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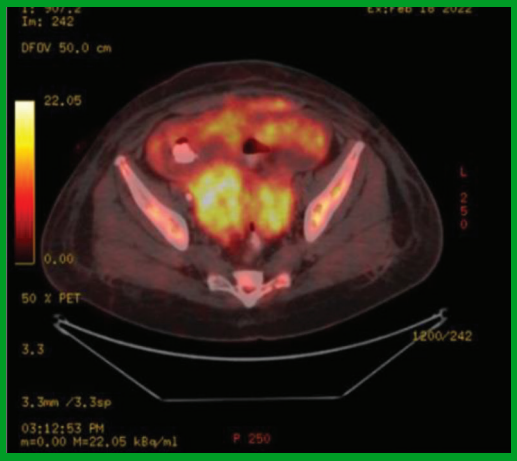

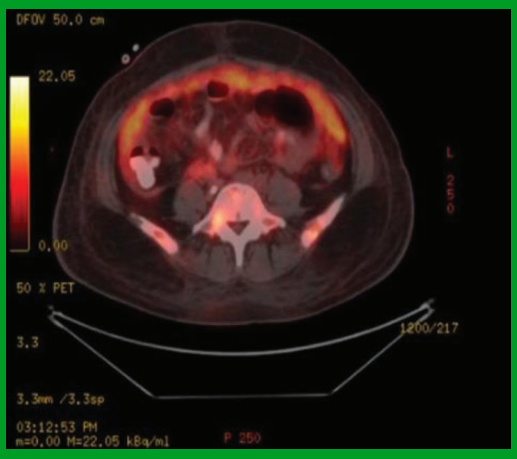

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EDITORIAL

Dear Readers;

We are back with the third issue of Bezmialem Science in 2025. This issue of our journal stands out with its structural innovations as much as its scientific content.

During this period, we have comprehensively updated our journal's editorial structure and scientific board. Our goal was to make the publication process more transparent, faster, and meet higher standards of academic quality. With our new team structure, we aim to conduct more rigorous peer-review processes thanks to the contributions of experienced scientists from diverse fields of expertise.

In this issue, we have featured articles that stand out for their latest and original content. Some of the key studies we have selected are:

- The study by **Şahin et al.**, "Atypic Primary Ovarian Lymphoma Presenting with Hypercalcemia: A Rare Case Report," is a rare case report that is important for clinical management.

  This article also inspired our cover image. This study, focusing on a case of diffuse large B-cell lymphoma (DLBCL) presenting with malignant hypercalcemia and bilateral ovarian involvement, is noteworthy for its diagnostic process and laboratory findings. This rare presentation is particularly important for shedding light on the mechanisms associated with hypercalcemia in various malignancies.

- The study by **Demirel et al.,** "Trends and Implications of Studies on Advanced Glycation End Products (AGEs) and Cancer: Bibliometric Analysis," presents important findings by examining the development of the scientific literature on the relationship between AGEs and cancer from a bibliometric perspective.

- The study by **Teoman and Ercin,** "Microsatellite Instability Status and Programmed Death Cell Ligand 1 Expression in Serous Ovarian Tumors," is also among our cover issues and is notable for its evaluation of current molecular parameters such as microsatellite instability and PD-L1 expression in serous ovarian tumors.

- The study by **Hösükler et al.,** "Evaluation of Injuries Due to Traffic Accidents with Trauma Scoring Systems," compared different scoring systems used in the evaluation of trauma cases. It stands out with its practical implications for emergency medicine and traumatology.

- The study by **Oba et al.,** "Nicotine Dependence Level and Sleep Quality in Patients Attending the Smoking Cessation Clinic," investigates the relationship between nicotine dependence level and sleep quality in individuals attending a smoking cessation clinic. It presents results that will guide clinical practice.

As Bezmialem Science, we are determinedly progressing towards our goal of becoming a scientific platform that grows stronger every day thanks to the contributions of you, our valued researchers. We would like to emphasize once again that every suggestion and contribution received by our new organization is valuable to us.

We hope that our new issue will inspire you scientifically and thank you for your contributions.

Stay with science,

Sincerely…

Prof. Dr. Adem AKÇAKAYA
Editor in Chief

Commentary

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The Role of Robotic Surgery in the Management of Hiatal Hernias

Hiatal Herni Ameliyatlarında Robotik Cerrahinin Yeri

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ABSTRACT

Robotic surgery (RS) has recently become an increasingly preferred minimally invasive approach for hiatal hernia repair. This commentary discusses the efficacy of RS compared to laparoscopic surgery (LS) in light of current meta-analyses and retrospective studies. RS offers technical advantages such as three-dimensional visualization, enhanced dexterity, and improved ergonomics, potentially providing superior precision for surgeons. Several studies have reported lower postoperative complication rates and, in some cases, shorter hospital stays in the RS group. However, operative times did not show a statistically significant difference between the two techniques. Large-scale meta-analyses indicated no clear clinical superiority of RS over LS, while costs associated with RS were significantly higher. Additionally, the retrospective nature of most studies and the heterogeneity in patient characteristics limit the generalizability of the findings. Despite its promising technical capabilities and increasing surgeon experience, further randomized controlled trials are necessary to establish the clinical benefits of RS. Nevertheless, RS represents a promising approach that may become more widely adopted in hiatal hernia surgery in the near future.

Keywords: Robotic surgery, hiatal hernia repair, laparoscopic surgery, minimally invasive techniques, postoperative outcomes

ÖZ

Robotik cerrahi (RC), son yıllarda hiatal herni onarımında giderek daha fazla tercih edilen minimal invaziv bir yöntem haline gelmiştir. Bu yorum yazısı, mevcut meta-analizler ve retrospektif çalışmalar ışığında RC'nin laparoskopik cerrahi (LC) ile karşılaştırmalı etkinliğini ele almaktadır. RC, cerrahlara daha üstün bir hassasiyet sunma potansiyeline sahip üç boyutlu görüntüleme, artırılmış el becerisi ve geliştirilmiş ergonomi gibi teknik avantajlar sağlamaktadır. Birçok çalışmada RC uygulanan hastalarda daha düşük postoperatif komplikasyon oranları ve bazı durumlarda daha kısa hastanede kalış süreleri bildirilmiştir. Ancak, her iki cerrahi teknik arasında operasyon süreleri açısından istatistiksel olarak anlamlı bir fark saptanmamıştır. Geniş ölçekli meta-analizler, RC'nin LC'ye karşı belirgin bir klinik üstünlüğünü göstermemekle birlikte, RC ile ilişkili maliyetlerin belirgin şekilde daha yüksek olduğunu ortaya koymuştur. Ayrıca, çalışmaların çoğunun retrospektif olması ve hasta özelliklerindeki heterojenlik, elde edilen bulguların genellenebilirliğini sınırlamaktadır. RC'nin umut vaat eden teknik yetkinlikleri ve cerrahların artan deneyimine rağmen, RC'nin klinik yararlarının net olarak ortaya konulabilmesi için daha fazla randomize kontrollü çalışmaya ihtiyaç duyulmaktadır. Bununla birlikte, RC hiatal herni cerrahisinde gelecekte daha yaygın olarak kullanılabilecek umut verici bir yaklaşım olarak değerlendirilmektedir.

Anahtar Kelimeler: Robotik cerrahi, hiatal herni onarımı, laparoskopik cerrahi, minimal invaziv teknikler, postoperatif sonuçlar

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Dear Readers,

In this issue, I will draw attention to robotic surgery (RS), which has become increasingly preferred in hiatal hernia surgeries with the effect of advancing technology and which we have recently started to apply in our own clinic. I will present an overview of the results of this minimally invasive approach, whose superiority is still controversial, compared to laparoscopic surgery (LS) in adult patients, taking into account the available literature.

A hiatal hernia is defined as the migration of the stomach or other abdominal organs through the esophageal hiatus into the thoracic cavity. An anatomical classification developed by Dr. Norman Barrett in 1954 categorized hiatal hernias into four types: sliding type I, paraesophageal type II, mixed type III, and herniation of organs other than the stomach type IV. Among these, sliding or type I hernias, in which the gastroesophageal junction migrates into the thorax, are the most common (95%) (1). Typical symptoms include reflux, regurgitation, pressure, and distension. Compression or volvulus can also create an unusual situation that can lead to ischemia. Surgical treatment is recommended for symptomatic hiatal hernias or those that have become ischemic. Traditionally, repair was performed via an open transabdominal or transthoracic approach, but with the advent of minimally invasive surgery, laparoscopic repair is now the standard. LS has been reported to offer fewer overall complications and a faster recovery compared to the open approach. However, LS has limitations, including less ergonomics due to the use of rigid instruments with limited range of motion, limitations in depth perception in two-dimensional imaging, the need for a trained camera assistant, and surgeon fatigue, leading researchers to explore alternative technologies. In the 2000s, the introduction of computer-assisted RS represented a significant advance in minimally invasive surgery by providing additional tools for performing minimally invasive surgery. RS appears to potentially overcome some of the limitations of traditional laparoscopy. Compared to the laparoscopic approach, RS offers improved three-dimensional imaging, motion scaling, vibration filtering, and improved ergonomics and rotation (2-5). These features are beneficial for the precise dissection and suturing required for procedures such as hiatal hernia repair. Despite its advantages, RS also presents its own challenges. While RS has been shown to result in longer operative times, higher costs, and less tactile feedback, the level of evidence definitively demonstrating its superiority in terms of clinical outcomes has not yet been reached. In this article, I will discuss three meta-analyses comparing RS and LS, and two retrospective studies that demonstrate the types of studies included in these analyses.

In this context, to the best of our knowledge, the first meta-analysis comparing the results of robotic and laparoscopic surgeries for hiatal hernia surgery (1) compared the operative time, intraoperative complications, 30-day re-admission, length of stay, and postoperative complications for hiatal hernia in published articles. In the study, which included a total of seven articles, 8166 patients underwent LS and 1945 patients underwent RS. In the postoperative complication analysis, which included five studies among the included studies, the rate was 4.25% (302/7111) in the LC group, while this rate was 3.49% (38/1088) in the RS group, indicating that the complication rate was significantly lower in the RS group (p=0.000). In three studies including 2096 patients, no significant difference was observed between the LS and RS groups when reporting operative time, and it was not found to be statistically significant (p=0.06). In three studies evaluating intraoperative complications; complications were observed in 10.67% of patients in the RS group and 9.09% of patients in the LS group, but the difference between the two groups was not found to be significant (p=0.89). In the results of the analysis where three studies including 2,176 patients were selected, hospital stay was reported and the mean hospital stay in these three studies was reported as 3.2 days in the RS group and 4.2 days in the LS group. The hospital stay was found to be significantly shorter in the RS group compared to the LS group (p=0.04). However, the analysis performed after excluding the study that increased statistical heterogeneity found no difference between the remaining two studies (p=0.97) in terms of length of hospital stay. In addition, in the analysis including two studies including 421 patients, 30-day re-admission was evaluated and no significant difference was noted between the RS and LS groups (p=0.53). This study has some limitations; the study lacked prospective randomized controlled trials directly comparing laparoscopic and robotic approaches. It contained significant heterogeneity in hospital stay and operative time, which could weaken the reliability of the results. It also lacked information on preoperative patient characteristics and intraoperative data, such as hernia size, comorbidities, posterior cruroplasty method, postoperative complications classified according to the Clavien-Dindo classification, etc. Despite these limitations, RS has been shown to be a better option, primarily due to decreased postoperative complications and length of stay.

A 2024 meta-analysis (6) aimed to compare the operative time, intraoperative complications, hospital stay, re-admission rates, overall complications, mortality, and costs associated with RS and LS for anti-reflux and hiatal hernia surgery. A total of fourteen articles and 555,368 patients were included. Of these patients, 66,725 underwent RS and 488,643 underwent LS. Eight studies, including 11,936 patients, evaluated operative time, and no statistically significant difference was found between the RS and LS groups (p=0.10). Intraoperative complications were excluded from the meta-analysis because they were documented only in a small subset of studies, comprising 0.02% of patients undergoing RS and 2% of patients undergoing RS. Length of hospital stay was reported in twelve studies and the mean was 3.7 days in the RS group and 3.5 days in the LS group, with no statistically significant difference observed (p=0.11). The results of the analysis of re-admission rates including a total of 539,673 patients from nine studies showed that there was no significant difference between the RS and LS groups (p=0.53). The results of the analysis of general postoperative complications including eleven studies also did not detect a significant difference between the RS and LS groups (p=0.62). In the analysis including twelve studies, mortality was compared for both groups and was determined as 0.4% (244/66,638) for the RS group and 0.3%

(1531/488,429) for the LS group. The analyses of seven studies that included cost reports also showed that the LS group had statistically significantly lower costs (p<0.00001). The limitations of this analysis are; while some of the included studies reported hiatal hernia types based on patient preoperative characteristics, no stratification was performed based on hiatal hernia type for various outcomes such as intraoperative and postoperative complications, operative time, length of stay, etc.

Awshah et al. (7), published in 2024, compared LS and RS for hiatal hernia and Heller myotomy in a meta-analysis of twenty-two studies involving 196,339 patients. The results of the analysis of seven of the thirteen hiatal hernia studies reporting perioperative complications revealed no significant difference between RS and LS in hiatal hernia repair; however, significant heterogeneity was highlighted. Similarly, in eleven hiatal hernia studies reporting morbidity, no significant difference was found between RS and LS, while significant heterogeneity was found. No significant difference was found in 10 studies comparing overall mortality in RS and LS. The results of studies comparing rates of reintervention/admission, recurrence, perioperative blood loss, operative time, and hospital stay were similar, with no significant differences found. A limitation of this meta-analysis is the paucity of randomized controlled trials and the retrospective nature of the included studies.

In the first of two retrospective studies, Benedix et al. (8) retrospectively examined 140 patients who underwent hiatal hernia and/or anti-reflux surgery in 2021. Of these patients, 85 (60.7%) underwent conventional LS, and 55 (39.3%) underwent RS. When the data obtained from this study were examined, it was observed that the mean operative time differed significantly between the LS and RS groups, with the mean operative time being longer in the RS group (p<0.01). However, it was noted that the procedure time decreased significantly over time in the RS group, with the mean operative time being 190.0 minutes for the first ten cases and 139.3 minutes for the last ten cases. The mean estimated intraoperative blood loss did not differ significantly between the LS and RS groups (p=0.25). Intraoperative complications occurred in 10 patients, 5 in each group (p=0.51). When postoperative outcomes and complications were examined, 15 patients (LS 8/9.4% vs. RS 7/12.7%; p=0.38) were transferred to the intermediate care unit due to pre-existing comorbidities. Furthermore, the mean length of hospital stay was not different between the two groups (p=0.2). Postoperative complications occurred in 11 (12.9%) and 6 (10.9%) patients in the LS and RS groups, respectively (p=0.8), and no mortality was observed. The current study has some limitations, including being a retrospective study examining the initial results from a single institution, the small number of patients in the RS group, and the study period coinciding with the initial introduction of the robotic system in the hospital. Similar parameters were examined in the analysis study by Tjeerdsma et al. (9) published in 2022, comparing the results of robotic-assisted and conventional laparoscopic hiatal hernia repair. In their three-year retrospective single-center study, in which they included a total of 58 patients, 42 of whom underwent LS and 16 who underwent RS, they determined the median hospital stay as 2.5 days for laparoscopic hiatal hernia repair and 3.0 days for robotic-assisted repair (p=0.301). Among the postoperative complications, five cases of pneumothorax, one patient with perforation, two patients with infection, and one patient with bleeding were reported in the conventional LS group. In the RS group, one case of pneumothorax and one patient with bleeding were observed. As a result of the analysis in which they also evaluated the parameter of admission to the intensive care unit; it was noted that the length of stay in the unit was longer in the conventional LS group, but the rate of admission to the unit tended to be higher in the RS group. Despite this, no mortality was reported in either group. Limitations of this study include its single-center nature and small sample size.

Conclusion

RS has become a powerful alternative for surgeons in hiatal hernia surgery, particularly in recent years, driven by increasing technological advancements. Significantly reducing the limitations of traditional LS, RS stands out with its technical advantages, including three-dimensional, high-resolution imaging, improved wrist mobility, tremor elimination, and motion scaling. These features facilitate more precise dissection and suturing in the anatomically complex diaphragmatic region, enabling a more effective translation of surgical skills into the field.

The low postoperative complication rates reported in studies and shorter hospital stays in some analyses suggest that RS may also have positive effects on patient comfort and recovery. As seen in the study by Benedix et al. (8), operative times were observed to be significantly shorter with experience in the RS group. However, it should be noted that these findings are not generalizable due to high heterogeneity rates and study quality limitations. In particular, the high levels of heterogeneity reported in Awshah et al. (7) meta-analysis clearly demonstrate the impact of differences in patient populations and surgical techniques on outcomes. This highlights the lack of standardization in studies evaluating the effectiveness of RS and the need for high-quality randomized controlled trials. Furthermore, while cost appears to be the current major limiting factor, it is also foreseeable that its technical appeal, surgeons' increasing experience, advances in robotic technology, and increased market competition will lead to a decrease in costs.

With the increasing prevalence of robotic systems and the increasing experience of surgeons, RS is likely to become a more frequently used standard for hiatal hernia repair in the near future. The technical advantages of RS, particularly in advanced hiatal hernias, reoperations, and anatomically challenging cases, will significantly influence surgeons' preferences.

Consequently, a significant portion of the existing literature is limited to single-center studies, making it difficult to draw a definitive conclusion about whether RS improves clinical outcomes. Although the clinical superiority of RS has not yet been clearly proven, its technical advantages and potential

healing benefits make RS a promising method for hiatal hernia surgery and a method that will be increasingly preferred in the future. While further prospective and randomized studies are needed in this area, it is clear that RS has solidified its place in the evolution of minimally invasive surgery.

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Original Article

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Trends and Implications of Studies on Advanced Glycation End Products (AGEs) and Cancer: Bibliometric Analysis

İleri Glikasyon Son Ürünleri (AGE'ler) ve Kanser Üzerine Yapılan Çalışmaların Eğilimleri ve Sonuçları: Bibliyometrik Analiz

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ABSTRACT

Objective: This study aims to analyze the current status of studies on the relationship between advanced glycation end products (AGEs) and cancer and to reveal the main trends in the field, the prominent authors, papers, affiliations, countries and collaborations and the most popular keywords related to the subject and changes in the popularity of keywords over time. In this context, the study aims to guide researchers who want to focus on the relevant field, and provide a basis for future research by facilitating access to information in the field.

Methods: Raw data were taken from the Web of Science (WoS) Core Collection database on April 30, 2024, and analyzed with programs such as Bibliometrix and VOSviewer. The data of the year 2024 were not included to be accurate regarding annual calculations.

Results: The first study on the subject in WoS was published in 1994. The United States of America (USA), China, and Japan stood out among countries, with Takeuchi M., Yamagishi S., and Kuniyasu H. among authors, and Kurume University among the institutions. The most collaboration on the subject was between the USA and China as countries and between Yamagishi S., and Matsui T. as authors.

Conclusion: Results from this bibliometric analysis emphasize the expanding importance of AGEs in cancer studies, pointing to potential avenues for further investigation and collaborative efforts in.

Keywords: Bibliometric analysis, cancer, oncology, advanced glycation end products, rage, nutrition

ÖZ

Amaç: Bu çalışmanın amacı ileri glikasyon son ürünleri (AGE) ve kanser ilişkisi üzerine yapılan çalışmaların mevcut durumunu analiz etmek ve alandaki ana eğilimleri, öne çıkan yazarları, makaleleri, kurumları, ülkeleri ve iş birliklerini ve konuyla ilgili en popüler anahtar kelimeleri ve anahtar kelimelerin zaman içinde popülerliğindeki değişimi ortaya koymaktır. Bu bağlamda, çalışma ilgili alana odaklanmak isteyen araştırmacılara rehberlik etmeyi ve alandaki bilgilere erişimi kolaylaştırarak gelecekteki araştırmalar için bir temel sağlamayı amaçlamaktadır.

Yöntemler: Ham veriler 30 Nisan 2024'te Web of Science (WoS) Core Collection veritabanından alınmış, Bibliometrix ve VOSviewer gibi programlarla analiz edilmiştir. Yıllık hesaplamalar açısından doğru olması için 2024 yılı verileri dahil edilmemiştir.

Bulgular: WoS'da konuyla ilgili ilk çalışma 1994 yılında yayınlanmıştır. Ülkeler arasında Amerika Birleşik Devletleri (ABD), Çin ve Japonya, yazarlar arasında Takeuchi M., Yamagishi S. ve Kuniyasu H. ve kurumlar arasında Kurume Üniversitesi öne çıkmaktadır. Konuyla ilgili en fazla iş birliği; ülkeler olarak ABD ve Çin arasında, yazarlar olarak Yamagishi S. ve Matsui T. arasındadır.

Sonuç: Bu bibliyometrik analizden elde edilen sonuçlar, AGE'lerin kanser çalışmalarındaki artan önemini vurgulayarak, daha fazla araştırma ve iş birliği çabası için potansiyel yollara işaret etmektedir.

Anahtar Kelimeler: Bibliyometrik analiz, kanser, onkoloji, ileri glikasyon son ürünleri, öfke, beslenme

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Introduction

Advanced glycation end products (AGEs) are a group of reactive compounds formed as a result of the non-enzymatic glycation of free amino groups of proteins and carbonyl groups of reducing sugars, known as the Maillard reaction (1,2). They can also form during non-enzymatic glycation and oxidation of lipids or nucleotides with sugars (3). Ne-(carboxyethyl)lysine, Ne-(carboxymethyl)lysine, fructosyl-lysine, and pyrraline are well-known types of AGEs (4). The formation of AGEs can occur exogenously during food processing, especially through heat treatment, or endogenously in the body due to high amounts of sugar intake (5,6). AGEs threaten human health in various ways by causing glycative stress (7). They are pro-inflammatory and pro-oxidant compounds that influence numerous biological responses by activating the receptor AGE (RAGE). They are causal in many chronic diseases, including cancer (8). Cancer, characterized by abnormal cell growth and proliferation beyond normal limits, which can subsequently invade surrounding tissues, is also referred to as malignant tumors and neoplasms (9). Recommendations are given to guide a healthy life to prevent cancer, such as changing nutritional patterns, reaching and maintaining a healthy body weight, reducing alcohol consumption, and increasing physical activity (10).

This study aims to analyze the current state of research on AGEs and cancer, revealing the main trends and identifying gaps in this field. The analysis may guide researchers who want to engage in this field and direct them to the right resources. In this context, the study's results will provide an idea of which articles and authors future researchers should focus on. As a result, this study aims to provide a basis for future research by facilitating access to information in the field.

Methods

This search was conducted in the Web of Science (WoS) Core Collection database on April 30, 2024. The search strategy and exclusion criteria are detailed in Table 1.

We searched the search query in title, abstract, and keywords without language restriction since all documents already contain English titles, abstracts, and keywords. Initially, 1,284 documents were identified. The data for 2024, when we conducted the analysis, were not included to be accurate regarding annual calculations, and the number of documents decreased to 1262. In order to address the historical development and evolution of research on AGEs and cancer, we did not choose to limit the study to a specific time period. The WoS database began indexing studies on this topic in 1994, and we considered this year as the starting point for analysis. By not applying a time restriction, we aimed to assess the progression of the field and identify key milestones that may have influenced the current state of research. Finally, arrangements were made according to document type. There were 1161 published documents from 584 sources related to "AGEs and cancer" from 1994 to 2023, and 242 were review articles.

Statistical Analysis

This study is based on bibliometric analysis, which does not involve conventional statistical hypothesis testing. Instead, descriptive bibliometric indicators such as the number of publications, citations, collaboration networks, and keyword

Table 1. The search strategy

OR		OR		OR	Excluded
advanced glycation end product$ glycosylation product$ glycoxidation product$ carboxymethyl-lysine carboxyethyl-lysine fructosyl-lysine pyrraline	And	cancer$ *carcinoma* tumor$ tumour$ neoplasm$ neoplasia neoplastic malignancy malignancies malignant melanoma leukemia lymphoma carcinogenesis onco*	Not	tumor necrosis factor tumour necrosis factor	Final publication year 2024 Meeting abstract Proceeding Paper Early access Editorial material Book chapters Letter Correction Data paper Note Publication with Expression of concern Retracted publication Retraction

: Was used to include all morphological variants of a word stem (e.g., onco for "oncology", "oncogene", etc., and *carcinoma* for all compound terms containing "carcinoma")
$: was used to include both singular and plural forms of words (e.g., cancer$ retrieves both "cancer" and "cancers"; tumor$ retrieves "tumor" and "tumors")
These wildcard characters ensured a comprehensive and inclusive search strategy by capturing different forms and variants of key terms, OR: Odds ratio

co-occurrence were analyzed. Raw data were exported in "plain.txt" format from WoS. These indicators were processed using WoS, RStudio 4.3.3 (Bibliometrix package) (11) and VOSviewer 1.6.20 (12) software. Besides, Microsoft Excel 365 was used for tabular presentations. No inferential statistical tests (e.g., t-tests, ANOVA) were conducted, as the objective was to evaluate publication and citation patterns rather than test statistical hypotheses.

Ethics Statement

This study does not involve human participants, animal experiments, or private or sensitive data collection. It is a bibliometric analysis based entirely on publicly available data from the WoS database. Therefore, ethical approval and informed consent were not required.

Results

Analysis of Documents

Figure 1 shows the number of documents produced on the subject by year. The first publication on the topic started in 1994 with 1 article. The number of publications increased over time and reached a peak of 106 documents in 2021. The annual growth rate was 16.46%.

While "local citation score (LCS)" reflects the citations made by the documents in the collection coming from WoS, the total citations (TC) they receive from documents indexed in WoS are called "global citation score (GCS)", also known as "TC". The top 10 most cited documents in terms of TCs in our data set are given in Table 2.

In Figure 2, 21 documents from our data set are visualized according to their citation relationships to each other and listed chronologically from left to right. The arrows show who is citing whom, and the direction of the arrow points to the document cited. The sizes of the nodes represent the LCS, Supplementary Table 1 is a detailed explanation of Figure 2. In this case, the article "Blockade of RAGE-amphoterin signaling suppresses tumor growth and metastases" published by Taguchi in 2000, ranked first in terms of both LCS and GCS.

Figure 3 shows the density analysis of the most cited references cited by the WoS collection. While some of these documents are already in our collection, some are from outside. The top 10 most local cited references are given in Supplementary Table 2.

Analysis of Authors

The number of authors publishing on "AGE and cancer" was 5789. The top 3 authors in terms of production were Yamagishi S. (n=28), Takeuchi M. (n=27), Kuniyasu H. (n=16). Figure 4 shows the authors and their publications over time. The line represents an author's timeline. The size of the circles represents the number of articles produced in the relevant year, and the color darkness represents the annual average number of citations for these articles.

Table 3 lists the top 10 authors according to their local impact. The ranking of the authors, whose h-indexes are calculated according to the number of articles related to the subject and the citations they receive from other authors in the collection, shows the author's local impact.

According to the results of the co-authorship analysis, 79 co-authors made at least five publications related to the subject together. Some of these 79 authors were not connected, and the largest set of connected items consisted of 7 authors (Figure 5). These seven authors were grouped into 2 clusters according to their relationships with each other. The authors in the first cluster were Takeuchi M., Sakasai-Sakai A., Takata T., and Takino J., and the authors in the second cluster were Yamagishi S., Matsui T., and Fukami K.

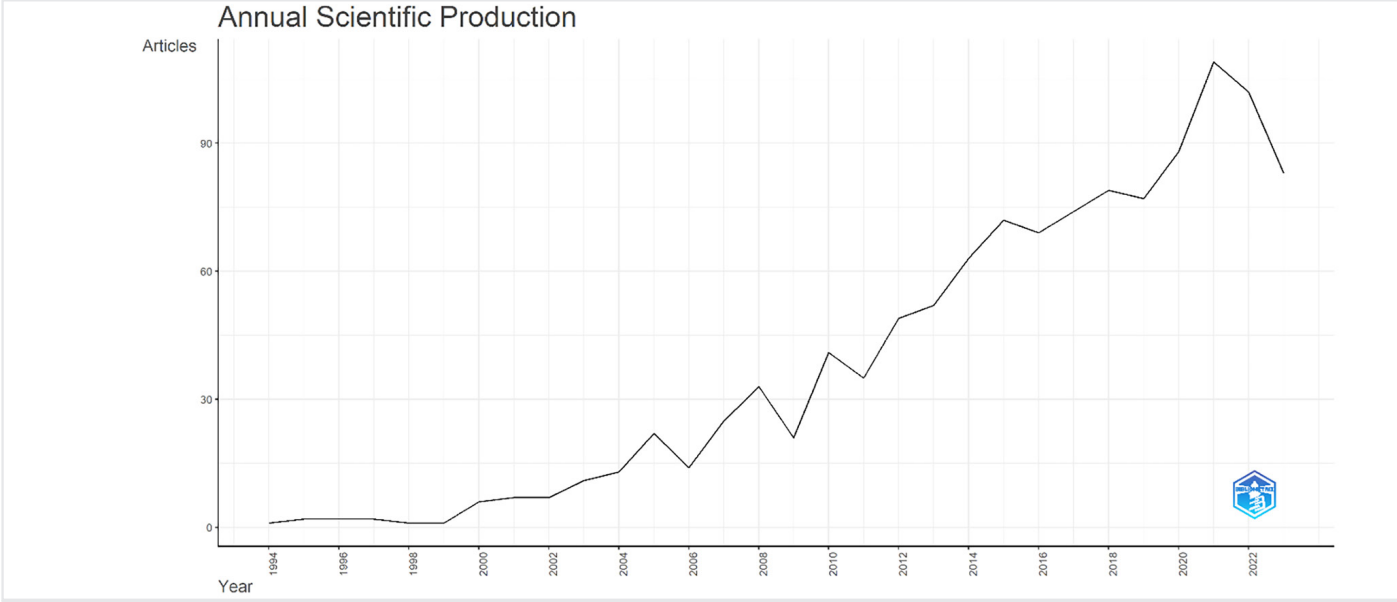

Figure 1. Annual scientific production

In Figure 5, colors ranging from purple to yellow provide information about the year of publication. The size of the nodes represents the number of documents that the authors have collaborated on regarding the subject; the lines between the nodes represent the connections between the collaborating authors; and the thickness of the lines represents the strength of these connections. In this respect, Yamagishi S., and Matsui T. had the closest collaboration. The ranking of these seven authors according to total link strength (TLS) was: Takeuchi M. (TLS=29) Yamagishi S. (TLS=22), Sakasai-Sakai A. (TLS=21), Takata T. (TLS=16), Takino J. (TLS=16), Matsui T. (TLS=15), and Fukami K. (TLS=9).

Analysis of Sources

The top 10 most productive sources were the International Journal of Molecular Sciences (n=34), PLoS One (n=22), Biochemical and Biophysical Research Communications (n=21), Scientific Reports (n=18), Journal of Biological Chemistry (n=15), Cells (n=14), Nutrients (n=13), Cancers (n=12), Medical Hypotheses (n=12), and Molecules (n=12), respectively. The production of these resources over time is given in Figure 6. While the International Journal of Molecular Sciences had eight publications in 2018, it experienced a turning point, increased rapidly in production, and ranked first with 34 publications in 2023. Journal of Biological Chemistry, Medical Hypotheses, Biochemical and Biophysical Research Communications, PLOS ONE, and Molecules have not published new publications on

Table 2. Top 10 most global cited documents

Author	Year	Title	TC	TC per year
Taguchi A	2000	Blockade of RAGE-amphoterin signalling suppresses tumour growth and metastases	1072	42,88
Bierhaus A	2005	Understanding RAGE, the receptor for advanced glycation end products	1010	50,50
Donato R	2013	Fuctions of S100 proteins	965	80,42
De Vos VM	2022	Gut microbiome and health: mechanistic insights	601	200,33
Van Remmen H	2003	Life-long reduction in MnSOD activity results in increased DNA damage and higher incidence of cancer but does not accelerate aging	564	25,64
Vauzour D	2010	Polyphenols and human health: prevention of disease and mechanisms of action	546	36,40
Huttunen HJ	2000	Coregulation of neurite outgrowth and cell survival by amphoterin and S100 proteins through receptor for advanced glycation end products (RAGE) activation	503	20,12
Lotze MT	2007	The grateful dead: damage-associated molecular pattern molecules and reduction/ oxidation regulate immunity	475	26,39
Negre-Salvayre A	2008	Advanced lipid peroxidation end products in oxidative damage to proteins. Potential role in diseases and therapeutic prospects for the inhibitors	464	27,29
Sinha P	2008	Proinflammatory S100 proteins regulate the accumulation of myeloid-derived suppressor cells	448	26,35

TC: Total citation

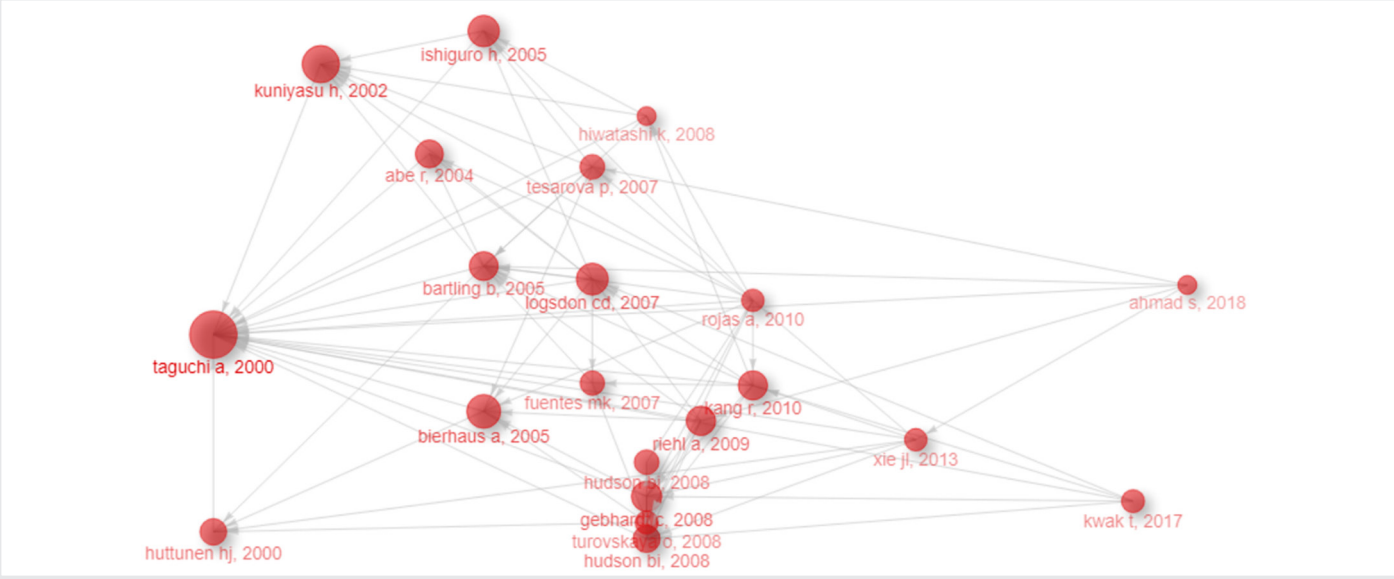

Figure 2. Historiograph of the documents

the subject after certain years, and the number of publications has remained constant.

The top 10 sources, according to their local impact, are given in Table 4. Among the top 10 sources in production, Cells, Cancers, and Molecules could not rank in the top 10 regarding local impact. Although Oncology Letters, Cancer Letters, and Carcinogenesis were not in the top 10 regarding production, they managed to be in the top 10 regarding local impact.

Analysis of Affiliations

The top 20 affiliations that published the most on "AGE and cancer" and their number of publications are shown in Figure 7.

Figure 8 shows the analysis of the collaborations. There were 114 affiliations that made at least five publications together related to the subject. Some 114 affiliations were not connected, and the largest set of connected items consisted of 104. These 104 affiliations were grouped under 11 clusters according to their relationships with each other.

In Figure 8, the size of the nodes represents the number of documents that the affiliations have collaborated on, the lines between the nodes represent the connections between the collaborating affiliations, and the thickness of the lines represents the strength of these connections. The top 5 affiliations according to their TLS were China Medical University, Taiwan (TLS=34), Asia University, Taiwan (TLS=26), Kurume University, Japan (TLS=25), National Chung Hsing University, Taiwan (TLS=25), Taichung Veterans General Hospital, Taiwan (TLS=19), respectively. The top 5 affiliations with the closest collaboration in terms of link strength (LS) were Kurume University-Hokuriku University (LS=8), National Tsing Hua University-China Medical University Taiwan (LS=8), Asia University Taiwan-China Medical University Taiwan (LS=8), National Chung Hsing University-Taichung Veterans General Hospital (LS=8),

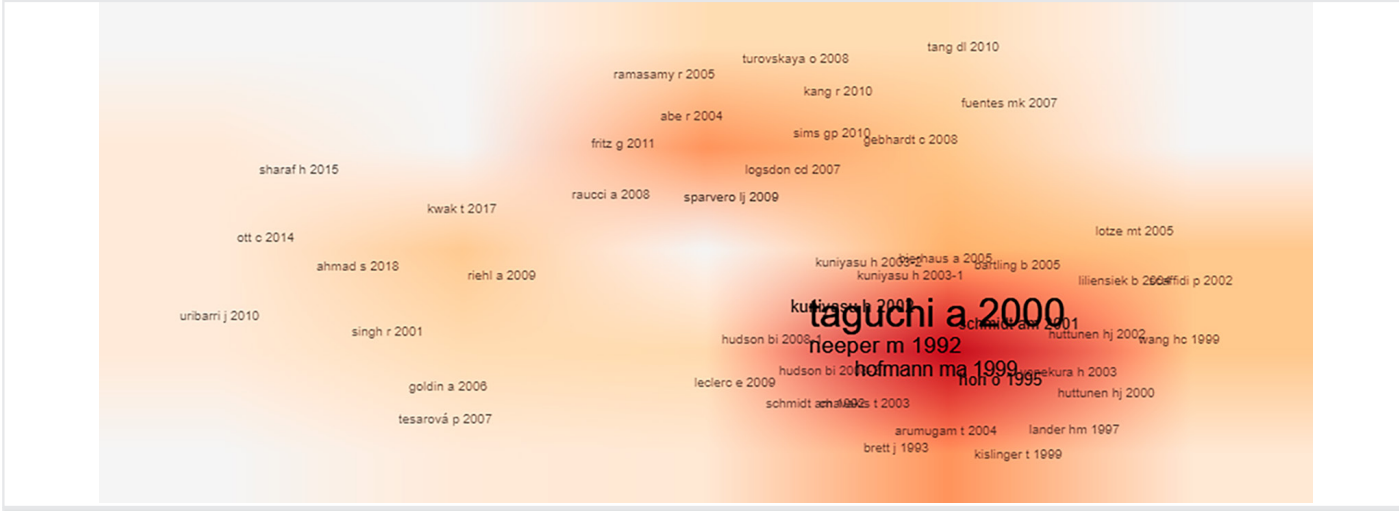

Figure 3. The density of most cited references which cited by the data set obtained from WoS

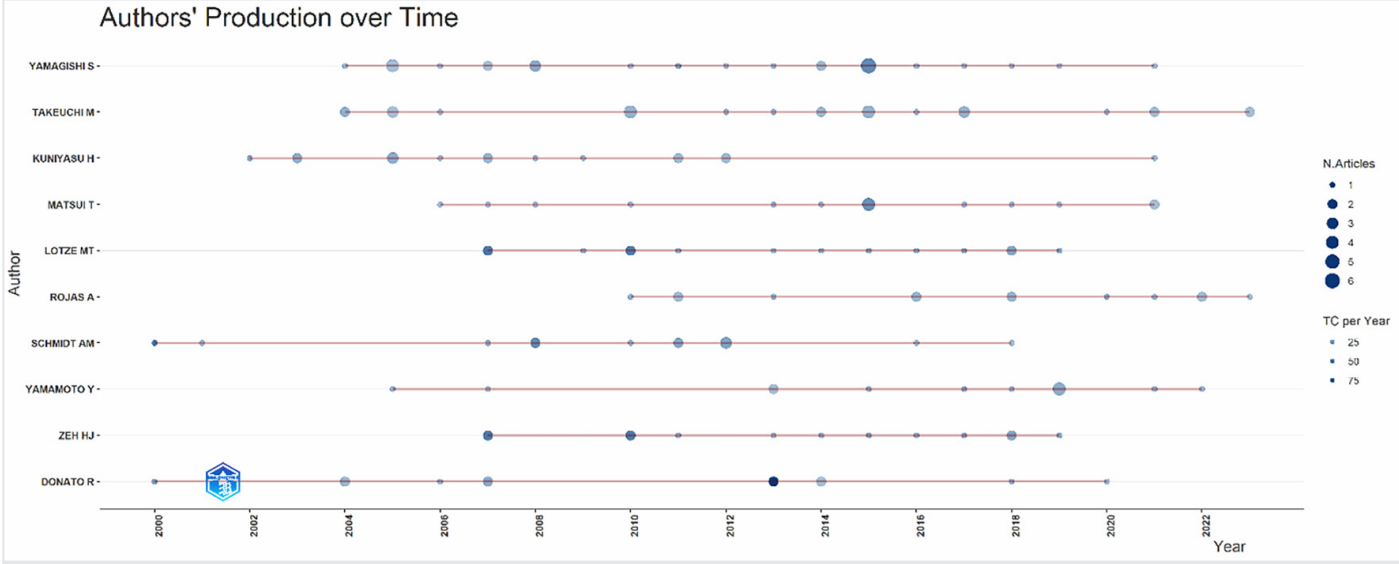

Figure 4. Authors' production over time

and Hiroshima Int University-Kanazawa Medical University (LS=7), respectively.

Analysis of Countries

Figure 9 shows the top 10 countries of the corresponding authors. Single-country publications (SCP) provide information about national collaboration, while multiple-country publications (MCP) provide information about international collaboration. The MCP and SCP rates of countries are shown in Supplementary Table 3. Countries with an MCP rate of 50% and above have high international collaboration (13). In this respect, the United Kingdom (UK) exceeded the threshold. The MCP ratios of China, the United States of America (USA), and Japan were 10%, 27.4%, and 10.3%, respectively.

Table 3. Author's local impact

Author	h-index	TC	NP	PY start
Takeuchi M	19	875	27	2004
Yamagishi S	19	1344	28	2004
Kuniyasu H	13	1136	16	2002
Lotze MT	13	2124	14	2007
Donato R	12	2288	12	2000
Zeh HJ	12	2039	13	2007
Matsui T	11	534	15	2006
Riuzzi F	11	1610	11	2004
Schmidt AM	11	2367	13	2000
Sorci G	11	2070	11	2000

TC: Total citation, NP: Number of paper, PY: Publication year

The top 10 countries that received the most citations on the subject are given in Figure 10. The first three most cited countries were the USA, China, and Japan. When we ranked them in terms of the average number of citations per article (CPA), the top 10 were Finland (CPA=136.90), Belgium (CPA=130.80), Ireland (CPA=99.30), New Zealand (CPA=94.00), the Netherlands (CPA=90.10), Switzerland (CPA=87.70), the UK (CPA=80.40), France (CPA=65.90), the USA (CPA=59.60), and Germany (CPA=58.70).

