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Internet-based Weight Control Intervention in "Bi'Kilo" Mobile App: A Qualitative Analysis of Usability, Acceptability, and User Experiences

"Bi'Kilo" Mobil Uygulamasında İnternet Tabanlı Kilo Kontrolü Müdahalesi: Kullanılabilirlik, Kabul Edilebilirlik ve Kullanıcı Deneyimlerine İlişkin Nitel Bir Analiz

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Abstract: The study aimed to evaluate the usability, acceptability, and user experiences of the "Bi'Kilo" mobile app, which is designed to facilitate weight management and encourage healthy lifestyle choices among its users. Employing a qualitative research design, the investigation involved in-depth interviews with eight users of the "Bi'Kilo" app. This approach gave a comprehensive understanding of participants' perceptions, experiences, and interactions with the application. Data from the interviews were meticulously analyzed to identify themes related to the app's usability, its impact on users' weight management efforts, and the overall user experience. This analysis was pivotal in understanding the strengths and weaknesses of the "Bi'Kilo" app from the perspective of its users. The findings revealed that users appreciated the app's role in promoting weight control and a healthy lifestyle, particularly highlighting personalized feedback and including multimedia content as beneficial features. Nonetheless, challenges were identified, including technical difficulties and a preference for more actionable advice over theoretical content. The study suggests several avenues for future research, including further refinement of the app to enhance its flexibility, integration of professional insights, and improvement in personalization to meet users' needs and preferences better. These components collectively provide a thorough examination of the "Bi'Kilo" app, offering valuable insights into its development and the broader health informatics field.
Keywords: Mobile Health Applications, Weight Management, User Experience, Usability, Acceptability

Özet: Bu çalışma, kullanıcılarının kilo kontrolünü kolaylaştırmak ve sağlıklı yaşam tarzı tercihlerini teşvik etmek amacıyla tasarlanan "Bi'Kilo" mobil uygulamasının kullanılabilirliğini, kabul edilebilirliğini ve kullanıcı deneyimlerini değerlendirmeyi amaçlamıştır. Nitel bir araştırma deseninin kullanıldığı araştırmada, "Bi'Kilo" uygulamasının sekiz kullanıcısı ile görüşmeler yapılmıştır. Bu yaklaşım, katılımcıların algılarının, deneyimlerinin ve uygulama ile etkileşimlerinin kapsamlı bir şekilde anlaşılmasını sağlamıştır. Görüşmelerden elde edilen veriler, uygulamanın kullanılabilirliği, kullanıcıların kilo kontrolü çabaları üzerindeki etkisi ve genel kullanıcı deneyimi ile ilgili temaları belirlemek için titizlikle analiz edilmiştir. Bu analiz, kullanıcıların bakış açısından "Bi'Kilo" uygulamasının güçlü ve zayıf yönlerini anlamada çok önemlidir. Bulgular, kullanıcıların uygulamayı kilo kontrolünü ve sağlıklı bir yaşam tarzını teşvik etmedeki rolü nedeniyle takdir ettiklerini, özellikle kişiselleştirilmiş geri bildirim ve multimedya içeriğinin faydalı özellikler olarak vurgulandığını ortaya koymuştur. Bununla birlikte, teknik aksaklıklar ve teorik içerik yerine daha çok uygulamaya dönük içeriklerin tercih edilmesi gibi konularda çeşitli güçlükler belirlenmiştir. Çalışma, uygulamanın daha da geliştirilerek işlevselliğinin artırılması, profesyonel görüşlerin entegrasyonu ve kullanıcıların gereksinim ve tercihlerinin daha iyi karşılanması için kişiselleştirmenin iyileştirilmesi gibi gelecekteki araştırmalar için çeşitli önerileri bildirmektedir. Bu bileşenler "Bi'Kilo" uygulamasının kapsamlı bir incelemesini sunmakta, uygulamanın geliştirilmesi ve daha geniş sağlık bilişim alanı için önemli görüşler sağlamaktadır.
Anahtar Kelimeler: Mobil Sağlık Uygulamaları, Kilo Kontrolü, Kullanıcı Deneyimi, Kullanılabilirlik, Kabul Edilebilirlik

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1. Introduction

Mobile health-mHealth software programs run on mobile devices and offer various health-related services (1). These services include collecting and sharing health data, providing health information and education, monitoring and managing health conditions, remote care and consultation, and promoting health and fitness (2). mHealth applications have revolutionized the delivery and management of health services, leveraging mobile technologies to provide accessible and cost-effective health services (3). These applications have increased the accessibility of health services by providing functionalities such as access to health information, self-monitoring, behavior tracking, and the delivery of interventions (4). mHealth applications offer effective interventions for health behaviors such as weight control, smoking cessation, and adherence to medication regimens (5). This is particularly important in managing chronic diseases such as diabetes, cardiovascular diseases, and certain types of cancer (6). Through features like personalized feedback, goal setting, motivational tips, and social support, they can personalize intervention strategies and contribute to improved health outcomes (7). The prevalence of smartphones and advancements in mobile technologies have facilitated the development of these applications and led to a paradigm shift in the delivery of health services (8). mHealth applications are becoming increasingly popular, offering innovative solutions in health services and covering a wide range of functionalities, including disease monitoring, health education, and lifestyle management (9). The use of applications indicates a significant change in health service delivery and patient engagement, particularly effective in weight control interventions (10).

The use of mHealth applications for self-care among special populations, such as pregnant women, has been extensively studied, showing effectiveness in weight control, providing educational information, and offering reminders and assessments related to services (3). Integrating applications into weight control interventions aligns with the broader trend of digital health solutions, offering functionalities ranging from tracking dietary intake and physical activity to providing personalized feedback and support. This facilitates self-monitoring, a key component in behavior change theories such as the Self-Determination Theory and the Theory of Planned Behavior (11, 12). As significant tools in weight control and management, these applications enable users to track dietary intake, physical activity, and body weight with capabilities like real-time feedback, personalized goal setting, and motivational support (13-15). mHealth applications in weight control promise to assist individuals in managing their weight by tracking physical activity and dietary intake and providing behavioral interventions. Studies have shown that mHealth interventions can effectively promote participation in physical activities and self-management of weight (13). As indicated by behavior change theories, mHealth applications in weight control offer effective opportunities for interventions in lifestyle changes, dietary habits, and physical activity (16). The popularity of applications in weight control is critically important in preventing and managing excessive weight and obesity, major risk factors for chronic diseases such as cardiovascular diseases, diabetes, and some cancers. According to the World Health Organization, in 2016, more than 1.9 billion adults were overweight, with 650 million being obese (17). Mobile applications for weight control can offer various advantages over traditional methods, including personalized feedback, special recommendations, real-time support, gamification, social networking, and rewards to increase user engagement and motivation (14).

Considering the prevalence and diversity of mHealth applications, as of October 2023, the Google Play Store contains over 30 million applications, approximately 10% of which, or 3 million, cover health topics and conditions (Google Play Store). A meta-analysis comparing these applications to traditional methods showed that users of weight control applications exhibited higher engagement and better outcomes than those using traditional diet and exercise diaries and were equally effective as traditional paper-pencil weight loss interventions (1). The effectiveness of applications suggests that mHealth applications can be as or more effective due to their convenience, real-time feedback, and interactive features (18). A 2021 meta-analysis found that mobile health technology interventions significantly reduced BMI in specific ethnic groups (2). When examining the advantages of mHealth applications over traditional interventions, it is observed that weight control applications demonstrate greater adherence to dietary and physical activity guidelines compared to users in traditional programs (19).

mHealth applications can enhance user engagement and motivation by providing personalized feedback, special recommendations, real-time support, gamification, social networking, and rewards (1,

20). Additionally, mobile applications benefit from the convenience of data collection and analysis by utilizing the built-in sensors and functionalities of mobile devices, such as cameras, GPS, accelerometers, and barcode scanners (21). One of the most significant conveniences of mobile applications is the ability to offer access and diversity to a broad and varied user base, regardless of location, time, and availability (22). Furthermore, a systematic review and meta-analysis of 17 randomized controlled trials indicate that mobile applications for weight loss are more effective than minimal interventions or usual care regarding efficacy and sustainability. However, the quality of evidence is low to moderate, highlighting the need for more rigorous and long-term studies (23).

Dennison et al. have highlighted that personalization enhances applications' relevance and effectiveness by addressing individual user needs and preferences, stating that personalized feedback and content are significant motivational factors for continuous use of the application (24). Users' adherence to the prescribed or recommended use of the application is important for engagement and critical for the success of any behavioral intervention (25). However, adherence to mobile applications can decrease over time, and users may encounter various barriers (26). The personalized support provided by mHealth applications, especially including specific diet and exercise recommendations, has the potential to increase user adherence significantly (27). Reminders and notifications in applications help maintain user engagement and encourage consistency in health behaviors. These features have improved body composition and adherence to health interventions (28). A user-friendly design of applications is seen as a critical factor for long-term commitment to mHealth interventions (29). An intuitive interface and easy navigation are among the key factors influencing the user's experience and continued application use (30).

Furthermore, the customization of the application interface and content according to the user's preferences, needs, and goals is a fundamental feature of personalization (31). This feature could enhance user satisfaction, adherence, and loyalty (29). Features such as personalization and user-friendly design are key factors in the success of mHealth applications in weight control (13, 32). These features are significant for encouraging user engagement and adherence.

Aim of the Study

This study emphasizes the growing importance of digital mental health services in today's world. In this context, it aims to evaluate the usability and acceptability of the mobile application named *"Bi'Kilo"*, developed by researchers for individuals who want to lose or control their weight. Conducted with a qualitative approach, this research seeks to gather information about the advantages, disadvantages, adaptability to life, expectations, suggestions and needs concerning the application. Based on this aim, the research seeks to answer the following central question: "How do users experience the usability and acceptability of the *"Bi'Kilo"* mobile application designed for weight control?"

1.2. *"Bi'Kilo"* Mobile Application

The *"Bi'Kilo"* mobile application is a self-guided, Turkish-language intervention designed to support weight control through educational and behavioral modules. It promotes healthy lifestyle changes through progressive, module-based learning. Users must engage with video animations and written content, answer related questions, and complete practice-based tasks to unlock subsequent modules.

The app comprises seven modules:

1. **Nutritional Education** – Covers energy balance, eating habits, goal setting, and dietary planning.
2. **Physical Activity** – Focuses on increasing activity levels, understanding benefits, and setting step goals.
3. **Mindful Eating** – Introduces principles and techniques of mindful eating.
4. **Emotional Eating** – Focuses on distinguishing between physical and emotional hunger.
5. **Cognitive Interventions** – Addresses sabotaging thoughts and environmental triggers.
6. **Thought Cards** – Encourages cognitive restructuring through alternative thinking strategies.
7. **Follow-up Phase** –Reinforces continued practice of acquired skills for maintaining weight control.

Each module includes structured self-monitoring practices (e.g., food logs, step counts, hunger scales), which must be completed to advance. The app also features a user profile with a weight progress graph, instructional mindful eating guidance, and technical support access.

2. Materials and Methods

2.1. Research Design

The research aims to qualitatively evaluate the usability and acceptability of the *"Bi'Kilo"* mobile application for individuals aiming for weight loss or weight control. The primary purpose of the study is to gain in-depth knowledge about the application's advantages and disadvantages, how it adapts to life, user expectations, suggestions, and needs. The research design is based on the qualitative research method, which Creswell and Poth describe as advantageous for collecting in-depth information about phenomena (33). These methods are designed to capture an individual's perspective and the meanings they attribute to their experiences, aiming to produce rich and nuanced data. The research methodology employs the phenomenological pattern defined by Patton (34). Phenomenology focuses on how people understand, describe, feel, judge, recall, make sense of, and talk about a particular phenomenon. Dağhan and Akkoyunlu define phenomenology as a method aimed at revealing the experiences, perceptions, and meanings individuals assign to a specific phenomenon (35). The research intensely focuses on the usability and acceptability of the *"Bi'Kilo"* application, user feedback, necessary adjustments, and innovations while examining the experiences and opinions of eight participants in detail. By adopting the phenomenological pattern, an ideal approach to comprehensively understand and interpret user experiences and perceptions, the study aims to provide significant information about the usability and acceptability of the "*Bi'Kilo"* application, illuminating its effectiveness and areas that need development.

2.2. Participants

The study's participants were carefully selected using criteria-based and maximum variation sampling methodologies. The purposive sampling approach, also known as intentional sampling, was used to intentionally select individuals with extensive expertise on a specific subject, thereby facilitating comprehensive research on the said subject. This method is widely accepted and suitable for qualitative research, especially phenomenological studies. Purposive sampling, categorized as a non-probability sampling technique, is designed to identify participants with significant and relevant firsthand experiences related to the phenomenon under investigation (34). As Yıldırım and Simsek state, criterion sampling requires selecting individuals based on precisely defined criteria (36). The selection criteria included being literate and possessing above-average technological literacy. Following the determination of eligibility criteria, invitations were sent to individuals who met the necessary prerequisites for participation. These invitations were distributed following notifications published on the researchers' official websites (www.bikilo.ogu.edu.tr), through private Instagram accounts (@bi.kilo), and other relevant social media profiles.

The principle of saturation, commonly used in qualitative research to determine sample size, was followed. Saturation is achieved when no new information or theme emerges from data collection and analysis (37). We conducted semi-structured interviews with participants and analyzed their responses using content analysis. After eight interviews, we reached saturation as no new insights or patterns were identified. Therefore, we concluded the interviews, deciding that the sample size provided rich and meaningful data to answer our research question. The participant group consisted of 8 women aged 22-32 years. Participants were informed about the scope of the research, assisted in installing the *"Bi'Kilo"* application on their smartphones, and explained how to use it. Table 1 presents participants' demographic characteristics.

Table 1. Participants' demographic characteristics

Participants	Age	Gender	Education Level
Participant 1	28	Female	PhD student
Participant 2	24	Female	Graduate student
Participant 3	26	Female	PhD student
Participant 4	32	Female	PhD student
Participant 5	23	Female	PhD student
Participant 6	25	Female	PhD student
Participant 7	22	Female	PhD student
Participant 8	24	Female	PhD student

2.3. Data Collection Tools

This research uses qualitative data to examine the usability and acceptability of the *"Bi'Kilo"* mobile application for weight loss and weight control goals. Phenomenological studies aim to explore the essence of participants' lived experiences; hence, this study preferred the qualitative interview method (36, 38). This approach allows us to deeply understand participants' meanings, interpretations, and experiences using the *"Bi'Kilo"* application, thus better comprehending the application's advantages, disadvantages, and alignment with user needs (39). The advantages of qualitative interviews include enabling the researcher to gain a more profound and holistic understanding of the studied phenomenon (33). Additionally, phenomenological research aims to reveal the essence or fundamental meaning of a phenomenon as experienced by an individual in a specific situation (40). Interviews were conducted by presenting standard questions to participants and using probing questions. Probing questions is important for better understanding the responses given by participants and exploring the reasons behind those responses (34). Data obtained from audio recordings and transcripts, after review and approval by participants, were used for analysis. This method ensured a rich and detailed understanding of participants' experiences, achieving a holistic understanding of the research.

The research sought answers to the following questions:

- Can you describe your experiences while using the *"Bi'Kilo"* mobile application?
- What can you say about the visual and technical aspects of the *"Bi'Kilo"* application?
- What parts/sections of the *"Bi'Kilo"* mobile application did you find useful?
- What parts/sections of the *"Bi'Kilo"* mobile application did you find useless?
- What do you think about the usability of the *"Bi'Kilo"* application?
- Do you think mobile application usage can be an alternative to face-to-face support? If not, why?

2.4. Data Collection Process

Following the 10-week usage period of the *"Bi'Kilo"* mobile application, qualitative data were collected through semi-structured interviews conducted online via *Zoom* and *Google Meet*. These interviews were conducted within a two-month period after participants completed the intervention. All interviews were audio-recorded and transcribed verbatim for analysis.

2.5. Data Analysis

Data were analyzed using inductive content analysis with *NVivo 11*. Coding was conducted based on the participants' verbatim responses, supported by in-vivo coding practices to preserve the authentic language used by participants. The resulting codes were organized into six overarching themes: Content, Useful Features, Technical-Application Issues, User Experience, Improvements, and Suggestions.

This analytic approach aimed to capture the diversity and complexity of users' lived experiences with the *"Bi'Kilo"* application and to ensure a grounded understanding of their feedback and suggestions.

3. Results

Codes obtained from interviews with participants were consolidated under the themes of Content, Useful Features, Technical-Application Issues, User Experience, Improvements, and Suggestions. Table 2 presents themes and their explanation.

Table 2.Themes and their explanation

Themes	Explanation of Themes
Content	The general structure and presentation of the *"Bi'Kilo"* application
Useful Features	Positive feedback from participants trying to lose weight with the *"Bi'Kilo"* application and the application's effective components and benefits to users
Technical-Application Issues	Criticisms related to the operation and content of the *"Bi'Kilo"* application, ranging from technical performance to content quality
User Experience	Practical usability and impact of the *"Bi'Kilo"* app through participants' experience
Improvements	Participants' encountered difficulties with the *"Bi'Kilo"* application and their suggested enhancements
Suggestions	Participants' feedback aimed at enhancing the development of the *"Bi'Kilo"* application

The Content theme addresses the general structure and presentation of the *"Bi'Kilo"* application based on participants' views. The theme highlights the "Visual and Technical Features" of the application, emphasizing its user-friendly and engaging qualities. Participants mentioned the smooth module sequence and how videos in each module increased user interest. Regarding "Content Being Good, Efficient, Clear" they appreciated the clarity and efficiency of information, though it sometimes remained theoretical. In "Information and Emotional Hunger" informative videos and texts, especially regarding emotional hunger, were found beneficial. Under "Comprehensiveness" the application's approach to not just being an eating log but addressing cognitive, physical, and emotional aspects of the user is emphasized. "Professionalism of Design" highlights the application's professional approach and ability to engage users. Table 3 presents the codes related to the Content theme and indicates from which participants they were obtained.

Table 3. Codes and participants related to the content theme

Code	Participant
Visual and technical features "The flow of the modules is generally very good. I think it is also very good that there is a video at the beginning of each module because reading a text alone can be boring.", "I think it is very good that visual and schematic expression is together.", "The design of the application is also good in generally", "I also liked that there was a text after the video."	1
Content is good, efficient, clear "I think it was good, it was productive. The messages were very clear, but they may remain too theoretical. If everyone is going to use it, I think it should be reduced to a theoretical language that everyone can understand."	1
Information, emotional hunger "As I said, the informative videos and articles were good. The fact that there was a survey afterwards was actually good in the sense of "Did I really understand?" It was also useful for me. I especially liked the informative parts, as I said." "Of course, some of it I had heard or read somewhere, some of it I didn't know at all. It was good for me to remind me, there were things I didn't know at all, especially in the parts about emotional hunger, for example, learning what triggers my eating attacks, these parts were very instructive for me." "Mostly the videos and what is written underneath like the description of the videos, I think I liked that part the most."	3

Comprehensiveness "I think it is very comprehensive, i mean, from the eating plan to physical activity, cognitive parts, thought cards, motivation, mindful eating" "So it's not a 'save and exit' app." "So it's just a self-monitoring app where the user keeps track of themselves and doesn't have to search and find out, "Okay, I took this many steps today, but what does that mean, how many steps should I have taken?" or "I recorded these meals, but what happens, I ate this much, but what happens?""""It is an application that also provides a really good education"	2
Professionalism of design "First of all, the program is very professionally designed. Whether it is video recordings, voice-overs, texts, questions that we can provide our feedback on what we listen to... I honestly believe it is very sufficient in this respect. In the same way, I think the fact that it asked us to participate actively, not just passively, and that we made some data entries and kept our records during the day were also positive features in this respect."	8

The "Useful Features" theme encompasses positive feedback from participants trying to lose weight with the *"Bi'Kilo"* application, covering the application's effective components and benefits to users. Under "Benefits to Weight Loss-Control" participants indicated that those with issues related to emotional eating might find the application more beneficial. The "Mindful Eating" section reflected that eating habits became more conscious and unnecessary eating was prevented. In "Applying What Was Learned" participants shared that they could integrate knowledge from the application into their daily lives, improving exercise and eating behaviors. "Integration into Daily Life and Awareness" emphasized the application's impact on their lives and how it increased their awareness. "Transcripts of Videos" showed that participants found the written content alongside videos useful. "Finding the Application Beneficial" stated that the application was effective in weight control and awareness and deemed professional and helpful by users. Table 4 presents codes related to the Useful Features theme and indicates from which participants they were obtained.

Table 4. The codes and participants related to the theme of useful features

Code	**Participant**
Benefit for weight loss-control "Definitely, I think people who have problems with emotional eating will benefit more. It is a good learning and tracking tool. I think it is passive in terms of awareness. If I have a control problem with eating, I don't log it, so notifications are important in this respect."	1
Mindful eating "I think especially the "Mindful eating" part is a nice part." "When I ate, I just ate. When I combined it with mindful eating, I stopped eating as soon as I was full and didn't eat unnecessarily."	4
Practice what was learned "I was able to integrate the information I learned in the application into my daily life. Yes, for example, there was a section on mindful eating, like watching something while eating. I pay more attention to it now, focusing only on eating." "When I started Bi'Kilo, I mean, when I started using the application, I was already doing sports, but I can say that it made it a little easier to track it. Because there was also the sports part"	7
Integration into daily life and awareness "I tried to increase my hiking." "I integrated it because I already downloaded this app for that purpose." "Some of it is still ongoing. Watching the same TV show while eating reminded me of eating later. When I saw that TV show, I became aware of that."	5
Transcripts of videos "Useful parts; first of all, the information parts, the videos, the transcripts given to us were very good, but when I was watching the videos, after a certain point I got bored and stopped and continued to read the transcript. But the information was very good, it was very good to read the transcript."	6

Considering the app useful "It is something that everyone will have when we say let's do an application about weight control, but what is really different for me and what the person can say "Oh, I am doing something different"; eating with awareness." "I think the thought cards and feedback are really good, thank you." "It is definitely a very useful and professional application, which is evident from the modules." "I think it can definitely be useful. Maybe, I guess it would definitely be useful, but it depends on the individual."	2

The "Technical-Application Issues" theme covers criticisms related to the operation and content of the *"Bi'Kilo"* application, ranging from technical performance to content quality. Issues like "Application Slowness and Crashing" caused discomfort due to unexpected shutdowns and errors, negatively affecting user experience. "Inability to Speed Up Videos" indicated limited information intake due to fixed video speeds. "Considering Thought Cards Redundant" and criticisms like "The Videos Were Kind of Boring" pointed to the content being unengaging or insufficient, with some participants already familiar with the information. "Questions Easily Answered" raised concerns about the instructional quality of the content, suggesting improvements to prevent misinformation. Table 5 presents codes related to the Technical-Application Issues theme and indicates from which participants they were obtained.

Table 5. The codes and participants related to the theme of technical-practical issues

Code	**Participant**
Application Slowness and Crashing "A couple of times I got an error notification while using the app. I took a screenshot but lost it. 3-4 times the app closed but I never experienced it afterwards."	1
Inability to speed up videos "The videos could have a faster narration."	1
Considering thought cards redundant "I couldn't reconcile the title with the content in the thought cards module. I thought I was going to be presented with mottoes that would increase my motivation or food intake. Other than that, there is no module that I would call unnecessary."	1
The videos were kind of boring "Another point is that the content of the videos seemed boring to me. It seemed very simple, I didn't learn anything new. Perhaps I think like that because I am interested in nutrition, but I didn't feel that I learned."	4
Questions answered easily "Also, I could answer questions without even watching the videos. I think you should be able to tell from those questions who watched the video"	4
Demotivation "It was a reminder for me when I wasn't paying attention, but my motivation dropped during the follow-up phase" "Technical issues were time-consuming and not moving on to the next module without doing what I disliked was demotivating."	4

"I thought, OK, I have learned it now, there is no need."	

The "User Experience" theme delves into participants' experiences using the *"Bi'Kilo"* application, emphasizing its practical usability and impact. Under the heading "Availability and willingness to use" it's mentioned that the application can be easily integrated into daily life and offers a unique approach. Participants highlighted the focus on not just weight loss but also increasing awareness about emotional eating. The "Preference Assessment" suggests the application could be an alternative to therapy, though face-to-face therapeutic support might still be necessary. In the "Experience - Reasons for Discontinuation" section, participants shared challenges related to continuous use, such as lack of time or forgetfulness. "Distinctive Aspect" underscores the comprehensive approach of the application and its features that enhance awareness of eating behaviors. Under "Data Entry Problems" some participants noted that data entry could be complex and repetitive. "Reasons for Using" emphasizes the application as an economic alternative to therapy access. Lastly, "Easy Time Allocation for Use" indicates that while the application does not require much time, some challenges were encountered. The "Improvement" theme has been developed to represent the difficulties encountered by participants with the *"Bi'Kilo"* application and their suggestions for its enhancement. Table 6 presents codes related to the User Experience Issues theme and indicates from which participants they were obtained.

Table 6. Codes and participants related to user experience theme

Code	**Participant**
Availability and willingness to use "It's nice to have an app like this at our fingertips, it can be used in daily life." "Yes, because I have already used a lot of such apps before and they were just "calorie tracking and recipes", but there are not many apps that aim to raise awareness like BiKilo. I think emotional eating will also attract people's attention." "People who want to lose weight immediately do not want to use it because this application is an application that is based on awareness and requires a long process."	5
Preferability assessment "I think it can be. I think that having at least one point in the day to focus on and being able to see them retrospectively, to see them collectively, can be useful for people who have a need in this regard." "For those who have difficulties or reservations about reaching a therapist, maybe the application may be a more attractive alternative, while those who may have difficulty in maintaining it on their own may be more interested in working with someone and progressing under someone's control, face to face with the therapist."	8
Experience - Reasons for Discontinuation "I don't follow it at the moment, I don't have much time." "Well, at first it was tempting, it was easy to enter it after every meal, but then I started to forget, I didn't have time at that moment, or I was out, I was meeting a friend, I couldn't enter it. When I couldn't enter it a few times like that, it didn't follow up."	3
Distinctive Aspect "I think it is different and meaningful and I think the thought cards are also useful, but they can be integrated more, so as I said, I think it is meaningful for the person in terms of providing motivation." "Oh, I'm doing something different"; eating with awareness. I think this will have an additional benefit and the thought cards are also useful." "I think it is very comprehensive, that is, from the eating plan to physical activity, cognitive parts, thought cards, motivation, eating with awareness, which is very important, I think it is useful to address them separately"	2

Dislike, data entry "The only thing that was challenging for me was this; we log in every day, you know, the parts we eat and drink, entering it over and over again after everything, because it asks for the same days over and over again, I forget, for example, "Did I write the same thing again?" It was a question mark. Actually, it can be easy to enter day by day, but it was challenging to enter the same days again after each tab." "No, I didn't have any difficulties, except for the part of re-entering them all one by one." "I will say it again, but as I said, it would be more comfortable if the data entry parts were just a separate tab. "Also, for example, if I want to write dinner, I can only write one thing there." "I think it would be better if; for example, these tabs could be in a separate thing, when I want to benefit from it, I should be able to enter these parts and listen to them, I should be able to read that part, but I think it would be better if the diary entry part was separate, that is, unconnected to each other."	3
Reasons for Using "They may prefer the application because it is free, I don't know if it will be free now, but it will be much more economical in every sense." "Apart from that, I think people have a little bit of difficulty in finding a psychiatrist or psychologist who is suitable for them and with whom they can really establish a telepathic relationship. Therefore, it is also good for them to progress on their own, they may prefer to apply it in that respect, and it is a process that spreads over a little more time, that is, it is something that they can use on the road during the day, not at certain hours with 1 or 2 checks a week, but "OK, let me see what I have done now"."	2
Easy Time Allocation for Use "But I don't think it's challenging or impossible for me not to make time for it."	8

The "Improvement" theme represented participants' encountered difficulties with the *"Bi'Kilo"* application and their suggested enhancements. "Notification and Planning Features" are needed to facilitate adaptation and include personalized exercise and eating plans, with weekly motivational messages also mentioned. "Progress Flexibility Within Modules" suggested that allowing users to proceed at their own pace could increase motivation and improve the experience. "Question-Answer Feedback" lack of feedback on right or wrong answers after animations hindered the learning process, necessitating development for accurate knowledge acquisition. The specific codes related to this theme and from which participants they were obtained will be detailed in Table 7.

Table 7. Codes and participants related to improvement theme

Code	**Participant**
Notification and planning features "There should be a stimulus so that the adaptation process is easier. If it is an application that everyone can use, there should be a plan for everyone. For the exercise plan, the weekly-monthly plan I mentioned in the meal plan can be made.", "Notification, exercise plan, eating plan-meal record comparison", "There can be a pool where people can enter their motivational phrases on a weekly basis, or a pool can be created and that motivational phrase can be added as the first notification of the day."	1
Progress flexibility within modules "It would have been more logical to complete this practice on a certain day. But as I said, as I don't have this motivation, maybe I need to finish it a little faster right now, because it is important for me to be able to complete it within a period of time and be able to make feedbacks, so the one-week periods restricted me a little bit, in that sense, I could have finished the application faster, in terms of being able to make these feedbacks."	8
Question-answer feedback "I will also say this about it; when I answered the questions in that section, I could not see what the correct answer was, this has been improved. I was saying "A" but I was saying "is it really A, did I do it right or wrong", this section can be looked at in order not to learn wrong information."	7

The "Suggestions" theme is predicated on participants' feedback to enhance the development of the *"Bi'Kilo"* application. The "Meal Plan-Record Comparison" suggests that participants find an integrated comparison between the meal plan and food record beneficial. Moreover, they indicate the possibility of having multiple entries for mindful eating, suggesting that separate entries could be made for each meal, necessitating the customization of the application according to the user's habits and the inclusion of reminders. The "Transition Between Sections" reveals participants' perception of the restriction in progressing to subsequent sections without entering specific records as a limitation, advocating for flexibility in this feature. The "Expert Feedback" underscores the need to enrich the application with feedback from dietitians or experts, enabling users to act more accurately and consciously. "Motivational Sentences" convey participants' belief in the potential of these sentences to boost morale and encourage users. "Areas or Features Requiring Improvement" reflect feedback on specific technical aspects of the application, such as video durations, notification frequency, activity suggestions, and other visual and functional features. In the "Recommending to Others" theme, while participants express a positive view of the application, this approval notably hinges on the user-friendliness of the application. The "Alternative to Face-to-Face Support" theme elucidates participants' views that mobile applications cannot fully replace face-to-face support. However, such applications offer advantages in terms of accessibility and convenience. The "Alternatives for Use" theme emphasizes the potential for mobile applications and face-to-face support to complement each other. The "Useless Parts of the *"Bi'Kilo"* Application" theme critiques technical issues and the lack of personalization within the application. The "Notifications, Increasing the Number of Records, Integrating a Pedometer" theme suggests that additional interactive features, recording options, and integration of a pedometer would be beneficial. Participants' feedback contains valuable suggestions for making the application more practical both technically and content-wise. Table 8 presents the codes related to the Suggestions theme and indicates from which participants they were obtained.

Table 8. Codes and participants related to the theme of suggestions

Code	**Participant**
Meal plan-record Comparison "I didn't like the design of the meal plan in the application. When entering each meal, you have to enter them one by one, but I think a person should be able to create their own scheme and have basic headings according to how many meals they consume (weekly/monthly) or be able to change these headings. There should also be times for these, and if there's no entry at those times, there should be a reminder. People might forget, it's not suitable for the sustainability of the application.", "I would also like a scheme where the meal plan and food record could be viewed more parallel. I have a meal plan and a separate food record that can be viewed from different channels, whereas I should be able to compare these two so I can see what I've planned, what I've eaten, how much I've eaten, and how much I'm sticking to the plan.", "There's only one entry for mindful eating in a day, yet a person can practice mindful eating at every meal.", "Weight tracking should also be added, and after entering the starting weight, a new entry can only be made after a certain period (like 15 days)."	1
Transition between sections "What I didn't like, well not that I didn't like but maybe it could be done differently, we couldn't proceed to the next section without entering a certain number of records. That feels a bit like a task to me, I might actually be more interested in the content of the next section and could benefit more from it, but if I don't enter my diet for five days, I can't proceed, which I think could change." "Actually, I was entering it every day, but as I said, especially after I started not being able to pass the section, I began entering it 2-3 times a day for meals. Normally, I would enter it every day, I mean if there wasn't such a restriction."	7
Expert feedback "Instead of the tracking phase being the same, there could be current changes, a dietician could give me feedback." "It could be possible if there is proper expert control because otherwise, I may not be aware of my own mistakes." "If you don't want to go to a dietician, there's an app that allows you to control and become aware of it on your own."	4

Motivational sentences "There could be a pool where people can enter their motivational sentences weekly, or a pool could be created and the first notification of the day could add that motivational sentence, like 'You can do it'."	1
Areas or Features Requiring Improvement "Definitely would be a plus. Especially reminders at times like 5 PM and 10 PM for eating-sleeping hours are very important." "Some videos are too long, it would be better if they didn't exceed 7-8 minutes." "At the beginning, the app was lagging, I was having trouble logging in, but then the content seemed to improve and it was smooth." "I didn't know this information, maybe it would be nice if such information was given right when you log into the app." "1) Setting the scale entry at the beginning 2) Shortening the video duration 3) Increasing the frequency of notifications" "I would suggest a small daily activity, like 10 minutes of 3 sets x movement per day."	5
Recommending to others "I would and I did because it's an application that will provide long-term benefits for us, it makes a person reflect on themselves. The content is good." P5 "I would. Generally, I would, even I mentioned it to my family. 'I participated in such a pilot study, there's this app, it's good.' My mom is trying to lose weight, sometimes she follows wrong diets, especially I would like to recommend it to my mom for her to get the right information." P7	5, 7
Alternative to face-to-face support (1, 5, 7) "It could be, but I don't know if it would be sufficient. I think people always need authority when making such a radical change in their lives or when they set a goal and want to achieve it. The app tells me what to do, but if I don't want to do it or can't, how will the app convince or force me? Also, the app only gives me information but doesn't understand my feelings or problems. Sometimes talking face to face and seeing the reactions of the person in front of me can be more effective." P1 "It could be because it saves time for people. It's easy to enter, and since it's aimed at my goal, it could be an option." "People who generally wouldn't prefer face-to-face might be those with high work pressure, who don't have or want to spare time... Those who want to use a mobile app might be people who need detailed conversations, motivation." P5 "Using a mobile app can definitely be an alternative. In terms of accessibility, I can't always reach a dietician or psychologist at any moment, but I can access a mobile app. I find it beneficial in this regard." "But since every person is individual and their needs are individual, I can't generalize it, 'This is the case for everyone,' but it could be an alternative for most." P7	1, 5, 7
Suggestions for improving the app "I think these new notifications are good. Because now every app is using it and it's definitely motivating." "Maybe there could be a separate graph for each day?" "The apps could be made bigger for easier access, etc." "Such as the hunger fullness scale, etc. Apart from that, thought cards, feedbacks were really on point, well done. Apart from that, the modules were pretty good, by the way. Regarding videos and content, definitely no feedback, everything is amazing in that part, I think no change is needed. Just a visual change could be made, in terms of colors, the design could be changed, apart from that, I don't think I have any feedback." P2 "Recipes suggested by a dietician could be added." "I thought about adding calories but it could be very triggering." "Alternative physical activities could be included. A notification could come with a new task. 'Do yoga, walk for 1 hour'" "Increasing notifications, giving daily tasks." P4	2, 4
Alternatives to use "I think the use of a mobile app and face-to-face support shouldn't be alternatives but could complement each other." "A person might have difficulty finding a suitable expert, obtaining an appointment or reaching them, might not afford the session fees, or might have trouble conforming to session times." "For obesity, for instance, 'I have weight issues but I actually have such a problem that I can't solve.' they might come in that way. From that perspective, face-to-face support might be preferred more and although it has been provided by a professional team, some people might want to see a professional in front of them, ask them a question because this can vary from person to person so I'm giving different answers."	2

Useless parts of the Bi'Kilo app "The useless parts; as I said, the record-keeping parts were very limited. Also, the app sometimes gave errors, lagged, or shut down. That was annoying." "Also, it could have been a bit more personalized. For example, I could enter my weight, height, age, etc., and it could offer me a program suitable for that. Or it could ask about my goals. For instance, I want to lose weight, maintain my weight, or eat healthily."	6
Notifications, increasing the number of records, integrating a pedometer "Some of the feedback I actually gave at the beginning, maybe the number of records we couldn't make more than once a day could be increased." "I don't know how possible it is, but could a pedometer or something similar be implemented into the program regarding exercise? It would have been nice to enter it because when we enter it now, we enter the approximate steps we do in exercise, but maybe a pedometer could be integrated into the program?"	8

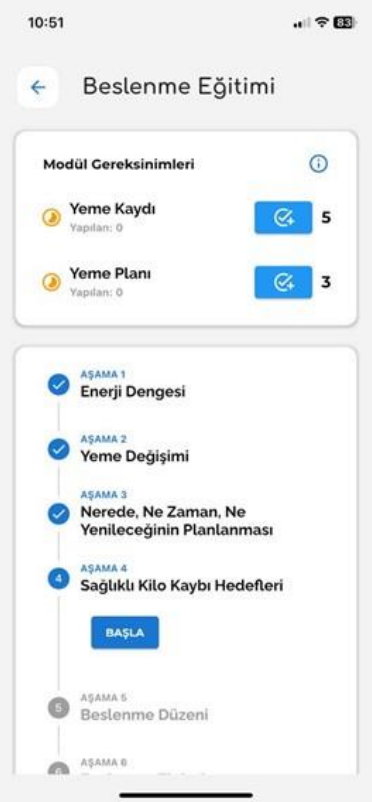

Figure 1. *Screenshot from the App-1, Nutrition Education Module Main Screen*

Figure 2. *Screenshot from the App-2, Practices Main Screen*

Figure 3. *Screenshot from the App-3, Hunger Fullness Scale*

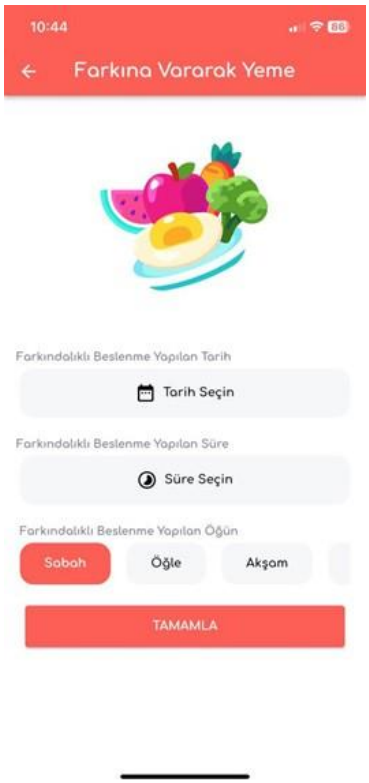

Figure 4. *Screenshot from the App-4, Mindful Eating Module*

Figure 5. *Screenshot from the App-5, User's Page*

4. Discussion

The findings from the *"Bi'Kilo"* mobile application study demonstrate that integrating visual and technical features, comprehensive content, and a focus on user interaction and engagement is consistent with current literature emphasizing the importance of these elements in digital health interventions (41). Particularly, the application's visual and technical features, the efficiency and clarity of content, and the sections addressing knowledge and emotional hunger have received positive user feedback. This corresponds with literature emphasizing the importance of clear information presentation and visual richness in health applications, supporting *"Bi'Kilo's*" success. Additionally, users' appreciation of the application's comprehensive and professional design underscores the necessity for such applications to be extensive and user-friendly. The findings provide significant insights into user perceptions and experiences with the *"Bi'Kilo"* mobile application for weight control. Overall, qualitative feedback indicates moderate to high usability, acceptability, and a positive impact on promoting healthy behaviors. Consistent with previous mHealth research, incorporating an interactive, self-monitoring approach has enhanced engagement with the application's design and content (41, 42). Features facilitating self-monitoring, such as food diaries and activity tracking, have been consistently highlighted as beneficial. The application's focus on mindful eating reflects evidence suggesting mindfulness techniques can improve eating behaviors and weight loss outcomes (43). However, some users have highlighted the content's theoretical nature, echoing Olson and Emery's findings on the need for user-centered content design in health applications, indicating a demand for more practical and relatable materials (43).

