < .05$), and the mediator variable was found to be statistically significant ($\beta = -.03$, 95% CI) (Figure).

Mediation analyses indicated that the association between borderline personality traits and the direct/straightforward sexual self-schema was explained in part by neuroticism and anger styles. Specifically, when neuroticism was included in the model, the beta value of borderline personality traits decreased from $\beta = -0.33$ to $\beta = -0.31$ ($p < .05$), and the indirect effect was statistically significant ($\beta = -0.02$, 95% CI). When Anger Styles were included, the beta value decreased to $\beta = -0.30$ ($p < .05$), with a statistically significant indirect effect ($\beta = -0.03$, 95% CI).

DISCUSSION

This study revealed a significant relationship between borderline personality traits, sexual self-schemas, personality traits, and anger expression styles. The findings indicated that individuals with borderline personality traits tend to exhibit sexual self-schemas characterized by loving/compassionate, sensual/stimulating, and direct/straightforward patterns. Prior research has consistently shown that neuroticism is linked to less adaptive emotion regulation strategies—such as rumination and suppression—rather than flexible approaches like reappraisal.⁵ Individuals high in neuroticism typically experience greater emotional instability, heightened stress reactivity, and a tendency to dwell on negative experiences, which may intensify both interpersonal and intrapersonal difficulties.⁴ Within the context of this study, such maladaptive regulation patterns may help explain the negative association observed between neuroticism and sexual self-schemas, as these strategies can hinder the development of positive sexual self-perceptions.¹¹ Considering that individuals with BPD often display low self-regulation and control,²⁰ the association

with the direct/straightforward sexual self-schema appears consistent with existing literature. Furthermore, it has been suggested that the link between borderline personality traits and the loving/compassionate sexual self-schema may stem from the inappropriate and frequent sexual behaviors often observed in borderline individuals,²¹ as well as from a heightened need for approval and validation.²²

This study identified the mediating role of anger in the relationship between borderline personality traits and sexual self-schemas, finding that individuals with borderline patterns, who also scored high on trait anger, displayed such patterns. Studies in the literature also show that an increase in borderline personality traits leads to higher levels of trait anger.²³ Consistent with these findings, the literature also indicates that individuals with borderline personality traits experience more difficulty in anger control compared to others.²⁴ The use of anger as a defense mechanism to cope with negative emotions can explain the negative relationship between anger control, borderline personality traits, and sexual self-schemas.²⁵ The findings of Howard et al.²⁶ explain the mediating role of anger, demonstrating that individuals with BPD display angry and aggressive behaviors towards others. Individuals with borderline traits outwardly express anger, which corresponds to the direct/straightforward dimension of sexual self-schemas.

Researchers have found that personality traits may function as a possible mechanism in the relationship between sexual self-schemas and borderline personality traits. In this context, it was determined that individuals with high neuroticism scores from the five-factor personality model have negative sexual self-schemas and exhibit borderline personality traits more frequently. Boldero et al.²⁷ concluded in their study that individuals with BPD behave impulsively and experience emotional inconsistency, supporting the relationship between neuroticism from the five-factor personality traits and borderline personality traits. Several studies suggest that individuals with neuroticism personality traits in the borderline pattern are more likely to have direct/straightforward sexual self-schemas. These studies relate borderline personality traits to early attachment styles, which in turn shape the sexual self-schemas assimilated in adulthood.²⁸

Moreover, the study has revealed the relationship between variables that have not been sufficiently studied in the literature by focusing on the behaviors of individuals with borderline personality traits and the underlying reasons for these behaviors.

Limitations

The study has certain limitations. The most significant limitation is the difficulty in forming the framework of the discussion section, which arises from the scarcity of articles that measure the relationship between the study variables during the literature review. On the other hand, the fact that the sub-dimensions of the SSSS differ between the original and the Turkish validity and reliability studies makes interpreting the literature more challenging. Another limitation is that only the characteristics measured by the scales are evaluated

in the study. Additionally, the sample was drawn from a single city (İstanbul) using a convenience sampling method, which may limit the generalizability of the findings to other populations.

CONCLUSION

The study's findings reveal that individuals with borderline personality traits often exhibit three sexual self-schemas: loving/compassionate, sensual/stimulating, and direct/straightforward. It was determined that anger styles play a mediating role in the relationship between borderline personality traits and sexual self-schemas. Additionally, neuroticism, among the five-factor personality traits, also plays a mediating role in this relationship.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the İstanbul Doğuş University Ethics Committee (Date 26.01.2024, Decision No: 2023/86).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The author have no conflicts of interest to declare.

Financial Disclosure

The author 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 ventricular repolarization parameters in patients with erectile dysfunction

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Cite this article as: Baran O, Yılmaz Y, Baydilli N, Yılmaz H, Keleşoğlu Ş. Evaluation of ventricular repolarization parameters in patients with erectile dysfunction. *J Med Palliat Care*. 2025;6(4):422-427.

Received: 20.06.2025

Accepted: 19.08.2025

Published: 31.08.2025

ABSTRACT

Aims: Erectile dysfunction (ED) is recognized as a good predictor of future cardiovascular disease (CVD). There are also studies showing that ventricular repolarization parameters on Electrocardiography (ECG) are associated with increased ventricular arrhythmogenesis and sudden death for various diseases. In this study, we will investigate the relationship between ED and Tp-e to QTc ratio, Tp-e interval/QT interval (Tp-e/QT) ratio and Tp-e interval.

Methods: The study included 87 patients admitted to the urology clinic of our hospital and diagnosed with vascular ED. The distance between the peak of the T wave and the end of the T wave was defined as the Tp-e interval. QT interval was defined as the interval from the beginning of the QRS complex to the end of the T wave and adjusted according to heart rate (QTc, Bazett formula).

Results: Tp-e-QTc ratio, Tp-e-QT ratio and Tp-e interval were statistically and significantly higher in patients with ED compared to the control group (overall $p < 0.01$). Our correlation analysis found significant negative correlations between IIEF-5 score and Tp-e-QTc ratio, Tp-e-QT ratio and Tp-e interval in patients with ED ($r = -0.714$, $p < 0.001$; $r = -0.729$, $p < 0.001$, $r = -0.776$, $p < 0.001$, respectively).

Conclusion: We found that Tp-e/QTc ratio, Tp-e/QT ratio and Tp-e interval, which are considered to be important for fatal ventricular arrhythmias on ECG, were significantly longer in emergency department patients.

Keywords: Sexual function, Tp-e to QTc ratio, Tp-e to QT ratio and Tp-e interval

INTRODUCTION

Erectile dysfunction (ED) is defined as the inability to achieve and/or maintain a penile erection for a satisfying sexual experience and can be considered an important diagnostic group as it affects the quality of life of middle/older age men.¹ It is the most common underlying cause in patients with vasculogenic ED.¹

Recent studies have shown that ED is a good predictor of cardiovascular disease (CVD) due to similar physiopathologic pathways, leading to an irrepressible desire for cardiologic evaluation of patients with ED.² Although limited in number, studies suggesting an association between ED and atherosclerotic CAD and cardiac arrhythmias are found in the literature.^{3,4} Furthermore, when ED is detected, it may be accompanied by silent CAD, and it is accepted that there is a not very long period of time (on average 2-5 years) between the detection of ED and the occurrence of a CAD-related event.⁴ ED also develops through similar pathophysiological mechanisms as atherosclerotic heart disease and arrhythmias.

Endothelial dysfunction is observed in patients with ED, and inflammatory markers and prothrombotic markers have been found to be elevated.⁵⁻⁷

Electrocardiography (ECG) is the most commonly used test in cardiology daily practice because it is a simple, inexpensive, practical, reproducible and easily accessible test. It is known that evaluation of ventricular recovery and repolarization starting with Q wave and ending with T wave on ECG may be a parameter that can be used to predict future ventricular arrhythmias.⁸ Recently, new ECG indices such as Tpeak-Tend (Tp-e) interval and Tp-e interval/QT interval (Tp-e/QT) ratio, Tp-e interval/QTc interval/(Tp-e/QTc ratio) are considered to indicate abnormal distribution of ventricular repolarization. Studies have also suggested that ECG parameters such as prolonged Tp-e interval and Tp-e/QTc ratio may be markers of ventricular arrhythmogenesis and sudden death.⁹⁻¹⁵

Some studies in the literature have suggested a possible association between supraventricular arrhythmias and

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ED.^{16,17} We hypothesize that patients with ED may exhibit prolonged ventricular repolarization parameters due to shared pathophysiological mechanisms with CVD, including endothelial dysfunction and systemic inflammation. However, to the best of our knowledge, no study in the literature has examined the ratio of Tp-e to QTc, the ratio of Tp-e to QT and the Tp-e interval to predict the risk of future ventricular arrhythmias/mortality in patients with ED.