Figure 11 shows collaboration between countries. Countries that collaborated more are marked in dark blue. The thickness of the connections represents the strength of collaboration. Supplementary Table 4 lists the ranking of the top 10 country pairs according to their frequency of collaboration.

Analysis of Author's Keywords

Figure 12 shows the word cloud, which consists of the author's keywords. The size of the words represents their frequency of use. The first 10 most frequently used keywords were rage (n=232), AGEs (n=96), cancer (n=90), high mobility group box 1 (HMGB1) (n=81), inflammation (n=72), ages (n=63), oxidative stress (n=60), diabetes (n=52), glycation (n=48), and breast cancer (n=40).

Figure 13 shows the trend of the author's keywords used over the years. The three most popular keywords per year used at least five times are shown in the figure. The location of the circles indicates the year in which the keywords were most popular, while the size of the circles represents the frequency of use of these keywords. The smallest circles belonged to the words "immunohistochemistry", "blood-brain barrier" and "glycoxidation" which were used five times each, and the largest circle belonged to the word "rage", which was used 232 times.

In Figure 14, keywords are divided into 9 clusters according to their co-occurrence. While different colors represent different

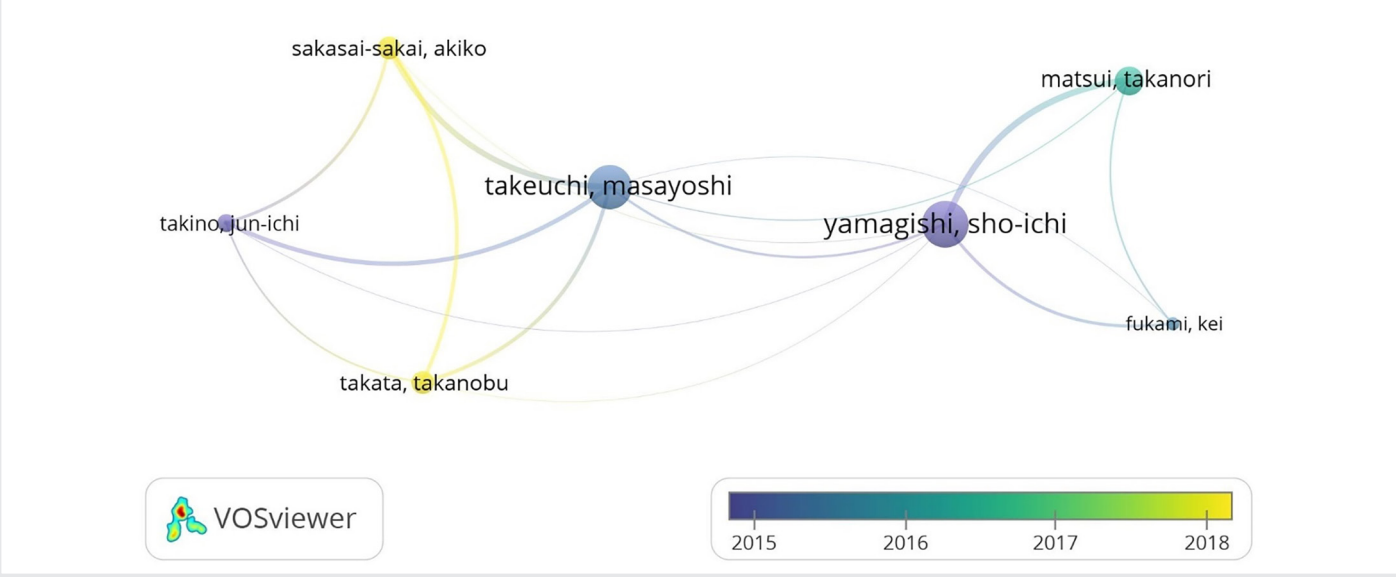

Figure 5. Co-authorship analysis of authors

clusters, the size of the nodes represents the TLS. The top 10 keywords in terms of TLS are rage, cancer, HMGB1, ages, AGEs, inflammation, diabetes, oxidative stress, glycation, and apoptosis, respectively. Lines between nodes show the recurrent relationship between words, meaning that the thicker the line, the more frequently the words were used together. Detailed information about Figure 14 is included in Supplementary Table 5.

Discussion

We have reported an increase over time in publications on AGEs and cancer; this trend has also been observed in bibliometric analyses of cancer and nutrition (14-16) and AGEs in obesity (17). According to the World Health Organization, approximately 1 in 5 people develop cancer in their lifetime. The International Agency for Research on Cancer projections for 2022 highlight the urgent need to address the escalating burden of cancer (18). The significance of cancer prevention and control was underscored at the third UN High-Level Meeting on Noncommunicable Diseases in 2018 (19) and the UN High-Level Meeting on Universal Health Coverage in 2019 (20). These factors likely contributed to the pronounced surge in publications observed between 2019 and 2021. Also, the dominance of ultra-processed foods rich in AGEs in the global food supply chain may have paved the way for more research over time (21,22). More than 35 million new cancer cases are projected to occur by 2050, representing a 77% increase from the estimated 20 million cases in 2022. This rapid escalation in the global cancer burden reflects both demographic aging and shifts in individuals'

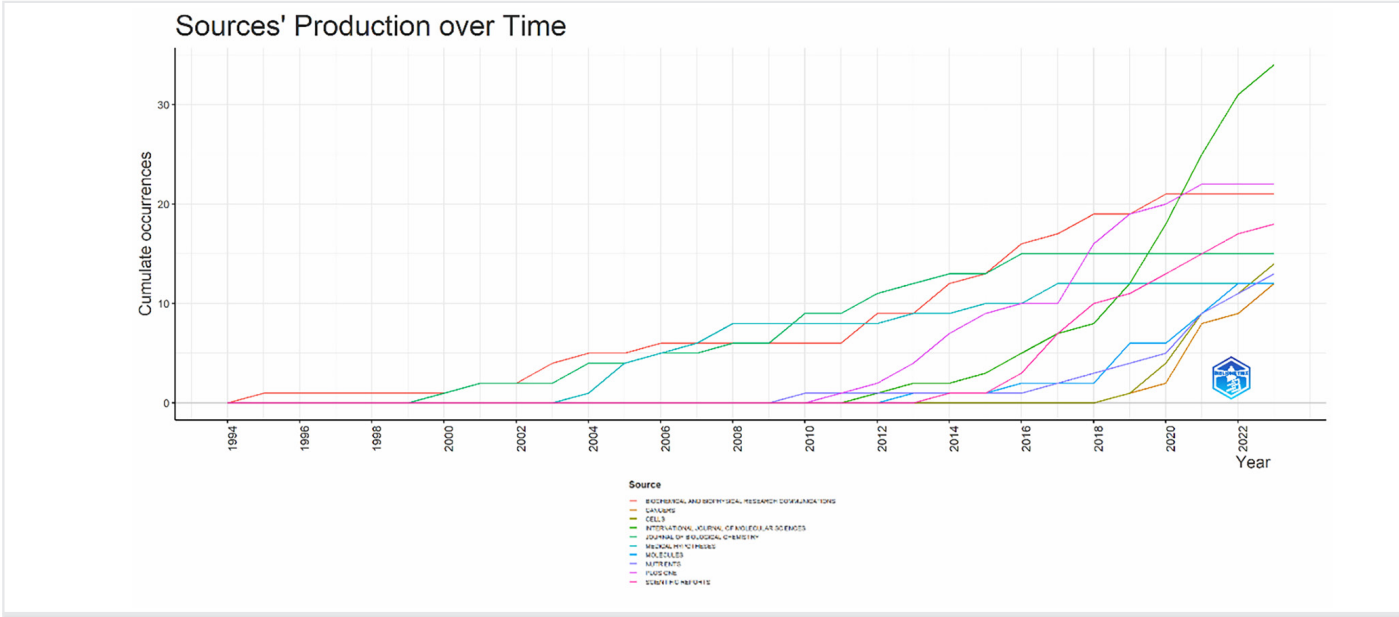

Figure 6. Sources' production over time

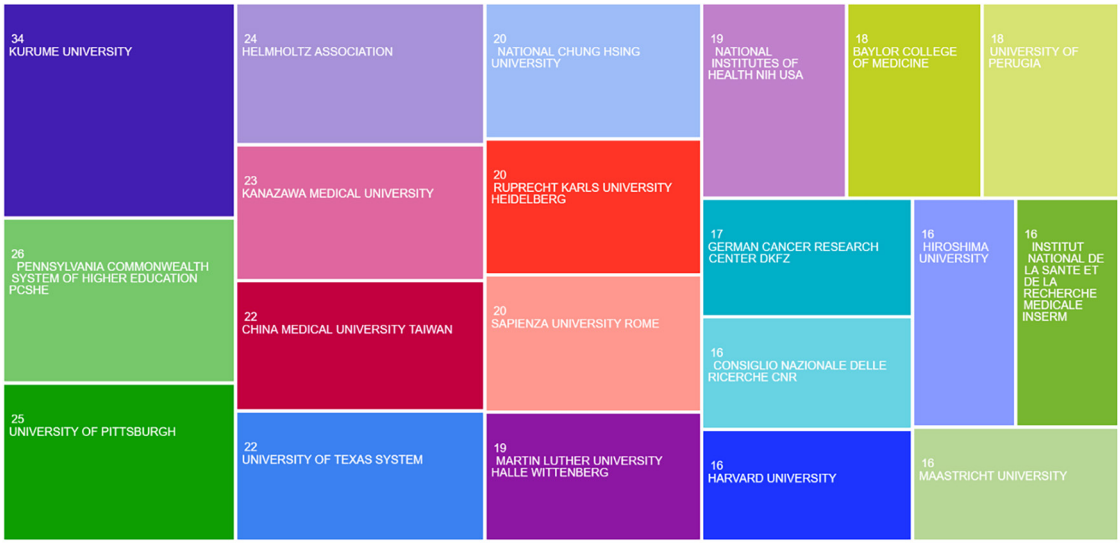

Figure 7. Publication of affiliations

Table 4. Sources' local impact

Sources	h-index	TC	NP	PY start
International Journal of Molecular Sciences	17	751	34	2012
Journal of Biological Chemistry	15	1742	15	2000
Biochemical and Biophysical Research Communication	14	716	21	1995
PLoS One	13	463	22	2011
Scientific Reports	11	405	18	2014
Medical Hypotheses	9	274	12	2004
Nutrients	9	761	13	2010
Oncology Letters	9	214	11	2012
Cancer Letters	8	361	8	2003
Carcinogenesis	8	775	9	2005

TC: Total citation, NP: Number of paper, PY: Publication year

exposure to risk factors (18). Given this context, research into the relationship between AGEs and cancer is anticipated to continue to garner significant attention in the years ahead.

The most cited study regarding TCs showed that co-localization of RAGE and amphoterin, also known as HMGB1, at the leading edge of advancing neurites contributes to cellular migration and pathologies such as tumor invasion. The authors also reported that RAGE-amphoterin blockade reduced the growth and metastasis of implanted and spontaneous tumors in susceptible mice (23). Amphoterin is a protein that enhances process elongation and migration in embryonic neurons and tumor cells by binding to RAGE, a multiligand transmembrane receptor (24).

The most cited document per year was a review article about gut microbiome and health. This study mentioned that AGEs interact with the colon epithelium by activating RAGE and increasing intestinal permeability, which in turn causes bacterial toxins to leak into the systemic circulation. It was also stated that

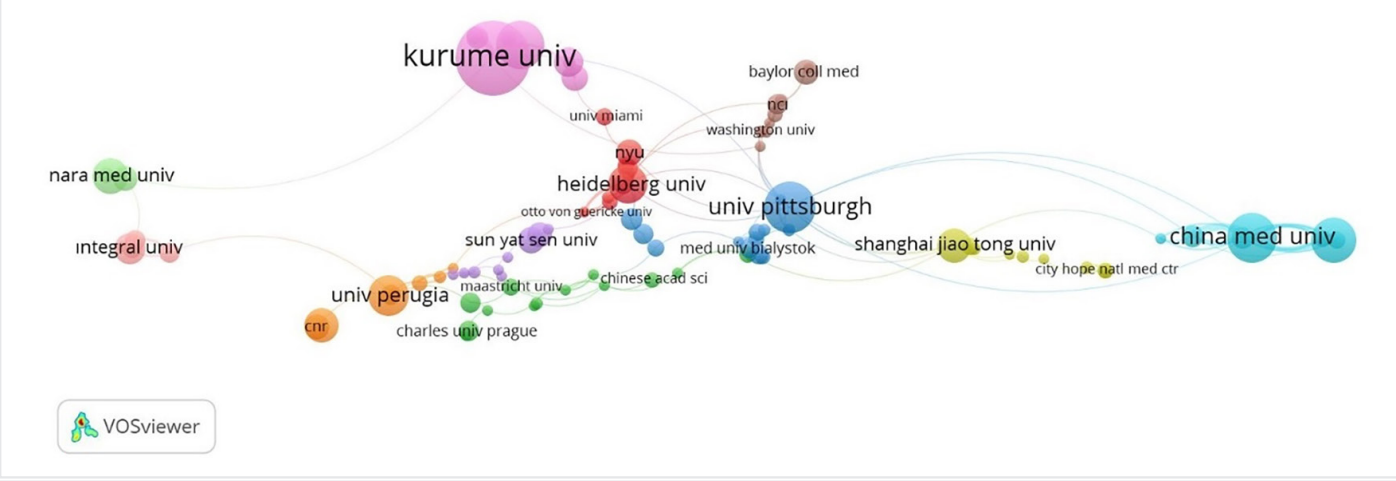

Figure 8. Collaboration of affiliations

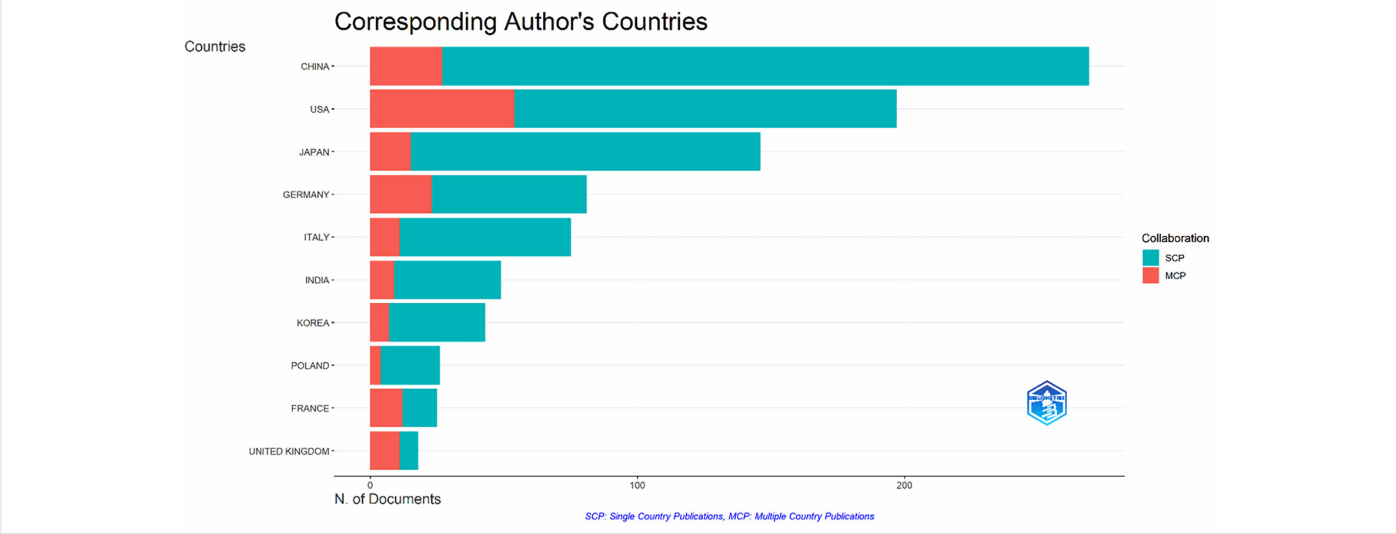

Figure 9. Top 10 corresponding authors' countries.
SCP: Single-country publications, MCP: Multiple-country publications

Escherichia coli could respire fructoselysine, a type of AGE, but this substance can be converted to butyrate by members of the genus Intestinimonas spp. in a new way as well (25).

The Journals Nutrients, PLoS One, Medical Hypotheses, and Scientific Reports, which ranked among the top 10 most productive sources in our study, were also in the top 15 in a bibliometric analysis of AGE and obesity (17). In a separate analysis on cancer and nutrition, Nutrients was among the top 10 sources (15), and in another, Nutrients, PLOS ONE, and Cancers were in the top 10 (16). As can be seen in Figure 6, some journals do not publish new studies related to the subject. If this continues, changes are expected in the list of the most productive sources.

Among the top 10 most influential authors, Schmidt AM., Yamagishi S., and Takeuchi M. (Table 3) were also prominent in another bibliometric analysis on AGE and obesity (17).

Kurume University, which has the most publications related to the subject, was ranked 3rd in terms of LS, and the institution it collaborated with the most was Hokuriku University. Kurume University is a prestigious university in Japan, founded in 1928 as Kyushu Medical School (26). The University of Texas System, in the top 10 regarding the number of publications in our collection, was also among the top 10 institutions in a bibliometric study analyzing the top 100 most cited articles (27). The University of Texas System was founded on September 15, 1883, in a real sense (28).

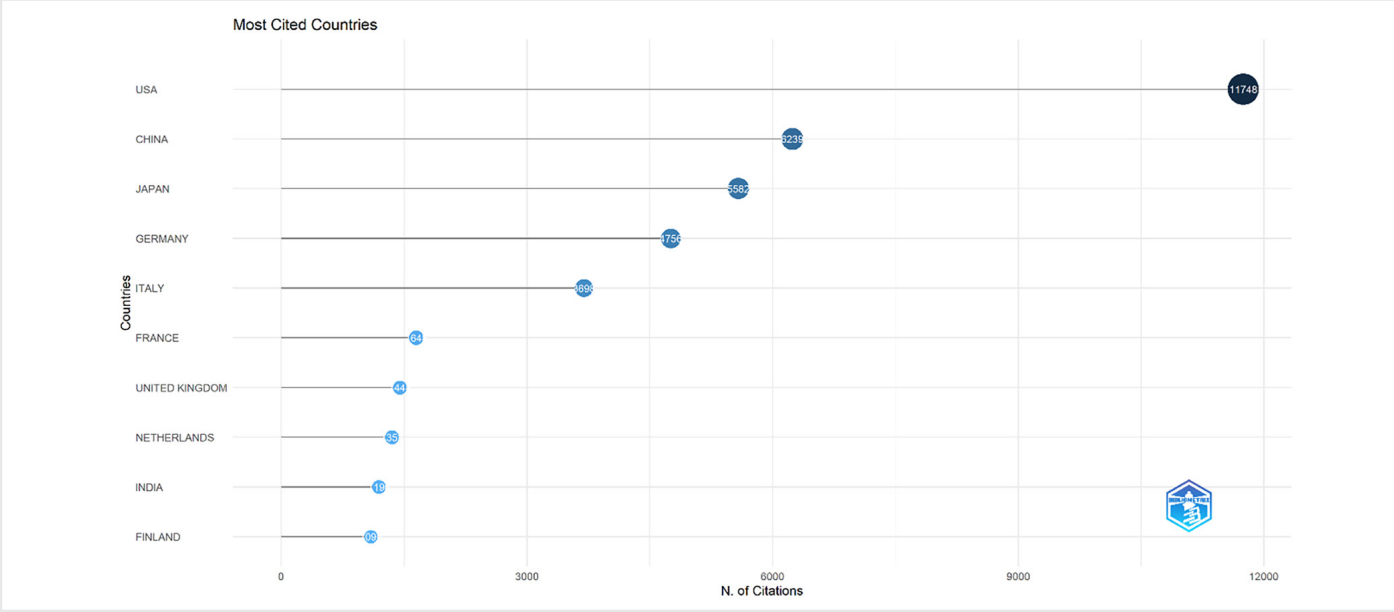

Figure 10. Most cited countries

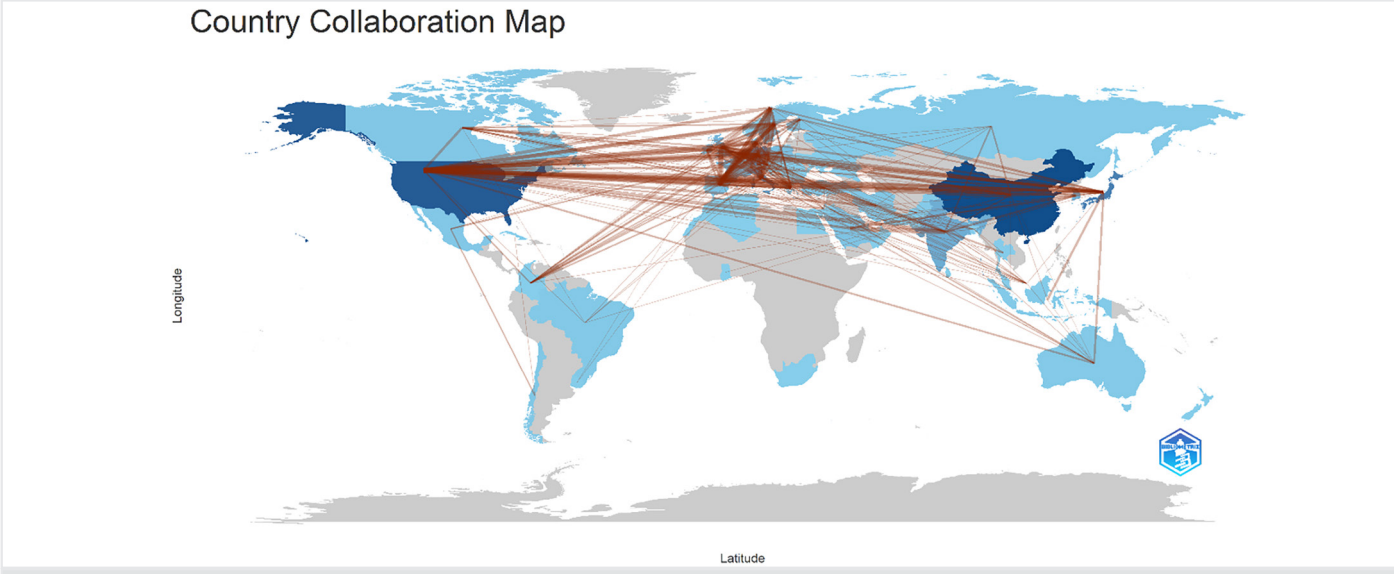

Figure 11. Country collaboration map

Although the most influential authors and the most productive institutions in the field were from Japan, as a result of the country analysis, Japan ranked 3rd in terms of both production and citations. The USA and China took the first two places. Our findings align with other bibliometric analyses on cancer and nutrition, where China, the USA, Japan, Germany, Italy, France, and the UK ranked among the top 10 (14-16). In the bibliometric analysis on AGE and obesity (17), the top 10 most cited countries included the USA, UK, Italy, Germany, Japan, China, France, the Netherlands, and India, as in our study. Cancer is the leading cause of death in China and developed countries (29). In 2019, when looking at the leading causes of premature death (between the ages of 30-70) in 183 countries, cancer ranked first in China, the USA, and Japan (30).

Supplementary Table 4 shows the top 10 most collaborative country pairs. Similar to our findings, a cancer and nutrition bibliometric study identified Italy-Germany, Italy-UK, UK-Germany, and UK-Spain as key collaborations (15). In our study, the USA and China were the leading cooperative countries, with the USA collaborating with various nations in the top four pairs. However, when the MCP rates of the countries are examined, it is seen that only the UK passes the 50% threshold and that international cooperation could be much higher. Despite the collaborative efforts observed among certain country pairs, there remains a need for increased international cooperation to address the complex challenges associated with AGEs and cancer.

The most frequently used keyword in our collection was "rage". This situation is natural, as in many studies, the mechanism of disease formation is explained through the activation of RAGE (8,23,25). Besides, the presence of breast cancer in the top 10 most frequently used keywords indicates that this type of cancer has been studied more than other types of cancer.

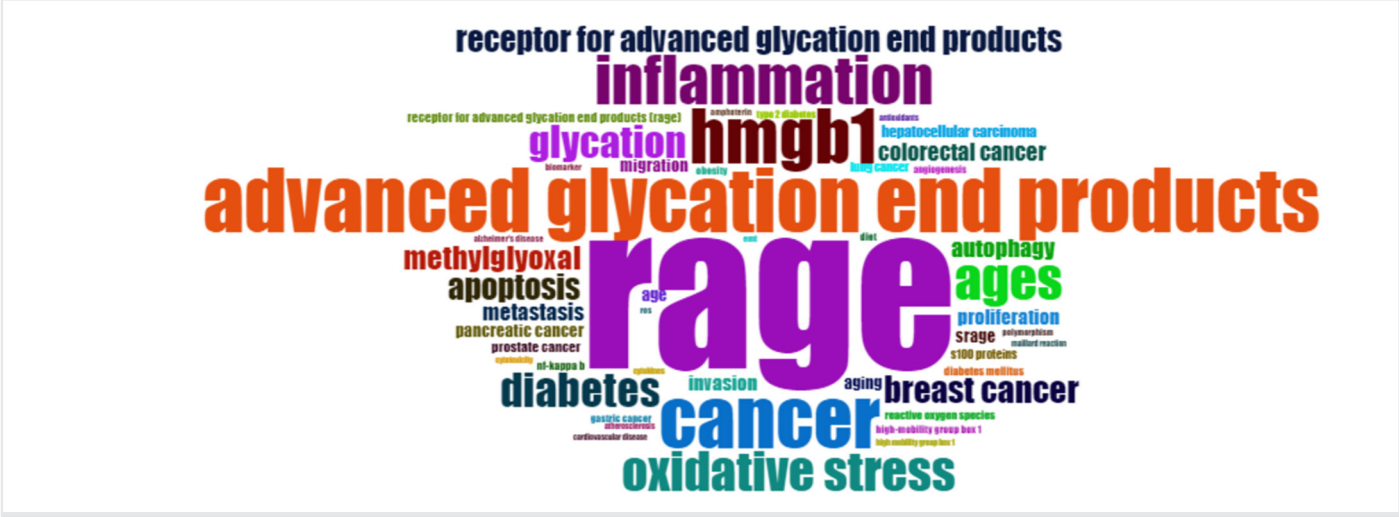

Figure 12. Word cloud of author's keywords

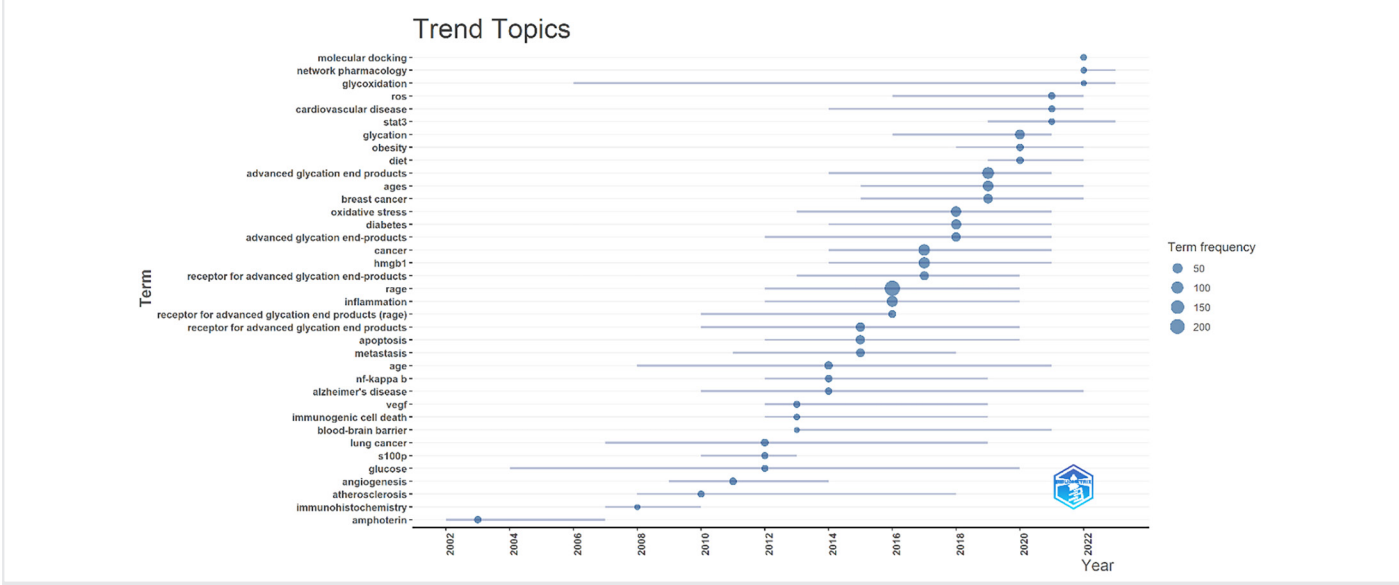

Figure 13. Trend topics of author's keywords

When the co-occurrence analysis of authors' keywords is examined in Figure 14, although different types of cancer are located in different clusters, all cancer types are in a central position. In this study, nine clusters emerged from the co-occurrences of keywords (Supplementary Table 5), and four study areas were revealed from these clusters.

In the first cluster, the research area includes studies and meta-analyses examining the relationship between cancer and diabetes, the effect of polymorphism in RAGE on cancer, and the effect of AGE, hyperglycemia, and glycation biomarkers in cancer formation. Gene polymorphisms in different parts of RAGE significantly increase the risk of cancer (31-33). A study examining the link between cancer and diabetes shows that patients with diabetes have a higher risk of developing cancer and that cancer patients with diabetes have higher mortality than cancer patients without diabetes (34).

In the second cluster, the research area examines cell migration, cell differentiation, and cell proliferation by induction RAGE and toll-like receptors by HMGB1. It also examines the effects of S100 proteins on malignant tumor proliferation, cell migration, metastasis, and the effects of factors promoting epithelial-mesenchymal transition (EMT) on micrometastasis. High mobility group box 1 is a pro-inflammatory cytokine and pro-angiogenic factor that can signal through RAGE and the toll-like receptors (35,36). It induces EMT, which plays an important role in cancer progression, especially colorectal cancer, through signaling pathways that increase the levels of snail, nuclear factor (NF)-kappaB, and matrix metalloproteinase 7 (36).

In the third cluster, the research area consists of studies examining the effect of the formation and accumulation of methylglyoxal, a strong inducer of AGEs, on diabetes and cancer formation, intervention studies that prevent the formation of methylglyoxal, and epidemiological studies on different types of cancer. An epidemiological study conducted in Japan examining dietary AGEs and cancer risk found a significant positive association between liver cancer risk and AGE consumption (37). Dietary intake of AGEs negatively affects the liver and increases the development of non-alcoholic fatty liver disease (38). Similarly, dietary AGE intake increases the risk of breast cancer (39). These results are intriguing, but studies on dietary AGEs and cancer are insufficient. Keywords such as "diet", "nutrition" or "dietary AGE" did not appear in the top 10 most frequently used authors' keywords, and Figure 13 shows that the word "diet" appeared in trends only between 2019-2022. These results support the idea that there are insufficient studies on dietary AGEs. Although some studies have shown a relationship between dietary AGE consumption and cancer risk, the formation mechanism has not been revealed. As a result, more studies on dietary AGEs are needed.

In the fourth cluster, the study area examines the effect of RAGE and amphoterin, on tumor invasion and metastasis of different types of cancer. Besides, S100 proteins, especially S100B, are abundantly expressed in the nervous system and are thought to function as cytokines with neurotrophic and neurotoxic effects. S100B is a signaling receptor for the toxic effects of RAGE (24).

When the trend topics graph in Figure 13 is examined, it seems that studies on amphoterin have not been studied as of 2007, but the keyword "amphoterin" referred to as "HMGB1" in the current literature. The keywords "immunohistochemistry", "angiogenesis", "atherosclerosis" and "S100p" are fields of study that are a little more of the past. Studies that reveal the relationship between glycation, diabetes, and cancer via AGEs in

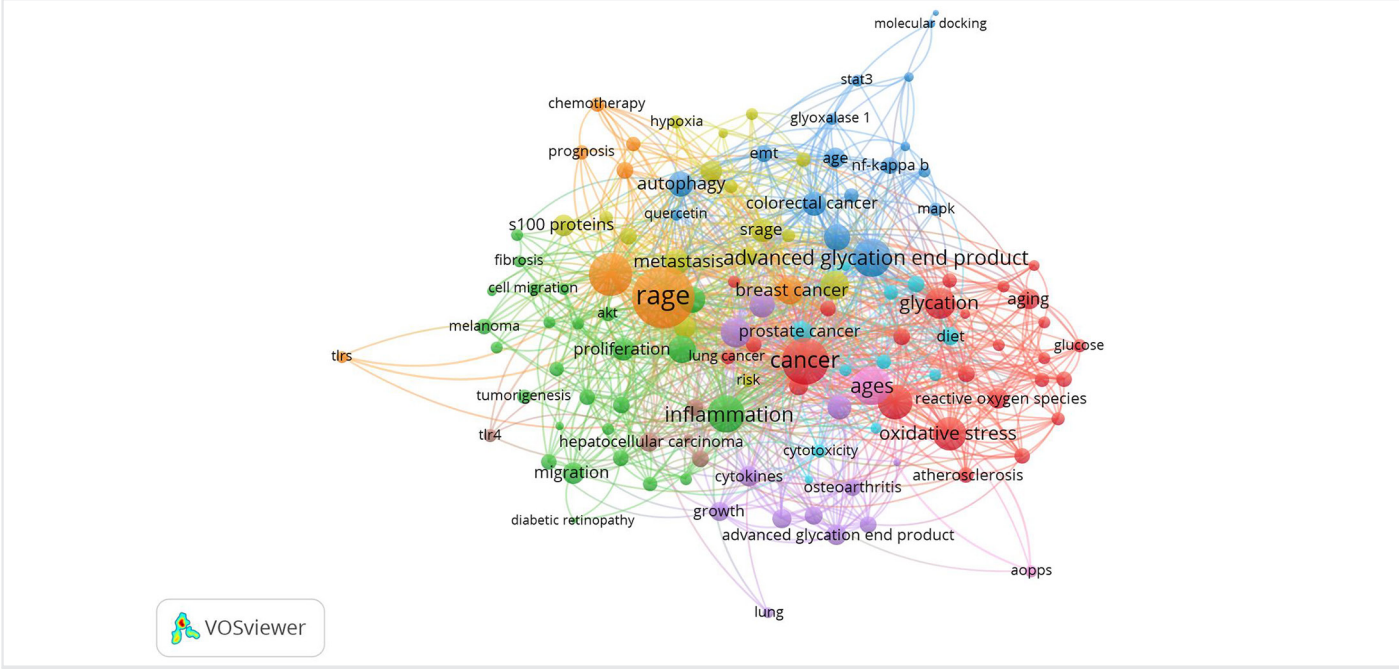

Figure 14. Co-occurrence analysis of author's keywords

the third cluster, are among the recently studied topics. Although "molecular docking" was among the trending keywords in 2022, this issue was not focused on much afterward. Network pharmacology, a term that has gained popularity recently, is an evolving approach used to explore the possible effects and mechanisms of natural products by conducting system-wide analyses of gene sets in herbs (40). Recent studies in our dataset have revealed that various active ingredients influence multiple mechanisms in the body, with some showing anticancer effects through the AGE-RAGE signaling pathway (40-42). Another currently popular keyword in our data was "signal transducer and activator of transcription 3 (STAT3)". The primary signaling pathways through which AGEs increase RAGE expression are NF-kappaB and STAT3 (43). In recent years, some cancer mechanisms have been explained through RAGE and STAT3 signaling pathways, and therefore STAT3 has become a popular word in current studies (44,45).

Generally, there is no keyword standard in the data set examined. The term "advanced glycation end product" is used alongside variations like "age," "ages," "AGEs," and "advanced glycation end-product," leading to similar keywords being grouped together. The lack of standardization in keyword usage underscores the importance of adopting consistent terminology to facilitate information retrieval and enhance the visibility of relevant research. To avoid this situation, authors can choose the most frequently used version of the keyword for their study through bibliometric research before publishing.

This study is the first bibliometric analysis of AGE and cancer. The fact that the WoS is a prestigious database with scientifically high-quality studies is one of the strengths of our study. Another strength of our study is that two researchers checked the data set separately, and the search strategy was created in great detail. Additionally, we could access more studies because we did not impose any language restrictions.

Study Limitations

The limitation of our study is that we only conducted bibliometric analysis based on the WoS database and did not include other publications on the subject from different databases. The exclusive use of the WoS database was primarily due to its high-quality, peer-reviewed content, and it is a widely accepted source for bibliometric analysis. Furthermore, WoS provides a comprehensive dataset for research in biomedical and health fields. However, future studies may consider incorporating additional databases for a broader comparison.

Conclusion

This bibliometric analysis highlights the growing significance of research into the relationship between AGEs and cancer, revealing key global trends in the field. While studies are increasing, much remains to be understood, particularly regarding the impact of dietary AGEs on cancer. The results underscore the need for greater international collaboration, with a special emphasis on expanding research in low- and middle-income countries. AGEs are emerging as a critical target for cancer prevention and treatment, reinforcing the importance of multidisciplinary studies to explore their biological effects in greater detail.

Our findings suggest that research on the AGEs-cancer connection will continue to expand. Studies focusing on molecules like RAGE and HMGB1 in cancer progression and metastasis have gained prominence. Further clinical validation of these targets could enhance treatment strategies. Future research will not only deepen our understanding of cancer's biological mechanisms but also help develop novel prevention and treatment approaches.

Ethics

Ethics Committee Approval: This study does not involve human participants, animal experiments, or private or sensitive data collection. It is a bibliometric analysis based entirely on publicly available data from the Web of Science database. Therefore, ethical approval were not required.

Informed Consent: This study does not involve human participants, animal experiments, or private or sensitive data collection. It is a bibliometric analysis based entirely on publicly available data from the Web of Science database. Therefore, informed consent were not required.

Footnotes

Authorship Contributions

Concept: Ş.N.D., Ş.A., Design: Ş.N.D., Ş.A., A.A.U., Data Collection or Processing: Ş.N.D., Analysis or Interpretation: Ş.N.D., Ş.A., A.A.U., Literature Search: Ş.N.D., A.A.U., Writing: Ş.N.D., A.A.U.

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Original Article

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Efficacy of Dual Triggering Versus hCG in Consecutive IVF Cycles in Women with Poor Ovarian Response

Düşük Overyan Yanıtı Olan Kadınlarda Art Arda IVF Sikluslarında Dual Tetiklemenin hCG'ye Karşı Etkinliği

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ABSTRACT

Objective: Bolus administration of gonadotrophin-releasing hormone (GnRH) analogs (GnRH-a) mimics physiological ovulation and reduces the risk of ovarian hyperstimulation syndrome. Adding GnRH-a to human chorionic gonadotropin (hCG) (dual triggering) to induce final oocyte maturation stimulates the luteinizing hormone surge and improves in vitro fertilization (IVF) outcomes by decreasing the rates of immature oocytes. The aim of this study was to compare the effects of hCG and dual triggering on cycle outcomes in patients with poor ovarian response (POR) in consecutive IVF cycles.

Methods: This retrospective cohort study included 54 patients with POR who underwent two consecutive IVF treatments within two years at the IVF Unit of Yeditepe University Hospitals. Two different triggering protocols (dual and hCG) were compared in terms of cycle outcomes.

Results: No statistically significant difference was found between the two triggering protocols in different IVF cycles of the same patients in terms of the total retrieved oocyte in the oocyte pick-up (dual: 3.72±2.96 vs hCG: 3.61±2.13, p>0.05), mature oocyte (dual: 2.88±2.40 vs hCG: 2.94±1.95, p>0.05), and normally fertilized oocyte (2 pronuclei) oocyte (dual: 2.83±1.91 vs hCG: 2.81±1.69, p>0.05) counts. No significant results were obtained

ÖZ

Amaç: Gonadotropin salgılatıcı hormon (GnRH) analoglarının (GnRH-a) bolus olarak uygulanması, fizyolojik ovulasyonu taklit eder ve ovaryen hiperstimülasyon sendromu riskini azaltır. Son oosit olgunlaşmasını indüklemek için insan koryonik gonadotropine (hCG) GnRH-a eklenmesi [ikili (dual) tetikleme], luteinize edici hormon (LH) dalgalanmasını uyarıp olgunlaşmamış oosit oranlarını azaltarak in vitro fertilizasyon (IVF) sonuçlarını iyileştirir. Bu çalışmada, düşük ovaryen yanıtı (DOY) olan olgularda hCG ve ikili tetiklemenin siklus sonuçlarına etkisinin hastaların ardışık IVF sikluslarında karşılaştırılması amaçlanmıştır.

Yöntemler: Bu retrospektif kohort çalışmasına, Yeditepe Üniversitesi Hastaneleri IVF Ünitesi'nde iki yıl içinde iki ardışık IVF tedavisi uygulanmış 54 DOY tanılı olgu dahil edilmiştir. İki farklı tetikleme protokolü (dual ve hCG) siklus sonuçları açısından karşılaştırılmıştır.

Bulgular: Aynı hastaların farklı IVF sikluslarında iki farklı tetikleme protokolü arasında oosit toplama işleminde (OTİ) alınan toplam oosit (değerleri: 3.72±2.96 ve hCG: 3.61±2.13, p>0.05), matür oosit (değerleri: 2.88±2.40 ve hCG: 2.94±1.95, p>0.05) ve normal olarak döllenen (2 pronükleus) oosit (dual: 2.83±1.91 ve hCG: 2.81±1.69 vs, p>0.05) sayılarında istatistiksel olarak anlamlı bir fark izlenmemiştir. Farklı tetikleyici grupları arasında pozitif

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ABSTRACT

in terms of positive β-hCG, implantation, clinical pregnancy, ongoing pregnancy, and abortion rates between different trigger groups (p>0.05).

Conclusion: Our findings showed that the different triggering methods did not significantly affect the cycle outcomes.

Keywords: Poor ovarian response, dual triggering, IVF, oocyte maturation, fertilization

ÖZ

β-hCG, implantasyon, klinik gebelik, devam eden gebelik ve abort oranları açısından anlamlı bir fark bulunamamıştır (p>0.05).

Sonuç: Bulgularımız, farklı tetikleme yöntemlerinin IVF siklus sonuçlarını önemli ölçüde etkilemediğini göstermiştir.

Anahtar Kelimeler: Düşük ovaryen yanıt, ikili tetikleme, IVF, oosit matürasyonu, fertilizasyon

Introduction

For many years, human chorionic gonadotropin (hCG) has been widely used in vitro fertilization (IVF) treatments to stimulate oocyte maturation and ovulation triggering by mimicking reproductive physiology and influencing the natural luteinizing hormone (LH) surge. Luteotropic effects of hCG, with its long half-life, result in an intrauterine environment that is optimal for pregnancy (1,2). The extended half-life of hCG is, however, a key contributor to the increased risk of ovarian hyperstimulation syndrome (OHSS) (3,4). Different medical approaches have been tried to prevent OHSS in oocyte pick-up (OPU) cycles, but no effective treatment method has been proven. To lower the incidence of OHSS, Shapiro et al. (5) put forward the administration of low-dose hCG and gonadotrophin-releasing hormone (GnRH) analogs (GnRH-a) on the same day of oocyte retrieval, so-called dual triggering. Shortly after, it was shown that patients with a history of recurrent empty follicles and immature oocyte rates achieved better results after dual triggering in terms of mature oocytes [metaphase II (MII)]. In another study, Griffin et al. (6) observed that by dual triggering, more mature oocytes were retrieved from the patients who had more than 25% immature oocytes in their previous OPU cycles.