Specifically, adding interactive modules and video content is understood to enhance user engagement and learning outcomes in digital health platforms, as indicated in Hutchesson et al. research in 2015 (19). The content and design of the application have significantly influenced user experience and engagement. Participants reported satisfaction with the orderly arrangement of modules and the presence of videos and texts that captured users' interest and effectively presented information. However, some technical issues and content criticisms have negatively impacted user motivation, leading to the discontinuation of the application. This underscores the importance of content and functionality in maintaining user engagement over time.

User feedback has highlighted various areas for improvement in the *"Bi'Kilo"* application. Technical issues like application crashes and the inability to adjust video speed were common concerns, similarly discussed by Payne et al. regarding the importance of technical reliability for user engagement (41). Users have also suggested personalizing content and enhancing interactive features. In line with the findings of Peng et al., specific content and interactive elements are emphasized as crucial for sustaining user engagement in digital health interventions (42). User feedback has revealed some critical limitations and areas needing improvement within the application. In particular, occasional slow performance and technical glitches negatively affected the user experience. Some users found the content monotonous or insufficient and requested more interactive elements in videos. Enhancements such as flexibility in module progression, displaying correct answers after animations, and more personalized content are necessary to increase user engagement and provide a more effective learning experience.

Additionally, offering more motivational messages and personalized feedback could further enhance the application's effectiveness. However, certain design limitations have impacted sustainable engagement. The requirement to complete a specific number of logs before progressing between modules was demotivating for some users. Increasing speed and content access flexibility could enhance engagement (41). Streamlining data entry systems is another recommended improvement. Further personalization based on user data, automatic feedback, and integration of expert input will assist in optimizing long-term efficacy (19). Features enabling comparison between diet plans and actual intakes could also enhance accountability. While promising for facilitating self-intervention, blending with human support where possible will ease progress and overcome barriers (43). The findings from the *"Bi'Kilo"* application present elements consistent with existing literature, highlighting how it can be improved based on user experiences and feedback. The results confirm the strengths of the *"Bi'Kilo"* application in providing a suitable, accessible platform for enhancing awareness and motivation, critical initial steps for lifestyle change. Maximizing flexibility and personalized support will further

reveal the potential for sustainable improvements in weight management behaviors. However, a notable limitation of the study is the small sample size, as it included only eight female participants, thereby limiting the generalizability of the results to broader populations.

The qualitative feedback from users of the *"Bi'Kilo"* mobile application demonstrates its promise in offering an accessible, versatile intervention for weight control. Principal findings indicate that participants perceive the application as moderately to highly usable and acceptable. The application's interactive components have enhanced awareness, knowledge, and motivation concerning dietary, activity, and mindful eating habits. Integrating tracking features and informative multimedia content has been particularly effective in facilitating initial behavior changes. The *"Bi'Kilo"* mobile application provides a comprehensive approach to weight control by integrating modules that address not only nutritional habits but also physical activity and cognitive-behavioral aspects. Users have appreciated the multimedia approach of the application, especially the use of videos and reflective exercises. However, some reported experiencing technical issues and desired more practical, less theoretical content. The application's design, professional layout, and encouragement of active user participation were generally well-received. Nonetheless, some limitations regarding sustained engagement and personalization have been recorded. Future iterations of the application should focus on enhancements that maximize content access and speed flexibility. Simplifying data entry systems and integrating additional expert input tailored to individual progress data could promote ongoing engagement. Further, including more reminders, integration with activity trackers, the ability to enter motivational statements, and the capability to make comparisons between diet plans and actual intakes are recommended. Adding social features for interaction with other users could facilitate accountability and motivation. Applications like *"Bi'Kilo"* play a significant role in modern health management, particularly in weight control, offering accessible and user-friendly platforms for individuals aiming to improve health behaviors. The effectiveness of applications relies on continuous improvement based on user feedback, technological advancements, and developments in health management practices. In applications, flexibility, personalized content, and behavioral science principles can significantly contribute to effective weight control and overall health. Insights from the *"Bi'Kilo"* application highlight the potential of mHealth solutions to empower individuals to take holistic and sustainable responsibility for their health. *"Bi'Kilo"* and mHealth applications are crucial in reducing barriers to accessing weight management interventions while optimizing mHealth tools with continuous user input and evidence-based behavioral design principles, critical for effective self-managed lifestyle change.

Furthermore, such mHealth tools can broadly impact a non-clinical sample level by expanding access to face-to-face programs. However, this impact depends on aligning content and features with user needs and preferences. Conclusions and recommendations emphasizing the need for ongoing development and adaptation underscore the potential and challenges of mHealth applications in the health sector.

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Comorbid Psychiatric Disorders in Children and Adolescents with Down Syndrome: A Retrospective Study

Down Sendromlu Çocuk ve Ergenlerde Eşlik Eden Psikiyatrik Bozukluklar; Retrospektif Bir Çalışma

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Abstract: Down syndrome is one of the most common chromosomal abnormalities accompanied by intellectual disability. However, limited information is available regarding the psychiatric diagnoses and follow-ups of children with Down syndrome, except for intellectual disability. This study aimed to investigate the data on degrees intellectual disability, comorbid psychiatric diagnoses, treatment, and clinical follow-ups of children with Down syndrome. This study was conducted with cases who applied to our hospital between January 2016 and December 2023, were under the age of 18 and diagnosed with Down syndrome. Sociodemographic, comorbid psychiatric and medical diagnosis, and treatment data of a total of 181 cases were retrospectively analyzed. A total of 181 individuals (102 males and 79 females) with Down syndrome were included in the study. When the cases were classified based on their intellectual disability levels, it was found that mild intellectual disability was the most common. 58% of the cases had at least one medical comorbidity, and 22.4% had a psychiatric comorbidity. It was found that the most frequently diagnosed comorbid psychiatric disorder was Attention Deficit Hyperactivity Disorder, and comorbid psychiatric disorders were not associated with gender or degrees intellectual disability.It was observed that hospital applications of individuals diagnosed with Down syndrome were through health board reports. It was determined that outpatient clinic applications for comorbid psychiatric disorders and treatments, other than intellectual disability, were low. As a result, it is recommended to develop health policies that ensure psychiatric follow-ups of individuals with Down syndrome to ensure their positive gains in later life.
Keywords: Adolescent, Child, Down syndrome, Intellectual disability

Özet: Down Sendromu zihinsel yetersizliğin eşlik ettiği en yaygın kromozomal anormalliklerden biridir. Ancak Down Sendromlu çocukların zihinsel yetersizlik dışında psikiyatrik tanı ve takipleri hakkında bilinenler kısıtlıdır. Bu çalışmada Down sendromlu çocukların zihinsel yetersizlik düzeyleri, komorbid psikiyatrik tanıları, tedavi ve klinik izlemlerine dair verilerin incelenmesi amaçlanmıştır. Bu çalışma Ocak 2016 ve Aralık 2023 tarihleri arasında hastanemize başvurusu olan, Down Sendromu tanısı almış 18 yaş altı olgularla yapılmıştır. Toplam 181 olgunun sosyodemografik verileri, komorbid psikiyatrik ve tıbbi tanı ve tedavi verileri geriye dönük olarak incelenmiştir. Çalışmaya toplam 102'si erkek (%56,4) olmak üzere 181 Down Sendromlu birey dahil edilmiştir. Olgularda zihinsel yetersizlik düzeylerine göre sınıflandırıldığında en sık hafif düzeyde zihinsel yetersizliğin görüldüğü bulunmuştur. Olguların %58 'ine en az bir tıbbi komorbidite, %22, 4'ünde ise psikiyatrik komorbidite bulunmuştur. En sık eşlik eden psikiyatrik tanının Dikkat Eksikliği Hiperaktivite Bozukluğu tanısı olduğu ve eşlik eden psikiyatrik bozukluk tanısının cinsiyet, zihinsel yetersizlik düzeyleri ile ilişkili olmadığı bulunmuştur. Down Sendromu tanılı bireylerin hastane başvurularının sağlık kurulu raporları üzerinden olduğu görülmüştür. Zihinsel yetersizlik dışındaki komorbid psikiyatrik bozukluklar ve tedaviler için poliklinik başvurularının az olduğu saptanmıştır. Sonuç olarak; Down sendromlu bireylerin ileri yaşlardaki olumlu kazanımlarını sağlamak amacıyla psikiyatrik takiplerini sağlayan sağlık politikaları geliştirilmesi önerilmektedir.
Anahtar Kelimeler: Çocuk, Down Sendromu, Ergen, Zihinsel yetersizlik

Ethics Committee Approval: The study was approved by Recep Tayyip Erdoğan University Noninterventional Clinical Research Ethical Committee (Decision no: 2024/32, Date: 08.02.2024).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

Authorship Contributions

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1. Introduction

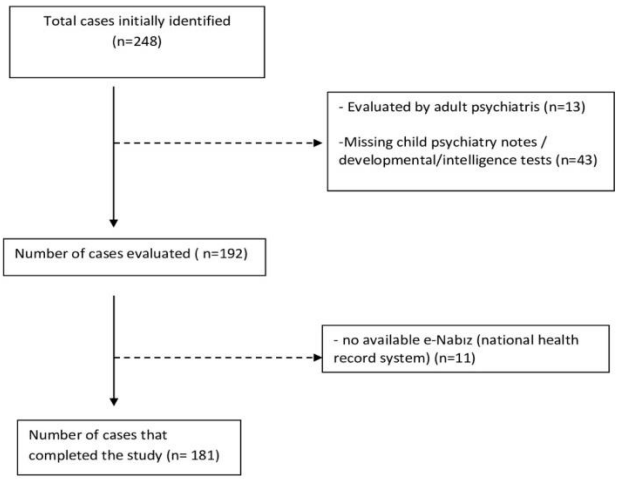
Down syndrome (DS) is the most common genetic cause of intellectual disability (ID) and it occurs due to the trisomy of chromosome 21 (1). Its worldwide prevalence is reported as approximately one in 800 live births (1). The genetic impairments associated with DS lead to problems related to increased comorbid medical conditions including craniofacial dysmorphic features as well as a range of neurological disorders, congenital heart diseases, endocrine disorders, and increased risk of infections (2). Individuals with DS experience impairments and difficulties in various developmental areas, particularly communication and comprehension skills, behavior and self-regulation, motor development, cognition, and attention (3,4). In addition to limitations in social and societal skills, these problems can lead to more frequent emotional and behavioral problems in individuals with DS (5,6). Furthermore, it has been reported that the achievements and difficulties experienced by these individuals, including the degree of ID, vary considerably within the population depending on the level of genetic impairment, and disorders and experienced difficulties increase with age (3,4). It has been revealed that the prevalence of psychiatric disorders seen in DS is higher than in the normal population, and when compared with other cases with ID, there are again some differences in the prevalence and severity of the disorders (3,4,7). In a study focusing on the frequency of psychiatric disorders in individuals with DS, it was reported that 8-23% of children with DS had a significant psychopathology (7). Another study found that 20-40% of children with DS had comorbid behavioral problems (8).

In the study conducted by Nærland et al. involving 674 children and adolescents diagnosed with Down syndrome (DS), it was reported that externalizing problems were most prevalent during the preschool period, with their rates decreasing with age, while internalizing problems increased with the onset of adolescence (9). In a smaller cross-sectional study conducted by Marino et al., the distribution and onset age of psychopathological risks were examined in a smaller sample of children with DS. It was found that 94% of the cases carried specific psychopathological risk factors, with externalizing problems such as Attention Deficit Hyperactivity Disorder (ADHD) and Oppositional Defiant Disorder (ODD) being more common in children, and internalizing problems such as anxiety and depression increasing during adolescence (10). Other studies conducted with children and adolescents with DS have also explored the prevalence of comorbid ADHD (11, 12) and Autism Spectrum Disorder (ASD) diagnoses (13) and externalizing problems (14,15); however, the number of such studies remains relatively limited.

Despite being the most common genetic disorder and the growing research interest in recent years, knowledge regarding the epidemiology, clinical presentation, and treatment approaches of psychiatric comorbidities in children and adolescents with Down syndrome (DS) remains limited. At the outset of our study, it was assumed that psychiatric referrals to child and adolescent psychiatry outpatient clinics were insufficient during the cognitive assessments of children with DS conducted within the scope of health board evaluations. This insufficiency may lead to delays in the diagnosis and treatment of psychiatric conditions in this population. In this context, our study aimed to examine the mode of referral, clinical follow-up, and treatment processes of patients aged 0–18 years in order to identify psychiatric comorbidities associated with DS. We believe that the findings obtained from this study will provide valuable data on the prevalence and treatment of comorbid psychiatric diagnoses in children and adolescents with DS and may serve as a foundation for future multi-center studies with larger sample sizes.

2. Materials and Methods

This study included cases who applied to Recep Tayyip Erdogan University Rize Training and Research Hospital between January 2016 and December 2023, were under the age of 18, and received a DS diagnosis with Q90.0, Q90.1, Q90.2, and Q90.9 ICD-10(International Classification of Disease-10) codes. The file data of the cases were retrospectively examined through the Hospital Information Recording System. The study initially included 248 cases; after excluding 67 cases, the final analysis comprised 181 cases (Figure 1).



Şekil 1.Flow chart of patient presented

The examined data of the cases included their ages, genders, comorbid pathologies with DS, ongoing treatments, applications for health board reports (Special Needs Report for Children as of 2019), their ages at the time of the first report, applications to the child psychiatry outpatient clinic, ages at the first application to psychiatric clinic, follow-ups, whether or not they had a diagnosis of intellectual disability as a result of psychiatric evaluation and its level, comorbid psychiatric disorders, and medication treatments used if any. The intellectual disability degree and psychiatric diagnoses of the cases were obtained from the child psychiatry's examination notes. Diagnoses were by re-evaluating patient anamnesis according to Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. The results were recorded in detail on data recording forms prepared by the researchers. The approval of the ethics committee of the Institution was obtained for the study (Ethics committee date: 08.02.2024; decision no: 2024/32). All procedures involving human participants in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later versions.

3.1. Statistical Analysis

The Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA, version 29.0) software was used for data analysis. Proportional data are presented as percentages, normally distributed data as mean ± standard deviation, and non-normally distributed data as median (minimum-maximum). The normality of data distribution was determined by the Kolmogorov-Smirnov test. The chi-square test was used to compare categorical data between groups. A p-value of <0.05 was considered statistically significant.

3.Results

It was determined that 56.4% (n=102) of the children were male and 43.6% (n=79) were female. The mean age at which cases first applied to the child psychiatry outpatient clinic was found to be 31.6 ± 35.7 months. When the nature of the applications was evaluated, it was determined that the most common reason for application was for a disability evaluation board application (%74.6, n=135). It was found that only 22.7% (n=41) of the cases applied to the child psychiatry outpatient clinic regularly attended follow-up appointments, while 2.8% (n=5) did not apply to the child psychiatry outpatient clinic at all. In our study, the mean age of cases for disability evaluation board applications was found to be 31.8 ± 36 months (minimum: 1 month / maximum: 115 months). Additionally, it was determined that 37% of the cases (n=65) were under 1 year old at the time of the application for the report.

Excluding psychiatric disorders, the comorbid medical pathologies of the cases were examined, and it was found that they were most frequently accompanied by cardiovascular system pathologies, followed by endocrine and urinary system pathologies, respectively. The distribution of comorbid medical pathologies by system is shown in Table 1. It was determined that 23.8% (n=43) of the cases had continuous medication usage due to their comorbid medical pathologies.

When the data regarding the intellectual disability levels of the cases were evaluated, it was determined that low level intellectual disability was the most

common comorbidity with DS (n=86, 47.5%). In the study, it was determined that 22.1% (n=40) of the cases had at least one psychiatric disorder in addition to ID, and 6.1% (n=11) had at least two different psychiatric disorders in addition to ID. The most common comorbid psychiatric disorder was found to be ADHD, and it was followed by Conduct Disorder (CD) and anxiety disorders, respectively. It was determined that 18.8% (n=34) of the cases received medication for comorbid psychiatric disorders, and 5% of these cases (n=9) used more than one medication. Table 2 shows the distributions of degree ID, comorbid psychiatric disorders and data related to medication treatments.

When the distribution of intellectual disability levels by gender was examined, no statistically significant difference was found between female and male cases (x^2=8.491, p=0.075). When the presence of comorbid psychiatric diagnosis by gender was examined, no statistically significant difference was found between females and males(x^2=0.25, p=0.517).

3.2 . Tables

Table 1. Distribution of medical pathologies comorbid with Down syndrome by different systems

	n	**%**
Comorbid medical pathology	105	58
Cardiovascular System	53	29.3
Endocrine System	30	16.6
Urinary System	10	5.5
Nervous system	9	5
Hearing System	9	5
Gastrointestinal System	7	3.9
Visual System	5	2.8
Skeletal System	3	1.7
Respiratory System	3	1.7
Skin Diseases	2	1.1

n: number of cases, %: percent

Table 2. Data on the degree of intellectual disability, comorbid psychiatric diagnoses, and psychotropic medication use in individuals with Down syndrome

	N	%
Intellectual Disability Degree		
Mild ID	86	47.5

Moderate ID	72	39.8
Severe ID	10	5.5
Borderline ID	8	4.4
Not received diagnosis because of age (age <6 months)	5	2.8
Comorbid Psychiatric Disorder		
ADHD	17	9.4
Conduct Disorder	15	8.3
Anxiety Disorder	9	5
ASD	4	2.2
Stuttering	2	1.1
Enuresis nokturna	2	1.1
OCD	1	0.5
ODD	1	0.5
Psychiatric medication used		
No	147	
Yes	34	
Distribution of psychotropic drugs used		
Antipsychotic	25	13.8
Methylphenidate-Atomoxetine	14	7.7
SSRI	2	1.1
Mood stabilizer	1	0.5

n: number of cases, %: percent, ADHD: Attention Deficiency Hyperactivity Disorder, ASD: Autism Spectrum Disorder, ID: Intellectual Disability, OCD: Obsessive Compulsive Disorder, ODD: Oppositional Defiant Disorder, SSRI: Selective Serotonin Reuptake Inhibitor

4. Discussion

In this study, a retrospective evaluation was conducted on individuals under 18 years of age diagnosed with DS at a tertiary healthcare center. Clinical data regarding comorbid psychiatric disorders, application types of patients, clinical follow-ups, and treatments used were examined. Results showed that the number of male cases was higher, and more than half of the cases had at least one medical pathology in addition to psychiatric disorders. When DS cases were evaluated according to their degree's intellectual disability, mild ID was found to be the most common, and no significant difference was found between genders in terms of ID levels. Approximately one-quarter of the cases had at least one comorbid psychiatric disorder and ADHD was the most common comorbid diagnosis.

The data obtained from the study revealed that the number of male cases was higher. This finding is consistent with the literature showing a higher prevalence of DS among males (2,13,16). In the study, it was determined that 74.7% of the cases were applied to the child psychiatry outpatient clinic through the disability evaluation board, while only 24.7% applied to the child psychiatry outpatient clinic for examination purposes. Similarly, in a study conducted in our country by Efendi et al. on children with DS, it was reported that 62.5% of the patients applied to the child psychiatry outpatient clinic for medical report (17). It was observed that data on psychiatric clinic applications, diagnoses, and follow-up of children with DS in our country is very limited in the literature. Considering this limited but valuable data from two studies conducted in our country, it can be assumed that if there were no individual special education and care fees that necessitate the health board application, a large majority of the cases would not have applied for mental health services (18). Among the underlying reasons for this situation, a primary barrier may be the lack of awareness among families regarding the psychiatric comorbidities that can accompany Down syndrome (DS), as well as the misconception that such issues are simply part of the natural course of DS. Secondly, the absence of routine psychiatric screening protocols for individuals with DS in our healthcare system, along with insufficient referral mechanisms within primary care services, constitutes systemic barriers to early diagnosis and intervention.To address the mental health needs of children with DS, certain interventions can be planned. Based on these findings, first, educational programs and awareness campaigns for families could be organized to increase understanding of psychiatric comorbidities in DS. Secondly, routine psychiatric screening protocols specifically for individuals with DS could be developed within primary care services, and access to child psychiatry consultations could be facilitated. The implementation of these recommendations may play a crucial role in improving the quality of life and supporting the long-term psychosocial functioning of individuals with DS.

The study found that the mean age at first application to the child psychiatry clinic was 31.6 ± 35.7 months, and the mean age at the application to the disability evaluation board was 31.8 ± 36 months. In a study conducted in our country, the mean age of the first psychiatric evaluation for children with DS was found to be 4.16 ± 2.8 years, while the mean age at which patients started individual special education was 20.15 ± 14.24 months. The study revealed that the difference between the age of initial psychiatric outpatient clinic application and the age of starting individual special education was primarily due to the fact that most patients initially sought services from pediatric departments to be eligible for government-funded special education (17). In this study, it was thought that the fact that the vast majority of initial psychiatric evaluations were conducted as a result of disability evaluation board applications explained the similarity between the mean ages of first psychiatric clinic application and disability evaluation board application.

Based on the data obtained in the study, it was found that nearly half of the individuals with DS had mild ID (47.5%), and this was followed by moderate (40%) and severe (5.5%) degrees of ID. In the study conducted by Efendi et al. with 72 children, differing from our results., moderate ID was observed in nearly half of the cases (45.7%), followed by mild ID (32.9%) and severe ID (21.4%) (17). In another study conducted with 16-19-year-old adolescents with DS, it was reported that the degree of ID was moderate in 43% of them, followed by severe (30%) and mild (17%) degrees of ID (19). There are differences in the prevalence of degrees ID between the results obtained from the literature. This situation may be related to the ages of the individuals included in the study and the differences in standardized tests used to assess ID. It is known that cognitive development is slower in individuals with DS compared to their normally developing peers. In addition to the individual variability in the degree of ID in DS, it is emphasized that intellectual development slows down as age increases, and the age at which the level of intellectual disability is assessed is important in this regard (20-22). Moreover, the improvement in healthcare conditions and the increased public awareness of DS have made it possible for individual special education to begin at an earlier age. This may have led to a higher diagnosis rate of mild ID in individuals with DS.

Research findings indicated that 22.1% of cases had at least one psychiatric disorder, and 6.1% had at least two different psychiatric disorders in addition to ID. It is seen that the number of studies on the prevalence of psychiatric disorders in children with DS is fewer compared to adults. In a scale-study conducted by Marino et al. with 97 children and adolescents with DS, it was reported that 94% of the participants had psychopathological risk factors (10). In the study by van Gameren-Oosterom et al.,

513 adolescents were evaluated, and problematic behavioral scale scores were obtained in 51% of the cases (19). Both studies are based on data obtained from scale scores rather than clinically structured assessments. In the study by Efendi et al., a psychiatric disorder diagnosis was found in 56% of cases with DS (17). In conclusion, there are widely varying rates reported across studies for comorbid psychiatric disorders and behavioral problems. It is reported that the fact that the studies were few in number, they were conducted with small sample sizes, and the diagnostic methods used were different may cause fluctuations in the results over wide ranges (23).

The results of this study revealed that ADHD was the most common comorbid psychiatric disorder, and it was observed in 9.4% of cases. In the study by Marino et al. showed that the prevalence of ADHD was 15% (10). Spinazzi et al reported this rate as 9.6% in their retrospective study on children with DS (24). In the study conducted by Startin et al. with DS children under the age of 15, the prevalence of ADHD was reported as 8.6% (2). Another study reported that 15.7% of participants already had an ADHD diagnosis, and the prevalence of ADHD obtained through the scales used in the study was 40.7% (12). Efendi et al. reported an ADHD diagnosis rate of 29.2% (17). In contrast to these results, In two different studies with smaller sample sizes, the ADHD diagnosis rate in children with DS was reported as 44% (11) and 34% (13). The results obtained from the studies report highly variable rates regarding the comorbidity of DS and ADHD. It is thought that these differences may have been due to the age distribution of the samples included in the studies, the use of structured interviews or scale applications as diagnostic methods, and the selection of different geographical region samples. In this study, it is considered that the fact that most of the cases were patients evaluated by a health board, only one-fifth had a child psychiatry appointment, and families had insufficient knowledge about comorbid psychiatric disorders in Down syndrome may have affected our results.

In this study, as an unexpected result, the prevalence rate of ASD was found to be 2.2%. Individuals with DS were characterized as having better social skills compared to individuals with other IDs. On the other hand, ASD is associated with limitations in communication skills in a range of social and societal areas (25). However, previous studies have reported that the prevalence of ASD in individuals with DS can vary between 16% and 42% and that the rate of ASD is higher in DS compared to the general population (25, 26). In the study by Marino et al. reported that in 7% of the cases, the scale scores obtained for ASD were above the clinical cut-off point (10). Spinazzi et al reported the prevalence rate of ASD was reported as 13% (24). This rate was reported as 5.7 % in the study by Startin et al (2). In a study conducted by Efendi et al., this rate was reported as 6.9% (17). The prevalence rates obtained in the literature vary considerably. The results obtained from this study, on the other hand, yielded a much lower value compared to the literature. It is thought that this situation may have been caused by the age group of the cases included in the study and the fact that the clinical appearance of OSB in children with DS is different. Regarding the comorbidity of DS and ASD, it has been reported that ASD diagnosis is made later in children with DS compared to children with only ASD, and that ASD may be more difficult to identify in this population due to the phenotypic social behavior patterns of DS (27, 28). The fact that the ASD frequency data was lower in this study compared to the literature may have been due to the difficulty of diagnosing ASD and the fact that the application rates of cases with DS for psychiatric examination were low outside the disability evaluation board.

In our study, it was found that 5% of the cases were diagnosed with anxiety disorder, but no case was diagnosed with a mood disorder. In the study conducted by Marino et al., in which the diagnosis was made using a scale, it was reported that mood disorders were observed in 9% of the cases and anxiety symptoms were observed in 36% of the cases (10). In the study of Spinnazi et al., the prevalence of depressive disorder was reported as 4.2% and anxiety disorder as 6.8% (24). In another study, the prevalence of depressive symptoms was reported as 9.6% between the ages of 5-11 and 7.6% between the ages of 12-21 (23). In a study conducted by Efendi et al., it was reported that 4.2% of the cases had anxiety disorder, and 1.4% of the cases had diagnosis of depressive disorder (17). Similar to the results of our study, in the study by Startin et al., it was reported that there were no children with Down syndrome diagnosed with depressive disorder, and anxiety disorder was detected in 2.9% of the cases (2). It has been revealed that depressive disorder diagnosis is seen at lower rates in children and adolescents with DS compared to adults with DS (29). It has also been reported that it is difficult to diagnose depressive disorder in individuals with intellectual disability due to the neurodevelopmental difficulties they experience, such as speech delay and inadequate nonverbal communication. Considering the age distribution of the cases included in the obtained results and the difficulty of diagnosing depressive disorder due to intellectual

disability, it is thought that this was a contributing factor.

In this study, it was found that ODD was comorbid in 0.5% of the cases, while CD was comorbid in 8.3% of the cases. There are limited number of studies investigating disruptive behaviors in children with DS in the literature. One of these studies was conducted with 100 children with DS aged 6-18, and it was reported that the prevalence of ODD was 8% and the prevalence of CD was 4% (14). In terms of the rates of DS and ODD comorbidity, a study conducted with 101 children with DS, using a semi-structured interview, found that 17% of the cases met the diagnostic criteria for ODD (15). In the study conducted by Marino et al., reported positive ODD symptoms in 26% of the sample (10). In our study, it was found that the prevalence of CD was higher compared to the literature, while the prevalence of ODD was much lower than expected. There are differences in the tools and methods used for diagnosis in the studies. This suggests that the differences in the results obtained may be related to the methodological approaches used. It is thought that the results of our study may have been affected by the fact that ODD and CD diagnoses were made by a child psychiatrist according to DSM-5 criteria, not by scale results, and that the diagnoses were obtained through medical records. In addition, it is thought that the lack of awareness of families about psychiatric comorbidities associated with DS and the low rates of application to psychiatric outpatient clinics other than the disabled health board may have contributed to these differences.

In this study, it was found that 18.2% of the cases were receiving psychiatric medication, and 5% of these cases were using more than one psychiatric medication. In the retrospective study of 832 children with DS, the rates of psychiatric medication use were reported as 17% for ages 5-11 and 25% for ages 12-21 (23). In the study by Efendi et al., it was reported that 44.4% of the cases required psychiatric medication (17). Cultural background plays a significant role in shaping Turkish families' general attitudes toward psychiatric medications. In Turkey, cultural values such as family honor, religious beliefs, and the social stigma surrounding mental health issues may influence a family's decision to seek or accept psychiatric treatment for their child with Down syndrome (30-33). In this context, the differences in medication use rates observed between the two studies may be attributed to the inclusion of families from different cultural regions of the country, where values such as family honor, religious beliefs, and stigma surrounding mental health issues may vary. Additionally, the differences observed in the rates of psychiatric medication use in the literature may be associated with various factors, such as methodological differences between studies, the low number of outpatient visits for psychiatric comorbidities among individuals with DS in this study, and the less frequent use of psychiatric medications in individuals with DS due to comorbid medical conditions and potential side effects. It is emphasized that there is insufficient data regarding the use of psychiatric medications in children with DS, and that more studies are needed to evaluate the efficacy and tolerability of these medications (3,23).

In this study, no significant difference was found between genders in terms of psychiatric disorder. While there are studies that report no significant differences similar to our results (34,35), some studies have reported significant differences between genders for psychiatric disorders (2,9,19,26). These results may have been due to the methodological differences between studies, such as age, geographic region, and diagnosis. In conclusion, it is thought that gender differences in comorbid psychiatric disorders in DS need to be investigated further.

The results of this study should be interpreted within the context of certain limitations. First and foremost, the retrospective nature of the data, obtained from hospital records, is a significant limitation. This may have led to a potential recording bias. Another limitation of the study is that the results obtained were not compared with those of individuals with other IDs. This could have contributed to a more detailed interpretation of the prevalence of comorbid psychiatric disorders determined. Finally, the fact that the study was conducted at a single center somewhat limits the generalizability of the results.

Despite these limitations, the findings of this study make a significant contribution to the literature by retrospectively examining comorbid psychiatric disorders in children and adolescents with Down syndrome (DS) at a tertiary care center. Due to the limited number of studies in our country regarding psychiatric referral patterns, diagnostic distributions, and treatment approaches in individuals with DS, this research represents an important step toward addressing the data gap in this field. It reveals that children with DS are predominantly evaluated through disability health board applications and that routine psychiatric follow-ups are largely insufficient. In the study, at least one psychiatric disorder was identified in approximately one-fourth of the DS cases, with ADHD being the most

frequently co-occurring diagnosis. Compared to the existing literature, the lower-than-expected prevalence of diagnoses such as ASD and mood disorders highlights the diagnostic challenges and referral tendencies specific to individuals with DS, which is a noteworthy point for clinical practice. The study highlights the importance of regular psychiatric follow-up for children with Down syndrome (DS) and underscores the need to develop early diagnosis and intervention programs. Recommendations such as utilizing disability health board evaluations as opportunities for psychiatric assessment and expanding family education programs stand out as original contributions to clinical practice. In conclusion, this study is a unique piece of research that provides a multidimensional examination of the psychiatric profiles of children and adolescents with DS, compares national data with the existing literature, and offers practical recommendations for clinical application. The findings obtained from this study are of guiding value for the development of policies aimed at meeting the mental health needs of individuals with DS.

5. Conclusion

It has been stated that having a comorbid psychiatric disorder predicts a lower quality of life for individuals with DS (36). It is accepted that psychiatric disorders negatively impact the ability of individuals with intellectual disabilities, including DS, to acquire skills such as daily living skills, adaptive functioning, and academic performance. Given these reasons, psychiatric clinic applications, recognition of comorbid psychiatric disorders, early appropriate interventions, and treatments are considered highly important for the DS population, just as much as applications and check-ups for other medical conditions. Considering that the difficulties experienced by individuals with DS increase with age, and that cognitive decline progresses negatively over time, early diagnosis and intervention for ID and comorbid psychiatric conditions become even more important. To this end, it is important that future studies are planned to be more comprehensive and methodologically robust. It is recommended that future research be conducted with larger sample sizes, incorporating standardized diagnostic tools and including control groups composed of individuals with other intellectual disabilities as well as typically developing peers. Additionally, it is considered essential to plan longitudinal follow-up studies that allow for the monitoring and tracking of clinical records, along with qualitative research exploring the barriers families face in accessing psychiatric services. These planned studies will not only provide a clearer understanding of the specific psychiatric profile of individuals with DS but will also allow for the evaluation of the effectiveness of intervention programs.

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The Dual Burden of Obesity and Asthma: Implications for Respiratory Health and Asthma Control in Adults with Asthma

Obezite ve Astımın İkili Yükü: Astımlı Yetişkinlerde Solunum Sağlığı ve Astım Kontrolü Üzerindeki Etkileri

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Abstract: Asthma and obesity are both highly prevalent conditions with significant public health implications, and obesity has been identified as an aggravating factor in the pathogenesis of asthma. The present study aims to investigate differences in pulmonary function, lung diffusion capacity, functional exercise capacity, and asthma control between obese and non-obese adults with asthma. Fifty asthma patients were divided equally into obese and non-obese groups. Participants performed pulmonary function test (PFT), lung diffusion capacity, six-minute walk test (6MWT), and Asthma Control Test (ACT). No significant differences were found among groups in terms of PFT, lung diffusion capacity, and ACT ($p>0.05$). Significant differences were observed between groups in end-test SpO_2 ($p = 0.045$), baseline and end-test systolic blood pressure ($p = 0.017$ and $p = 0.002$), end-test respiratory rate ($p = 0.002$), perceptions of dyspnea and fatigue at both baseline and end-test (all $p < 0.05$), end-test leg pain ($p = 0.045$), and total walking distance ($p = 0.038$). A moderate and statistically significant negative correlation was found between body mass index (BMI) and the 6MWT distance ($r = –0.592$, $p = 0.028$). This study reveals that functional capacity is significantly impaired in patients with mild asthma, and obesity further aggravates this limitation. These results highlight the need for early functional evaluation and reinforce the importance of incorporating structured exercise and weight control into comprehensive asthma rehabilitation programs.
Keywords: Asthma, Asthma control, Functional exercise capacity, Lung diffusion capacity, Obesity, Pulmonary function test

Özet: : Astım ve obezite, her ikisi de önemli halk sağlığı sorunları olan yaygın durumlardır ve obezitenin astımın patogenezinde kötüleştirici bir faktör olduğu belirlenmiştir. Bu çalışma, astımı olan obez ve obez olmayan yetişkinler arasında akciğer fonksiyonları, akciğer diffüzyon kapasitesi, fonksiyonel egzersiz kapasitesi ve astım kontrolü açısından farklılıkları araştırmayı amaçlamaktadır. Elli astım hastası eşit şekilde obez ve obez olmayan iki gruba ayrılmıştır. Katılımcılara solunum fonksiyon testi (SFT), akciğer diffüzyon kapasitesi testi, altı dakikalık yürüme testi (6DYT) ve Astım Kontrol Testi (AKT) uygulanmıştır. Gruplar arasında SFT, akciğer diffüzyon kapasitesi ve AKT açısından anlamlı bir fark bulunmamıştır ($p>0.05$). Gruplar arasında test sonu SpO_2 ($p = 0.045$), başlangıç ve test sonu sistolik kan basıncı ($p = 0.017$ ve $p = 0.002$), test sonu solunum hızı ($p = 0.002$), hem başlangıç hem de test sonunda nefes darlığı ve yorgunluk algısı (tüm $p < 0.05$), test sonu bacak ağrısı ($p = 0.045$) ve toplam yürüme mesafesi ($p = 0.038$) açısından anlamlı farklar gözlemlenmiştir. Vücut kitle indeksi (VKİ) ile 6DYT mesafesi arasında orta düzeyde ve istatistiksel olarak anlamlı negatif bir korelasyon bulunmuştur ($r = –0.592$, $p = 0.028$). Bu çalışma, hafif astımı olan hastalarda fonksiyonel kapasitenin belirgin şekilde bozulduğunu ve obezitenin bu kısıtlamayı daha da kötüleştirdiğini ortaya koymaktadır. Bu sonuçlar, erken fonksiyonel değerlendirme gerekliliğini vurgulamakta ve yapılandırılmış egzersiz ile kilo kontrolünü içeren kapsamlı astım rehabilitasyon programlarının önemini pekiştirmektedir.
Anahtar Kelimeler: Akciğer Difüzyon Kapasitesi, Astım, Astım kontrolü, Fonksiyonel egzersiz kapasitesi, Obezite, Solunum Fonksiyon Testi

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1. Introduction

Asthma is a heterogeneous, chronic inflammatory airway disease marked by variable airflow obstruction and bronchial hyperresponsiveness. Clinically, it presents with symptoms such as dyspnea, wheezing, chest tightness, and cough, which tend to worsen at night or in the early morning hours (1). The global burden of asthma continues to rise, currently affecting approximately 339 million people, with prevalence rates varying between 1% and 20% depending on geographic and environmental conditions (2).