This study aimed to assess whether ventricular repolarization heterogeneity would be increased in men with ED without known CAD or significant structural heart disease and to assess whether potential changes in repolarization indices (Tp-e interval and Tp-e/QT and Tp-e/QTc ratios) would be associated with ED severity.

METHODS

Ethics

Approval for this study was obtained from the Erciyes University Clinical Researches Ethics Committee (Date: 16.12.2020, Decision No: 2020/634). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

The study included retrospective analysis of data from 87 patients with vascular ED who presented to our hospital's urology clinic between October 2020 and May 2021. Physical examination findings, medical history and laboratory characteristics of the study and control groups were obtained from the hospital archive and computer records and recorded in the protocol files. The control group consisted of 69 patients who were similar to the patient group in terms of demographic characteristics and did not have ED. When the control and patient groups were evaluated in terms of CAD, their history/physical examination findings/ECGs and Transthoracic Echocardiography test results were evaluated as normal.

Exclusion criteria were as follows: left bundle branch block, presence of a pacemaker, uninterpretable ECG such as U waves and negative T waves, CAD, severe heart failure, severe valvular heart disease, severe organ failure such as kidney, liver, lung, malignancy, urinary problems, use of drugs for depression or other neuropsychiatric disorders, use of drugs that may affect the QT interval, electrolyte disorders that may affect the QT interval.

Assessment of Erectile Dysfunction

We included ED patients with documented vascular ED lasting at least 6 months. Etiologic causes other than vascular ED were excluded. These included: neuropathy, neuropathic disorders, morbid obesity, history of surgery (pelvic, retroperitoneal or perineal), radiotherapy and cryotherapy, or taking medications that may affect erectile function.

The International Index of Erectile Function (IIEF-5) questionnaire was used to diagnose the presence of ED in the control groups. In addition, the same questionnaire was used to determine the severity of the disease in ED patients. The

threshold for normal erectile function was an IIEF-5 score of ≥ 22 .¹⁸

Electrocardiogram Analysis

All standard 12-lead ECGs were recorded simultaneously while the patients were resting in the supine position and using a calibrated recorder (Philips brand device) (ECG recording standard; paper speed: 25 mm/sec and voltage: 1 mV/cm). All ECGs were scanned and transferred to a personal computer.

To record ECG waveform measurements, ECGs were first magnified and measurements were made using an electronic caliper (Cardio Calipers, version 3.3 software; Iconico.com, Philadelphia, PA, USA). ECG results were read by 2 cardiologists blinded to clinical data.

Tp-e interval is the distance between the peak of the T wave and the end of the T wave. Tp-e intervals were best measured using the T wave in lead V5.⁸ If lead V5 was not suitable for Tp-e analysis, other leads were evaluated (V4 or V6).

The QT interval is usually measured in lead V6, which is known to best reflect the transmural axis of the left ventricle. Adjusted for heart rate (Bazett formula); the interval from the beginning of the QRS complex to the end of the T wave: $cQT = QT\sqrt{(R-R \text{ interval})}$. The Tp-e/QT ratio (Tp-e divided by QT) and Tp-e/QTc (Tp-e divided by QTc) were calculated based on these measurements.

Echocardiography

Conventional echocardiography images were obtained from parasternal and apical views for each patient and healthy volunteers. All measurements were performed using a device equipped with a 3.5 MHz transducer (Vivid 7, GE Medical System, Horten, Norway) available at our hospital. Two-dimensional echocardiographic measurements were performed to evaluate left ventricular ejection fraction and valvular pathologies. Ejection fraction was calculated using Simpson's method.¹⁹

Statistical Analysis

SPSS Statistics Software kit, package version 21.0 (SPSS Inc, Chicago, IL, USA) was used to perform statistical analyses. Data distribution characteristics were determined using the Kolmogorov-Smirnov test. Independent sample t-test was used for parametric scale variables, while χ^2 (chi-square) test was used for univariate analysis of categorical variables. Mean $\pm$ SD (standard deviation) for parametric variables and percentages for categorical variables were reported. Correlation analyses were evaluated using Pearson and Spearman coefficients. Two-tailed p values were used for all analyses. A probability value of $p < 0.05$ was required for test results to be considered significant.

RESULTS

The study included 87 patients with a mean age of 55.4 ± 12.5 years who suffered from ED and 69 control patients with a mean age of 52.6 ± 9.4 years who did not suffer from ED. [Table 1](#) shows the main demographic and clinical variables of the

study groups. There was no statistically significant difference between the patients and the control group in terms of risk factors such as age, smoking, DM and HT ($p>0.05$). The mean IIEF-5 score of the ED group was 12 ± 3.2 , while that of the control group was 23.9 ± 1.9 ($p<0.001$).

Table 1. Study groups baseline clinical and demographic characteristics of the study groups

Variables	Control group (n=69)	ED (n=87)	p value
Age (years)	52.6 $\pm$ 9.4	55.4 $\pm$ 12.5	0.122
HT (n, %)	16	22	0.762
DM (n, %)	15	21	0.724
Smoking (n, %)	7	7	0.649
Systolic blood pressure (mm/hg)	119.5 $\pm$ 10.2	122.6 $\pm$ 11.5	0.201
Diastolic blood pressure (mm/hg)	73.7 $\pm$ 7.2	74.7 $\pm$ 6.3	0.507
Glucose (mg/dl)	93.3 $\pm$ 22.7	99.4 $\pm$ 16.8	0.053
Body-mass index (kg/m ²)	26.6 $\pm$ 4.3	27.9 $\pm$ 4.8	0.096
Serum creatinine, (mg/dl)	0.82 $\pm$ 0.18	0.88 $\pm$ 0.26	0.104
AST (U/L)	21.1 $\pm$ 6	23.5 $\pm$ 11.8	0.125
ALT (U/L)	19.8 $\pm$ 8.5	22.1 $\pm$ 15.1	0.263
Total cholesterol (mg/dl)	172.8 $\pm$ 47.3	179.1 $\pm$ 48.1	0.438
Triglycerides (mg/dl)	124.2 $\pm$ 69.4	137.7 $\pm$ 68.9	0.245
Low density lipoprotein (mg/dl)	113.4 $\pm$ 42.7	114.8 $\pm$ 42.1	0.840
High density lipoprotein (mg/dl)	38.3 $\pm$ 25	36.1 $\pm$ 9.8	0.470
White blood cell (10 ³ / μ L)	8.1 $\pm$ 2.3	8.8 $\pm$ 2.5	0.076
Hemoglobin (g/L)	13.6 $\pm$ 1.4	14 $\pm$ 2	0.177
Platelets (10 ³ / μ L)	231.5 $\pm$ 67.6	244.1 $\pm$ 61.2	0.233
IIEF-5 score	23.9 $\pm$ 1.9	12 $\pm$ 3.2	<0.001

ED: Erectile dysfunction, DM: Diabetes mellitus, HT: Hypertension, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, IIEF: International Index of Erectile Function, $p<0.05$ was considered significant.

Table 1 lists the laboratory results of the study groups. There was no significant difference between the two groups in terms of basic laboratory parameters ($p>0.05$). When the two groups were evaluated in terms of echocardiographic variables, no statistically significant difference was found between the groups ($p>0.05$) (**Table 2**).