Studies until today aimed to investigate the effects of dual triggering to prevent OHSS in patients who had high, normal, or low responses to controlled ovarian hyperstimulation (COH). Through those studies, the effect of dual triggering on oocyte maturation has been brought to light. While investigating the live birth rates in patients who had normal responses to dual triggering, Lin et al. (7) found a statistically significant increase in the total number of oocytes and the number of mature (MII) oocytes retrieved. Recently, the first prospective, double-blinded, randomized controlled study on normal responders to dual triggering (n=155) demonstrated the increase in oocytes per follicle, MII oocytes, and total oocyte counts, with no reported cases of OHSS (8). However, the effects of different triggering methods on the same poor responder patients' oocytes have not been evaluated and compared before. Our aim in this study is to apply two different triggering methods in consecutive COH cycles to poor responder patients and compare the total, mature (MII), and normally fertilized [2 pronuclei (2PN)] oocyte counts as well as cycle outcomes after each treatment.

Methods

Patient Selection

A total of 54 patients who had two consecutive treatment cycles within two years with different triggering protocols each were included in this single-centered, retrospective cohort study that was conducted at the IVF Unit of Yeditepe University Hospitals, İstanbul, Türkiye, between 2014 and 2021. The Ethical Committee of Yeditepe University approved the study protocol (approval no: 2022/12, date: 17.03.2022). The protocol was consistent with the World Medical Association Declaration of Helsinki's "Ethical Principles for Medical Research Involving Human Subjects". All participants received medical approval from their physicians and gave written, informed consent before they participated in the study. Every patient in this study was categorized as having poor ovarian response (POR) based on the Bologna Criteria, which were created in 2011. For the purposes of this study, patients were deemed to have POR if they met two of the three criteria outlined in the Bologna definition, which offer a precise framework for diagnosing POR.

Women 40 years of age or older meet the first criterion for the diagnosis of POR. Other risk factors that can make people more susceptible to a decreased ovarian reserve were also taken into account. These variables could include a history of radiation, chemotherapy, or ovarian surgery. The second criterion relies on past reproductive history. Specifically, POR is defined as the retrieval of 3 or fewer oocytes after 1 or more cycles of ovarian stimulation based on a conventional stimulation protocol. An inadequate number of oocytes retrieved with adequate stimulation is consistent with a diminished ovarian reserve, with an inability to respond adequately to traditional IVF protocols. Laboratory assessments of ovarian reserve include the third diagnostic criterion. If a patient's anti-Müllerian hormone (AMH) levels were <0.5-1.1 ng/mL or their antral follicle count (AFC) was ≤5-7, they were deemed to fit this condition. Since both AFC and AMH levels are correlated with the number and quality of a woman's remaining oocytes, these indicators are commonly accepted in clinical practice as being suggestive of a reduced ovarian reserve (5).

Among all patients with POR, patients who were treated with hCG mono for ovulation induction in their first COH protocol and who used dual trigger for the next, that is, consecutive

treatment, were included in this study. Patients who had not met the above-given criteria, and identified a genetic mutation regarding the oocyte maturation or had more than two years between those consecutive treatment cycles were excluded from the study.

Treatment Protocol

Patients were evaluated ultrasonographically on the 2nd or 3rd day of their menstrual cycle. COH was initiated to patients who did not have any contraindications for treatment. Appropriate dosage was determined according to the patients' characteristics. Recombinant follicle-stimulating hormone (FSH) (GONAL-f, merck-serono) and/or human menopausal gonadotropin (merional, IBSA) were/was used for COH.

Patients who were scheduled for flexible GnRH-antagonist protocol for pituitary suppression were evaluated ultrasonographically on the 5th or 6th days of their menstrual cycles. GnRH-antagonist (cetrotide, merck-serono or orgalutran, MSD) 0.25 mg subcutaneously daily was administered if at least one follicle was ≥14 mm. Ultrasonography was performed at regular intervals to follow up the follicular developments. When at least two dominant follicles of 17 mm were observed; standard 10.000 IU hCG (pregnyl 10.000 IU, merck or ovitrelle 500 mcg, Merck) or dual triggering was planned. Dual triggering was accomplished by the simultaneous injections of 10.000 IU hCG (pregnyl 10.000 IU, merck or ovitrelle 500 mcg, merck) and 0.2 mg triptorelin acetate (gonapeptyl, ferring). Three of the individuals who met the criteria had their ovulation induction induced by 500 mcg of choriogonadotropin alfa in the hCG mono arm. For the remaining 51 individuals, hCG was administered. To induce ovulation in each patient, 10.000 IU hCG and 0.2 mg triptorelin acetate were administered in successive doses. OPU was performed 36-38 hours after ovulation triggering.

On the second or third day of the menstrual cycle, oral estradiol (E2) (estrofem® 6 mg) was given to prepare the endometrium. When the endometrial thickness surpassed 7 mm on day 12 or 13, 400 mg of intravaginal progesterone (progestan 200 mg) and 50 mg of subcutaneous progesterone (prolutex® 25 mg) were administered daily. A frozen embryo from day five was thawed and transferred on day six of the progesterone regimen. Up to six weeks after conception, luteal-phase support was maintained using oral E2, subcutaneous, and intravaginal progesterone.

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences software (SPSS, version 25, IBM Corp, Armonk, NY, USA). Non-parametric Wilcoxon signed ranks test was used for the comparisons of two different triggering protocols that were applied to the same patients. A chi-square test was performed for the comparisons of IVF results of fresh embryo transfers between two different triggering methods. A p-value of <0.05 was considered statistically significant. The primary outcome was the effect of dual triggering on oocyte maturation, hence on mature oocyte counts.

Results

The comparison of demographics and clinical characteristics of the patients in each treatment is given in Table 1. The vast majority of patients [77.8% (n=42)] had primary infertility and the remaining ones [22.2% (n=12)] had secondary infertility. The average infertility duration of patients was 6.81±4.89 (mean ± standard deviation) years. Other concomitant pathologies to POR were advanced maternal age [44.4% (n=24)], endometrioma [3.7% (n=2)], absolute tubal factor [3.7% (n=2)], and male factor [3.7% (n=2)]. Although a statistically significant difference was observed between the ages of patients in their consecutive IVF cycles (dual vs hCG triggering), it did not have a clinical significance (38.80±3.72 vs 38.17±3.75, p<0.001, respectively). AMH (ng/mL) levels and body mass index (BMI) (kg/m^2) were found similar between dual and hCG triggering groups (AMH: 0.4565±0.30 vs 0.4561±0.30, BMI: 29.86±3.76 vs 29.24±4.23, respectively). Basal FSH and E2 levels were not statistically significant between the two treatment groups (p>0.05). Total gonadotropin doses were higher in dual triggering group than hCG triggering group (3955.56±963.78 vs 3619.81±911.27, p=0.011), however, stimulation days were similar (10.24±1.45 vs 9.98±1.18, respectively). No statistically significant difference was found between the dual triggering protocol and hCG protocol in different assisted reproductive technology cycles of the same patients in terms of total retrieved oocytes (dual: 3.72±2.96 vs hCG: 3.61±2.13, p>0.05) and mature oocytes (dual: 2.88±2.40 vs hCG: 2.94±1.95, p>0.05) (Table 1).

Of 108 COH cycles (54 cases in each group), no oocyte was obtained in six (5.5%) [hCG: 1 (1.9%), dual: 5 (9.3%)], no MII oocyte was obtained in two (1.9%) (both patients were in hCG group), no 2PN was observed in three (2.8%) [hCG:1 (1.9%), dual: 2 (3.7%)], oocyte vitrification was performed in six (5.5%) [3 (5.5%) in each group], cleavage arrest occurred in sixteen (15.2%) [8 (14.8%) in each group], total embryo freezing was applied in forty-one (38%) [hCG:21 (38.9%), dual: 20 (37%)] and embryos transfer was applied in forty-three (39.8%) [hCG: 23 (42.6%), dual: 20 (37%)] cases.

Regarding the normal fertilization, no statistical significance was observed in terms of 2PN oocyte count between two trigger methods in the COH cycles of 47 patients (hCG: 2.81±1.69 vs dual: 2.83±1.91, p>0.05) (Table 1).

When we evaluated the fresh embryo transfer results according to different trigger methods, rates of positive β-hCG, implantation, clinical pregnancy, and ongoing pregnancy were higher, while biochemical and clinical miscarriage rates were lower in the dual trigger group than hCG group. However, the differences were not found statistically significant (p>0.05). Similarly, the day of transfers and number of transferred embryos were not found statistically significant (p>0.05) (Table 2). Of 54 patients only eight patients (14.8%) had embryo transfers in both IVF cycles with different trigger methods. In the hCG triggering group, only two of them had positive β-hCG (25%). The implantation rate of 15 embryos that were transferred was 13.3%. However,

Table 1. The comparison of demographics, clinical characteristics and cycle outcomes of the patients in their COH cycles with dual vs hCG trigger

(n=54)	Dual triggering	hCG triggering	p-value
Age (years)	38.80±3.72	38.17±3.75	**<0.001**
AMH (ng/mL)	0.4561±0.30	0.4565±0.30	NS
BMI (kg/m²)	29.86±3.76	29.24±4.23	NS
Basal FSH (mIU/mL)	10.74±4.10	9.71±3.85	NS
Basal E2 (pg/mL)	36.76±17.64	43.06±19.52	NS
Total gonadotropin dose (units)	3955.56±963.78	3619.81±911.27	**0.011**
Duration of stimulation (days)	10.24±1.45	9.98±1.18	NS
Total retrieved oocytes (n)	3.72±2.96	3.61±2.13	NS
MII oocyte (n) (%)	2.88±2.40 (77.4%)	2.94±1.95 (81.4%)	NS
2PN oocyte (n)	2.83±1.91	2.81±1.69	NS

Values were given as mean ± standard deviation (SD)
Wilcoxon signed rank test was applied for the two related sample comparisons. Bold values are statistically significant (p<0.05)
COH: Controlled ovarian hyperstimulation, hCG: Human chorionic gonadotropin, AMH: Anti-Mullerian hormone, BMI: Body mass index, FSH: Follicle-stimulating hormone, E2: Estradiol hormone, MII: Metaphase II, NS: Statistically non-significant, n: Number, 2PN: 2 pronuclei

Table 2. Comparing the fresh embryo transfer results between hCG and dual triggering protocols

	Dual triggering (n=20)	hCG triggering (n=23)	p-value
β-hCG positive %	8/20 (40%)	7/23 (30.4%)	NS
Implantation %	6/32 (18.8%)	6/40 (15.0%)	NS
Clinical pregnancy %	8/20 (40%)	6/23 (26.1%)	NS
Biochemical miscarriage %	0/8	1/7 (14.3%)	-
Clinical miscarriage %	4/8 (50%)	5/6 (71.4%)	NS
Ongoing pregnancy %	4/20 (20%)	1/23 (4.3%)	NS
Day of transfer (n)			
Day 2/3	14	18	NS
Day 4	-	2	
Day 5	6	3	
Number of the embryos transferred	1.60±0.50	1.73±0.44	NS

Chi-square test was used for the comparisons. p<0.05 was accepted as statistical significance
NS: Non-significant, hCG: Human chorionic gonadotropin

all these pregnancies resulted with clinical miscarriage. In the dual triggering group, four patients had positive β-hCG (50%). The implantation rate was calculated as 30.8% with a total number of 13 embryos that were transferred. Only one of the four pregnancies was ongoing (12.5%), remaining three resulted with clinical miscarriage.

Discussion

GnRH-a have shown promise in reducing the risk of OHSS associated with hCG triggering. The concept of dual triggering, combining GnRH-a and hCG, has gained attention for its potential to enhance IVF outcomes, especially in cases of POR.

While previous studies have indicated positive effects of dual triggering on oocyte maturation and overall IVF success, the current study underscores that such benefits might not extend uniformly to patients with POR.

As the landscape of IVF continues to evolve, further investigation is warranted to fully understand the nuances of triggering methods in different patient populations. By shedding light on the specific circumstances of poor responder patients, this study contributes to the broader dialogue surrounding IVF protocols and the optimization of outcomes. However, it is important to note that this study mainly focused on oocyte-related outcomes due to the limited number of embryo transfers in our study groups (hCG: 23, dual: 20 embryo transfers). On the other hand, the potential impact on implantation, ongoing pregnancies, and live birth rates warrants additional exploration, especially considering the potential effects of GnRH-a triggering on luteal phase support and endometrial receptivity.

In Shapiro's research, the study group consisted of high-responder patients. In ovulation induction, the lowest doses of hCG paired with GnRH agonists were modified for each patient based on their weight and the probability of developing OHSS. In the study, there is no uniform dose application. There is no other group or treatment approach that can be used to compare the total number of oocytes collected, the number of mature oocytes, or fertilization rates (5).

Gonen et al. (9) demonstrated the physiological effects of GnRH-a on follicle maturation and oocyte triggering. Since the LH surge occurred within natural limits, the risk of OHSS was shown to be lower with GnRH-a triggering. Later studies demonstrated that endogenous LH surge and the following increase in FSH due to GnRH-a triggering also resulted in increased numbers of MII oocytes (10,11). However, due to inadequate corpus luteum formation, GnRH-a triggering is known to be associated with luteal phase deficiencies. Progesterone support and endometrial stabilization cannot be provided which may result in poor implantation rates and early pregnancy losses in fresh embryo transfers (10,12-14). In a systematic review, it was demonstrated that the administration of GnRH-a as a single triggering agent had negative effects on implantation rates, ongoing pregnancy rates, and live birth rates (15). Adding hCG or E2 and progesterone combinations to the treatment are some of the preventive measures that have been tried over the past years to solve this problem. Freezing all embryos and postponing embryo transfers are some of the common approaches in GnRH-a triggered cycles.

In a study conducted by Griffin (16), in 2012, he divided the patients into two groups and used GnRH agonist (1 mg leuprolide acetate) alone for ovulation induction in one group and GnRH agonist (1 mg leuprolide acetate and 1000 IU hCG) in combination with low dose hCG for ovulation induction in the other. The effects of GnRH-a triggering of high-responder patients, in contrast, showed a positive relationship of GnRH-a triggering with ongoing pregnancy rates and live birth rates without any OHSS case.

Schachter et al. (17) also proved a similar positive relationship between GnRH-a triggering and ongoing pregnancy rates in the normoresponder group. In Lin et al.'s (7) research published in 2013, the study population was normoresponders and the contribution of dual trigger ovulation induction to live birth rates was questioned as the main outcome. Apart from this, the clinical pregnancy rate, the implantation rate, the OHSS incidence, and the blastocyst progression rate were also calculated. In the study, standard doses of hCG (6500 IU of recombinant hCG) and dual trigger (0.2 mg of triptorelin and 6500 IU of recombinant hCG) were applied to two different normoresponder patient population groups. As a result, the total number of retrieved oocytes and the number of mature oocytes in the dual trigger applied group were statistically significantly higher than the hCG group. In the study, all embryo transfers were made as fresh cycles, and implantation rates, clinical pregnancy rates, and live birth rates were found to be statistically significantly higher (7). Dual triggering was associated with a considerably higher number of retrieved oocytes, mature oocytes, pregnancy rate, and live birth rate than the standard hCG trigger, according to the current meta-analysis (18).

In Shapiro et al. (19) retrospective cohort study published in 2021, clinical pregnancy rates and live birth rates were investigated as the main outcome in the hCG mono (10.000 IU hCG / 250-500 mcg ovidrel) and GnRH-a trigger combined with low dose hCG (1000 IU hCG +2 mg GnRH-a) groups (19). Although the number of retrieved oocytes and fertilization rates were higher in the dual triggering group, clinical pregnancy, and live birth outcomes were found to be statistically significantly lower.

Our initial aim in this study was to apply both hCG and dual triggering to poor responder patients in their consecutive COH cycles to compare the total and mature oocyte counts, that were obtained after each triggering method. Previous studies compared the effects of hCG and dual triggering in consecutive cycles of different patient populations. However, retrieved oocytes and MII/total oocyte counts of the different triggering protocols that were applied to the same patients with POR were compared for the first time. Although some publications demonstrate the increased total oocyte counts and MII oocyte rates after dual triggering in different patient groups; we found that the triggering method did not significantly affect the results in patients with POR.

Previous studies demonstrated the different effects of GnRH-a triggering on implantation rates, ongoing pregnancy rates, and live birth rates of high-responders and normal-responders. When we evaluated the cycle outcomes in the limited number of cases that had fresh embryo transfers (hCG: 23, dual: 20), positive β-hCG, implantation, clinical pregnancy, and ongoing pregnancy rates were higher, on the other hand, biochemical and clinical miscarriage rates were lower in Dual group than hCG group. However, the differences were not found statistically significant ($p>0.05$) (Table 2). Although there is a tendency that dual trigger could decrease clinical miscarriage, our results might

have increased statistical error due to the low number of patients. We could not compare the results of different trigger methods in the same patients since only eight patients had embryo transfers in their both IVF cycles. In the hCG triggering group, only two of them had positive β-hCG (25%) while it was four (50%) in the dual triggering group. The implantation rate was 13.3% for hCG and 30.8% for dual triggering. Only one of the four pregnancies was ongoing (12.5%) in the dual group, remaining ones and all two pregnancies in the hCG group resulted with clinical miscarriage.

Study Limitations

The major limitation of the study is that it was conducted with a small number of cases due to the difficulty of finding patients with two consecutive IVF treatments within two years with different triggering protocols in the same center. Our results should be confirmed in further large-scale studies due to the possibility of statistical errors that may arise from the small sample size.

Conclusion

Our results demonstrated that the choice of triggering method, whether hCG or dual triggering, did not significantly influence either the retrieved / mature / 2PN oocyte counts or clinical IVF outcomes in patients with POR. Our findings emphasize the complexity of IVF treatment and the need for tailored approaches to trigger methods based on individual patient characteristics. While the present investigation adds valuable insights to the field, further research is needed to comprehensively address the multifaceted aspects of triggering methods and their influence on diverse patient cohorts undergoing IVF.

Ethics

Ethics Committee Approval: The Ethical Committee of Yeditepe University approved the study protocol (approval no: 2022/12, date: 17.03.2022).

Informed Consent: All participants received medical approval from their physicians and gave written, informed consent before they participated in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.G.K.Y., M.Y., E.A., Concept: M.G.K.Y., G.Ö., M.Y., E.G.Ç., O.A., E.A., Design: M.G.K.Y., G.Ö., M.Y., E.G.Ç., O.A., E.A., Data Collection or Processing: M.G.K.Y., G.Ö., M.Y., E.G.Ç., O.A., E.A., Analysis or Interpretation: M.G.K.Y., G.Ö., M.Y., E.G.Ç., O.A., E.A., Literature Search: M.G.K.Y., G.Ö., M.Y., E.G.Ç., Writing: M.G.K.Y., G.Ö.

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Original Article

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Evaluation of the Factors Preventing the Opening of Health Facilities by SWARA Method

Sağlık Tesislerinin Açılışını Engelleyen Faktörlerin SWARA Yöntemi ile Değerlendirilmesi

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ABSTRACT

Objective: This study aims to prioritize the critical factors preventing the operation of healthcare facilities in Türkiye using the Step-Wise Weight Assessment Ratio Analysis (SWARA) method. Issues such as infrastructure, supply, geographical location, procurement processes, medical equipment supply, licensing and legal procedures, financial and human resource challenges encountered from the construction phase to service delivery are examined.

Methods: The SWARA method was used to identify and prioritize the factors hindering healthcare facilities' service delivery based on expert opinions, ranking these factors according to their importance. A total of eight criteria, derived from a comprehensive literature review, were assessed by five experts with relevant experience. The experts evaluated and ranked these factors, and the final prioritization was determined by calculating the geometric mean of their assessments.

Results: According to the analysis, financial issues were found to be the most significant factor affecting the service delivery process, with a weight of 29%. This was followed by licensing and legal procedures at 19%, material supply issues at 14%, and infrastructure problems at 12%. Human resource issues were identified as the least important factor, with a weight of 3%.

Conclusion: In line with the results obtained, stakeholders involved in the opening process have the opportunity to focus on and eliminate the problems related to them. At the same time, it also provides critical information about where those who plan the process should concentrate on inspections. In this way, health facilities will be able to start service provision at any time within the plan.

Keywords: Healthcare facilities, service delivery, SWARA method

ÖZ

Amaç: Bu çalışma, Türkiye'deki sağlık tesislerinin hizmet sunumuna geçişini engelleyen kritik faktörleri Aşamalı Ağırlık Değerlendirme Oran Analizi (SWARA) yöntemi ile önceliklendirmeyi amaçlamaktadır. Sağlık tesislerinin inşaat aşamasından hizmet sunumuna geçene kadar karşılaştığı altyapı, tedarik, coğrafi konum, ihale süreçleri, tıbbi malzeme tedariği, ruhsatlandırma ve yasal süreçler, finansal ve insan kaynağı sorunları incelenmiştir.

Yöntemler: SWARA yöntemi, sağlık tesislerinin hizmet sunumunu engelleyen faktörleri belirlemek ve önem sırasına göre ağırlıklandırmak amacıyla kullanılmıştır. Literatür taraması sonucunda belirlenen toplam sekiz kriter, ilgili alanda tecrübeli beş uzman tarafından değerlendirilmiştir. Uzmanlar, bu kriterleri önem derecelerine göre sıralamış ve nihai önceliklendirme, değerlendirmelerin geometrik ortalaması alınarak yapılmıştır.

Bulgular: Analiz sonuçlarına göre, sağlık tesislerinin hizmet sunum sürecini en fazla etkileyen faktör %29 ağırlıkla finansal sorunlar olmuştur. Bunu %19 ile ruhsatlandırma ve yasal süreçler, %14 ile yapı malzemeleri tedariği, %12 ile altyapı sorunları takip etmiştir. İnsan kaynağı sorunları ise %3 ağırlıkla en düşük öneme sahip faktör olarak belirlenmiştir.

Sonuç: Elde edilen sonuçlar doğrultusunda, açılış sürecinde görev alan paydaşların kendisi ile ilgili sorunlara odaklanması ve ortadan kaldırması imkanı doğmaktadır. Aynı zamanda süreci planlayanların ise hangi noktalardaki denetimlere yoğunlaşması gerektiği hakkında da kritik bilgiler sunmaktadır. Bu sayede sağlık tesisleri plan dahilinde istenildiği zamanda hizmet sunumuna başlayabilecektir.

Anahtar Kelimeler: Sağlık tesisleri, hizmet sunumu, SWARA yöntemi

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Introduction

Health facilities are critical structures for the protection and improvement of public health. This ensures that health facilities are indispensable elements of the modern society structure. The main purpose of health facilities is to provide all kinds of health services. Since people's health has a significant impact on their lives, the value of modern health facilities is increasing at both public and state level. For this reason, many new health facilities have been planned and constructed in Türkiye in recent years (1). However, many mishaps may occur in the process from the stage when a health facility is planned to the moment when it will actively provide service provision. Such situations prolong the time for the health facility to enter the service provision phase (2). Health facilities projects often require significant investment. Lack of financial resources can be a significant obstacle to their construction and implementation. The complexity and size of the structure to be built may cause the planned construction time to be extended. Such situations usually occur after disruptions in the procurement processes of the required building materials. Health facilities in the relevant area are expected to serve thousands of people a day. For this reason, the relevant facility should be built in the most suitable geographical area in terms of infrastructure. After the completion of the construction phase of the mentioned health facilities, there are some factors that prevent the transition to service provision. In particular, problems in the procurement and tendering of medical equipment required for service provision prolong the process. Moreover, the opening of new modern health facilities further increases the need for professional human resources. Finally, deficiencies in the legal procedures of a completed health facility also constitute an obstacle in the transition to service provision.

The failure of a health facility to start service delivery on schedule has serious negative impacts on community health and the economy. From a public health perspective, a delayed facility can prevent individuals in the area from accessing timely and adequate healthcare, triggering the spread of diseases and the progression of health problems. On the financial side, delays lead to budget losses at the government level, while for investors they mean additional costs and wasted resources. Moreover, the burden of out-of-service facilities is transferred to other health facilities in the surrounding area, leading to overcrowding in existing facilities, increased workload on staff and a decline in the quality of health services. These critical impacts underscore the importance of ensuring timely and effective transition of health facilities to service delivery.

In order for the planned health facilities to be able to provide services on time, it is necessary to take measures to minimize this obstacle. In this context, correct planning of legal procedures should be made. At the same time, necessary improvements should be made during the construction phase or the subsequent material procurement phase. All these planning and improvements increase the cost. Therefore, it is not financially reasonable for those who plan, build and implement health facilities to take too many measures together. Therefore, it is necessary to transfer the budget to more important factors when making an investment plan. For this reason, a priority analysis should be conducted to determine the order of importance of the factors that hinder the service delivery of a health facility. However, it is seen that there are not enough studies focusing on this issue in the literature. Accordingly, this study aims to identify and prioritise the critical obstacles in front of the health facilities that are in the construction phase or even if the construction has been completed but cannot start the service delivery process due to various reasons by using Step-Wise Weight Assessment Ratio Analysis (SWARA) method. In this way, it fills the gap in the literature in the relevant field. The research offers not only theoretical contributions but also practical guidance for policy makers and practitioners.

In the first part of this study, there is an introductory section in which the subject is generally stated. It is followed by the title of literature review in which current sources related to the subject are reviewed. In the third section, the SWARA method used in the study is explained. The analysis results and findings obtained from the study are presented in the fourth section. Finally, there is a discussion section where the findings of the study are evaluated and a conclusion section where a general evaluation is made.

Literature Review

Infrastructure problems are one of the critical factors that prevent health facilities from providing services effectively. The infrastructure of health facilities covers a wide range from the basic structural elements of the building to technological investments, from the number of beds and medical devices to electricity resources (3). Infrastructure deficiencies can directly affect the functioning of health facilities and the quality of health services. According to Altsoy and Taştan Boz (4), infrastructure problem is an important factor in the effective operation of hospitals and should be supported. Infrastructure deficiencies may delay the opening of health facilities on planned dates and cause disruptions in the provision of health services. Buzcu and Birdir (5) in their study examining the problems of medical tourism in Türkiye, stated that the lack of physical and technological infrastructure in hospitals had a negative impact on health service delivery. In the study conducted by Küçük (6) it was seen that health facilities should be strengthened and supported in terms of personnel, physical infrastructure and medical equipment in order to secure long-term health services. According to the study conducted by Kurt (7), infrastructure improvements are crucial for enhancing both safety standars and service quality; therefore, it is important to address infrastructure problems during the opening process of the facility.

Supply and construction maintenance issues in facility building materials can significantly impact the timely completion of healthcare facility construction projects. Building materials are critical to ensure the durability and safety of healthcare facilities. Olanrewaju et al. (8) stated that poor quality or inadequate materials could shorten the life of facilities, increase maintenance costs, and even pose a risk to patient safety. Therefore, necessary precautions and planning should be made facility-oriented. In this context, maintenance management of hospital buildings

presents different challenges compared to other building types. The analysis of defective components of buildings to be used for healthcare facilities, maintenance plans and the supply of necessary building materials should be provided as soon as possible (9). Furthermore, Halıcıoğlu and Kuntay's (10) research shows that material shortages and price fluctuations can lead to serious disruptions in the construction process. Therefore, solving maintenance and supply problems in building materials plays a major role in the completion and opening of facilities on planned dates.

The geographical location and transportation of the facility play an important role in the opening of health facilities and providing accessible services. Location and ease of transportation is one of the criteria that patients consider when choosing a health institution (11). While this situation provides many advantages for hospitals with easy access, it may cause disruptions in opening processes and patient flow for health facilities in remote areas where transportation is difficult. Karaman (12), in his study on city hospitals, stated that hospitals had negative evaluations due to the fact that they were located in remote areas of the city. In their study, Chen et al. (13) stated that the geographical distribution of the population and the location of health resources directly affected the accessibility of health services and emphasized that these factors should be considered in local health planning. Additionally, it was contended in their work that improving transportation infrastructure could enhance access to healthcare by making it easier for residents of remote areas to reach healthcare services. In another study, Weiss et al. (14) examined the travel time of patients to health facilities and stated that geographical factors were a measure of welfare in accessing services. In a study conducted by Cheng et al. (15) in China, it was emphasised that the spatial distribution of healthcare facilities in the region was critical for patients' access to services and the economic sustainability of facilities. Such geographical challenges can make it difficult for facilities to provide services effectively and open on time.

Tender processes play an important role in the construction and operational processes of healthcare facilities. The complexity of tender processes prolongs the completion time of projects (16). Legal disputes at the tender stage and delays in the evaluation of bids can lead to disruptions in the process. There are various models such as public-private partnership in the health sector in Türkiye. Various uncertainties and incompatibilities that may occur in these tender implementation regulations may increase the costs and extend the duration of the project (17). According to Adebayo et al. (18), tender procedures have a big impact on the acquisition of necessary medical equipment and supplies, which in turn affects how efficiently healthcare facilities operate. Effective tendering can lower costs and improve supply chain management, but complicated processes can cause delays and increase administrative workloads. Kulaksız and Küçükkocaoğlu's (19) research shows that in order to minimise possible problems that may be experienced in healthcare institutions, tender processes should be managed effectively, the appropriate model should be selected and projects should be completed on time.

Problems in the supply of medical supplies are critical for healthcare facilities to provide effective services. Medical supplies directly affect the quality of patient care; therefore, it is necessary to supply these supplies on time and in sufficient quantity (20). The entire process from the production of a medical equipment in healthcare organisations to its delivery to patients is considered within the scope of the supply chain process (21). Since the consumer group is the patient, planning and implementation of the supply of medical equipment is extremely important. According to a study conducted by Modutlwa (22), issues in the supply of medical supplies lead to shortages of essential equipment, compromising patient care and increasing health risks. These supply chain problems also result in ineffective treatment, limited therapy options, higher costs, and ultimately, worsened patient outcomes, contributing to increased morbidity and mortality rates. Göncü's (23) study on supplier relationship management shows that disruptions in material supply can cause major problems both in emergencies and in daily operations. In this context, regular and reliable procurement of medical supplies is of great importance to improve the quality of patient care and the operational efficiency of the facility.

Licensing and legal processes required for the opening of health facilities are a critical step for the facilities to operate in accordance with legal and regulatory standards. Licensing in healthcare facilities is also associated with minimum standards for physical and structural requirements such as physical structure, number of personnel, medical equipment and devices (24). Delays in licensing processes can significantly disrupt the provision of health services. The reasons for licensing delays include the complexity of bureaucratic processes, lack of communication between regulatory bodies, and problems in legal compliance processes (25). The complexity of these processes may prolong the opening time of the facility, delaying the service provided to the community and increasing operating costs. In order to meet sustainable public health and public health requirements, zoning and legal processes must be handled in a timely manner (26). Therefore, accelerating and making legal and licensing processes more efficient is critical to ensure that facilities are opened on time.

Financial management and planning is a critical factor affecting the opening process and operational efficiency of facilities. In this context, efficient financing mechanisms are required for health institutions in order to avoid disruptions in the services provided (27). As a matter of fact, studies on unmet needs have revealed that economic inadequacies in health services are not only individual but also health facility-related (28). The study by Calabrese et al. (29) discusses constraints such as resource limitations, demand, efficiency, capacity, distance and cost that prevent the optimal location of health facilities. These factors, which are influenced by economic management and planning, hinder sustainability and the establishment of new health services in various regions. Insufficient financial resources may cause the facility to have difficulty in meeting equipment and personnel needs. In their literature review, Cansever and Gökkaya (30) stated that hospital construction required a good economic analysis and cost plan. In

another study, Yousefli et al. (31) emphasised the importance of budget planning for healthcare facilities due to the criticality of the service they provide.

Human resource issues are a critical element for healthcare facilities to provide effective services. Difficulties in recruiting healthcare professionals can directly affect the quality of patient care and service efficiency (32). In addition, administrative staff shortages may cause disruptions in operational processes, which may delay the opening of facilities. Armağan Kaygusuz (33) stated in his study that the most important factor for an organisation aiming to provide sustainable and efficient service delivery was human resources. Sünter (34) emphasised that health facilities in developed societies should provide a safe working environment by taking the necessary precautions for their employees. In this context, human resource management and planning should be carried out for the aims and objectives of the organisation. A study by Hassan et al. (35) concluded that all stakeholders in the healthcare sector should prioritize retention factors when designing or reviewing strategies and policies, including management initiatives, innovation-driven soft human resource management, and job satisfaction, to address the significant losses caused by high employee turnover rates. In another study, Üner (36) stated that the process of recruitment and selection of qualified personnel was important to increase the operational efficiency and service quality of healthcare facilities.

Methods

In this study, it is aimed to determine the critical obstacles in front of the health facilities that are in the construction phase or cannot start the service delivery process for various reasons even if the construction is completed and to prioritise them by SWARA method. At this stage, the obstacles in front of the service delivery process were determined as a result of the literature review. These criteria are infrastructure problems, problems in the building materials of the facility, geographical location of the facility, tender processes, procurement of medical supplies in the facility, licensing and legal processes, financial problems, human resource problems. The determined criteria and criteria descriptions are given in Table 1.

The criteria determined within the scope of this study were prioritised using the SWARA method. At this stage, the opinions of 5 experts who have in-depth knowledge on the subject were consulted. In similar studies in the literature, it is stated that the experts who will make the evaluation should have at least 5 years of experience and the opinions of at least 3-6 experts are needed. The professional and occupational distribution of the experts was also carefully considered during the selection process. Two of the experts included in the study were professors and three were assistant professors. All experts had academic and professional experience in the field of health management, and each of them had at least 5 years of sectoral knowledge. These characteristics ensured that the experts had in-depth knowledge on the subject and were able to make reliable assessments (37-39).

The data obtained from the expert opinions guided the process of weighting and prioritisation of the criteria.

Since the article did not use data, scales or subjects, ethics committee permission and patient consent were not required.

Statistical Analysis

In this study, SWARA method, which is one of the multi-criteria decision-making techniques, was used in the data analysis phase. SWARA, which is one of the criterion weighting methods, has been frequently used in recent years. The main reason for choosing the SWARA method in our study is that this method provides a structured and systematic process for determining the importance of criteria. The SWARA method determines the criteria weights by progressively processing the evaluations obtained from the experts and thus provides a more understandable approach to the decision-making process (40). SWARA method consists of 5 steps. These steps are:

Step 1: Ranking the criteria from most important to least important according to the level of importance:

In the first step of SWARA method, experts rank the criteria from most important to least important. When more than one expert evaluates, each expert ranks the criteria according to their own importance and at the end of this process, as many rankings are

Table 1. Problems that prevent health facilities from providing health services

Categories	Explanations	Sources
Infrastructure problems	Deficiencies in basic infrastructure needs of the facility such as electricity, water and roads	(3-7)
Procurement and other problems in the building materials of the facility	Problems in the quality or suitability of materials used in construction	(8-10)
Geographical location of the facility	Distance of the facility to settlements, transport networks and emergency services	(11-15)
Tender processes	Bureaucratic problems or delays at the tender stage	(16-19)
Medical equipment supply problems in the facility	Difficulties in procurement of medical devices and materials needed by the facility	(20-23)
Licensing and legal processes	Problems encountered in the official permits and legal processes required for the facility to start operation	(24-26)
Financial challenges	Inadequate financial resources required for the construction or operation of the facility	(27-31)
Human resource problems	Deficiencies in the provision of health and support staff of the facility	(32-36)

obtained as the number of experts. By taking the geometric mean of these rankings, an overall ranking is obtained for the criteria.

Step 2: Determining the relative importance levels of the criteria:

In the second step of the SWARA method, the criteria are compared among themselves in order to determine the relative importance levels of the criteria. At this stage, it is determined how important criterion j is compared to criterion (j+1). Keršuliene et al. (40) named this ratio as "comparative importance of the average value" and expressed it with the symbol s_j.

Step 3: Calculation of k_j Coefficient:

In the third step of SWARA method, k_j coefficient is calculated for each criterion. At this stage, the following equation (1) is utilised. The k_j coefficient of the criterion with the highest importance in the ranking of the criteria is assigned as 1.

$$k_j = \begin{cases} 1, & j = 1 \\ s_{j+1}, & j > 1 \end{cases} \quad (1)$$

Step 4: Calculation of q_j values of the criteria:

The q_j values showing the weights of the criteria are calculated by utilising equation (2).

$$q_j = \begin{cases} 1, & j = 1 \\ \frac{q_{j-1}}{k_j}, & j > 1 \end{cases} \quad (2)$$

Step 5: Determining the relative weight values of the criteria:

In the last stage of SWARA method, the relative weight values (w_j) of each criterion are calculated. W_j value indicates the relative importance of criterion j. It is calculated with the help of equation (3) below.

$$\frac{q_j}{\sum_{k=1}^{n} q_k} \quad (3)$$

Results

In this study, the critical obstacles in front of the health facilities which were under construction or even if the construction was completed but service delivery process could not start due to various reasons were identified and prioritised by SWARA method. Within the scope of SWARA method, firstly, 5 expert opinions were obtained for the evaluation of the criteria obtained as a result of the literature review. Each expert was asked to rank the 8 criteria in descending order of importance. Since there was more than one decision maker, in order to obtain a general ranking, the geometric mean of these procedures was taken and the final ranking result was obtained as shown in Table 2.

In the next stage of SWARA method, the relative importance level of each criterion is determined. In order to determine the relative importance levels of the criteria, experts are expected to make comparisons between the criteria. Each criterion is compared with the criterion above it and their importance levels are determined. For example, in this study, the financial problems criterion ranked first in the ranking made by the experts. Experts were asked how important the financial problems criterion was compared to the licensing and legal processes criterion. Table 3 shows the evaluations of the experts.

After the s_j values are obtained in the SWARA method, the stage of calculating the k_j coefficient comes. At this stage, the k_j value of the financial problems criterion, which has the highest importance in the criterion ranking, is taken as 1 according to the method. The k_j values of the other criteria are obtained by adding 1 to the s_j values as in Equation (1). The k_j values are followed by the calculation of q_j values. At this stage, the q_j value of the financial problems criterion, which ranks first, is assigned as 1 according to the method. The q_j values of the following criteria are calculated by utilising equation (2). The final weight values of the criteria are also calculated using equation (3). The q_j value of each criterion is divided by the sum of q_j values. Below is the table showing the steps of SWARA method as a result of the evaluations made by the experts.

Table 2. Expert evaluations

Criteria	Expert 1	Expert 2	Expert 3	Expert 4	Expert 5	Geometric mean	Final ranking
Infrastructure problems	4	8	5	2	2	4.2	4
Procurement and other problems in the building materials of the facility	5	1	3	5	5	3.8	3
Geographical location of the facility	8	3	7	6	7	6.2	7
Tender processes	3	6	6	8	4	5.4	5
Medical equipment supply problems in the facility	6	7	4	4	6	5.4	6
Licensing and legal processes	2	2	2	3	3	2.4	2
Financial challenges	1	4	1	1	1	1.6	1
Human resource problems	7	5	8	7	8	7	8

As a result of the analyses, it was determined that the most important obstacle for health facilities to transition to the service delivery process is financial problems with a criterion weight of 0.28. This was followed by the criterion of licensing and legal processes with a criterion weight of 0.19. The least important criterion was found to be human resource problems with a criterion weight of 0.04. The final criteria weights in Table 4 show the prioritization of the obstacles encountered in the establishment process of health facilities. According to the results of the analysis, financial problems were identified as the most critical barrier with a weight of 0.28. This situation points to factors such as high capital requirements, investment costs and limited financing resources in the establishment process of health facilities. Establishing the infrastructure of health services, technology and equipment purchases, maintenance and operating expenses constitute a significant financial burden. In addition, limited access to financial resources in this process stands out as an important factor that slows down or stops the establishment processes.

Discussion

In this study, it was aimed to identify and prioritize the critical obstacles in front of the health facilities were under construction or even if the construction was completed but service delivery process could not start due to various reasons were identified and prioritised by SWARA method. It was concluded that the criterion with the highest degree of importance among the criteria was "financial difficulties" and the criterion with the lowest importance was "human resource problems", "licensing and legal processes" and "supply problems in building materials" were found to be the second and third most important criteria. According to the results of the analysis, financial difficulties were found to be the criterion with the highest degree of importance faced by health facilities that were under construction or even if the construction was completed but service delivery process could not start due to various reasons. In order to overcome the difficulties related to this criterion, effective financial planning is required. In the study conducted by Emek (41), it was stated that only 12 of the 20 public-private partnership contracts in 2017 were able to obtain the necessary financing, and that the investments proposed in line with the contracts and the budget planning envisaged could not be realized. Yeşiltaş (42) examined the financial, legal and economic criticisms of public-private partnerships and city hospitals. As a result of this examination, it was revealed that financial institutions were reluctant to fund these partnerships. Emin Kurt and Demirhan (43) conducted a strengths, weaknesses, opportunities, threats analysis for the planned city hospital in Diyarbakır. As a result of the analysis, it is emphasized that the high-cost city hospital will create an economic burden and may cause problems in terms of financial sustainability as it requires a certain occupancy rate. Aliefendioğlu and Bostancı (44) examined the formation process of city hospitals in Türkiye and found that the most important problem encountered in the construction of hospitals was the problem of finding financial resources. When the results of the studies in the literature are analyzed, they are similar to the results of this study.

Table 3. S_j values

s_j	Expert 1	Expert 2	Expert 3	Expert 4	Expert 5
Financial challenges					
Licensing and legal processes	0.80	0.80	0.70	0.20	0.25
Procurement and other problems in the building materials of the facility	0.70	0.30	0.50	0.25	0.30
Infrastructure problems	0.45	0.10	0.50	0.05	0.05
Tender processes	0.35	0.70	0.60	0.10	0.25
Medical equipment supply problems in the facility	0.55	0.55	0.55	0.30	0.30
Geographical location of the facility	0.50	0.55	0.05	0.40	0.30
Human resource problems	0.30	0.10	0.40	0.05	0.05

Table 4. Final criteria weights

	s_j	k_j	q_j	w_j
Financial challenges		1	1	0.28
Licensing and legal processes	0.46	1.45	0.68	0.19
Procurement and other problems in the building materials of the facility	0.34	1.34	0.51	0.14
Infrastructure problems	0.19	1.19	0.42	0.12
Tender processes	0.33	1.33	0.32	0.09
Medical equipment supply problems in the facility	0.38	1.37	0.23	0.06
Geographical location of the facility	0.30	1.3	0.17	0.05
Human resource problems	0.15	1.15	0.15	0.04

Within the framework of the findings, policy makers can develop sustainable financing models in public-private cooperation. In addition to these models to be developed, policy makers can develop risk-sharing and incentive policies to gain the trust of investors or institutions. Feasibility studies can be conducted for the estimated budget plans. Alternative income channels can be created to reduce the financial pressure on health facilities.