Obesity has been identified as a significant modifiable factor influencing asthma development and progression. An asthma-obesity phenotype has been described, characterized by more severe symptoms, reduced response to standard therapies and asthma control, and lower quality. Of life, and increased healthcare utilization (3). Mechanistically, obesity contributes to systemic inflammation, airway remodeling, and altered immune responses, all of which may exacerbate asthma severity and frequency of exacerbations (4, 5). Furthermore, obesity-related comorbidities such as gastroesophageal reflux disease, obstructive sleep apnea, and metabolic syndrome may further contribute to the worsening of asthma symptoms (6).

Several studies have reported an inverse association between body mass index (BMI) and pulmonary function, functional capacity, and asthma control, suggesting that increased adiposity negatively affects respiratory health (7, 8). Excess weight has been linked to increased airway resistance, reduced lung compliance, and physical inactivity, which may amplify systemic inflammation and respiratory symptoms (9). However, findings across the literature remain inconsistent regarding the magnitude and nature of these effects, particularly concerning lung diffusion capacity and exercise capacity (10).

Given these ambiguities, further research is warranted to clarify the impact of obesity on key physiological and clinical parameters in asthma. The present study aims to investigate differences in pulmonary function, lung diffusion capacity, functional exercise capacity, and asthma control between obese and non-obese adults with asthma, thereby contributing to a more nuanced understanding of the asthma-obesity phenotype.

2. Materials and Methods

Study design and subjects

This study was conducted as a prospective and cross-sectional study. Fifty patients who met the inclusion criteria among 58 asthma patients referred from the Department of Chest Diseases of a university hospital between January 2024 and June 2024 were included in the study. The criteria for selecting the subjects were as follows: being diagnosed with asthma, age at more than 18 years old, and being able to read and understand written and spoken language. Subjects were excluded if they were unable to complete the tests or exercises due to diagnosed comorbid conditions, had experienced a disease exacerbation in the past 8 weeks, were currently involved in, or had participated in a regular exercise training program within the past year. After the initial assessments, patients were divided into two groups: either the obese (n=25) or the non-obese (n=25) group. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). According to the World Health Organization (WHO) criteria (11), individuals with a BMI of 30 kg/m^2 or higher were classified as obese, while those with a BMI below 30 kg/m^2 were considered non-obese.

The study was conducted by the tenets of the Declaration of Helsinki and approved by the Ethics Committee of Atlas University (date: 09.10.2023, protocol number: 08.07). All participants provided written informed consent.

Outcome measures

Asthma Severity

Asthma severity was assessed using the GINA criteria, which categorize patients into four groups—mild intermittent, mild persistent, moderate persistent, and severe persistent—based on clinical symptoms and spirometric measurements reflecting the degree of airway obstruction (12).

Asthma Control Test

The Asthma Control Test (ACT) is a five-item questionnaire that evaluates asthma control based on symptoms, medication use, and daily functioning. Each item is scored on a 5-point scale, yielding a total score between 5 and 25.

Scores ≥ 20 indicate well-controlled asthma, while scores < 20 suggest poor control (13).

Pulmonary Function Test (PFT)

Pulmonary function was assessed with a spirometer (COSMED Pony FX) following American Thoracic Society (ATS) and European Respiratory Society (ERS) standards (14). Parameters such as forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC ratio, peak expiratory flow (PEF), and forced expiratory flow between 25% and 75% (FEF_{25-75}) were recorded and expressed as percentages of predicted values.

Lung Diffusing Capacity

Lung diffusing capacity for carbon monoxide (DLCO) was measured using the single-breath technique with an automated device (CareFusion, Hochberg, Germany). Participants first breathed normally for 4–5 breaths, then exhaled fully to residual volume. They were then instructed to inhale a test gas mixture rapidly to total lung capacity, hold their breath for 4 seconds, and exhale steadily back to residual volume (15).

Functional Exercise Capacity

The 6-Minute Walk Test (6MWT), recommended by the ATS to evaluate functional exercise capacity (16), was conducted along a 30-meter straight corridor. Participants were instructed to walk as fast as possible at their own pace without running for 6 minutes. Physiological parameters including oxygen saturation (SpO_2), heart rate (HR), systolic (SBP) and diastolic blood pressure (DBP), respiratory rate (RR), dyspnea, fatigue (via the Modified Borg Scale), and leg pain (via the Visual Analogue Scale) were measured before and after the test. The total walking distance covered in 6 minutes was recorded in meters (m).

Statistics and sample size

Statistical analyses were performed using the SPSS 16.0 software package. The normality of data distribution was assessed using the Shapiro-Wilk test. Categorical variables were analyzed using the Chi-square (χ^2) test. For comparisons between groups, the Independent Samples T-test was applied when data followed a normal distribution; otherwise, the Mann-Whitney U test was used. The One-Sample T-test was conducted to compare results with reference values from a healthy population. Correlations between variables were assessed using either Pearson or Spearman correlation tests, depending on data distribution. Correlation strength was categorized based on the correlation coefficient (r) as follows: weak ($r < 0.3$), moderate ($r = 0.3–0.5$), and strong ($r = 0.5–1.0$). A p-value of <0.05 was considered statistically significant.

G*Power 3.1 software was used to calculate the sample size. (University of Düsseldorf, Germany). Sava et al. (17) reported a significant difference in functional exercise capacity between obese and non-obese patients with COPD in which an effect size was 0.843 (342 ± 79 m vs 407 ± 75 m). We calculated that at least 24 participants per group would be required to detect this difference with %80 power and 95% confidence in the study.

3. Results

Fifty-eight asthma patients were assessed for eligibility; a total of eight patients were excluded for not meeting the inclusion criteria or refusing to participate. Twenty-five patients for each group (obese and non-obese) were included in the study (Figure 1). The demographic and clinical characteristics of the patients are shown in Table 1. No significant difference was found between the two groups' demographic and clinical data except for BMI.

There was no statistically significant difference between the two groups in terms of PFT parameters and lung diffusion capacity (Table 2).

The comparison of 6MWT results between obese and non-obese asthma patients is presented in Table 3. A significant difference was observed in end-test SpO_2 levels, with the non-obese group having higher oxygen saturation compared to the obese group ($p = 0.045$). Both baseline and end values of systolic blood pressure (SBP) were significantly higher in the obese group ($p = 0.017$ and $p = 0.002$, respectively). Additionally, the respiratory rate at the end of the test was significantly elevated in the obese group ($p = 0.002$). Perceptions of dyspnea and fatigue were significantly more pronounced in the obese group at both the beginning ($p = 0.004$ and $p = 0.018$, respectively) and at the end of the test ($p = 0.010$ and $p = 0.026$, respectively). End-test leg pain was also significantly higher among obese patients ($p = 0.045$). Furthermore, the total walking distance was significantly shorter in the obese group compared to the non-obese group ($p = 0.038$), indicating reduced functional exercise capacity.

The relationship between BMI and PFT, lung diffusion capacity, and functional exercise

capacity is presented in Table 4. A moderate and statistically significant negative correlation was found between BMI and the 6MWT distance (r = –0.592, p = 0.028).

Table 1. Demographic and clinical characteristics of the groups

	Obese group (n=25)	**Non-obese group** (n=25)	**p value**
Age (years)	42.84±13.13	38.88±12.69	0.218
Gender			
Female Male	17 (68%) 8 (32%)	15 (60%) 10 (40%)	0.556
Body Composition			
Weight (kg)	95.08±21.33	68.53±11.21	**<0.001***
Height (cm)	166.60±8.36	168.28±8.65	0.600
BMI (kg/m2)	34.25±7.52	24.24±3.04	**<0.001***
Disease duration (year)	7.60±9.48	4.84±6.01	0.434
Smoking history (pack-years)	20.85±14.47	19.07±10.29	0.903
Number of asthma attacks in the previous year	1.48±0.65	1.68±0.69	0.270
Drugs, number of users, n (%)			
Inhaled corticosteroids β2 agonists	15 (60%) 6 (24%)	21 (84%) 4 (16%)	0.269
GINA classification			
Mild intermittent Mild persistent Moderate persistent Severe persistent	13 (52%) 5 (20%) 6 (24%) 1 (4%)	14 (56%) 3 (12%) 6 (24%) 2 (8%)	0.833
ACT	20.17±3.78	21.25±2.72	0.930

*Data are presented as mean ± standard deviation or n (%). *$p \leq 0.05$.*
Abbreviations: BMI: Body mass index; cm: centimeter; kg: kilogram., GINA: Global Initiative for Asthma; ACT: Asthma Control Test

Table 2. Comparison of pulmonary function and lung diffusion capacity between the groups

	Obese group (n=25)	**Non-obese group (n=25)**	**p value**
Pulmonary function			
FVC (% predicted)	91.80±15.49	90.96±11.96	0.831
FEV_1 (% predicted)	84.52±13.30	84.72±13.62	0.763
FEV_1 / FVC (%)	78.35±8.06	79.01±9.20	0.808
PEF (% predicted)	75.28±15.81	72.64±17.35	0.884
FEF_{25-75} (% predicted)	64.80±26.09	69.92±28.69	0.515
Lung Diffusion Capacity	5.68±1.93	5.72±2.13	0.907
DLCO (% predicted)	81.68±16.66	79.04±15.61	0.554

*Data are presented as mean ± standard deviation or n (%). *$p \leq 0.05$.*
Abbreviations: FVC: forced vital capacity; FEV_1: forced expiratory volume in 1s; PEF: peak expiratory flow. FEF_{25-75} : forced expiratory flow between 25% and 75; DLCO: diffusing capacity for carbon monoxide.

Table 3. Comparison of 6MWT results between the groups

	Time	Obese group (n=25)	Non-obese group (n=25)	p value
HR (beats/min)	**Rest**	94.40±14.86	89.92±14.09	0.203
	End	116.56±22.07	111.48±18	0.197
SpO_2 (%)	**Rest**	97.44±1.28	96.48±1.89	0.400
	End	95.92±4.74	96.68±2.86	**0.045***
SBP (mmHg)	**Rest**	12±0.57	11.40±0.91	**0.017***
	End	13.08±1.32	12.04±1.48	**0.002***
DBP (mmHg)	**Rest**	8.60±1.29	8.16±1.34	0.080
	End	9.68±1.34	8.92±1.15	0.058
RR (breaths/min)	**Rest**	15.76±1.92	14.92±1.70	0.099
	End	21.60±3.08	19.20±2.85	**0.002***
Dyspnoea (M. Borg)	**Rest**	0.35±0.61	0.010±0.020	**0.004***
	End	2.17±1.65	0.98±0.95	**0.010***
Fatigue (M. Borg)	**Rest**	0.27±0.65	0.01±0.01	**0.018***
	End	2.33±1.93	1.15±1.45	**0.026***
Leg pain (VAS)	**Rest**	0.01±0.01	0	0.153
	End	1.12±0.08	0.42±0.94	**0.045***
6MWT distance (m)		414.16±71.81	459.52±67.86	**0.038***

*Data are presented as mean ± standard deviation or n (%). *$p \leq 0.05$.*
Abbreviations: HR: heart rate; min: minute; SpO_2: Peripheral Capillary Oxygen Saturation; SBP: systolic blood pressure; DBP: diastolic blood pressure; RR: respiratory rate; M. Borg: Modified Borg Scale; VAS: Visual Analogue Scale; 6MWT: 6 minute walk test; m: meter.

Table 4. Correlation of the BMI with pulmonary function, lung diffusion capacity, and functional exercise capacity

	BMI	
	r	**p**
Pulmonary function		
FVC (% predicted)	-0.064	0.659
FEV_1 (% predicted)	-0.077	0.594
FEV_1/FVC (%)	-0.098	0.497
PEF (% predicted)	0.057	0.692
FEF_{25-75} (% predicted)	-0.156	0.279
Lung diffusion capacity		
DLCO (% predicted)	0.199	0.165
Functional exercise capacity		
6MWT distance (m)	-0.592	**0.028***

*Abbreviations: BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1s; PEF: peak expiratory flow. FEF_{25-75} : forced expiratory flow between 25% and 75; DLCO: diffusing capacity for carbon monoxide; 6MWT: 6 minute walk test; m:meter. *$p \leq 0.05$.*

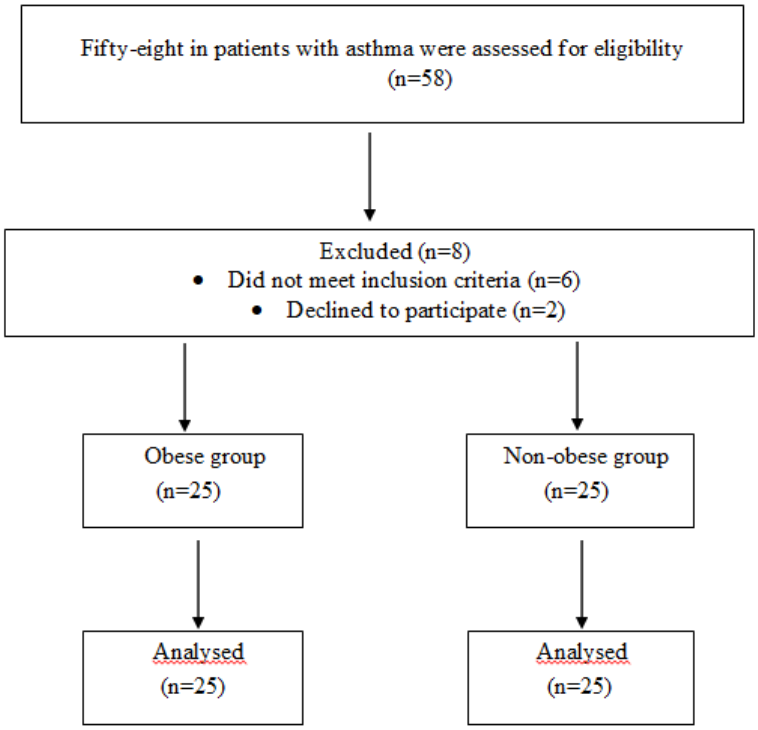

Figure 1. Flow diagram of study design.

4. Discussion

This study set out with the aim of investigating the impact of obesity on pulmonary function, lung diffusion capacity, functional exercise capacity, and asthma control in adults with asthma, involving 50 participants aged 18–65 years, including 25 obese and 25 non-obese individuals. Significant differences—favoring the non-obese group—were identified between the groups in several 6MWT variables. Specifically, end-test SpO_2 levels were significantly lower in obese individuals compared to non-obese individuals. Both baseline and end-test systolic blood pressure (SBP) values were significantly higher in the obese group. The respiratory rate at the end of the test, as well as perceived dyspnea and fatigue at both the beginning and end of the test, were also significantly elevated in obese participants. In addition, leg pain at the end of the test was greater, and total walking distance was shorter in the obese group. These findings collectively indicate impaired functional performance and increased perceived exertion in obese asthma patients.

Obesity is known to negatively affect the respiratory system, primarily through the mechanical compression resulting from increased adipose tissue in the thoracic and abdominal regions. This mechanical burden can impair the mobility of the chest wall and diaphragm, subsequently reducing lung volumes and respiratory capacity (3). In patients with asthma, excess body weight may further compromise diaphragmatic function. Previous studies have demonstrated that obesity leads to both a reduction in diaphragm muscle fiber number and size, as well as increased pulmonary blood flow. Consequently, diaphragmatic activity is elevated in obese individuals compared to those of normal weight, reflecting a compensatory mechanism due to inefficient ventilation (18). Another mechanism through which obesity may influence asthma involves changes in airway smooth muscle. The increase in fat mass may alter respiratory mechanics and impair contractile properties of airway muscles, leading to disrupted actin-myosin interactions, weakened respiratory muscle strength, and compromised pulmonary function (19).

However, the literature presents conflicting evidence on whether obesity further impairs pulmonary function in individuals with asthma. Several studies have reported a negative correlation between increased BMI and parameters such as functional residual capacity (FRC) and expiratory reserve volume (ERV) in patients with asthma (20). Rastogi et al. observed that normal-weight individuals with

asthma had significantly higher predicted values of FEV_1, FEV_1/FVC, and $FEF_{25–75}$ compared to their obese counterparts (21). Similarly, studies have shown negative correlations between BMI and predicted FVC and FEV_1/FVC values in mildly and moderately obese individuals, reinforcing these findings (22). Schachter et al., in a study involving 1971 healthy participants, found that obese individuals had significantly lower FEV_1 and FVC values compared to those with normal BMI (23). These results were further supported by Steier et al., who reported statistically significant differences in FEV_1, FVC, and FEV_1/FVC between obese and non-obese participants (24). In contrast, some studies have reported no significant changes in pulmonary function following weight loss in obese asthmatic individuals (25), and others found no difference in PFT parameters between obese and non-obese asthmatic patients (26). Ghabashi et al. reported no correlation between BMI and any PFT parameter (27). In our study, consistent with these findings, no significant differences were found in any pulmonary function parameters between the obese and non-obese asthmatic groups. Pulmonary function decline in patients with asthma is often associated with disease severity, symptom burden, and poor asthma control (28). Grzelewska-Rzymowska et al. reported that well-controlled asthma was associated with FEV_1 values remaining within the expected range, whereas disease duration longer than 20 years, particularly in cases of moderate persistent asthma, was linked to a decline in pulmonary function (29). In our study, consistent with these findings, no significant differences were found in any pulmonary function parameters between the obese and non-obese asthmatic groups. This result may be explained by the fact that the majority of participants in both the obese (52%) and non-obese (56%) groups were classified as having mild intermittent asthma. Additionally, similar ACT scores and comparable numbers of asthma exacerbations in the past year between the two groups may have contributed to the absence of statistically significant differences. In addition to similar asthma severity and control scores, no significant differences were observed between the obese and non-obese groups in smoking history, number of asthma attacks in the previous year, or medication use (including inhaled corticosteroids and β2 agonists). This clinical similarity likely contributed to the absence of differences in pulmonary function and asthma control. Supporting these findings, previous studies have emphasized that asthma-related outcomes such as lung function and symptom control are more strongly influenced by disease severity and treatment adherence than by BMI alone, particularly in populations with similar medication regimens and exacerbation history (30,31). Moreover, asthma severity classification based on GINA criteria did not differ significantly between the obese and non-obese groups, as shown in Table 1. This clinical similarity likely contributed to the comparable pulmonary function outcomes observed in our study.

DLCO plays a significant role in the early diagnosis of various pulmonary diseases, including emphysema, cystic fibrosis, pulmonary embolism, and COPD, where it is typically reduced. Although its primary use in asthma is limited, DLCO measurements can be particularly helpful in differentiating asthma from COPD (32). In COPD patients, especially those with emphysema, DLCO values are often decreased, whereas in asthma, values are generally normal or even increased in early stages. This increase has been linked to increased pulmonary blood flow and elevated cardiac output, commonly seen in asthma. However, in elderly patients with asthma or in severe disease, ventilation-perfusion mismatching may lead to decreased DLCO values (33). While some clinical studies have reported increased DLCO in asthma and obesity, others have presented contradictory results (34). While DLCO is typically decreased in patients with severe obstruction compared to those with mild obstruction, other studies found no significant differences in DLCO across groups with varying degrees of obstruction (35). Viegi et al. observed elevated DLCO values in individuals with FEV_1/FVC ratios between 65% and 75%, suggesting only a weak association between DLCO and the degree of airway obstruction (36). Schultz et al. reported decreased DLCO in asthmatic patients with FEV_1 below 40%, supporting the notion that DLCO remains largely unaffected in mild to moderate obstruction (37). Similarly, in a study by Kanat et al., which included 91 asthmatic patients and 47 healthy controls without any comorbid conditions affecting DLCO or smoking history, no statistically significant difference in DLCO was found between the groups (38). In line with the existing literature, our study also found no significant difference in DLCO between the obese and non-obese asthma groups. A possible explanation for this result is that the majority of patients in both groups were classified as having mild intermittent asthma and exhibited only mild airway obstruction (mean FEV_1 % predicted: 84.52 in the obese group vs. 84.72 in the non-obese group), suggesting that DLCO remains stable in cases of mild disease severity and mild airflow obstruction.

Previous literature has demonstrated that individuals with asthma generally exhibit lower functional exercise capacity compared to healthy controls. This

limitation is likely due to exercise-induced bronchospasm, heightened dyspnea perception, medication side effects, asthma-related symptoms, kinesiophobia, and subsequent physical inactivity (39). In our study, functional exercise capacity was assessed using the 6MWT, a validated and routinely applied field test in asthma populations 40). The mean 6MWT distance was 414.14 m in the obese group and 459.52 m in the non-obese group. Notably, the literature reports an average 6MWT distance of approximately 627.8 m in healthy adults aged 18–70 years (41). Statistical analysis confirmed that both asthma groups demonstrated significantly lower than normative values 6MWT distances compared to healthy norms (One-sample t-test; $p < 0.001$). Recent findings suggest that overweight and obese adults are more likely to identify exercise as an asthma trigger and therefore engage in avoidant behaviors more frequently than normal-weight individuals (42). A study reported a stepwise decline in 6MWT distances according to weight classification: 613.4 ± 45.9 m in underweight, 532.3 ± 62.7 m in obese, and 462.8 ± 68.2 m in morbidly obese participants. These differences were statistically significant between underweight individuals and the other two groups (43). In line with these findings, our study revealed a statistically significant difference in 6MWT distances between obese and non-obese asthma groups. Supporting prior studies, our results suggest that BMI may be a primary determinant of reduced functional capacity in asthmatic individuals (44, 45). For instance, Santuz et al. found no association between BMI and asthma severity or FEV_1, but did identify a correlation between BMI and functional capacity in obese asthma patients (46). A lack of significant association between PFT and 6MWT performance in our study may be explained by factors such as the low number of asthma exacerbations in the past year and the classification of patients within the partially controlled asthma category based on ACT scores. Additionally, the homogeneity in medication uses and clinical characteristics between groups enabled a more accurate assessment of the independent effect of obesity on functional capacity, separate from PFT parameters.

In the context of asthma, obesity is associated with a complex, multifactorial phenotype involving diverse pathophysiological mechanisms and subphenotypes (47). Numerous physiological alterations linked to obesity can negatively influence cardiopulmonary responses during physical activity. Studies consistently report that obese individuals exhibit greater increases in heart rate and blood pressure during exercise, as well as heightened perceptions of fatigue and dyspnea, contributing to lower functional capacity compared to non-obese individuals (48). One study reported a positive correlation between BMI and both pre- and post-test SBP and HR during the 6MWT. Individuals with the highest BMI experienced more pronounced fatigue and dyspnea and exhibited resting heart rates approximately 12% higher than those with lower BMI. These participants also showed greater increases in perceived exertion and fatigue (49).

Our findings further confirmed that resting HR values were significantly and consistently elevated in the obese asthma group relative to their non-obese counterparts. Lindgren et al. further emphasized the prognostic implications of elevated resting HR and SBP, suggesting these variables, when coupled with high BMI and low cardiorespiratory fitness, may indicate an increased risk of future heart failure and all-cause mortality (50). The interaction between higher BMI and reduced 6MWT performance has been reinforced by several studies, which attribute this reduction to factors such as a sedentary lifestyle, and increased perception of fatigue, dyspnea, and pain during walking (51). Similar physiological limitations have also been reported in studies involving obese patients with chronic obstructive pulmonary disease (COPD), indicating shorter walking distances compared to patients with normal BMI during exercise testing (52). Further supporting these findings, Seres et al. (53) reported that decreased exercise capacity in morbidly obese individuals was associated with increased oxygen consumption, heart rate, systolic blood pressure, and minute ventilation. They concluded that the increased energy demand required to mobilize excess body mass may underlie the reduced physical performance in this population (53). Likewise, another study demonstrated that even well-controlled asthmatic individuals with obesity had lower functional capacity and greater leg fatigue compared to normal-weight asthmatics, likely due to the elevated metabolic demand required to move heavier limbs during activity (54). Although research on oxygen saturation changes during exercise in obese asthmatic individuals is limited, studies in healthy populations provide relevant insight. For instance, recent research in healthy adults reported that those with higher BMI experienced greater declines in oxygen saturation following the 6MWT compared to those with normal BMI (55). Additionally, a study involving children aged 5–9 years showed that overweight participants had higher SBP and lower oxygen saturation both at

rest and end-6MWT compared to their normal-weight counterparts (56). Consistent with the literature, the present study revealed statistically significant differences between obese and non-obese asthma groups in multiple post-exercise physiological parameters. These included lower end-of-test SpO_2, higher pre- and post-test SBP, elevated end-test RR, as well as notably greater perceived dyspnea, more intense leg fatigue, and significantly increased leg pain in obese participants. These findings support prior research indicating that obesity contributes to an altered physiological and perceptual response to exercise, ultimately impairing functional capacity in individuals with asthma.

An increasing number of studies suggest a potential link between obesity and asthma, although the exact nature of this relationship remains unclear. Several studies have demonstrated that higher BMI is linked to poorer asthma control, increased symptom burden, and greater medication use, independent of asthma severity (57-59). Additionally, Boulet and Franssen found reduced responsiveness to inhaled corticosteroids in obese asthmatic patients compared to their non-obese counterparts (60). In contrast, our study found no significant difference in asthma control between obese and non-obese groups. One likely explanation for this discrepancy is the lower prevalence of class II and III obesity in our study population. In addition to comparable ACT scores, both groups also shared similar asthma severity profiles, with no statistically significant difference in GINA-based asthma staging. Supporting our findings, multiple studies have also reported no association between obesity and asthma control, severity, or symptom expression (61-63). These include both cross-sectional and cohort studies assessing symptom frequency, medication use, exacerbations, and pulmonary function. One possible explanation is that similar clinical characteristics across BMI groups, such as disease severity, treatment regimen, and exacerbation history, may diminish observable differences. These factors likely minimized confounding effects and enabled a clearer interpretation of obesity's impact on asthma control in a relatively homogeneous sample.

Our study has several limitations. First, body composition was assessed solely through height and weight measurements, without evaluating more specific parameters such as basal metabolic rate, body fat percentage, or fat mass. This limited the exploration of more nuanced relationships between obesity and asthma-related outcomes. Second, although previous studies have demonstrated that physical activity level is a significant determinant of pulmonary function, functional capacity, and asthma control, we did not assess participants' physical activity levels using either subjective or objective methods. The absence of this data may have prevented us from accounting for an important confounding variable that could influence the study outcomes. Subsequent research could incorporate body composition assessments, such as BIA or DEXA, to better distinguish fat and lean mass. Similarly, the use of wearable devices or accelerometers may allow for objective monitoring of physical activity and its relationship to asthma outcomes.

5. Conclusion

This study demonstrates that even in patients with mild asthma, functional capacity is significantly reduced compared to healthy individuals, and the presence of obesity further exacerbates this impairment. Given the increasing prevalence of obesity worldwide, these findings underscore the importance of early functional assessment and the integration of structured exercise and weight management into asthma rehabilitation. Although current guidelines emphasize the role of exercise in asthma care, our results highlight the need for a more comprehensive approach that addresses both respiratory limitations and obesity-related physical constraints. We believe this study raises clinical awareness about the dual burden of asthma and obesity and supports the development of tailored rehabilitation strategies. Further research is warranted to explore how varying degrees of obesity influence respiratory health and asthma control, ideally through studies with larger and more diverse populations to enhance the generalizability of findings and deepen our understanding of this complex interaction.

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Patients with Chronic Myeloid Leukemia Diagnosed with Predominant Thrombocytosis without Marked Leukocytosis: Case Series

Belirgin Lökositoz Olmaksizin Baskin Trombositozla Tani Alan Kronik Miyeloid Lösemili Hastalar: Vaka Serisi

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Abstract: Chronic myeloid leukemia (CML) is a clonal hematopoietic pluripotent stem cell disease characterized by excessive and uncontrolled proliferation of myeloid lineage cells. Platelet count is increased in more than half of patients and the appearance of platelets is variable. When patients present with predominant thrombocytosis without marked leukocytosis, they should be tested for the Philadelphia chromosome or (breakpoint cluster region- Abelson) BCR-ABL to distinguish cases of CML. In this study, the data of 215 patients diagnosed with CML between 2010 and 2023 were retrospectively evaluated. The study enrolled patients aged ≥18 years with leukocyte count <40 x109/L and platelet count >500 x109/L at the time of diagnosis. While investigating the etiology of predominant thrombocytosis and no significant leukocytosis, 13 patients diagnosed with CML were identified. The proportion of these patients among all patients with CML was 6%. This study showed that CML should be considered in the differential diagnosis of patients with predominant thrombocytosis without marked leukocytosis. In these patients, the Ph chromosome should definitely be checked before ET is diagnosed. Making a correct diagnosis in this patient group is important in order to start tyrosine kinase inhibitor treatment before it progresses to accelerated or blastic phases.
Keywords: Chronic Myeloid Leukemia, Myeloproliferative Disorders, Essential Thrombocythemia, Thrombosis, Tyrosine Kinase İnhibitor

Özet: Kronik miyeloid lösemi (KML), miyeloid seri hücrelerinin aşırı ve kontrolsüz çoğalmasıyla karakterize klonal hematopoietik pluripotent bir kök hücre hastalığıdır. Hastaların yarısından fazlasında trombosit sayısı artmıştır ve trombositlerin görünümü değişkendir. Hastalarda belirgin lökositoz olmaksızın baskın trombositoz mevcutsa, KML vakalarını ayırt etmek için Philadelphia kromozomu veya (breakpoint cluster region -Abelson) BCR-ABL testi yapılmalıdır. Bu çalışmada 2010-2023 yılları arasında KML tanısı almış 215 hastanın verileri retrospektif olarak değerlendirildi. Çalışmaya tanı anında lökosit sayısı <40 x109/L ve trombosit sayısı >500 x109/L olan ≥18 yaş hastalar dahil edildi. Belirgin lökositoz olmadan baskın trombositozla tetkik edilirken KML tanısı alan 13 hasta belirlendi. Bu hastaların tüm KML hastaları içindeki oranı %6 bulundu. Bu çalışma, belirgin lökositoz olmaksızın baskın trombositozu olan hastaların ayırıcı tanısında KML'nin düşünülmesi gerektiğini göstermektedir. Bu hastalarda ET tanısı konulmadan önce mutlaka Ph kromozomuna bakılmalıdır. Bu hasta grubunda doğru tanı koymak, hastalığın akselere veya blastik faza ilerlemeden tirozin kinaz inhibitörü tedavisine başlanması açısından önemlidir.
Anahtar Kelimeler: Kronik Miyeloid Lösemi, Miyeloproliferatif Hastalık, Esansiyel Trombositoz, Tromboz, Triozin Kinaz İnhibitörü

Ethics Committee Approval: The study was approved by Eskişehir Osmangazi University Noninterventional Clinical Research Ethical Committee (Decision no: 37, Date: 21.02.2023).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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1. Introduction

Chronic myeloid leukemia (CML) is a clonal hematopoietic pluripotent stem cell disease characterized by excessive and uncontrolled proliferation of myeloid lineage cells(1). It is among the myeloproliferative disorders (MPDs), which are clonal disorders of myeloid origin, including essential thrombocythemia, polycythemia vera and myelofibrosis(2). The Philadelphia (Ph) chromosome, an abnormal chromosome 22 resulting from a reciprocal translocation [t(9;22)q34;q11)] leading to the fusion of the Abelson (ABL) protooncogene on chromosome 9 and the breakpoint cluster region (BCR) gene on chromosome 22, is detected in approximately 95% of CML cases(3). The resulting product of this chimeric gene is a protein with tyrosine kinase activity and a molecular weight of 210 kDa (p210) and is responsible for the development of the leukemic phenotype in CML. Depending on the cleavage sites in the BCR and ABL genes, different BCR-ABL fusion transcripts are formed. The most well-known are the p190, p210, and p230 fusion transcripts.

The annual incidence for CML is 1-2/100,000 and accounts for 15-20% of adult leukemias. It is more common in men than women (Male/Female=3/2) and can develop at any age, although patients are often diagnosed in their 50s and 60s(4).

The clinical course of the disease has 3 stages. These three stages are the chronic stage, which represents the majority of patients at the time of diagnosis, the accelerated stage, which can be observed when the disease is left untreated and allowed to run its natural course or when there is no response to treatment, and the blastic stage, which indicates disease progression. The diagnosis is usually made by leukocytosis detected during routine tests and 20-40% of these patients are asymptomatic at the time of diagnosis. The most common symptoms are weakness due to anemia, decreased exercise capacity, abdominal swelling due to splenomegaly, pain, and rapid satiety(5).

In CML, leukocytosis is the typical finding at the time of diagnosis and there is a picture of granulocytosis in which all stages of granulocytic series maturation from blasts to fragmented neutrophils can be observed. The basophil count is always elevated and can be detected in the early stages of the disease even before the leukocyte count increases. Platelet count is increased in more than half of patients and the appearance of platelets is variable(6).

When patients present with isolated thrombocytosis, they should be tested for the Philadelphia chromosome or BCR-ABL to distinguish cases of CML(7). Literature includes a few case reports of patients with CML presenting with isolated thrombocytosis at the time of diagnosis(8,9). This study reviews the clinical and laboratory findings, treatment and prognosis of patients with CML diagnosed with isolated thrombocytosis without significant leukocytosis.

2. Materials and Methods

In this study, the data of 215 patients diagnosed with CML between 2010 and 2023 in Eskişehir Osmangazi University, Department of Internal Medicine, Division of Hematology were retrospectively evaluated. Demographic and clinical properties of the patients were retrieved from patient files and hospital information record system. The study enrolled patients aged ≥18 years with leukocyte count <35 $x10^9$/L and platelet count >500 $x10^9$/L at the time of diagnosis. Overall survival (OS) was defined as the time from the date of initial diagnosis to the date of last visit or death.

Approval for the study was obtained from the Eskişehir Osmangazi University Non-Interventional Ethics Committee with the number 21.02.2023-37.

Statistical Analysis

The study evaluated the patients' age at diagnosis, bone marrow pathology, hemogram results, lactate dehydrogenase, cytogenetic analysis and polymerase chain reaction (PCR) results from bone marrow aspiration at diagnosis, Janus Kinase-2 (JAK-2), calreticulin (CALR), myeloproliferative leukemia (MPL), comorbid diseases, SOKAL, HASFORD, ELTS scores, history of thrombosis and bleeding, PCR results at 3 months, 6 months and 12 months, treatments and clinical responses.

Results were analyzed using SPSS (Statistical Package for Social Sciences) for Windows 24 program. For descriptive statistics, numerical data were expressed as median (min-max) and categorical data were expressed as number and percentage.

3. Results

After exclusion, 13 patients who were diagnosed with CML while being examined for isolated thrombocytosis without significant leukocytosis were detected. The proportion of these patients

among all patients with CML was 6%. The mean age at diagnosis was 53.5 (26-79) years. Six (46%) patients were over 60 years of age at diagnosis. Of the patients, 84% (n=11) were female. Female to male ratio was 11:2.

One patient (7%) was examined for hematuria and fever on admission. Twelve patients (93%) were asymptomatic. Three patients (23%) had mild splenomegaly, while 77% had none. No thrombosis was detected on admission. The mean platelet count was 1068x10^9/L (582-2392 x10^9/L). Four patients (30%) had a platelet count above 1000 x10^9/L. Six patients (46%) had anemia. The lowest hemoglobin value was 10.3 g/dL. The mean leukocyte count was 20.4 x10^9/L (8.0-31.2 x10^9/L). Eight patients (61%) had elevated lactate dehydrogenase (LDH) levels at the time of diagnosis. Table-1 shows the clinical and demographic properties and laboratory results of the patients.

All patients (100%) were positive for BCR-ABL translocation and all had chronic phase CML at the time of diagnosis. Eight patients (61%) were tested for JAK-2 mutation and all of them were negative. No patient was tested for CALR and MPL gene mutations. Cytogenetic analysis was performed on 11 patients at diagnosis, but it was observed that metaphase plates could not be obtained in 3 of these cases. Cytogenetics study showed Ph chromosome t(9,22) in 7 patients (53%). In one patient, the cytogenetic results were normal. Of the 13 patients tested for t(9,22) translocation by fluorescence in situ hybridization (FISH), 12 (92.3%) were positive.

The mean t(9,22) positivity rate by FISH in bone marrow was 80.63% (22.44-99.5%). All patients were tested for p210 by PCR. p210 results were positive in 7 patients. Results of 6 patients could not be reached. One patient had normal FISH and normal cytogenetics. This patient was diagnosed with CML due to p210 positivity.

Bone marrow biopsy results were available for 11 patients (Table-1). The risk score results are shown in Table-1 and no significant correlation was shown Sokal and Hasford risk scores and OS (p>0.05). However, low ELTS score was associated with increased OS (p=0.017) (Figure-1).

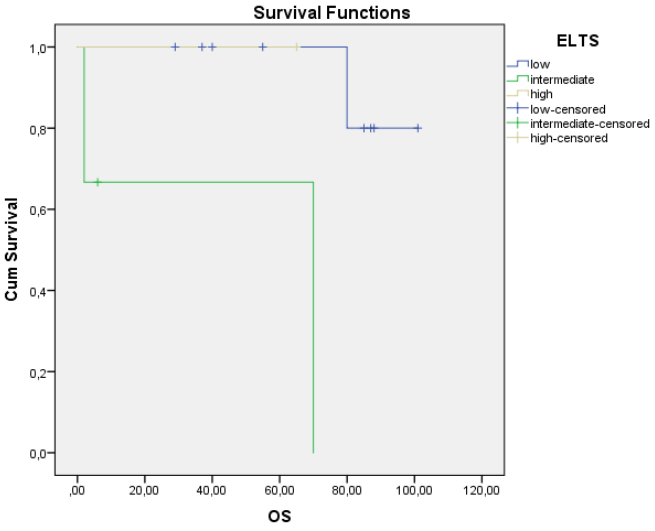

Figure-1. Low ELTS score was associated with increased OS (p=0.017).