Table 2. Echocardiographic characteristics of the study population

Variables	Control group (n=69)	ED (n=87)	p value
LVEDD, mm	4.73 $\pm$ 0.41	4.80 $\pm$ 0.44	0.198
LVESD, mm	3.11 $\pm$ 0.41	3.14 $\pm$ 0.32	0.463
IVSD, mm	1.05 $\pm$ 0.97	1.05 $\pm$ 0.18	0.871
PWD, mm	1.01 $\pm$ 0.84	1.01 $\pm$ 0.17	0.915
LVEF %	63.3 $\pm$ 3.1	61.3 $\pm$ 4.1	0.514

ED: Erectile dysfunction, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end-systolic diameter, IVSD: Interventricular septal diameter, PWD: Posterior wall diameter, LVEF: Left ventricular ejection fraction

ECG parameters of the groups are shown in **Table 3**. Heart rate and QRS duration were similar between the groups ($p=0.130$ and $p=0.869$, respectively). In addition, there was no difference between QT interval and QTc duration ($p>0.05$). Tp-e/QTc ratio, Tp-e/QT ratio and Tp-e interval were statistically and significantly higher in patients with ED

compared to the control group (all $p<0.01$). Our correlation analysis found significant negative correlations between IIEF-5 score and Tp-e-QTc ratio, Tp-e-QT ratio and Tp-e interval in patients with ED ($r=-0.714$, $p<0.001$; $r=-0.729$, $p<0.001$, $r=-0.776$, $p<0.001$, respectively) (**Table 4**).

Table 3. Electrocardiographic characteristics of the study group

Variables	Control group (n=69)	ED (n=87)	p value
Heart rate (beats/min)	75.2 $\pm$ 10	72.8 $\pm$ 9.7	0.130
QRS duration (ms)	89.7 $\pm$ 32.8	88.8 $\pm$ 35	0.869
QT interval (ms)	379.7 $\pm$ 23.9	380.6 $\pm$ 27.7	0.828
QTc interval (ms)	419 $\pm$ 16.1	416 $\pm$ 23.9	0.385
Tp-e (ms)	73.2 $\pm$ 4.7	83.9 $\pm$ 4.5	<0.001
TPe/QTc ratio (ms)	0.20 $\pm$ 0.01	0.17 $\pm$ 0.01	<0.001
TPe/QT ratio (ms)	0.19 $\pm$ 0.01	0.22 $\pm$ 0.01	<0.001

ED: Erectile dysfunction, Tp-e: T wave interval peak to peak, c=corrected, $p<0.05$ was considered significant.

Table 4. Correlation analysis results of study parameters with IIEF-5 score

Variables	r	p
Tp-e (ms)	-0.714	<0.001
TPe/QTc ratio (ms)	-0.776	<0.001
TPe/QT ratio (ms)	-0.729	<0.001

IIEF: International Index of Erectile Function, Tp-e: T-wave interval from peak to end, c: Adjusted, $p<0.05$ was considered significant.

DISCUSSION

This is the first study to show that Tp-e/QTc ratio, Tp-e/QT ratio and Tp-e interval durations, which indicate the repolarization period, which is considered the most sensitive period for fatal ventricular arrhythmias on ECG, are significantly prolonged in ED patients. The study also makes an important contribution to the existing body of knowledge by showing that there may be a link between the severity of ED and arrhythmia markers.

ED has been shown to be commonly associated with CVD. The pathophysiology of the disease shares some similarities with CVD, including atherosclerosis, endothelial dysfunction, structural vascular damage and subclinical inflammation.²⁰⁻²⁴ In addition, patients with a range of risk factors such as CVD, HT, DM, obesity and dyslipidemia have been found to have a higher incidence of ED.²⁵⁻²⁸ This suggests that there may be an association between these diseases and ED.

Dong et al.²⁹ conducted twelve prospective cohort studies with 36,744 subjects. In their meta-analysis, they reported that men with EDs were significantly more likely to suffer from CVD, CAD, stroke and death compared to men without EDs. This translated into 46% for CAD, 48% for CVD, 35% for stroke and 19% for all-cause mortality, strikingly independent of traditional CVD risk factors. Uddin et al.² reached similar results. They showed that ED is an important predictor of future CVD events independent of traditional CVD risk factors. Thompson et al.³⁰ showed an increased incidence of future myocardial infarction (MI), angina and stroke in people

with ED. Another study showed that ED was an independent risk factor for silent MI in DM patients with ED.²⁴ The authors of the study even argued that the presence of ED was the most effective predictor of CAD in men with DM. Although not as robust as the data on the aforementioned diseases, emerging data also associate ED with cardiac arrhythmias.

A study by Lin et al.³¹ showed that ED is more common in people with atrial fibrillation (AF). Furthermore, a recent MESA study that followed patients for four years showed that ED patients were associated with an increased risk of AF.³² Altunkol et al.³³ found a prolongation of atrial conduction time in ED patients, which is considered a predictor of AF. Meanwhile, Schouten et al.³⁴ found an increased risk of MI and stroke as well as sudden cardiac death in patients with ED. Although the groups in this study were similar in terms of ED-related comorbidities such as DM, HT, CAD, obesity and smoking, we found a prolonged Tp-e-QTc ratio, Tp-e-QT ratio and Tp-e interval in patients with ED compared to the control group, all of which are ECG indicators of ventricular arrhythmogenesis and sudden death.

Ventricular arrhythmias, a common cause of sudden cardiac death, can occur in apparently healthy individuals. It may be possible to predict the development of ventricular arrhythmias by analyzing various indicators of ventricular repolarization on the ECG. Of these, QT interval, QTc interval and QT interval dispersion have been extensively investigated in previous studies.³⁵ Recent studies have proposed the use of Tp-e interval and Tp-e/QTc ratio as a new index of transmural dispersion of repolarization. When the literature is reviewed, there are studies reporting that prolonged Tp-e/QTc ratio, Tp-e/QT ratio and Tp-e interval are associated with ventricular arrhythmias.⁹⁻¹⁵

The mechanisms leading to ventricular arrhythmias have a complex pathophysiology with many risk factors (remodeling of ventricular structure, ion channel functions, electrophysiologic mechanisms, etc.).³⁶ On this basis, ventricular arrhythmias can also affect people without ED. However, as shown in this study, the prolongation of ventricular arrhythmia predictive parameters such as Tp-e/QTc ratio, Tp-e/QT ratio and Tp-e interval in patients with ED may be attributed to several reasons. Although the control and patient groups were similar in terms of CVD risk factors, it was determined that ventricular arrhythmias were prolonged in ED patients, suggesting that this may be independent of the traditional CVD risk.

The increased inflammation and increased oxidative stress that contribute to the impairment of endothelial function in patients with ED, which may be associated with an increased risk of cardiac arrhythmias.^{7,38} Because a recent study has shown that ventricular repolarization indices are associated with systemic inflammation. Moreover, increased inflammatory activity has been implicated in the pathogenesis of cardiac arrhythmias either through direct arrhythmogenic action or through induction of oxidative stress.^{39,40} Inflammation may explain the heterogeneity of ventricular repolarization in ED patients, but the issue itself requires further analysis. Prospective studies that include

systematic ischemia testing and long-term arrhythmic outcomes are necessary to determine whether this association is truly independent of CAD.

Recent studies have shown that ED is a precursor to cardiovascular clinical events in some men and the presence of ED in patients warrants screening for CVD risk factors. This study also found that predictive parameters of ventricular arrhythmia, such as Tp-e/QTc ratio, Tp-e/QT ratio and Tp-e interval, which have been widely associated with sudden cardiac death in recent years, are prolonged in patients with ED. Considering the available studies, it can be concluded that patients with ED are at increased risk of ventricular arrhythmias. Analysis of these simple, easily measured ECG parameters can be used to classify ED patients without known arrhythmias as being at high risk for future development of ventricular arrhythmias. Our findings may encourage physicians to further consider ventricular arrhythmia screening in high-risk populations for ED.

Limitations

The primary limitation of the study is the small sample size. Another limitation is the study method used for ED diagnosis. The IIEF-5, a subjective questionnaire, was used in the study, whereas using a more objective tool such as penile Doppler USG would have been a better alternative. Additional tests such as exercise stress testing, myocardial perfusion scintigraphy, or coronary computed tomography were not performed to exclude suspected coronary artery disease in the included patient/control group. We believe that larger studies with objective criteria will shed light on this study and support its findings.