According to the results of the study, licensing and legal processes were the second most important criteria for health facilities that were under construction or even if the construction was completed but service delivery process could not start due to various reason. Legal processes are critical for the functionality of health facilities. The licensing processes required for a health facility to become operational involve long and complex procedures. This situation also makes it difficult to transition to service delivery of health facilities whose construction is completed. Sonğur and Top (45) revealed the opinions of stakeholders on public-private partnership and integrated health campus practices. According to the results of the study, failure to ensure transparency in contracts is predicted to lead to failures related to the process. In addition, long tender processes are among the problems related to public-private partnership in the health sector. In the study conducted by Sungur (46), it was stated that the complexity of public-private partnership contracts and the long joint operation period pave the way for many risks in health facilities. Kaya (47) aimed to present an analysis of strengths/weaknesses and opportunities/threats for city hospitals built through public-private partnership. According to the results of the analysis of that study, long contract periods, uncertainties at the end of the contract, disorganized legal infrastructure and lack of transparency of the contracts were stated as weaknesses. The results of the study are in line with the results of the analyzed studies. For licensing and legal processes, policy makers can reduce the impact of bureaucracy by relaxing the procedures applied. In addition, flexibilities should be created for long tender processes. Managing complex processes in an open and transparent manner and strengthening coordination and communication between institutions will facilitate the process. Carrying out all processes within the framework of determined standards and ensuring the participation of all stakeholders in the changes to be made in legislation and legal regulations can minimise the problems that may be experienced.

According to the results obtained from the analyses, it has been determined that the third most important criterion faced by health facilities in the service delivery process or opening to service is the supply problems in the building materials of the facility. The inability to purchase materials for the construction of health facilities on time, fluctuations in prices and disruptions in the supply chain process cause the facilities to experience some difficulties in the opening or service process. In the study conducted by Bilen and Solmaz (48), supply and distribution problems are among the problems experienced by small and medium-sized enterprises Yılmaz et al. (49) found that the lack of a comprehensive evaluation model that should be used in the construction process of buildings caused some problems. Olanrewaju et al. (50) stated that poor quality materials used in the study could create problems for the facility and even increase maintenance costs. Accordingly, maintenance organizations and procurement procedures should be redesigned to meet the needs. Integration of digital technologies in building material procurement processes can prevent operational disruptions. Agreements can be made with alternative companies against unpredictable delays. An accurate and effective supply management model should be established. Managers can minimise possible risks by making agreements with suppliers by considering price, delivery time and quality factors. In addition, tender processes with suppliers should be open and transparent.

Study Limitations

Health facilities are classified according to many factors such as size, ownership and scope. However, within the scope of applicability in the study, all health facilities were examined in a single study without a separate evaluation. These situations constitute an important limitation of the study. Another limitation of the study is the evaluation of 5 experts' opinions as decision makers.

Conclusion

According to the findings of the study, there are some fundamental problems in both the construction phase and the transition to operationalization of health facilities. These problems delay the opening process of health facilities, leading to loss of time and exceeding existing budgets. As a matter of fact, the increase in costs directly affects the sustainability of the facility. Effective management of financial resources is an important issue for successful and timely service delivery. Financing sources can be diversified through the use of digital financial instruments, cooperation with international institutions and organisations, and green financing models. A performance-based incentive system can be created for contractors or intermediary companies. Common funds or state-backed loans can be offered to reduce risks for sector investors. Making strategic decisions by conducting a feasibility study for the region where a health facility will be planned can eliminate unnecessary financial burden. In order to reduce the problems experienced in legal processes, there is a need for flexible and ambiguity-free legislative arrangements. In order to improve supply processes for the facility, a good planning system, predictable demand forecasting and the use of alternative supply channels come to the fore. These measures will minimize the problems encountered in procurement processes and facilitate the timely delivery of the project. As a result, the elimination of these barriers will ensure the desired efficiency of health facilities and the effective delivery of services. Considering these critical factors in the strategic planning process plays a critical role in increasing the sustainability of the facility and achieving the desired performance. For future studies, other multi-criteria decision-making techniques such as decision making trial and evaluation laboratory, analytic hierarchy process (AHP) or fuzzy AHP can be used to compare the research results. In the literature, it is criticised that expert opinions are taken equally. The level of knowledge of experts varies according to qualifications such as

experience, education and title. For this reason, it is suggested that artificial intelligence-based models that also weight expert opinions should be used in future studies. In addition, this study was evaluated within the scope of the health sector and sectoral differences can be revealed by conducting studies on other sectors.

Ethics

Ethics Committee Approval: Ethics committee permission was not required since the article did not use elements such as data, scales or subjects.

Informed Consent: Since the article did not use data, scales or subjects, informed consent of patients was not required.

Footnotes

Authorship Contributions

Concept: K.Ş., B.S., Y.D.U., S.K., Design: K.Ş., B.S., Y.D.U., S.K., Data Collection or Processing: S.K., Analysis or Interpretation: K.Ş., B.S., S.A., Writing: K.Ş., Y.D.U., S.A.

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Original Article

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Evaluation of Injuries Due to Traffic Accidents with Trauma Scoring Systems

Trafik Kazalarına Bağlı Yaralanmaların Travma Skorlama Sistemleri ile Değerlendirilmesi

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ABSTRACT

Objective: The purpose of this study was to examine the common traits of individuals admitted to our Forensic Medicine Clinic as a result of traffic accidents and the seriousness of their injuries.

Methods: This study covered the cases at the Forensic Medicine Clinic between 2015 and 2021 where a forensic report was made due to a traffic accident.

Results: In this study, 802 cases were included: 69.20% (n=555) of the cases were male with the mean age of 36.10±19.62 years (min.:1, max.:90). Seat belts were not buckled up in 62.30% (329/528) of the in-vehicle traffic accident cases. In 71.43% (55/77) of the motorcycle accident cases, helmets and safety gear were not used. A significant difference was noted in injury severity across various age groups ($p<0.001$). Motorcycle and off-vehicle traffic accidents had significantly higher Injury Severity Score (ISS) and New ISS values ($p<0.001$).

Conclusion: The findings of this research indicated that most individuals involved in traffic accidents did not utilize seat belts, helmets, or safety gear. This demonstrates the apparent necessity for social education and advertisements to be increased, road safety policies should be re-evaluated, and safety belt and helmet checks in traffic should be increased to ensure seat belts, helmets, and safety gear use.

Keywords: Traffic accident, injury, trauma scores, seat belt, helmet, forensic medicine

ÖZ

Amaç: Bu çalışmada, Adli Tıp Kliniği'mize trafik kazası nedeniyle başvuran olguların genel karakteristik özelliklerinin ve travma skorlama sistemleri kullanılarak yaralanma şiddetlerinin değerlendirilmesi amaçlanmıştır.

Yöntemler: 2015-2021 yılları arasında Adli Tıp Kliniği'nde trafik kazası nedeniyle adli rapor düzenlenen olgular çalışmaya dahil edildi.

Bulgular: Çalışmaya 802 olgu dahil edilmiş olup, %69,20'si (n=555) erkek, yaş ortalaması 36,10±19,62'dir (min.:1, max.:90). Araç içi trafik kazası geçiren mağdurların %62,30'unda (329/528) emniyet kemeri takılı değildi. Motosiklet kazası geçiren olguların %71,43'ünde (55/77) kask ve koruyucu ekipman bulunmamaktaydı. Yaş grupları ile yaralanma şiddeti arasında istatistiki olarak anlamlı bir farklılık tespit edilmiştir ($p<0,001$). Araç dışı trafik kazalarında ve motosiklet kazalarında Yaralanma Ciddiyeti Skoru (YCS) ve Yeni YCS şiddeti anlamlı derecede daha yüksekti ($p<0,001$).

Sonuç: Bu çalışmanın sonuçları, trafik kazası mağdurlarının çoğunluğunun emniyet kemeri, kask veya koruyucu ekipman kullanmadığını göstermiştir. Bu nedenle emniyet kemeri, kask ve koruyucu ekipman kullanımının yaygınlaştırılması için toplumsal eğitimlerin ve reklamların arttırılması, karayolu güvenlik politikalarının yeniden değerlendirilmesi ve trafikte emniyet kemeri ve kask denetimlerinin daha da sıklaştırılması gerektiği düşüncesindeyiz.

Anahtar Kelimeler: Trafik kazası, yaralanma, travma skorları, emniyet kemeri, kask, adli tıp

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Introduction

Traffic accident-related deaths and injuries are major public health issues (1). While traffic accident deaths increase each year in middle- and low-income countries, they are decreasing significantly in high-income countries such as Germany due to strict road safety measures (2). In Türkiye, traffic accidents cause injuries of tens of thousands and the deaths of thousands of people every year. According to the data from the Turkish Statistical Institute, a total of 983,808 road accidents took place in Türkiye in 2020, 4,866 people lost their lives and 226,266 people were injured (3). Excessive speed, poor road conditions, young drivers, carelessness, distraction, alcohol or drug use, not using a helmet or seat belt, and lack of airbags are among the most important causes of serious injuries, including death in traffic accident (4,5).

The reduction of serious injuries due to road traffic accidents may only be possible by determining the causes and applying road safety policies in this context (2). Trauma scoring systems like Injury Severity Score (ISS) and New ISS (NISS) help determine the degree of trauma (6). AIS is an anatomical-based coding system developed by the Association for the Advancement of Automotive Medicine in the mid-1960s to track injuries in automotive and aircraft accidents. It rates each type of damage on a six-point scale based on body region (7). The squares of the Abbreviated Injury Score (AIS) scores for the three body parts with the most severe injuries are summed to determine the ISS [ISS= (AIS body resgion 1)^2 + (AIS body resgion 2)^2 + (AIS body resgion 3)^2] (8). Regardless of which body part is injured, the NISS represents the sum of the squares of the three most severe injuries. Thus, NISS may be equal to or greater than ISS (9). Li and Ma (10) reported that NISS was more valuable than ISS in predicting mortality in patients with severe blunt trauma. Evaluation of traffic accident victims' injuries using trauma scores may help to better understand the circumstances that lead to severe trauma and to define the necessary precautions to avoid severe injuries. This study's objective was to determine the general characteristics of forensic cases admitted to a forensic medicine clinic due to traffic accidents and to evaluate the injury severity in these cases.

Methods

This research was conducted at the Forensic Medicine Clinic of Bolu Abant Izzet Baysal University's Faculty of Medicine. We did not establish an informed consent form because our study was designed retrospectively. Approval for the study was granted by the Clinical Research Ethics Committee of Bolu Abant Izzet Baysal University (decision number: 2022/105, dated: 26.04.2022). Our research adhered to the ethical criteria outlined in the Helsinki Declaration of 1964, as revised in 2013.

This retrospective cohort study analyzed 802 forensic cases from January 01, 2015, to December 31, 2021. Cases were excluded if there was no traumatic injury or data were incomplete. The records of the hospital automation system, the records of the forensic medicine clinics, and the medical files of the cases featured in the study were reviewed retrospectively.

Simple demographic data (age, gender), injury characteristics, victims' position, the use of safety belts, helmets, and safety gear, extent of forensic trauma, and trauma scores were evaluated. The AIS 2008 update was used to calculate the ISS and NISS.

Statistical Analysis

Statistical Package for Social Science (SPSS) for Windows, version 21.0 software (IBM Corporation., Armonk, NY, USA) was used to analyze the study's data. Using the analytical (Kolmogorov-Smirnov / Shapiro-Wilk test) and visual (histograms, plots) approaches were used to determine whether the variables' distributions were normal. The frequency, percentage, mean, median, and standard deviation values were displayed in descriptive statistics.

The chi-square test was used to compare categorical variables. The non-parametric Mann-Whitney U test and the Kruskal-Wallis test (post-hoc: Dunn-Bonferroni test) were used to compare groups that did not exhibit a normal distribution. The categorical variables were reported as frequency and percentage, and the continuous variables as median interquartile range values. A significance level of $p<0.05$ was considered statistical.

Results

The study included 802 cases: 69.20% (n=555) of the cases were male, with the mean age of the cases was 36.10±19.62 (min.:1, max.:90). The age range from 21 to 30 was the most prevalent group (n=171, 21.30%) (Table 1). More than one site of injury was reported in 36.28% of the cases (n=291) (Table 1). Considering all the injuries separately after multiple site injuries were distributed, 58.98% of the victims suffered extremity injuries (n=473), 46.23% had head and neck injuries (n=371), 24.68% had chest injuries, and 5.36% had abdominal injuries.

Passengers (36.29%) and drivers (29.55%) were the most often injured in traffic accidents (Table 1). Seat belts were not buckled up in 62.30% (329/528) of the in-vehicle traffic accident cases. In 71.43% (55/77) of the motorcycle accident cases, helmets and protective equipment were not used. Life-threatening trauma was detected in 21.93% of the cases (Table 1).

Upper extremity fractures occurred in 16.58% (n=133) of the cases followed by lower extremity fractures in 16.33% (n=131), skull bone fractures in 5.60% (n=45), rib fractures in 10.83% (n=87), internal organ injury in 12.09% (n=97), and cerebral hemorrhage (epidural, subdural, etc.) in 2% (n=16). The distribution of injuries according to the type of traffic accident is displayed in Table 2. Motorcycle accident cases had more severe bone trauma than in-vehicle accident victims ($p<0.05$) (Table 3).

ISS and NISS Score

The mean ISS was 6.45±8.22, and the mean NISS was 8.44±10.69. There was no remarkable difference among gender in terms of ISS and NISS values ($p>0.05$) (Table 4). A significant difference was noted in injury severity across various age groups. Cases aged ≥60 years were determined with significantly more severe trauma than those aged ≤10 years and the 21-30 and 31-

40 years age groups (p<0.001) (Table 4). Compared to instances with isolated head-neck damage, isolated extremities injury, and isolated abdominal-chest injury, those with multiple traumas had substantially higher ISS and NISS values (p<0.001) (Table 4). The ISS and NISS values were also significantly higher in abdominal-chest trauma than in head-neck and extremity injuries (p<0.001). Motorcycle and off-vehicle traffic accidents had significantly higher ISS and NISS values (p<0.001) (Table 4). The ISS and NISS values escalated with an increasing extent of forensic trauma (p<0.001). ISS value ≥8.5 (sensitivity: 92%, specificity: 86.6%) and NISS value ≥9.5 (sensitivity: 86.4%, specificity: 87.2%) may be useful in defining life-threatening injuries (Table 5).

Table 1. Characteristics of traffic accidents

	In-vehicle driver		Passenger		Off-vehicle pedestrian		Bicyclist		Motorcycle rider		p-value
Gender	n	%	n	%	n	%	n	%	n	%	
Male	211	26.31	140	17.46	109	13.59	25	3.12	70	8.73	<0.001
Female	26	3.24	151	18.83	60	7.48	3	0.37	7	0.87	
Age	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
0-10 years	0	0.00	30	3.74	29	3.62	6	0.75	3	0.37	<0.001
11-20years	9	1.12	52	6.48	22	2.74	11	1.37	35	4.36	
21-30 years	66	8.24	68	8.48	17	2.12	2	0.25	18	2.25	
31-40 years	45	5.61	49	6.11	21	2.62	2	0.25	8	1.00	
41-50 years	44	5.48	31	3.87	16	1.99	2	0.25	8	1.00	
51-60 years	40	4.99	34	4.24	17	2.12	2	0.25	3	0.37	
>60 years	33	4.11	27	3.37	47	5.86	3	0.37	2	0.25	
Injury site	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Isolated head-neck	59	7.36	76	9.48	25	3.12	7	0.87	13	1.62	<0.001
Isolated extremity	62	7.73	82	10.23	72	8.98	13	1.62	30	3.74	
Isolated chest-abdomen	30	3.74	35	4.36	5	0.62	0	0.00	2	0.25	
Multiple	86	10.72	98	12.22	67	8.35	8	1.00	32	3.99	
Degree of forensic injuries	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Cured by simple medical intervention	117	14.59	145	18.08	62	7.73	9	1.12	22	2.74	<0.01
Not cured by simple medical intervention	70	8.73	95	11.85	61	7.61	14	1.75	31	3.87	
Life-threatening	50	6.23	51	6.36	46	5.73	5	0.62	24	2.99	
Total	237	29.55	291	36.29	169	21.07	28	3.49	77	9.60	

Table 2. Distribution of injuries in traffic accident victims

	In-vehicle driver		Passenger		Off-vehicle pedestrian		Bicyclist		Motorcycle rider		p-value
Upper extremity fracture	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Yes	26	3.24	52	6.49	36	4.49	5	0.62	14	1.74	0.071
No	211	26.31	239	29.80	133	16.58	23	2.87	63	7.86	
Lower extremity fracture	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Yes	24	2.99	27	3.37	50	6.23	4	0.50	26	3.24	<0.001
No	213	26.56	264	32.92	119	14.84	24	2.99	51	6.36	
Skull fracture	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Yes	7	0.87	7	0.87	13	1.62	3	0.37	15	1.87	<0.001
No	230	28.68	284	35.42	156	19.45	25	3.12	62	7.73	

Table 2. Continued

	In-vehicle driver		Passenger		Off-vehicle pedestrian		Bicyclist		Motorcycle rider		p-value
Rib fracture	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Yes	32	3.99	33	4.11	16	1.99	1	0.12	5	0.62	0.334
No	205	25.56	258	32.17	153	19.08	27	3.37	72	8.98	
Visceral organ injuries	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Yes	26	3.24	29	3.61	27	3.37	2	0.25	13	1.62	0.183
No	211	26.31	262	32.67	142	17.70	26	3.24	64	7.98	
Cerebral heamorrhage	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Yes	4	0.50	2	0.25	6	0.75	0	0.00	4	0.50	0.053
No	233	29.05	289	36.04	163	20.32	28	3.49	73	9.10	
Total	237	29.55	291	36.29	169	21.07	28	3.49	77	9.60	

Table 3. Distribution of bone fracture score according to traffic accident types

Mean		Bone fracture score					p-value[1]
		SD	Median	25th per	75th per		
Traffic accident	In-vehicle	3.47	1.62	3.00	2.00	5.00	0.023
	Off-vehicle	3.79	1.60	4.00	2.00	5.00	
	Motorcycle	4.13	1.62	4.00	3.00	6.00	

[1]Kruskal-wallis test, per: Percentile, SD: Standard deviation

Table 4. Distribution of ISS and NISS according to gender, age group, injury site, traffic accident, degree of forensic injuries.

		Injury Severity Score (ISS)					p-value[1]
		Mean	SD	Median	25th per	75th per	
Gender	Male	6.66	±8.57	4.00	1.00	9.00	0.600
	Female	5.97	±7.35	3.00	1.00	9.00	
Age group	0-10 years	5.88	±8.87	1.00	1.00	5.75	<0.001
	11-20years	8.06	±10.82	4.00	1.00	9.00	
	21-30 years	4.64	±5.72	2.00	1.00	6.00	
	31-40 years	4.27	±5.32	2.00	1.00	5.00	
	41-50 years	6.85	±7.20	4.00	1.00	9.00	
	51-60 years	7.66	±8.79	4.00	1.00	12.25	
	60 years and older	8.71	±9.50	4.50	1.00	13.00	
Injury site	Isolated head–neck	2.77	±3.88	1.00	1.00	4.00	<0.001
	Isolated Extremity	3.71	±4.23	1.00	1.00	4.00	
	Isolated chest-abdomen	6.58	±6.00	4.00	1.00	9.00	
	Multiple	11.12	±10.75	8.00	3.00	17.00	
Traffic accident	In-vehicle	5.23	±6.51	2.00	1.00	9.00	<0.001
	Off-vehicle	8.29	±10.17	4.00	1.00	9.50	
	Motorcycle	10.03	±10.94	8.00	2.50	13.50	
Degree of forensic injuries	Cured by simple medical intervention	1.34	±.60	1.00	1.00	2.00	<0.001
	Not cured by simple medical intervention	6.07	±4.40	4.00	4.00	9.00	
	Life-threatening	17.33	±10.32	13.00	9.00	22.00	

Table 4. Continued

		New Injury Severity Score (NISS)					p-value[2]
		Mean	SD	Median	25th per	75th per	
Gender	Male	8.80	±11.07	4.00	1.00	12.00	0.201
	Female	7.63	±9.76	3.00	1.00	10.00	
Age group	0-10 years	7.80	±12.22	2.00	1.00	7.50	<0.001
	11-20 years	10.27	±13.00	4.00	2.00	13.00	
	21-30 years	6.29	±8.34	3.00	1.00	9.00	
	31-40 years	5.87	±8.01	3.00	1.00	6.00	
	41-50 years	9.42	±10.04	5.00	2.00	12.50	
	51-60 years	9.77	±11.77	4.00	1.00	16.00	
	60 years and older	10.83	±11.21	8.00	2.00	17.00	
Injury site	Isolated head-neck	4.77	±8.34	1.00	1.00	4.00	<0.001
	Isolated extremity	4.78	±5.36	3.00	1.00	8.00	
	Isolated chest-abdomen	8.63	±8.09	8.00	1.00	12.75	
	Multiple	13.91	±13.45	10.00	3.00	22.00	
Traffic accident	In-vehicle	6.94	±9.11	3.00	1.00	9.00	<0.001
	Off-vehicle	10.39	±12.41	5.00	2.00	13.50	
	Motorcycle	13.67	±13.37	9.00	3.00	22.00	
Degree of forensic injuries	Cured by simple medical intervention	1.64	±0.83	1.00	1.00	2.00	<0.001
	Not cured by simple medical intervention	7.97	±5.83	6.00	4.00	12.00	
	Life-threatening	22.96	±12.78	22.00	13.00	27.00	

[1]Mann-Whitney U test, [2]Kruskal-wallis test, per: Percentile, SD: Standard deviation, ISS: Injury Severity Score, NISS: New Injury Severity Score

Table 5. Distribution of ISS and NISS according to degree of forensic injuries

		Injury Severity Score (ISS)					p-value[1]
		Mean	S.D.	Median	25th per	75th per	
Degree of forensic injuries	Cured by simple medical intervention	1.34	±0.60	1.00	1.00	2.00	<0.001
	Not cured by simple medical intervention	6.07	±4.40	4.00	4.00	9.00	
	Life-threatening	17.33	±10.32	13.00	9.00	22.00	
		New Injury Severity Score (NISS)					p-value[1]
		Mean	S.D.	Median	25th per	75th per	
Degree of forensic injuries	Cured by simple medical intervention	1.64	±0.83	1.00	1.00	2.00	<0.001
	Not cured by simple medical intervention	7.97	±5.83	6.00	4.00	12.00	
	Life-threatening	22.96	±12.78	22.00	13.00	27.00	

		Sensitivity (%)	Specifity (%)	Positive predictive value (%)	Negative predictive value (%)
ISS	Cut off : 8.5	92	86.6	65.9	97.5
NISS	Cut off: 9.5	86.4	87.2	61.4	98.3

[1]Kruskal-wallis test, per: Percentile, SD: Standard deviation

Discussion

In a study conducted in Korea, females (52.4%) constituted more than half of traffic accident injury cases (11). Males (78%) constituted the majority of the victims who presented at hospital due to traffic accidents in India (12) and in another study in Nepal, the majority of people injured in traffic accidents were male (13). According to research conducted in Türkiye, the majority of people injured in traffic accidents were male (1,14-17). In this study, the majority of the traffic accident victims (69.20%) were male, which was consistent with the literature.

In Helsinki, the mean age of seriously injured traffic accident victims was 44.3±20.2 years old (18). Traffic accident victims in Athens were most frequently in the 25-34 years age group (28.4%) (5) and in Ethiopia, mostly in the 20-29 age group (33.7%) (12). In a previous study in Türkiye, the mean age of traffic accident fatalities in Aydın was 44.39 years old, and they

were most frequently in the 21-30 years age group (16). Similarly, in this study, the mean age of the cases was 36.10±19.62 years old (min.:1, max.:90) and the most common age group was 21-30 years old (n=171, 21.30%).

In general, the most injured body parts due to traffic accidents are the extremities and the head (19). In a study conducted in Korea, major injuries were determined most frequently in the extremities (36.8%) and head (35.9%) (11). Yaşar and Büken (15) reported that traffic accident victims frequently suffered injuries in the extremities (43%) and head and neck region (30.22%). In a study involving 1,338 traffic accident victims, the most common injury sites were the extremities (45.9%) and head and neck region (53.1%) (14). In this study, 36.29% (n=291) of the cases had multiple site injuries, in line with the literature, extremity injuries were determined in 58.98% (n=473) and head-neck injuries in 46.23% (n=371).

In a study conducted in Singapore, the majority of traffic accident victims were motorcyclists (50.10%), pedestrians (21.80%), and cyclists (9.90%) (20). In Nepal, most traffic accident-related injuries appeared to motorcyclists and pedestrians (13). In Yemen, the most frequent injuries as a result of traffic accidents were invehicle passengers (38%) and pedestrians (32%) (21). In Helsinki, severely injured cases due to traffic accidents were most often the drivers or passengers (38.60%) (18). The previous study in Aydın, Türkiye, reported that traffic accident deaths were most frequent in pedestrians (32.90%) and motorcyclists (20.10%) (16). In this study, passengers (36.29%) and drivers (29.55%) were most frequently injured due to traffic accidents.

In Aydın, 13.5% of the cases who died as a result of traffic accidents had upper extremity fractures, 37.7% had rib fractures and, 34.8% had lower extremity bone fractures (16). In a study of 1338 traffic accident cases, 7.62% of the cases (n=102) had extremity fractures, 2.16% (n=29) had rib fractures, 1.35% (n=18) had intracranial hemorrhage, and 0.90% (n=12) had skull fractures (14). In another study involving 1567 cases, 6.2% of the cases (n=99) had lower extremity fractures, %6 (n=95) had upper extremity fractures, 3.8% (n=60) had rib fractures, 3.5% (n=56) had skull fractures, 2.7% (n=43) had lung contusion, 2.4% (n=39) had intracranial haemorrhage (22). In this study, upper extremity fractures were determined in 16.58% (n=133) of the cases, followed by lower extremity fractures in 16.33% (n=131), skull bone fractures in 5.60% (n=45), rib fractures in 10.83% (n=87), internal organ injury in 12.09% (n=97), and cerebral haemorrhage (epidural, subdural, etc.) in 2% (n=16). Skull fractures were more common in motorcycle-related traffic accidents in Athens (5). The development of skull fractures varied greatly among the cases in this study, with motorcycle riders having a much greater incidence of both skull and lower extremities fractures. Moreover, motorcycle accident victims had more severe bone trauma than in-vehicle accident victims.

Among the victims of traffic accident injuries in Athens, only 29.80% of motorcycle drivers and only 5.70% of motorcycle passengers wore helmets, while 26.30% of automobile drivers and only 14.10% of automobile passengers wore seat belts (5). In a study conducted in Yemen, none of the traffic accident victims wore a seat belt or helmet (21). While 84.50% of motorcycle accident victims in Iran were not using a helmet, 77.20% did not have a driver's licence (23). Aygencel et al. (17) reported that 93.10% of cases presenting at the emergency service due to traffic accidents were not wearing seat belts. In this study, seat belts were not buckled up in 62.30% (329/528) of the in-vehicle traffic accident cases and in 71.43% (55/77) of motorcycle accident cases, helmets and safety gear were not available. While it is legally required in Türkiye for motorcyclists to wear helmets and for drivers and passengers to buckle up, the evidence gathered for this study indicates that society does not enforce these laws. Therefore, there is a clear need for the provision of public education and for traffic checks to be increased to ensure the use of helmets and seat belts.

Atik et al. (24) reported that the mean ISS value of 453 traffic accident victims aged 0-17 years was 3.32±3.76. The median ISS value of 1,063 traffic accident victims in Helsinki was 22, and the median NISS score was 27 (18). In an another study (25) of 162,695 traffic accident victims, the average ISS value was eight. In this study, the mean ISS value was 6.45±8.22, and the mean NISS value was 8.44±10.69. Kong et al. (26) demonstrated that the incidence of serious injury in small motor vehicle accidents was 1.6 times higher in elderly patients than in non-elderly. In a study conducted in Korea, there was a significant difference between age groups and ISS in adult traffic accident cases, and the ISS values increased after the age of 40 years (11). In this study, a significant difference was noted in injury severity across various age groups. Cases aged ≥60 years were determined with significantly more severe trauma than those aged <10 years age and in the 21-30 and 31-40 years age groups. In addition, it is noteworthy that the ISS and NISS values increased with age after 30 years, which may be related to the fact that people are more fragile with age and thus suffer more severe injuries.

Varlık et al. (14) reported that the males mortality rate was higher in traffic accidents. Atik et al. (24) discovered no statistically significant variation in ISS across genders among children who sustained injuries from traffic incidents. Mogaka et al. (27) also reported no discrepancy in the severity of injuries between male and female traffic accident cases. In this study, there was no remarkable difference among gender in terms of ISS and NISS values.

Dirlik et al. (16) reported that the leading cause of death due to traffic accidents was multiple injuries (44.3%). In this study, the ISS and NISS values of the cases with multiple injuries were significantly higher (Table 4).

In Helsinki, of cases with serious traffic accident injuries, the highest NISS values were determined in pedestrians, followed by cyclists, motorcyclists, and motor vehicle passengers (18). Mogaka et al. (27) reported that unprotected road users (pedestrians and two-wheelers) had a significantly higher median ISS value than those injured inside vehicles. In this study, motorcycle and off-vehicle traffic accidents had significantly higher ISS and NISS values (Table 4).

Bilgin et al. (28) demonstrated that evaluation of injury severity using the ISS was a useful method for distinguishing between life-threatening and non-life-threatening conditions. According to Fedakar et al. (29) the ISS and NISS may be used to identify life-threatening injuries stated in the Turkish Penal Code, and those were more effective in proving them than the Glasgow Coma Scale, revised trauma score, and trauma and injury score. In this study, the ISS and NISS values escalated with an increasing extent of forensic trauma and an ISS value >8.5 (sensitivity: 92%, specificity: 86.6%) and NISS >9.5 (sensitivity: 86.4%, specificity: 87.2%). These values may be useful in defining life-threatening parameters. The ISS and NISS can be employed to ascertain whether a life-threatening situation is present, particularly in instances where the guidelines applied in Türkiye are inadequate.

Study Limitations

This study had some limitations. First, it was prepared retrospectively, conducted in a single clinic, and only included forensic cases. Therefore, it cannot be said that it represents the entire trauma population resulting from traffic accidents. The study included cases that had survived the traffic accident, not the individuals who died after the traffic accident. Therefore, while the results provide information about the severity of trauma in traffic accident injuries, they cannot provide information about the mortality rate.

Conclusion

The consequences of this study demonstrated that among the victims of traffic accidents, those who had out-of-vehicle and motorcycle accidents were exposed to more severe trauma. Motorcyclists had a higher incidence of skull and lower extremity fractures and more severe bone fractures. We found that the majority of the victims did not use seat belts, helmets and safety gear. Therefore, there is a need to increase social education and advertisements, road safety policies should be re-evaluated, and seat belt and helmet checks in traffic should be increased to ensure seat belts, helmets and safety gear use. The ISS and NISS can be considered a useful evaluation method in traffic accident injuries to determine both the life-threatening injuries and simple medical interventions specified in the Turkish Penal Code.

Ethics

Ethics Committee Approval: Approval for the study was granted by the Clinical Research Ethics Committee of Bolu Abant İzzet Baysal University (decision no: 2022/105, dated: 26.04.2022).

Informed Consent: Did not establish an informed consent form because our study was designed retrospectively.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.H., Z.Z.E., A.Y., Concept: E.H., Z.Z.E., E.Ş., Design: E.H., Z.Z.E., A.Y., Data Collection or Processing: E.H., Z.Z.E., E.Ş., Analysis or Interpretation: E.H., Z.Z.E., A.Y., E.Ş., Literature Search: E.H., Z.Z.E., A.Y., E.Ş., Writing: E.H., Z.Z.E.

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Original Article

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Maturity-onset Diabetes of the Young (MODY): How Much Can We Detect?

Gençlerde Başlayan Erişkin Tipi Diyabet (MODY): Ne Kadarını Yakalayabiliyoruz?

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ABSTRACT

Objective: This study aims to assess the characteristics of patients who underwent genetic analysis with suspicion of maturity-onset diabetes of the young (MODY).

Methods: Forty patients who met the criteria of measurable serum fasting C-peptide levels, positive family history, and autoantibody negativity and were diagnosed with diabetes at a young age were analyzed for demographic, clinical, laboratory and molecular test results. A comprehensive MODY panel examining a total of 21 genes [*hepatocyte nuclear factor 4 alpha (HNF4A), glucokinase (GCK), HNF 1 alpha (HNF1A), pancreatic and duodenal homeobox 1, HNF 1 beta (HNF1B), neurogenic differentiation 1, kruppel-like factor 11, carboxyl ester lipase, paired box gene 4, insulin, B-lymphocyte kinase, adenosine triphosphate binding cassette sub-family C member 8, potassium inwardly rectifying channel subfamily J member 11, AKT2, GLI-similar 3, glutamate dehydrogenase 1, hydroxyacyl-CoA dehydrogenase, insulin receptor, solute carrier family 2 member 2, wolfram syndrome 1, zinc finger protein 57*] in 30 patients (75%) with next-generation sequencing method and variants detected in 10 patients (25%) using a short panel including *GCK, HNF1A, HNF1B and HNF4A* genes were analyzed using different databases (online mendelian inheritance in man, database of single nucleotide polymorphisms, genome aggregation database, human gene mutation database).

Results: Overall, 11 variants in 7 different genes were detected in 10 patients (25%). Sixty per cent (n=6) of the mutation-positive patients were treated with insulin. Serum fasting C-peptide levels (1.18 vs 1.26 ng/mL, p=0.891) and age at diabetes diagnosis (26.5

ÖZ

Amaç: Bu çalışmanın amacı gençlerde başlayan erişkin tipi diyabet (MODY) şüphesi ile genetik analiz yapılan hastaların özelliklerini değerlendirmektir.

Yöntemler: Ölçülebilir serum açlık C-peptid düzeyleri, pozitif aile öyküsü, otoantikor negatifliği gibi kriterlere uyan ve genç yaşta diyabet tanısı alan 40 hastanın demografik, klinik, laboratuvar ve moleküler test sonuçları incelendi. Tamamı yeni nesil dizileme yöntemi ile 30 hastada (%75), 21 genin [*hepatosit nükleer faktör 4 alfa (HNF4A), glukokinaz (GCK), HNF 1 alfa (HNF1A), pankreatik ve duodenal homeobox 1, HNF 1 beta (HNF1B), nörojenik farklılaşma 1, kruppel benzeri faktör 11, karboksil ester lipaz, paired box proteini 4, insülin, B lenfoid tirozin kinaz, adenozin trifosfat bağlı kompaktörü subfamilisi C üyesi 8, potasyum inwardly rectifying kanal subfamiliyası J üyesi 11, AKT2, GLIS ailesi çinko parmak proteini 3, glutamat dehidrogenaz 1, hidroksi asil-koa dehidrogenaz , insülin reseptörü, sitozol membran taşıyıcı 2 , wolfram sendrom 1 proteini, çinko parmağı proteini 57*] incelendiği kapsamlı MODY paneli ve 10 hastada (%25) *GCK, HNF1A, HNF1B ve HNF4A* genlerini içeren kısa panel kullanılarak saptanan varyantlar, farklı veri tabanları (insanlarda çevrim içi mendel kalıtımı veritabanı, tek nükleotid polimorfizmi veritabanı, genom toplulaştırma veritabanı, insan gen mutasyonları veritabanı) kullanılarak analiz edildi.

Bulgular: Tüm hastalar içinde 10 hastada (%25) toplam 7 ayrı gende, 11 varyant tespit edildi. Mutasyon pozitif hastaların %60'ı (n=6) insülin kullanmaktaydı. Mutasyon pozitif ve negatif gruplar arasındaki serum açlık C-peptid düzeyleri (1,18'e 1,26 ng/mL,

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ABSTRACT

vs 29.0 years, p=0.860) were not different between the mutation-positive and mutation-negative groups.

Conclusion: Despite the improved diagnosis, MODY diagnosis is still missed and a significant number of patients are unnecessarily treated with insulin. In particular, individuals diagnosed with diabetes at a young age, with negative autoantibodies and measurable serum C-peptide levels, should be evaluated for MODY.

Keywords: MODY, next-generation sequence analysis, *GCK, HNF1A, HNF4A*

ÖZ

p=0,891) ve diyabet tanısı aldıkları yaşlar (26,5'e 29,0 yıl, p=0,860) arasında fark yoktu.

Sonuç: Gelişen tanı imkânlarına rağmen MODY hastaları hala gözden kaçmakta ve önemli bir kısmı gereksiz yere insülin ile tedavi edilmektedir. Özellikle genç yaşta diyabet tanısı alan, otoantikorları negatif, ölçülebilir serum C-peptid düzeyleri olan hastalar, MODY açısından gözden geçirilmelidir.

Anahtar Kelimeler: MODY, yeni nesil dizi analizi, *GCK, HNF1A, HNF4A*

Introduction

Diabetes is a chronic, progressive metabolic disease caused by interacting genetic and environmental factors. It is characterized by hyperglycemia and associated with impaired lipid, protein and carbohydrate metabolism. So far, more than 300 polymorphisms have been identified in type 2 diabetes that may play a role in its pathophysiology (1-3). Highly penetrant monogenic forms of diabetes, such as maturity-onset diabetes of the young (MODY), provide evidence that rare genetic variants can cause diabetes. Developments in the field of genetics will provide a better understanding of the role of genetics in diabetes in the future (2).

MODY describes a genetic disorder with early onset of diabetes (usually before age 25), a positive family history, autosomal dominant inheritance, and a lack of ketosis without significant insulin deficiency (1,4-6).

Currently, there are 14 genes definitively associated with MODY types; *hepatocyte nuclear factor 4 alpha (HNF4A), glucokinase (GCK), HNF 1 alpha (HNF1A), pancreatic and duodenal homeobox 1 (PDX1), HNF 1 beta (HNF1B), neurogenic differentiation 1 (NEUROD1), kruppel-like factor 11 (KLF11), carboxyl ester lipase (CEL), paired box gene 4 (PAX4), insulin (INS), B lymphocyte kinase (BLK), adenosine triphosphate binding cassette sub-family C member 8 (ABCC8), potassium inwardly rectifying channel subfamily J member 11 (KCNJ11), and adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1* (7-11). The most common mutations in MODY are in *HNF1A, GCK, HNF4A, HNF1B and INS* genes. Almost all cases in the literature that can be definitively linked to MODY have a mutation in one of these 5 genes (10,12,13). The most common MODY gene mutations are *GCK* and *HNF1A* mutations. *GCK* mutations seem to be at the forefront in some countries, while *HNF1A* mutations are reported more frequently in others (14). The most common mutation, *GCK*, has been found in a relatively small number of studies in our country (15-17).

The only accepted method in diagnosing MODY is detecting the genetic mutation using a molecular test. Classically, clinical MODY is characterized by onset before the age of 25 years, the presence of diabetes in two consecutive generations, the absence of beta-cell autoantibodies and the preservation of endogenous insulin secretion (fasting serum C-peptide levels ≥0.6 ng/mL) (4-6). However, clinical criteria alone are insufficient for diagnosing MODY (13). Studies have shown that up to 95% of MODY patients are misdiagnosed and receive unnecessary insulin treatment (18,19). Misclassification will likely cause over-intervention or unnecessary increases in health care and treatment costs (20).

There has been evidence of the efficacy of sulfonylurea treatment in MODY patients since the 1990s, and there has been no significant change in treatment to date (21,22). It is well known that the tendency towards more expensive and complex treatments for diabetes is increasing worldwide. The use of sulfonylureas has halved in the last decade, and this situation leads to patients with undiagnosed monogenic diabetes receiving more costly and unindicated treatments unnecessarily every day (23-25).

Although it is a relatively expensive test, genetic analysis in correctly selected patients is a cost-effective method of avoiding unnecessary treatment and screening for comorbidities, but its effectiveness in reducing longevity and comorbidities has not been demonstrated (26).

Our study aimed to investigate the characteristics of patients who underwent genetic analysis with suspicion of MODY and to investigate the genotype-phenotype relationship of the detected variants.

Methods

Study Design

The medical records and genetic results of patients who underwent genetic analysis for suspected MODY at the Internal Medicine and Endocrinology Outpatient Departments of the İstanbul Medeniyet University, Göztepe Prof. Dr. Süleyman Yalçın City Hospital were retrospectively analyzed.

Age, age at onset of diabetes, sex, body mass index (BMI), waist circumference (cm), systolic and diastolic blood pressure (mmHg), family history of diabetes, history of diabetic ketoacidosis (DKA), history of previous diseases and operations, and previous treatments were noted. Biochemical analyses of the patients were as follows: glucose (mg/dL), glycated hemoglobin A1c (HbA1c, %), islet cell antibody (ICA, positive/negative), glutamic acid decarboxylase antibody (GADA, IU/mL), insulin autoantibody (IAA, IU/mL), serum C-peptide (ng/

mL), low-density lipoprotein cholesterol (LDL-C, mg/dL), high DL-C (HDL-C, mg/dL), triglycerides (TG, mg/dL), alanine aminotransferase (ALT, IU/L), aspartate aminotransferase (IU/L), spot urine protein-to-creatinine ratio, and C-reactive protein (CRP, mg/dL) values were recorded in the database. For all patients diagnosed with diabetes under 35 (as it cannot be calculated above this age), the probability of MODY was calculated using the model at https://www.diabetesgenes.org/ and added to the patient data.

Ethics committee approval was obtained from the Ethics Committee of İstanbul Medeniyet University (no: 2020/0619, date: 26.10.2020). This study was conducted according to the principles of the Declaration of Helsinki.

Inclusion and Exclusion Criteria

Patients with suspected MODY who underwent genetic analysis were included. Since the study was conducted in an adult outpatient clinic, patients under 18 years of age were not included.

Genetic Analysis

The main MODY panel (*GCK, HNF1A, HNF1B and HNF4A*) and the comprehensive MODY panel (*HNF4A, GCK, HNF1A, PDX1, HNF1B, NEUROD1, KLF11, CEL, PAX4, INS, BLK, ABCC8, KCNJ11, AKT2, GLI-similar 3, glutamate dehydrogenase 1, hydroxyacyl-CoA dehydrogenase, INS receptor, solute carrier family 2 member 2, wolfram syndrome 1 (WFS1), zinc finger protein 57*) were used for genetic analysis.

Deoxyribonucleic acid was routinely isolated from the patients' peripheral blood for genetic analysis. The genes in the test panel were amplified by exon-specific (amplicon) multiplex polymerase chain reaction and analyzed on the IlluminaMiseq next-generation sequencing platform using the capture-based method. The Mutation Taster model, available at http://www.mutationtaster.org/, was used as an in silico bioinformatics program using sequence conservation and structure-based algorithms to calculate the pathogenicity probabilities of new variants detected during the study (27).

The resulting data were analyzed using Burrows-Wheeler aligner (0.7.12-r1034), PicardTools 2.17.3, Genome Analysis Tool Kit 3.7 and ANNOVAR. The analysis was reported using the human genome hg19 and several databases [OMIM, single nucleotide polymorphism database (dbSNP), ClinVar, dbNSFP, Genome Aggregation Database (gnomAD), 1000 Genomes, Exome Sequencing Project, Exome Aggregation Consortium, Ensembl, HapMap CEU and Human Gene Mutation Database (HGMD)]. Variants were also reported according to the American College of Medical Genetics and Genomics (ACMG) classification to assess the level of pathogenicity (28). We re-used these databases and updated the analyses of the variants before the publication date of the study.