Until the results of genetic tests are available five patients (38%) received hydroxyurea treatment. One patient was initially misdiagnosed with ET and briefly received anagrelide prior to confirmation of CML. Upon diagnosis of CML, all patients were started on imatinib. Three patients (23%) did not respond to imatinib treatment at the end of 12 months. Two of them were switched to nilotinib and one patient was switched to dasatinib. Bosutinib was started in one of the patients on nilotinib because of loss of response at 5 years of nilotinib treatment. At the 2nd year of dasatinib treatment, the patient developed plerual effusion and was switched to nilotinib. There were no other patients with complications. No patient developed accelerated or blastic phase CML during follow-up. None of the patients underwent allogeneic stem cell transplantation.

The mean follow-up period was 57.3 months (2-101 months). Ten patients (76%) were alive and followed for chronic phase CML. Three patients (23%) died during the chronic phase. One patient died due to COVID pneumonia and one patient died due to urinary tract infection. The cause of death of the third patient was not available. All deceased patients were >70 years old (72-79 years).

Table-1: Clinical and laboratory characteristics of patients

Patient#	Age	Gender	Symptom	SM	PLT ($x10^9$/L)	Hgb (g/dL)	WBC ($x10^9$/L)	NEU# ($x10^9$/L)	LYMP# ($x10^9$/L)	EOS# ($x10^9$/L)	BAS# ($x10^9$/L)	Diagnostic cytogenetics	Diagnostic Ph	Diagnostic p210 (%)
1	72	E	A	None	1418	13.8	14.40	10.2	3	0.4	0.1	46,XY,t(9;22)(q34;q11)[16]	22.44%	NA
2	77	K	A	Yes	734	12.7	18.22	8.88	5.31	0.6	2.52	46,XX,t(9;22)(q34;q11)[15]	93.89%	16.529
3	45	K	A	None	2392	10.9	12.8	9.7	2.1	0.4	0.1	46,XX,t(9;22)(q34;q11)[20]	55%	NA
4	29	K	Hematuria, fever	Yes	1669	11.1	27.23	19.47	5.84	0.46	0.99	No plaque	99.50%	100
5	66	E	A	None	824	16.8	27.6	18.6	3.1	1.2	4.2	46,XY,t(9;22)(q34;q11)[11]	99.50%	195.17
6	26	K	A	None	582	11.9	24.37	19.01	3.79	0.07	0.43	NA	99%	NA
7	63	K	A	Yes	892	10.3	24.58	20.6	1.8	0.1	0.7	46,XX,t(9;22)(q34;q11)[5]	94.33%	NA
8	39	K	A	None	733	11.2	31.2	27.6	1.5	1.7	0.2	46,XX,t(9;22)(q34;q11)[20]	95.67%	200
9	75	K	A	None	615	13.6	21.7	16.9	3	0.3	0.3	NA	41.8%	NA
10	45	K	A	None	772	12.9	8	4.5	2.2	0.3	0.4	46,XX,t(9;22)(q34;q11)[13]	85.87%	51.41
11	79	K	A	None	1477	11.1	15.1	12.9	1.2	0.7	0.8	No plaque	99.50%	17.64
12	43	K	A	None	895	12.2	26.8	20.7	3.6	0.6	1.3	46,XX[7]	Negative	NA
13	37	K	A	None	888	13.5	13.9	9.69	2.87	0.24	0.16	No plaque	99.50%	100

Table-1: Clinical and laboratory characteristics of patients (continued)

Patient#	Month 3 p210 (%)	Month 6 p210 (%)	Month 12 p210 (%)	Bone Marrow	SOKAL	HASFORD	ELTS	Treatment	Complication	Follow up (months)	Result
1	NA	NA	NA	Normocellular, megakaryostic hyperplasia, small and dysplastic megakaryocytes	1.7 H	782.24 I	1.27 L	imatinib/dasatinib/nilotinib	pleural effusion with dasatinib	80	R/D
2	NA	NA	NA	Hypercellular, myeloid and megakaryocytic hyperplasia, M/E:10/1, small megakaryocytes, stage 1 reticulin fibrosis	1.1 I	1048.79 I	1.68 I	imatinib	None	6	R/A
3	0.158	0.36	0.953	megakaryocytic hyperplasia, small megakaryocytes, stage 1 reticulin fibrosis	5.3 H	1223.63 I	0.49 L	HU/anagralide/imatinib/nilotinib/bosutinib	None	101	R/A
4	100	100	23,54 *	Hypercellular, myeloid and megakaryocytic hyperplasia, stage 1 reticulin fibrosis	1.8 H	1453.71 I	0.50 L	HU/imatinib	None	37	R/A
5	57.12	3.066	0.01	Hypercellular, megakaryocytic hyperplasia, small megakaryocytes, stage 2 reticulin fibrosis	1.1 I	978.46 I	2.74 H	HU/imatinib	None	65	R/A
6	NA	NA	NA	NA	0.5 L	12.39 L	0.58 L	imatinib	None	29	R/A
7	36.03	40.54	56.54	Hypercellular, granulocytic and megakaryocytic hyperplasia, stage 1 reticulin fibrosis	1.2 I	762.99 L	1.18 L	HU/imatinib/nilotinib	None	88	R/A
8	4.53	2.283	0.34	Hypercellular, granulocytic and megakaryocytic hyperplasia, small megakaryocytes	0.8 I	302.89 L	0.75 L	imatinib	None	87	R/A
9	NA	NA	NA	NA	1.0 I	728.55 L	1.57 İ	imatinib	None	70	R/D
10	0.06	Negative	Negative	Hypercellular, granulocytic and megakaryocytic hyperplasia, small megakaryocytes, pleomorphic megakaryocytes	0.7 L	348.45 L	0.69 L	imatinib	None	55	R/A
11	NA	NA	NA	Hypercellular, granulocytic and megakaryocytic hyperplasia, small megakaryocytes, pleomorphic megakaryocytes	2.0 H	899.41 I	1.57 I	HU/imatinib	None	2	D**
12	6.780	30.93	0.10	Granulocytic hyperplasia	0.8 I	298.89 L	0.63 L	imatinib	None	85	R/A
13	Negative	Negative	Negative	Suboptimal	0.7 L	70.21 L	0.56 L	imatinib	None	40	R/A

** The fourth patient did not receive imatinib treatment regularly and remained BCR-ABL translocation positive until year 1. During follow-up, the patient turned negative after starting to take medication regularly.*

***Patient died of urosepsis at 2 months of treatment before response could be evaluated.*

PLT: Platelet count, Hgb: Hemoglobin, WBC: Leukocyte count, NEU#: Neutrophil count, LYMP#: Lymphocyte count, EOS#: Eosinophil count, BAS#: Basophil count, Ph: Philadelphia chromosome, A: Asymptomatic, NA: Not available, SM: Splenomegaly, H: High, I: Intermediate, L: Low, HU: Hydroxyurea, R/A: In

4. Discussion

Leukocytosis is a typical finding in patients with CML and they are usually diagnosed with leukocyte counts higher than $100x10^9$/L(11). Thrombocytosis is a common finding at the time of diagnosis of CML, but rarely exceeds 1000×10^9/L(5). In CML, the bone marrow is hypercellular and the myeloid to erythroid cell ratio is increased in favor of the myeloid series. Reticulin fibrosis may be seen in the bone marrow(12). Megakaryocytes are typically hypolobulated nuclei and smaller than normal(13).

In this study, the proportion of patients diagnosed with predominant thrombocytosis was 6%, the mean platelet count was $1068x10^9$/L ($582\text{-}2392x10^9$/L). No thrombotic events were observed. In this study, similar to the literature, megakaryocytes were small in size in seven patients (63%) and hypolobulated in five (45%) in addition, pleomorphic megakaryocytes were detected in two (18%) patients. Reticulin fibrosis was observed in five patients (45%). Two patients (18%) showed signs of dysplasia.

In the review by Findakly and Arslan, the mean age was 40.5 years and the mean platelet count was $1923x10^9$/L ($584\text{-}8688\ x10^9$/L). 50% of patients were asymptomatic. Women accounted for 65%. Splenomegaly was found in 13.3% of patients(8). Megakaryocytes in bone marrow were 71.4% small, 21.4% pleomorphic and 7.1% dysplastic. It is known that CML diagnosed with isolated thrombocytosis is more common in young people and in women(10). In this study, splenomegaly was more common in women and the rate of splenomegaly was similar to the literature. However, in contrast to the literature, the proportion of elderly patients was higher in this study. The mean age was 53.5 years (26-79) and 46% of patients were older than 60 years at diagnosis. The proportion of asymptomatic patients in our study was also high (93%).

Hydroxyurea may be used in the treatment of these patients with very high platelet values ($>1000x10^9$/L). Platelet apheresis can be performed in patients showing significant symptoms of leukostasis. Imatinib, nilotinib, dasatinib may be preferred as first-line treatment agents(14). Hydroxyurea treatment was given to five patients in this study. Imatinib was started in all patients after Ph chromosome was detected positive. In patients unresponsive to imatinib treatment, nilotinib and dasatinib were used. All the patients in the study were followed up for chronic phase CML. No patient progressed to accelerated phase or blastic phase.

Among the risk scores, the ELTS score was found to be low in 69% of the patients at the time of diagnosis. Hasford risk score was low in 53% and Sokal risk score was low in 23% of patients. Risk scores were not calculated in other studies. In this study, ELTS score was found to be associated with OS.

In patients with predominant thrombocytosis without marked leukocytosis, the Ph chromosome should definitely be checked before ET is diagnosed. One case from the literature(15) and one of our cases was negative for Ph chromosome by FISH and the patient was diagnosed with BCR-ABL fusion gene. Atypical transcripts and RNA sample of poor quality can also cause false negative results(16). Therefore, patients with isolated thrombocytosis should be assessed by bone marrow biopsy to avoid missing the diagnosis of CML. In addition, Ph chromosome along with JAK-2 should be requested in all patients presenting with thrombocytosis before CALR and MPL studies. p190 and p230 should definitely be checked in patients with negative p210 results.

5. Conclusion

This study showed that CML should be definitely considered in the differential diagnosis of patients with predominant thrombocytosis without marked leukocytosis. The diagnosis should include a bone marrow biopsy and genetic testing for the BCR-ABL fusion gene. In patients with small hypolobulated megakaryocytes and basophilia, CML rather than ET with large hyperlobulated megakaryocytes should be considered in the prediagnosis.

CML is a disease in which a average OS similar to the general population can be achieved with a daily, single, oral medication. Although it may present like ET at the time of diagnosis, they may be misdiagnosed if Ph is not requested. Patients from being mistakenly diagnosed and treated Ph-negative MPD which could result highly progressive clinical scenarios such as accelerated and blastic phases. In these patients, thrombotic events and bleeding disorders may occur. In this patient group, correct diagnosis and rapid initiation of tyrosine kinase inhibitor therapy may help prevent problems that may lead to serious morbidity and mortality.

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Assessment of Four Different eGFR Equations in Older Turkish Adults

Yaşlı Türk Bireylerde Dört Farklı eGFR Formülünün Değerlendirilmesi

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Abstract: Age-related physiologic changes and comorbidities make it difficult to estimate the glomerular filtration rate(GFR) in older adults. Although inulin clearance is accepted as the gold standard for measuring GFR, it is impractical in clinical practice. A total of 228 patients who underwent a 24-hour creatinine clearance test for the measured GFR (mGFR) were included in the study.The estimated GFR(eGFR) was calculated according to the Modification of Diet in Renal Disease(MDRD) and Chronic Kidney Disease Epidemiology Collaboration(CKD-epi), Berlin Initiative Study-1(BIS-1) and Full Age Spectrum(FAS) formula. The medians of the differences between mGFR and each eGFR equation were used for assessing the bias, and the interquartile range(IQR) of the differences was used for expressing the precision of each equation. The mean age was 76.98±7.83 years and the frequency of female patients was 58.20%. In all patients, FAS[bias=0.40(1.09%), IQR= 26.55 (%52.49)] and BIS-1[bias=1.36(4.27%), IQR=26.71 (%55.28)] were less biased.In the mGFR≥60 mL/min/1.73 m2 subgroup, MDRD was the most precise[bias= -1.73(-1.69%), IQR=25.14 (%49.75)]. in four equations.In patients younger than 75 years, MDRD and CKD-epi equations were less biased, and the CKD-epi equation had the smallest IQR[bias=2.80(4.52%),bias= -2.93(-4.29%), IQR=32.97(49.94%)], whereas, in those older than 75 years, BIS-1 and FAS equations were less biased. However, for the patients 30≤mGFR<60 and mGFR<30 mL/min/1.73 m2, BIS-1 had the lowest bias and smallest IQRs[bias=3.49(7.81%),IQR=14.28(33.20%) and bias=7.60(40.11%), IQR=13.81(39.59%)]. In conclusion, BIS-1 and FAS equations were less biased in older patients with mGFR<60 mL/min/1.73 m2, and MDRD and CKD-epi were less biased in patients with mGFR≥60 mL/min/1.73 m2.
Keywords: Glomerular filtration rate; Older adults; Creatinine clearance; Glomerular filtration rate equation.

Özet: Yaşla ilişkili fizyolojik değişiklikler ve eşlik eden hastalıklar, yaşlı bireylerde glomerüler filtrasyon hızının (GFH) tahmin edilmesini güçleştirmektedir. Klinik uygulamada altın standart olarak kabul edilen inülin klirensi, pratikte kullanımı zor olduğundan tercih edilmemektedir. Bu çalışmada, ölçülen GFH (mGFH) için 24 saatlik kreatinin klirens testi uygulanan toplam 228 hasta değerlendirilmiştir. Tahmini GFH (eGFH), Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI Berlin Initiative Study-1 (BIS-1) ve Full Age Spectrum (FAS) formüllerine göre hesaplanmıştır. MGFH ile her bir eGFH formülü arasındaki farkların medyanı yanlılığı, interkuartil aralığı (IQR) ise her formülün hassasiyetini göstermek amacıyla kullanılmıştır. Hastaların ortalama yaşı 76.98±7.83 yıl olup, kadın hasta sıklığı %58.20'dir. Tüm hastalarda FAS [yanlılık=0.40 (1.09%) IQR=26.55 (%52.49)] ve BIS-1 [yanlılık=1.36 (4.27%) IQR=26.71 (%55.28)], formülleri daha az yanlılık göstermiştir. mGFH ≥60 mL/dk/1,73 m² alt grubunda, MDRD formülü dört formül arasında en hassas olanıdır [yanlılık= -1.73 (-1.69%), IQR=25.14 (%49.75)]. 75 yaş altı hastalarda MDRD ve CKD-EPI formülleri daha az yanlılık göstermiş, CKD-EPI formülü en dar IQR değerine sahip olmuştur [yanlılık=2.80 (4.52%), yanlılık= -2.93 (-4.29%), IQR=32.97 (49.94%)]. Ayrıca, 75 yaş üzerindeki bireylerde BIS-1 ve FAS formülleri daha az yanlılık göstermiştir. mGFH 30≤mGFH<60 ve mGFH<30 mL/dk/1.73 m² olan hastalarda ise, BIS-1 formülü en düşük yanlılık ve en dar IQR değerleriyle öne çıkmıştır [sırasıyla yanlılık=3.49 (7.81%), IQR=14.28 (33.20%) ve yanlılık=7.60 (40.11%), IQR=13.81 (39.59%)]. Sonuç olarak, mGFH <60 mL/dk/1.73 m² olan yaşlı hastalarda BIS-1 ve FAS formülleri daha az yanlılık gösterirken, mGFH ≥60 mL/dk/1.73 m² olan hastalarda MDRD ve CKD-EPI formülleri daha doğru sonuçlar vermektedir.
Anahtar Kelimeler: Glomerüler filtrasyon hızı; Yaşlı bireyler; Kreatinin klirensi; Glomerüler filtrasyon hızı formülleri

Ethics Committee Approval: This study was conducted in conformity with the Declaration of Helsinki and was approved by the local ethics committee (IRB number: 2023/01-13).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

Authorship Contributions: The authors confirm contribution to the paper as follows: study conception and design: ATI; data collection: FSD, FM, MSO; analysis and interpretation of results: IY, FSD; draft manuscript preparation: FSD, EAB; critical revision: ATI. All authors reviewed the results and approved the final version of the manuscript.

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1. Introduction

Age-related changes occur in the urinary system, as in all systems. The number of nephrons decreases by 50%, and compensatory hypertrophy develops in the remaining nephrons [1]. After the age of 40 years, creatinine clearance decreases by 1 mL/min/1.73 m^2 each year [2]. In addition, comorbidities such as chronic kidney disease (CKD), type 2 diabetes mellitus (T2DM), hypertension (HT), and the number of drugs increase with aging [3]. Among individuals with advanced CKD, older adults form the most significant demographic. These changes make it difficult to evaluate the glomerular filtration rate (GFR), the key to the diagnosis of CKD, the adjustment of drug dosage, and the administration of intravenous contrast in older adults [4–6].

Various procedures for measured GFR (mGFR) are available. In the assessment of renal function, inulin clearance is the gold standard measurement; however, it is too complicated for clinical practice [7]. Creatinine, one of the most commonly used markers, is the end product of creatine phosphate in muscle [8]. It is freely filtered from the glomeruli, whereas it is actively secreted from the peritubular capillaries [9]. This appears as an excess of 10-20% in the GFR calculation. Despite this situation, creatinine is frequently the preferred marker for GFR calculation because of its ease of measurement and use. Also, the 24-hour creatinine clearance test is expensive and urine collection is difficult due to mobility, gait and balance problems, and cognitive impairment in older adults. Urinary tract catheterization to collect urine is impractical because of the many complications in older patients [10]. Due to these challenging issues, estimated GFR (eGFR) is more prominent in older adults than mGFR.

Accurate estimation of GFR is important for drug dose adjustment and rationalization of pharmacotherapy in older adults. Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-epi) are the most used creatinine-based equations for estimating GFR [11,12]. Additionally, Berlin Initiative Study (BIS) and Full Age Spectrum (FAS) are other systems based on creatinine equations [13,14]. However, which equation is optimal for accurate assessment of GFR in Turkish older adults has not yet been studied in detail. In this study, we aimed to define the most precise equation among MDRD, CKD-EPI, BIS-1, and FAS, at various GFR ranges in Turkish older adults.

2. Materials and Methods

2.1.Participants and Study Design

This is a retrospective and cross-sectional study. Between January 2013 and October 2021, patients who were hospitalized in our geriatric clinic for any reason were screened. A total of 228 patients who underwent a 24-hour creatinine clearance test were included in the study (Figure 1). The 24-hour urine collection process was conducted under the supervision of nurses and doctors for hospitalized patients. All data were collected retrospectively from the patients' medical records, including descriptive information, comorbidities, Charlson Comorbidity Index (CCI), blood tests, and 24-hour creatinine clearance test results. Exclusion criteria included undergoing kidneyreplacement therapy, acute kidney failure, acute glomerulonephritis, cirrhosis, congestive heart failure, hypovolemia, cachexia, muscle disease, and sepsis.

2.2. Measurement of GFR

The 24-hour urinary creatinine clearance test was performed to evaluate hypertensive nephropathy, diabetic nephropathy, and stage of chronic kidney disease, and to adjust the drug dose. Creatinine levels were measured using a Diagnostic Modular System AutoAnalyzer (Roche E170 and P 800, Switzerland) immunoassay (IUD).

MGFR was calculated using the following formula:

Creatinine clearance = urinary creatinine (mg/dL) x 24-hour urinary volume (mL)/ plasma creatinine (mg/dL) x 1440

2.2.1. Estimation of GFR

The GFR was estimated according to the MDRD, CKD-epi, BIS-1, and FAS formulas. The formulas are as follows:

MDRD= 175 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x 0.742 (if female) [11]

CKD-epi= 141 x min (serum creatinine /k,1)$^{\alpha}$ x max (serum creatinine /k, 1)$^{-1.209}$ x 0.993^{Age} x 1.018 (if female) ($k = 0.7$ for females and 0.9 for males, $\alpha = 0.329$ for females and 0.411 for males)[12]

BIS-1 GFR= 3736 x creatinine$^{-0.87}$ x age$^{-0.95}$ x 0.82 (if female)[13]

FAS−eGFR= (107.3/(serum creatinine /Q)) x $0.988^{(Age-40)}$ for age >40 years where Q is 0.70 mg/dL for females and 0.90 mg/dL for males.[14]

2.3. Statistical Analysis

The data were analyzed using the IBM SPSS software. For quantitative data, descriptive measures are given as means±standard deviations and the proportions for qualitative data are provided. For normally distributed data, t-tests were employed. The differences between eGFR and mGFR were tested using the Wilcoxon signed-rank test for matched pairs because normality was violated. The medians of the differences between mGFR and each eGFR equation are used for assessing bias and the interquartile range (IQR) of the differences was used for expressing the precision of each equation. The IQR of the difference was calculated as the difference between the 75^{th} and 25^{th} percentiles. GFR and positive values indicate cases of overestimating. A bias close to zero is therefore preferred and smaller IQRs indicate better precision. Bland-Altman plots for the differences against the means were produced for both the raw and percentage differences. Simple linear regression models between the differences between each eGFR and mGFR and the respective means were built to evaluate proportional bias. Subgroup analyses were conducted for age groups (<75 years and ≥75 years) and different mGFR (mGFR≥60, 30≤mGFR<60, mGFR<30 mL/min/1.73 m^2) ranges. A significance level of $p<0.05$ was applied in all analyses.

3. Results

A total of 228 consecutive patients were included in the study. The mean age was 76.98±7.83 years and the frequency of female patients was 58.20%. The demographic features of the patients measured and eGFR results are shown in Table 1.

3.1. Overall patients

The comparison of mGFR and four equations showed that BIS-1 and FAS were not significantly different (p=0.853 and p=0.582, respectively), but the MDRD and CKD-epi were significantly different (p<0.001 for each) (Table 2). Bland–Altman plots of four equations against mGFR are given in Figures 1 and 2 for the differences and percentage differences, respectively. We observed that the spread of differences varied strongly with the averages when raw differences were plotted as in Figure 1; therefore, the percentage differences in Bland–Altman plots in both age groups were also considered and plotted in Figure 2. Using the one-sample t-test, mean differences between the four equations and mGFR were tested and the differences between BIS-1 and mGFR and FAS and mGFR were not statistically significant (p=0.199 and p=0.189 respectively) (Table 4). Regression analysis of the differences between mGFR and each eGFR was conducted using the means of the mGFR and eGFR as predictors to investigate proportional bias (Table 3). The bias and precision were investigated separately for the subgroups with respect to mGFR levels in addition to the overall assessments because all models yielded significant coefficients. In all patients and various mGFR ranges, FAS [bias=0.40 (1.09%)] and BIS-1 [bias=1.36 (4.27%)] were less biased. Regarding precision, the MDRD equation had the smallest IQR in all patients [IQR=25.14 (49.75%)]. In the mGFR ≥60 mL/min/1.73 m^2 subgroup, MDRD was better in the estimation of GFR than other equations [bias= -1.73 (-1.69%)]; FAS had the smallest IQR [25.35 (29.38%)]. For estimating the mGFR in 30≤mGFR<60 mL/min/1.73 m^2 and mGFR <30 mL/min/1.73 m^2, FAS had less bias than the other equations [bias= 3.72 and 8.43 (8.21% and 43.35%)] and BIS-1 was more precise [IQR=16.53 and 16.07 (32.89% and 36.46%)] (Table 5).

3.2. Participants aged <75 years

In patients younger than 75 years (n=89) and various mGFR ranges, MDRD and CKD-epi equations were less biased, and the CKD-epi equation had the smallest IQR (bias=2.80 (4.52%), bias=-2.93 (-4.29%), IQR=32.97 (49.94%) respectively). For the subgroup 30≤mGFR<60 mL/min/1.73 m^2, BIS-1, and FAS were less biased, and BIS-1 had the smallest IQR (bias=9.32 (17.86%) and bias=7.60 (14.81%), and IQR=22.76 (44.96%) respectively) (Table 5). For patients with mGFR<30 mL/min/1.73 m^2, the FAS equation was less biased [bias=21.49 (56.76%)], and the BIS-1 equation had the smallest IQR [IQR=27.50 (76.74%)]. For the subgroup mGFR ≥60 mL/min/1.73 m^2, MDRD was less biased [bias= -7.33 (-7.06%) and FAS was more precise [IQR=26.30 (28.18%)].

3.3. Participants aged ≥75 years

In patients older than 75 years (n= 139) and various mGFR ranges, BIS-1 and FAS equations were less biased, but the IQRs of the equations were similar. For the mGFR>60 mL/min/1.73 m^2 subgroup, MDRD, and CKD-epi equations were less biased, but BIS-1 and FAS had the smallest IQRs [bias=5.75 (5.86%), bias= -1.89 (-2.87%), IQR=23.24 (30.04%) and IQR=23.48 (30.92%), respectively]. For the patients with 30≤mGFR<60 mL/min/1.73 m^2, BIS-1 and FAS were less biased and had the smallest IQRs

[bias=4.23 (8.63%), bias=3.49 (7.81%), IQR=14.07 (28.89%), and IQR=14.28 (33.20%), respectively]. For the remaining patients with mGFR<30, FAS had the least bias [bias=7.60 (40.11%)], whereas BIS-1 had the smallest IQR [IQR=12.32 (35.75%)]. Table 5 summarizes the bias and precision of the equations.

Table 1. Patient characteristics of the study.

Parameter	All (n=228)
Sex (female) (%)	58.20
Age (year)*	76.98±7.83
Serum creatinine	1.17±0.70
HT (%)	82.00
DM (%)	76.30
CKD (%)	30.70
CCI	2.38±1.26
mGFR (CrCl-24h) mL/min/1.73 m² *	58.15±34.02
eGFR mL/min/1.73 m² *	
CKD-epi*	62.81±24.93
MDRD*	68.61±29.71
FAS*	56.17±23.06
BIS-1*	56.02±20.79

CCI: Charlson Comorbidity Index; BIS-1: Berlin Initiative Study 1; CKD: Chronic kidney disease; CKD-epi: The Chronic Kidney Disease Epidemiology Collaboration; CrCl-24h: Creatinine Clearance from a 24-hour urine collection; DM: Diabetes Mellitus; eGFR: Estimated glomerular filtration rate; Fas: Full Age Spectrum; HT: Hypertension; MDRD: The original Modification of Diet in Renal Disease; mGFR: Measured glomerular filtration rate.

**mean±SD*

Table 2. Comparison of measured GFR and estimated GFR values

Comparison	P value	Wilcoxon signed-rank statistic
mGFR-MDRD	<0.001	-6.603
mGFR-CKD-epi	<0.001	-3.814
mGFR-BIS-1	0.853	-0.186
mGFR-FAS	0.582	-0.550

BIS-1: Berlin Initiative Study 1; CKD-epi: The Chronic Kidney Disease Epidemiology Collaboration; FAS: Full Age Spectrum; MDRD: The original Modification of Diet in Renal Disease; mGFR: Measured glomerular filtration rate.

Table 3. Regression analysis between the differences and the means and the differences (percentage) and the means

	The differences and the means		**The differences (percentage) and the means**	
Variable	**Beta**	**p**	**Beta**	**p**
Mean (MDRD, mGFR)	-0.153	0.005	-0.452	< 0.001
Mean (CKD-epi, mGFR)	-0.354	< 0.001	-0.582	< 0.001
Mean (BIS-1, mGFR)	-0.544	< 0.001	-0.887	< 0.001
Mean (FAS, mGFR)	-0.436	< 0.001	-0.671	< 0.001

BIS-1: Berlin Initiative Study 1; CKD-epi: The Chronic Kidney Disease Epidemiology Collaboration; FAS: Full Age Spectrum; MDRD: The original Modification of Diet in Renal Disease; mGFR: Measured glomerular filtration rate.

Table 4. One-sample tests for the mean differences

	Mean Difference	**95% CI**	**p**
MDRD-mGFR	10.69	7.49-13.88	< 0.001
CKD-EPI-mGFR	4.83	1.78-7.88	< 0.001
BIS-1-mGFR	-1.94	-4.93-1.03	0.199
FAS-mGFR	-1.97	-4.93-0.98	0.189

BIS-1: Berlin Initiative Study 1; CKD-epi: The Chronic Kidney Disease Epidemiology Collaboration; FAS: Full Age Spectrum; MDRD: The original Modification of Diet in Renal Disease; mGFR: Measured glomerular filtration rate.

Table 5. Bias and precisions of equations compared with measured GFR

	Overall (n=228)	mGFR≥60 (n=93)	30≤mGFR<60 (n=83)	mGFR<30 (n=52)
		All Participants		
		Bias (median differences)		
MDRD	9.42	-1.73	15.23	13.17
CKD-epi	5.39	-9.39	11.59	11.40
BIS-1	1.36	-17.41	4.93	10.90
FAS	0.40	-15.44	3.72	8.43
		Precision (IQR of differences)		
MDRD	25.14	30.50	24.94	22.68
CKD-epi	26.31	30.24	24.24	24.81
BIS-1	26.71	25.52	16.53	16.07
FAS	26.55	25.35	18.06	18.11
		Bias (median percentage difference)		
MDRD	18.91	-1.69	31.38	57.21
CKD-epi	13.14	-11.16	24.83	43.62
BIS-1	4.27	-23.69	12.13	46.45
FAS	1.09	-22.57	8.21	43.35
		Precision (IQR of percentage differences)		
MDRD	49.75	32.55	43.72	42.21
CKD-epi	52.66	36.92	42.07	53.07
BIS-1	55.28	28.47	32.89	36.46
FAS	52.49	29.38	36.47	42.33
		Participants <75 years		
		Bias (median differences)		
MDRD	2.80	-7.33	13.72	27.63
CKD-epi	-2.93	-13.55	13.47	25.88
BIS-1	-5.90	-22.01	9.32	23.38
FAS	-5.61	-18.92	7.60	21.49
		Precision (IQR of differences)		
MDRD	34.30	31.92	30.86	36.78
CKD-epi	32.97	31.71	31.57	34.34
BIS-1	38.58	27.33	22.76	27.50
FAS	36.50	26.30	25.10	29.50
		Bias (median percentage difference)		
MDRD	4.52	-7.06	25.22	48.90
CKD-epi	-4.29	-15.88	24.83	64.61
BIS-1	-8.40	-24.02	17.86	60.26
FAS	-9.72	-22.57	14.81	56.76
		Precision (IQR of percentage differences)		
MDRD	55.43	32.42	50.94	91.97
CKD-epi	49.94	31.08	51.31	94.78
BIS-1	52.09	27.98	44.96	76.74
FAS	53.23	28.18	47.31	85.74
		Participants ≥75 years		
		Bias (median differences)		
MDRD	11.04	5.75	16.24	11.32
CKD-epi	8.12	-1.89	11.41	8.76
BIS-1	4.93	-12.95	4.23	10.08
FAS	3.32	-12.91	3.49	7.60
		Precision (IQR of differences)		

MDRD	20.14	27.60	21.56	18.47
CKD-epi	19.53	25.98	21.27	16.90
BIS-1	20.20	23.24	14.07	12.32
FAS	19.44	23.48	14.28	13.81
		Bias (median percentage difference)		
MDRD	31.38	5.86	31.40	52.41
CKD-epi	18.76	-2.87	24.41	40.80
BIS-1	14.18	-22.35	8.63	46.36
FAS	9.30	-21.54	7.81	40.11
		Precision (IQR of percentage differences)		
MDRD	44.15	33.65	36.09	38.73
CKD-epi	43.40	38.41	39.81	48.49
BIS-1	45.77	30.04	28.89	35.75
FAS	46.64	30.92	33.20	39.59

BIS-1: Berlin Initiative Study 1; CKD-epi: The Chronic Kidney Disease Epidemiology Collaboration; CrCl-24h: Creatinine Clearance from a 24-hour urine collection; Fas: Full Age Spectrum; MDRD: The original Modification of Diet in Renal Disease; mGFR: Measured glomerular filtration rate.

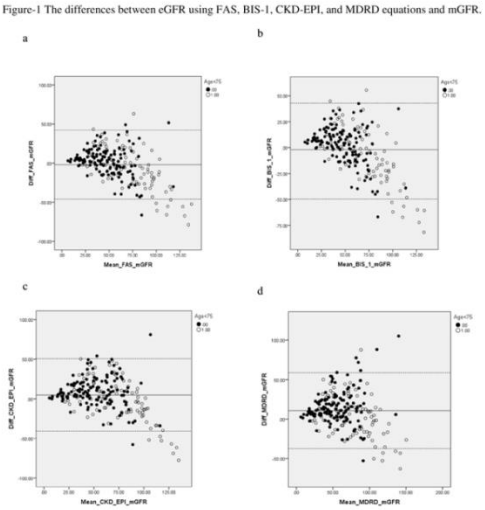

Fig. 1 *Bland–Altman plots reveal the differences between estimated glomerular filtration rate (eGFR) using a FAS equation, b BIS-1 equation, c CKD-EPI equation, and d MDRD equation, and measured GFR (mGFR), plotted against the mean of mGFR and eGFR. All values are expressed in ml/min/1.73 m^2. Horizontal solid lines stand for the mean of bias, and horizontal dash lines represent the 95% confidence interval of bias. Participants <75 years are represented by a hollow circle and those≥75 years by a filled square.*

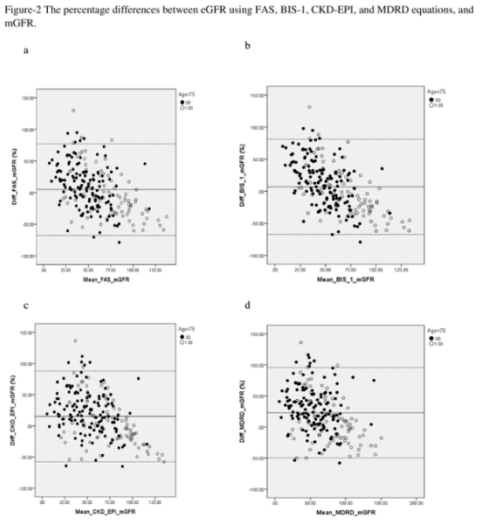

Fig. 2 *Bland–Altman plots reveal the percentage differences between estimated glomerular filtration rate (eGFR) using a FAS equation, b BIS-1 equation, c CKD-EPI equation, and d MDRD equation, and measured GFR (mGFR), plotted against the mean of mGFR and eGFR. All values are expressed in ml/min/1.73 m^2. Horizontal solid lines stand for the mean of bias, and horizontal dash lines represent the 95% confidence interval of bias. Participants <75 years are represented by a hollow circle and those≥75 years by a filled square*

4. Discussion

This cross-sectional and retrospective study evaluating the capacity of BIS-1, FAS, MDRD, and CKD-epi to accurately assess GFR in older adults found that BIS-1 and FAS equations were less biased in the patients. Patients with mGFR≥60 mL/min/1.73 m^2, MDRD, and CKD-epi equations were less biased, and for those with mGFR<60 mL/min/1.73 m^2, BIS-1, and FAS were less biased. Nevertheless, in those older than 75 years, however, MDRD and CKD-epi equations were less biased, and BIS-1 and FAS had the smallest IQRs in mGFR≥60 mL/min/1.73 m^2.

It is known that after the age of 40 years, there is a decrease in creatinine clearance every year (7.5 to 10 mL per minute per decade). In addition to physiologic changes, other comorbidities, as well as CKD, are common in older adults [15]. The management of CKD is closely related to renal functions [6,16,17], and most antibiotics require dose adjustment based on renal function [18]. Considering all these situations, accurate and practical GFR measurement becomes even more crucial for these patients. The limited applicability of the 24-hour urine collecting methods increases the importance of estimated GFR methods. Accordingly, although cystatin-based measurement methods are considered more reliable, creatinine-based eGFR equations are the most commonly used worldwide. Within this context, the organization Kidney Disease: Improving Global Outcomes (KDIGO) recommends using CKD-epi as an eGFR equation for the entire population, and if eGFR is below 60 mL/min/1.73 m^2, it recommends cystatin C measurements [19]. However, it is worth noting that only 13% of patients were aged 65 years or older in the study conducted for the CKD-epi equation [20]. Moreover, patients older than 70 years were excluded from the MDRD equation study [21]. This may be why those equations are poorly related to mGFR in older adults, especially those with lower GFR.

Apart from age-related changes in the kidney system, changes in the muscle and diet can affect serum creatinine, thus measurement methods in older individuals may differ from those in younger individuals. Therefore, the BIS-1 and BIS-2 equations were developed for patients older than 70 years; BIS-2 was reported to be a reliable equation in patients with eGFR greater than 30 mL/min per 1.73 m^2, and the BIS-1 equation was reported as an acceptable alternative in older patients with normal or mild-to-moderately reduced kidney function [13,22]. Also, the FAS equation was developed to eliminate the effect of age and sex on creatinine clearance [23]. The FAS and BIS-1 equations were recommended as accurate equations to estimate GFR in older patients, especially for those with moderately reduced kidney function [24]. Nevertheless, the present study demonstrated that the BIS-1 and FAS equations were less biased in older adults with mGFR <60 mL/min/1.73 m^2.

In a study, Guan et al. found that the BIS-2 might be optimal for Chinese older adults (≥75 years) with mGFR ≥ 30 mL/min/1.73 m^2, and CKD-epi could yield better performance than the BIS-2 equation, especially in those aged <75 years with mGFR <30 mL/min/1.73 m^2. In that study, mGFR was evaluated using a renal dynamic imaging method, with 99 m Tc-diethylene-tri- amine pentaacetic acid (99m Tc-DTPA).[15] In our study, we could perform neither 99 m Tc-DTPA nor cystatin-based equations, but both studies showed that most used equations (MDRD and CKD-epi) might not be optimal for all ages and in various mGFR subgroups. Another recent study reported that MDRD, CKD-epi, and BIS-1 could not be considered interchangeable for assessing eGFR in Chinese centenarians [25].