CONCLUSION

Our findings suggest that Tp-e/QTc ratio, Tp-e/QT ratio and Tp-e interval, which can be obtained by ECG, which is a cheap and repeatable test that can be found in almost all health institutions, can provide information about cardiac arrhythmia risk in ED patients at earlier periods. Larger sample and long-term follow-up studies are needed to observe the clinical consequences of these findings and perhaps reach an earlier medical treatment decision.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approval for this study was obtained from the Erciyes University Clinical Researches Ethics Committee (Date: 16.12.2020, Decision No: 2020/634).

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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Can red cell distribution width (RDW) and immature granulocyte parameters predict mortality in patients with pleural effusion?

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Cite this article as: Dal İ, Gülten S. Can red cell distribution width (RDW) and immature granulocyte parameters predict mortality in patients with pleural effusion? *J Med Palliat Care.* 2025;6(4):428-433.

Received: 28.07.2025

Accepted: 20.08.2025

Published: 31.08.2025

ABSTRACT

Aims: Pleural effusion is a frequent clinical manifestation with variable etiologies and prognoses. Identifying reliable, accessible prognostic biomarkers is critical for early risk stratification. This study aimed to assess the prognostic significance of red cell distribution width (RDW) and immature granulocyte (IG) parameters in predicting in-hospital mortality in patients with pleural effusion.

Methods: A retrospective analysis was conducted on 107 adult patients who underwent diagnostic thoracentesis. Hematologic data including RDW-CV, RDW-SD, IG percentage (IG%), and IG absolute count (IG#) were obtained within 24 hours of thoracentesis. Patients were categorized based on in-hospital survival status. Receiver operating characteristic (ROC) analysis was used to evaluate the predictive performance of these parameters.

Results: In-hospital mortality occurred in 21.5% of patients. Non-survivors exhibited significantly higher RDW-CV, RDW-SD, IG%, and IG# values ($p < 0.001$ for all). RDW-CV demonstrated the highest prognostic accuracy (AUC=0.793), with an optimal cut-off value of 16.1% (sensitivity: 70.2%, specificity: 82.6%). RDW-SD showed an AUC of 0.782, with a cut-off of 55.8 fL (sensitivity: 88.1%, specificity: 60.9%). Among IG parameters, IG% (AUC=0.770) had a cut-off of 1.1% (sensitivity: 81.0%, specificity: 65.2%) and IG# (AUC=0.752) had a cut-off of $0.055 \times 10^3/\mu\text{L}$ (sensitivity: 61.9%, specificity: 87.0%).

Conclusion: Elevated RDW and IG parameters independently predict in-hospital mortality in patients with pleural effusion. These readily available and cost-effective markers may serve as valuable tools for early prognostic assessment, particularly in settings where advanced diagnostic resources are limited.

Keywords: Pleural effusion, red cell distribution width, immature granulocytes, prognostic biomarkers, in-hospital mortality, hematologic indices

INTRODUCTION

Pleural effusion is a common clinical manifestation of various diseases, including heart failure, infections, and malignancies, and poses significant diagnostic and prognostic challenges in daily practice.¹ While thoracentesis with biochemical and cytological analysis remains the cornerstone of initial evaluation, its diagnostic sensitivity, particularly in malignant pleural effusions (MPEs), is limited.^{2,3} Advanced imaging, thoracoscopy, and biomarker analysis have been proposed to improve diagnostic yield, but these are often invasive, resource-intensive, or unavailable in many healthcare settings.⁴

To address these limitations, attention has increasingly shifted toward peripheral blood-based biomarkers, which offer simplicity, accessibility, and potential for early risk stratification.^{5,6} Numerous hematologic indices derived from complete blood count (CBC) parameters—such as

the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and red cell distribution width (RDW)—have been studied in recent years for their diagnostic and prognostic relevance in malignant and inflammatory diseases.⁷⁻⁹ RDW, in particular, reflects the heterogeneity of erythrocyte size and has been linked to poor outcomes in cancer, cardiovascular disease, and sepsis.^{10,11} Its elevation is thought to represent ineffective erythropoiesis, chronic inflammation, or oxidative stress, all of which are common in advanced malignancies.¹¹

In addition to red blood cell indices, IGs have garnered interest as emerging biomarkers of systemic inflammation and stress-induced myelopoiesis.¹² IGs—including promyelocytes, myelocytes, and metamyelocytes—are typically absent in healthy individuals but may appear in peripheral blood during acute infections, sepsis, or malignant infiltration.¹² Recent

studies have demonstrated the diagnostic and prognostic value of IG counts in sepsis, respiratory failure, and cancer-related complications.^{13,14}

Despite these promising findings, few studies have explored the combined prognostic utility of RDW and IG parameters in patients with pleural effusion. Given their availability through routine automated hematology analyzers, these indices may offer non-invasive tools for early mortality prediction and clinical risk stratification. Moreover, understanding their performance in distinguishing benign from malignant effusions and their relationship with clinical outcomes could provide valuable insights for decision-making in pleural disease management.

Pleural effusion carries heterogeneous prognoses, and cytology has limited sensitivity; therefore, accessible blood-based markers that reflect systemic inflammation and disordered erythropoiesis could aid early risk stratification.¹⁴ RDW captures anisocytosis and inflammatory stress, while IG indices reflect stress-induced myelopoiesis; both have been linked to adverse outcomes across malignant and inflammatory conditions.

We hypothesized that higher baseline RDW (RDW-CV, RDW-SD) and IG parameters (IG% and IG#) are independently associated with in-hospital mortality among patients with pleural effusion. To test this hypothesis, we evaluated the prognostic performance of RDW and IG indices for predicting in-hospital mortality in pleural effusion.

METHODS

Ethics

This was a retrospective observational study conducted at a tertiary university hospital between January 1, 2022, and December 31, 2023. The study has been approved by the Kastamonu University Clinical Researches Ethics Committee (Date: 14.12.2022, Decision No: 2022-KAEK-117) and was conducted in accordance with the principles of the Declaration of Helsinki.

Study Population

Adult patients (≥ 18 years) who underwent diagnostic thoracentesis for pleural effusion during the study period were screened. Inclusion criteria were: (1) availability of CBC results including IG parameters obtained within 24 hours of thoracentesis; and (2) definitive diagnostic classification of the pleural effusion as benign, malignant, or cytologically suspicious, based on cytological or histopathological findings.

Exclusion criteria included: (1) hematologic malignancy involving the bone marrow; (2) systemic infection at the time of sampling; and (3) incomplete clinical or laboratory data. No patients were excluded due to recent chemotherapy or radiotherapy, as no such cases were identified in the study cohort.

Patients were categorized into survivor and non-survivor groups based on in-hospital mortality, defined as death occurring during the index hospitalization in which thoracentesis was performed.

A total of 214 patients who underwent evaluation for pleural effusion between January 2022 and December 2023 were initially screened. After excluding 65 patients with incomplete outcome data, 24 patients with active systemic infection, 13 patients with missing CBC or IG measurements, and 5 patients with hematologic malignancies, a total of 107 patients met the eligibility criteria and were included in the final analysis. The patient selection process is summarized in [Figure 1](#).

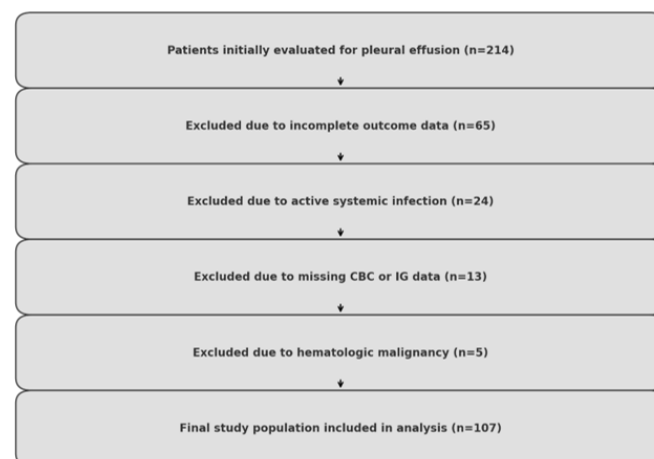


Figure 1. Patient flow diagram demonstrating inclusion and exclusion criteria diagnostic classification

Patients were followed from the time of admission until discharge or in-hospital death. No post-discharge follow-up was included in this study.