Statistical Analysis

Analyses were performed using the IBM SPSS version 22 program (IBM Corp., Armonk, NY, USA). Descriptive statistical methods used to analyze the data were number, percentage, minimum and maximum, median, mean and standard deviation. The conformity of the quantitative data to the normal distribution was tested using the Shapiro-Wilk test, the Box-Plot test, histogram plots, the number of cases in the study, and the mean and standard deviation values (29). T-test (two-tailed Student's t-test) for parametric variables and Mann-Whitney U test for non-parametric variables were used for statistical comparisons between mutation-positive and mutation-negative groups. A p-value of 0.05 was accepted as the threshold for statistical significance. In addition, the analyses were performed again, excluding the two siblings who were found to be involved in the analysis and similar results were found (data not shown).

Results

A total of 40 patients were included in the analysis. Demographic and clinical characteristics, including sex distribution, current age, and age at diagnosis, are summarized in Table 1.

A positive family history of diabetes was present in 90% (n=36) of the patients. There was no family history of diabetes in 10% of the patients (n=4). A history of DKA was present in 5% (n=2) of the patients.

Chronic diseases other than diabetes were present in 60% (n=24) of the patients; dyslipidemia (n=10), hypertension (n=9), hypothyroidism (n=4), allergic rhinitis or rheumatoid arthritis (n=2 each), and other conditions (n=12). Treatment for comorbidities other than diabetes was recorded in 42.5% (n=17) of the patients; 9 patients had a history of statin use, 9 had a history of angiotensin-converting enzyme inhibitor or

Table 1. Clinical, physical and laboratory characteristics of patients suspected of having MODY

Characteristics	Mean or % ± SD (Min.-Max.)
Female	48%
Age, year	40.1 (19-62)
Age at diagnosis of diabetes, year	28.4 (13-48)
HbA1c	8.5±2.3%
FPG, mg/dL	179.6±89.7
C-peptide, ng/mL	1.24±0.76
Insulin therapy	50%
Family history of diabetes	90%
Statin use	23%
BMI, kg/m^2	25.3 (18.4-40.3)
Waist circumference, cm	
Male	87.6 (78-101)
Female	84.0 (68-120)
Systolic blood pressure, mmHg	120.3±10.8
Diastolic blood pressure, mmHg	77.6±7.9

MODY: Maturity-onset diabetes of the young, SD: Standard deviation, Min.: Minimum, Max: Maximum, HbA1c: Glycated hemoglobin, FPG: Fasting plasma glucose, BMI: Body mass index

angiotensin receptor blocker use, 2 had a history of thiazide diuretic use, 1 had a history of calcium channel blocker use, and 1 had a history of beta-blocker use. In the analysis of complications of diabetes, 20% of patients (n=8) had a history of complications; 3 patients had retinopathy or neuropathy, and 1 patient had nephropathy or peripheral arterial disease.

The mean MODY probability percentage of the patients sent for gene analysis was 30.8±27.1%. The percentage of four patients could not be calculated because the calculator could not calculate those diagnosed above the age of 35 years.

Physical measurements such as BMI, waist circumference, and blood pressure are summarized in Table 1.

Laboratory characteristics including HbA1c, fasting plasma glucose, and serum C-peptide levels are presented in Table 2.

When the cases were analyzed regarding the 3 diabetes autoantibody tests (ICA, GADA, IAA) performed in our hospital, it was observed that 60% (n=24) were negative for all three autoantibodies. One autoantibody was positive in 10% (n=4), and two autoantibodies were positive in 2.5% (n=1) of cases; none of the patients were positive for all three autoantibodies.

Table 2. Laboratory characteristics of patients suspected of having MODY

Characteristics	Mean or % ± SD (Min.-Max.)
Diabetes-specific autoantibodies	
ICA	3%
GADA	8%
IAA	5%
CRP, mg/dL	2.11±0.93
Spot urine protein/creatinine	0.18±0.16
ALT, U/L	21.8±19.6
LDL, mg/dL	116.5±30.4
HDL, mg/dL	53.4±14.1
TG, mg/dL	169.0±139.8

Spot urine protein (mg/dL), creatinine (mg/dL)
MODY: Maturity-onset diabetes of the young, ICA: Islet cell cytoplasmic autoantibodies, GADA: Glutamic acid decarboxylase autoantibody, IAA: Insulin autoantibody, LDL: Low-density lipoprotein cholesterol, HDL: High-density lipoprotein cholesterol, TG: Triglyceride, ALT: Alanine transaminase, CRP: C-reactive protein

Table 3. Genetic test result distribution in patients with suspected MODY

Result	**Mutation-negative**	**n=30**	**25%**
	Mutation-positive	**n=10**	**75%**
ACMG classification of positive variants	Pathogenic	2	
	Potentially pathogenic	6	
	VUS	2	

VUS: A variant of uncertain clinical significance, ACMG: American College of Medical Genetics

Among the cases sent for molecular analysis, one patient (2.5%) had ICA positive, and three patients (7.5%) had GADA positive. IAA was positive in two patients (5%) who were known to receive insulin treatment. The autoantibody titer was in the borderline positive range in cases with positive autoantibodies.

Genetic variants were detected in 25% (n=10) of patients. Details of the identified variants and their ACMG classifications are presented in Table 3.

When the patients were compared between those mutation-positive and mutation-negative, it was found that the waist circumference of mutation-positive female patients was significantly thinner (87.7±13.0 vs 73.0±8.0 cm, p=0.011). No differences were observed regarding gender, age, age at diagnosis of diabetes, HbA1c, average plasma glucose, serum C-peptide, history of DKA, insulin treatment, how long insulin has been in use since diagnosis, family history of diabetes, history of non-diabetes chronic diseases, in diabetes complications, MODY probability percentage, BMI, a waist circumference of male patients, systolic and diastolic blood pressure, autoantibodies, CRP, spot urine protein/creatinine ratio, ALT, LDL-C, HDL-C, TG, statin use. A detailed comparison of mutation-positive and mutation-negative patients is provided in Supplementary Table.

In 10 cases (25%), 11 rare heterozygote sequence variants were identified in 7 genes. Two variants were observed in the *GCK* gene, two in the *HNF1A* gene, two in the *HNF4A* gene, one in the *BLK* gene, two in the *ABCC8* gene, one in the *INSR* gene and two in the *WFS1* gene. These consisted of 9 missenses (82%), 1 nonsense (9%) and 1 deletion-frameshift (9%) variant. Eight of them (*GCK* c.943C>T, *HNF1A* c.864delG, *HNF1A* c.1513C>A, *BLK* c.T1013C, *ABCC8* c.2539G>A, *ABCC8* c.1252T>C, *WFS1* c.1672C>T, *WFS1* c.2020G>A) were registered in databases. According to the ACMG classification of the 3 new variants, *GCK* c.91A>T was considered pathogenic, *HNF4A* c.1004G>A was considered potentially pathogenic, and *INSR* c.913G>A was considered variants of uncertain significance (VUS). The mutations identified by the bioinformatics program were predicted to be "damaging" and likely to affect protein function. There were 12 variants detected in the study, but two separate cases carried the same variant in the *WFS1* gene (Tables 4 and 5).

Discussion

Our study revealed the presence of a genetic factor in 10 (25%) of 40 patients who underwent genetic analysis with clinical suspicion of MODY. Prospective and retrospective studies in Türkiye have shown mutation detection rates ranging from 17 to 65%, while international studies have shown mutation detection rates ranging from 7 to 97% (14-17). The observed differences between studies are most likely explained by the different selection criteria used for genetic testing. The mutation detection rates in studies with patient selection by physician decision, such as ours, are similar to or lower than those in our study (13,30). This may be attributed to the fact that genetic testing is often performed without adherence to the standardized patient selection criteria

recommended by MODY guidelines. Additionally, there appears to be a lack of awareness regarding MODY and other forms of monogenic diabetes among physicians working in adult outpatient clinics. It was also thought that some genes related to MODY may not yet have been discovered, or limitations related to testing panels may also contribute to this. The next-generation sequencing method used in the genetic analysis of patients can detect single nucleotide changes with 99% accuracy, as well as small deletions and insertions (up to 10-15 bases). However, detecting large deletions, duplications, insertions, changes in long homopolymer sequences and copy number variants in genes is insufficient. This suggests that some of the remaining mutation-negative patients may have mutations in MODY genes that have not yet been identified.

Although next-generation sequencing has revolutionized clinical diagnostic testing, kits examining deep intronic sequence and promoter variations have not yet become widespread due to cost.

As kits examining these regions become more common in the future, the proportion of variants that can be detected in similar

Table 4. Genetic characteristics of patients with variants and their equivalents in databases

No	Gene (locus)	Associated phenotype (#OMIM no)	DNA exchange AA exchange	Mutation type Zygosity	HGMD	dbSNP	ACMG classification*
2	*GCK* (NM_000162)	MODY, type 2 (# 125851)	c.91A>T p.Lys31*	Nonsense Heterozygote	No information available	No information available	PVS1, PM1, PM2, PP3 "pathogenic"
14	*GCK* (NM_000162.5)	MODY, type 2 (# 125851)	c.943C>T p.L315F	Missense Heterozygote	CM064013 "MODY 2"	Rs1583594350 "VUS"	PM1, PM2, PP2, BP3, PP5, PM5 "potentially pathogenic"
17	*HNF1A* (NM_000545)	MODY, type 3 (#600496)	c.864delG p.P291Qfs*51	Del-FS Heterozygote	CM082856 "MODY 3"	Rs762703502 "pathogenic"	PVS1, PP5, PM2 "pathogenic"
40	HNF1A (NM_000545.6)	MODY, Type. 3 (#600496)	c.1513C>A p.H505N	Missense Heterozygote	CM082823 "MODY 3"	No information available	PM2, PP2, PP3, PP5 "potentially pathogenic"
20	*HNF4A* (NM_000457.4) *BLK* (NM_001715)	MODY, type 1 (# 125850) MODY, type 11 (#613375)	c.1004G>A p.G335E c.T1013C p.I338T	Missense Heterozygote Missense Heterozygote	No information available CM1416414 "Autism spectrum disorder"	No information available No information available	PM1, PM2, PP2, PP3 "potentially pathogenic" PM2, PP3 "VUS"
11	*ABCC8* (NM_000352.4)	DM, non-insulin-dependant (#125853)	c.l252T>C p.C418R	Missense Heterozygote	CM994414 "Hypoglycemia persistent hyperinsulinemic"	RS67254669 "VUS"	PM2, PP2 "VUS"
31	*ABCC8* (NM_000352.6)	DM, non-insulin-dependant (#125853)	Cc.2539G>A p.A847T	Missense Heterozygote	CM148394 "Hyperinsulinemic hypoglycemia"	RS561593131 "VUS"	PS1, PM1, PM2, PP2, BP4 "potentially pathogenic"
39	*INSR* (NM_000208.4)	DM, insulin-resistant (#610549)	c.913G>A P.V305I	Missense Heterozygote	No information available	No information available	PM1, PM2 "VUS"
37	*WFS1* (NM_006005.3)	DM, non-insulin-dependant (#125853)	c.1672C>T p.R558C	Missense Heterozygote	CM015264 "Wolfram's syndrome"	Rs199946797 "pathogenic"	PM2, PM5, PP5, PP3 "potentially pathogenic"
21	*WFS1* (NM_006005.3)	DM, non-insulin-dependant (#125853)	c.2020G>A p.G674R	Missense Heterozygote	CM011519 "Wolfram's syndrome"	RS200672755 "pathogenic"	PM2, PP3, PP5 "potentially pathogenic"
			c.1672C>T p.R558C	Missense Heterozygote	CM015264 "Wolfram's syndrome"	Rs199946797 "pathogenic"	PM2, PM5, PP2, PP3 "potentially pathogenic"

*In the recommendations of the ACMG standards and guidelines, each pathogenic criterion is classified as very strong (PVS1), strong (PS1-4), moderate (PM1-6) or supportive (PP1-5), and each benign criterion as benign (BP1-5).
OMIM no: Online mendelian inheritance in man phenotype number, DNA: Deoxyribonucleic acid, AA: Amino acid, HGMD: Human gene mutation database (access code given if the information is available in the database), dbSNP: Single nucleotide polymorphism database (access code given if the information is available in the database), ACMG: American College of Medical Genetics, Del-FS: Deletion/frameshift,VUS: A variant of uncertain clinical significance,

studies will increase.

Of the variants identified as "disease cause for MODY" by the HGMD database, 3 were detected in patients 14, 17 and 40 (*GCK* c.943C>T; p.L315F, *HNF1A* c.864delG; p.P291Qfs*51 and *HNF1A* c.1513C>A; p.H505N, respectively). The variants of the other 7 patients were registered as probable for MODY or of uncertain clinical significance.

A review of clinicians' decisions to perform genetic testing revealed that 90% of patients had a family history of diabetes, and the mean age at diagnosis was 28.4±7.6 years. Since diabetes is a common disease, the presence of diabetes in a few family members does not necessarily indicate hereditary diabetes. However family history is an accurate first approach to selecting patients with MODY (31). Mutation-positive patients in our study were diagnosed with diabetes approximately 2.5 years (26.5±8.8 vs. 29.0±7.2 years) earlier. This supports a genetic basis in these patients.

Most variants in this study were missense mutations (82%), which can affect protein stability or cause loss of critical catalytic domains. These results were similar to studies in other European populations where missense mutations predominate (32-34). In addition, nonsense and a frameshift mutation were identified that can cause premature termination of protein synthesis or the formation of nonsense ribonucleic acid (35).

Two patients (5%) who underwent molecular testing with suspicion of MODY but no mutation was detected had a history of hospitalization with suspected DKA. A history of DKA in patients with MODY is usually not an expected finding because endogenous insulin production may continue for years, but history alone does not exclude MODY (36). The reason for this is

Table 5: Clinical and laboratory characteristics of patients with variants

No	G	Age	AD	BMI	WC	A1c	C-p	Chronic D	Complication	MO%	Affected relative	Treat	Gene	Variant	Mut
2	F	32	18	18.4	68	7.2	0.88	-	-	75.5	Mother, father, uncle, brother	OAD+ Insulin	*GCK*	c.91A>T p.Lys31*	Nons
14	F	28	22	21.9	68	6.8	1.12	-	-	75.5	Father, sibling	OAD	*GCK*	C.943C>T P.L315F	Miss
17	F	41	35	19.7	70	8.2	1.33	-	-	24.4	Mother, father, brother, sister	OAD	*HNF1A*	c.864delG p.P291Qfs*51	Del/ Fr.
40	F	28	16	25.8	0	6.8	0.62	-	-	75.5	Mother, father, brother, sister	Insulin	*HNF1A*	C.1513C>A P.H505N	Miss
20	F	58	26	20.1	72	7.6	0.63	Dyslipidemia HT Hypothyroid	NP	62.4	Father	OAD+ Insulin	*HNF4A* *BLK*	c.l004G>A P.G335E C.T1013C P.I338T	Miss
11	M	19	13	33.1	101	13.2	3.11	Autism epilepsy	-	0.7	Grandfather, mother, father, uncle	OAD+ insulin	*ABCC8*	c.1252T>C P.C418R	Miss
31	M	38	35	27.0	94	7.4	1.99	-	-	15.1	Grandmother, father	LSM	*ABCC8*	C.2539G>A P.A847T	Miss
39	F	62	32	26.7	87	8.3	0.27	Dyslipidemia	PAD	4.6	Father, uncle, daughter	OAD+ Insulin	*INSR*	c.913G>A P.V305I	Miss
37	M	46	38	19.3	78	10.2	1.10	A. Rhinitis		Ø	Sibling	LSM	*WFS1*	c.1672C>T P.R558C	Miss
21	M	56	30	24.2	85	8.2	0.72	HT	RP	15.1	Sibling	Insulin	*WFS1*	c.2020G>A P.G674R C1672C>T P.R558C	Miss

G: Gender, F: Female, M: Male; AD: Age at diagnosis of diabetes (years); BMI: Body mass index (kg/m^2); WC: Waist circumference (cm), A1c: Glycated hemoglobin (%), C-p: Serum fasting C-peptide (ng/mL), Chronic D: Chronic disease, MO%: MODY probability percentage, Treat: Treatment for diabetes, Mut: Mutation type; ACMG: American College of Medical Genetics classification, HT: Hypertension, A. rhinitis: Allergic rhinitis, NP: Neuropathy, PAD: Peripheral arterial disease, RP: Retinopathy, OAD: Oral antidiabetic drug, LSM: Lifestyle modification, Miss: Missense, Del: Deletion, Fr: Frameshift, Ø: Unknown or incalculable

that there have been reports in the literature of cases of *HNF1A*-MODY, the majority of which had DKA with insulin deficiency in the later stages of the disease (37).

The first case (no: 22) was a 30-year-old diabetic patient with 25 years of diabetes mellitus and a fasting serum C-peptide level of 0.42 ng/mL, who was prescribed insulin 10 years after diagnosis and had DKA in the 21st year after diagnosis and the second case (no: 28) was a 27-year-old diabetic patient with 29 years of diabetes mellitus and a fasting serum C-peptide level of 0.48 ng/mL, who was prescribed insulin during hospitalization with DKA 10 years after diagnosis. No variant was detected in the genetic analysis of both cases.

In case 2, the *GCK* variant was a novel mutation causing premature stop codon formation. It is known that the HbA1c level of *GCK*-MODY patients rarely exceeds 7.5%, and there are even publications in the literature that set a limit of 7.3% for requesting genetic testing (9,38). This case was a 32-year-old, 14-year-old diabetic patient with a serum fasting C-peptide level of 0.88 ng/mL and an HbA1c level of 7.2% under metformin, sitagliptin and insulin glargine treatment. This new mutation (c.91A>T; p.Lys31*) was not a primary missense mutation but a nonsense mutation causing a termination codon resulting in reduced functional glucokinase protein (39). This supports the possibility of high pathogenicity. Several studies have shown that insulin secretion in patients with nonsense and frameshift mutations in the MODY genes is impaired more severely or at an earlier stage than in those with missense mutations. This is more likely to lead to the use of insulin (40-42). This is explained by the fact that a MODY patient with *GCK* mutation was diagnosed under insulin therapy, for whom treatment is not usually recommended (43).

Case 14, who had a different variant in the *GCK* gene, was a patient being followed up with metformin and dapagliflozin treatment and underwent genetic analysis on suspicion of MODY. A c.943C>T; p.L315F missense variant was found and classified as a "disease-causing mutation" in the HGMD database and VUS in the dbSNP database.

Case 17 was a 35-year-old patient diagnosed with *HNF1A*-MODY by detecting c.864delG; p.P291Qfs*51 deletion, frameshift variant when the HbA1c level was 8.2, who had been on diabetes treatment for 6 years, and who showed dramatic improvement in glycemic control after switching to gliclazide treatment. Unlike missense mutations, this mutation, which is classified as pathogenic according to ACMG criteria and the dbSNP database as in patient 2, causes a loss-of-function mutation (PVS1) of the gene product due to deletion of a guanine nucleotide, resulting in a frameshift in protein translation and a change in protein length. The presence of individuals diagnosed with diabetes in the family also supports the presence of this variant with a high risk of phenotyping.

The c.1513C>A; p.H505N variant in the *HNF1A* gene detected in patient 40 was "potentially pathogenic" according to ACMG criteria and had a frequency of 0.0000797 (gnomAD). This mutation, whose functional effect is mostly considered "damaging" by in silico prediction tools, was registered as a "disease-causing mutation" for MODY 3 in the HGMD database. The fasting serum C-peptide level was 0.62 ng/mL, and the postprandial C-peptide level was 1.76 ng/mL, while the pre-treatment HbA1c level was 12.6%, and it was 6.8% under basal insulin glargine treatment only.

Interestingly, case 20 had an HNF4A variant (c.1004G>A; p.G335E) and a BLK variant (c.T1013C; p.I338T) that were not previously included in databases and could not be classified as pathogenic. Although the patient had two variants associated with MODY and predicted to be "damaging" by in silico prediction tools, and had diabetes for 32 years, the possible reason for the delayed diagnosis of MODY was the increased prevalence of genetic testing in recent years and the presence of comorbidities such as dyslipidemia and hypertension, which are common with type 2 diabetes mellitus (T2DM). This pattern was compatible with MODY type 1 and type 11 disease, which may present with signs of insulin resistance such as dyslipidemia, weight gain and high insulin requirement. This may also be an additive effect of mutations. Previously, cases with two different MODY mutations and developing different or more severe presentations than expected have been reported in the literature (44-46). All this evidence suggests the importance of screening for other genes, especially for patients with an unexplained or severe clinical pattern.

Case 11 with a 3-gen family history of diabetes, epilepsy and autism since age 2, diagnosed with diabetes at age 13, heterozygous c.1252T>C (p.C418R) missense mutation in *ABCC8* gene, eating disorder secondary to Autism, had no evidence of insulin resistance other than obesity. The *ABCC8* gene mutation associated with MODY type 12 has been reported many times before. According to the literature, the clinical features of our case resemble the reported cases of MODY with *ABCC8* gene mutation (17,47-49). The slight differences between the reported cases suggest that the location of the mutation may be the cause. It should be noted that environmental and epigenetic factors also influence these differences. In addition, neurologic involvement was present in this case, as in previously reported cases. A review of the literature on the role of the sulfonylurea receptor in developing the central nervous system suggests that the two conditions may be related (50). The presence of *ABCC8* gene mutation in developmental delay, epilepsy, and neonatal diabetes (DEND) syndrome with DEND also suggests the same relationship (51). The same variant was previously diagnosed by Özdemir et al. (17). in a Turkish patient, a 13-year-old female with diabetes mellitus, BMI 30.3, fasting serum C-peptide 4.64 ng/mL and HbA1c 12% on oral antidiabetic drug and insulin therapy; the high degree of similarity with the clinical presentation of this case was noteworthy and supported the idea that the variant may be involved. In silico evaluations of this variant, which has a frequency of 0.0006-0.0010 in the community, cannot help determine the exact effect of this "damaging" mutation. More case reports and functional analyses are needed to elucidate their impact.

Another patient with a mutation in the *ABCC8* gene was patient number 31, carrying the c.2539G>A p.A847T variant. The patient, who had a history of diabetes at an early age in 2 previous generations but had hypertriglyceridemia and was overweight and compatible with T2DM, did not receive drug treatment for 3 years since the age of 35 when s/he was diagnosed with diabetes but metformin and gliclazide treatment was started after genetic diagnosis. The *ABCC8* gene is still generally considered by pediatric endocrinologists in the genetic etiology of NDM, but several studies have identified similar *ABCC8* missense mutations with early and late-onset diabetes (52-54).

Case 39 was a 62-year-old patient with diabetes for 30 years whose serum fasting C-peptide level had decreased by approximately 70% from 0.97 ng/mL to 0.27 ng/mL in the last 9 years, with negative autoantibodies. The patient, whose postprandial C-peptide was 2.23 ng/mL and who needed insulin approximately 10 years after the diagnosis, was found to have a c.913G>A; p.V305I missense variant in the *INSR* gene, which was not previously included in the databases and classified as "of uncertain clinical significance" according to ACMG. This was supported by the fact that the father and daughter of the patient with this variant, which was predicted to be "damaging" by in silico analysis programs, had similar early-onset diabetes. In contrast to the conditions associated with insulin response disorders caused by the *INSR* gene, there is a need for more relevant family studies, and case reports in the literature to understand under which disease group this novel variant, which produces an insulin secretion defect phenotype, will be classified in the future (55-57).

A careful review of the clinical features of patients 31 and 39 shows that some features are compatible with the characteristics of MODY and some with the characteristics of T2DM. Furthermore, in addition to the pathogenicity prediction calculation results, the rarity of these variants in large population databases supports that they are pathogenic mutations rather than common benign polymorphisms (58).

Eight mutation-positive cases had parents with diabetes, consistent with OD inheritance of MODY. It was interesting to note that two patients with heterozygote *WFS1* mutations, no: 21 (c.2020G>A; p.G674R and c.1672C>T; p.R558C) and no: 37 (c.1672C>T; p.R558C), had no history of diabetes in their parents. However, these variants were not considered de novo mutations but a penetrance deficiency because both patients had a history of diabetes in their siblings. Especially patient 21 had two variants in the same gene. It was evaluated that this patient, who had no history of diabetes in either parents, might have a phenotype with increased penetrance by inheriting one variant from the mother and one from the father. In the literature, it was previously reported that heterozygous WFS1 mutations like these caused type 2 diabetes–like patterns with early onset (59-61).

Study Limitations

There are some limitations to this study. First, analyzes of existing data were carried out because some of the patients' clinical and laboratory information was not sufficient or accessible. Another limitation is that genetic analysis could not be performed on the family or relatives of the patients with the detected mutations. This situation led to inadequate genotype and phenotype analysis.

Conclusion

In conclusion, genetic variants were identified in 10 (25%) of 40 patients with clinically suspected MODY. Three new variants (*GCK*, c.91A>T;p.Lys31*, *HNF4A*, c.1004G>A;p.G335E and *INSR* c.913G>A;p.V305I) contributed to the literature.

In addition, the findings of this study suggest that clinicians may underutilize genetic testing for MODY and that genetic tests are not sufficiently developed in variant detection.

Our study's results may help better understand the clinical features and genetics of MODY and allow for a more personalized approach to treatment and genetic counselling of patients.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Ethics Committee of İstanbul Medeniyet University (no: 2020/0619, date: 26.10.2020). This study was conducted according to the principles of the Declaration of Helsinki.

Informed Consent: As this was a retrospective study based on anonymized data, individual informed consent was not required.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.U., A.A., M.K., Concept: G.U., Design: G.U., M.K., Data Collection or Processing: G.U., A.A., Analysis or Interpretation: G.U., A.A., M.K., Literature Search: G.U., M.K., Writing: G.U.

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Supplementary Table: https://d2v96fxpocvxx.cloudfront.net/bd1986e1-0bc1-4f4d-af66-3a184850a065/content-images/5251b73c-5244-470c-a518-fd2be5ff3040.pdf

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Antimicrobial Susceptibility Profiles of Microorganisms Isolated from Patients Treated in Intensive Care Units Before and During the COVID-19 Pandemic: A Single-center Retrospective Study

Türkiye'de COVID-19 Pandemisi Öncesi ve Sırasında Yoğun Bakım Ünitesinde Tedavi Edilen Hastalardan İzole Edilen Mikroorganizmaların Antimikrobiyal Duyarlılık Profilleri: Tek Merkezli Retrospektif Bir Çalışma

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ABSTRACT

Objective: The global coronavirus disease-2019 (COVID-19) pandemic has increased public health challenges, especially in intensive care units (ICU) where COVID-19 patients are at increased risk of infectious complications. This study aimed to identify, compare, and evaluate antimicrobial susceptibility profiles of microbial isolates from ICU patients of a tertiary hospital in Türkiye before and during the COVID-19 pandemic.

Methods: In this retrospective analysis, we analyzed data from 1462 patients who were admitted to the ICU of Sivas Cumhuriyet University Faculty of Medicine Application and Research Hospital between January 2018 and December 2022. In this analysis, demographic and clinical variables including age, gender, and antimicrobial susceptibility test results, as well as the annual distribution and antimicrobial resistance profiles of clinical isolates were determined.

Results: Among the 1687 sputum, 1396 urine, and 1307 blood cultures analyzed, there was a significant increase in sputum cultures during the pandemic (21.94%; p=0.012). The proportion of Gram-negative bacteria was high in all cultures. *Pseudomonas aeruginosa*

ÖZ

Amaç: Küresel koronavirüs hastalığı-2019 (COVID-19) pandemisi, özellikle COVID-19 hastalarının enfeksiyöz komplikasyon riskini artırdığı için yoğun bakım ünitelerindeki halk sağlığı sorunlarını da artırmıştır. Bu çalışmanın amacı, COVID-19 pandemisi öncesinde ve pandemi sırasında Türkiye'deki üçüncü basamak bir hastanenin yoğun bakım ünitesindeki (YBÜ) hastalarından izole edilen mikrobiyal izolatların antimikrobiyal duyarlılık profillerinin değerlendirilmesidir.

Yöntemler: Bu retrospektif çalışmada, Ocak 2018 ile Aralık 2022 tarihleri arasında Sivas Cumhuriyet Üniversitesi Tıp Fakültesi Uygulama ve Araştırma Hastanesi YBÜ'ye kabul edilen 1462 hastaya ait veriler analiz edilmiştir. Bu amaçla hastalara ait yaş, cinsiyet ve antimikrobiyal duyarlılık testi sonuçlarını içeren demografik ve klinik değişkenlerin yanı sıra klinik izolatların yıllık dağılımı ve antimikrobiyal direnç profilleri belirlenmiştir.

Bulgular: Analiz edilen 1687 balgam, 1396 idrar ve 1307 kan kültürü arasında, pandemi sırasında balgam kültürlerinde önemli bir artış olmuştur (%21,94; p=0,012). Gram-negatif bakterilerin oranı tüm kültürlerde yüksek tespit edilmiştir. Balgam kültürlerinde

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(P. aeruginosa) was common in sputum cultures, *Escherichia coli (E. coli)* in urine cultures, and coagulase-negative staphylococci (CoNS) in blood cultures. Gram-negative bacteria gradually increased in all cultures from 2018 to 2022. There was a decrease in Gram-positive bacteria. In general, antibiotic resistance of *P. aeruginosa* and *E. coli* isolates increased before the pandemic but decreased during the pandemic.

Conclusion: Our study shows that infection profiles before and during the pandemic are different from each other. Continuous monitoring of resistance patterns will contribute to developing infection control strategies to prevent the development of antimicrobial resistance.

Keywords: Antimicrobial resistance, intensive care unit, COVID-19, antimicrobial susceptibility profile

Pseudomonas aeruginosa (P. aeruginosa), idrar kültürlerinde *Escherichia coli (E. coli)* ve kan kültürlerinde koagülaz-negatif Stafilokoklar yaygın bulunmuştur. Gram-negatif bakteriler 2018'den 2022'ye kadar tüm kültürlerde kademeli olarak artmıştır. Gram-pozitif bakterilerde ise azalma görülmüştür. Genel olarak, *P. aeruginosa* ve *E. coli* izolatlarının antibiyotik direnci pandemi öncesinde artmış ancak pandemi sırasında azalmıştır.

Sonuç: Çalışmamız pandemi öncesi ve pandemi sırasındaki enfeksiyon profillerinin birbirinden farklı olduğunu göstermektedir. Direnç paternlerinin sürekli izlenmesi, antimikrobiyal direnç gelişimini önlemek için enfeksiyon kontrol stratejilerinin geliştirilmesine katkıda bulunacaktır.

Anahtar Kelimeler: Antimikrobiyal direnç, yoğun bakım ünitesi, COVID-19, antimikrobiyal duyarlılık profili

Introduction

Antimicrobial resistance is an important public health problem that is increasing daily (1). Uncontrolled use of antimicrobial agents in the treatment of infectious diseases is one of the leading factors causing the development of antimicrobial resistance (2). Nosocomial infections cause serious mortality and morbidity by prolonging the hospital stay of patients (3). Infections in intensive care units (ICUs) account for 25% of nosocomial infections (4). Patients hospitalized in ICUs are usually immunocompromised individuals who have undergone interventional procedures and receive broad-spectrum antibiotic treatment (2). Intensive use of antibiotics in ICUs is one of the leading factors in the emergence and development of antimicrobial resistance. *Acinetobacter baumannii (A. baumannii), Pseudomonas aeruginosa (P. aeruginosa), Klebsiella pneumoniae (K. pneumoniae),* methicillin-resistant *Staphylococcus aureus (S. aureus), Escherichia coli (E. coli),* Vancomycin-Resistant *Enterococcus, Serratia marcescens, Enterobacter cloacae (E. cloacae)* are among the microorganisms causing nosocomial infections (4,5). Antimicrobial resistance profiles of the microorganisms causing these infections vary regionally (4). Identifying these microorganisms and determining their antimicrobial susceptibility profiles are essential for clinicians to control nosocomial infections and determine infectious disease treatment plans (6). With the emergence of the coronavirus disease-2019 (COVID-19) pandemic, researchers have warned of the risks of inappropriate antibiotic use and the risks that may occur, based on experience from past outbreaks (7). Especially the low immunity of patients treated in ICUs and the effect of invasive interventions applied to these patients cause an increased risk of infectious diseases in these patients. This leads to more antimicrobial agents (2). Monitoring and evaluating the use of antimicrobial agents in critical situations such as pandemics, where infectious diseases are widespread throughout society, is essential for the continuation of public health. As a result of research conducted in different countries, it is stated that the use of antimicrobial agents has increased during the COVID-19 pandemic (8). In this study, it was aimed to retrospectively investigate the microorganisms isolated from the samples sent to the microbiology laboratory and antimicrobial susceptibility profiles of patients who were being treated in the ICUs of Sivas Cumhuriyet University Faculty of Medicine Application and Research Hospital before and during the COVID-19 pandemic.

Methods

Study Design and Setting

In this study, we retrospectively analyzed the reports of patients treated in the ICU of Sivas Cumhuriyet University Faculty of Medicine Application and Research Hospital. The study was conducted to determine the resistance profiles of microorganisms isolated from sputum, urine, and blood cultures. Sivas Cumhuriyet University Faculty of Medicine Application and Research Hospital is a tertiary care teaching hospital with 1050 beds. We surveyed samples, demographic characteristics, and results of culture tests of patients treated in the ICU of the hospital between January 2018 and December 2022. In Türkiye, the period before this date was considered pre-pandemic since the pandemic was declared on March 11, 2020.

Inclusion Criteria

This study included isolates from sputum, urine, and blood culture samples. Two blood cultures with the same results were included in the study. The first samples from recurrent patient samples were accepted into the study, and the others were excluded. In addition, samples considered to be contaminated were excluded.

Bacterial Identification, and Antimicrobial Susceptibility Tests

Clinical isolates in the samples sent to the microbiology laboratory were identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) using Microflex LT MALDI-TOF MS (Bruker Daltonics, Germany) according to the manufacturer's operating procedures. Antimicrobial susceptibility tests of the identified bacterial isolates were analyzed using Phoenix 100® (Becton Dickinson, USA), and yeast isolates were analyzed using Micronaut (Bruker Daltonics, Germany) test kits according to the manufacturer's procedures. Antimicrobial susceptibilities of the isolates were evaluated according to the European Committee on Antimicrobial Susceptibility Testing criteria (9).

Data Collection

Demographic information such as age, and gender, and clinical information such as antimicrobial susceptibility test results were collected from the electronic medical records of the hospital. This study was conducted in compliance with the Helsinki Declaration and informed consent was obtained from all participants before starting the study.

Ethical Principles of the Research

Before initiating the study, ethical permission for the research was obtained from the Sivas Cumhuriyet University Ethical Committee of Non-invasive Clinical Research (decision no: 2023-10/03, date: 19.10.2023).

Statistical Analysis

Statistical analyses were conducted using GraphPad Prism (version 8) software package. Descriptive analyses were presented using frequencies and percentages. Changes in antimicrobial resistance before and during the pandemic were analyzed using x^2 or Fisher's exact test. The significance level was accepted at a $p< 0.05$.

Results

Demographics of the Study Population

As presented in Table 1, the study population was nearly equally distributed by sex and predominantly elderly. A total of 4405 microbiological culture results were included in the study (38.43% sputum, 32.8% urine, 29.77% blood). The sputum culture rate was higher in the pre-pandemic period (16.49%) than in pandemic period (21.94 %) (p=0.012).

Clinical Isolates

Gram-negative bacteria were the most frequently isolated microorganisms from sputum, urine, and blood cultures in the ICU. Gram-positive bacteria were more common in blood cultures (46.31%) than in sputum, and urine cultures. During the pandemic period, the proportion of Gram-negative bacteria grown in sputum, urine, and blood cultures increased (77.26%, 75%, and 56.52%, respectively) (Table 2, Figure 1).

As shown in Figure 1 and Table 2, the dominant pathogens varied by specimen: *P. aeruginosa, S. aureus* and *K. pneumoniae* were common in sputum; *E. coli, K. pneumoniae* and *Enterococcus faecium (E. faecium)* in urine; and CoNS, *K. pneumoniae* and *S. aureus* in blood cultures.

Antimicrobial Resistance in Bacteria

Antimicrobial Resistance Profile of Gram-positive Bacteria

Antimicrobial resistance status of Gram-positive bacteria commonly grown in sputum, urine, and blood cultures were analyzed. Overall, *S. aureus* isolates grown in sputum, urine and blood cultures were susceptible to vancomycin, teicoplanin, tigecycline and trimethoprim-sulfamethoxazole, but showed high resistance to penicillin (99.2% sputum; 100% urine; 99.0% blood cultures) and ampicillin (99.2% sputum; 100% urine; 99.1% blood cultures) (Figure 2).

E. faecium grown in urine culture showed increased resistance to teicoplanin (0.0% pre-pandemic; 14.3% pandemic; p=0.007) and decreased resistance to amoxicillin-clavulanate (97.9% pre-pandemic; 84.9% pandemic; p=0.032) during the pandemic (Figure 2).

Resistance to trimethoprim-sulfamethoxazole (9.8% pre-pandemic; 32.3% pandemic; p<0.001) and teicoplanin (3.9% pre-pandemic; 11.4% pandemic; p=0.031) increased, while resistance to clindamycin (69.6% pre-pandemic; 54.4% pandemic; p=0.008) decreased in CoNS grown in blood cultures. A decrease in amoxicillin-clavulanate (12.9% pre-pandemic; 0.0% pandemic; p=0.032) resistance was also observed in *Enterococcus faecalis (E. faecalis)* grown in blood cultures (Figure 2).

Antimicrobial Resistance of Gram-negative Bacteria

Antimicrobial resistance profiles of the most frequently grown six Gram-negative bacteria in sputum, urine, and blood cultures are shown in Figure 2. During the pandemic, *P. aeruginosa* in sputum cultures showed a decrease in cephalosporin resistance (42.3% pre-pandemic; 27.6% pandemic; p<0.001) and an increase in gentamicin resistance (16.7% pre-pandemic; 47.6% pandemic; p<0.001). *K. pneumoniae* grown in sputum cultures showed a decrease in levofloxacin resistance (83.3% pre-pandemic; 60.6% pandemic; p<0.001). *E. coli* grown in sputum cultures showed decreasing resistance to β-lactam/adjuvant antibiotics (69.4% pre-pandemic; 44.1% pandemic; p<0.001) and ciprofloxacin (70.8% pre-pandemic; 50.5% pandemic; p=0.013). During the pandemic period, *E. cloacae* isolates were resistant to carbapenems (2.8% pre-pandemic; 39.4% pandemic; p<0.001) and ceftazidime (16.7% pre-pandemic; 61.9% pandemic; p=0.027), while *Proteus mirabilis* (*P. mirabilis)* isolates had increased resistance to cefuroxime (0.0% pre-pandemic; 19.05% pandemic; p=0.018) and gentamicin (25.9% pre-pandemic; 54.8% pandemic; p=0.034).

E. coli grown in urine cultures were resistant to trimethoprim-sulfamethoxazole (56.9% pre-pandemic; 43.6% pandemic; p=0.008), β-lactam/adjuvant (43.4% pre-pandemic; 28.7% pandemic; p<0.001), ampicillin (83.9% pre-pandemic; 71.1% pandemic; p=0.002) and ciprofloxacin (55.4% pre-pandemic; 44.1% pandemic; p=0.025) significantly decreased during the pandemic period. However, resistance to ceftazidime (44.3% pre-pandemic; 88.9% pandemic; p<0.001) increased. Ceftazidime (75.2% pre-pandemic; 98.5% pandemic; p<0.001) resistance of *K. pneumoniae* grown in urine cultures increased, while levofloxacin (90.9% pre-pandemic; 61.5% pandemic; p<0.001) resistance decreased. Piperacillin/tazobactam (62.7% pre-pandemic; 3.4% pandemic; p<0.001) and ceftazidime (47.1% pre-pandemic; 12.7% pandemic; p<0.001) resistance of *P. aeruginosa* isolates grown in urine cultures decreased during the pandemic period. Trimethoprim-sulfamethoxazole (57.8% pre-pandemic; 81.8% pandemic; p=0.025) resistance of *P. mirabilis* isolates increased.

In blood cultures, piperacillin/tazobactam (47.1% pre-pandemic; 37.7% pandemic; p=0.001) and ceftazidime (37.7% pre-pandemic; 19.0% pandemic; p=0.002) resistance of *P. aeruginosa* decreased, while tigecycline (8.3% pre-pandemic; 33.3% pandemic; p<0.001) resistance of *E. coli* increased.

Table 1. Characteristics of patients hospitalized in ICU

Characteristics		Pre-pandemic (%)	During-pandemic (%)	Total (%)	p-value
Total n (%)		566 (38.71)	896 (61.29)	1462	
Gender n (%)	Female	287 (19.63)	415 (28.39)	702 (48.02)	0.107
	Male	279 (19.08)	481 (32.90)	760 (51.98)	
Age group n (%)	≤44	37 (2.53)	94 (6.43)	131 (8.96)	0.089
	45-64	120 (8.21)	197 (13.47)	316 (21.68)	
	65-74	139 (9.51)	220 (15.05)	362 (24.56)	
	75-84	168 (11.49)	246 (16.83)	414 (28.32)	
	≥85	102 (6.98)	139 (9.51)	242 (16.48)	
	Median (IQR)	74 (20)	72 (21)	72 (20)	
Culture type n (%)	Sputum culture	724 (16.49)	963 (21.94)	1687 (38.43)	0.012*
	Urine culture	660 (15.03)	736 (16.77)	1396 (32.80)	
	Blood culture	624 (14.21)	683 (15.56)	1307 (29.77)	
	Total cultures	2008 (45.74)	2382 (54.26)	4390	

The x^2 test was used to analyze the data. *: p<0.05
ICU: Intensive care unit, IQR: Interquartile range

Table 2. Distribution of clinical isolates according to samples

	Sputum (%)		Urine (%)		Blood (%)	
Pathogens	**Pre-pandemic (n=724)**	**During-pandemic (n=963)**	**Pre-pandemic (n=663)**	**During-pandemic (n=748)**	**Pre-pandemic (n=624)**	**During-pandemic (n=683)**
Gram-positive bacteria	**26.93**	**22.74**	**17.27**	**19.57**	**46.31**	**40.56**
Staphylococcus aureus	13.95	17.76	0.76	1.90	8.01	9.52
CoNS	0.83	0.10	1.82	2.45	25.80	18.30
Enterococcus faecalis	0.41	0.10	6.21	5.84	4.97	6.00
Enterococcus faecium	0.41	0.10	7.58	7.74	1.12	3.22
Streptococcus pneumoniae	0.97	1.97	0.00	0.00	0.80	0.44
Corynebacterium striatum	8.98	1.87	0.61	0.27	3.53	1.76
Others	1.38	0.83	0.30	1.36	2.08	1.32
Gram-negative bacteria	**72.93**	**77.26**	**69.39**	**75.00**	**50.96**	**56.52**
Pseudomonas aeruginosa	19.06	16.10	7.42	9.51	8.49	8.78
Acinetobacter baumannii	11.19	14.75	4.39	4.21	6.09	7.61
Klebsiella pneumoniae	12.15	14.33	13.94	18.34	10.90	12.30
Escherichia coli	9.94	9.66	26.52	30.03	8.49	7.03
Stenotrophomonas maltophilia	3.73	4.15	0.15	0.14	3.53	5.86
Enterobacter cloacae	1.66	2.28	1.06	1.36	1.76	2.49
Proteus mirabilis	3.73	4.36	6.97	5.98	1.28	1.90
Others	11.46	11.63	8.94	5.43	10.42	10.54
Fungi	**0.14**	**0.00**	**13.33**	**5.43**	**2.72**	**2.93**
Candida albicans	0.14	0.00	7.42	2.72	1.12	0.88
Others	0.00	0.00	5.91	2.72	1.60	2.05

Bold values mean total percentages of Gram-positive, Gram-negative, and fungi
CoNS: Coagulase-negative staphylococci

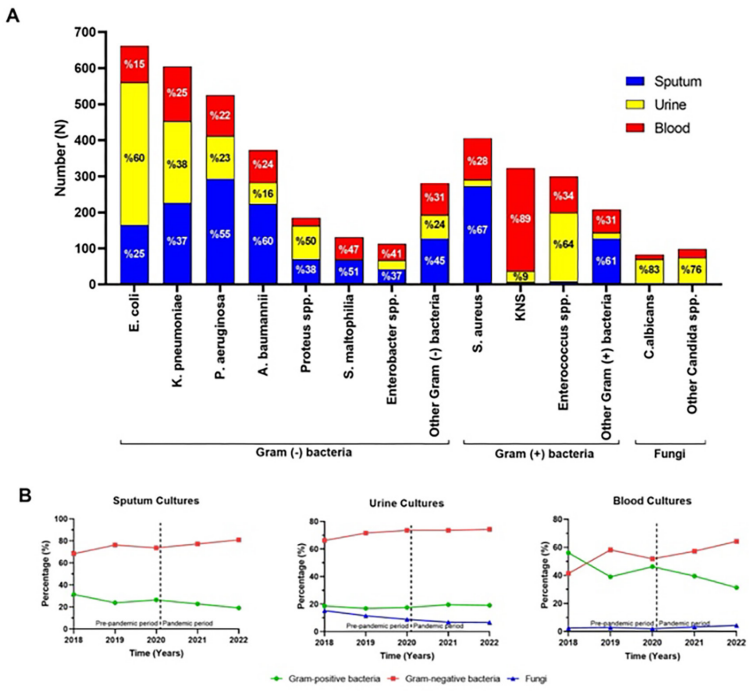

Figure 1. Clinical isolate types in ICU

(A) The composition of all pathogens. (B) Distribution of pathogens before and during the pandemic (2018-2022).