Scarr et al. reported an unexpected finding in a study. In their study, MDRD, CKD-epi creatinine (CKD-epi-cr), CKD-epi cystatin C (CKD-epi-cys), CKD-EPI-cr-cys, and β2 microglobulin were performed for eGFR in Canadian older adults with type 1 diabetes. All these equations underestimated mGFR and were related to greater negative bias and lower accuracy in higher mGFR [26].

In an older multi-ethnic group, MDRD and Cockcroft–Gault (CG) had discordant results in 60% of patients [27]. Although CG is not the most reliable and used equation, it is an important study in that it showed that measurement methods could be inconsistent with each other in older patients and the study was conducted on a multi-ethnic group. In accordance with the present study, the BIS-1 equation was reported to be most accurate in Chinese older adults among CKD-epi, Lund-Malmö Revised (LMR), BIS-1, and FAS equations based on serum creatinine when GFR was measured using the dual plasma sample clearance method with Technetium-99 m-diethylenetriamine-pentaacetic acid (Tc-99 m-DTPA) [28]. Another study concluded that the BIS-1 equation was more accurate than the MDRD and CKD-epi in patients older than 80 years with a GFR<60mL/min/1.73m^2 [29].

When the literature is reviewed, there is no consensus on a gold standard equation for GFR in older individuals. Different results in groups with different characteristics suggest that biomarkers used in equations also relate to age, sex, comorbid conditions, various mGFRs, and ethnicity. In our study, we evaluated the various mGFR values in older adults by dividing by age, those older than 75 years, and those who were aged 75 years and younger, using four different equations. Compatible with the literature, this study showed that BIS-1 and FAS equations were suitable for older adults with moderately reduced kidney function.

4.1. Strengths and limitations

This study is the first study on Turkish older adults to define the most precise eGFR equation. Four of the most commonly used equations were assessed for this purpose, and the GFR was measured using 24-hour creatinine clearance. Also, this study had some limitations. First, it was a cross-sectional and retrospective study. After that, a single laboratory measurement was used to calculate the mGFR and eGFR equations, and muscle mass was not evaluated. The next issue, inulin clearance, the gold standard method, was not measured. Finally, all participants were hospitalized, and the results might not reflect the entire population. Prospective studies with a larger population are needed.

5. Conclusion

BIS-1 and FAS equations were found to be less biased in older patients with mGFR<60 mL/min/1.73 m^2, and MDRD and CKD-epi were less biased in patients with mGFR≥60 mL/min/1.73 m^2. These equations may become valuable in older adults for the estimation of GFR. Moreover, equations may be combined to obtain accurate eGFR.

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Could the First Trimester Complete Blood Cell Indices Be Used to Predict Adverse Outcomes in Pregnant Women with Asthma?

Astımlı gebe kadınlarda birinci trimester tam kan sayımı indeksleri olumsuz sonuçları tahmin etmek için kullanılabilir mi?

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Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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[RŞ, OOÖ, ZA, ŞK] assisted in statistical analysis, data interpretation, and manuscript revisions.
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Abstract: The objective of this study was to investigate the efficacy of complete blood cell indices, specifically the neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and systemic immune-response index (SIRI), in predicting composite adverse outcomes in pregnant women with asthma. This study employed a retrospective cohort design, enrolling 307 low-risk pregnant women and 97 pregnant women with asthma. The neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and systemic immune-response index (SIRI) were compared between pregnant women with asthma and the low-risk pregnancy group in the first trimester. A significant difference was observed in the first trimester SII between pregnant women with asthma and the low-risk pregnancy group (p=0.034). The neutrophil-to-lymphocyte ratio (NLR) and systemic immune response index (SIRI) demonstrated no significant differences between the groups. Moreover, pregnant women with asthma had significantly higher eosinophil count values as expected. The first trimester white blood cell count (WBC) and platelet count (PLT) were found to be significantly higher in the asthma group (p=0.014 and p=0.031, respectively). In the asthma group, no significant difference was found between the composite adverse pregnancy outcomes due to SII, SIRI, and NLR. Pregnant women with asthma exhibited significantly elevated values for SII, WBC, PLT and eosinophils. In our study, we observed no association between groups in complete blood cell indices due to the composite adverse effects of pregnancy. Further studies with larger groups are required to evaluate the efficacy of complete blood cell indices in pregnant women with asthma.
Keywords: Asthma, pregnancy, complete blood cell indices, perinatology, immune system

Özet: Bu çalışmanın amacı, astımlı gebelerde tam kan sayımı indekslerinin, özellikle nötrofil-lenfosit oranı (NLR), sistemik immün-inflamasyon indeksi (SII) ve sistemik immün-yanıt indeksinin (SIRI) bileşik olumsuz sonuçları öngörmedeki etkinliğini araştırmaktır. Bu çalışmada retrospektif bir kohort tasarımı kullanılmış ve 307 düşük riskli gebe ile 97 astımlı gebe çalışmaya dahil edilmiştir. Nötrofil-lenfosit oranı (NLR), sistemik immün-inflamasyon indeksi (SII) ve sistemik immün-yanıt indeksi (SIRI) ilk trimesterde astımlı gebeler ile düşük riskli gebelik grubu arasında karşılaştırıldı. Astımlı gebeler ile düşük riskli gebelik grubu arasında ilk trimester SII açısından anlamlı bir fark gözlendi (p=0.034). Nötrofil-lenfosit oranı (NLR) ve sistemik inflamasyon yanıt indeksi (SIRI) gruplar arasında anlamlı farklılık göstermedi. Ayrıca, astımlı gebelerde eozinofil sayısı beklendiği gibi anlamlı derecede yüksekti. İlk trimester beyaz küre sayısı (WBC) ve trombosit sayısı (PLT) astım grubunda anlamlı olarak daha yüksek bulunmuştur (sırasıyla p=0,014 ve p=0,031). Astım grubunda, SII, SIRI ve NLR'ye bağlı bileşik olumsuz gebelik sonuçları arasında anlamlı bir fark bulunmamıştır. Astımlı gebelerde SII, WBC, PLT ve eozinofil değerleri anlamlı derecede yüksek bulunmuştur. Çalışmamızda, gebeliğin bileşik yan etkilerine bağlı olarak tam kan hücresi indekslerinde gruplar arasında bir ilişki gözlenmemiştir. Astımlı gebelerde tam kan hücresi indekslerinin etkinliğini değerlendirmek için daha büyük gruplarla yapılacak ileri çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Astım, gebelik, tam kan sayımı indeksleri, perinatoloji, immün sistem

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1. Introduction

Asthma is a chronic respiratory disease that affects approximately 300 million people worldwide. The disease and its symptoms cannot be attributed to a single environmental or genetic cause. Rather, the essential diagnosis is made based on three major characteristics: (i) reversible airway obstruction, (ii) inflammation of the airway, and (iii) increased airway response due to variable stimuli (1). Asthma is one of the most prevalent comorbidities among pregnant women, affecting between 3% to 6% of pregnant women worldwide (2). Pregnant women with asthma are at an increased risk of adverse outcomes of pregnancy, both for the mother and the fetus. (3)

It is a well-documented phenomenon that asthma control levels often change during pregnancy. It is commonly accepted that approximately one-third of asthma patients experience exacerbation during pregnancy, with the majority of these occurring during the middle of the pregnancy. Conversely, approximately one-third of patients experience improvement, with no significant changes observed in the remaining one-third. However, a recent multicase-control study has demonstrated that the percentage of asthma cases that worsen during pregnancy is 18.8%, a figure that is lower than previous estimates. Furthermore, the study has indicated that the severity of the disease is significantly associated with the likelihood of asthma worsening during pregnancy (4). It is of paramount importance to treat asthma and to reduce the incidence of exacerbations during pregnancy, as this has a significant impact on the outcome of pregnancy. (5)

The complete blood count (CBC) is a commonly employed and readily accessible diagnostic tool. Its indices may indicate the presence of inflammation, tissue repair, cytokine secretion, and cell regeneration processes. (6) The three complete blood cell indices, namely the neutrophil-to-lymphocyte ratio (NLR), the systemic immune-inflammation index (SII), and the systemic immune-response index (SIRI), have been employed in clinical practice in recent years. (7) It is possible that these indexes may indicate an excessive inflammatory response within the human body.

A recent study has demonstrated that in individuals with asthma, elevated levels of SII and SIRI are associated with an increased prevalence of stroke. This association was particularly pronounced in individuals with coexisting obesity and hyperlipidemia. SII and SIRI are relatively stable novel inflammatory markers in the asthmatic population. SIRI demonstrates superior predictive value for stroke prevalence compared to SII (8).

The objective of this study was to assess the predictive value of NLR, SII, and SIRI in identifying composite adverse outcomes in pregnant women with asthma.

2. Materials and Methods

This retrospective case-control study was conducted at Ankara Bilkent City Hospital's perinatology clinic between 2020 and March 2023. All pregnant women with asthma who provided written informed consent to participate in the study were included. The demographic features, clinical characteristics, laboratory results, and complete blood cell indices were compared to a gestational age-matched control group who were followed up in the perinatology clinic during the study period. The study protocol was approved by the institutional ethics committee, which assigned reference number E2-23-4338.

The diagnosis of asthma was made in accordance with the GINA guidelines.(9) Asthma severity is classified according to the parameters defined by the National Asthma Education and Prevention Program Working Group on Asthma and Pregnancy. These parameters define four categories: mild, moderate, moderate with additional therapy, and severe. At the time of the initial blood sample collection during the first trimester, all patients were asymptomatic for SARS-CoV-2, or SARS-CoV-2 PCR results were negative. Moreover, cases with severe asthma were excluded from the study as the severity of the disease has significant impact on the complete blood count parameters and adverse pregnancy outcomes.

A composite adverse outcome was defined as the presence of at least one of the following pregnancy complications: preterm delivery, gestational hypertension, intrauterine fetal demise, fetal growth restriction, and oligohydramnios.

A comparison was conducted between the study and control groups regarding maternal age, gravidity, parity, live births, first-trimester complete blood cell parameters, neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and systemic immune response index (SIRI). The following formulae were employed to calculate SII and SIRI:

SII = (platelet count x neutrophil count)/lymphocyte count

SIRI = (neutrophil count x monocyte count)/lymphocyte count

All blood samples were collected between 8 and 14 weeks of gestation during the patient's first admission to the hospital. Neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and systemic immune response index (SIRI) were calculated based on first-trimester complete blood cell results. Additionally, the asthma group was divided into subgroups based on adverse pregnancy outcomes, which were then compared between the subgroups.

All patients with asthma were managed by a multidisciplinary team, comprising a pulmonary diseases specialist and a perinatologist.

All statistical analyses were performed by SPSS 22 (IBM Statistics, Chicago, USA). As the data were found to be normally distributed according to Shapiro Wilk Test, mean and standard deviation values were used to present continuous variables, and the student t-test was used to compare mean values between the groups. Categorical variables were presented as numbers and percentages. A chi-square test was performed to compare categorical values. A p-value <0.05 was considered statistically significant.

3. Results

A total of 92 pregnant women with asthma were compared to a gestational age-matched low-risk control group of 307 pregnant women. Table 1 presents a comparison of the demographic features, laboratory results, and complete blood cell indices between the study and control groups. Statistically significant higher values were observed for maternal age, white blood cell count, platelet count, eosinophils and SII in the asthma group compared to the low-risk group.

Table 1. Comparison of demographic features, and ultrasonographic measurements between the groups

	Control (n=307)	Asthma (n=92)	P
Maternal age (years)	28 (7)	30 (10)	**<0.001**
Gravidity	2 (2)	2 (2)	0.25
Parity	1 (2)	1 (2)	0.082
Wbc	9.04 (2.74)	9.69 (3.55)	**0.014**
Neutrophile	6.51 (2.35)	6.83 (2.92)	0.031
Lymphocyte	1.78 64)	1.79 (0.7)	0.64
Eosinophils	0.08 (0.1)	0.15 (0.13)	**<0.001**
Hgb	12.2 (1.8)	11.8 (1.5)	0.11
Hct	36.5 (5.7)	36 (3.6)	0.28
Plt	249 (89)	267 (131)	**0.031**
NLR	3.63 (1.89)	3.56 (2.1)	0.57
SII	904 (577)	1018 (682)	**0.034**
SIRI	1.6 (1.05)	1.71 (1.33)	0.086

Hb: hemoglobin, Hct: hematocrit, WBC: white blood cell, Plt: platelet, NLR: neutrophil to lymphocyte ratio, SIRI: Systemic immune response index, SII: Systemic immune-inflammation index

In the asthma group, 35 (38%) of the pregnant women had a composite adverse outcome in their pregnancy. A total of 20 cases (21%) of preterm birth, 18 cases (19%) of intrauterine growth restriction, 6 cases of preeclampsia and 23 cases (25%) of low-birth-weight newborns were recorded. Additionally, 13 cases presented with oligohydramnios and one case resulted in intrauterine fetal demise. A comparison of demographic features, clinical characteristics, laboratory values, and complete blood cell indices between asthmatic patients with and without composite adverse outcome is presented in Table 2. It was observed that the composite outcome group exhibited higher numerical values with respect to complete blood count indexes. Nevertheless, despite the numerical higher values, no statistically significant difference was identified between the two groups. Conversely, the gestational age at birth, birth weight and 1st minute APGAR scores were markedly elevated in the asthmatic cohort that had not experienced a composite adverse outcome.

Table 2. Comparison of complete blood cell indices in pregnant women with asthma according to the presence or absence of composite adverse outcome

	Asthma without composite adverse outcome (n=57)	Asthma with composite adverse outcome (n=35)	p
Maternal age (years)	28.9±4.5	29.1±4.6	0.71
Gravidity	2±1.3	2±1.2	0.87
Parity	0.6±0.8	0.7±0.7	0.43
WBC	9.8±2.9	8.7±2.6	0.16
Neutrophil	9.21±2.83	7.66±4.34	0.23
Lymphocyte	1.53±0.31	1.74±0.51	0.2
Eosinophils	0.13± 0.15	0.16± 0.14	0.11
Hgb	11.7±2.3	12±1.9	0.6
Hct	35.3±3.2	36.2±3.9	0.43
Platelet	267±78	255±74	0.093
SII	1007 ±1053	1049 ±817	0.41
SIRI	1.63 ±1.41	1.77 ±1.37	0.32
NLR	3.44 ±2.43	3.66 ±1.73	0.27
Week of birth	37.3±2.3	38.8±1.1	**0.016**
Birth weight	2790±614	3244±402	**0.021**
APGAR 1st min	7.73±0.63	7.59±0.32	**0.043**
APGAR 5th min	8.87±0.44	8.71±0.5	0.17

Hb: hemoglobin, Hct: hematocrit, WBC: white blood cell, Pct: plateletcrit, NLR: neutrophil to lymphocyte ratio, SIRI: Systemic immune response index, SII: Systemic immune-inflammation index

4. Discussion

The development of asthma is significantly influenced by inflammatory processes. Asthma is a chronic inflammatory disease that affects the number and mechanism of eosinophils, neutrophils, lymphocytes, and macrophages and their components.(10). In recent years eosinophils were the essential marker for asthma in complete blood cell count (CBC) studies(11). Meanwhile more recent studies focus on complete blood cell indices such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune response index (SIRI), and systemic immune-inflammation index (SII) etc. These CBC associated inflammatory biomarkers have been used to assess disease severity, exacerbations and predict morbidity and mortality(12).

Asthma is most common comorbidity in pregnancy. Approximately 4-8% of pregnant women are affected by this disease(13). In addition to the effect of maternal asthma on pregnancy outcomes, pregnancy may affect the course of asthma. The severity of asthma may improve, worsen, or remain unchanged during pregnancy; the mechanisms underlying changes in the severity of asthma during pregnancy remain undefined. Acute exacerbations have been observed in almost half of the patients and are a major problem during pregnancy. This leads the patients seek for medical assistance. Asthma in pregnancy also have a higher obstetric adverse outcome rate such as preterm delivery, gestational hypertension, gestational diabetes and low birth weight(14).

Complete blood cell indices show their clinical importance in various fields of medicine(15). Despite the numerous positive findings that have been obtained in the clinical application of complete blood cell indices, it is still unclear what role they play in the development and prognosis of diseases (16). It is still non-specific and heterogeneous in each disease. Nevertheless, studies to understand the total blood cell count in specific patient groups are necessary to obtain more meaningful results.

The association between asthma and adverse pregnancy outcomes has been known for decades, and there are numerous studies that have investigated this. Because of the oxygen requirements of the fetus, maternal oxygen levels are critical for the fetal oxygenation. This is a serious problem in acute exacerbations in pregnant women with asthma(17). Asthma is known to be associated with preeclampsia(18,19), placental abruption, placenta previa(20) and obstetric hemorrhage. A large cohort study from Canada of more than 15,000 women with asthma found an increased risk of spontaneous abortion (21).

In a single center retrospective cohort study, more than 2000 pregnant women with asthma were compared with more than 8000 randomly selected pregnant women. Maternal asthma has been found significantly associated with several composite adverse outcomes, including preterm birth, low-weight-birth infants whom small for their gestational

age, cesarean delivery and gestational hypertension (14).

A retrospective cohort study was conducted using the Health Care Cost and Utilization Project-Nationwide Inpatient Sample (HCUP-NIS) database. The study population comprised 7,772,999 pregnant women, of whom 223,236 (2.9%) had asthma between 2003 and 2011. In the present study, the authors reported the discovery of statistically significant associations between composite adverse outcomes and maternal asthma (22).

A retrospective cohort study of pregnant women with asthma was conducted in a single center between 2009 and 2018. One of the findings of this study was that oligohydramnios rates were higher in moderate and severe asthma groups compared to the mild asthma group ($p<0.001$) (23). The authors claimed that they expected oligohydramnios and other composite adverse outcomes to include inadequate placental perfusion intrauterine growth restriction, gestational hypertension, and preeclampsia. This is a consequence of inadequate oxygenation of the placental vascular tree due to maternal asthmatic exacerbations. This situation might be correlated with asthma severity, number of exacerbations, type of medication, smoking status, asthma-related hospitalizations and air pollution (24).

A study found that a high blood eosinophil count was a risk factor for increased asthma exacerbations or hospital admissions in people with uncontrolled asthma. Furthermore, a high blood eosinophil count was identified as an independent risk factor for two or more asthma exacerbations, as well as any asthma emergency department visit or hospitalization (25). As anticipated, eosinophil counts were elevated in the asthma group in our study. However, no significant difference was observed in asthmatic pregnant women with and without composite adverse outcome. It is hypothesized that this discrepancy may be attributed to the fact that the asthma group encompasses patients with mild and moderate asthma.

In recent years, our knowledge of the role of complete blood cell indices has improved, and new indices such as SII and SIRI have entered the field. In a recent retrospective cohort study including a total of 48,305 participants found that the prevalence of asthma was found to be positively associated with these complete blood cell indices: NLR, PLR, MLR, SIRI and SII (12). Also, in this study gradient of these complete blood cell indices were associated with a higher percentile risk of mortality.

Considering the autoimmune and inflammatory background of the asthma, pregnant women have potential to be negatively affected by disease specific complications and relatively low oxygen levels. Moreover, physiologic changes observed during pregnancy may affect the prognosis of asthma. As complete blood cell indices reflect excessive inflammatory processes in the human body, the authors of the present manuscript aimed to investigate their possible role in the prediction of composite adverse outcomes in pregnant women with asthma. Furthermore, the severity of asthma was found to be closely associated with adverse outcomes in pregnant population. Thus, complete blood cell indices may be useful as they may represent the degree of inflammation in the maternal blood.

The asthmatic group exhibited significantly elevated white blood cell (WBC), platelet, eosinophil, and systemic immune index (SII) levels compared to the control group. No significant difference was observed in SIRI and NLR values between the two groups. Among asthmatic patients, there was no significant difference between the groups with and without composite adverse outcomes for NLR, SII, and SIRI. The limited number of patients in the asthma group and the exclusion of severe cases may be contributing factors.

5. Conclusion

This study's most notable strength was its incorporation of innovative indices, the inclusion of a substantial number of study parameters, and the incorporation of initial acceptance parameters. The principal limitation of this study was that it was conducted at a single center and included a relatively small number of participants. As a result, the severity of asthma in the patients included in the study was not sufficiently varied. In conclusion, further multicenter studies with larger patient populations are required to ascertain the efficacy of SII, SIRI, and NLR in predicting composite adverse outcomes in pregnant women with asthma.

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Kliniğimizde Non-Melanom Malign Kutanöz Cilt Lezyonlarında Frozen Negatif Gelen Hastaların Nihai Patolojisinde Cerrahi Sınır Pozitifliğinin Retrospektif Çalışılması

Retrospective Study of Surgical Margin Positivity in Final Pathology of Patients with Frozen Negative Non-Melanoma Cutaneous Skin Lesions in Our Clinic

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Abstract: Basal cell carcinoma, squamous cell carcinoma, and malignant melanoma are the most common subtypes of cutaneous malignancies and are generally examined in two main subtypes: non-melanoma and melanoma. The adequacy of surgical margins after excision of the lesion is one of the main factors determining the success of treatment. Frozen section analysis is an effective method used to determine intraoperative surgical margins and plays an important role in assessing the adequacy of excision and minimizing the risk of recurrence. This study aimed to evaluate the reliability and efficacy of this method by examining the relationship between frozen section analysis and pathological diagnosis in patients who underwent surgery for basal cell carcinoma or squamous cell carcinoma. Patient demographics, tumor localization, tumor size, histopathological subtype, surgical margin, reconstruction method, frozen section analysis, and final pathology results were obtained. A total of 898 lesions were evaluated in 763 patients who underwent surgery for non-melanoma cutaneous malignancies. Of the patients, 65% were men and 35% were women. The most common malignancy was basal cell carcinoma, which accounted for 72.8% of all lesions. The correlation between frozen section analysis and final pathological evaluation was 94.2%, and the false-negative rate was 5.8%. In conclusion, this study demonstrates that frozen section analysis is a reliable tool for the surgical management of non-melanoma malignant cutaneous lesions. However, considering the limitations of the method, the histological subtype of the lesion, its location, and patient risk factors, a multidisciplinary approach to surgical margin management is recommended.
Keywords: Skin neoplasm, Basal cell carcinoma, Squamous cell carcinoma, Frozen section

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Özet: Kutanöz maligniteler arasında bazal hücreli karsinom, skuamöz hücreli karsinom ve malign melanom en sık görülen alt tipler olmakla birlikte, cilt kanserleri genellikle non-melanom ve melanom olmak üzere iki ana alt tipte incelenmektedirler. Lezyonun eksizyonu sonrası cerrahi sınırların yeterli olması, tedavi başarısını belirleyen ana faktörlerden biridir. Frozen kesit analizi, intraoperatif cerrahi sınırları ortaya koymak adına kullanılan etkili bir yöntem olup, eksizyonun yeterliliğini sorgulama ve nüks riskini en aza indirme açısından önemli bir rol oynar. Çalışmamızın amacı, bazal hücreli karsinom veya skuamöz hücreli karsinom nedeniyle opere edilen hastalarda frozen kesit analizi ile nihai patolojik tanı arasındaki ilişkiyi inceleyerek, yöntemin güvenilirliğini ve etkinliğini değerlendirmektir. Hastaların demografik verileri, tümör lokalizasyonu, tümör boyutu, histopatolojik alt tipi, cerrahi sınır marjini, rekonstrüksiyon yöntemi, frozen kesit analizi ve nihai patoloji sonuçları retrospektif olarak elde edilmiştir. Melanom dışı kutanöz maligniteler nedeniyle cerrahi müdahale yapılan 763 hastada toplamda 898 lezyon değerlendirilmiştir. Hastaların %65'i erkek ve %35'i kadın olarak belirlenmiştir. Nihai patolojik incelemeye göre, en yaygın malignite bazal hücreli karsinom olup, tüm lezyonların %72,8'ini oluşturmuştur. Frozen kesit analizi ile nihai patolojik değerlendirme arasında %94,2 oranında korelasyon tespit edilmiş olup, frozen kesit analizi ile nihai patoloji arasındaki yalancı negatiflik oranı %5,8 olarak hesaplanmıştır. Sonuç olarak bu çalışma, frozen kesit analizinin, melanom dışı malign kutanöz lezyonların cerrahi yönetiminde güvenilir bir araç olduğunu göstermektedir. Ancak, yöntemin sınırlılıklarını dikkate alarak ve lezyonun histolojik alt tipi, lokalizasyonu, hastaya ait risk faktörleri gibi durumlar da göz önünde bulundurularak, cerrahi sınır yönetiminde multidisipliner bir yaklaşımın benimsenmesi önerilmektedir.
Anahtar Kelimeler: Cilt neoplazmı, Bazal hücreli karsinom, Skuamöz hücreli karsinom, Frozen kesit

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1. Giriş

Kutanöz maligniteler, dünya genelinde epitel kökenli malign tümörler arasında en yaygın görülen kanserler arasında yer almakta ve genellikle keratinosit veya glandüler adneksiyal hücrelerden köken almaktadır(1, 2). Gelişmiş ülkelerde özellikle ortalama yaşam süresinin uzaması, ultraviyole (UV) ışınlarına artan maruziyet ve ozon tabakasındaki incelmenin etkisiyle bu malignitelerin görülme sıklığı da artmaktadır(3, 4). Özellikle açık ten rengine sahip bireyler ve immünsuprese hastalar kutanöz maligniteler açısından yüksek risk taşımaktadır(1). Kutanöz maligniteler arasında bazal hücreli karsinom (BHK), skuamöz hücreli karsinom (SHK) ve malign melanom en sık görülen alt tipler olmakla birlikte, malign melanom, BHK ve SHK'dan farklı seyir göstermesi nedeniyle, cilt kanserleri genellikle non-melanom ve melanom olmak üzere iki ana alt tipte incelenmektedirler(5). Non-melanom cilt maligniteleri arasında BHK, düşük metastatik potansiyeline rağmen lokal invaziv ilerleyebilmekte, SHK ise metastaz yapma potansiyeli ile daha agresif bir klinik seyir gösterebilmektedir(6).

Cilt kanserlerinin tedavisinde cerrahi eksizyon, tedavinin önemli bir parçası olup, cerrahi sınırların yeterli olması, tedavi başarısını belirleyen ana faktörlerden biridir(7). Ancak bu sınırlar, tümörün histolojik alt tipi, lokalizasyonu ve çevre dokularla ilişkisi gibi çeşitli faktörlere göre değişiklik gösterebilmektedir(2). Cerrahi sınırların intraoperatif olarak değerlendirilmesi, özellikle yüz ve el gibi estetik ve fonksiyonel açıdan önemli bölgelerde büyük önem taşımaktadır(8). Frozen kesit analizi, intraoperatif dönemde cerrahi sınırların durumunu ortaya koymak adına kullanılan etkili bir yöntemdir(7, 9). Bu sayede, cerrahi sırasında lezyonun sınırlarının değerlendirilmesine olanak tanıyarak, eksizyonun yeterliliğini sorgulama ve nüks riskini en aza indirme açısından önemli bir rol oynar(10). Frozen kesit analizi yönteminin, özellikle burun, kulak, alt göz kapağı gibi rekonstrüktif açıdan zorlayıcı anatomik bölgelerde kullanımı, estetik ve fonksiyonel sonuçların korunması açısından bir avantaj sunmaktadır(11). Bu alanlarda dokunun aşırı eksizyonu hem estetik hem de işlevsel kayıplara yol açabileceğinden, frozen kesit analizi, cerrahın dokuların optimal şekilde çıkarılmasını sağlamasına yardımcı olur. Ancak frozen kesit analizinin bazı sınırlamaları bulunmaktadır. Yöntem, dokunun sınırlı bir alanını değerlendirdiğinden, yanlış negatif sonuçlar verebilmekte, bu analize rağmen cerrahi sınır pozitifliği gibi önemli klinik sonuçları olabilmektedir(11). Ayrıca, frozen kesit analizinin teknik zorlukları, cerrah ve patolog bağımlı olması, yöntemin doğruluğunu etkileyebilmektedir(10).

Bu bağlamda çalışmamızın amacı, kliniğimizde melanom dışı malign cilt lezyonları nedeniyle opere edilen hastalarda frozen kesit analizi ile nihai patolojik tanı arasındaki ilişkiyi inceleyerek, yöntemin güvenilirliğini ve etkinliğini değerlendirmektir. Çalışmanın sonuçlarının, cerrahi sınır yönetimi ve cerrahi planlama süreçlerine katkılar sağlaması beklenmektedir.

2. Gereç ve Yöntem

Bu retrospektif çalışma, 01.01.2018 ile 31.12.2023 tarihleri arasında kliniğimizde melanom dışı kutanöz maligniteler nedeniyle opere edilen hastaların verilerini kapsamaktadır. Çalışma protokolü, Helsinki Bildirgesi'ne uygun olarak hazırlanmış ve ilgili etik kurul tarafından onaylanmıştır (Karar No: E-24/102). Çalışmaya, daha önce biyopsi ile BHK veya SHK tanısı alan ve frozen kesit prosedürü uygulanmış hastalar dahil edilmiştir. İntraoperatif frozen kesit analizi yapılmamış olan hastalar, nihai patoloji sonucu benign lezyon veya melanom olarak raporlanan vakalar, eksik veri içeren hastalar ve önceki cerrahi prosedür nedeniyle tam patolojik değerlendirme yapılamayan hastalar dahil edilmemiştir.

Hastaların demografik verileri, tümör lokalizasyonu, tümör boyutu, histopatolojik alt tipi, cerrahi sınır marjini, rekonstrüksiyon yöntemi, frozen kesit analizi ve nihai patoloji sonuçları retrospektif olarak elde edilmiştir. Ayrıca hastaların eşlik eden komorbiditeleri, nüks ve metastaz durumları ile cerrahi sonrası takip süreleri de kaydedilmiştir.

Cerrahi prosedür sırasında, Amerikan Ulusal Kapsamlı Kanser Ağı kılavuzunda önerilen sınırlar göz önünde bulundurularak eksizyon yapılmıştır. BHK vakalarında ≥4 mm, SHK vakalarında ise ≥6-10 mm cerrahi sınır uygulanmıştır. Ayrıca, Amerikan Ulusal Kapsamlı Kanser Ağı kılavuzuna göre, tümör boyutunun 2 cm'den büyük olması, tümörün kalınlığının >6 mm olması, perinöral invazyon varlığı, lokalizasyonun kulak veya dudak gibi yüksek riskli alanlarda olması, kötü diferansiye histolojik tip, immünsüpresyon ve önceki tedaviye rağmen nüks gelişmiş olması gibi özellikler kötü prognoz kriterleri arasında yer alan lezyonlarda daha geniş cerrahi sınır uygulanmıştır(12, 13). Frozen kesit analizi ile, intraoperatif dönemde cerrahi sınırların negatif olduğunu doğrulamak amacıyla,

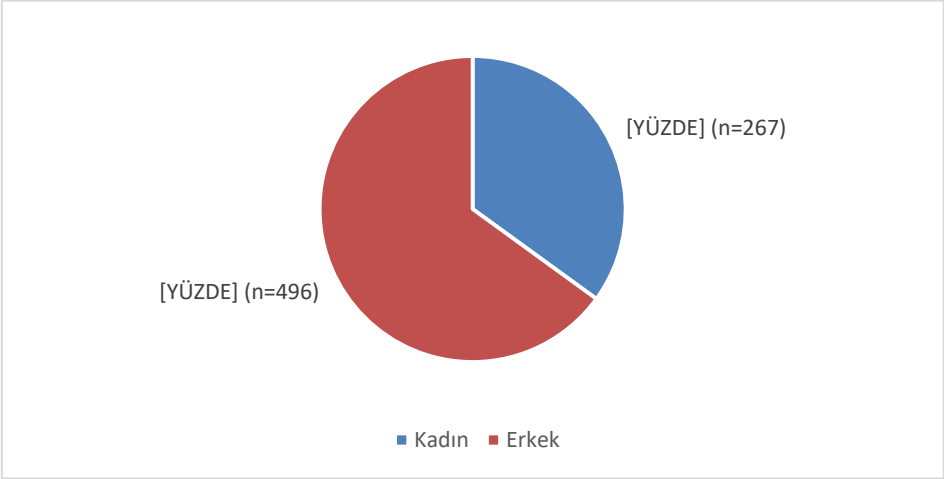
lezyonun eksizyonu sonrası geride kalan dokunun hem periferik hem de derin cerrahi sınırlarından örnek alınarak patolojik değerlendirme yapılmıştır. Nihai patolojik değerlendirme, cerrahiden sonra alınan dokuların standart formalinle fikse edilmesi ve parafin bloklara gömülmesiyle gerçekleştirilmiştir. Kesitler hematoksilen-eozin (H&E) boyası ile boyanmış ve tümörün histopatolojik tipi, cerrahi sınır durumu ve diğer mikroskobik özellikler detaylı olarak incelenmiştir. Frozen kesit ile nihai patolojik tanı arasındaki uyum, korelasyon analizi ile değerlendirilmiştir.

2.1 İstatistiksel Analiz

Elde edilen veriler SPSS (Statistical Package for the Social Sciences, IBM) versiyon 26.0 yazılımı kullanılarak analiz edilmiştir. Kategorik veriler sayı ve yüzde olarak, sürekli veriler ise ortalama ± standart sapma (SD) olarak ifade edilmiştir. Yalancı negatiflik ve yalancı pozitiflik oranları hesaplanmıştır.

3. Bulgular

Melanom dışı kutanöz maligniteler nedeniyle cerrahi müdahale yapılan 763 hastada toplamda 898 lezyon değerlendirilmiştir. Çalışmaya dahil edilen hastaların %65'i erkek ve %35'i kadın olarak belirlenmiştir (Grafik 1). Hastaların yaş ortalaması 65,2 ± 12,8 yıl olarak hesaplanmıştır.



Grafik 1. Cinsiyet Dağılımı

Lezyonların anatomik dağılımı incelendiğinde en sık lokalizasyonun burun (%23,4), skalp (%12,9), malar (%10,2), infraorbital bölge (%10) ve kulak (%9,8) olduğu görülmüştür (Tablo 1).

Tablo 1. Lezyonların yüzdeki anatomik dağılımları

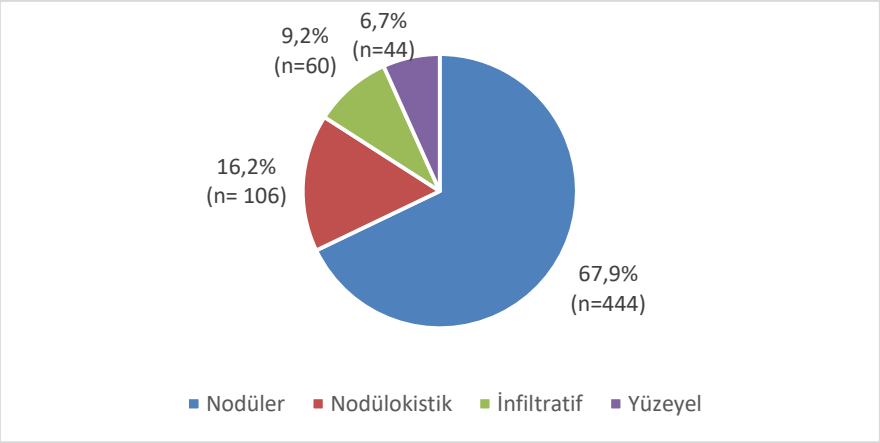
Lokalizasyon	% (n)
Burun	%23,4 (210)
Skalp	%12,9 (116)
Malar	%10,2 (92)
İnfraorbital	%10 (90)
Kulak	%9,8 (88)
Diğer	%33,7 (302)

Nihai patolojik incelemeye göre, en yaygın malignite BHK olup, tüm lezyonların %72,8'ini oluşturmuştur. İkinci sıklıkta ise SHK %26,2 ve nadiren gözlenen bazoskuamöz karsinom (BSHK) ise toplam lezyonların %1'ini oluşturmuştur (Tablo 2).

Tablo 2. Lezyonların patolojik alt tiplere göre dağılımları

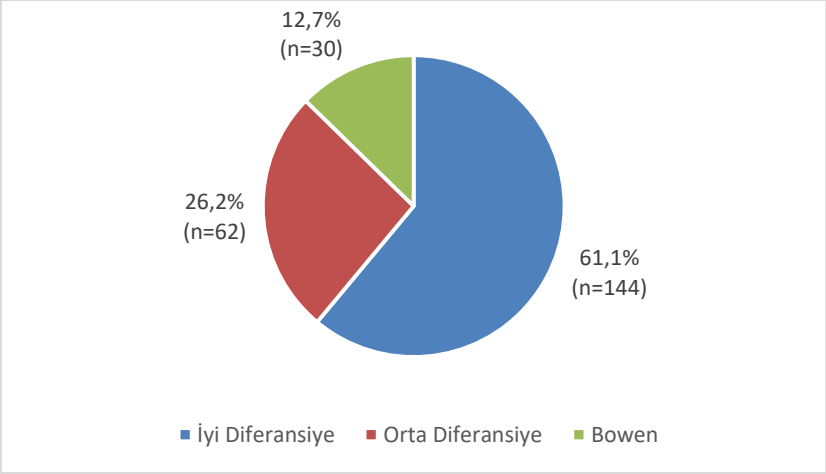
Malignite Türleri	% (n)
Bazal Hücreli Karsinom (BHK)	%72,8 (654)
Skuamöz Hücreli Karsinom (SHK)	%26,2 (236)
Bazoskuamöz Hücreli Karsinom (BSHK)	%1 (8)

BHK alt tipleri değerlendirildiğinde, en yaygın histolojik alt tipin nodüler (%67,9) olduğu görülmüştür. Nodülokistik (%16,2) ve infiltratif (%9,2) alt tipler nodüler alt tipi takip etmekte, en az görülen alt tip ise yüzeyel yayılan BHK (%6,7) olarak bulunmuştur (Grafik 2).



Grafik 2. BHK Histolojik Alt Tipleri

SHK alt tiplerinde ise iyi diferansiye alt tip %61,1 ile en yaygın alt tip olarak görülmüştür. Orta derecede diferansiye (%26,2) ve in situ SHK (%12,7) alt tipleri sıklık sırasıyla izlenmiştir (Grafik 3).