Malignant pleural effusion (MPE) was defined as the presence of malignant cells in pleural fluid cytology and/or histological confirmation of malignancy via pleural biopsy. Benign pleural effusions (BPE) were diagnosed based on negative cytology/histology and corroborative clinical or microbiological evidence (e.g., heart failure, parapneumonic effusion, or tuberculosis). Cases with non-diagnostic or inconclusive pathology results and those with insufficient follow-up were excluded from the study. However, cases that were cytologically categorized as suspicious for malignancy were included in the analysis.

Data Collection

Demographic and clinical variables (age, sex, comorbidities, and etiology of effusion) were extracted from the hospital's electronic medical records. Laboratory data were collected from blood samples obtained on the same day as thoracentesis. Parameters of interest included:

CBC with automated differential, including: white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin (HGB), hematocrit (HCT), red cell distribution width (RDW-CV and RDW-SD), platelet count (PLT), and indices such as mean platelet volume (MPV), plateletcrit (PCT), neutrophil and lymphocyte percentages, and derived ratios (NLR, PLR, SII, and PANS).

IG percentage and absolute count, obtained using the Sysmex XN-Series automated hematology analyzers via fluorescence flow cytometry.

Pleural fluid cytology results were used as the diagnostic reference standard.

All blood samples were processed within two hours of collection to ensure measurement accuracy.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Normality of distribution was assessed using the Kolmogorov–Smirnov test. Continuous variables were reported as median and interquartile range (IQR), and compared using the Mann–Whitney U test. Categorical variables were expressed as counts and percentages, and compared using Pearson’s Chi-square test or Fisher’s exact test, where appropriate.

To assess the prognostic performance of selected hematologic parameters in predicting in-hospital mortality, receiver operating characteristic (ROC) curve analysis was performed. Area under the curve (AUC) values were calculated along with optimal cut-off values determined using Youden’s index. Sensitivity, specificity, and 95% confidence intervals were reported for each variable. A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

A total of 107 patients who underwent pleural fluid analysis were included in the study, of whom 84 survived and 23 died during the follow-up period. There were no statistically significant differences in age or sex distribution between the survivor and in-hospital mortality groups. The median age was 81.0 (IQR: 73.25–86.00) years in survivors and 82.0 (IQR: 77.00–88.00) years in those who died (p=0.436). Although the proportion of males was higher among survivors, and females predominated in the in-hospital mortality group, this difference did not reach statistical significance (p=0.114). Pathological classification of pleural effusions revealed a higher frequency of malignant and suspicious cases in the in-hospital mortality group; however, this difference was also not statistically significant (p=0.094) (Table 1).

Table 1. Demographic and pathological characteristics of the study population			
Variable	Survivors (n=84)	In-hospital mortality (n=23)	p value
Age, median (IQR)	81.00 (73.25–86.00)	82.00 (77.00–88.00)	0.436
Gender			
Male, %	26 (30.9)	3 (13)	0.114
Female, %	58 (69.1)	20 (87)	
Pathology			
Malign, %	10 (11.9)	3 (13)	0.094
Benign, %	71 (84.5)	16 (69.6)	
Suspicious, %	3 (3.6)	4 (17.4)	
IQR: Inter quartile range			

Hematological parameters obtained at the time of pleural fluid sampling revealed several significant differences between the groups. RBC count, HGB, and HCT levels were significantly lower in the in-hospital mortality group compared to

survivors (p=0.011, p=0.025, and p=0.030, respectively), indicating a greater degree of anemia in non-survivors. Platelet counts were also significantly lower in the in-hospital mortality group (p=0.014). Notably, both RDW-SD (fL) and RDW-CV (%), markers of RBC distribution variability, were significantly elevated in patients who died (p<0.001 for both).

Markers of bone marrow activation and inflammation, particularly those related to IGs, showed strong discriminatory potential. IG# ($\times 10^3/\mu\text{L}$) and IG% (%) were significantly higher in the in-hospital mortality group (median IG#: 0.14 vs. $0.04 \times 10^3/\mu\text{L}$; IG%: 1.60 vs. 0.50 %), with both parameters reaching high levels of statistical significance (p<0.001). Lymphocyte percentage (LYMPH%, %) was significantly reduced in the in-hospital mortality group (p=0.019), while NLR and macrocytic red cell percentage (MacroR, %) were elevated (p=0.022 and p=0.031, respectively). Other derived inflammatory indices such as PLR, SII, and PANS did not differ significantly between groups (Table 2).

ROC curve analysis was performed to assess the diagnostic performance of selected hematological parameters in predicting mortality. RDW-CV demonstrated the highest diagnostic accuracy, with an AUC of 0.793 (95% CI: 0.706–0.880; p<0.001), followed closely by RDW-SD (AUC=0.782; 95% CI: 0.678–0.887; p<0.001). Among the IG indices, IG% (%) yielded an AUC of 0.770 (95% CI: 0.666–0.875), and IG# ($\times 10^3/\mu\text{L}$) an AUC of 0.752 (95% CI: 0.646–0.857), both statistically significant (p<0.001), indicating moderate to good discriminatory ability (Table 3, Figure 2).

Corresponding optimal cut-off values derived from the ROC analysis were 55.8 fL for RDW-SD (sensitivity: 88.1%, specificity: 60.9%), 16.1% for RDW-CV (sensitivity: 70.2%, specificity: 82.6%), $0.055 \times 10^3/\mu\text{L}$ for IG# (sensitivity: 61.9%, specificity: 87.0%), and 1.1% for IG% (sensitivity: 81.0%, specificity: 65.2%).

We compared RDW and IG indices between benign (n=87) and malignant (n=13) pleural effusion groups. The mean RDW-SD values were 50.4 ± 8.9 fL in the benign group and 50.5 ± 12.8 fL in the malignant group (p=0.619). RDW-CV values were $16.0 \pm 1.3\%$ vs. $16.3 \pm 1.5\%$ (p=0.535). IG# levels were $0.09 \pm 0.17 \times 10^3/\mu\text{L}$ vs. $0.11 \pm 0.41 \times 10^3/\mu\text{L}$ (p=0.707), and IG% values were $1.1 \pm 1.3\%$ vs. $4.2 \pm 12.6\%$ (p=0.596) in benign and malignant groups, respectively. None of these differences reached statistical significance.

DISCUSSION

This study investigated the prognostic significance of RDW indices and IG parameters in patients with pleural effusion. The results demonstrated that elevated RDW-CV, RDW-SD, IG percentage, and IG absolute count were significantly associated with mortality. These findings suggest that simple hematological parameters, routinely obtained in clinical practice, may offer valuable prognostic information in pleural effusion evaluation.