ICU: Intensive care unit

Annually Antimicrobial Resistance Distribution of Clinical Isolates

As shown in Figure 3, the annual variation in antibiotic resistance rates of *P. aeruginosa*, *E. coli*, and *K. pneumoniae* isolates frequently grown in sputum, urine, and blood cultures were analyzed.

In all types of cultures, β-lactam/adjuvant antibiotic resistance in *P. aeruginosa* isolates across all cultures decreased after 2019. Resistance to fluoroquinolones steadily increased before the pandemic but showed a continuous decrease during the pandemic period. Nevertheless, fluoroquinolones resistance rates in sputum and urine cultures in 2022 were higher than those in 2018. Carbapenem resistance in isolates from sputum cultures increased before the pandemic but remained stable during the pandemic period. The highest carbapenem resistance in isolates from blood cultures was observed in 2021. Cephalosporin resistance in isolates from sputum cultures decreased from 48.42% in 2019 to 24.78% in 2022, while the resistance rate in urine cultures decreased to 8% in 2022. Cephalosporin resistance rate in blood cultures decreased from 51.72% in 2019 to 17.5% in 2022. The resistance of *P. aeruginosa* isolates to aminoglycosides increased from 2018 to 2020, but after 2020; it decreased again to the resistance rates observed in 2018 (Figure 3).

While the antifolate, cephalosporins, and aminoglycosides resistance of *E. coli* isolates grown in urine and blood cultures increased before the pandemic, it decreased to its lowest rate in 2021 and then rose again in 2022. Specifically, antifolate resistance decreased from 60% to 36% in urine isolates and from 66.6% to 29.4% in blood isolates. Similarly, cephalosporin resistance dropped from 56.8% to 48.6% in urine and from 57.1% to 23.6% in blood samples. For aminoglycosides, resistance fell from 12% to 6.4% in urine cultures and from 25% to 5.5% in blood cultures. Antifolate resistance rate of *E. coli* isolates in sputum cultures was the highest (67%) in 2019 and decreased to the lowest level (35%) in 2022. Additionally, the rate of cephalosporin resistance in sputum cultures decreased from 57.7% in 2020 to 23.5% in 2022. There was no significant change in aminoglycoside resistance. While the β-lactam/adjuvant, and fluoroquinolone resistance rates of *E. coli* isolates growing in all cultures were highest in the pre-pandemic period, they decreased during the pandemic. Resistance rates of *E. coli* isolates to carbapenems were the lowest compared to other antimicrobials. In 2019, carbapenem resistance (22.6%) increased in sputum isolates (Figure 3).

There was no significant change in the antifolate resistance of *K. pneumoniae* isolates grown in sputum cultures. In urine and blood cultures, antifolate resistance increased in a fluctuating manner. The distribution of β-lactam/adjuvant antibiotic resistance in *K. pneumoniae* isolates grown in all culture types showed a similar pattern. Fluoroquinolone resistance distribution was similar across all culture types. The highest fluoroquinolone resistance was observed in isolates obtained from urine cultures, with a rate of 91.1% in 2019. Carbapenem resistance of isolates grown in sputum, urine, and blood cultures increased gradually over the years. In 2022, the resistance rates were 62.8%, 50%, and 56.4%, respectively. Cephalosporin resistance rates decreased during the pandemic period; however, an increase started to

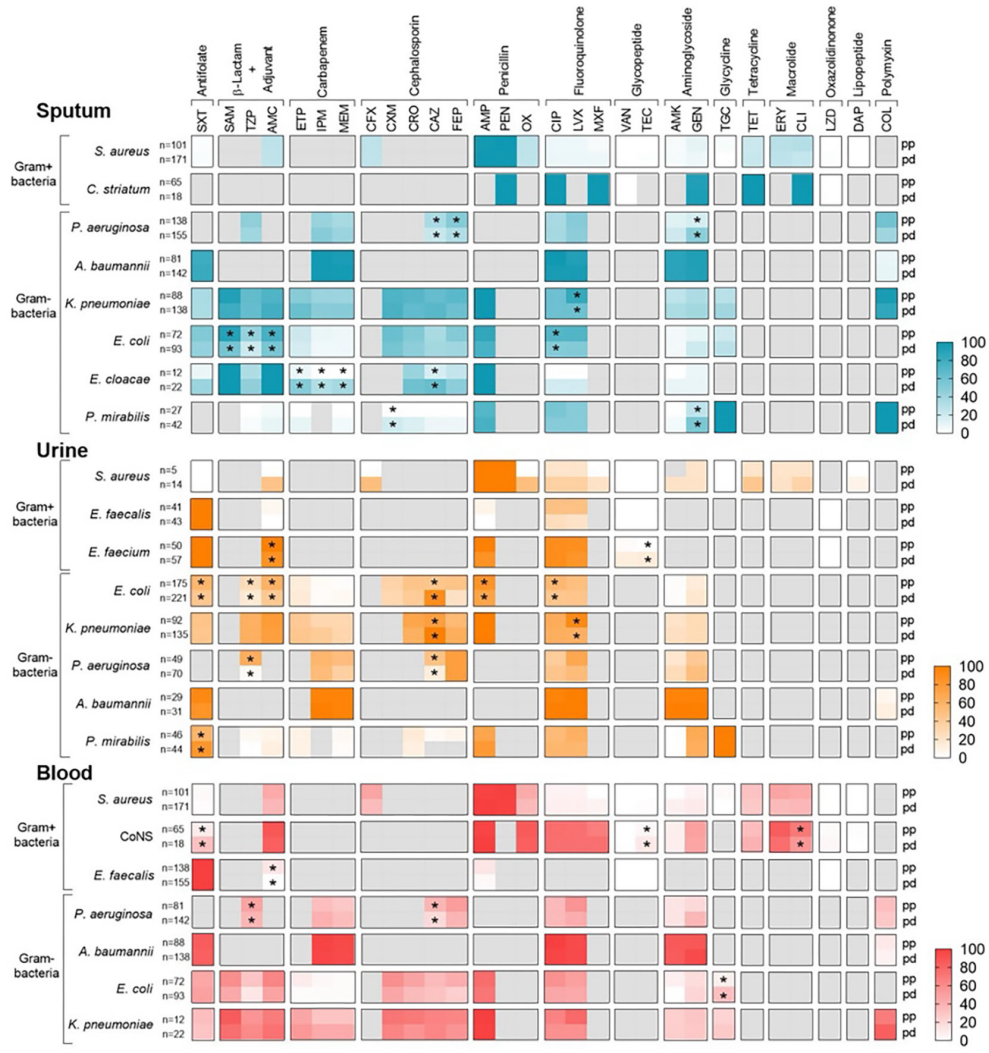

Figure 2. Antimicrobial resistance profile of Gram-positive, and Gram-negative bacteria grown in sputum, urine, and blood cultures

In the heatmap, the color of each cell shows the percentages of resistant strains grouped according to the antimicrobial classification indicated in the columns. Gray cells indicate that the bacteria were not tested with the antimicrobial listed in the column. Pre-pandemic period (pp) and pandemic period (pd) were compared in each bacterial group. Asterisked cells indicate isolates with a significantly different resistance profile to the indicated antimicrobial during the pandemic compared to the pre-pandemic period (analyzed by chi-square and Fisher's exact test)

occur again in 2022. The aminoglycoside resistance rates of *K. pneumoniae* isolates grown in sputum, urine, and blood cultures were 9.3%, 13.9%, and 7.7%, respectively, in 2018. However, in 2022, the resistance rates had increased to 48.9%, 36.1%, and 42.3%, respectively (Figure 3).

Antimicrobial Resistance in Fungi

Antimicrobial resistance of *Candida albicans (C. albicans)* and other Candida isolated from urine and blood cultures were analyzed. *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, and *C. krusei* were included among another Candida. Although the resistance rates of *C. albicans* isolates grown in urine cultures to azoles (43.8% pre-pandemic; 37.5% pandemic; p=0.341), echinocandins (17.7% pre-pandemic; 10.0% pandemic; p=0.432), and amphotericin B (2.0% pre-pandemic; 0.0% pandemic; p>0.999) decreased during the pandemic period, there was no significant change (Figure 4). On the other hand, the resistance rates of *C. albicans* isolates grown in blood culture to azoles (32.14% pre-pandemic; 70.8% pandemic; p=0.012) and echinocandins (7.7% pre-pandemic; 25.0% pandemic; p=0.321) increased during the pandemic period. All blood culture isolates were susceptible to amphotericin B (Figure 4).

Discussion

Antibiotic resistance poses a significant global public health threat and leads to increased mortality, hospitalizations, and prolonged hospital stays due to infections caused by resistant bacteria (1). The emergence of the COVID-19 pandemic has put great pressure on healthcare systems and led to a significant increase in empirical antibiotic treatments, especially among

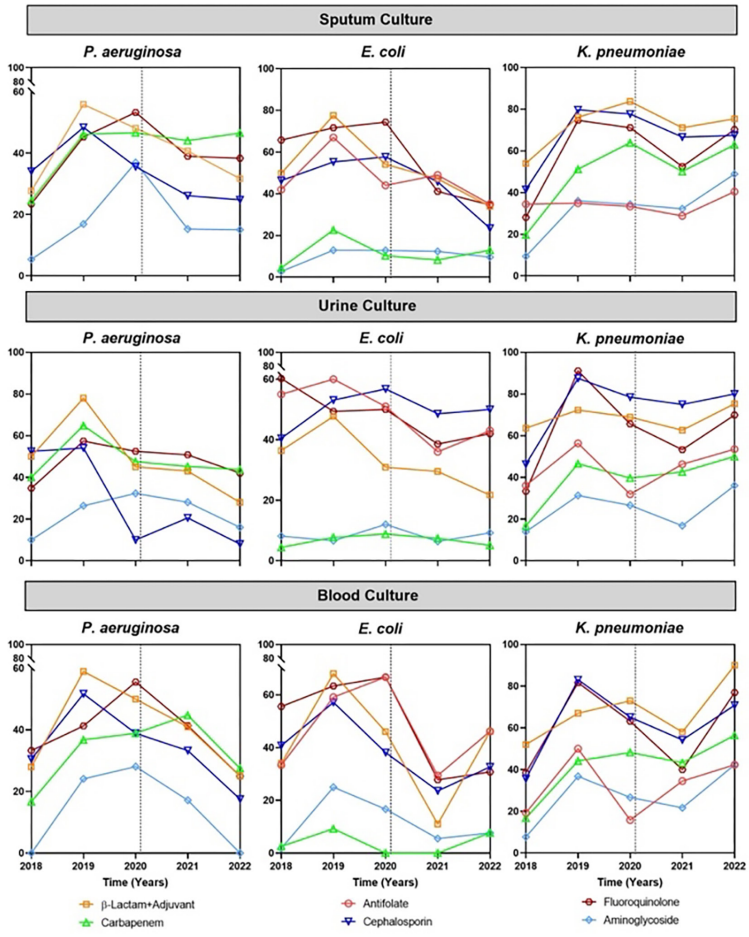

Figure 3. Annual change in resistance to antimicrobial classes of some of the most common isolates grown in sputum, urine, and blood cultures

The dashed line indicates the beginning of the pandemic period

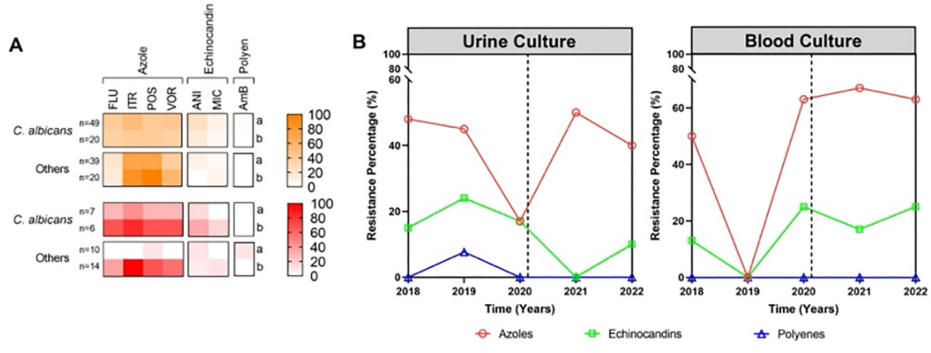

Figure 4. (A) Antimicrobial resistance profile of fungi grown in urine and blood cultures. (B) Annual change in antimicrobial resistance of *C. albicans* grown in urine and blood cultures

Antimicrobial resistance profile of fungi grown in urine and blood cultures, and annual change in antimicrobial resistance of C. albicans. In the heatmap, the color of each cell shows the percentages of resistant strains grouped according to the antimicrobial classification indicated in the columns. Orange color represents urine cultures, and red color represents blood cultures. Pre-pandemic period (pp) and pandemic period (pd) were compared in each bacterial group. Time-antimicrobial resistance graphs show the annual change in antimicrobial resistance of C. albicans grown in urine and blood cultures. The dashed line indicates the beginning of the pandemic period

intensive-care patients (10). Despite this increase in antibiotic use, our study did not observe an overall significant increase in resistance development during the pandemic, consistent with findings in Taiwan however, a notable exception was noted in *K. pneumoniae* showing an increase in resistance during this period, which is consistent with findings from a separate study (10,11).

Our study revealed a significant increase in the number of sputum cultures during the pandemic, possibly attributable to the increased frequency of respiratory sampling required by the pandemic. Gram-negative bacteria were isolated more frequently than Gram-positive bacteria in all cultures, which is consistent with previous studies conducted in ICU patients (12,13). Consistent with previous studies, *P. aeruginosa* was found to be the most frequently isolated bacterium from sputum samples in our study (14,15). Urinary tract infections constitute an important part of nosocomial infections in ICU settings (16). In our study, *E. coli* and *K. pneumoniae* were the most frequently isolated bacteria in urine cultures to previous findings (17,18). Bloodstream infections constitute an important burden on human health and the most frequently isolated organism in our study was CoNS, followed by *S. aureus* and *P. aeruginosa*; this is consistent with similar studies showing that Gram-positive bacteria are predominant in blood cultures (19,20).

Regarding antimicrobial resistance patterns, our findings revealed that *S. aureus* isolates were susceptible to trimethoprim-sulfamethoxazole, vancomycin, teicoplanin, and tigecycline and showed marked resistance to ampicillin which was also shown in previous studies (12). In contrast, we observed a significant increase in trimethoprim-sulfamethoxazole and teicoplanin resistance and a significant decrease in clindamycin resistance rate among CoNS isolated from blood cultures. Teicoplanin resistance also increased in a post-COVID-19 study, consistent with our findings (11).

Similar to the findings of a study conducted in Romania, a decrease in penicillin resistance among *Enterococcus species* was observed in our study. Furthermore, consistent with the study conducted in Colombia, an increase in vancomycin and teicoplanin resistance was recorded among *E. faecium* isolates (11,21).

The resistance rates of *A. baumannii* isolates to antifolates, carbapenems, fluoroquinolones, and aminoglycosides were found to be quite high in other studies (22). Specifically, no significant change in antimicrobial resistance was observed among *A. baumannii* isolates in our study.

Regarding *P. aeruginosa* isolates, our study revealed a significant decrease in piperacillin-tazobactam and ceftazidime resistance in isolates obtained from blood and urine cultures. However, in sputum culture isolates, resistance to ceftazidime and cefepime decreased significantly, while gentamicin resistance showed a significant increase. These findings are consistent with another study covering the years 2016-2020, which observed a decrease in resistance rates in many antibiotic groups, except amikacin, in *P. aeruginosa* strains during the pandemic period (23).

In terms of *E. coli* isolates our study showed a significant decrease in resistance to antifolate, β-lactam/adjuvant antibiotics, ciprofloxacin, and ampicillin during the pandemic period. However, resistance to ceftazidime increased. Similarly, as reported in other studies on *K. pneumoniae* isolates; a high level of ampicillin resistance was found in our study (17,18). In particular, *K. pneumoniae* exhibited a high resistance rate against many commonly used antimicrobials. While ceftazidime resistance increased in our study, levofloxacin resistance decreased significantly. Unlike our study, there is another study showing an increase in levofloxacin resistance (11).

Regarding fungal infections, *C. albicans* was the most frequently isolated yeast fungus in our study, which is consistent with previous studies showing its prevalence, especially in ICU patients (24). *C. albicans* isolates obtained from urine cultures generally showed decreased antimicrobial resistance during the pandemic, while those obtained from blood cultures showed increased resistance.

Study Limitations

Despite the valuable data provided by our study, some limitations should be noted, including small sample sizes for some isolates and limitations in generalizing the findings due to the single-center nature of the study. Nevertheless, our study highlights the importance of comprehensive research on antimicrobial resistance patterns both before and during pandemics and provides valuable information to address this global health challenge.

Conclusion

While most of the microorganisms analyzed (*S. aureus*, *C. striatum*, *A. baumannii*, *E. faecalis*) showed no significant change in resistance patterns before and during the pandemic, *P. aeruginosa* and *E. coli* isolates showed a downward trend, while *K. pneumoniae* showed an increase in resistance after 2022. This is thought to be due to the irrational use of antibiotics. In addition to the development of strategies for the control of infectious diseases, it is necessary to raise awareness among healthcare professionals and the public on the rational use of antibiotics. Furthermore, further research is needed to elucidate the development of antimicrobial resistance.

Ethics

Ethical Committee Approval: Each stage of the study was conducted with ethical principles. Before initiating the study, written permission was obtained from the Sivas Cumhuriyet University Ethical Committee of Non-invasive Clinical Research (decision no: 2023-10/03, date: 19.10.2023).

Informed Consent: Informed consent was obtained from all participants before starting the study.

Footnotes

Authorship Contributions

Concept: A.Ç., R.E.A., R.A., Design: A.Ç., R.E.A., R.A., Data Collection or Processing: A.Ç., R.E.A., Analysis or Interpretation: A.Ç., R.E.A., R.A., Literature Search: A.Ç., R.E.A., R.A., M.H., A.H.T.K., Writing: A.Ç., R.E.A., R.A., M.H., A.H.T.K.

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Original Article

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Nicotine Dependence Level and Sleep Quality in Patients Attending the Smoking Cessation Clinic

Sigara Bırakma Polikliniğine Gelen Hastalarda Nikotin Bağımlılık Düzeyi ve Uyku Kalitesi

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ABSTRACT

Objective: In our study, the aim is to investigate the impact of nicotine dependence level, smoking habits, and the desire to quit smoking on sleep quality, as well as their relationship with anxiety and depression levels.

Methods: The study is a prospective case control research. Two hundred twenty-eight individuals who were admitted to family medicine and smoking cessation clinics (SCC) were included in the study, forming three different groups: those who smoked and visited the SCC, those who smoked, and those who did not smoke. Participants were administered Fagerstrom Nicotine Dependence Test, Pittsburgh Sleep Quality Index (PSQI), and Hospital Anxiety and Depression Scale.

Results: In our study, the PSQI score of patients who wished to quit smoking and were admitted to the SCC was 5.29, while the PSQI score of other smokers was 4.58, and the PSQI score of non-smokers was 4.54. Although the PSQI scores of patients who were admitted to the SCC were higher, this wasn't statistically significant (p=0.479). Statistically significant results were found regarding anxiety and depression levels between those who were admitted to the SCC and the other groups (p<0.001, p=0.015). The dependence level of the group smoking and visiting the SCC was significantly higher than that of the other group of smokers (p<0.001).

Conclusion: Anxiety, depression, physical activity, and nocturnal eating are factors associated with sleep quality. Individuals who visit the SCC have higher scores for cigarette addiction, anxiety, depression, and questioning and treating their symptoms in this direction will be beneficial for the patient's sleep pattern.

Keywords: Cigarette smoking, sleep quality, smoking cessation

ÖZ

Amaç: Çalışmamızda, nikotin bağımlılık düzeyi, sigara kullanımı ve sigara bırakma isteğinin uyku kalitesine etkisi ve anksiyete depresyon düzeyleri ile ilişkisinin incelenmesi hedeflenmiştir.

Yöntemler: Çalışmamız prospektif, olgu kontrol tipte bir araştırmadır. İki yüz yirmi sekiz kişi, aile hekimliği ve sigara bırakma polikliniklerine (SBP) başvurmuş ve çalışmaya dahil edilmiştir. Bu kişiler arasında, SBP'ye gelip sigara içenler, sigara içenler ve sigara içmeyenler olmak üzere üç farklı grup oluşturulmuştur. Katılımcılara Fagerstrom Nikotin Bağımlılık Testi (FNBT), Pittsburgh Uyku Kalitesi İndeksi (PUKİ), Hastane Anksiyete ve Depresyon Ölçeği uygulanmıştır.

Bulgular: Çalışmamızda sigara bırakma isteği olup SBP'ye başvuran hastaların PUKİ skoru 5,29, diğer sigara içenlerin PUKİ skoru 4,58, sigara içmeyenlerin PUKİ skoru 4,54 idi. SBP'ye başvuran hastaların PUKİ skorları daha yüksek olmasına rağmen istatistiksel olarak anlamlı çıkmamıştır (p=0,479). SBP'ye başvuranlar ve diğer gruplar arasında anksiyete ve depresyon düzeyleri açısından istatistiksel açıdan anlamlı sonuçlar çıkmıştır (p<0,001 ve p=0,015). SBP'ye gelip sigara içen grubun bağımlılık düzeyi diğer sigara içen gruptan anlamlı yüksektir (p<0,001).

Sonuç: Anksiyete, depresyon, fiziksel aktivite ve gece yemek yeme uyku kalitesiyle ilişkili faktörlerdir. SBP'ye gelen kişilerin sigara bağımlılığı, anksiyete, depresyon ve PUKİ uyku bozukluğu skorları yüksek olup, bu yönde semptomlarının sorgulanması ve tedavisi hastanın uyku düzeni için yarar sağlayacaktır.

Anahtar Kelimeler: Sigara içme, uyku kalitesi, sigara bırakma

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Introduction

Sleep disorders are directly associated with socioeconomic status, psychiatric diseases, obesity, smoking addiction, stress, and drug use (1).

The effects of nicotine and nicotine deprivation on sleep and the tendency of nonsmokers to be more awake in the morning indicate a relationship between smoking and sleep disorders (2). Also, because of the nicotine it contains, smoking is among the factors that might affect sleep quality negatively by stimulating the central nervous system (3). It was reported in previous studies that smokers had sleep problems such as difficulty falling asleep, falling asleep, waking up early, and daytime sleepiness (4). Nicotine stimulates the release of neurotransmitters such as dopamine, which cause sleep disorders. For this reason, smokers can stay awake longer than non-smokers, wake up frequently at night, and experience insomnia (5). Although there are studies in the literature conducted on the relationship between smoking and sleep quality, no study was detected that included smokers who wanted to quit smoking.

Individuals who have psychiatric problems tend to start smoking at an earlier age, smoke more heavily, and be more addicted to cigarettes than the general population (6). It has been confirmed that smoking is highly comorbid with anxiety and depression and that this relationship is moderated by factors such as the smoker's age, type of disorder, and level of nicotine dependence (7). Previous studies reported an association between smoking and increased anxiety symptoms or disorders. In this context, early life exposure predisposes to anxiety in later life (8). The anxiolytic and antidepressant effects of smoking are often described by smokers. Depression causes people to smoke to treat their symptoms, but later smoking increases the risk of depression through changes in neurotransmitter pathways after chronic exposure. Acute or occasional tobacco use might reduce the negative effects, but chronic use exacerbates anxiety and depression (9).

The present study aimed to examine the relationship between nicotine addiction levels, smoking, and desire to quit smoking on sleep quality and anxiety and depression levels.

Methods

The study had a prospective cross-sectional design and the participants were included in the study with the simple random sampling method among those who were admitted to family medicine and smoking cessation clinics (SCC) of family medicine between 27.07.2022 and 27.09.2022. When the 562 people who were admitted to the clinics were accepted as the study population, the confidence interval was calculated as 95%, the deviation amount was calculated as 0.05, and the minimum number of people required was calculated as 228. The patients were divided into three different groups as smokers who were admitted to SCC, smokers who were not admitted to SCC, and non-smokers, (76 participants in each group). Patients between the ages of 18-65 who volunteered for the study were included, and those with mental retardation, communication limitations, active psychiatric disease, body mass index (BMI) ≥35, asthma and chronic obstructive pulmonary disease, and pregnant women were not included in the study. Also, those who had known sleep disorder diagnosis, substance abuse other than smoking, shift work that would disrupt sleep patterns or long-distance travel requirements, or acute or chronic diseases that would disrupt sleep patterns were not included in the study. Face-to-face interview technique and survey design were used in the study.

After the informed consent forms were approved, a participant information collection form was used, including sociodemographic data, chronic disease, and medication use status, and the results were recorded. This form consisted of questions on the sociodemographic characteristics, height-weight status, chronic diseases, regular medication, and smoking status, physical activity, and general health status of the individuals. Fagerstrom Test for Nicotine Dependence (FTND), Pittsburgh Sleep Quality Index (PSQI), and Hospital Anxiety and Depression Scale (HADS) were admitted to the participants.

The Turkish validity and reliability study of FTND was conducted by Uysal et al. (10) to be used as a measurement tool in the evaluation of nicotine addiction. The score range that can be obtained from the test, which consists of a total of 6 questions, is between "0" and "10". A higher score indicates an increase in addiction.

The PSQI is a self-report scale used to evaluate sleep quality and sleep disturbance over one month. The PSQI was developed by Buysse et al. (11) and was shown to have adequate internal consistency, test-retest reliability, and validity. The Turkish validity and reliability study of the scale was conducted by Ağargün et al. (12) and it was determined that it was suitable for the Turkish population. It consists of a total of 11 questions and 7 subcomponents. These components consist of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping pills, and daytime dysfunction. The total score on the scale ranges from 0 to 21. The scores of the 7 components are added together, and values >5 indicate poor sleep quality.

The HADS consists of 14 questions, where single-digit questions measure anxiety (HADS-A) level and double-digit questions measure depression (HADS-D) level, each question consisting of 4 options. Participants' anxiety and depression levels are considered normal between 0-7 points, borderline between 8-10 points, and abnormal if 11 and above. The Turkish validity and reliability study was conducted by Aydemir and Güvenir (13).

The study was conducted in line with the Declaration of Helsinki and the principles of good clinical practice. Approval was received from the Ethics Committee of a University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital (decision no: 2022/141, date: 27.06.2022).

Statistical Analysis

Statistical analyses were made by using the IBM SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA). Demographic variables

such as sex and PSQI classification were summarized by using frequencies (n) and percentages (%) to illustrate the distribution of the participants. The distribution of the continuous variables including age, BMI, FTND, HADS and PSQI scores was evaluated graphically and with the Shapiro-Wilk test. Descriptive statistics were expressed as mean ± standard deviation because these variables did not meet the criteria for normal distribution. For group comparisons, nonparametric tests were applied because of the non-normal distribution of continuous variables. The Mann-Whitney U test was used to compare two independent groups, and the Kruskal-Wallis test was used for comparisons involving more than two independent groups. Post-hoc pairwise comparisons were adjusted by using the Bonferroni correction and were then analyzed with the Mann-Whitney U test. The Spearman's rank-order relationship coefficient was made use of to examine the relationships between scale scores. Multivariate logistic regression analysis was conducted to identify predictors of poor sleep quality. The independent variables included in the model were HADS-A score, HADS-D score, FTND score, age, sex, marital status, BMI, regular exercise, nighttime eating, and phone use before sleeping. Statistical significance was set at $p<0.05$.

Results

The study included 76 individuals who were admitted to SCC and smoked, 76 individuals who were not admitted to SCC and smoked, and 76 individuals who did not smoke and a total of 57.9% of the individuals (n=132) were female, the average sleep duration of the individuals was 7.16±1.24 hours. According to the PSQI scale score classification, 70.2% (n=160) were in the healthy sleep class, and 29.8% (n=68) were in the poor sleep class.

The comparison of the demographic characteristics of the individuals and the PSQI scores of other variables that might affect sleep quality is given in Table 1. No statistically significant differences were detected between the PSQI scores and the other variables except for "do you exercise regularly?", "do you have a habit of eating at night?", "do you actively use your mobile phone, television, or computer in the last hour before going to sleep?" ($p>0.05$). The sleep quality of those who answered "every day" to the question "do you exercise regularly?" was better than those who said "no" or "occasionally" ($p=0.007$ and $p=0.012$).

Comparisons were made between the groups (smokers who were admitted to SCC, smokers, non-smokers) in terms of total PSQI, subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, daytime dysfunction, HADS-A, HADS-D and FTND scores (Table 2). No significant differences were detected between the groups in terms of total PSQI scores ($p=0.479$). However, when we look at its subcomponents, there was a significant difference between the groups in terms of sleep latency, habitual sleep efficiency, and sleep disturbance scores. Sleep latency scores were significantly higher in the group who were admitted to SCC and smoked compared to non-smokers, and habitual sleep efficiency scores were significantly higher in the group

Table 1. The comparison of the PSQI scores of the individuals in variable groups

		PSQI score	
		Mean ± SD	p-value
Sex	Female	4.97±2.71	0.316
	Male	4.57±2.33	
Educational status	Not literate	5.67±4.72	0.441
	Primary school	5.35±2.43	
	Middle school	5.00±4.09	
	High school	4.53±2.54	
	Bachelor's degree and above	4.82±2.31	
Marital status	Married	4.77±2.58	0.459
	Single	4.68±2.32	
	Divorced	5.08±3.15	
	Spouse passed away	7.00±3.94	
Living environment	Alone	4.41±2.00	0.501
	With spouse	4.00±1.94	
	Nuclear family	4.82±2.58	
	Extended family	5.21±3.14	
	Other	5.17±2.81	
Income status	Less than MW	5.44±3.03	0.875
	MW	4.80±2.96	
	More than MW	4.73±2.51	
	2 times and more than MW	4.78±2.21	
	3 times and more than MW	4.45±1.82	
Regular exercise	No	5.16±2.68	**0.023**
	Every day	3.60±1.27	
	At least three days a week	4.18±2.16	
	At least five days a week	4.63±2.27	
	Once in a while	5.26±2.98	
Smoking	Yes	4.93±2.54	0.369
	No	4.54±2.59	
Consuming tea one hour before sleep	Yes	4.99±2.38	0.347
	No	4.53±2.50	
	Sometimes	5.00±3.09	
Consuming coffee one hour before sleep	Yes	5.13±2.14	0.272
	No	4.74±2.60	
	Sometimes	4.72±2.79	
Chronic disease	Yes	5.28±2.99	0.494
	No	4.76±2.52	
Night eating habit	Yes	5.68±2.85	**0.002**
	No	4.51±2.39	
Screen before sleep*	Yes	5.03±2.59	**0.001**
	No	3.78±2.10	

*Screen exposure in the last hour before sleep, SD: Standard deviation, MW: Minimum wage, PSQI: Pittsburgh sleep quality index

who were admitted to SCC and smoked compared to non-smokers (p=0.013 and p=0.030). Sleep disturbance scores were significantly higher in the group who were admitted to SCC and smoked compared to smokers and non-smokers (p=0.029 and p=0.037). HADS-A, HADS-D, and FTND scores of the group that were admitted to SCC and smoked were significantly higher than the group that did not smoke (p<0.001, p=0.015 and p<0.001).

A statistically significant and positive relationship was detected between FTND score and sleep disturbance (rho: 0.189, p=0.019). No statistically significant relationship was found between FTND score and subjective sleep quality, sleep latency, sleep duration, and habitual sleep efficiency (rho: 0.033, p=0.683; rho: 0.147, p=0.071; rho: -0.003, p=0.970; rho: -0.037; p=0.654, respectively).

The results of the multivariate logistic regression model, which included variables such as HADS-A score, HADS-D score, FTND score, age, sex, marital status, BMI, regular exercise, eating at night, using the phone before going to sleep, etc., whose effects on poor sleep status were investigated, are given in Table 3.

The explanatory power of the model was evaluated by using the Cox and Snell or Nagelkerke R^2 values. The Nagelkerke R^2 value of 0.523 in the logistic regression model indicated that the multivariate model explained the response variable (poor sleep status) very well.

Table 2. Comparison of PSQI (total and subcomponents), HADS-A, HADS-D, and FTND scores between the groups

	Coming to SCC and smoking	Smoker	Non-smoking	Test statistics
	Mean ± SD	Mean ± SD	Mean ± SD	p-value
Total PSQI	5.29±2.97	4.58±1.96	4.54±2.59	0.479
Subjective sleep quality	1.10±0.72	1.10±0.42	0.99±0.62	**0.441**
Sleep latency	1.32±0.91[a]	1.07±0.87	0.91±0.94[a]	**0.017**
Sleep duration	0.74±0.72	0.83±0.62	0.80±0.67	**0.437**
Habitual sleep activity	0.34±0.77	0.09±0.33[a]	0.33±0.66[a]	**0.024**
Sleep disorder	1.24±0.49[a,b]	1.00±0.49[a]	1.03±0.63[b]	**0.013**
Daytime dysfunction	0.41±0.66	0.45±0.79	0.46±0.72	**0.878**
HADS-A	7.78±3.82[a]	5.37±3.05[a]	6.50±4.14	**<0.001**
HADS-D	6.67±3.62[a]	4.96±3.05[a]	5.69±3.84	**0.019**
FTND	6.37±2.28	4.43±3.07		**<0.001**

[a,b]: Mann-Whitney U-test statistics, Kruskal-Wallis test statistics, same letters indicate significant difference between groups, PSQI: Pittsburgh sleep quality index, HADS-A: Hospital anxiety and depression scale - anxiety, HADS-D: Hospital anxiety and depression scale - depression, FTND: Fagerstrom test for nicotine dependence

Table 3. Potential risk factors predicting poor sleep status in the multivariate logistic regression model

Variables	β	Standard error	Wald	p-value	Exp (B)	95% Confidence interval for Exp (B)	
						Lower	Upper
Constant	-9.261	2.315	16.005	**<0.001**	0.001		
HADS-A	0.269	0.088	9.415	**0.002**	1.309	1.102	1.555
HADS-D	0.223	0.099	5.051	**0.025**	1.249	1.029	1.517
FTND	0.027	0.094	0.085	0.771	1.028	0.854	1.236
Age	0.010	0.028	0.119	0.730	1.010	0.956	1.066
Sex (male)	0.093	0.513	0.033	0.855	1.098	0.402	2.998
Marital status (married)	-0.784	0.529	2.195	0.138	0.456	0.162	1.288
BMI	0.098	0.059	2.769	0.096	1.103	0.983	1.238
Regular exercise (yes)	-1.066	0.513	4.315	**0.038**	0.344	0.126	0.942
Eating at night (yes)	1.632	0.536	9.284	**0.002**	5.113	1.790	14.604
Use of phone etc. before going to sleep (yes)	2.109	1.135	3.450	0.063	8.238	0.890	76.252

β: The estimated coefficient for the predictor, SE: Standard error, Wald: $(\beta/S.E)^2$, Exp (B): Odds ratio, HADS-A: Hospital anxiety and depression scale - anxiety, HADS-D: Hospital anxiety and depression scale - depression, FTND: Fagerstrom test for nicotine dependence, BMI: Body mass index

Discussion

A total of 29.8% of the participants were in the poor sleep class in terms of PSQI score evaluation in the study. According to the results of the multivariate logistic regression analysis, it was found that the HADS-A score increased the risk of poor sleep by 1.31 times, and the HADS-D score increased by 1.25 times. Individuals who ate at night were more likely to have poor sleep than those who did not. The risk of having poor sleep was found to be 5.11 times higher. The risk of having poor sleep was reduced by 65.6% (1-0.34) in those who exercised regularly compared to those who do not.

In a previous study that was conducted by Dugas et al. (14), higher cigarette consumption, more frequent deprival symptoms, and higher FTND scores were associated with poor sleep quality. In another study conducted by Riedel et al. (15), it was reported that total sleep time was shorter in those who smoked less than 15 cigarettes per day and that heavy smokers did not tend to have insomnia. They attributed this to heavy smokers consuming cigarettes on a more consistent schedule. In the study, the FTND score was not one of the potential risk factors predicting poor sleep status. However, "sleep disturbance", which is one of the subcomponents of PSQI, was higher in SCC patients with high FTND scores and smokers compared to the other groups. Although there were patients with SCC patients with the highest PSQI scores among the three groups in the study and they smoked, it was not statistically significant. In other studies conducted in our country comparing smokers and non-smokers, the relationship between poor sleep and smoking was not significant (16-18). In a study conducted by Sujarwoto (19) on approximately 39,000 individuals, the probability of experiencing sleep disturbance was almost 1.5 times higher in current smokers than in non-smokers, and this rate almost doubled among heavy smokers. The finding in the same study that poverty was also associated with poor sleep suggests that differences in socioeconomic levels between the study participant groups may be the cause of this.

In a study that was conducted by Kwan et al. (20), it was found that students with night eating syndrome (NES) had worse sleep quality. In another study conducted by Şen and Kabaran (21), it was found that there were positive relationships between the carbohydrate intake of male participants and night eating, mood, and sleep disorder scores. In the study conducted by Basatemür and Güneş (22), sleep quality was found to be lower in those with night eating habits. Similar to these results in the present study, the PSQI score of individuals with night eating habits was higher than those without. In the regression model created in the present study, it was found that the risk of poor sleep was 5.11 times higher in individuals who ate at night compared to those who did not.

In the study that was conducted by Wu et al. (23), it was found that screen exposure reduced sleep quality. Low physical activity also reduces sleep quality statistically significantly. Rafique et al. (24) concluded that using mobile screens for 8 hours or more per day and using mobile phones for at least 30 minutes before going to sleep were associated with poor sleep quality. In the present study, those who were exposed to screens in the last hour before going to sleep had higher PSQI scores and lower sleep quality than those who were not exposed to screens.

The study of Brand et al. (25) reported that continuous intense exercise was positively associated with patients' sleep and psychological functioning. It was also found that men with low exercise levels were at risk for increased sleep complaints and poorer psychological functioning. Banno et al. (26) meta-analysis of nine studies concluded that exercise improved sleep quality without significant side effects. Lederman et al. (27) meta-analysis of eight studies reported that exercise significantly improved sleep quality in patients. In the regression model we created, exercise increased sleep quality by 65%. In the present study, similar to the literature data, as exercise level increased, it positively affected sleep quality.

Previous studies show a strong association between nicotine addiction and psychiatric diseases such as stress, anxiety, and depression (1,28). In the meta-analysis conducted by Fluharty et al. (6), half of the studies show that initial depression or anxiety is associated with subsequent smoking behavior in the form of starting to smoke or strong cigarette addiction. In the present study, the HADS-A and HADS-D scores of individuals who were admitted to SCC were found to be significantly higher than those in the smoking group. This may be because individuals who were admitted to SCC were highly dependent or that comorbid conditions caused by smoking increased anxiety and depression. Some of the patients who were admitted to SCC were admitted to our outpatient clinic because of symptoms resulting from smoking. In the study conducted by Esen et al. (29), it was concluded that the health anxiety levels of those who were admitted to SCC because of fear of chronic disease were significantly higher and that the health anxiety levels of these patients were similar to those with chronic diseases.

The smokers who had the worst sleep quality were those who were admitted to SCC among the groups, but the total PSQI scores were not statistically significant. However, there were significant results in sleep latency, habitual sleep efficiency, and sleep disturbance scores between the groups. Anxiety, depression, physical activity, and night eating are factors associated with sleep quality.

Study Limitations

The fact that the study was conducted in one single center in the provincial borders of İstanbul, was based on volunteering, and the PSQI scale, which provides a subjective assessment of sleep quality, might have affected the results.

Conclusion

People who are admitted to SCC have high scores for smoking addiction, anxiety, depression, and sleep disorders, and questioning and treating their symptoms will benefit the patient's sleep pattern. Questioning and adjusting lifestyles such as exercise status, eating habits, and screen exposure may be recommended for patients with sleep disorders.

Ethics

Ethics Committee Approval: Approval was received from the Ethics Committee of a University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital (decision no: 2022/141, date: 27.06.2022).

Informed Consent: Informed consent forms were approved, a participant information collection form was used, including sociodemographic data, chronic disease, and medication use status, and the results were recorded.

Footnotes

Authorship Contributions

Concept: Y.O., Ö.B.D., A.D., Design: Y.O., Ö.B.D., A.D., Data Collection or Processing: Y.O., Analysis or Interpretation: Y.O., Ö.B.D., A.D., Literature Search: Y.O., Ö.B.D., A.D., Writing: Y.O., Ö.B.D., A.D.

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Original Article

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Microsatellite Instability Status and Programmed Death Cell Ligand 1 Expression in Serous Ovarian Tumors

Seröz Over Tümörlerinde Mikrosatellit İnstabilite Durumu ve Programlanmış Ölüm- Ligand 1 Ekspresyonu

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ABSTRACT

Objective: The goal is to find out more about the microsatellite instability (MSI) and programmed death cell ligand 1 (PD-L1) expression in ovarian serous tumors so that we can better understand the tumor microenvironment and possibly come up with new ways to treat it. This study examines how PD-L1 expression and DNA mismatch repair (dMMR) are related in ovarian serous tumors. The goal is to figure out how these two factors affect the immune system of the tumor.