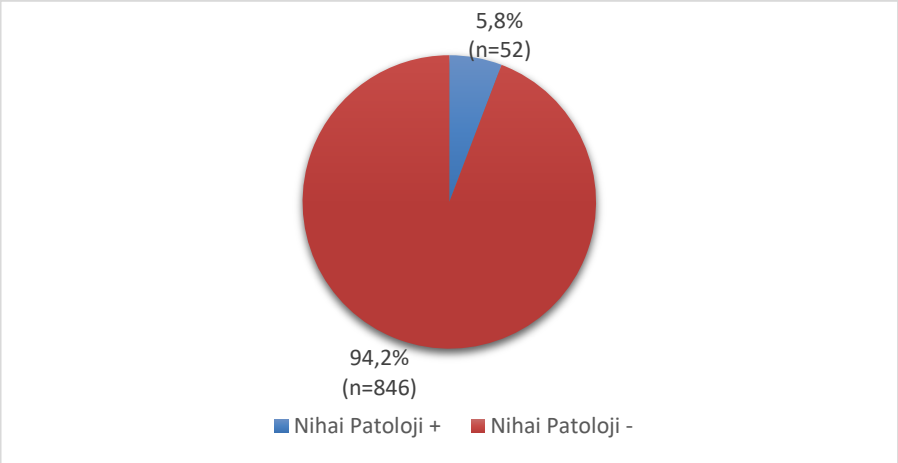


Grafik 3. SHK Histolojik Alt Tipleri

Cerrahi işlem sırasında, BHK lezyonlarının %66,8'i 5 mm cerrahi sınır ile, SHK lezyonları ise %62,7 ile en sık 10 mm cerrahi sınır ile eksize edilmiştir. Rekonstrüksiyon yöntemleri incelendiğinde, en sık

kullanılan yöntemin flep ile onarım (%49,8) olduğu belirlenmiştir. Bunu greft ile onarım (%28,7) ve primer kapatma yöntemi (%21,3) takip etmiştir.

Frozen kesit analizi sonuçlarına göre, 898 lezyonun 813 tanesi ilk eksizyon sonrası negatif, 85 tanesinde ise intraoperatif frozen kesit analizi sonucu pozitif gelmesi üzerine aynı seansta re-eksizyon uygulanmış ve nihai frozen kesit analizi sonucu negatif olarak raporlanmıştır. Nihai patoloji sonuçlarına göre, cerrahi sınırların %94,2'si negatif raporlanmış hem intraoperatif frozen kesit analizi hem nihai patolojik sonuçlarında cerrahi sınırlar negatif olarak değerlendirilmiştir. Lezyonların %5,8'inde ise frozen kesit analizi negatif olarak raporlanmasına rağmen, nihai patolojide pozitif cerrahi sınır tespit edilmiştir (Grafik 4).



Grafik 4. Frozen Negatif Hastaların Nihai Patoloji Cerrahi Sınırları

Bu doğrultuda frozen kesit analizi ile nihai patolojik değerlendirme arasında %94,2 oranında korelasyon tespit edilmiş olup, frozen kesit analizi ile nihai patoloji arasındaki yalancı negatiflik oranı %5,8 olarak hesaplanmıştır. Frozen kesit analizi ile nihai patolojik değerlendirme arasında korelasyon tespit edilen hastaların, net sınırlı ve daha küçük boyutlu, histopatolojik olarak ise nodüler tip BHK ve in situ SHK tümörlerde olduğu görülmüştür. Yalancı negatiflik ise, daha kötü sınırlara sahip, infiltratif veya mikronodüler büyüme paterni gösteren BHK alt tipleri ile orta derecede diferansiye SHK lezyonlarında saptanmıştır.

Takip süreleri boyunca hastaların %4,1'inde nüks gözlenmiş, %1,3'ünde ise uzak metastaz bildirilmiştir. Nükslerin büyük çoğunluğu SHK hastalarında görülmüş olup, en sık nüks, yüzdeki lezyonlarda meydana gelmiştir.

4. Tartışma ve Sonuç

Bu çalışmada, melanom dışı malign cilt lezyonlarında frozen kesit analizinin güvenilirliği ve nihai patolojik sonuçlarla uyumu retrospektif olarak değerlendirilmiştir. Bulgularımız, frozen kesit analizinin cerrahi sınırların intraoperatif değerlendirilmesinde yüksek bir doğruluk oranına sahip olduğunu ve yalancı negatiflik oranlarının kabul edilebilir düzeylerde olduğunu göstermektedir (%5,8). Bu sonuçlar, literatürdeki verilerle uyumlu olup, frozen kesit analizinin klinik pratikteki önemini desteklemektedir(9).

Non-melanom cilt lezyonlarının lokalizasyonları incelendiğinde yüz ve skalpin, UV ışınlarına da sık maruziyetleri nedeniyle, bu lezyonların en sık izlendiği bölgeler olduğu görülmüştür(14). Çalışmamızda literatüre paralel olarak, lezyonların en sık görüldüğü bölgeler arasında burun (%23,3) ve skalp (%12,9) olduğu gözlenmiştir.

Histopatolojik tipler açısından, BHK %72,8 ile en sık görülen malignite türü olurken, ikinci sırada %26,2 ile SHK yer almıştır. Çalışmamızda BHK'nın en yaygın alt tipi %67,8 oranıyla nodüler tip olarak bulunmuştur. Bunu nodülokistik (%16,2) ve infiltratif (%9,2) alt tipler takip etmiştir. Literatürde de nodüler BHK'nın en sık görülen histolojik alt tip olduğu, ancak infiltratif tipin cerrahi sınır pozitifliği ve nüks riski açısından daha riskli olduğu belirtilmektedir. SHK alt tiplerinde ise iyi diferansiye alt tipin %61,1 ile en yaygın olduğu belirlenmiştir. Bununla birlikte, çalışmamızda nihai

patoloji değerlendirmesinde kötü diferansiye SHK alt tipine rastlanmamış olması diferansiyasyon derecelerinin patoloji uzmanları arasında farklılık gösterebilmesi ile, olguların çoğunlukla orta derecede diferansiye gruba dahil edilmiş olma olasılığı da göz önünde bulundurulmalıdır. Ayrıca, çalışmaya dahil edilen SHK hasta grubunda, in situ SHK lezyonları da dahil edilmiş olup, bu hastalar için de frozen kesit analizinin doğruluğu çalışılmıştır.

Frozen kesit analizinin güvenilirliği üzerine yapılan önceki çalışmalarla kıyaslandığında, Onajin ve ark. yaptıkları çalışmada, frozen kesit analizi ile nihai patoloji arasındaki uyum oranının %94,3 olduğu belirtilmiştir(9). Çalışmamızda elde edilen %94,2'lik uyum oranı, bu sonuçlarla paralellik göstermekte ve frozen kesit analizinin intraoperatif dönemde cerrahi sınırların doğru bir şekilde değerlendirilmesinde etkili bir araç olduğunu doğrulamaktadır. Yalancı negatiflik oranları açısından, çalışmamızda %5,8 oranında yalancı negatiflik bildirilmiştir. Bu oran, literatürde bildirilen %3-7 arasındaki yalancı negatiflik oranları ile uyumlu bulunmuştur. Yalancı negatif sonuçlar, özellikle tümörün infiltratif veya mikronodüler büyüme paterni gösterdiği durumlarda, tüm tümör sınırlarının frozen örneklemesine dahil edilmesi güçleşmektedir. Ayrıca, lezyonun cerrah tarafından eksize edilen kısmı ile patolog tarafından değerlendirilen kesit arasında uyumsuzluk olabileceği gibi, teknik sınırlılıklar (örneğin kesit kalınlığı, donma artefaktları) da frozen kesit analizinde tümör dokusunun gözden kaçmasına neden olabilir. Onajin ve arkadaşlarının çalışmasında da benzer şekilde infiltratif tümörlerin daha yüksek yalancı negatiflik oranlarına yol açtığı bildirilmiştir. Bu bulgular, frozen kesit analizinin özellikle histopatolojik olarak sınırları belirsiz ya da agresif alt tipler içeren tümörlerde dikkatle yorumlanması gerektiğini göstermektedir.(9, 10).

Çalışmamızda frozen kesit analizinin genel doğruluk oranı yüksek olmakla birlikte, bu yöntemin bazı hasta gruplarında daha güvenilir olduğu gözlemlenmiştir. Özellikle nodüler alt tipe sahip BHK lezyonları, net sınırlı ve küçük boyutlu lezyonlar ile yüzeyel yerleşimli tümörlerde frozen kesit analizi ile nihai patoloji sonuçları arasında yüksek korelasyon saptanmıştır. Buna karşılık, infiltratif veya mikronodüler büyüme paterni gösteren BHK alt tipleri ile kötü sınırlı özellikleri olan SHK lezyonlarında, tümörün çevre dokulara mikroskobik yayılımı frozen kesitlerde gözden kaçabileceğinden, bu analiz daha sınırlı kalabilmektedir. Benzer şekilde Petitjean ve arkadaşlarının çalışmasında da frozen kesitin nodüler BHK ve iyi sınırlı SHK lezyonlarında daha güvenilir sonuçlar verdiği; ancak infiltratif ve agresif alt tiplerde yalancı negatiflik oranının arttığı bildirilmiştir(10).

Rekonstrüksiyon yöntemleri açısından, çalışmamızda flep ile onarımın en sık tercih edilen yöntem olduğu görülmüştür. Netscher ve ark. çalışmasında, yüz bölgesi lezyonlarında estetik sonuçları optimize etmek için flep rekonstrüksiyonunun yaygın olarak kullanıldığı vurgulanmıştır(15). Bu durum, yüz gibi estetik açıdan kritik alanlarda frozen kesit analizinin önemini bir kez daha ortaya koymaktadır.

Cerrahi sınır marjinlerine yönelik değerlendirmede, BHK lezyonlarında en sık 5 mm, SHK lezyonlarında ise 10 mm sınır uygulandığı belirlenmiştir. Literatürdeki çalışmalarda da benzer şekilde, SHK için daha geniş cerrahi sınırlar önerilmektedir(16, 17). Nüks oranlarının analizinde, SHK'nın daha yüksek nüks oranına sahip olduğu gözlemlenmiştir. Bu durum, SHK'nın histolojik olarak daha agresif bir doğaya sahip olması ve daha geniş cerrahi sınırlar gerektirmesiyle ilişkilendirilebilir. Literatürde de SHK'nın daha sık nüks ve metastaz yapma potansiyeline sahip olduğu vurgulanmaktadır(18). Bu bağlamda, literatürle de paralel olarak SHK lezyonlarında özellikle yüzdeki lezyonlarda nüks oranlarının daha yüksek olduğu, önemli bir klinik çıkarım olarak gözlenmiştir.

Frozen kesit analizinin avantajları olmakla birlikte, birtakım sınırlılıkları da bulunmaktadır. Frozen kesit analizi, dokunun yalnızca belirli bir bölgesini değerlendirdiğinden, tüm cerrahi sınırların eksiksiz bir şekilde incelenmesini garanti edememektedir. Bu nedenle, daha geniş kapsamlı cerrahi sınır incelemesi gerektiren durumlarda yöntem sınırlı kalabilir. Ayrıca lezyonun eksizyonunu gerçekleştiren cerrah ve frozen kesit analizini gerçekleştiren patoloğa göre de sonuçlar etkilenebilmektedir.

Çalışmamızın kısıtlılıkları arasında, verilerin retrospektif olarak alınması ve çalışmanın tek merkezli olarak yürütülmesi bulunmaktadır.

Sonuç olarak bu çalışma, frozen kesit analizinin, melanom dışı malign kutanöz lezyonların cerrahi yönetiminde güvenilir bir araç olduğunu göstermektedir. Ancak, yöntemin sınırlılıklarını dikkate alarak ve lezyonun histolojik alt tipi, lokalizasyonu, hastaya ait risk faktörleri gibi durumlar da göz önünde bulundurularak, cerrahi sınır yönetiminde multidisipliner bir yaklaşımın benimsenmesi önerilmektedir. Gelecekte daha geniş örneklem boyutlarına sahip prospektif çalışmalar,

frozen kesit yönteminin etkinliğini daha kapsamlı bir şekilde değerlendirebilir.

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Bir Üniversite Hastanesine Başvuran Erişkin Hastalarda Sağlık Haberleri Algısı ve Sağlık Okuryazarlığı Düzeyinin Değerlendirilmesi

Evaluation of Health News Perception and Health Literacy Level in Adult Patients Admitted to a University Hospital.

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Abstract: This study aimed to determine the level of health news perception in patients applying to a university hospital, to examine some variables thought to be related and to evaluate the level of health literacy. The study was a cross-sectional study conducted on adult patients admitted to ESOGU Health, Practice, and Research Hospital between 01 November - 30 December 2022. The study group consisted of 398 volunteer adult patients. The level of patients' perception of health news was assessed with the Health News Perception Scale and the level of health literacy was assessed with the Health Literacy Scale - Short FormOf the study group, 232 (58.3%) were female and 166 (41.7%) were male. Their ages ranged between 18-78 years and the mean age was 37.0±14.8 years. The scores obtained by the patients from the Health News Perception Scale ranged between 36.0 and 126.0. The mean score was 78.9±14.8 (median: 79.0). As a result of multiple linear regression analysis the variables found to be associated with the level of perception of health news, being male and being 45 years of age or older were found to be significant predictors of the perception of health news (p: 0.002, R2: 0.051, F: 3.469). It was found that there was a weak negative relationship between the scores obtained from the Health News Perception Scale and the Health Literacy Scale. It can be said that the perception of health news in the study group is at a medium level. It may be useful to carry out information activities to increase the perception of health news. As health literacy increases, patients' perception of negative health news decreases, even if it is low.
Keywords: Patient, Health News, Health Literacy, Eskişehir

Etik Kurul Onayı: Çalışma Eskişehir Osmangazi Üniversitesi Klinik Araştırmalar Etik Kurulu tarafından onaylanmıştır (Sayı: 54, Tarih: 22.11.2022).
Onam: Yazarlar retrospektif bir çalışma olduğu için olgulardan imzalı onam almadıklarını beyan etmişlerdir.
Telif Hakkı Devir Formu: Tüm yazarlar tarafından Telif Hakkı Devir Formu imzalanmıştır.
Hakem Değerlendirmesi: Hakem değerlendirmesinden geçmiştir.
Yazar Katkı Oranları: Veri toplama: MB, ES, SS. Konsept: MB, ES, SS, AK. Tasarım: MB, AÜ, DA. Veri İşleme: MB, ES.
Analiz veya Yorum: MB, ES, SS, AÜ, DA. Literatür Taraması: MB, ES, SS, AK. Yazma: MB, AÜ.
Çıkar Çatışması Bildirimi: Yazarlar çıkar çatışması olmadığını beyan etmişlerdir.
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Özet: Bir üniversite hastanesine başvuran hastalarda sağlık haberleri algısı düzeyinin saptanması, ilişkili olduğu düşünülen bazı değişkenlerin incelenmesi ve sağlık okuryazarlığı düzeyinin değerlendirilmesi amaçlanmıştır. Çalışma, 01 Kasım – 30 Aralık 2022 tarihleri arasında, ESOGÜ Sağlık, Uygulama ve Araştırma Hastanesi'ne başvuran erişkin hastalarda yapılan kesitsel bir araştırmadır. Çalışma grubu 398 gönüllü erişkin hastadan oluşmuştur. Hastaların sağlık haberleri algısı düzeyi, Sağlık Haberleri Algısı Ölçeği ile sağlık okuryazarlık düzeyi ise Sağlık Okuryazarlığı Ölçeği – Kısa Formu ile değerlendirilmiştir. Çalışma grubunu oluşturanların 232'si (%58,3) kadın, 166'sı (%41,7) erkektir. Yaşları 18-78 arasında değişmekte olup ortalama 37,0±14,8 yıl idi. Hastaların Sağlık Haberleri Algısı Ölçeği'nden aldıkları puanlar 36,0-126,0 arasında değişmekte olup ortalama 78,9±14,8 (ortanca: 79,0) puan idi. Sağlık haberleri algı düzeyi ile ilişkili olduğu saptanan değişkenlerle yapılan çoklu doğrusal regresyon analizi sonucunda erkek olmak ve 45 yaş ve üzerinde olmak sağlık haberleri algısının önemli yordayıcıları olarak bulunmuştur (p:0,002, R2: 0,051, F: 3,469). Sağlık Haberleri Algısı Ölçeği ile Sağlık Okuryazarlığı Ölçeğinden alınan puanlar arasında negatif yönde zayıf derecede bir ilişki olduğu saptanmıştır. Çalışma grubundakilerin sağlık haberleri algılarının orta düzeyde olduğu söylenebilir. Sağlık haberleri algısını artırmak için bilgilendirme çalışmalarının yapılması yararlı olabilir. Sağlık okuryazarlık düzeyi arttıkça düşük de olsa hastaların olumsuz sağlık haberleri algısı azalmaktadır.
Anahtar Kelimeler: Hasta, Sağlık Haberleri, Sağlık Okuryazarlığı, Eskişehir

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1. Giriş

Sağlıkla ilgili bilgilerin aranması, anlaşılması ve kullanılması sağlık konusunda karar vermede önemli bir yere sahiptir. Sağlık bilgisine erişimde seçeneklerin çok olması ile insanların bunlara erişmede tercih ettiği farklı yollar bulunmaktadır. Sağlık bilgisine erişmede önemli yollardan biri "sağlık haberciliğidir" (1,2). Sağlık haberciliği, insan sağlığı ve sağlıkla bağlantılı yaşam kalitesine dair her türlü konuyu ele alan haber faaliyetlerini kapsar. Bu alanın temel amaçları arasında bireyleri sağlık konusunda bilgilendirmek, halk sağlığına yönelik farkındalık oluşturmak, bilinç seviyesini artırmak ve gerekli durumlarda toplumu uyarmak yer almaktadır. Sağlıkla ilgili yayımlanan birçok haber, milyonlarca kişiye ulaşarak güncel bilgilerin başlıca kaynaklarından biri haline gelmektedir. (3).

İnsanlar güvendikleri kaynaklardan sağlık bilgilerine ulaşarak sağlıkla ilgili inanç, tutum ve davranışlarını şekillendirme eğilimindedirler. Sağlıklı bir yaşam sürmek ve sağlıklı yaşama yönelik bilgi sahibi olabilmek için sağlıkla ilgili haberlerin takip edilmesi çok önemlidir. Sağlık konusunda yeterli bilgiye sahip olma ile sağlık sorunlarına daha kolay çözüm bulunması, kişisel bakım ve hastalıkların önlenmesi, kişisel risk faktörlerinin ve önleyici stratejilerin daha kolay anlaşılması mümkün hale gelebilir. Ayrıca sağlıkla ilgili yeterli bilgi sahibi olunması; hastalıkların teşhis ve tedavi süreçlerine uyumu arttırmakta ve prognozların tahmin edilmesini kolaylaştırmaktadır (1,2,4).

Günümüzde medya, insanların sağlıkla ilgili konular hakkında bilgi edinme kaynakları arasında sağlık temalı içeriklerin artışıyla birincil haber kaynağı olarak ön plana çıkarken, sağlık alanında uzman kişilerden edinilen bilgiler daha geri planda kalmaya başlamıştır (5). Medyadaki haber kaynakları arasında internet, sosyal medya ve televizyon önde gelmektedir. Teknolojinin çok hızlı gelişimine paralel olarak özellikle sosyal medya kullanımı, dünyanın her yerindeki bilgi ve gelişmelere sınırsız erişim sağlamasıyla birlikte sağlık konusunda da önemli bir kaynak olarak ilgi çekmektedir. (6,7).

Sağlık haberleri algısı, bireylerin medyada yer alan sağlıkla ilgili haberleri nasıl değerlendirdiği, haberlere duyduğu güven ve haberlerin sağlık davranışlarına etkilerini kapsar. Sağlıkla ilgili haberlere kolay ulaşım; dezenformasyon, yanlış bilgilendirme gibi sorunlara yol açabilmektedir. Haberlerin doğru, objektif, çıkar çatışması olmadan kamusal yararın gözetilmesi gibi ilkeler ve toplumun demografik yapısı ile uyumlu olarak yapılması bireylerin haberlere olan algılarını olumlu yönde etkileyebilmektedir. Buna karşın haberler hazırlanırken etik ilkelerin gözetilmemesi, hatalı veya eksik bilgilerle toplumu yanlış sağlık görüşlerine yönlendirmesi ise olumsuz algı oluşturabilmektedir (6,8).

Sağlık haberleri algısını etkileyen en önemli faktörler arasında bireylerin sağlık okuryazarlık düzeyi olduğu bilinmektedir. Dünya Sağlık Örgütünün sağlık okuryazarlığı tanımı bireylerin sağlığını koruyup geliştirebilmesi için bilgiye erişme, anlama ve kullanma yeteneğini ile motivasyonunu şekillendiren bilişsel ve sosyal becerilerini kapsamaktadır (9). Sağlık haberlerinin yanıltıcı veya hatalı bilgiler içerebilmesi nedeniyle sağlık okuryazarlığı, sağlıklı yaşam ve sağlıkla ilgili kararlar açısından büyük bir öneme sahiptir (10).Sağlık okuryazarlığı, sadece bireyin kendisine sunulan tıbbi bir bilgiyi okuması ve anlaması değil aynı zamanda kendi sağlığının farkında olması, sağlığı hakkında karar alabilmesi, hastalığını bilmesi ve tanımlayabilmesi, sağlık sistemini kullanabilmesi ve sistemden en etkin şekilde nasıl yararlanabileceğini de bilmesini gerektiren bir alandır (11).

Bu çalışma ile hastaneye başvuran erişkin hastaların sağlık haberleri algısı düzeyinin saptanması, ilişkili olduğu düşünülen bazı değişkenlerin incelenmesi ve sağlık okuryazarlığı düzeyinin değerlendirilmesi amaçlanmıştır.

2. Gereç ve yöntem

Çalışma, 09 Kasım – 30 Aralık 2022 tarihleri arasında, ESOGÜ Sağlık, Uygulama ve Araştırma Hastanesi'ne başvuran erişkin hastalarda yapılan kesitsel tipte bir araştırmadır. Çalışma için ESOGÜ Girişimsel Olmayan Klinik Araştırmalar Etik Kurulunun 22.11.2022 tarih ve E-25403353-050.99-415416 sayılı onayı ve veri toplanabilmesi için de hastane başhekimliğinin yazılı izni alınmıştır.

Bu çalışma için ulaşılması gereken minimum hasta sayısı 384 olarak hesaplandı (yeterli sağlık haberleri algısı sıklığı 0.50, güven aralığı %95 ve hata payı 0.05). Veri toplama süresince hastaneye başvuran ve çalışmaya katılmayı kabul eden 398 erişkin hasta çalışma grubunu oluşturdu.

Çalışmada veri toplama aracı olarak kullanılan anket form literatürden de faydalanılarak oluşturuldu (5-7,9). Anket formda hastaların bazı sosyodemografik özellikleri, sağlık haberleri algısı ile ilişkili olduğu

düşünülen bazı faktörler, Sağlık Haberleri Algısı Ölçeği ve Sağlık Okuryazarlığı Ölçeğinin soruları yer almaktadır. Çalışmanın bağımlı değişkeni sağlık haberleri algısı iken bağımsız değişkenleri sosyodemografik özellikler, sağlık haberleri algısıyla ilişkili olabilecek faktörler ve sağlık okuryazarlığıdır.

Çalışma veri toplama süresince hastaneye başvuran erişkin hastalara polikliniklerin bekleme salonlarında çalışmanın konusu ve amacı hakkında bilgi verilmesinin ardından çalışmaya katılmayı kabul edenlerden sözel onamları alındı. Anket formlar, hastalar tarafından yaklaşık 5-7 dakikada dolduruldu.

Hastaların sağlık haberleri algı düzeyleri, Sağlık Haberleri Algısı Ölçeği kullanılarak değerlendirildi. Bu ölçek, 2018 yılında Çınar ile arkadaşları tarafından geliştirilmiştir. Ölçek, 5'li Likert tipi ve 26 sorudan oluşmaktadır. Ölçekten alınabilecek puan aralığı 26 ile 130 arasında değişmekte olup, yüksek puanlar daha yüksek düzeyde olumsuz sağlık haberleri algısını göstermektedir (12).

Çalışmamızda sağlık okuryazarlık düzeyinin değerlendirilmesi için Sağlık Okuryazarlığı Ölçeği Kısa Form kullanıldı. Bu ölçek, 2019 yılında Duong ve arkadaşları tarafından geliştirilmiş ve geçerlilik-güvenilirlik çalışması 2021 yılında Yılmaz ve Eskici tarafından yapılmıştır (13, 14). Ölçek, 4'lü Likert tipinde 12 sorudan oluşmaktadır. Ölçek sorularına verilebilecek cevaplar "çok zor" 1 puan, "oldukça zor" 2 puan, "oldukça kolay" 3 puan ve "çok kolay" 4 puan şeklinde değerlendirilir. Ölçeğin değerlendirilmesinde "İndeks = (Ortalama-1) x 50/3)" formülü kullanılmaktadır. Ortalama; ölçek toplam puanı ölçek madde sayısına bölünerek hesaplanır. Formül kullanılarak hesaplanan indeks değeri 0 ile 50 arasında değişmekte olup, puan yükseldikçe sağlık okuryazarlığı düzeyi de artmaktadır.

Bu çalışmada, hastaların aile gelir durumu ve genel sağlık durumları kendi algılarına göre değerlendirmiş olup "kötü", "orta" ve "iyi" şeklinde sınıflandırıldı. Günlük en az bir adet sigara tüketenler sigara içen bireyler olarak değerlendirildi. Haftada en az üç kez, 30 dakika veya daha uzun süre tempolu yürüyüş yapanlar düzenli egzersiz yapan bireyler olarak kabul edildi. Vücut kitle indeksi (VKİ) 30 ve üzeri olan kişiler ise obez olarak tanımlandı. (15,16).

Elde edilen veriler, SPSS (v 15.0) İstatistik Paket Programı programına aktarılarak değerlendirildi. Verilerin normal dağılıma uygunluğu Kolmogorov-Smirnov Testi ile kontrol edildi. İstatistiksel analizlerde Mann-Whitney U testi, Kruskal-Wallis testi, Spearman korelasyon analizi ve çoklu lineer regresyon analizi kullanıldı. İstatiksel anlamlılık değeri $p<0,05$ kabul edildi.

3. Bulgular

Çalışma grubundakilerin 231'i (%58,0) kadın, 167'i (%42,0) ise erkektir. Yaşları 18-78 arasında değişmekte olup ortalama 37,0±14,8 yıl idi. Hastaların Sağlık Haberleri Algısı Ölçeğinden aldıkları puanlar 36,0-126,0 arasında değişmekte olup ortalama 78,9±14,8 (ortanca: 79,0) puandır. Çalışma grubundakilerin Sağlık Haberleri Algısı Ölçeğinden aldıkları puanların bazı sosyodemografik özelliklere göre dağılımı Tablo 1'de verilmiştir.

Tablo 1. Çalışma grubundakilerin Sağlık Haberleri Algısı Ölçeğinden aldıkları puanların bazı sosyodemografik özelliklere göre dağılımı

Bazı sosyodemografik özellikler	**n (%)**	**Sağlık Haberleri Algısı Ölçek Puanı** Ortanca (min-max)	**Test değeri z / KW ; p**
Yaş grubu			
29 ve altı	154 (38,7)	78,0 (36,0-117,0)	**7,046; 0,030**
30-44	127 (31,9)	80,0 (41,0-126,0)	
45 ve üzeri	117 (29,4)	81,0 (50,0-126,0)	
Cinsiyeti			
Kadın	232 (58,3)	78,0 (36,0-126,0)	**2,219; 0,027**
Erkek	166 (41,7)	80,0 (57,0-126,0)	
Medeni durumu			
Evli değil	181 (45,5)	78,0 (36,0-114,0)	**2,108; 0,035**
Evli	217 (54,5)	80,0 (41,0-126,0)	
Öğrenim durumu			
İlkokul ve altı	27 (6,8)	78,0 (41,0-126,0)	0,272; 2,604
Ortaokul-Lise	169 (42,4)	79,0 (47,0-126,0)	
Üniversite	202 (50,8)	79,0 (36,0-114,0)	
Çalışma durumu			

Çalışmıyor	214 (53,8)	78,0 (41,0-126,0)	0,916; 0,360
Çalışıyor	184 (46,2)	80,0 (36,0-126,0)	
Aile gelir durumu			
Kötü	111 (27,9)	80,0 (50,0-126,0)	0,979; 0,613
Orta	184 (46,2)	78,0 (36,0-123,0)	
İyi	103 (25,9)	79,0 (36,0-118,0)	
Yaşadığı yer			
İl merkezi	315 (79,1)	78,0 (36,0-126,0)	**7,030; 0,030**
İlçe merkezi	61 (15,3)	78,0 (50,0-123,0)	
Belde / köy	22 (5,5)	90,0 (58,0-126,0)	
Obezite			
Yok	357 (89,7)	79,0 (36,0-123,0)	0,839; 0,402
Var	41 (10,3)	81,0 (50,0-126,0)	
Sigara içme durumu			
İçmiyor	234 (58,8)	79,0 (36,0-126,0)	0,478; 0,633
İçiyor	164 (41,2)	79,0 (41,0-126,0)	
Düzenli egzersiz yapma durumu			
Yapmıyor	214 (53,8)	79,0 (36,0-126,0)	0,348; 0,728
Yapıyor	184 (46,2)	79,0 (36,0-115,0)	
Kronik hastalık öyküsü			
Yok	251 (63,1)	78,0 (41,0-126,0)	**2,174; 0,030**
Var	147 (36,9)	82,0 (36,0-126,0)	
Ruhsal hastalık öyküsü			
Yok	341 (85,7)	79,0 (36,0-126,0)	1,078; 0,281
Var	57 (14,3)	76,0 (50,0-115,0)	
Toplam	398 (100,0)	79,0 (36,0-126,0)	

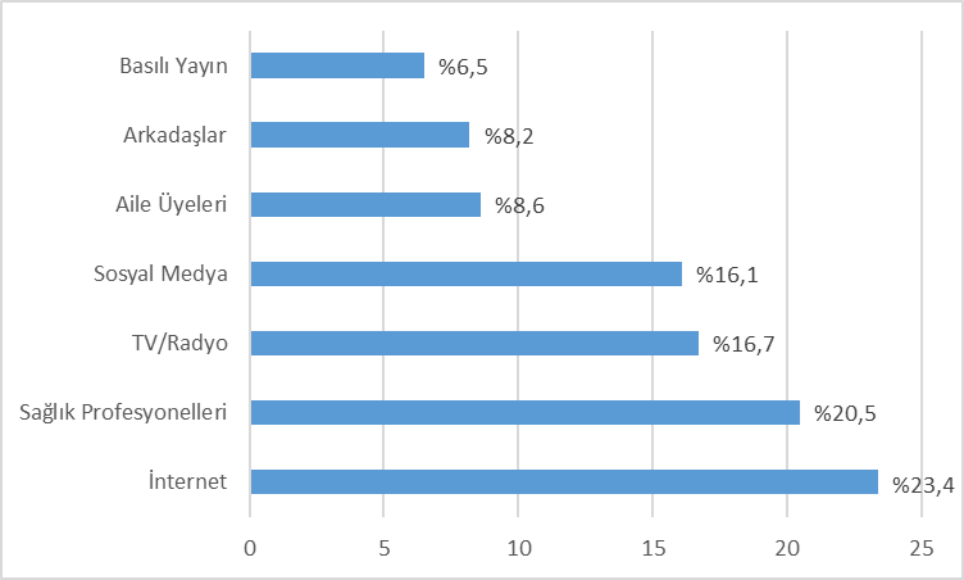
Çalışma grubunu oluşturanların 71'i (%17,8) her gün sağlıkla ilgili haberleri okuduğunu / izlediğini / dinlediğini, 245'i (%61,6) sağlıkla ilgili haberlerine güvendiğini, 167'si (%42,0) ise daha önce sağlıkla ilgili herhangi bir haber ve programda tavsiye edilenleri uyguladığını beyan etmiştir. Çalışma grubundakilerin Sağlık Haberleri Algısı Ölçeğinden aldıkları puanların sağlık haberleri algısı ile ilişkili olduğu düşünülen bazı değişkenlere göre dağılımı Tablo 2'de verilmiştir.

Tablo 2. Çalışma grubundakilerin Sağlık Haberleri Algısı Ölçeğinden aldıkları puanların sağlık haberleri algısı ile ilişkili olduğu düşünülen bazı değişkenlere göre dağılımı

Sağlık haberleri algısı ile ilişkili bazı değişkenler	**n (%)**	**Sağlık Haberleri Algısı Ölçek Puanı** Ortanca (min-max)	**Test değeri z / KW ; p**
Bakmakla yükümlü olduğu kişi varlığı			
Yok	288 (71,9)	79,0 (36,0-119,0)	0,972; 0,331
Var	112 (28,1)	79,0 (47,0-126,0)	
Genel sağlık durumunuzu nasıl tanımlarsınız?			
Kötü	33 (8,3)	83,0 (36,0-119,0)	2,051; 0,359
Orta	150 (37,7)	80,0 (36,0-126,0)	
İyi	215 (54,0)	78,0 (41,0-123,0)	
Sağlıklı beslendiğinizi düşünüyor musunuz?			
Hayır	164 (41,2)	81,0 (36,0-126,0)	1,273; 0,203
Evet	234 (58,8)	77,0 (41,0-126,0)	
Sağlıkla ilgili haberleri okuma / izleme / dinleme sıklığı			
Hiç izlemiyor	38 (9,5)	81,0 (58,0-106,0)	2,435; 0,487
Ayda en az 1 kez	86 (21,6)	78,0 (41,0-113,0)	
Haftada en az 1 kez	203 (51,0)	79,0 (36,0-126,0)	
Her gün	71 (17,8)	78,0 (52,0-126,0)	

Sağlıkla ilgili haberlere güveniyor musunuz?			
Güvenmiyorum	153 (38,7)	81,0 (50,0-126,0)	**2,248; 0,025**
Güveniyorum	245 (61,3)	77,0 (36,0-119,0)	
Sağlıkla ilgili herhangi bir haber ve programda tavsiye edilenleri uygulama durumu			
Uygulamam	231 (58,0)	78,0 (36,0-126,0)	0,584; 0,559
Uygularım	167 (42,0)	80,0 (41,0-123,0)	
Toplam	398 (100,0)	79,0 (36,0-126,0)	-

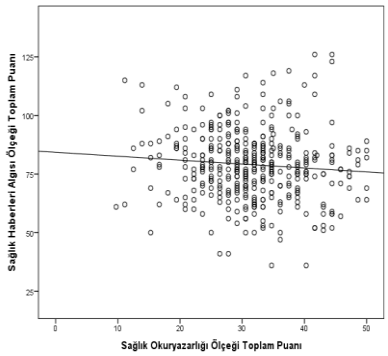
Çalışma grubundakilerin sağlıkla ilgili haberleri edindikleri kaynaklar arasında en çok internet (%23,4), sağlık profesyonelleri (%20,5) ve TV/radyo (%16,7) olduğu görülmüştür. Hastaların sağlıkla ilgili haberleri edindikleri kaynakların dağılımı Grafik 1'de verilmiştir.



Grafik 1. Sağlıkla ilgili haberlerin edinildiği kaynaklar*

*Sayılar kişiler üzerinden değil verilen cevaplar üzerinden değerlendirilmiştir.

Hastaların Sağlık Okuryazarlığı Ölçeğinden aldıkları puanlar 10,0-50,0 arasında değişmekte olup, ortalama 31,6±7,8 (ortanca: 30,5) puan idi. Sağlık Haberleri Algısı Ölçeği ve Sağlık Okuryazarlığı Ölçeğinden alınan puanlar arasında negatif yönde zayıf bir ilişki olduğu saptandı (r=-0,110, p=0,028). Çalışma grubundakilerin Sağlık Haberleri Algısı Ölçeğinden ve Sağlık Okuryazarlığı Ölçeğinden aldıkları puanların dağılımı Grafik 2'de verilmiştir.



Grafik 2. Hastaların Sağlık Haberleri Algısı

Ölçeğinden aldıkları puanlar ile Sağlık Okuryazarlığı Ölçeği'nden aldıkları puanların dağılımı

Yapılan istatistiksel analizlerde Sağlık Haberleri Algısı Ölçeğinden alınan puanlarla ilişkili olduğu saptanan değişkenlerle (cinsiyet, yaş grubu, medeni durum, yaşadığı yer, kronik hastalık öyküsü ve sağlıkla ilgili haberlere güvenme durumu) oluşturulan çoklu doğrusal regresyon analizi sonucunda yaş ve cinsiyetin sağlık haberleri algı düzeyinin yordayıcısı olduğu bulundu ($p<0,05$). İlgili regresyon analizi sonuçları Tablo 3'te sunulmuştur.

Tablo 3. Çalışma grubundakilerin Sağlık Haberleri Algısı Ölçeğinden alınan puanlarla ilişkili olduğu tespit edilen değişkenlerle oluşturulan çoklu doğrusal regresyon analizi sonuçları

Sağlık haberleri algısı ile ilişkili değişkenler	**Sağlık Haberleri Algısı Ölçeği Puanı**			
	Unstandardize beta	**Standardize beta**	**%95 GA**	**p**
Cinsiyet	**0,018**	**0,104**	**0,001-0,035**	**0,037**
Yaş grubu	**0,013**	**0,128**	**0,001-0,026**	**0,042**
Medeni durumu	-0,001	-0,008	-0,022-0,019	0,892
Yaşadığı yer	0,010	0,067	-0,005-0,026	0,191
Kronik hastalık öyküsü	0,006	0,032	-0,013-0,024	0,544
Sağlıkla ilgili haberlere güvenme durumu	-0,015	-0,087	-0,032-0,002	0,086
R^2	**0,051**			**0,001**
F	**3,935**			-

4. Tartışma

Sağlık haberleri, haber içerikleri arasında önemli bir yere sahiptir. Sağlıkla ilgili yayınların medyada yer alması, bu konulara verilen önemi artırmanın yanı sıra toplumun inanç, tutum ve davranışlarını da olumlu yönde şekillendirebilmektedir (17,18). Bu çalışmada, hastaların sağlık haberleri algısı düzeyinin saptanması, ilgili olduğu düşünülen bazı değişkenlerin incelenmesi ve sağlık okuryazarlığının değerlendirilmesi amaçlanmıştır.