The observed in-hospital mortality rate of 21.5% in our cohort appears relatively high compared to some prior reports. However, this finding may be explained by the advanced median age (81 years), the high proportion of malignant or

Table 2. Comparison of hematological parameters between survivors and in-hospital mortality groups

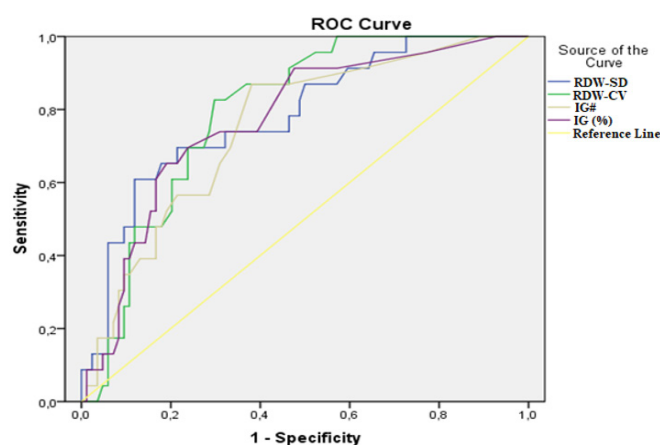
Parameter	Survivors (n=84)	In-hospital mortality (n=23)	p-value
WBC ($\times 10^3/\mu\text{L}$)	8.61 (6.76–11.87)	9.39 (6.54–11.67)	0.441
RBC ($\times 10^6/\mu\text{L}$)	4.21 (3.64–4.77)	3.91 (2.96–4.30)	0.011
HGB (g/dl)	11.10 (10.12–13.00)	10.10 (8.90–11.50)	0.025
HCT (%)	35.75 (31.85–40.77)	32.60 (26.70–36.70)	0.030
MCV (fL)	85.95 (81.00–89.97)	89.90 (82.30–94.50)	0.114
MCH (pg)	27.65 (26.12–29.45)	28.00 (26.70–29.40)	0.313
MCHC (g/dl)	32.30 (31.10–33.10)	31.50 (30.60–32.70)	0.271
PLT ($\times 10^3/\mu\text{L}$)	250.00 (175.75–302.00)	139.00 (121.00–282.00)	0.014
RDW-SD (fL)	47.15 (43.12–51.88)	57.60 (48.30–63.10)	<0.001
RDW-CV (%)	15.20 (13.75–16.48)	17.20 (16.20–19.60)	<0.001
PDW (%)	10.90 (9.50–12.60)	11.45 (10.33–12.85)	0.319
MPV (fL)	9.90 (9.40–10.60)	10.40 (9.50–10.97)	0.257
P_LCR (%)	24.50 (19.70–30.50)	28.45 (20.70–33.17)	0.248
PCT (%)	0.25 (0.19–0.30)	0.18 (0.14–0.30)	0.065
NRBC# ($\times 10^3/\mu\text{L}$)	0.00 (0.00–0.00)	0.00 (0.00–0.03)	<0.001
NRBC (%)	0.00 (0.00–0.00)	0.00 (0.00–0.30)	<0.001
NEUT# ($\times 10^3/\mu\text{L}$)	6.28 (4.89–8.79)	7.52 (4.80–9.49)	0.349
LYMPH# ($\times 10^3/\mu\text{L}$)	1.04 (0.75–1.47)	1.00 (0.55–1.32)	0.237
MONO# ($\times 10^3/\mu\text{L}$)	0.68 (0.50–0.88)	0.80 (0.51–0.99)	0.183
EO# ($\times 10^3/\mu\text{L}$)	0.07 (0.02–0.15)	0.03 (0.00–0.17)	0.162
BASO# ($\times 10^3/\mu\text{L}$)	0.04 (0.02–0.05)	0.04 (0.02–0.05)	0.727
NEUT (%)	75.55 (69.22–83.23)	80.40 (74.10–88.40)	0.091
LYMPH (%)	13.55 (8.70–17.30)	9.70 (5.60–14.10)	0.019
MONO (%)	7.90 (6.05–9.97)	8.30 (4.80–11.80)	0.847
EO (%)	0.95 (0.10–1.98)	0.30 (0.00–1.40)	0.072
BASO (%)	0.40 (0.30–0.70)	0.30 (0.20–0.60)	0.227
IG# ($\times 10^3/\mu\text{L}$)	0.04 (0.03–0.12)	0.14 (0.06–0.29)	<0.001
IG (%)	0.50 (0.40–0.90)	1.60 (0.60–3.10)	<0.001
MicroR (%)	3.90 (2.20–8.50)	4.50 (2.80–7.10)	0.590
MacroR (%)	3.80 (3.40–4.20)	4.50 (3.50–7.70)	0.031
NLR	6.00 (4.00–9.75)	8.00 (6.00–16.00)	0.022
PLR	215.50 (161.00–363.00)	195.00 (111.00–279.00)	0.167
SII	1289.50 (796.75–2727.00)	1483.00 (642.00–2543.00)	0.964
PANS	798.50 (495.25–1800.00)	1215.00 (673.00–1443.00)	0.288

Data are presented as median (IQR). WBC: White blood cell, RBC: Red blood cell, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, PLT: Platelet count, RDW-SD: Red cell distribution width-standard deviation, RDW-CV: Red cell distribution width-coefficient of variation, PDW: Platelet distribution width, MPV: Mean platelet volume, P_LCR: Platelet large cell ratio, PCT: Plateletcrit, NRBC#: Nucleated red blood cell count, NRBC: Nucleated red blood cell percentage, NEUT#: Neutrophil count (absolute), LYMPH#: Lymphocyte count (absolute), MONO#: Monocyte count (absolute), EO#: Eosinophil count (absolute), BASO#: Basophil count (absolute), NEUT: Neutrophil percentage, LYMPH: Lymphocyte percentage, MONO: Monocyte percentage, EO: Eosinophil percentage, BASO: Basophil percentage, IG#: Immature granulocyte count, IG: Immature granulocyte percentage, MicroR: Microcytic red cells, MacroR: Macrocytic red cells, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, PANS: Platelet $\times$ neutrophil/lymphocyte score

Table 3. Diagnostic performance of selected hematological parameters based on ROC curve analysis

Test result variable(s)	AUC	Std. error	Asymptotic Sig.b	Asymptotic 95% CI	
				Lower bound	Upper bound
RDW-SD (fL)	0.782	0.053	<0.001	0.678	0.887
RDW-CV (%)	0.793	0.044	<0.001	0.706	0.880
IG# ($\times 10^3/\mu\text{L}$)	0.752	0.054	<0.001	0.646	0.857
IG (%)	0.770	0.053	<0.001	0.666	0.875

ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval, RDW-SD: Red cell distribution width-standard deviation, RDW-CV: Red cell distribution width-coefficient of variation, IG#: Immature granulocyte count, IG: Immature granulocyte percentage

**Figure 2.** Receiver operating characteristic (ROC) curves of RDW and immature granulocyte parameters for predicting in-hospital mortality
ROC: Receiver operating characteristic, RDW-SD: Red cell distribution width-standard deviation, RDW-CV: Red cell distribution width-coefficient of variation, IG#: Immature granulocyte count, IG: Immature granulocyte percentage

cytologically suspicious effusions, and the likely presence of multiple comorbid conditions. Previous studies have reported short-term mortality rates ranging from 8% to 20% in similar high-risk populations, suggesting that our findings, while elevated, remain within a plausible clinical spectrum.

Pleural effusion is a common clinical condition with a wide range of underlying etiologies, including infections, heart failure, and malignancies.^{15,16} Differentiating MPE from benign causes remains a diagnostic challenge, particularly given the limitations of cytology, which has suboptimal sensitivity in many cases.³ While imaging and thoracoscopy can improve diagnostic yield, they are not always feasible or available, particularly in resource-limited settings.¹⁷ Therefore, accessible and non-invasive biomarkers are increasingly sought to support clinical decision-making.

In this context, RDW has emerged as a potentially informative marker of both inflammatory activity and disordered erythropoiesis.^{18,19} Our findings reinforce its clinical value: both RDW-CV and RDW-SD were significantly higher in the in-hospital mortality group, with RDW-CV showing the highest area under the ROC curve (AUC=0.793). At the optimal cut-off of 16.1%, RDW-CV yielded a sensitivity of 70.2% and a specificity of 82.6%, highlighting its strong discriminatory performance. Similarly, RDW-SD demonstrated an AUC of

0.782, with a sensitivity of 88.1% and specificity of 60.9% at a cut-off of 55.8 fL. These values are consistent with previous studies indicating that elevated RDW reflects chronic inflammation, oxidative stress, and poor clinical outcomes in malignancy and other systemic illnesses.²⁰

Alongside RDW, IGs have gained attention as indicators of bone marrow activation and systemic inflammation.²¹ IGs, including promyelocytes, myelocytes, and metamyelocytes, are typically absent in the peripheral blood of healthy individuals but appear in various pathologic states, including infections, sepsis, and cancer.^{12,14,22} In our study, both IG% and IG# were significantly elevated in the non-survivor group, with AUCs of 0.770 and 0.752, respectively. At a cut-off of 1.1%, IG% showed a sensitivity of 81.0% and specificity of 65.2%, while IG# at a threshold of $0.055 \times 10^3/\mu\text{L}$ had a specificity of 87.0% and sensitivity of 61.9%. These results align with emerging literature highlighting the prognostic relevance of IGs in inflammatory and oncologic conditions.