Methods: We used immunohistochemistry to examine MMR proteins and PD-L1 in 37 people with serous ovarian tumors. Of these, 14 had high-grade serous carcinoma, 6 had low-grade serous carcinoma, 8 had borderline serous tumors, and 9 had serous cystadenomas.

Results: In our study, only four cases (10.8%) showed loss of MMR protein expression, indicative of dMMR. We found no significant relationship between MSI status and tumor size, ovarian localization, International Federation of Gynecology and Obstetrics stage, or PD-L1 expression.

Conclusion: In this study, loss of MMR protein expression was not associated with prognostic parameters or PD-L1 expression. Although some studies have compared the MSI status of tumors with various prognostic parameters, a consensus has yet to be reached. Understanding the interplay between MSI and PD-L1 expression could guide personalized treatment approaches, offering new avenues for precision medicine in ovarian cancer.

Keywords: Microsatellite instability, PD-L1, serous ovarian cancer, immunohistochemistry

ÖZ

Amaç: Seröz over tümörlerinde mikrosatellit instabilitesi (MSI) ve programlanmış ölüm- ligand 1 (PD-L1) ekspresyonu hakkında daha fazla bilgi edinmek, böylece tümör mikroçevresini daha iyi anlayabilmek ve tedavi etmek için olası yeni yollar bulmaktır. Bu çalışmada seröz over tümörlerinde PD-L1 ekspresyonu ve DNA uyumsuzluk onarımının (dMMR) ilişkisi incelenmiş ve bu iki faktörün tümör içi immün sistemi nasıl etkilediğini bulmak hedeflenmiştir.

Yöntemler: Seröz over tümörü olan 37 hastada MMR proteinleri ve PD-L1 düzeylerine bakmak için immünohistokimyasal yöntemler kullandık. Bunlardan 14'ünde yüksek dereceli seröz karsinom, 6'sında düşük dereceli seröz karsinom, 8'inde borderline seröz tümör ve 9'unda seröz kistadenom vardı.

Bulgular: Çalışmamızda sadece dört olguda (%10,8) dMMR'yi gösteren MMR protein ekspresyon kaybı saptandı. MSI durumu ile tümör boyutu, over lokalizasyonu, Uluslararası Jinekoloji ve Obstetrik Federasyonu evresi veya PD-L1 ekspresyonu arasında anlamlı bir ilişki bulunamadı.

Sonuç: Bu çalışmada, MMR protein ekspresyonu kaybı prognostik parametreler veya PD-L1 ekspresyonu ile ilişkili saptanmadı. Bazı çalışmalarda tümörlerin MSI durumu çeşitli prognostik parametrelerle karşılaştırılmış olsa da aralarındaki ilişki için henüz bir fikir birliğine varılamamıştır. MSI ve PD-L1 ekspresyonu arasındaki etkileşimi anlamak, over kanserinde hedefe yönelik kişiselleştirilmiş tedavi yaklaşımlarına rehberlik edebilir.

Anahtar Kelimeler: Mikrosatellit instabilite, PD-L1, seröz over kanseri, immünohistokimya

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Introduction

Ovarian cancer is the second most prevalent form of cancer among gynecological malignancies and is the most lethal gynecological malignancy that affects women (1). The subtype of serous ovarian cancer is the most common within this category (2). Although early-stage diagnosis plays a crucial role in ovarian malignancies, patients frequently acquire diagnoses at advanced stages. (3). The prognosis for advanced ovarian cancer is significantly unfavorable, with diminished efficacy of standard treatments such as chemotherapy and radiotherapy. Therefore, advancing novel therapeutic methods, such as immunotherapy, has been paramount. Recent research has discovered that microsatellite instability (MSI) and programmed death cell ligand 1 (PD-L1) expression play a crucial role in how tumors interact with the immune system. MSI, which stands for defective DNA mismatch repair (dMMR), has attracted attention because it correlates with increased immunogenicity and improves responsiveness to immune checkpoint inhibitors in different types of cancer.

The PD-L1, a protein found on the surface of cancer cells, interacts with the PD-1 receptor on immune cells. This interaction suppresses the immune response and allows the cancer cells to avoid being attacked by the immune system. Understanding the complex connection between MMR protein expression and PD-L1 status in ovarian cancer is crucial for deciphering the immune system's characteristics and investigating potential treatment options. Nevertheless, the specific location and significance of dMMR and MSI status in ovarian cancer are not fully comprehended. The clinicopathologic characteristics of dMMR ovarian tumors are still not well understood, as there is conflicting information regarding the agreement between MMR deficiency and MSI status. Moreover, there is still ambiguity regarding the potential effectiveness of PD-1/PD-L1 inhibition in treating ovarian malignancies with MMR deficiency, as previous studies have only demonstrated mild responses in ovarian carcinomas (4).

The documented prevalence of MSI in ovarian cancer varies from 2% to 20% (2). Endometrioid and clear-cell ovarian carcinomas are the predominant subtypes of ovarian malignancies that have been found to display MSI, as reported in many publications (5). However, there is limited research explicitly addressing serous ovarian carcinomas with MSI.

This study's objective is to examine the frequency of dMMR and PD-L1 expression in ovarian serous tumors and assess their relationship with other prognostic factors.

Methods

Collection of Materials

Our pathology department diagnosed 37 instances between 2012 and 2020, including 14 high-grade serous carcinomas, six low-grade serous carcinomas, eight borderline serous tumors, and nine serous cystadenomas. These cases were selected based on their sufficient clinical knowledge. The hematoxylin and eosin (H&E)-stained case preparations were reassessed, and suitable blocks that accurately represented the tumor were chosen for immunohistochemical (IHC) investigation.

Compliance with Ethical Standards

All the authors declare that this study complied with the Declaration of Helsinki, as approved by the Karadeniz Technical University Ethics Committee (protocol number: 2020/251, date: 06.11.2020). Written informed consent was obtained for the study.

Immunohistochemistry (IHC) and Scoring

IHC experiments were conducted using the Ventana BenchMark Ultra, a fully automated staining system manufactured by Ventana Medical Systems, Inc. in the United States. Four micrometer thick slices were obtained from tissue blocks using a polymer-coated lamella to do this. After removing the paraffin, the IHC staining process was started.

The assessment of MMR protein expressions was conducted in the following manner: Positive staining or intact nuclear expression for each antibody was determined based on the existence of nuclear staining. The absence of nuclear staining in tumor cells was characterized as a lack of MMR protein expression. MMR protein expression is typically detected in lymphocytes and/or stromal cells, which serves as a positive internal control.

The outcomes are commonly categorized in the following manner:

1-Proficient Mismatch Repair (pMMR): This term describes tumors that show complete expression of all four MMR proteins. pMMR status signifies the operational state of the MMR system and the tumor's ability to correct DNA replication mistakes effectively.

2-Deficient Mismatch Repair (dMMR): This term describes tumors that lack the expression of one or more MMR proteins. An instance of dMMR classification occurs when a tumor exhibits the absence of MutL homolog 1 (MLH1) and postmeiotic segregation increased 2 (PMS2) expression while maintaining the expression of MutS homolog 2 (MSH2) and MutS homolog 6 (MSH6).

The PD-L1 antibody clone 28-8 was utilized. The PD-L1 expression was evaluated by scoring the sections based on the percentages of tumor cells showing entire circumferential or partial linear plasma membrane staining. A tumor is classified as PD-L1 positive when 5% or more of its cells show staining for PD-L1. The tonsillar tissue was utilized as the external positive control.

Statistical Analysis

The data analysis was conducted using the SPSS 22.00 statistical analysis tool. When comparing numerical variables between two independent groups, the Student's t-test is used if the normal distribution requirement is satisfied. If the normal distribution condition is not met, the Mann-Whitney U test is used instead. The ANOVA test was conducted by comparing at least three

groups to see if the normal distribution assumption was fulfilled. In contrast, the Kruskal-Wallis test was utilized if this assumption was not maintained. The chi-square test was applied to compare categorical data. A p-value of less than 0.05 was considered statistically significant.

Results

Clinicopathological Parameters

Fourteen, 6, 8, and 9 cases of high-grade serous carcinoma, low-grade serous carcinoma, borderline serous tumor, and serous cystadenoma were diagnosed, respectively. The International Federation of Gynecology and Obstetrics (FIGO) stage I/II was identified in 16 cases (high-grade 4 cases, low-grade 5 cases, borderline 7 cases). FIGO stage III/IV was determined in 12 cases (high-grade 10 cases, low-grade 1 cases, and borderline 1 cases). The characteristics of patients are summarized in Table 1.

Expression of PD-L1

Four cases (10.8%) (high-grade serous carcinoma) were identified as PD-L1 positive by IHC, as shown in Figure 1. There was no significant relationship between PD-L1 expression and tumor size (p=0.282), FIGO stage (p=0.053), or localization (p=0.276).

Expression of MMR proteins

The IHC identified four cases (10.8%) (3 in high-grade serous carcinoma and 1 in low-grade serous carcinoma) as dMMR.

Table 1. Characteristics of the study population

Characteristics	Number of patients	Percentage of patients (%)
Age at diagnosis		
<50	13	35.1
≥50	24	64.9
Histology		
High grade serous	14	38
Low grade serous	6	16
Borderline	8	22
Serous cystadenoma	9	24
FIGO state		
I, II	16	43
III, IV	12	32
Localization		
Right ovary	12	32
Left ovary	11	30
Bilateral	14	38
Tumor size		
<10cm	25	68
≥10cm	12	32
Total	37	100

FIGO: International Federation of Gynecology and Obstetrics

The expression loss distribution in immune markers in these cases was as follows (Table 2).

-Isolated loss in PMS2 in 3 cases is shown in Figure 2 (all the cases are in high grade).

-Loss in MLH1 and PMS2 expressions in 1 case (low grade)

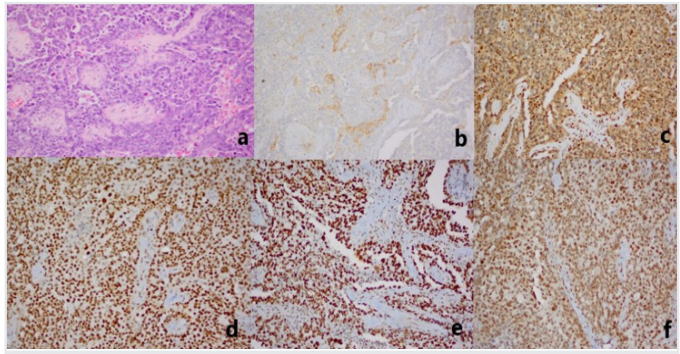

Figure 1. High grade serous ovarian carcinoma a) H&E x200, b) PD-L1x200 (positive staining), c) PMS2x200, d) MSH-2x200, e) MSH-6x200, f) MLH-1x200. No loss of MMR protein expression

H&E: Hematoxylin and eosin, PD-L1: Programmed death cell ligand 1, PMS2: Postmeiotic segregation increased 2, MSH: MutS homolog, MLH: MutL homolog, MMR: Mismatch repair

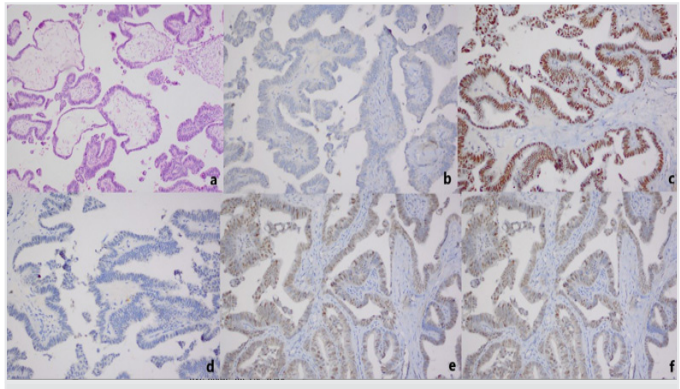

Figure 2. High grade serous ovarian carcinoma a) H&E x200, b) PD-L1x200 (negative staining), c) MSH-6x200, d) PMS-2x200 (loss of PMS-2 expression), e) MLH-1x200, f) MSH-2x200

H&E: Hematoxylin and eosin, PD-L1: Programmed death cell ligand 1, MSH: MutS homolog, PMS2: Postmeiotic segregation increased 2, MLH: MutL homolog

Table 2. The MMR expression status of cases with dMMR

	MLH1 loss	MSH2 loss	MSH6 loss	PMS2 loss
Case 1	-	-	-	+
Case 2	-	-	-	+
Case 3	-	-	-	+
Case 4	+	-	-	+

dMMR: DNA mismatch repair, MLH1: MutL homolog 1, MSH2: MutS homolog 2, MSH6: MutS homolog 6, PMS2: Postmeiotic segregation increased 2

-There was no significant relationship between dMMR and tumor size (p=0.582), localization (p=0.625), FIGO stage (p=0.464).

Relationship between dMMR and Expression of PD-L1

There was no significiant relationship between MSI status and expression of PD-L1 (p=1.000). While PD-L1 was positive in 4 of 37 cases which did not show loss of MMR protein expression.

Discussion

Our study, which examined how dMMR and PD-L1 expression were related in ovarian serous tumors, revealed a fascinating finding: there was no significant link between these two molecular markers. This finding prompts a comprehensive discussion of potential explanations and the broader implications for understanding the tumor microenvironment in ovarian cancer.

Ovarian serous tumors are known for their molecular heterogeneity, which can significantly impact the expression patterns of various biomarkers. The fact that our study found no link between dMMR and PD-L1 expression might show how different the molecular landscape was in this group of ovarian cancers. This variety can be caused by changes in underlying genes, tumor growth, and effects on the microenvironment. This is one reason why there isn't a single link between dMMR and PD-L1.

Understanding the lack of correlation between dMMR and PD-L1 in ovarian serous tumors is crucial for guiding therapeutic strategies. The absence of a direct correlation suggests that a comprehensive molecular profiling approach may be necessary to identify patients who may benefit from immune checkpoint inhibitors. When dMMR and PD-L1 don't match, looking into other immunotherapeutic targets and combination therapies tailored to each tumor's molecular makeup may be more helpful.

Vierkoetter et al. (7) found that patients with dMMR were younger than those with pMMR (mean age: 47 and 58 years, respectively) (p=0.0014). However, in our study, the four patients with dMMR were 67, 64, 63, and 58, with a mean age of 63. Contrary to the previous research, our findings indicated that cases with dMMR were older than those with pMMR.

Norquist et al. (8) identified MMR gene mutations in eight out of 1,915 patients with ovarian cancer, with 88% of these patients showing defects in the PMS2 and MSH6 genes. The tumor type in four patients with PMS2 mutations was high-grade serous carcinoma. Our study used MLH1, MSH2, MSH6, and PMS2 markers for IHC analysis. Three patients with MMR loss only had PMS2 protein expression loss, while one had both PMS2 and MLH1 loss.

In the study by Ryan et al. (9), MSI was most often found in the endometrioid subtype, but it was also found in high-grade serous ovarian carcinomas, which was a statistically important finding. Although not statistically significant, three out of four cases with MMR loss in our study were in the high-grade serous ovarian carcinoma subtype. More extensive studies ought to support this finding.

Study Limitations

Considering the temporal and spatial dynamics of dMMR and PD-L1 expression is essential. Tumor evolution and the dynamic nature of the immune response may lead to temporal variations in these molecular markers. Additionally, spatial heterogeneity within the tumor microenvironment can contribute to divergent expression patterns, complicating efforts to establish a straightforward correlation. More in-depth studies that look at both space and time may give us a better understanding of how dMMR and PD-L1 are connected in ovarian serous tumors.

The lack of a link could also mean that immune evasion in ovarian serous tumors isn't just dependent on the PD-L1/PD-1 axis in patients with dMMR. Alternative immune checkpoint pathways, tumor-intrinsic factors, or additional immune evasion mechanisms could have a role. Looking into other immunomodulatory molecules and pathways in the tumor microenvironment might reveal more layers of complexity in the immune response and help explain why dMMR and PD-L1 don't work together in this case (6).

Conclusion

This research contributes to our existing knowledge of the intricate molecular characteristics of ovarian serous tumors and highlights the significance of gaining a deeper understanding of the correlation between dMMR and PD-L1 expression. The absence of this link demonstrates the complexity of the interplay between the tumor and the immune system in ovarian cancer, emphasizing the importance of continued research to uncover the various mechanisms through which the immune system can overcome this challenge.

Ethics

Ethics Committee Approval: All the authors declare that this study complied with the Declaration of Helsinki, as approved by the Karadeniz Technical University Ethics Committee (protocol number: 2020/251, date: 06.11.2020).

Informed Consent: Written informed consent was obtained for the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.T., Concept: G.T., Design: G.T., Data Collection or Processing: G.T., M.E.E., Analysis or Interpretation: G.T., Literature Search: G.T., M.E.E., Writing: G.T.

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

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Original Article

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A Comparison of the Stomatognathic and Neck Functions between Smokers and Non-smokers

Sigara Kullanan ve Kullanmayanların Stomatognatik ve Boyun Fonksiyonlarının Karşılaştırılması

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ABSTRACT

Objective: This study aimed to compare smokers' and non-smokers' stomatognathic and neck functions.

Methods: The study included 100 smokers and 96 non-smokers who did not have any chronic diseases. Temporomandibular and swallowing functions were evaluated as stomatognathic function components. Temporomandibular function with Fonseca Anamnestic Index (FAI) and swallowing function with Eating Assessment Tool (EAT-10) were assessed. The Neck Disability Index (NDI) was used to evaluate neck functions.

Results: The FAI score of smokers was higher than non-smokers (p=0.005). According to FAI scores, 68 (68%) of smokers had the risk of temporomandibular disorder (TMD), whereas 48 (50%) of non-smokers had the risk of TMD. The risk of TMD was higher in smokers (p=0.013). The EAT-10 scores of smokers and non-smokers were similar (p=0.692). Four participants among smokers (4%) and 4 participants among non-smokers (4.1%) had a risk for the swallowing disorder. The risk for the swallowing disorder of smokers and non-smokers was similar (p>0.999). The NDI scores were similar between smokers and non-smokers (p=0.833). According to NDI, 38 (38%) and 38 (39.6%) participants in both smokers and non-smokers had no functional neck disability.

ÖZ

Amaç: Bu çalışmada sigara kullanan ve kullanmayanların stomatognatik ve boyun fonksiyonlarının karşılaştırılması amaçlandı.

Yöntemler: Çalışmaya herhangi bir kronik hastalığı olmayan 100 sigara içen ve 96 sigara içmeyen kişi dahil edildi. Temporomandibular fonksiyon ve yutma fonksiyonu stomatognatik fonksiyon bileşenleri olarak değerlendirildi. Temporomandibular fonksiyon Fonseca Anamnestik Anketi (FAI) ile, yutma fonksiyonu ise Yutma Fonksiyonu Tarama Testi (EAT-10) ile değerlendirildi. Boyun fonksiyonlarını değerlendirmek için Boyun Engellilik Göstergesi (NDI) kullanıldı.

Bulgular: Sigara kullananların FAI skoru kullanmayanlara göre daha yüksekti (p=0,005). FAI skorlarına göre sigara kullananların 68'inde (%68) temporomandibular bozukluk (TMB) riski bulunurken, sigara kullanmayanların 48'inde (%50) TMB riski vardı. Sigara kullananlarda TMB riski daha yüksekti (p=0,013). Sigara kullanan ve kullanmayanların EAT-10 puanları benzerdi (p=0,692). Sigara kullanan 4 hastada (%4) ve sigara kullanmayan 4 hastada (%4,1) yutma bozukluğu riski vardı. Sigara kullanan ve kullanmayanların yutma bozukluğu riski benzerdi (p>0,999). Sigara kullanan ve kullanmayanların NDI skorları benzerdi

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ABSTRACT

The rate of functional neck disability of the groups was similar (p=0.304).

Conclusion: It was found that the risk of temporomandibular dysfunction was higher in smokers than in non-smokers, but not for swallowing and neck function. Even in the absence of chronic disease, the risk of developing temporomandibular dysfunction in smokers should be kept in mind.

Keywords: Neck, smoking, stomatognathic system, swallowing, temporomandibular disorder

ÖZ

(p=0,833). NDI'ye göre sigara kullananların 38'inde (%38) ve kullanmayanların 38'inde (%39,6) fonksiyonel boyun engelliliği yoktu. Grupların fonksiyonel boyun engelliliği oranı benzerdi (p=0,304).

Sonuç: Sigara kullananlarda temporomandibular disfonksiyon riskinin sigara kullanmayanlara göre daha yüksek olduğu ancak yutma ve boyun fonksiyonları için bu durumun söz konusu olmadığı bulundu. Kronik hastalık olmasa bile sigara kullananlarda temporomandibular disfonksiyon gelişme riski akılda tutulmalıdır.

Anahtar Kelimeler: Boyun, sigara içme, stomatognatik sistem, yutma, temporomandibular bozukluk

Introduction

Smoking is a harmful addiction that causes global drivers of premature disability and death. It is associated with many pathological factors that cause mortality and pave the way for the formation and progression of many diseases, especially neurological, cardiovascular, and lung diseases. Smoking is largely responsible for all deaths caused by lung cancer and chronic obstructive pulmonary disease (COPD) (1-3). However, not much focus has been given to the impact of smoking on smokers without any chronic disease, who may have smoking-related health issues even if they don't have any chronic diseases. Although smokers may seem healthy due to the absence of common smoking-induced chronic diseases like COPD, smoking harmfully exposes them to risks from the early stages of smoking (4). Smoking is not only a risk factor for many well-known chronic diseases, but also it may cause physical impairment and pain aggravation (5,6) due to its numerous hazardous ingredients causing impaired tissue healing, alteration in pain processing, and inflammation (4,7). Previous clinical researches have demonstrated this (5,8).

The stomatognathic system consists of muscles around the head and neck, chewing muscles, bone structures (lower and upper jaw), temporomandibular joint (TMJ), and soft tissues (salivary glands, vascular and nerve structures) (9,10). Chewing and swallowing, which are physiologically interconnected, are the most prominent functional parts of the stomatognathic system. TMJ is critical in the functionality of this connection (11,12). TMJ, connected to the cervical region by muscles and ligaments, is also included in the structure of the functional complex called the "cranio-cervical-mandibular system" (10,13). Additionally, the convergence of trigeminal and upper cervical nerve inputs in the trigeminocervical nucleus creates neurophysiological connections between TMJ and the cervical spine (14). With its biomechanical, neurophysiological, and functional relationship, TMJ is critical for stomatognathic and neck functions (10-14).

It is hypothesized that smoking may have an impact on gustatory and olfactory perception, as well as masticatory behavior. Consequently, the oral phase of swallowing can be affected, leading to stomatognathic dysfunction (11). Studies investigating the effect of smoking on stomatognathic function generally focused on TMJ (8,15-17). Studies indicated that smoking might increase symptoms and aggravate the pain of patients with TMJ disorders (8,15). However, the findings of the studies comparing the presence of TMJ disorders in smokers and non-smokers are contradictory (16,18). To the authors' knowledge, no study has compared swallowing and neck functions in smokers and non-smokers. Therefore, we aimed to compare stomatognathic (temporomandibular and swallowing) and neck functions in smokers and non-smokers.

Methods

Study Design

This case-controlled research was conducted web-based using an online form. The data collection was performed in February and March 2024. The ethical protocol of the study was approved by the Ankara Yıldırım Beyazıt University Health Science Ethics Committee (protocol number: 01-560, date: 16.01.2024) and this study was performed strictly under the declaration of Helsinki. Participants were informed about the study and their consent was obtained.

Participants

The 18-65 aged healthy participants were invited to the study. The participants were called for the study from the community via an announcement and they were recruited randomly through the snowball sampling method due to eligible criteria. The participants were divided into two groups based on their smoking status: current smokers and non-smokers. All patients were asked a series of questions, including "Do you currently smoke?", "Have you ever smoked?", and if they had smoked before, "For how many years have you smoked in total?" and "What is the average number of cigarettes you smoke per day?". Patients were also asked about their smoking cessation history, including "Have you ever quit smoking?" and "If yes, how long ago did you quit smoking?". Patients who currently smoked and had smoked at least 100 cigarettes in the past year were classified as smokers. Non-smokers verified that they had never smoked. Furthermore, participants who were not current smokers were not classified as non-smokers if they confirmed that they were ex-smokers (19).

Participants were excluded if they (a) had any diagnosed chronic diseases such as cardiovascular disease [hypertension (HT), history of myocardial infarcts, and any cardiovascular surgery, etc.], pulmonary disease (COPD, asthıma, etc.), endocrine disease [diabetes mellitus (DM), hypo/hyperthyroid, etc.], allergic (allergic rhinitis, etc.), rheumatic, oncologic, neurologic diseases, (b) had a history of any surgery or trauma related to the stomatognathic system (chin, jaw, throat, etc.), or cervical spine (c), had congenital spine deformity, (d) had a major psychiatric disorder, (e) had missing data in the assessment form, and (f) were not volunteer.

Measurements

The demographic, physical, and medical characteristics of the participants [sex, age, height, weight, body mass index, education level, medical history (chronic disease, surgery history), smoking features number of cigarettes smoked per day, years of smoking, history of quitting smoking, and smoking index] were questioned. The smoking index was recorded using the Brinkman formula, which multiplies the number of cigarettes smoked daily by the total number of smoking years. This index was divided into three categories: light smoking (≤200), moderate smoking (200-599), and heavy smoking (≥600) (20). Temporomandibular, swallowing, and neck functions were evaluated with patient-based questionnaires.

Temporomandibular Function

The Fonseca Anamnestic Index (FAI) is used to evaluate the temporomandibular function. It includes 10 items with three response options: "yes" (10 points), "sometimes" (5 points), and "no" (0 points). The score is calculated by adding up the points from all items, and it can classify the results into four categories: no signs or symptoms of temporomandibular disorder (TMD) (0-15 points), mild TMD (20-45 points), moderate TMD (50-65 points), and severe TMD (70-100 points). A total of more than 15 points means a risk for TMD. A higher score indicates higher temporomandibular dysfunction (21).

Swallowing Function

The swallowing function was evaluated with the Eating Assessment Tool (EAT-10) commonly known as EAT-10. It was designed to evaluate the swallowing disorders under 10 questions. Each question is given a score from 0 to 4 based on the severity of the problem (0= no problem, 4= severe problem). The total score is obtained by adding up the points given to each item. A total of 3 points and above means a risk for swallowing disorder. As the total score increases, the severity of swallowing dysfunction increases (22).

Neck Function

Neck function was assessed with the Neck Disability Index (NDI) developed to evaluate neck problems' effects on daily living activities. It consists of 10 items with 6 possible answers for each item ranged 0 to 5 points (0= no pain and no functional disability; 5= worst pain and maximum disability). The sum of the scores corresponding to the response to each item gives the NDI score. If NDI scores are between 0-4, 5-14, 15-24, 25-34, and over 35 points, they are classified as having no, mild, moderate, severe, or complete disability, respectively. Higher scores indicate greater functional neck disability (23).

Statistical Analysis

The sample size needed for the study was determined using a statistical power analysis program (G*Power Version 3.0.10, Franz Faul, Universität Kiel, Germany) (24). A pilot study was conducted with five randomly selected participants from each group, and their FAI scores were utilized to estimate it. A sample size of one hundred ninety participants (ninety-five per group) with a 10% drop rate was required to achieve 80% power with d=0.432 effect size, α=0.05 type I error, and β =0.20 type II error.

Statistical analysis software (IBM Corp. Released in 2012, IBM SPSS Statistics for Windows, Version 22.0) was used for data analysis and calculations. The Kolmogorov-Smirnov test, histogram, detrended normal quantile-quantile graph, skewness and kurtosis coefficients, and coefficient of variation were utilized to examine the distribution of data. Continuous values that followed a normal distribution were represented as mean ± standard deviation (X ± SD), while those that did not follow a normal distribution were represented as median (interquartile range). Categorical variables were represented as frequency (n) and percentage (%). The chi-square or Fischer's exact tests were used to compare categorical variables. For continuous variables, the independent sample t-test was employed to compare the variables of different groups, provided that the assumption of normal distribution was met. If the assumption of normal distribution was not met, the Mann-Whitney U test was used. A result was considered statistically significant if the overall p-value was less than 0.05.

Results

Three hundred-four participants were evaluated for the study's eligibility criteria. Firstly, 3 participants were excluded due to having missing data (n=1) and not being volunteers (n=2). According to their smoking status, participants were assigned into the smoker (n=145), and non-smoker (n=156) groups. Of 145 active smokers 45 were excluded due to having a chronic disease [cardio-pulmonary diseases (CPD) (n=8), HT (n=10), DM (n=4), hypo/hyper thyroid (n=4)], history of chin, face, or neck surgery or trauma (n=15), having allergenic rhinitis (n=4). Because 60 of non-smokers were not suitable for non-smokers group, 96 non-smokers were involved. Of a group of 60 participants, 27 had chronic conditions [rheumatic disease (n=4), CPD (n=6), DM (n=6), hypo/hyper thyroid (n=7), HT (n=4)], history of chin, face, or neck surgery or trauma (n=13), having allergenic rhinitis (n=5), having history of smoking (n=15). The study ultimately included 100 smokers and 96 never smokers. A flowchart illustrating the process from assessing eligibility criteria to data analysis for the study is provided in Figure 1.

Out of a total of 100 smokers, 42 (42%) were female and 58 (58%) were male. The educational level of the smokers was as follows: 13 (13%) had completed primary school, 20 (20%)

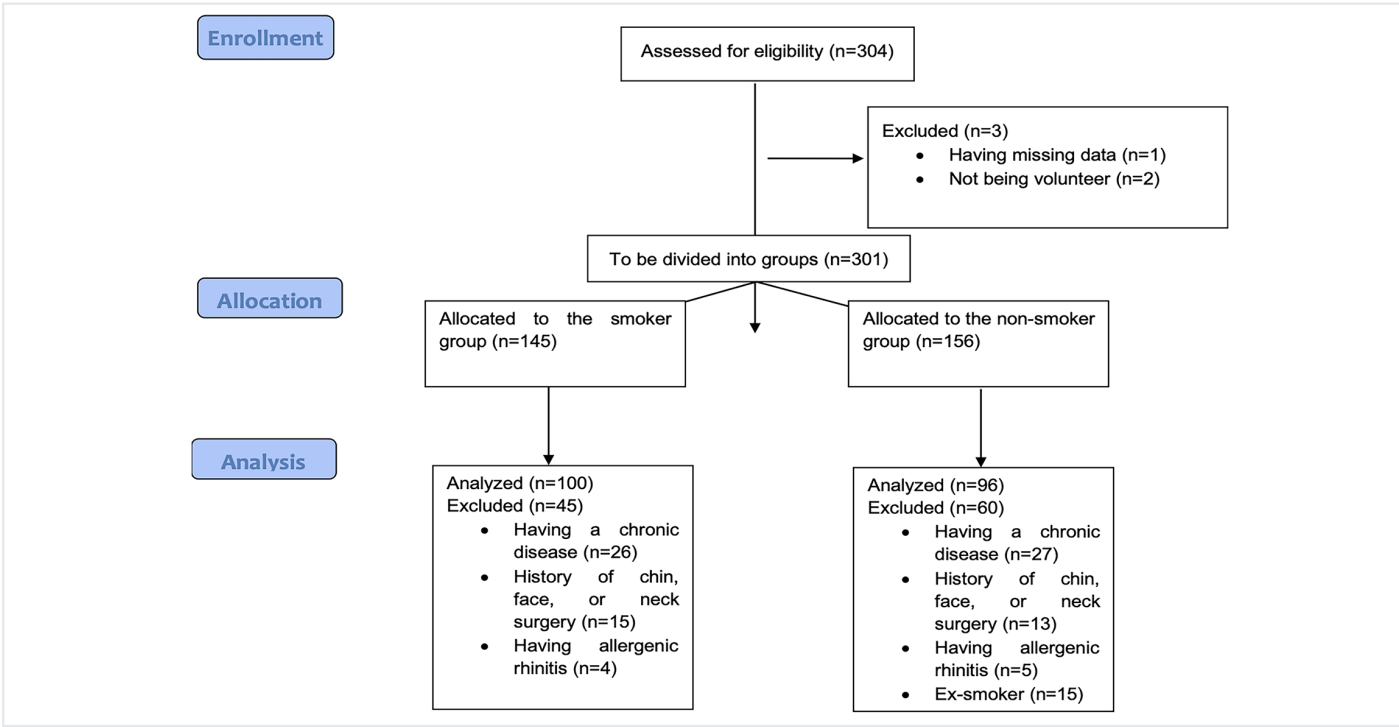

Figure 1. The flowchart of the study

had completed high school, 55 (55%) had obtained a bachelor's degree, and 12 (12%) had obtained a master's degree (Table 1). The mean of cigarettes smoked per day was 17.20±9.32, the smoking year was 16.38±10.32, and the smoking index was 311.30±287.76. Of the smokers, 51 (51%), 34 (34%), and 15 (15%) were light, moderate, and heavy smokers, respectively (Table 2). Out of 96 non-smokers, 68 (70.8%) were females and 28 (29.2%) were males. Six (6.3%) completed primary school, 13 (13.5%) completed high school, 61 (63.5%) had a bachelor's degree, and 16 (16.7%) had a master's degree (Table 1).

In the group of smokers, 32 participants (32%) reported no symptoms of TMD, 48 (48%) reported mild symptoms, 16 (16%) reported moderate symptoms, and only 4 (4%) reported severe TMD. On the other hand, no cases of severe TMD were reported in the non-smoker group. Out of the non-smokers, 36 participants (37.5%) had mild TMD symptoms, 12 (12.5%) had moderate symptoms, and 48 (50%) showed no symptoms of TMD. Sixty eight (68%) of smokers had the risk of TMD, whereas 48 (50%) of non-smokers had the risk of TMD. The presence of TMD (p=0.013) and TMD severity (p=0.024) was different between smokers and non-smokers. FAI score evaluating temporomandibular dysfunction was higher in smokers than non-smokers (p=0.005) (Table 3).

According to the EAT-10 score, 4 participants among smokers (4%) and 4 participants among non-smokers 4.1% had a risk for the swallowing disorder. The risk for the swallowing disorder of smokers and non-smokers was similar (p>0.999). The EAT-10 score evaluating swallowing function was similar between smokers and non-smokers (p=0.692) (Table 3).

Out of the smokers, 38 participants (38%) had no, 44 (44%) had mild, and 18 (18%) had moderate functional neck disability. Whereas, non-smokers reported no 38 (39.6%), mild 48 (50%), and moderate 10 (10.4%) functional neck disability. In both groups, no severe functional disability was found. The rate of functional neck disability of the groups was similar (p=0.304). The NDI scores evaluating neck function were similar between smokers and non-smokers (p=0.833) (Table 3).

Discussion

The purpose of this study was to compare stomatognathic (temporomandibular and swallowing) and neck functions in smokers and non-smokers who did not have any chronic diseases. We found that the percentage of TMD was higher in smokers compared to non-smokers. Additionally, the severity of TMD in smokers, according to the FAI score, was also higher. However, no significant difference was observed between smokers and non-smokers in the swallowing and neck functions. Therefore, we reported that smoking could cause temporomandibular dysfunction, but it didn't affect swallowing and neck function.

Studies suggest that smokers experience more severe pain in the presence of TMD than non-smokers, indicating that smoking is a risk factor for exacerbating temporomandibular symptoms (8,25). Although smoking was accepted as a risk factor for aggravating pain and dysfunction in patients with TMD, they focused on the effects of smoking on the severity of temporomandibular dysfunction. The findings of studies comparing temporomandibular function between smokers and non-smokers were contradictory (16,18). Sachdeva et al. (16) reported that smokers (56.9%) had higher TMD incidence than

Table 1. The comparison of the demographic and medical characteristics of groups

	Smokers (n=100)	Non-smokers (n=96)	p-value
Age (year), median (IQR)	37.00 (13.00)	30.00 (15.00)	**<0.001**[a*]
Body mass index (kg/m^2), median (IQR)	24.87 (4.64)	24.45 (5.68)	0.412[a]
Sex, N (percentage)			
Female	42 (42)	68 (70.8)	**<0.001**[b]
Male	58 (58)	28 (29.2)	
Education level, N (percentage)			
Primary school	13 (13)	6 (6.3)	
High school	20 (20)	13 (13.5)	0.182[c]
Bachelor	55 (55)	61 (63.5)	
Master	12 (12)	16 (16.7)	

* p<0.05, [a]: Mann-Whitney U test, [b]: Fischer exact test, [c]: Chi-square test, N: Frequency, IQR: Inter-quartile range

Table 2. The smoking characteristics of smokers

	Smokers (n=100)
Mean of cigarettes smoked per day, X ± SD	17.20±9.32
Smoking years, X ± SD	16.38±10.32
Smoking index, median (IQR)	240 (405)
Smoking index category, N (percentage)	
Light	51 (51)
Moderate	34 (34)
Heavy	15 (15)

N: Frequency, X: Mean, SD: Standard deviation, IQR: Inter-quartile range

non-smokers (43.1%). Göğremiş and Sönmez (18) determined that 91.7% of smokers and 85.4% of non-smokers had TMD and they concluded that there was no significant difference in the incidence of TMD between smokers and non-smokers. Our findings were consistent with the study of Sachdeva et al. (16). We discovered that the risk rate of TMD was 68% in smokers, whereas it was 50% in non-smokers. Furthermore, our study also revealed that the severity of TMD was higher in smokers as compared to non-smokers. Smoking has been associated with aggravating chronic pain by acting on pain via hypersensitivity and inflammatory pathways. It also impairs the healing process, and this leads to aggravating chronic pain and dysfunction (7,26). Smoking can cause changes in the pattern of mastication behavior, a major function of the TMJ. Smokers exhibit atypical patterns in both functions compared to non-smokers (11). Our findings suggest that the higher incidence and severity of TMD in smokers than non-smokers can be attributed to the physiological (7,26) and biomechanical (11) effects of smoking on the TMJ.

We investigated the swallowing function in smokers and non-smokers. We found that the swallowing functions of smokers and non-smokers were similar. Moreover, we found that only a small percentage of both smokers (4%) and non-smokers (4.1%) were at risk of developing a swallowing disorder. Although as yet, no study has compared the swallowing function in smokers and non-smokers participants without COPD, studies reported that patients with COPD which is a smoking-induced disease had impaired swallowing function (27,28). In COPD patients, laryngopharyngeal mechanosensitivity may be reduced and swallowing function may be impaired, characterized mainly by pharyngeal stasis (29). So we may comment that smokers without COPD had similar swallowing functions as those of non-smokers. No differences in swallowing function between smokers and non-smokers can be attributed to our method for assessing swallowing function using the EAT-10. Smoking may impair taste and smell perception during the oral phase of swallowing (30). However, since swallowing is a submaximal function, this impairment might not lead to any functional problems. Alternatively, smoking may have impacted the spatial and temporal parameters of swallowing, which are not detectable by the EAT-10 (22).

We compared the self-reported neck function of smokers and non-smokers and found no difference. To the best of our knowledge, no studies have been conducted to compare neck function between smokers and non-smokers. Previous research has primarily focused on comparing neck pain rates and intensity (31,32). It was reported that smokers compared to non-smokers have more risk for musculoskeletal pain, especially spine pain (31). A study found that smokers had a 1.39 times higher risk of neck pain than non-smokers (32). Due to the negative effects of smoking on pain development and the aggravation of pain intensity (33,34), we had assumed that smoking could also affect neck function, but we did not find any differences between smokers and non-smokers. One possible explanation for the lack of significant differences in neck function between smokers and non-smokers is that neck function is influenced by multiple determinants, such as individual, clinical, and emotional factors (35). Also, we assessed neck function with a self-reported questionnaire. Therefore, our results should be questioned with objective methods.

Study Limitations

It is important to note that our study had some limitations that must be considered. Firstly, due to the cross-sectional design

Table 3. Comparison of temporomandibular, swallowing, and neck functions of groups

	Smokers (n=100)	Non-smokers (n=96)	p-value
Fonseca Amnestic Index Score, median (IQR)	25.00 (25.00)	17.50 (28.75)	**0.005**[a*]
The presence of temporomandibular disorder, N (percentage)			
Available	68 (68)	48 (50)	**0.013**[b*]
Absent	32 (32)	48 (50)	
Eating assessment tool score, median (IQR)	0.00 (0.00)	0.00 (0.00)	0.692[a]
The presence of swallowing disorder, N (percentage)			
Available	4 (4)	4 (4.1)	>0.999[b]
Absent	96 (96)	92 (95.9)	
Neck Disability Index Score, median (IQR)	6.00 (8.00)	7.00 (7.50)	0.833[a]
The presence of functional neck disability, N (percentage)			
Available	62 (62)	38 (39.6)	0.304[c]
Absent	38 (38)	58 (60.4)	

[*] p<0.05, [a]: Mann-Whitney U test, [b]: Fischer exact test, [c]: Chi-square test, N: Frequency, IQR: Inter-quartile range

of the study, it is challenging to make causal inferences based on the data and analyses. Moreover, two groups in this study exhibited differences in certain demographic characteristics, such as age and gender. Since this is a cross-sectional study with a randomly selected sample from the broader population, these differences are expected. However, it is important to consider this when interpreting the results. Future studies should focus on participants of the same gender or within a narrower age range for more accurate comparisons. Additionally, the study only relied on self-reported measures to examine the stomatognathic and neck functions. The study was limited to patients' perceptions of these factors. As a result, future studies should consider using objective measurement methods. A thorough clinical examination of TMJ dysfunction should be conducted to address this limitation. Lastly, it is important to consider the possibility of selection bias as the patients in the study were limited to those who could fill out an online form via a web-based survey method.

Conclusion

We found that smokers had higher temporomandibular dysfunction than non-smokers. Additionally, we revealed that the severity of TMD was higher in smokers as compared to non-smokers. However, swallowing and neck functions were similar between smokers and non-smokers. We choose a study sample without any diagnosed chronic disease like COPD. So, we may comment that even in the absence of chronic disease smoking may cause a risk of temporomandibular dysfunction. So, the risk of developing temporomandibular dysfunction in smokers even in the absence of chronic disease should be kept in mind. In addition, the recommendations of healthcare professionals to quit smoking habits in their patients with TMD are very valuable.

Ethics

Ethics Commitee Approval: The ethical aproval of the study was obtained from the Ankara Yıldırım Beyazıt University Health Science Ethic Comitte (protocol number: 01-560, date: 16.01.2024).

Informed constent: Participants' informed consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.M., E.İ.H., S.Ç., S.A., N.Ö.Ü., Concept: O.M., N.Ö.Ü., Design: O.M., E.İ.H.,

N.Ö.Ü., Data Collection or Processing: O.M., E.İ.H., S.Ç., S.A., N.Ö.Ü., Analysis or Interpretation: O.M., S.Ç., N.Ö.Ü., Literature Search: O.M., E.İ.H., S.Ç., S.A., N.Ö.Ü., Writing: O.M., E.İ.H., S.Ç., S.A., N.Ö.Ü.