Yaşam süresinin uzaması özellikle ileri yaşlarda birçok sağlık sorununu da beraberinde getirmektedir. Kronik sağlık sorunlarının yanında ölüm korkusu da artmaktadır. Bu durum insanların sağlıkla ilgili konulara karşı ilgilerinin artmasına ve sağlık haberlerinin takibiyle davranış değişikliklerine neden olabilmektedir (19,20). Çalışmamızda 45 ve üzeri yaş grubunda olanların sağlık haberleri algısının daha olumsuz olduğu saptandı. Bujnowska-Fedak ve Kurpas'ın Polonya'da 50 yaş üstü bireyler arasında yaptıkları bir çalışmada sağlık haberleri algısının daha olumlu olduğunu raporlamışlardır (21). Ertaş ve arkadaşlarının Konya'da yaptıkları çalışmada ise yaş grupları ve sağlık haberleri algısı arasında bir fark bulunamadığı bildirilmiştir (17). Çalışmalardaki farklı sonuçların nedenlerinden biri çalışma gruplarında sağlıkla ilgili yaşanılan kişisel deneyimlerdeki değişiklikler olabilir.

Kadınlar, hem kendi hem de aile üyelerinin sağlığından esas sorumlunun kendileri olduğunu benimsedikleri için sağlıkla ilgili programlarda hedef kitle olarak değerlendirilmektedirler (22). Bu sorumluluğun gereği olarak kadınların, kendisi ve aile üyeleri için doğru haber ve bilgiye ulaşma düşüncesiyle sağlık haberlerine daha dikkatli yaklaşmaları olasıdır. Bu çalışmada kadınların sağlık haberleri algısının erkeklere göre daha olumsuz olduğu saptandı. Yapılan bazı çalışmalarda ise sağlık haberleri algısı açısından kadınlarla erkekler arasında bir fark bulunamadığı bilidrilmiştir (6,18,23). Zaman içinde ailede primer bakım verenlerin rolündeki değişiklikler meydana gelmesi bildirilen farklı sonuçların nedenleri arasında sayılabilir.

İnsan sağlığı ve uzun yaşam süresi ile ilişkili olan sosyal faktörlerden birinin de insanların medeni durumları olduğu bilinmektedir. Yapılan bazı çalışmalarda evli olanların evli olmayan akranlarından daha iyi sağlık sonuçlarına sahip olduğu rapor edilmektedir (24,25). Bizim çalışmamızda evli olanların sağlık haberleri

algılarının evli olmayanlara göre daha olumsuz olduğu saptanmıştır. Oysa yapılan ileri analiz sonucunda sağlık haberleri algısı ile medeni durum arasındaki farkın ortadan kalktığı görülmüştür. Balcı ve Bekiroğlu'nun yaptıkları çalışmada evli olanlar arasında sağlık haberleri ile ilgili olumsuz algıların sağlıkla ilgili davranış değişikliğinde bekarlara göre daha etkili olduğu bildirilmiştir (6). Sağlık haberleri algı düzeyi ve medeni durum arasında bir ilişki bulunamadığını bildiren çalışmalar da mevcuttur (17,26). Yapılan çalışmalarda bulunan farklı sonuçların nedenlerinden biri çalışma gruplarını oluşturanların ailelerindeki sosyokültürel yapıların çeşitlilik göstermesi olabilir.

Kırsal kesimde yaşayanların sosyoekonomik durumlarının kentlerde yaşayanlardan daha kötü olduğu düşünüldüğünde sağlıkla ilgili bilgilere erişimlerinin ve kullanımlarının daha sınırlı olduğu bilinen bir gerçektir (27). Dolayısıyla yaşanılan yerin büyüklüğü ve gelişmişlik düzeyi bireylerin sağlık haberleri algısını ve sağlıklı olma davranışlarını etkilemesi olasıdır**.** Bu çalışmada belde / köyde yaşayanların sağlık haberleri algısının diğer gruplara göre daha olumsuz olduğu bulundu. Ancak yapılan ileri analiz sonucunda sağlık haberleri algısı ile yaşanılan yer arasındaki farkın ortadan kalktığı görülmüştür. Literatürde yaşanılan yerin özellikleri ile sağlık haberleri algısı ilişkisini ortaya koyan bir çalışmaya rastlanamamış olsa da özellikle kırsal alanlarda yaşayanların bireysel özellikleri ve bölgesel farklılıklarının sağlık kaynaklarına erişimi ve haber algısını etkileyeceğini bildiren araştırmacılar da vardır (28, 29).

Kronik herhangi bir hastalığı olanların özellikle sağlıkla ilgili bilgi kaynaklarına ulaşmada seçici davranarak sağlık bilgilerini daha iyi anlaması, değerlendirmesi ve kullanması olasıdır (30). Dolayısıyla bu hastaların sağlık haberleri algılarının daha olumsuz olması beklenebilecek bir durumdur. Çalışma grubunda kronik hastalık öyküsü olanların sağlık haberleri algılarının olmayanlara göre daha olumsuz olduğu bulundu. Yapılan çoklu lineer regresyon analizi sonucunda kronik hastalık varlığı ile sağlık haberleri algısı arasındaki farkın ortadan kalktığı görülmüştür. Kırılmaz ve Yıldırımın yaptıkları çalışmada kronik hastalığı olanlar arasında sağlık haberleri algısının olmayanlara göre daha olumlu olduğu raporlanmıştır (26). Vehof ve arkadaşları yaptıkları bir çalışmada kronik hastalığı olanların sağlık haberlerini güvenilir olmayan kaynaklardan edindiklerinde daha olumsuz bir tutuma yol açtığı raporlanmıştır (31).

Bir haberin kaynağının güvenilir olması, o habere olan algının olumlu yönde etkilenmesi açısından çok önemlidir. Sağlık haberinin o konuda uzman kişiler tarafından yapıldığı inancı yaygın olsa da medyadaki bilgi kirliliği nedeniyle bireylerin sağlık haberlerine olan algıları olumsuz yönde etkilenmektedir (8). Çalışma grubunda sağlıkla ilgili haberlere güvenmeyenlerin sağlık haberleri algılarının güvenenlere göre daha olumsuz olduğu bulundu. Ancak ileri analiz sonucunda bu farkın ortadan kalktığı görülmüştür. Ertaş ve arkadaşlarının yaptıkları çalışmada da benzer sonuçlar raporlanmıştır (17). Çıkrıkçı Işık ve arkadaşları sağlık sektöründe çalışanların sağlıkla ilgili haberleri güvenilir bulmadığı ve sağlık haberleri algılarının daha olumsuz olduğunu rapor etmişlerdir (32). Chang'ın Tayvan'da yaptığı bir çalışmada ise katılımcıların bilgi için genel olarak haber medyasına güvendikleri ancak medya tarafından geleneksel ve çevrimiçi sağlık haberlerinin daha çarpıcı ve abartılı hale getirildiğini bildirmiştir (33). Çalışmalarda benzer şekilde sağlık haberleri algısının olumsuz olmasının nedenlerden biri medyada yer alan haberlerin doğru bilgi vermekten çok halkın dikkatini çekme odaklı yapılması olabilir.

Teknolojinin hızla gelişmesi ve teknolojiye erişimin her geçen gün kolaylaşması nedeniyle haber algılarını etkileyen kaynaklar arasında kitle iletişim araçlarının öne çıktığı görülmektedir (7). Çalışmamızda sağlıkla ilgili haberlerin edinildiği kaynaklar arasında en çok sırasıyla; internet, sağlık profesyonelleri, TV/radyo ve sosyal medya olduğu saptandı. Yüksel ve arkadaşları sağlıkla ilgili haberlerin edinildiği kaynaklar arasında en çok sırasıyla; TV, gazete ve internet olduğunu bildirmişlerdir (34). Ferreira ve Borges'in COVID 19 pandemisi sürecinde yaptıkları çalışmada insanların ana sağlık haber kaynağı olarak televizyon ve gazeteleri kullandıkları bildirilmiştir (35). Nguyen ve arkadaşlarının Vietnamda yaptıkları bir çalışmada sağlık bilgisi edinme kaynakları arasında televizyon ve internetin ön plana çıktığını raporlamışlardır (36). Wang ve arkadaşları ise Hong Kong'da Çin'li erişkinler arasında sağlıkla ilgili bilgilerin en çok sırasıyla; gazete/dergi, televizyon, radyo ve internetten edinildiğini bildirmişlerdir (37).

Sağlık okuryazarlığı düzeyi azaldıkça bireylerin, sağlık bilgilerini okuma, anlama ve yorumlama becerilerinin de azalması beklenir (32). Dolayısıyla bu kişilerin sağlıkla ilgili haberlere olan algılarında da zorluk yaşamaları olasıdır**.** Çalışma grubundakilerin sağlık okuryazarlık düzeyleri arttıkça düşük de olsa sağlık haberleri algılarının olumlu yönde arttığı saptandı. Diviani ile arkadaşlarının yaptıkları çalışmada da sağlık okuryazarlık düzeyi arttıkça sağlık haberleri

algısının olumlu yönde arttığı raporlanmıştır (38). Chen ve arkadaşları sağlık okuryazarlık düzeyi düşük olanlarda sağlık haberleri algısının haber edinme kaynaklarının kalitesi arttıkça olumlu yönde değiştiğini bildirmişlerdir (1).

5. Kısıtlılıklar

Çalışmanın kesitsel tipte olması, sadece bir şehirde ve bir sağlık kurumuna başvuranlarda yapılmış olması çalışmanın genellenebilirliği açısından kısıtlılıklardır.

6. Sonuç ve öneriler

Çalışma grubundakilerin sağlık haberleri algısı orta düzeyde olduğu söylenebilir. Yapılan çoklu doğrusal regresyon analizi sonucuna göre yaş ve cinsiyetin sağlık haberleri algı düzeyinin yordayıcısı olduğu bulundu. Sağlıkla ilgili haberlerin edinildiği kaynaklar sırasıyla; internet, sağlık profesyonelleri ve TV/radyo idi. Hastaların sağlık okuryazarlık düzeyleri arttıkça düşük de olsa sağlık haberleri algılarının olumlu yönde artmaktadır. Sağlık profesyonellerinin hastalara sağlık okuryazarlığı düzeyinin arttırılması ve sağlık haberleri algısını olumlu yönde etkileyebileceği bilgi kaynakları ve haber platformlarını önermesi yararlı olabilir. Ayrıca hastane içerisinde görsel destekli içerikler (infografikler, kısa videolar) ve kısa mesajlarla sağlık bilgileri ileterek daha etkili ve kolay anlaşılır hale getirilebileceği düşünülmektedir. Sağlık haberleri algısı ve sağlık okuryazarlığı ilişkisinin ortaya konabilmesi için toplum tabanlı kapsamlı çeşitli çalışmalara ihtiyaç vardır.

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The Effects of Vortioxetine on Rotenone-Induced Inflammatory Changes in Rat-Derived Enteroglial Cells: The Role of the TLR4/NFκB Signaling Pathway

Sıçan Kökenli Enteroglial Hücrelerde Rotenon ile İndüklenen İnflamatuvar Değişiklikler Üzerine Vortioksetinin Etkileri: TLR4/NFκB Sinyal Yolağının Rolü

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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder with both motor and non-motor symptoms, and currently, there is currently no disease-modifying therapy. Due to their potential anti-inflammatory effects, antidepressants have gained attention as therapeutic agents in inflammation-related neurological conditions. In this study, we aimed to investigate the effects of vortioxetine on rotenone-induced enteric inflammation in an *in vitro* model using enteric glial cells and whether these effects involve modulation of the TLR4/NF-κB signaling pathway. Cells were treated with rotenone (10 μM) and vortioxetine (1 and 5 μM). TLR4 and NF-κB mRNA expression levels were analyzed by RT-qPCR, and the levels of TNF-α, IL-1β, and IL-6 were measured via ELISA. The findings showed that rotenone significantly suppressed TLR4 and NF-κB expression by impairing the immune responses of glial cells, and the administration of 5 μM vortioxetine further enhanced this effect. Additionally, the decrease observed in TNF-α and IL-1β levels in the rotenone groups was reversed by vortioxetine administration. The results suggest that vortioxetine may regulate inflammatory responses in enteric glial cells through the TLR4/NF-κB pathways and could be investigated as a potential therapeutic compound in inflammation-based models of the gut-brain axis in PD.
Keywords: Enteric inflammation, Enteric glia, Rotenone, Toll-like receptor, Vortioxetine

Özet: Parkinson hastalığı (PH) progresif bir nörodejeneratif hastalık olup günümüzde hastalığı durdurmaya yönelik kesin bir tedavi seçeneği bulunmamaktadır. Gastrointestinal inflamasyon, PH ile ilişkili motor-olmayan bulgulardan biridir. Son yıllarda antidepresanların potansiyel antiinflamatuvar etkileri nedeniyle nörodejeneratif hastalıkların tedavisinde kullanılabileceğine dair ilgi artmıştır. Bu çalışmada, vortioksetinin enterik glia hücrelerinde rotenon ile indüklenen inflamatuvar yanıtlar üzerindeki etkisi ve bu etkisinde TLR4/NF-κB sinyal yolağının rolü araştırılmıştır. Rotenon (10 μM) ve vortioksetin (1 ve 5 μM) ile muamele edilmiş hücre örneklerinde TLR4 ve NF-κB mRNA ekspresyonları RT-qPCR ile, TNF-α, IL-1β ve IL-6 düzeyleri ise ELISA yöntemiyle değerlendirilmiştir. Bulgular, rotenonun glial hücrelerin immün yanıtlarını bozarak TLR4 ve NF-κB ekspresyonunu belirgin şekilde baskıladığını ve bu etkinin 5 μM vortioksetin uygulamasıyla daha da arttığını göstermiştir. Ayrıca rotenon gruplarında TNF-α ve IL-1β düzeylerinde gözlenen düşüş, vortioksetin uygulaması ile tersine dönmüştür. Sonuçlar, vortioksetinin enterik glia hücrelerinde TLR4/NF-κB yolakları üzerinden inflamatuvar yanıtı düzenleyebileceğini ve PH'nin bağırsak-beyin eksenine dayalı inflamasyon modelinde potansiyel bir terapötik madde olarak çalışılabileceğini göstermektedir.
Anahtar Kelimeler: Enterik inflamasyon, Enterik glia, Rotenon, Toll-benzeri reseptör, Vortioksetin.

Ethics Committee Approval: This study was conducted using a commercially available cell line. No human participants, human-derived tissues, or animal models were involved. Therefore, ethical approval was not required for the experimental procedures described. We confirm that all methods were carried out in accordance with relevant guidelines and regulations.
Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.
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1. Introduction

Post-mortem studies have shown that Lewy body pathology, a characteristic feature of Parkinson's disease (PD), exists in the enteric nervous system (ENS) beyond the central nervous system (CNS) in nearly all PD patients (1). The ENS referred to as the "second brain" functions as the intrinsic neural network of the gastrointestinal tract and exhibits numerous similarities to the CNS (2). The ENS has a very large number of neurons and a larger population of glial cells (3). Enteric glial cells (EGCs) closely resemble CNS astrocytes and microglia in both structure and function (4). During inflammation, EGCs activate signaling pathways that result in the release of cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and IL-6 (5).

Gastrointestinal dysfunction, which belongs to the non-motor symptoms of PD, is believed to emerge years before the onset of motor symptoms (6). With the identification of Lewy body pathology in enteric neurons obtained from biopsies of PD patients, the potential involvement of the ENS in PD pathophysiology has gained attention (7). Studies have shown that EGCs actively regulate the neuroimmune axis via pattern recognition receptors such as Toll-like receptors (TLRs) (8). TLR4 plays a crucial role in the pathogenesis of PD by mediating neuroinflammation, responding to alpha-synuclein aggregates, and contributing to both CNS and ENS dysfunction, making it a promising therapeutic target (9, 10).

Pharmacological approaches have been used to develop experimental models that mimic nigrostriatal neurodegeneration and PD-like pathology in animals (2). Exposure to rotenone, a pesticide, is widely utilized both *in vitro* and *in vivo* as a disease model because it replicates key pathological and behavioral features of PD (11, 12). Rotenone administration has been shown to induce pathological alterations not only in the CNS but also in the ENS, leading to both motor and non-motor symptoms, including gastrointestinal dysfunction (6, 13). Rotenone is a highly lipophilic molecule and a well-characterized inhibitor of mitochondrial complex I. In addition to inducing dopaminergic neurodegeneration, rotenone exposure activates inflammatory pathways through mechanisms such as p38 MAPK activation and mTOR inhibition, leading to increased oxidative stress, ATP depletion, and apoptosis (14). Furthermore, rotenone exposure has been shown to upregulate pro-inflammatory cytokines and TLR-related signaling in both neuronal and glial cells (15). In enteric neuronal cell cultures, rotenone exposure has been shown to increase the number of α-synuclein inclusions within non-neuronal (16). Moreover, following rotenone exposure, TLR4 knockout mice displayed reduced intestinal inflammation, gut and motor dysfunction, neuroinflammation, and neurodegeneration compared to wild-type mice (17), indicating that PD symptomatology could be related to disrupted immune responses mediated by EGCs (8).

Experimental studies have shown that certain antidepressants can reduce proinflammatory cytokine levels in inflammatory conditions (18). Vortioxetine is an antidepressant that works in multiple ways by blocking 5-HT_3, 5-HT_7, and 5-HT_{1D} receptors with 5-HT_{1B} partial agonism and 5-HT_{1A} agonism. It also inhibits the serotonin transporter (SERT) (19). Previous research has reported that vortioxetine may exert beneficial effects on TLR2-mediated inflammatory mechanisms (20, 21). Identifying strategies that can prevent enteric neurodegeneration may contribute to the development of new therapeutic principles for neurodegenerative diseases. This study aims to investigate the inhibitory effects of vortioxetine on rotenone-induced inflammatory changes in EGCs through modulation of the TLR4/NFκB signaling pathway.

2. Materials and Methods

2.1. *In vitro* studies

2.1.1. Chemicals and reagents

Vortioxetine was sourced by H. Lundbeck A/S (Denmark). For experimental treatments, rotenone and the solvent dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Vortioxetine was prepared in 10% 2-hydroxypropyl-β-cyclodextrin, while rotenone was dissolved in DMSO. The final concentration of DMSO in the culture medium was kept below 0.2% to prevent cytotoxicity.

2.1.2. Enteroglial cell culture

The EGC cell line used in this study, derived from rat tissue, was generously obtained from Dr. Luca Antonioli (University of Pisa). Cells were cultured in DMEM enriched with 10% fetal bovine serum (FBS), 2 mM L-glutamine, and 100 U/mL penicillin-streptomycin. Cultures were maintained at 37 °C in a humidified incubator with 5% CO_2. When cells

reached 70–80% confluency, they were detached using trypsin-EDTA and subsequently seeded into T-25 flasks or 96-well plates for experimental procedures.

2.1.3. Study design

The selection of rotenone and vortioxetine concentrations was based on our previous study, where we optimized these concentrations through viability and functional assays (21). The experimental groups established for the study are detailed in Table 1.

Table 1. Experimental groups

Group	Treatment
I. CONTROL	Culture medium without any additives
II. ROTENON	Culture medium containing 10 μM rotenone
III. VORTIOXETINE (V1)	Culture medium containing 1 μM vortioxetine
IV. VORTIOXETINE (V2)	Culture medium containing 5 μM vortioxetine
V. ROT+V1	Culture medium containing 10 μM rotenone and 1 μM vortioxetine
VI. ROT+V2	Culture medium containing 10 μM rotenone and 5 μM vortioxetine

2.1.4. Reverse transcription quantitative polymerase chain reaction (RT-qPCR)

Total RNA was isolated from cultured cells using a commercial RNA extraction kit (HibriGen, Cat. No. MG-RNA-01-100) in accordance with the supplier's guidelines. After cell lysis, RNA was collected using spin column-based purification. RNA quality and quantity were evaluated using spectrophotometric analysis, and only samples with a 260/280 absorbance ratio between 1.7 and 2.0 were selected for subsequent steps. For cDNA synthesis, 1 μg of RNA was converted to cDNA using the OneScript® Plus cDNA synthesis kit (ABM, G236). Reverse transcription was performed at 25 °C for 10 min, 50 °C for 15 min, and 85 °C for 5 min. cDNA was stored at −80 °C until further use.

Specific primers for TLR4 and NFκB that are used in the study are listed in Table 2. PCR amplification was performed using a Roche LightCycler 96 system. Cycling conditions included an initial denaturation at 95 °C for 5 min, followed by 40 cycles of 95 °C for 15 s and 60 °C for 20 s. A melting curve analysis (60 °C to 95 °C, with 0.5 °C/s increments) confirmed specificity. Gene expression levels were quantified using the $2^{-\Delta\Delta CT}$ method (22) using the reference gene beta-actin (β-act) for normalization.

Table 2. Primer sequences used for RT-qPCR

Gene	Primer Sequence
TLR4	F: GGATGATGCCTCTCTTGCAT
	R: TGATCCATGCATTGGTAGGTAA
NFκB	F: GCCTGACACCAGCATTTGA
	R: CAAACCAAACAGCCTCACG
β-actin	F: CGGCAATGAGCGGTTCC
	R: TGCCACAGGATTCCATACCC

2.1.5. Measurements of TNF-α, IL-1β, and IL-6 levels

Levels of TNF-α, IL-1β, and IL-6 in EGC lysates were measured using enzyme-linked immunosorbent assay (ELISA) kits (BT Lab; TNF-α: E0764Ra, IL-1β: E0119Ra, IL-6: E0135Ra), following the manufacturers' protocols. Briefly, cells were washed with PBS, detached with trypsin, and collected by centrifugation at 1000 g for 5 minutes. After discarding the supernatant, cells were washed three times with PBS. A total of 1×10^6 cells were resuspended in PBS and subjected to three freeze-thaw cycles. Lysates were centrifuged at 1500 g for 10 minutes at 2–8 °C, and the resulting supernatants were collected and stored at −20 °C until analysis. All measurements were performed in duplicate.

2.3. Statistical Analysis

All data were expressed as mean ± standard error of the mean (SEM). The Kolmogorov–Smirnov test was used to assess the normality of distribution. Group differences were assessed with one-way

ANOVA followed by Tukey's post-hoc test. For non-normally distributed data, the Kruskal–Wallis test was applied, followed by Dunn's post-hoc test for multiple comparisons. Statistical analyses were performed on GraphPad Prism 10.0 software (SanDiego, CA, USA), and a p-value < 0.05 was considered statistically significant.

3. Results

3.1 Changes in TLR4 and NFκB mRNA expression

The mRNA expression levels of TLR4 and NFκB were assessed in EGCs to compare differences among experimental groups. As shown in Figure 1a, Rotenone exposure caused a marked decrease in TLR4 expression ($p < 0.0001$), indicating a toxic impairment of inflammatory signaling in EGCs. Co-administration of vortioxetine (5 µM) with rotenone further decreased TLR4 expression ($p < 0.05$ vs. rotenone alone), suggesting that vortioxetine potentiated the rotenone-induced TLR4 downregulation rather than reversing it. Interestingly, vortioxetine administered alone at both concentrations (1 µM and 5 µM) also significantly reduced TLR4 expression compared to the control group ($p < 0.0001$ for both), indicating that vortioxetine may directly modulate basal TLR4 signaling even in the absence of rotenone Unlike TLR4, NF-κB expression did not show significant differences between groups (Figure 1b). However, in the rotenone-treated group, NF-κB expression was reduced by 48.83%, indicating a marked toxic effect. When high-concentration vortioxetine (5 µM) was co-administered with rotenone, NF-κB levels decreased even further (52.67% reduction), suggesting that vortioxetine at this concentration did not mitigate, and may even potentiate, rotenone-induced suppression. Interestingly, the combination of rotenone with a lower concentration of vortioxetine (1 µM) resulted in a slight 18.61% increase in NF-κB expression compared to rotenone alone; however, this change did not reach statistical significance ($p > 0.05$).

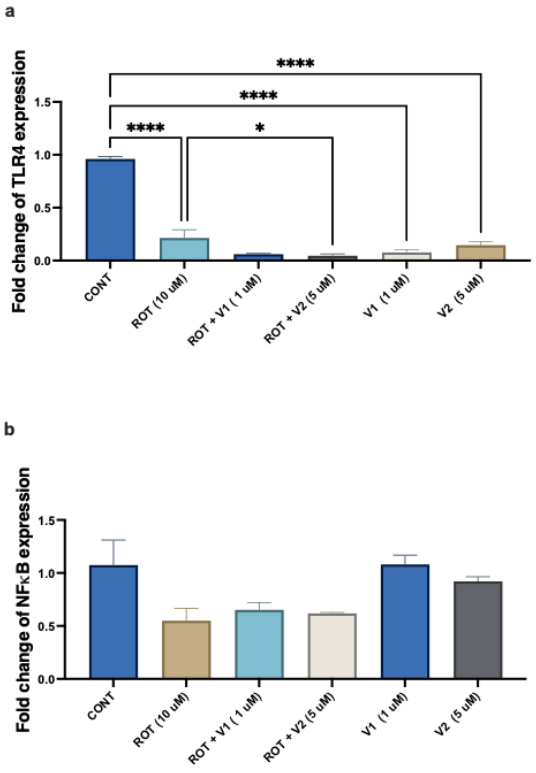

Figure 1. Fold changes in TLR4 and NF-κB mRNA levels in EGCs. Data are presented as mean ± SEM. Experiments were performed in duplicate and repeated three times. Statistically significant results are marked with an asterisk (*). CONT: Control, ROT: 10 µM Rotenone, V1: 1 µM vortioxetine. V2: 5 µM vortioxetine. *$p < 0.05$, ****$p < 0.0001$.

3.2. Changes in proinflammatory cytokines levels in EGCs

TNF-α levels were significantly reduced in the rotenone-treated group compared to the control ($p < 0.05$), indicating a suppressive effect of rotenone alone (Figure 2a). When vortioxetine was co-administered with rotenone, both low (1 µM) and high (5 µM) concentrations, did not change the TNF-α levels. Moreover, vortioxetine alone (at both concentrations) did not significantly alter TNF-α levels compared to the control group.

For IL-1β levels, although there was a 32% reduction following rotenone administration compared to the control group, which may be considered physiologically relevant, the difference did not reach statistical significance (Figure 2b). Co-treatment with vortioxetine at 1 µM significantly increased IL-1β levels compared to rotenone alone ($p < 0.01$), while 5 µM vortioxetine showed non-significant reversal. Vortioxetine alone (at both concentrations) did not significantly alter IL-1β levels compared to the control group.

IL-6 levels did not differ significantly between the treatment groups, indicating that neither rotenone nor its combination with vortioxetine led to a significant modulation of IL-6 expression (Figure 2c).

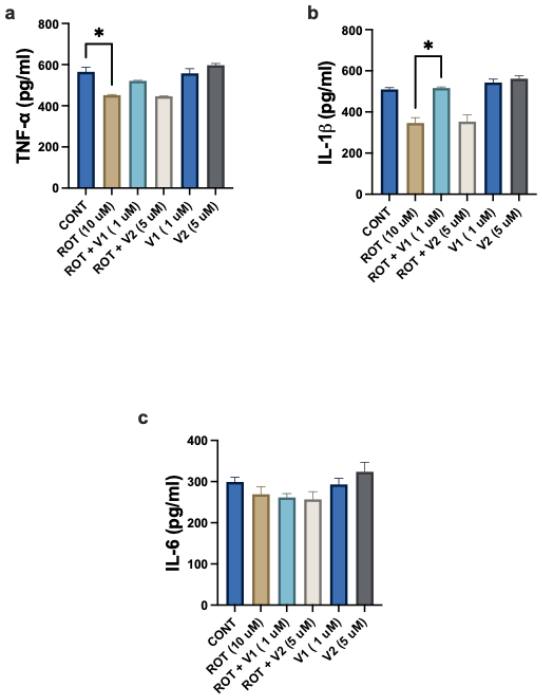

Figure 2. Changes in TNF-α (a), IL-1β (b) and IL-6 (c) levels in enteric glial cells. Data are presented as mean ± SEM. Experiments were performed in duplicate and repeated three times. Statistically significant results are marked with an asterisk (*). CONT: Control, ROT: 10 µM Rotenone, V1: 1 µM vortioxetine. V2: 5 µM vortioxetine. *$p < 0.05$.

4. Discussion

PD pathology is estimated to begin in the ENS and transfer to the CNS via vagal nerve (23) supported by the research indicating pathological α-synuclein aggregates detected in gastrointestinal tissues several years prior to clinical diagnosis of PD (24). Given the importance of ENS in the disease progression, our study provides valuable insight into the potential neuroprotective role of vortioxetine in rotenone-induced EGC dysfunction. By examining both gene expression and inflammatory cytokine levels, our findings demonstrated that rotenone, a complex I inhibitor, disrupted the cellular inflammatory response and led to a reduction in inflammatory marker levels. On the other hand, vortioxetine appeared to enhance this response, as indicated by an increase in the expression of these markers. These findings highlight vortioxetine's potential in modulating early enteric inflammatory pathways relevant to PD pathogenesis.

Rotenone is a pesticide that inhibits the complex I of the mitochondrial electron transport chain. It is widely used in research to model PD because it can replicate many of the disease's key features (25). Exposing the stomach to the rotenone caused the propagation of α-synuclein to the brain (26, 27). Rotenone has also been shown to induce pathological changes in enteric neuronal culture (16, 28) and primary enteric neurons (29). In our previous study, we also demonstrated the toxic

effects of rotenone on EGCs (21). We performed this study in EGCs due to their essential roles in the gut inflammation (30). These cells functionally and morphologically resemble astrocytes in the CNS and are activated during inflammation through TLRs (31). Especially, the TLR4/NF-κB pathway plays a significant role in the pathogenesis of PD by mediating neuroinflammation and contributing to neuron damage (32). The TLR4/NF-κB pathway is activated in response to α-synuclein and other inflammatory stimuli, leading to increased expression of inflammatory genes and cytokines such as TNF-α and IL-1β (33, 34). Perez-Pardo et al. demonstrated that patients with PD exhibit increased intestinal TLR4 expression, mucosal immune activation, and disrupted gut barrier integrity, all of which were replicated in rotenone-treated wild-type mice (17). Our results showed that rotenone reduced TLR4 and NFκB levels in EGCs, suggesting that exposure to neurotoxins like rotenone may impair glial responses to inflammation by disrupting mitochondrial function. Consistent with our study, Rabaneda-Lombarte et al. demonstrated that rotenone impairs glial immune responses by disrupting cellular metabolism and interfering the metabolic reprogramming essential for glial activation (35, 36). The reduction of TLR4 expression observed with vortioxetine alone, as well as the further reduction seen with its co-administration alongside rotenone, might be explained by vortioxetine's intrinsic serotonergic immunomodulatory effects. In fact, chronic antidepressant treatment (including SSRIs) has been shown to attenuate TLR4 levels (37). This potentiation may also reflect a compensatory mechanism to prevent an exaggerated inflammatory response under toxic conditions in which cells can develop tolerance by reducing TLR4 receptor levels or responsiveness (38). In addition to its known central effects, recent clinical evidence suggests that vortioxetine may also exert therapeutic actions by modulating the gut microbiota composition (39). These findings raise the possibility that vortioxetine's immunomodulatory effects against gut-related inflammatory responses.

Proinflammatory cytokines are known to be increased in PD patients in serum (40), cerebrospinal fluid (41), brain (42) and even colon tissue (43). However, *in vitro* systems may fail to mimic these inflammatory responses because they lack the intricate cellular interactions present *in vivo*. Previous studies have demonstrated that rotenone-induced neurotoxicity is significantly amplified in the presence of glial cells, particularly microglia, through mechanisms involving oxidative stress and activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (44). Given the functional parallels between EGCs and CNS glia, it is plausible that rotenone may also activate inflammatory signaling and oxidative responses in EGCs, thereby exacerbating cellular damage. This could explain why we observed a significant decrease in the levels of TNF-α and IL-1β in our model. Administration of a low concentration of vortioxetine increased the IL-1β levels in rotenone group, suggesting that it helps to regain cells to produce a response against inflammation. These findings highlight the relevance of glial cell type in shaping cellular vulnerability to mitochondrial toxins and emphasize the importance of considering glial contributions when modeling gut-related aspects of PD.

This study has some limitations. The findings are based on a single *in vitro* model using rat-derived EGCs, which, although highly relevant to the enteric nervous system, do not fully replicate the complex multicellular and microenvironmental interactions observed *in vivo*. Moreover, the glial response to rotenone and vortioxetine was assessed at the mRNA and cytokine levels; however, additional analyses would provide a more comprehensive understanding of the underlying mechanisms.

In conclusion, our findings provide novel insights into the effects of rotenone and vortioxetine on inflammatory responses in EGCs, highlighting the involvement of the TLR4/NF-κB pathway. Rotenone-induced suppression of inflammatory signaling suggests that mitochondrial toxins impair glial capacity to respond to environmental stressors. Importantly, co-treatment with vortioxetine, particularly at low concentrations, partially restored TLR4 expression and increased IL-1β levels, suggesting a potential modulatory role on glial-driven inflammation. These results support the hypothesis that targeting enteric glia and gut inflammation may offer promising avenues for early intervention in PD.

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Yardımcı Üreme Tedavisi Sonuçlarında Zayıf Yanıt Veren Olgularda Over Rezerv Belirteçlerinin Öngörü Potansiyeli

The Predictive Potential of Ovarian Reserve Markers for Poor Responders in the Assisted Reproductive Treatment Outcomes

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Abstract: To evaluate the predictive power of baseline age, FSH, AMH, and AFC on total retrieved oocyte numbers and treatment outcomes in women with poor ovarian response (POR) according to the Bologna criteria. In this retrospective study, 181 IVF cycles meeting the Bologna POR criteria were analyzed at the Eskişehir Osmangazi University Reproductive Health Center between January 2017 and December 2024. Baseline parameters (age, FSH, AMH, AFC) were correlated with total and MII oocyte counts using correlation and logistic regression analyses. POR prediction (≤3 retrieved oocytes) was assessed by ROC analysis. Pregnancy outcomes (biochemical, clinical pregnancy, live birth) were recorded based on serum β-hCG measurements 12 days post-transfer and ultrasonographic findings. The mean age was 35.9 ± 4.6 years, basal FSH 9.9 ± 4.1 IU/L, AMH 0.88 ± 0.33 ng/mL, and AFC 5.5 ± 2.5. Mean total oocyte count was 2.54 ± 1.28 and MII oocyte count 1.50 ± 1.27. AFC showed a significant correlation with total oocyte count ($r = 0.247$, $p < 0.001$). AMH (AUC = 0.716, $p = 0.003$) and FSH (AUC = 0.687, $p = 0.002$) predicted POR cycles with ≤3 oocytes, demonstrating slightly lower AUC values compared to AFC. Clinical pregnancy rate was 28.9% and live birth rate was 18.1%. In women with POR, AFC was the strongest predictor of oocyte yield, while AMH and FSH showed comparable and higher performance in identifying very POR cycles. These findings underscore the importance of combined assessment of basal ovarian reserve markers for personalized IVF protocol planning.

Keywords: Ovarian Reserve; Antral Follicle Count(AFC); Anti-Müllerian Hormone(AMH); Follicle Stimulating Hormone(FSH); Poor Ovarian Response; İn Vitro Fertilization

Özet: Bu çalışmanın amacı, Bologna kriterlerine göre düşük over yanıtı tanısına uyan kadınlarda bazal yaş, FSH, AMH ve AFC değerlerinin toplanan oosit sayısı bağlantılı tedavi sonuçlarını öngörme gücünü değerlendirmektir. Eskişehir Osmangazi Üniversitesi Üreme Sağlığı Merkezi'ne Ocak 2017–Aralık 2024 tarihleri arasında başvuran, Bologna kriterlerine göre düşük over yanıt durumuna sahip 181 tüp bebek siklusu retrospektif olarak incelendi. Bazal parametreler (yaş, FSH, AMH, AFC) ile toplanan oosit sayıları arasındaki ilişki korelasyon ve lojistik regresyon analizleri ile; çok düşük over yanıtı (≤3 oosit) öngörüsü ROC analizi ile değerlendirildi. Gebelik sonuçları (biyokimyasal, klinik gebelik, canlı doğum) embriyo transferinden 12 gün sonraki β-hCG ve ultrasonografik bulgulara göre kaydedildi. Katılımcıların ortalama yaş 35.9±4.6 yıl, bazal FSH 9.9±4.1 IU/L, AMH 0.88±0.33 ng/mL, AFC 5.5±2.5 olarak tespit edildi. Ortalama toplam oosit sayısı 2.54±1.28, matür oosit sayısı 1.50±1.27 idi. AFC, toplam oosit sayısı ile anlamlı korelasyon ($r=0.247$, $p<0.001$) gösterirken; AMH (AUC=0.716, $p=0.003$) ve FSH (AUC=0.687, $p=0.002$) 3 ve altı oosit elde edilen döngüleri öngörmede AFC'ye göre daha yüksek öngörü potansiyeli sergiledi. Klinik gebelik oranı %28.9, canlı doğum oranı %18.1 olarak bulundu. Düşük over yanıtlı vakalarda AFC, toplam oosit sayısını öngörmede en güçlü belirteç iken; düşük yanıtlı döngülerin tanımlanmasında AMH ve FSH değerleri AFC'den daha iyi bir öngörü potansiyeli gösterdi. Bu veriler, IVF protokollerinin kişiselleştirilmesinde bazal over rezerv belirteçlerinin birlikte değerlendirilmesinin önemini vurgulamaktadır.