The prognostic utility of IGs may also reflect the immunological landscape of pleural malignancies. IGs are phenotypically similar to myeloid-derived suppressor cells (MDSCs), which are known to accumulate in malignant effusions and contribute to immune evasion and tumor progression.^{23,24} Thus, elevated IG levels may signal a suppressed immune microenvironment, supporting their role as indirect markers of malignancy and poor outcome.

Other inflammatory indices such as the NLR and macrocytic red cells (MacroR) were also significantly associated with mortality, consistent with prior studies that link these markers to systemic inflammation and impaired hematopoiesis.^{25,26} However, platelet-related indices like PLR, SII, and PANS did not show significant prognostic value in this cohort, possibly due to underlying variability in platelet counts from non-malignant causes.

Regarding clinical applicability, our findings suggest that hematological parameters such as RDW and IG indices should be interpreted as risk indicators rather than absolute triggers for specific interventions. For instance, an RDW-CV value above the identified cut-off of 16.1% was associated with significantly increased mortality risk in our cohort. However, this does not directly translate into a recommendation for ICU admission in isolation. Instead, such results may warrant closer clinical monitoring, early identification of deterioration, and integration into comprehensive risk assessment alongside other clinical and laboratory findings. These markers therefore provide a practical, cost-effective adjunct to guide clinical decision-making, especially in settings where advanced diagnostic modalities are not readily available.

This study has notable strengths, including its pathology-confirmed diagnoses, the use of widely available hematological parameters, and the dual focus on both diagnostic and prognostic implications. However, it is limited by its retrospective design and modest sample size. Prospective multicenter studies are needed to validate these findings and determine whether integration of RDW and IG parameters into clinical risk models can improve patient stratification and management.

CONCLUSION

The present study highlights that readily available hematological parameters, particularly RDW and IG indices, serve as significant predictors of in-hospital mortality in patients with pleural effusion. Their combined use may offer a practical, cost-effective approach to enhance clinical assessment, guide further diagnostic evaluation, and inform prognosis, especially in resource-limited settings.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study has been approved by the Kastamonu University Clinical Researches Ethics Committee (Date: 14.12.2022, Decision No: 2022-KAEK-117).

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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The use of virtual reality in clinical skills training for nursing students

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Received: 12.07.2025

Accepted: 26.07.2025

Published: 31.08.2025

ABSTRACT

This review examines the contributions of virtual reality technology to clinical skills training in nursing students. Virtual reality allows students to safely develop psychomotor and cognitive skills by providing three-dimensional and interactive learning environments. The literature shows that virtual reality supported education increases learning motivation, reduces anxiety about making mistakes and improves practical skills. It is also important in terms of providing reproducible experience without compromising patient safety. In this context, the review aims to evaluate the role of virtual reality in gaining clinical skills as an innovative and effective method in nursing education.

Keywords: Nursing, clinical skills, nurse education, virtual reality

INTRODUCTION

Today's health systems are changing with technological developments. As a matter of fact, this change is also effective in the education process of health professionals.¹ Especially nursing education includes a complex and challenging learning process in which theoretical knowledge and clinical practice are integrated. In this process, the ability of students to acquire clinical skills in a safe, effective and ethical manner is directly related to the quality of educational environments.² However, many difficulties such as patient safety, student anxiety, lack of guidance and limitations of practice environments may prevent nursing students from gaining sufficient experience in clinical practice.³

In this context, innovations in information technologies have brought the use of alternative and complementary methods in nursing education. Virtual reality technology, which has been increasingly used in recent years, offers realistic and interactive learning environments that allow students to experience complex clinical situations. Virtual reality provides the user with a sense of presence in a three-dimensional environment, enabling the application of clinical skills in a risk-free and reproducible manner; thus, it both strengthens the learning process and increases student safety.⁴

In this review study, the integration of virtual reality technology into nursing education and especially its role in gaining clinical skills will be discussed. The aim was to present innovative and evidence-based recommendations to improve the quality of health education by revealing the

potential of virtual reality-based educational applications for nursing students.

VIRTUAL REALITY

Virtual reality is a computer-based technology that allows users to feel as if they are physically present in a three-dimensional, interactive environment.⁵ During a virtual reality experience, users are usually required to wear a half-helmet-like head-mounted display connected to a computer interface. With the incorporation of tracking software and haptic or touch control technologies, users can navigate a computer-aided three-dimensional environment designed to be responsive to head movements.⁶

In the definition of hardware-based virtual reality, two basic psychological concepts come to the fore: our mental perception and the body. While our mental perception is shaped by our cognition and senses related to the environment, the body as a part of perception takes part in the representation of the mind. It is suggested that these sensory processes, providing synchronized sensory stimulation in a three-dimensional environment and tracking body movements with sufficient degrees of freedom are based on two interconnected hardware capabilities.⁷

For a sensory stimulation to be effective in virtual reality, the virtual reality hardware should be capable of blocking visual stimuli in the physical environment. This enhances the virtual reality experience by reducing distractions and is a key differentiator that distinguishes the technology from

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television, computers or augmented reality. Virtual reality's ability to neutralize visual stimuli should work consistently and synchronously with synchronized sensory stimulation and motion support.^{8,9}

In virtual reality applications, various technological components are utilized to increase the interaction and perceptual experience of users with the virtual environment. These components include interactive 360-degree content systems that allow virtual elements to be viewed in all aspect,¹⁰ virtual reality glasses, which are imaging devices worn on the head or integrated into the helmet,¹¹ joysticks that enable users to move in the environment and interact with objects, body tracking systems that enable the representation of the individual's own body in the virtual environment, and virtual reality gloves that enable natural interaction by sensing hand movements precisely.¹²

When the literature is examined, it is seen that the usage areas of virtual reality technology spread over a wide range. This technology is effectively used in various fields ranging from supporting the personal skills of individuals with balance disorders and autism spectrum disorders, training military personnel, visualizing the interior and exterior designs of architectural structures, treating phobias, and supporting the development of emotion and empathy. In addition, there are many application areas such as reinforcing surgical practices in the field of medicine and training new surgeons, providing experiential learning in the tourism sector and educational environments.¹³

VIRTUAL REALITY AND EDUCATION

Unlike other learning digital learning platforms, virtual reality is a unique method in that it offers an immersion that enhances the sense of presence through realistic experiences, allows the user to interact with the environment to change location and pick up or manipulate objects, and provides multi-sensory feedback: visual, auditory and tactile.¹⁴ Virtual reality is a particularly effective method for developing creativity. It engages users in multi-sensory experiences, tangible and three-dimensional spatial cognition, allowing them to expand their perspectives and generate new ideas.¹⁵

Virtual reality can be particularly useful for individuals who can mentally visualize objects, shapes, and relationships in space¹⁶ or for those who learn more effectively through hands-on activities.¹⁷ From a broader perspective, it is argued that the discovery-based and curiosity-inducing structure of virtual reality makes significant contributions to the learning process and allows individuals to feel freer in processes such as generating ideas, research and evaluation.¹⁸

Compared to traditional training methods, virtual simulation-based training offers significant advantages such as time savings, safety, cost-effectiveness and efficiency in training, as they can be completed in less time.¹⁹ Recent developments in motivation theory suggest that understanding how to harness the affective effectiveness of e-learning tools such as virtual reality is a central issue for learning and teaching.²⁰ The cognitive and affective theory of learning with media emphasizes that learning is not only a cognitive but also

an affective process.²¹ A student's emotional response to the learning process can have a great impact on academic achievement. Two key features are important in instructional design. One is to give students a sense of autonomy and the other is to evoke a sense of intrinsic value for the learning task and content.²² Integrating these two features into instructional design can help reduce negative emotions such as anger and frustration in students, while increasing motivation and enjoyment of the learning process. In particular, virtual reality is suitable for creating educational models in accordance with cognitive and affective theory.²³

IMPORTANCE OF NURSING EDUCATION

Nursing is one of the most versatile professions in the health care workforce. Since Florence Nightingale developed and put into practice the concept of educated nursing, the nursing profession has continuously restructured itself with the transformations in the health system.²⁴ Nursing education is of strategic importance not only to support individual professional development but also to protect public health, ensure patient safety and contribute to the sustainability of the health system. A qualified nursing education ensures the acquisition of basic professional competencies such as critical thinking, clinical decision making, ethical sensitivity and communication skills.²⁵ The International Council of Nurses emphasizes that nursing education plays a critical role in providing up-to-date knowledge, leadership skills and the ability to deal with emergencies.²⁶ Similarly, Jefferies et al.²⁷ draw attention to the decisive role of higher education standards in nursing education by revealing that academic literacy, critical thinking and clinical competence are directly related to professional practices. In this context, nursing education directly affects the quality and effectiveness of health services not only at the individual but also at the societal level.