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

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Original Article

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Evaluation of Nursing Students' Attitudes Toward Health Technologies in Clinical Practice and Individual Innovative Behaviors: A Cross-sectional and Correlational Study

Hemşirelik Öğrencilerinin Klinik Uygulamalarda Sağlık Teknolojilerine Yönelik Tutumlarının ve Bireysel Yenilikçi Davranışlarının Değerlendirilmesi: Kesitsel ve Korelasyonel Bir Çalışma

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ABSTRACT

Objective: Future nurses' effective use of health technologies requires sufficient knowledge, positive attitudes, individual innovativeness, and self-efficacy behaviors toward these technologies. This study examined nursing students' health technology attitudes and individual innovativeness behaviors.

Methods: This cross-sectional and correlational study involved 346 students with practice experience in the nursing department of a university. Identification form, the Health Personnel Health Technology Assessment Attitude Scale, and the Individual Innovativeness Scale (IIS) were used. Descriptive statistics and correlation test were used.

Results: The mean total score of the Healthcare Personnel Health Technologies Assessment Attitude Scale was 99.58±10.65, and the mean total score of the IIS was 63.65±9.40. A weak positive correlation was found between students' health technology evaluation attitudes and individual innovativeness behaviors.

Conclusion: Health technology should be included in the education of future nurses to teach technological tools, eliminate barriers to their use, and develop innovative behaviors. Positive attitudes will bring along innovative behaviors and ensure faster

ÖZ

Amaç: Geleceğin hemşirelerinin sağlık teknolojilerini etkin bir şekilde kullanabilmeleri, bu teknolojilere yönelik yeterli bilgi, olumlu tutum, bireysel yenilikçilik ve öz yeterlilik davranışlarını gerektirmektedir. Bu çalışmada hemşirelik öğrencilerinin sağlık teknolojilerine yönelik tutumları ve bireysel yenilikçilik davranışları incelenmiştir.

Yöntemler: Kesitsel ve korelasyonel bir çalışmadır. Bir üniversitenin hemşirelik bölümünde uygulama deneyimi olan 346 öğrenciyi kapsamaktadır. Tanımlama formu, Sağlık Personeli Sağlık Teknolojisi Değerlendirme Tutum Ölçeği ve Bireysel Yenilikçilik Ölçeği (BYÖ) kullanıldı. Tanımlayıcı istatistikler ve korelasyon testi kullanıldı.

Bulgular: Sağlık Personeli Sağlık Teknolojileri Değerlendirme Tutum Ölçeği toplam puan ortalaması 99,58±10,65, BYÖ toplam puan ortalaması 63,65±9,40'tır. Öğrencilerin sağlık teknolojilerini değerlendirme tutumları ile bireysel yenilikçilik davranışları arasında pozitif yönde zayıf bir korelasyon bulunmuştur.

Sonuç: Teknolojik araçların öğretilmesi, kullanımının önündeki engellerin kaldırılması ve yenilikçi davranışların geliştirilmesi için geleceğin hemşirelerinin eğitiminde sağlık teknolojisine yer

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ABSTRACT

adoption of developments in health technologies. At this point, it is imperative to support the existing positive attitudes of students and encourage their innovative behaviors.

Keywords: Innovation, nursing, nursing students, health technology, technology

ÖZ

verilmelidir. Olumlu tutumlar yenilikçi davranışları beraberinde getirecek ve sağlık teknolojilerindeki gelişmelerin daha hızlı benimsenmesini sağlayacaktır. Bu noktada öğrencilerin var olan olumlu tutumlarının desteklenmesi ve yenilikçi davranışlarının teşvik edilmesi zorunludur.

Anahtar Kelimeler: İnovasyon, hemşirelik, hemşirelik öğrencileri, sağlık teknolojisi, teknoloji

Introduction

The rapid advancement of health technologies has transformed healthcare delivery, making it more efficient, accurate, and patient-centered. Health technologies encompass not just physical devices but also digital systems and applications that support various aspects of patient care. These include telehealth services that enable remote patient monitoring, mobile health applications that provide real-time data to healthcare providers, and electronic health records that streamline patient information management. The adoption of these technologies in healthcare settings has been driven by the need to improve patient outcomes, reduce medical errors, and enhance the overall quality of care (1,2).

Innovation in nursing is closely linked to the use of these technologies. It involves not only adopting new technologies but also integrating them into daily practice in ways that enhance care delivery (3). Innovative nurses are those who can identify the potential of new technologies, adapt them to their specific clinical settings, and create new solutions that improve patient care (4,5). For nursing students, developing this innovative capacity is crucial, as it prepares them to face the challenges of a rapidly changing healthcare landscape.

Technology is a process developed according to individuals' time, interests, and needs. It involves creating effective and efficient tools and services that simplify life (2,6). The resources society uses in all areas of life are combined with technological knowledge. Innovations brought about by technology and information in healthcare are essential for delivering health services. Healthcare organizations adopt new technologies to improve the quality of patient care. Technology enables healthcare professionals to manage large volumes of data, facilitates workflow, and reduces medical errors, ultimately increasing patient safety and satisfaction (7).

Health technologies include various processes, such as devices, vaccines, medications, clinical practices, procedures, public health practices, and the application of skills and knowledge organized in systems to address health problems and improve quality of life (2,6,8). Many applications and field-specific technologies are involved in every stage of routine care processes (7,9). Nurses utilize technology in diverse ways to provide care to individuals (10,11). In this study, health technologies are defined based on the World Health Organization's definition, including devices such as pulse oximeters, glucometers, and monitors used in clinical applications (8). These technological devices are continually evolving with advancements in technology, necessitating an innovative approach from nurses.

The dynamic nature of health technology requires a proactive approach in the nursing profession, compelling nurses to not only respond to technological advancements but also anticipate and effectively integrate these changes into patient care. This ensures that nurses remain at the forefront of healthcare innovation, continually improving the quality of care they provide (12). Nurses should be competent in using digital and technological solutions to provide effective and patient-centered care (1). Competence in these areas is not merely a skill but a critical component for the survival and advancement of the nursing profession in the modern healthcare landscape (13). Technologies are integrated into profession-specific practices, and adapting and utilizing technological developments to meet the needs of individuals receiving services while following innovative approaches are among the skills and competencies required by the profession (14). These competencies emphasize the importance of flexibility and continuous learning, which are essential for nurses to meet the evolving demands of healthcare. Nurses can improve their professional skills by increasing their individual innovativeness levels.

Individual innovativeness refers to nurses' capacity to embrace change, take calculated risks, and implement new technologies and methodologies in their practice (15). It embodies the willingness not only to accept innovations but also to actively seek out and apply new ideas that can enhance patient care and professional practice. This is particularly important as the knowledge base in healthcare expands and practices evolve, making innovation a necessary component of nursing. As knowledge increases and healthcare practices continuously change, innovation and creativity have become necessities (16). In this context, innovation in nursing transcends mere technological adoption; it involves the thoughtful application of new ideas, processes, and tools to improve care efficiency, meet patient needs more effectively, and reduce operational costs. Innovation in nursing is the application of new ideas, procedures, or techniques to fulfill individuals' needs, reduce costs, and increase work efficiency (3). This innovation is vital not only for improving the quality and sustainability of nursing care but also for ensuring that nursing professionals can keep pace with the rapidly changing demands

of healthcare (4). Studies show that innovation in nursing can enhance treatment effectiveness, quality of care, and professional productivity, facilitating access to health services and reducing care costs (1,5,17). In a rapidly developing world, the nursing profession should emphasize innovation and professionalism (4).

Nursing education plays a crucial role in fostering innovation. To prepare future nurses for the challenges of modern healthcare, educational programs must incorporate innovative strategies that reflect the current and future needs of the profession. This includes integrating health technologies into the curriculum and encouraging students to develop the skills necessary to use these technologies effectively. Nursing education should include innovative strategies according to the profession's needs (4). Furthermore, nursing students should not only be aware of health technologies used in clinical practice but also be encouraged to cultivate a proactive, innovative mindset that enables them to adapt to and even drive change in their future careers. Nursing students should be aware of health technologies utilized in clinical practice, be open to enhancing their skills in these areas, and adopt positive attitudes. A literature review showed that studies of nursing students frequently evaluated the use of information and communication technologies, computer usage, and attitudes toward technology in nursing education (7,10,15,18-21). There are studies (15,22-28), showing the individual innovativeness behaviors of nursing students and nurses and their relationships with different variables. However, while there is substantial research in these areas, a gap remains in understanding how nursing students' attitudes toward evaluating health technologies are linked to their individual innovativeness behaviors in clinical practice. This study aims to fill that gap by exploring these relationships in depth, thereby contributing to a more comprehensive understanding of how technology and innovation intersect in nursing education and practice.

The aim of this study was to explore the relationship between nursing students' attitudes toward health technologies and their individual innovativeness.

Research questions;

1) What are nursing students' attitudes toward health technologies?
2) What is the use of health technology by undergraduate nursing students?
3) What are the individual innovativeness levels of nursing students?
4) What is the relationship between attitudes towards health technologies and individual innovativeness behaviors?

Methods

Study Design

This was a cross-sectional and correlational study. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting checklist (29).

Participants and Sample Size

The study population consisted of second, third, and fourth-year students (n=571) enrolled in the nursing department of a state university in the 2021-2022 academic year. The criteria for inclusion in the sample included being an active second, third or fourth grades student in the fall and spring semesters of the 2021-2022 academic year, and voluntary participation. The exclusion criterion was being a foreign student. The study's sample size was calculated with the G*Power 3.1.9.7 program by establishing a two-way hypothesis (30). The calculation made with a correlation value of 0.30, a margin of error (α) of 0.05, and a power (1-β) of 0.95 determined that the sample size should be at least 330.

Data Collection Procedure

Data were collected through self-report with nursing students between May 20 and June 20, 2022. Students were informed about the study, and informed consent was obtained from those who agreed to participate in the study. Data were collected face-to-face. After informed consent was obtained, the questionnaires were completed. Data collection took about 15 minutes.

Instruments or Data Collection Tools

Data were collected using an identification form, the Health Personnel Health Technologies Assessment Attitude Scale (HPHTAAS) and the Individual Innovativeness Scale (IIS).

Identification Form

The researchers developed the identification form by reviewing the relevant literature (7,10,18-21). This form asked participants nine questions about socio-demographic characteristics and eight about technology.

Health Personnel Health Technologies Assessment Attitude Scale

The scale was developed by Kuşcu et al. (6). It aims to evaluate the attitudes of healthcare professionals toward health technologies. The five-point Likert-type scale consists of 23 items and 3 sub-dimensions. Questions 1-4 constitute the scope dimension, 5-11 constitute the awareness dimension, and 12-23 constitute the benefit dimension. There are no reverse items in the evaluation of the scale. Each response receives a score: 1 for "strongly disagree", 2 for "disagree", 3 for "undecided", 4 for "agree", and 5 for "strongly agree." It is reported that when the average responses to the item approach 1, the level of health technology assessment is low, and when the average responses to the item approach 5, the level of health technology assessment is high. The Cronbach's alpha for the overall scale was 0.95, and for the benefit, awareness, and scope dimensions, they were 0.93, 0.90, and 0.84, respectively. In our study, the Cronbach's alpha for the overall scale was 0.90, with values of 0.90 for the scope dimension, 0.89 for the awareness dimension, and 0.82 for the benefit dimension.

Individual Innovativeness Scale

The scale was developed by Hurt et al. (31) to assess individual innovativeness among teachers and university students. The scale

was adapted into Turkish by Sarıoğlu Kemer and Altuntaş (32) to assess the individual innovativeness of nurses. The Turkish-adapted version includes 18 items, the five-point Likert-type and is structured into three sub-dimensions: thought leadership (items 1,3,4,7,8,10,11), resistance to change (items 5,6,9,12,13,15,18), and risk-taking (items 2,14,16,17). Eleven items of the scale are positive (1,2,3,4,7,8,10,11,14,16,17) and seven items (5,6,9,12,13,15,18) were negative. Negative items are reverse-scored. Scale sub-dimension and total score values are obtained by summing the scores from each item. A minimum of 18 and a maximum of 90 points are obtained from the scale. According to their scores, individuals are categorized as "innovative" with 82 and above, "pioneer" with 75-82, "questioner" with 66-74, "skeptic" with 58-65, and "traditionalist" with 57 and below. As the scores obtained from the scale increase, the innovativeness level of individuals also increases (32). The original scale consists of 20 items with Cronbach's alpha value of 0.89 for the total scale. The Turkish-adapted version the Cronbach's alpha value of was between 0.82 for the total scale and 0.72 and 0.80 for the sub-dimensions. In this study, the Cronbach's alpha value was 0.84 for the overall scale, 0.85 for thought leadership, 0.80 for resistance to change, and 0.85 for the risk-taking sub-dimension.

Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study's purpose and the content of the forms were explained to the students. They then gave consent for participation. Students were explained that they could leave the study at any time. Ethical permission was obtained from Pamukkale University Ethics Committee (decision number: E-60116787-020-208262, date: 17.05.2022). Permissions from the place where the data would be collected and from the authors to use the scale were taken.

Statistical Analysis

The data were evaluated with the Statistical Package for the Social Sciences (SSPS) version 29.0 program. Descriptive statistics were used to analyze the data, including number, percentage, mean, and standard deviation. Normal distribution was tested with skewness (0.81-2.00) and kurtosis (1.12-1.65) values, and it was accepted that the data were normally distributed (33). The relationship between the measured variables was evaluated using Pearson correlation analysis. Pearson correlation value ranges are 0.1 small, 0.3 medium and 0.5 large correlation. A value of $p<0.05$ was considered statistically significant in all analyses.

Results

Students' Characteristics

A total of 359 students who matched the inclusion criteria participated in the study. The responses of 13 students contained incorrect and incomplete data, and these students were not included in the study. The study included 346 students. The nursing students that took part in the study had an average age of 21.32±1.52 years. Table 1 gives the socio-demographic characteristics of the students.

Technological devices were used daily by 67.6% of nursing students. Of the students interviewed, 55.8% found the technological equipment in health institutions insufficient. The most common uses of technology were for obtaining information (17.9%), research (17.1%), and sharing information among students (12.4%). Among the barriers to the use of technology, 31.0% ranked the limited number of technological devices, and 22.0% ranked not knowing how to use them. While 82.4% of the students stated they did not receive information about using technological devices, 85.5% wanted to receive training (Table 2).

Health Technology Assessment Attitudes and Individual Innovative Behaviors

The mean total score of the nursing students in the HPHTAAS was 99.58±10.65. This score indicated that their attitude towards evaluating health technologies was high. The mean total score of the IIS was 63.65±9.40. According to the score above this average, students were in the category of "skeptical" about innovation. (Table 3).

The Relationship Between Health Technology Assessment Attitudes and Individual Innovative Behaviors

A weak positive correlation was found between the total score of health technology evaluation attitudes and opinion leadership ($r=0.178$, $p<0.01$), risk-taking ($r=0.187$, $p<0.01$), and individual innovativeness total score ($r=0.158$, $p<0.01$). A weak positive relationship was found between the individual innovativeness total score and the sub-dimensions of scope ($r=0.134$, $p<0.05$),

Table 1. Socio-demographic characteristics

	n	%
Gender		
Female	295	85.3
Male	51	14.7
Year of study		
2nd year	125	36.1
3rd year	131	37.9
4th year	90	26.0
Employment status		
Yes	18	5.2
No	328	94.8
Place of living		
City	140	40.5
Small town	124	35.8
Village	82	23.7
Insurance		
Yes	218	63.0
No	128	37.0
Incoming		
Income more than expenditure	34	9.8
Income equal to expenditure	204	59.0
Income less than expenditure	108	31.2

Table 2. Students' use of technology

	n	%
Frequency of technological device use in nursing practices		
Daily	234	67.6
Once a week	74	21.4
Rarely	38	11.0
Technological devices used in patient care*		
Phone	173	7.1
Computer	141	5.8
Glucometer	259	10.6
Pulse oximeter	322	13.2
Monitor	302	12.4
Digital thermometer	317	13.0
Digital blood pressure meter	187	7.7
Air/Adjustable bed	188	7.7
Pump Device	196	8.0
Pneumatic system (system that transports blood samples to the relevant laboratory)	123	5.0
Bedside aspiration and oxygen systems	233	9.5
Finding technological devices sufficient		
Yes	153	44.2
No	191	55.8
Reason for using the technological device*		
Sharing information among students	204	12.4
Obtaining information	294	17.9
Planning patient care	195	11.9
Research	281	17.1
Providing patient care	159	9.7
Planning the treatment	118	7.2
Making treatment	136	8.3
Accepting samples (blood, urine, stool, etc.)	73	4.4
To follow the results of the patient's procedures	184	11.2
The barriers to the use of technology*		
Being costly	83	9.6
Not knowing how to use them	190	22.0
Lack of calibration	98	11.4
The limited number of them	267	31.0
The language of the device is not Turkish	50	5.8
Complexity of the operating system	72	8.4
Not authorized to use the device	102	11.8
From whom/where they get support in using technology*		
Biomedical engineer	14	1.7
Work colleague	261	31.8
Charge nurse	325	39.5
Information Processing Unit	37	4.5
The Internet	142	17.3
Instruction manual of the device	43	5.2
Getting information about the use of technological devices		
Yes	61	17.6
No	285	82.4
Desire to receive training in biomedical technology		
Yes	296	85.5
No	50	14.5

*: More than one answer was given

awareness (r=0.154, p<0.01), and utility (r=0.125, p<0.05) (Table 4).

Discussion

This study examined the health technology evaluation attitudes and individual innovation behaviors of nursing students. The results showed while nursing students' attitudes toward technology use were high, their innovation behavior was "skeptical". The most important barriers to students' use of health technologies were identified as limited number of devices and not knowing how to use them. There was a weak positive association found between students' health technology evaluation attitudes and individual innovativeness behaviors.

The use of Health Technologies and The Barriers to the use of Health Technology

It is essential to apply technology at all stages of nursing education and to evaluate the results. Technology use in the clinical environment helps students develop critical thinking, clinical reasoning skills, and problem-solving skills. (34). In this study, most nursing students use technological devices in their clinical practices, including pulse oximeters, digital thermometers, monitors, and glucometers. Students take an active role in patient monitoring. Additionally, they use health technology to obtain information and conduct research. However, students use patient care devices less frequently because they participate in care procedures alongside licensed nurses and primarily focus on follow-ups. As they are not yet professional nurses, they cannot be independent in the use of these devices. Student nurses learn clinical and technological skills from clinical educators and clinician nurses who serve as professional role models (35).

Future nurses' adoption, understanding, and application of the use of technology in the provision of health services will enable them to be competent and effective (36). To successfully implement health technologies, nurses should have positive attitudes, sufficient knowledge, basic competence, appropriate behaviors, digital self-efficacy and technology-specific self-efficacy (1). Health technology assessment attitude and individual innovation behaviors are other factors they should have.

In the modern digital age, many students find health technology insufficient in the institutions where they practice. Many factors can contribute to this insufficiency. For example, the increased cost associated with rapidly developing technology makes it difficult for institutions to maintain equipment that is suitable for technological advancements (35). In this study, students identified the lack of technological devices, high costs, and inadequate calibration as barriers to the use of technology. Factors such as hospital capacity and the high number of patients may also contribute to the insufficiency of existing health technology. In addition, clinical educators and nurses may find it challenging to accept and integrate new technologies into practice.

In this study, more than half the students stated that not knowing how to use a technological device was an obstacle. Students did not receive sufficient education on this subject. Students often receive support from clinical educators, charge nurses, and other students in accessing information about the use of technology. Literature supports that using technology can be learned through role models and peer support (37). However, courses and training related to health technologies should be added to the curriculum. Another study suggested that digital technologies should be fully integrated into the nursing curriculum. However, this is delayed due to inconsistencies and irregularities between

Table 3. Descriptive data of scales and subscales

Variables	Mean	SD	Min.	Max.
Thought leadership	24.58	4.65	8.00	35.00
Resistance to change	23.26	5.23	7.00	35.00
Risk-taking	15.81	3.09	4.00	20.00
Total score of IIS	63.65	9.40	38.00	89.00
Scope	17.26	2.27	4.00	20.00
Awareness	31.28	3.58	7.00	35.00
Benefit	51.03	6.67	34.00	88.00
Total score of HPHTAAS	99.58	10.65	67.00	132.00

SD: Standard deviation, Min.: Minimum, Max.: Maximum, HPHTAAS: Health Personnel Health Technologies Assessment Attitude Scale, IIS: Individual Innovativeness Scale

Table 4. Correlation between the scales

	Thought leadership	Resistance to change	Risk-taking	Total score of IIS
Scope	0.068	0.113*	0.114*	0.134*
Awareness	0.112*	0.097	0.137*	0.154**
Benefit	0.198**	-0.063	0.187**	0.125*
Total score of HPHTAAS	0.178**	0.014	0.187**	0.158**

*: Correlation is significant at 0.05 level, **: Correlation is significant at the 0.01 level, HPHTAAS: Health Personnel Health Technologies Assessment Attitude Scale, IIS: Individual Innovativeness Scale

nursing education programs and institutions (35). Adding relevant objectives and courses to updated nursing education programs is recommended (25,38). Students' willingness to learn biomedical technology supports this. Shen et al. (25) emphasized that the innovative education program played an important role in increasing nursing students' innovative behaviors, self-efficacy, and professionalism. Accordingly, the nursing education curriculum should be updated regularly and should be able to follow innovations.

As a Factor Associated with Health Technology Evaluation Attitudes: Individual Innovative Behaviors

The literature shows that nursing students and nurses have different scores and are in different categories regarding innovativeness. The adoption of innovations varies among individuals; those who fear uncertainty may resist change (36). According to a survey, nurses' opinions on the purposeful use of technology vary; some are excited, while others are apprehensive or opposed (39). A study attributes the slow adoption of digital technologies to resistance primarily due to economic problems and fear of machines potentially "taking over in work" (35). The skeptical approach to innovative behaviors shows that the innovation is not adopted until others accept, use, and benefit from it. In this case, a supportive approach is important for nursing students to practice their profession.

Studies evaluating innovation behavior in nursing students generally found skeptical (26,27) or questioning (15,23,24) behavior. They determined that individual innovativeness in nursing students was positively associated with 21st century skills (22) professionalism (25) entrepreneurial tendencies (24), and attitudes toward evidence-based nursing (40) and negatively associated with using technological equipment (15). The individual innovation approach affects students positively. For educators and clinician nurses to be suitable role models in increasing the innovation behaviors of nursing students, training on awareness, information, adoption, and use of health technologies should be provided.

While nursing students' attitudes toward technology use were high, their innovation behavior was "skeptical". In skeptical behavior, the individual needs to believe and trust to adopt innovation and needs reliable support and resources to adopt the innovations brought by technology (41,42). The fact that students are in the internet generation-generation z and use technology for visual and verbal communication (43) explains their high technology attitudes. Value judgments, attitudes, and expectations differ between generations depending on the developments and innovations in the environment. This also affects their adaptation processes and ability to innovate (23). A positive attitude is important in increasing technological solutions, increasing efficiency reducing errors and improving patient care (1). In the digital age, when nursing students are informed about the effectiveness and usefulness of the technology used in clinical practice, their individual innovation levels will increase.

Students' health technology attitudes positively increase their innovativeness behaviors. Students' health technology attitudes and innovation behaviors are related, although not strongly. The environment in which nurses work is impacted by developments in science, technology, and health. They frequently come across advances in their work practices and make good use of them (44). Health technology adoption and use is more likely among nurses who are receptive to learning new skills and technologies. However, nurses with low self-efficacy or resistance to change can be more reluctant to adopt these tools (1). Based on the positive relationship between innovation and innovation, high health technology attitudes of student nurses may increase their innovation behaviors. Positive attitudes will bring along innovative behaviors and ensure faster adoption of developments in health technologies. At this point, it is imperative to support the existing positive attitudes of students and encourage their innovative behaviors.

Study Limitations

This study had some limitations. It did not consider the possible effects of demographic variables on the dependent variables. Participants were selected through random sampling; since this is a weak sampling method, it may have affected the reliability of the results. A further limitation is that the outcomes can only be generalized to nursing students of one university.

Conclusion

The use of technology in health services will prepare students and future nurses to be more competent and effective. This study revealed that students' knowledge of health technologies was not sufficient, and they wanted more information. A positive relationship existed between students' health technology evaluation attitudes and individual innovativeness behaviors. Health technologies should be included in nursing education, especially technological tools used in patient care. Factors preventing their use should be eliminated. Nurses should increase their digital literacy and be open to innovations that will maximize care. Increasing individual innovativeness will positively affect the attitude towards health technologies. A positive increase in nurses' use of technology and their attitudes towards evaluating health technologies will facilitate adaptation to the digitalizing world. Nurses and nursing students should be followers of health technologies and every technological development affecting health care.

Ethics

Ethics Committee Approval: Ethical permission was obtained from Pamukkale University ethics committee (decision number: E-60116787-020-208262, date: 17.05.2022).

Informed Consent: Students were informed about the study, and informed consent was obtained from those who agreed to participate in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.Ö.Ç., F.H.İ., N.K., E.Ö.B., Concept: İ.Ö.Ç., F.H.İ., N.K., E.Ö.B., Design: İ.Ö.Ç., F.H.İ., N.K., E.Ö.B., Data Collection or Processing: İ.Ö.Ç., F.H.İ., N.K., E.Ö.B., Analysis or Interpretation: İ.Ö.Ç., F.H.İ., N.K., E.Ö.B., Literature Search: İ.Ö.Ç., F.H.İ., N.K., E.Ö.B., Writing: İ.Ö.Ç., F.H.İ., N.K., E.Ö.B.

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Case Report

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Atypic Primary Ovarian Lymphoma Presenting with Hypercalcemia: A Rare Case Report

Hiperkalsemi ile Başvuran Nadir Bir Atipik Over Lenfoma Olgusu

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ABSTRACT

Here, we present a rare case of primary ovarian lymphoma with bilateral ovarian involvement, which manifested with malignant hypercalcemia. A 39-year-old female patient presented to our hospital with lower abdominal pain. Hypercalcemia, anemia, and thrombocytopenia were observed during the examinations. Abdominal ultrasound revealed a mass lesion thought to be associated with an abscess or malignancy in both adnexal areas, as well as mass lesions in bilateral ovaries, along with paraaortic and paraaortocaval lymphadenomegaly on abdominal computed tomography (CT). In the positron emission tomography CT examination, increased fluorodeoxyglucose uptake (SUV_{max} ranging between 11.5 and 9.5) was observed in the lesions defined on abdominal CT. Bone marrow biopsy performed for thrombocytopenia was found to be compatible with diffuse large B-cell lymphoma (DLBCL). Although this case demonstrates that hypercalcemia can be observed in the course of DLBCL with bilateral ovarian involvement, which is a rare condition, it is also considered significant as it is inconsistent with most of the hypercalcemia mechanisms associated with malignancies described today.

Keywords: Bilateral ovarian lymphoma, hypercalcemia, non-Hodgkin lymphoma

ÖZ

Burada, malign hiperkalsemi ile başvuran bilateral over tutulumu olan nadir bir primer lenfoma olgusunu sunuyoruz. Otuz dokuz yaşında kadın hasta karın ağrısı şikayeti ile hastanemize başvurmuştur. Muayenesinde hiperkalsemi, anemi ve trombositopeni saptanmıştır. Abdominal ultrasonda ve bilgisayarlı tomografide (BT) bilateral adneksiyal alanda apse veya malignite ile ilişkili olabileceği düşünülen kitle lezyon ve paraaortik ve paraaortakaval alanlarda lenfadenomegali saptanmıştır. Pozitron emisyon tomografisi BT'de Batın BT'de tanımlanan lezyonlarda artmış fluorodeoksiglukoz tutulumu (SUV_{maks} 11,5 ile 9,5 arasında değişmekte) gözlendi. Trombositopeni de olması nedeniyle yapılan kemik iliği biyopsisi bulguları diffüz büyük B-hücreli lenfoma (DBBHL) ile uyumlu bulundu. Bu olgu bilateral over tutulumlu DBBHL seyrinde hiperkalseminin görülebileceğini gösterse de bu nadir bir durumdur; aynı zamanda günümüzde tanımlanan çoğu malignite ile ilişkili hiperkalsemi mekanizması ile uyumsuzluk taşıması nedeniyle de önem arz etmektedir.

Anahtar Kelimeler: Bilateral over lenfoması, hiperkalsemi, Hodgkin dışı lenfoma

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Introduction

Hypercalcemia is a common condition that can occur in 20% to 30% of patients diagnosed as having malignancy. It can manifest in patients with either solid or hematological malignancies. The most common cancers associated with hypercalcemia are breast, kidney and lung cancers, and multiple myeloma (1,2). The release of parathyroid hormone-related peptide and 1.25 dihydroxyvitamin D (calcitriol) in tumor cells, or osteolytic metastases caused by secreted cytokines are three separate major mechanisms implicated in the development of hypercalcemia due to malignancy.

The mechanism of non-Hodgkin lymphoma (NHL)-associated hypercalcemia is currently not clearly understood. In the literature, cases of NHL presenting with severe hypercalcemia are limited.

While ovarian involvement can be observed in the course of diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma among NHLs, bilateral primary ovarian lymphoma is an extremely rare condition. Cases reported in the literature are limited to a few. In this article, we describe a rare case of DLBCL with bilateral ovarian involvement presenting with hypercalcemia.

Case Report

A 39-year-old female patient with no known history of chronic disease was admitted to the clinic with complaints of pain in the lower abdomen and groin. She had no family history of malignancy. She did not smoke or drink alcohol. Laboratory tests revealed hypercalcemia, normochromic normocytic anemia, thrombocytopenia, elevated creatinine and increased acute phase reactants. Laboratory findings are summarized in Table 1. In the abdominal ultrasound ultrasonography (USG); bilateral kidney size and parenchymal echogenicity was normal. The uterus was normal, but a densely loculated collection area around the uterus with internal soft tissue echoes measuring approximately 81x65x103 mm filling the entire adnexal lodge was detected. In transvaginal USG, it was stated that there were tuboovarian abscesses or bilateral mass lesions suspicious for malignancy, measuring 97x62 mm in the left ovary and 71x57 mm in the right ovary. In the examinations of tumor markers, carcinoembryonic antigen level was: 3.54 µg/L (normal range <3.8) cancer antigen (CA) 15.3 level: 11.4 U/mL (normal range <25) CA 125 level: 134 U/mL (normal range <35). Abdominal computed tomography (CT) performed without contrast due to acute renal failure revealed lesions suggesting abscess or suspicious lesions in terms of malignancy in both adnexal areas, which were of 8x5

Table 1. Laboratory results

		Normal range			Normal range
Glucose	98 mg/dL	74-106	Ferritin	**1837 µg/L**	10-120
Creatinine	**2.66 mg/dL**	0.5-1	CRP	**212 mg/L**	0-5
AST	62 mg/dL	0-32	Procalcitonine	0.4 ng/mL	<0.5
ALT	23.7 mg/dL	0-33	Sedimentation	**36 mm/sa**	0-20
ALP	91 mg/dL	35-104	Total protein	6.7 mg/dL	6.4-8.3
GGT	18 mg/dL	0-36	Albumin	3.2 mg/dL	3.9-4.9
LDH	**670 mg/dL**	306	PHT related peptide	2 pmol/L	4.9±0.5
Total bilirubin	0.45 mg/dL	<1.2	Magnesium	2.12 mg/dL	1.6-2.6
Direct bilirubin	0.6 mg/dL	0-0.3	Potassium	4.5 mg/dL	3.5-5.1
PTH	**8.04 pg/mL**	15-65	Sodium	136 mg/dL	136-146
25 OH D vitamin	**3.47 µg/L**	20-80	Phosphorus	**4.9 mg/dL**	2.6-4.5
1.25 OH D vitamin	**<5 pg/mL**	19-73	Calcium	**19 mg/dL**	8.6-10
Hemogram					
Hemoglobin	**8 g/dL**	10.8-14.2	Neutrophils	3.51 10^3/uL	1.63-6.96
Hemotocrit	**24.6%**	35-45	Lymphocytes	**0.49 10^3/uL**	1.09-2.99
MCV	81.7 fl	81-96	Monocytes	0.18 10^3/uL	0.24-0.79
Total leucocytes	4.21 10^3/uL	3.7-10.1	Eosinophiles	0.02 10^3/uL	0.03-0.44
Platelet count	**60 10^3/uL**	155-366			
Coagulation					
PT	16.9 sn	11-16	D-dimer	1.92 µg	0-0.5
aPTT	37 sn	24-36	Fibrinogen	**574 mg/dL**	200-400
INR	**1.25**	0.8-1.2			

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, LDH: Lactate dehydrogenase, OH: Hydroxyvitamin, MCV: Mean corpuscular volume, PT: Prothrombin time, aPTT: Activated partial thromboplastin time, INR: International normalized ratio, PHT: Parathormone, CRP: C-reaktif protein, PTH: Parathyroid hormone

cm on the right side and 7x5 cm on the left side. Lymph nodes in the paraaortic and paraaortocaval spaces, the largest of which was 19x7.5 mm in size at the paraaortic level were detected. Diffuse heterogeneous increases in density, contamination, free fluid densities and hypodense lesions causing irregularities in the cortex were detected in the perihepatic-perisplenic areas and mesenteric fat tissues in the lower abdominal quadrant. No pathology was detected in thorax CT except bilateral 2 cm pleural effusions. Intensely increased fluorodeoxyglucose (FDG) uptake in the 8.5x6.5 cm diameter lesion filling the right adnexal area and the 7x5 cm lesion observed in the left adnexal area in positron emission tomography (PET) CT taken to evaluate for malignancy due to a dirty appearance in the omentum were detected (SUV_{max}: 11.9 and 13 respectively). Increased FDG uptakes in the upper, middle and lower quadrants of the abdomen at the level of areas of diffuse density increase, mostly diffusely focalized in the mesenteric fatty tissues (SUV_{max}: 6.7), in the right and left anterior diaphragmatic areas in the abdomen in prevertebral, paraaortic and aortacaval areas, in multiple lymph nodes (maximum SUV_{max}: 7.9) in the paracaval areas, bilateral common iliac areas, in places conglomerate, the long axis of the larger one reaching 2.5 cm, in the cranial bones, bilateral

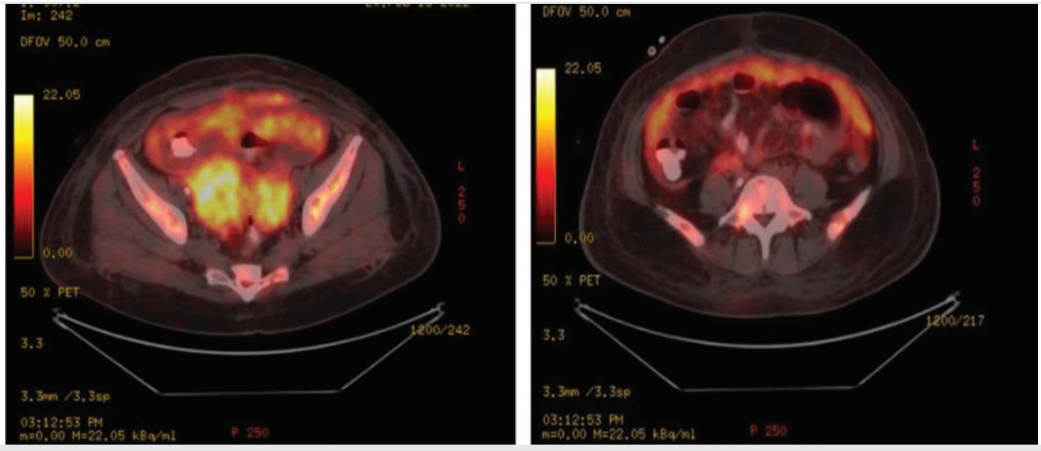

Figure 1. PET-CT images of bilateral ovaries and anterior abdomen-omentum

PET-CT: Positron emission tomography-computed tomography

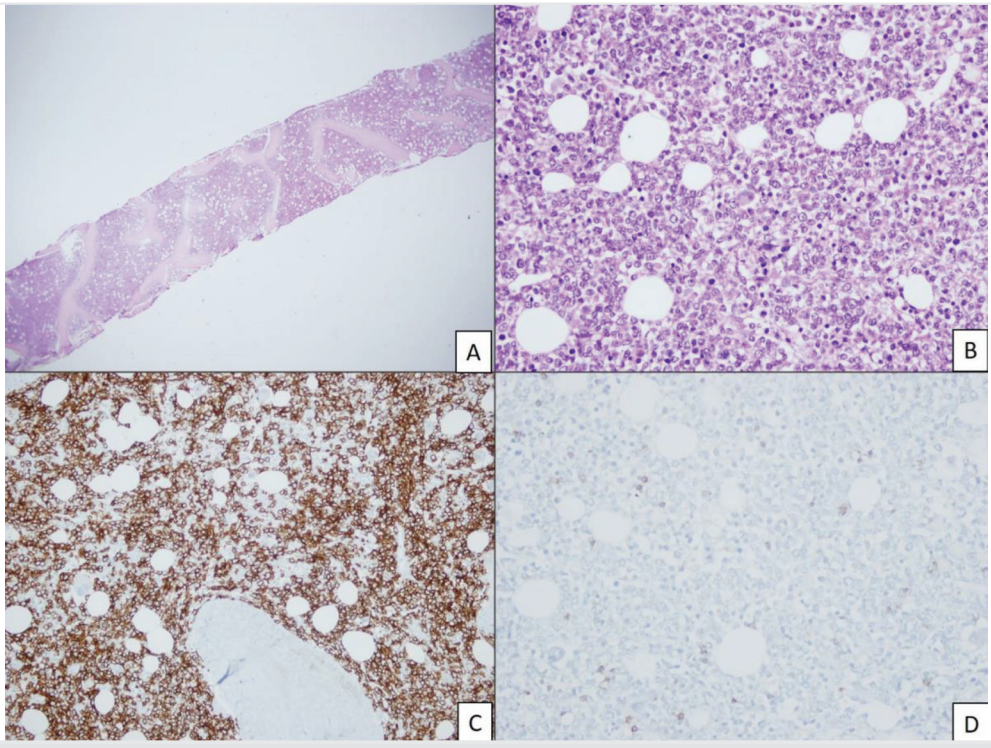

Figure 2. Hypercellular bone marrow biopsy (A, H&E, 2X magnification), revealed diffuse infiltration of neoplastic lymphoid cells (B, H&E, 40X magnification), which were positive for CD20 (C, 20X magnification), and negative for CD3 (D, 20X magnification)

H&E: Hematoxylin and eosin, CD20: Cluster of differentiation 20, CD3: Cluster of differentiation 3

humerus, sternum, bilateral scapulas and clavicles, vertebral colon, ribs, and pelvic bones at the level of extensive lesion areas, mostly lytic, in multiple foci G involvements (maximum SUV_{max}: 9.5) were detected (Figure 1). No pathological findings were observed in gastroscopy and colonoscopy which was performed to screen for gastrointestinal system malignancies. The patient's general condition was poor due to high creatinine level and hypercalcemia. Since she also had bilateral ovarian involvement, needle biopsy was postponed because of the thought that it might cause new implantation. Due to the thrombocytopenia at peripheral blood and bone involvement at PET-CT, bone marrow biopsy was performed. Atypical cells were not observed. Due to the thrombocytopenia and bone involvement at PET-CT, bone marrow biopsy was performed. In the H&E stained sections of the bone marrow, diffuse infiltration characterized by large to medium-sized cells with vesicular nuclei and prominent nucleoli was observed. Immunohistochemically neoplastic cells were cluster of differentiation (CD)20 (+), CD3 (-), CD5 (-), CD30 (-), CD10 (-), BCL-6 (-), multiple myeloma oncogene 1 (-), BCL-2 weak (+), epstein-barr virus-latent membrane protein (EBV-LMP) (-), CD38 (-), c-myc (-), terminal deoxynucleotidyl transferase (TdT) (-), cyclinD-1 (-). Ki-67 proliferation index was evaluated as 60%. The findings were found to be consistent with DLBCL (Figure 2).

Acute renal failure was thought to be due to prerenal renal failure secondary to vasoconstriction and postrenal renal failure due to compression. Despite intensive intravenous (IV) hydration and IV furosemide 40 mg twice a day, the patient's hypercalcemia did not regress. She underwent hemodialysis 6 times due to persistence of hypercalcemia findings. Subsequently, IV 4 mg zoledronic acid was administered once. With the diagnosis of DLBCL with bilateral ovarian, omental and diffuse paraaortic lymph node involvement, the patient was started on rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Under these treatments, the initial calcium level decreased from 19 mg/dL to 10.5. After one cure of standard-dose R-CHOP treatment, the patient developed high fever and shortness of breath during the cytopenia period, and died due to coronavirus disease 2019 pneumonia and sepsis forty days after the initial diagnosis.

Discussion

Primary ovarian lymphoma is one of the rare malignancies of the ovary, constituting 0.5% of NHL and 1.5% of ovarian malignancies (3,4). It is generally thought as a manifestation of systemic disease, most commonly associated with DLBCL and Burkitt lymphoma (5). In our case, similar to the literature, DLBCL was detected as the histological subtype of NHL.

Hypercalcemia is a common condition that can occur in 20% to 30% of patients with malignancy. Hypercalcemia as a paraneoplastic finding has been associated with many malignancies; however, hypercalcemia observed in the context of ovarian cancer is a rare condition. Only a few cases were reported in the literature, so its incidence is not clearly known (1,6,7). In most of these few reported cases, the histologic type was clear cell adenocarcinoma. NHL was detected in one case, where calcitriol levels were found to be high, and hypercalcemia was correlated with it (8-10).

The mechanism of hypercalcemia in NHLs has not been fully elucidated. In one study, calcitriol levels were found to be high in all patients with HL presenting with hypercalcemia and in one-third of patients with NHL. In similar studies, it has been reported that there may be a relationship between hypercalcemia and parathormone associated peptide (PTHrP) levels in some individuals with HL and NHL (11-15). When all these studies are evaluated together, it can be said that hypercalcemia observed in the context of NHL may be associated with an increase in calcitriol or PTHrP. However, in a study by Shallis et al. (15). involving patients with NHL, no relationship was found between calcitriol and PTHrP levels and hypercalcemia. It was reported that hypercalcemia was observed in individuals with aggressive disease, and it was suggested that there might be an association between disease activity and hypercalcemia. In our case, despite the severe hypercalcemia observed, similar to the findings of that study, calcitriol and PTHrP levels were low.

Conclusion

We aimed to contribute to the literature by reporting this rare and interesting DLBCL case, notable for both bilateral ovarian involvement and its presentation with severe hypercalcemia.

Ethics

Informed Consent: Patient consent obtained.

Footnotes

Authorship Contributions

Concept: E.Ş., Ş.A.Y., Design: E.Ş., Ş.A.Y., Data Collection or Processing: E.Ş., F.K., E.K., G.Y., Analysis or Interpretation: E.Ş., F.K., E.G., G.Y., Literature Search: F.K., E.G., Writing: E.Ş., F.K., E.K., E.G., Ş.A.Y., G.Y.

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Erratum

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The article titled **"The Relationship Between Thirst Distress and Severity and Compliance with Fluid Control and Interdialytic Weight Gain in Hemodialysis Patients,"** published in Bezmialem Science, Volume 13, Issue 2, 2025, has been retracted and returned to the author due to the unauthorised use of a proprietary scale without obtaining the necessary permission from the original copyright holder. To avoid a potential breach of publication ethics and ensure compliance with intellectual property standards, the manuscript has been returned to the author.