CLINICAL SKILLS TRAINING IN NURSING EDUCATION

Clinical skills are difficult to be acquired by students as they consist of components of psychomotor, cognitive and affective learning domains.²⁸ Therefore, clinical skills acquisition is a complex process that requires students to integrate knowledge and critical thinking skills with practical performance. In addition to practicing in both hospitals and home care facilities, clinical skills laboratories are one of the most commonly used settings for developing nursing students' clinical skills.²⁹

Nursing education requires comprehensive preparation and training for nursing students to gain proficiency in specific clinical skills in clinical settings. Although lecture and demonstration methods are traditionally used to teach clinical nursing skills, these methods do not always meet learning needs and therefore may be inadequate.³⁰ With the development of multimedia technology, technological developments such as computer-assisted learning,³¹ video-assisted learning,³² simulation,³³ augmented³⁴ support the efficiency and effectiveness of clinical skills training.

Clinical practice is a fundamental and indispensable component of nursing education. However, especially in the first clinical experiences, factors such as the intensity of the practice areas, students' sense of inadequacy, fear of making mistakes or harming the patient, and the imbalance in the student/faculty ratio increase the level of anxiety in students. This anxiety may cause students to be unable to adequately reflect their knowledge and skills to real patient care.³⁵ In addition, the direct application of some interventions that violate bodily integrity on the patient carries serious risks in terms of patient privacy and safety. Therefore, making sure that students act by respecting patient rights and values during clinical practice is of great importance in terms of providing safe care. In line with all these reasons, the use of skills laboratories in the development of clinical skills of nursing students is becoming increasingly important. Inadequate planning of clinical education in clinical skills training, organizational problems, inappropriate assessment methods, unsupportive learning environment, inadequate clinical guidance and difficulties in transferring theoretical knowledge to practice are among the main obstacles that negatively affect the clinical learning process.³⁶

CLINICAL SKILLS TRAINING IN NURSING AND VIRTUAL REALITY

Rapid developments in information technologies, especially with innovations such as virtual reality, bring a different pedagogical perspective to nursing education. This technology provides nursing students with hands-on learning opportunities by offering interactive and realistic clinical scenarios, while eliminating the need for direct patient participation. Thus, it not only allows clinical nurses to use their time efficiently, but also reduces the challenges associated with traditional patient-based education.³⁷

This technology allows students to practice their clinical skills, improve their decision-making in simulated patient care scenarios, and explore different medical conditions. Virtual reality encourages the active participation of nursing students in realistic and interactive learning processes, enabling them to better grasp theoretical knowledge and receive hands-on training in a safe, controlled environment. Moreover, the interactive nature of virtual reality enriches students' intuitive and experience-based learning processes by supporting traditional didactic methods.³⁸

A good learning process requires a sense of security.³⁹ Providing feedback on a completed clinical practice is not only a technical process but also an advanced competence that requires an understanding of the complexity behind the practice and skill. Showed that the feedback process enhances learning in both givers and receivers. Effective feedback allows for critical evaluation and integration of theory and practice.⁴⁰

Research shows that virtual simulation in nursing education and clinical practice can be similarly effective to traditional simulation methods, and in some cases even superior.⁴¹⁻⁴³ This technology allows participants to practice repeatedly in a safe and supervised environment by realistically simulating complex medical procedures and nursing

scenarios, thus contributing to the development of their clinical skills, decision-making abilities and critical thinking capacities.⁴⁴ Among the positive functions of virtual reality is the development of clinical reasoning. Levett-Jones et al.⁴⁵ conceptualized clinical reasoning as a process in which a person collects clues, processes information, identifies the problem, plans and performs actions, evaluates the results, and reflects on and learns from the process. The nursing process includes clinical reasoning stages. This cognitive and meta-cognitive process, which involves synthesizing information and patient data related to specific clinical situations, plays a critical role for nurses to respond appropriately to clinical changes and make effective care management decisions. Therefore, it is of great importance to improve the clinical reasoning skills of both nursing students and clinical practitioner nurses so that they can make evidence-based decisions by making correct inferences and provide safe, quality care.⁴⁶ Virtual simulation is an application-based teaching method that aims to improve learners' clinical decision-making skills to diagnose patient problems and their performance in outcome-oriented care management through clinical scenarios that are structured based on explicit learning objectives, reproducible and adaptable to individual needs. Virtual reality supports repetitive and deliberate practice in a safe environment with scenarios that can be adapted according to the level of complexity.⁴⁷ These scenarios offer expert rationales and feedback that facilitate the development of clinical reasoning. The structure of the virtual simulation is in line with best practices for healthcare simulation and experiential learning theory. Learners gain experience through active participation, make sense of these experiences through feedback, and integrate the acquired knowledge into their cognitive structures for use in real clinical settings.⁴⁸ In a meta-analysis of twelve randomized controlled trials (RCTs), virtual reality applications were found to be effective in improving clinical reasoning skills in nursing. It has been stated that the design features of virtual reality simulations include structured content for patient management, systematic implementation of various clinical scenarios, experience durations of more than 30 minutes, and structured feedback processes after the scenario is completed. It is emphasized that these design elements can significantly increase the effectiveness of virtual reality-based simulations in education.⁴⁹ In one of the studies on virtual reality-supported nursing education, it was determined that the simulation-based training program conducted with the participation of 90 nurses had a significant effect on nursing competence in isolation services.⁵⁰ In a systematic review of eight RCTs, it was revealed that virtual reality-based education provided significant improvement in nursing students' clinical skills, knowledge level, and perceptions of psychological and emotional safety.⁵¹ In a meta-analysis and meta-regression study in which 11 RCTs focusing on virtual reality training were examined, it was found that virtual reality applications significantly increased the clinical skills performance of nursing students with a medium-high level effect.⁵² In a systematic review and meta-analysis of 22 studies examining virtual reality simulations for nursing students, it was determined that virtual reality-based training significantly

increased nursing competence.⁵³ In a study conducted with a quasi-experimental design and involving 76 second-year nursing students, students performed basic clinical skills such as intravenous catheter application, nasogastric feeding and nelaton catheterization on a virtual reality-based platform; a significant performance increase was observed especially in nasogastric feeding and nelaton catheterization applications.⁵⁴ In a randomized controlled study examining the effect of virtual reality-based learning tool on nursing students' thorax and lung physical examination knowledge and skills with 80 student participation, virtual reality was found to be effective in skill development.⁵⁵

CONCLUSION

It shows that virtual reality supported education programs are effective in improving the clinical skills of nursing students. The realistic and interactive environment provided by this technology enables students to safely practice complex health processes. In addition, virtual simulations strengthen the learning process by providing repetition and immediate feedback, thus increasing students' confidence in practice and decision-making competence. These results suggest that virtual reality technology has significant potential as a complementary and remedial tool to traditional methods in nursing education and contributes to the training of graduates who are more prepared for clinical practice. It is necessary to investigate the effect of hybrid approaches in which virtual reality is integrated with applied education. Therefore, it is important to consider the strengths and limitations of each technology and utilize best practices when integrating virtual reality with traditional educational methods. It should investigate how virtual reality can be integrated more effectively into the educational process and how innovation and progress can be achieved in nursing education.

ETHICAL DECLARATIONS

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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