Anahtar Kelimeler: Over Rezervi; Antral Folikül Sayısı(AFC); Anti-Mülleryan Hormone(AMH); Folikül Stimüle Edici Hormone(FSH); Poor Ovarian Response; İn Vitro Fertilizasyon

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1. Giriş

Tüp bebek tedavilerinde düşük over rezervi ve buna bağlı düşük over yanıtı, tedavi başarısını etkileyen karmaşık bir klinik problemdir. Yıllar içerisinde over rezervini değerlendirmek ve ayrıca IVF(in-vitro fertilizasyon)/ICSI(intrasitoplazmik sperm injeksiyonu) tedavi süreçlerinde oosit eldesi ve gebelik sonuçlarını öngörmek için bir çok over rezerv testleri geliştirilmiştir. Yardımcı üreme tedavileri(YÜT) sikluslarında uygulanan overyan stimülasyonda overyan yanıt önemli bir durumdur(1). Klinik, hormonal ve ultrasonografik birtakım belirteçler over rezervini değerlendirmek için kullanılmaktadır(2–4). Over yanıtını öngörmek için de yine yaş, antral folikül sayısı(AFC), bazal FSH(folikül stimüle edici hormone), inhibin B ve AMH(antimülleryen hormon) gibi over rezerv testleri kullanılmaktadır. Avrupa İnsan Üreme ve Embriyoloji Derneği(ESHRE) tarafından YÜT'de düşük over yanıtlı olguları tanımlamak için Bologna kriterleri ortaya konmuştur(5). Düşük over yanıtını standartlaştırarak hasta sınıflandırması ve tedavi planlaması için yol gösterici olmaktadır. Artan kadın yaşı ve beklenmedik bazı problemler ile azalmış over rezervi ve bunun neticesinde de düşük over yanıtı ile karşılaşmak olası hale gelmektedir(6,7). Literatürde AFC'nin, over rezervinin nicelik ve kalite boyutlarını birlikte öngörmede tutarlı bir belirteç olduğu; AMH'nın ise özellikle ölçüm stabilitesi ve siklus içi varyasyonunun düşük olması nedeniyle yaygın kullanıldığı vurgulanmaktadır(8,9). Yaş artışı ve over rezervinin azalması ile FSH seviyelerinde bir artış, AFC ve AMH değerlerinde de bir azalma olduğu bilinmektedir. Bununla birlikte, farklı kohort ve protokollerde AFC ve AMH'nın overyan yanıt açısından öngörü performansında değişiklikler rapor edilmiş; bazı çalışmalarda bazal FSH ve anne yaşının kombine modellerde anlamlı katkı sağladığı ifade edilmiştir(10). Hala over rezerv testleri açısından mükemmel bir test bulunmamakla birlikte, AFC ve AMH değerlerinin ve kombinasyonlarının iyi bir prediksiyon sağlayabileceği düşünülmektedir. Özellikle düşük over yanıtının IVF olgularında %10-20 arasında gözlenmekte ve yaşla birlikte de arttığı görülmektedir. Bu bağlamda, düşük over yanıt tahmininde hangi parametrenin klinik uygulamada öncelikli olarak kullanılacağı konusunda görüş birliği oluşmamıştır(11). Over rezervinin ve over yanıtının öngörüsünde ve de tedavi süreçlerinde stimülasyonun kişiselleştirilmesi amaçlı bu belirteçler ve de verecekleri sonuçlar önem arz etmektedir. Bu çalışma, Bologna kriterlerine göre düşük over yanıtlı kadınlarda özellikle FSH, AMH ve AFC değerlerinin elde edilen oosit sayısını ne ölçüde öngörebildiğini retrospektif veriler ışığında değerlendirerek, hasta danışmanlığı ve tedavi stratejilerinin kişiselleştirilmesine katkı sağlamayı amaçlamaktadır.

2. Gereç ve Yöntem

Bu çalışma retrospektif ve gözlemsel bir çalışma olarak tasarlanmıştır. Eskişehir Osmangazi Üniversitesi Üreme Sağlığı Merkezi'ne Ocak 2017 ile Aralık 2024 tarihleri arasında başvuran hastalara ait tüp bebek tedavi verileri geriye dönük olarak incelenmiştir. Bu çalışma için Eskişehir Osmangazi Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'ndan 2024-343 karar numarası ile etik onay alınmıştır. Belirtilen tarihler arasında oosit toplama (OPU) işlemi gerçekleştirilen 1405 siklus taranmış, Bologna kriterlerine göre düşük over rezervi tanımına tam olarak uyan 181 tüp bebek siklusu çalışmaya dâhil edilmiştir. Çalışmaya 20–44 yaş aralığında yer alan kadınlar dâhil edilmiştir.

Bologna kriterleri, Avrupa İnsan Üremesi ve Embriyoloji Derneği (ESHRE) tarafından 2011 yılında tanımlanmış olup(5), düşük over yanıtının (poor ovarian response – POR) tanımlanabilmesi için aşağıdaki üç kriterden en az ikisinin karşılanması önerilmektedir: 1. İleri anne yaşı (≥40 yaş) veya POR için diğer risk faktörlerinin varlığı, (2) Önceki bir siklusta ≤3 oosit elde edilmesi, (3) Anormal over rezerv test sonuçları (Antral folikül sayısı <5–7 ve/veya AMH düzeyi <0.5–1.1 ng/mL). Bu kriterleri karşılayan olgular çalışmaya dahil edilmiştir.

Dahil edilme kriterleri: Bologna düşük overyan yanıt kriterlerinin tümünü karşılayan, 20–44 yaş aralığında olan ve çalışmanın yürütüldüğü merkezde tüp bebek tedavisi görmüş hastalardır.

Dışlanma kriterleri: Vücut kitle indeksi ≥40 kg/m², geçirilmiş reprodüktif cerrahi öyküsü, normal veya yüksek over rezervi, anovulasyon, erkeğe ait ciddi sperm bozuklukları ve cerrahi sperm elde edilmesini gerektiren durumlar olarak belirlenmiştir.

Hastalara agonist veya antagonist protokolü ile kontrollü over stimülasyon protokolleri uygulanmıştır. Menstrüel siklusun 2. veya 3. günü, 150–350 IU dozunda rFSH veya HMG ile tedaviye başlanmıştır. Agonist protokol uygulanan hastalarda kısa protokol kapsamında siklus başında GnRH agonist verilerek tedavi devam edilmiştir.

Antagonist protokol uygulanan hastalarda, estradiol düzeyine ve/veya dominant folikül çapına göre fleksibl antagonist protokol uygulanmıştır. En az üç folikül ≥18 mm çapa ulaştığında ovulasyon rekombinant hCG ile tetiklenmiş ve 36 saat sonra OPU işlemi gerçekleştirilmiştir. Elde edilen oositler takip edilmiş, embriyo gelişim süreçleri ve gebelik durumları kaydedilmiştir.

Çalışmada, hastaların demografik özellikleri (yaş, infertilite tipi, sigara kullanımı, daha önceki tedavi öyküsü, infertilite süresi ve tipi), bazal hormon düzeyleri (FSH, LH, estradiol, AMH), antral folikül sayıları, siklus sonunda elde edilen toplam ve matür oosit sayıları ile matürasyon oranları kaydedilmiştir. Embriyo gelişim durumu ve laboratuvar değerlendirmesine göre klinik durum doğrultusunda 3. gün veya 5. gün embriyo transferi uygulanmıştır.

İkincil sonuçlar olarak, tedavi sonucunda elde edilen gebelik oranları da değerlendirilmiştir. Gebelik durumu, embriyo transferinden 12 gün sonra yapılan serum β-hCG ölçümü ile ve ardından ultrasonografide gebelik kesesi ve fetal kardiyak aktivitenin saptanması ile belirlenmiş ve kaydedilmiştir. Hastaların doğum verileri de kayıtlardan incelenerek canlı doğum oranları da tespit edilmiştir.

Bu çalışmada, siklus başlangıcında ölçülen FSH, AMH ve antral folikül sayılarının siklus sonunda elde edilen oosit sayıları ile ilişkisi ve öngörü kapasiteleri karşılaştırılmıştır. Tüm veriler merkezin hasta takip veritabanından retrospektif olarak elde edilmiştir.

İstatistiksel analizler SPSS v25.0 (IBM Corp., Armonk, NY, ABD) istatistik programı kullanılarak gerçekleştirilmiştir. Verilerin dağılımı normallik testleri ile değerlendirilmiştir. Normal dağılım gösteren ceriler için t-Test, normal dağılıma uymayan veriler için de Mann-Whitney testi uygulanmıştır. Siklus başındaki over rezerv belirteçleri ile siklus sonunda elde edilen oosti sayıları arasındaki ilişkiyi saptamak için sürekli değişkenler için uygun korelasyon analizleri (Pearson veya Spearman) uygulanmıştır. Oosit sayısını öngören bağımsız değişkenleri belirlemek amacıyla lojistik regresyon analizi yapılmıştır. Parametrelerin oosit öngörüsündeki gücü ROC eğrileri kullanılarak değerlendirilmiştir. $p<0.05$ değeri istatistiksel olarak anlamlı kabul edilmiştir.

3. Bulgular

Çalışmaya toplam 181 tüp bebek siklusu dâhil edilmiştir. Katılımcıların demografik verileri incelendiğinde; yaş ortalaması 35.94±4.57 yıl, vücut kitle indeksi 26.26±4.96 kg/m² olarak bulunmuştur. Siklus başlangıcı yapılan değerlendirme sonuçları da; ortalama bazal FSH düzeyi 9.87±4.12 IU/L, bazal estradiol 46.05±34.79 pg/mL, antral folikül sayısı (AFC) 5.5±2.5, ve AMH düzeyi 0.88±0.33 ng/mL olarak saptanmıştır(Tablo 1).

Tablo 1. Demografik ve Klinik Parametreler

Parametreler	**n:181**
	Ort±SD / n(%)
Yaş (yıl)	35.94±4.57 (37)
VKİ (kg/m^2)	26.26±4.96 (25.5)
Sigara, n(%)	
İçiyor	53 (29.3)
İçmiyor	128 (70.7)
İnfertilite süresi (yıl)	4.74±4.21
İnfertilite tipi, n(%)	
Primer	119 (65.7)
Sekonder	62 (34.3)
Bazal FSH (IU/l)	9.87±4.12 (9.1)
Bazal Estradiol (pg/ml)	46.05±34.79 (40)
Antral Folikül Sayısı	5.5±2.5 (5)
AMH(Anti-Mülleryen Hormon)	0.88±0.33 (0.51)

Veriler n(%) veya Ortalama±Standart sapma veya n(%) olarak verilmiştir.

Overyan stimülasyon ve laboratuar sonuçlarına bakıldığında ise; toplam stimülasyon süresi ortalama 9.17±1.92 gün, kullanılan toplam gonadotropin dozu 2766.56±720.41 IU idi. Tetikleme günü estradiol düzeyi 1008.79±499.88 pg/mL olarak hesaplanmıştır. Tedavi sonuç aşamasında uygulanan oosit toplama işleminde ortalama 2.54±1.28 adet toplam oosit, 1.50±1.27 adet metafaz II (matür) oosit elde edilmiş ve ortalama matürasyon oranı %55.89±38.93 olarak kaydedilmiştir (Tablo 2). Toplam 83 hastada(%45.9) embriyo transferi aşamasına gelinmiştir. Bu olgularında %83.8'inde klivaj evresi, %16.2'sinde ise blastosist evresi transferi gerçekleştirilmiştir.

Tablo 2. Stimülasyon ve laboratuar sonuçları

Parametreler	**n:181**
	Ort±SD / n(%)
Toplam Stimülasyon Süresi (gün)	9.17±1.92
Toplam Gonadotropin Dozu (IU)	2766.56±720.41
Tetikleme günü Estradiol (pg/ml)	1008.79±499.88
Toplam Oosit Sayısı	2.54±1.28
Toplam Metafaz II Oosit Sayısı	1.50±1.27
Matürasyon oranı (%)	55.89±38.93
Fertilizasyon oranı (%)	65.79±44.9
Klivaj oranı (%)	69.75±46.07
Embriyo transferi yapılma oranı, n (%)	83 (45.9)
Embriyo transfer günü, n(%)	
Klivaj evresi	68 (83.8)
Blastosist evresi	15 (16.2)

Veriler n(%) veya Ortalama±Standart sapma veya n(%) olarak verilmiştir.

Toplam oosit sayısı üzerine etki etmesi muhtemel bazal faktörlerin incelenmesi amaçlanarak yaş, siklus 2.-3. günü bakılan FSH, antral folikül sayısı ve AMH değerlerinin oosit sayıları ile korelasyonu analiz edilmiştir. İlginç şekilde beklenenin aksine yaş ile zayıf pozitif yönde anlamlı korelasyon (r=0.220, p=0.003) tespit edilmiştir. AFC ile ise zayıf-orta düzeyde pozitif ve anlamlı bir korelasyon (r=0.247, p<0.001) tespit edilmiştir. AMH düzeyi ile toplam oosit sayısı arasında istatistiksel olarak anlamlı olmasa da pozitif yönde bir ilişki gözlenmiştir (r=0.144, p=0.056). Bazal FSH düzeyi ile toplam oosit sayısı arasında negatif yönde ancak anlamlı olmayan korelasyon bulunmuştur (r=–0.098, p=0.189) (Tablo 3).

Tablo 3.Toplanan Oosit ile Faktörler arası Korelasyon Analizi

	Pearson Korelasyon Katsayısı	**p**
Bazal FSH	-0.098	0.189
Bazal AFC	0.247	<0.001
AMH	0.144	0.056

Toplam oosit sayısını etkileyebilecek bu faktörlerin lineer regresyon analizi ile değerlendirilmesi neticesinde ise; FSH, AMH ve AFC'nin hem düzeltilmemiş (unadjusted) hem de düzeltilmiş (adjusted) analizleri gerçekleştirilmiştir. Bazal FSH seviyesinin bu öngörüde gerek düzeltilmemiş gerekse de düzeltilmiş analizde anlamlı seviyede FSH seviyelerindeki artışın %20 oranında oosit sayısında düşüş ile ilişkili olduğu tespit edilmiştir(Tablo 4).

Tablo 2. Toplam Oosit sayısının Lojistik Regresyon Analizi (3 ve daha düşük oosit eldesi öngörüsü)

		Düzeltilmemiş		**Düzeltilmiş**	
Lojistik Regresyon	**Değişken**	**OR**	**p**	**aOR**	**p**
	Bazal FSH	1.20	0.043	1.21	0.032
	Bazal AFC	0.97	0.770		
	AMH	0.81	0.134		

Over yanıtı değerlendiren bu belirteçlerin öngörü potansiyellerine yönelik gerçekleştirilen ROC analizlerinde de FSH, AFC ve AMH için eşik değerleri ve de hassasiyet değerleri belirlenmiştir. Bu analizde toplam oosit sayıları 3 ve altında olan olgular ile 4 ve üstü olan olgular kategorize edilerek 3 ve altı daha düşük over yanıtı elde edilen olguların parametreler ile öngörülebilme potansiyelleri değerlendirilmiştir. Bazal FSH değeri için elde edilen eğri altındaki alan(AUC) 0.687 olarak belirlenmiştir(p=0.002). Hassasiyet ve özgüllük değerleri de sırasıyla %76.2 ve %64.7 olarak bulunmuştur. FSH için 7.86 seviyesi ve üstü olması, 3 ve altı oosit eldesi için bir eşik değer olarak tespit

edilmiştir (Şekil 1). AFC için bu değerlendirmede AUC 0.526 olarak bulunmuş(p=0.711) ancak istatistiksel anlamlılık bulunamamıştır. Hassasiyet ve özgüllük değerleri ise %10.9 ve %100 olarak tespit edilmiştir. AMH için yapılan analizde ise AUC 0.716 ile diğer parametrelere göre daha yüksek tespit edilmiştir(p=0.003). Oosit sayısı olarak 3 ve altını öngörmek için eşik değer de 0.76 ve altı olarak tespit edilmiştir.

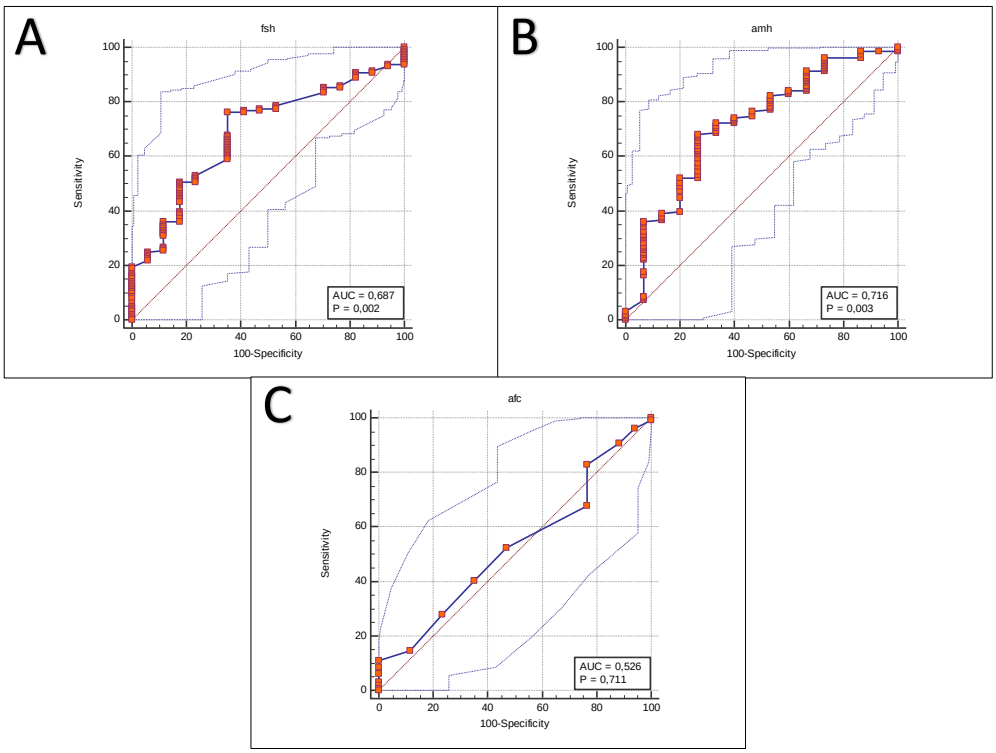

Figure 1. Over rezerv belirteçlerinin 3 ve altı oosit sayısını öngörme etkinlikleri, ROC eğrileri (A. Folikül stümüle edici hormone, B. Antimülleryen hormon, C. Antral folikül sayısı)

Embriyo transferi yapılan 83 hastanın gebelik sonuçları incelendiğinde ise; transfer başına hCG pozitifliği gelişen %30.1 oranında olgu tespit edilmiştir. Klinik gebelik ve canlı doğum oranları ise sırasıyla; %28.9 ve %18.1 olarak belirlenmiştir.

4. Tartışma ve Sonuç

Bu çalışmada, Bologna kriterlerine uyan olgularda ART sikluslarında siklus başında değerlendirilen bazal parametreler içinde AFC, FSH ve AMH değerlerinin toplam oosit sayısını öngörmede etkinlikleri değerlendirilmiştir. Toplam oosit sayıları ile en güçlü korelasyon AFC ile gözlenmiş ve güçlü bir belirteç olduğu (r=0.247, p<0.001) ortaya konmuştur; bu bulgu, düşük over rezervli popülasyonda AFC'nin klinik değerine dikkat çekmektedir. Ayrıca 3 ve altı oosit eldesi olarak çok düşük yanıt veren olguların öngörüsünde ise AMH ve de FSH değeri bu öngörüyü sağlamada AFC'ye göre daha etkin olarak bulunmuştur. AUC değerlerine göre de en etkin parametre AMH tespit edilmiştir.

ART sikluslarında tedavi sonuçlarını öngörmek için bir çok test kullanılmaktadır(12–14). Kadın yaşının kötü oosit kalitesi prediksiyonunda en iyi belirteç olduğu bilinse de over rezerv belirteçlerinin oosit kantitesinin belirlenmesinde sıklıkla kullanıldığı bilinmektedir(15). Anne yaşı, IVF çıktıları üzerinde etkili bir faktör olarak kabul edilir; çalışmamızda yaş ile toplam oosit sayısı arasında zayıf pozitif korelasyon bulunmuştur (r=0.220, p=0.003). Ferraretti ve ark. tarafından bildirildiği üzere, ileri yaşın over yanıtını olumsuz etkilediği ve öngörü modellerinde yaşın da önemli bir değişken olduğu vurgulanmıştır (5).

Siklus başında değerlendirilen basit bazal testlerden olan FSH seviyeleri, siklus içerisinde ve sikluslar arasında belirgin farklılıklar göstermesi de belirteç olarak kullanımında birtakım kısıtlılıklar

oluşturmaktadır. Bazı çalışmalarda ise bazal FSH seviyelerinin özellikle düşük yanıtlı olguları belirlemek için tek başına belirleyici olmadığı bulunmuştur(16). Bazal FSH düzeyinin öngörücü değeri sınırlı kalmıştır; çalışmamızda FSH ile toplam oosit sayısı arasında anlamlı bir korelasyon saptanmamıştır (r=–0.098, p=0.189). Ancak 3 ve oosit altı oosit eldesini öngörmede anlamlı bir etkinlik göstermiştir(AUC=0.687, p=0.002). Literatürde de FSH'ın over rezervi tahmininde AUC değerinin genellikle 0.60–0.70 arasında olduğu, diğer belirteçlere kıyasla daha düşük performans gösterdiği bildirilmektedir (5,8).

Bir diğer önemli bir over rezerv belirteci de AMH seviyelerinin tespit edilmesidir. AMH, granüloza hücrelerinden salgılanan (özellikle preantral ve antral foliküler hücrelerden) menstrüel siklus süresince göreceli olarak stabil olan bir hormondur. AMH'ın absolü değeri primer foliküllerin sayısı ile direk olarak oransal ilişkilidir, ve foliküllerin matürasyonu ve gelişimi üzerinde düzenleyici fonksiyonu bulunmaktadır ve böylelikle overyan yanıt ve over rezerv fonksiyonunun değerlendirilmesi için öncelikli bir serolojik belirteç olarak görünmektedir(17,18). AMH, over rezervinin non-invaziv belirteci olarak kabul edilmekle birlikte, düşük rezervli gruplarda performansı değişkenlik göstermektedir. Düşük AMH seviyelerinin düşük over rezervini ve overyan hiperstimülasyona muhtemel düşük over yanıtını öngörebileceği belirtilmekte ve de yeterli yanıt alınabilmesi için daha fazla gonadotropin kullanımı gerekebileceği bildirilmiştir(15).

Over rezerv belirteçleri tek başlarına kullanılabilmekle birlikte kombinasyonlar halinde değerlendirme de muhtemel düşük over yanıtını öngörebilmek için mantıklı görünmektedir. AFC ve AMH belirteçlerinin ayrı ayrı veya kombine şekilde over yanıtını değerlendirebileceği ve böylelikle de overyan stimülasyon sikluslarında bireyselleştirme uygunabileceği bildirilmiştir(19). Bununla birlikte bazı infertilite merkezlerince; yalnızca AFC kullanılarak yapılan over yanıt öngörüsünün altın standart yaklaşımı olduğuna inanılmaktadır(20,21). AFC oldukça iyi bir over rezerv ve yanıt belirteci olsa da siklustan siklusa değişmesi ve uygulayıcı bağımlı olarak subjektif bir belirteç olması negatif yönleri olarak karşımıza çıkmaktadır. AFC ve AMH'nın oosit sayısını yansıtma ve benzer değerler sunması ve oosit sayısı ile yüksek korelasyon göstermesi de vurgulanmaktadır(22). Bu kapsamda, AMH'nın AFC ile karşılaştırılmasında siklus içi ve sikluslar arası değişkenliğinin daha az olması bir avantaj olarak karşımıza çıkmaktadır(23,24). Bu nedenle AFC'nin bu değişkenliğinin daha fazla olması özellikle tanısal süreçte bu öngörüyü sağlamada özellikle düşük over yanıtlı olgularda dikkate alınması gereken bir durumdur(24,25). Birtakım çalışmalar da AMH ve AFC'nin prediktif değeri karşılaştırılmıştır. Çalışmaların bir kısmında genel eğilim AMH değerlerinin over yanıtını öngörmede AFC değerlerine göre daha güçlü olduğu bulunsa da diğer bazı çalışmalarda ise AFC'nin daha güçlü bir öngörü sağladığı bulunmuştur(3,21,26–28). Mutlu ve ark. yaptığı bir çalışmada da düşük over yanıtını öngörmede AFC'nin AMH'dan daha iyi olduğu tespit edilmiştir(12). Buna karşıt şekilde bazı çalışmalarda da AMH seviyelerinin over yanıtı değerlendirmede AFC'den daha iyi bir belirteç olduğu tartışılmaktadır(29,30). Liu ve ark. yaptığı bir meta-analizde ise, düşük over yanıtı 4 oositin altı olarak tanımlandığı durumda AFC'nin AMH değerlerinden daha iyi sensitivite ve spesifisite değerleri verdiğini bulmuşlardır(11). Biz de çalışmamızda benzer şekilde 3 ve altı oosit eldesini eşik kabul edip gerçekleştirdiğimiz analizde AMH değerini önemli bir öngörü belirteci olarak bulurken(AUC=0.716, p=0.003), AFC ise bu öngörüde anlamlı etkinlik gösterememiştir(AUC=0.526,p=0.711).

Düşük over yanıtı predikte etmek için eşik değerlerin belirlenmesi ile ilgili yapılan çalışmalar 5 ile 7 arası ve daha az AFC tespit edilmesine genel olarak dayandırılmaktadır(31). AMH için ise 0.7-1.3 ng/mL değerinin ART sikluslarında öngörü için makul seviyeler olduğu kabul edilmektedir(19,32). Bizim çalışmamızda ise AFC için 9 değeri, AMH için de 0.76 ng/mL değeri eşik olarak belirlenmiştir. Serum AMH değerinin de overyan yanıtı öngörebilecek şekilde elde edilen oosit sayıları ile pozitif korele olduğu net şekilde ortaya konmuştur. Honnma ve ark. tarafından yapılan bir çalışmada ise serum AMH değerlerinin yaş ile kombine edilmesinin tek başına AMH'ya göre daha iyi bir indikatör olacağı düşünülmüştür(33). Keane ve ark. yaptığı IVF sonuçlarını değerlendirdikleri çalışmada ise hem AFC hem de AMH değerlerinin elde edilen oosit sayıları ile pozitif ilişkili olduğu ancak eğer kombine edilirlerse en iyi doğrulukla over yanıtını öngörebilecekleri sonucuna varmışlardır(34). Salemi ve ark. over yanıtını değerlendirmek için yaptıkları yeni bir meta-analizde AFC, AMH, FSH ve estradiol değerlerini incelemişlerdir. Çalışmada bu over rezerv ve yanıt belirteçleri arasında en etkili belirteçlerin yüksek doğruluk öngörüsü ile AFC ve AMH olduğunu tespit etmişlerdir(10).

Yaş ve over rezervi arasında değişen bir ilişki olması ve over rezerv testlerinin farklı yaş ve klinik olgu gruplarında farklı potansiyellere sahip olması da önemli bir durum olarak karşımıza çıkmaktadır(6,7).

Bu durum özellkle over yanıtında farklı sonuçlar ile karşılaşılabilecek düşük yanıtlı olgularda daha önemli bir durumdur. Optimal tedavi sonucunu elde edebilmek için over yanıtını siklus başında öngörebilmek önemlidir ve böylece de kişiye özel tedavi planlaması uygulanabilir(35,36). Çiftlerin ART süreçlerinin yetersiz yanıta bağlı olarak iptali, kesintiye uğraması gibi durumlar ciddi fiziksel ve psikolojik etkiler ortaya çıkarabilmektedir. Bu nedenle anormal yanıt durumunu azaltmak tedavideki kayıp durumlarını da azaltmak için önemli hale gelmektedir. Siklus başında bazı belirteçler ile elde edilecek oosit sayısını öngörebilmek özellikle siklus iptalinin göreceli daha sık olduğu düşük over yanıtlı olgular için çok daha kritik olmaktadır(37).

Bu olgu gruplarında gebelik oranlarının da göreceli olarak daha düşük tespit edildiği bildirilmiştir. Bozdağ ve ark. yaptığı geniş çaplı bir retrospektif çalışmada Bologna kriterlerini sağlayan olgularda canlı doğum oranları %2.3-8.7 olarak bulunmuştur. Bizim çalışmamızda ise literatür verilerine göre bir miktar da olsa yüksek bir oranda canlı doğum oranı %18.1 olarak bulunmuştur.

Bu çalışmanın güçlü yönleri arasında, Bologna kriterlerine uygun büyük bir kohortun (n=181) incelenmesi ve hem korelasyon hem de de lineer regresyon analizlerinin birlikte kullanılarak öngörü gücünün kapsamlı değerlendirilmesi yer almaktadır. Sınırlılıklar olarak, retrospektif ve tek merkezli tasarımın potansiyel seçilim yanlılıklarına açık olması ve OSI/ORPI gibi kombine indekslerin ölçülmemiş olması sayılabilir.

ART sikluslarında özellikle de düşük over yanıtı beklenen olgularda over rezervini siklus başında iyi şekilde değerlendirip tedaviyi ona göre planlamak tedavi sonuçlarını iyileştirmekte ve de olası iptalleri mümkün olduğunca azaltmaktadır. Biz de çalışmamızda Bologna kriterlerini karşılayan düşük yanıtlı olgularda siklus başı değerlendirdiğimiz over rezerv belirteçlerinin siklus sonuçlarını öngörme güçlerini değerlendirdik. Oosit sayıları ile en korele belirteçin AFC olduğu bulunurken, çok düşük yanıtlı 3 ve altı oosit sayısını öngörmede ise AMH en iyi belirteç olarak öne çıkarken AMH ve AFC anlamlı bir öngörü sağladığı tespit edilmiştir. Buradan anlaşıldığı gibi AMH siklus bağımsız olması nedenli özellikle düşük yanıtlı olgularda anlamlı bir öngörüyü sağlayabilmektedir. İdeal bir over rezerv testinin kolay ulaşılabilir, tekrarlanabilir, düşük siklus içi ve sikluslar arası değişkenlik göstermesi gerektiği bilinmektedir. Düşük over yanıtlı olguları en iyi şekilde öngörebilmek de bu kapsamda oldukça önemli olmaktadır. Ama literature de baktığımızda tamamiyle ideal ve altın standart bir test özellikle düşük over yanıtlı olgularda henüz ortaya konabilmiş değildir. Bu konuda kapsamlı çalışmalar ile gelecekte daha iyi sonuçlar elde edilebileceği düşünülmektedir.

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Brucellosis in Children: A Single-Center Experience and Clinical Evaluation in A Tertiary Care Hospital

Çocuklarda Bruselloz: Üçüncü Basamak Bir Hastanede Tek Merkez Deneyimi ve Klinik Değerlendirme

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Abstract: Brucellosis is a prevalent zoonotic disease in childhood, particularly in endemic regions. This study aimed to compare the clinical, laboratory, and serological features of bacteremic and non-bacteremic pediatric brucellosis patients.This retrospective study included 117 pediatric patients diagnosed with brucellosis between February 2017 and July 2024. Patients were classified into bacteremic (n=38) and non-bacteremic (n=79) groups according to blood culture results. Statistical analyses were performed using R version 4.5.0. Normality of continuous variables was assessed using the Shapiro–Wilk test. The independent samples t-test was used for normally distributed variables, and the Wilcoxon rank-sum test for non-normal distributions. Categorical variables were compared using the Pearson Chi-square or Fisher's exact test, as appropriate. A p-value of <0.05 was considered statistically significant.Hospitalization was significantly more common in the bacteremic group (39.5%) than in the non-bacteremic group (11.4%) (p = 0.001), and hospital stay distribution also differed between groups (p = 0.035). Splenomegaly (p = 0.004) and arthritis (p = 0.001) were more frequently observed in the non-bacteremic group. Laboratory analyses revealed significantly lower hemoglobin (p = 0.037) and MPV (mean platelet volume) (p = 0.048) levels in bacteremic patients. No significant differences were found in CRP, ESR, WBC counts, or serological test results.Bacteremic pediatric brucellosis cases may present with fewer localized symptoms but require longer hospitalization. Reduced hemoglobin and MPV values may serve as potential indicators of bacteremia. These findings contribute to the understanding of the clinical variability of pediatric brucellosis and support early risk stratification.
Keywords: Brucellosis, childhood, Brucella melitensis, blood culture, zoonotic infection

Özet: Bruselloz, çocukluk çağında endemik bölgelerde sık görülen önemli bir zoonotik enfeksiyondur. Bu çalışmada, bakteriyemik ve bakteriyemik olmayan çocukluk çağı bruselloz olgularının klinik, laboratuvar ve serolojik özelliklerinin karşılaştırılması amaçlanmıştır.Bu retrospektif çalışmada, Şubat 2017 - Temmuz 2024 tarihleri arasında bruselloz tanısı almış 117 çocuk hasta değerlendirildi. Hastalar, kan kültürü sonucuna göre bakteriyemik (n=38) ve bakteriyemik olmayan (n=79) olarak iki gruba ayrıldı. Verilerin analizinde R versiyon 4.5.0 yazılımı kullanıldı. Sürekli değişkenlerde normallik dağılımı Shapiro–Wilk testi ile değerlendirildi. İkili karşılaştırmalarda parametrik veriler için bağımsız gruplar t-testi, parametrik olmayanlar için Wilcoxon testi kullanıldı. Kategorik değişkenlerde Pearson ki-kare veya Fisher exact testleri uygulandı. p<0,05 anlamlı kabul edildi.Bakteriyemik hastalarda hastaneye yatış oranı (%39,5), bakteriyemik olmayanlara göre (%11,4) anlamlı olarak yüksekti (p=0,001). Yatış süresi dağılımı da gruplar arasında farklıydı (p=0,035). Splenomegali (p=0,004) ve artrit (p=0,001), bakteriyemik olmayan grupta daha sık görüldü. Laboratuvar bulgularında, bakteriyemik grupta hemoglobin düzeyi (p=0,037) ve MPV (ortalama trombosit hacmi) (p=0,048) anlamlı olarak daha düşüktü. CRP, ESR, WBC ve serolojik test sonuçlarında gruplar arasında anlamlı fark saptanmadı.Bakteriyemik çocukluk çağı bruselloz olgularında lokal bulgular daha az izlenmekte ancak hastaneye yatış ihtiyacı daha fazla olmaktadır. Düşük hemoglobin ve MPV değerleri, bakteriyeminin olası göstergeleri olarak düşünülebilir. Elde edilen bulgular, çocukluk çağı brusellozunun klinik çeşitliliğine ışık tutmakta ve erken risk sınıflaması açısından katkı sağlamaktadır.
Anahtar Kelimeler: Bruselloz, çocukluk çağı, Brucella melitensis, kan kültürü, zoonotik enfeksiyon

Ethics Committee Approval: This study was approved by the Ethics Committee of Toros University (Protocol No: E-25.09.2024/163).
Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.
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1. Introduction

Brucellosis is a zoonotic infection caused by Brucella species, which are Gram-negative coccobacilli affecting both humans and animals. Transmission occurs through direct contact with infected animals, consumption of contaminated animal products particularly unpasteurized milk and dairy products or inhalation of aerosols. The disease is more prevalent in rural communities engaged in livestock farming and poses a significant public health concern in these regions [1,2].Although childhood brucellosis is reported less frequently than adult cases, it remains an important source of infection in endemic areas, especially due to the consumption of raw dairy products. The immature immune system of children increases their susceptibility to infection. Brucellosis in children often presents with nonspecific symptoms such as fever, arthralgia, fatigue, and sweating, which can lead to diagnostic delays [3,4].Diagnosis is primarily based on serological tests and/or blood cultures. The standard tube agglutination test (STA) is the most commonly used method in pediatric cases. However, interpretation of serological titers must be supported by clinical findings. While blood culture is considered the gold standard for diagnosis, it is time-consuming and may have limited sensitivity. Bacteremia is more frequently observed in cases with positive cultures [5–7].Complications of childhood brucellosis include osteoarticular involvement (arthritis, sacroiliitis), hepatosplenomegaly, lymphadenopathy, and, rarely, neurobrucellosis. Treatment typically involves combination antibiotic therapy. Despite appropriate treatment, relapses may occur, increasing the disease burden [8–10].In countries where brucellosis is endemic, such as Turkey, assessing the clinical course, diagnostic approaches, complications, and relapse rates in pediatric patients is crucial for improving clinical management. This study aims to retrospectively evaluate the clinical and laboratory features, diagnostic methods, and relapse rates of childhood brucellosis, thereby contributing to the existing body of knowledge.

2. Materials and Methods

2.1 Study Design and Population

This retrospective study included 117 pediatric patients aged between 1 month and 18 years who were diagnosed with brucellosis and admitted to the Pediatric Infectious Diseases or General Pediatrics Outpatient Clinics of Toros Training and Research Hospital between February 2017 and July 2024.

2.2 Diagnostic Criteria

Brucellosis was diagnosed in patients who presented with clinical findings consistent with the disease (e.g., fever, night sweats, fatigue, arthralgia) and who had either:

•A positive Brucella standard tube agglutination test (STA) at a titer of ≥1:160,

and/or

•A positive blood culture isolating Brucella species [7].

Additional symptoms such as weight loss, abdominal pain, headache, and back pain were considered supportive of brucellosis. Physical examination findings including hepatomegaly, splenomegaly, lymphadenopathy, and arthritis were also considered diagnostic indicators.

2.3 Data Collection

Demographic characteristics, clinical findings, laboratory parameters, microbiological results, treatment approaches, and duration of hospitalization were reviewed from the hospital's electronic medical records. Laboratory data included ALT (Alanine Aminotransferase), AST (Aspartate Aminotransferase), CRP (C-Reactive Protein), ESR (Erythrocyte Sedimentation Rate), MPV (Mean Platelet Volume), WBC (White Blood Cell Count).

2.3 Ethical Approval

This study was approved by the Ethics Committee of Toros University (Protocol No: E-25.09.2024/163).

2.4 Statistical Analysis

All statistical analyses, data management, visualization, and reporting procedures were conducted using R version 4.5.0. Several R packages were employed to facilitate a structured and reproducible workflow. The R6 package was utilized to construct modular and reusable object-oriented structures, enabling a more flexible statistical pipeline. The rstatix package provided a streamlined interface for conducting inferential statistical tests, while flextable was used to generate publication-ready summary tables formatted in accordance with journal standards.

Inferential statistics were applied to examine associations and differences between groups. The

choice of statistical tests was based on the distribution of the data and the underlying assumptions of each test. Normality of numerical variables was assessed using the Shapiro–Wilk test. For normally distributed data, independent samples t-tests were used to compare two groups, and ANOVA was applied for comparisons across more than two groups. When the data were not normally distributed, the Wilcoxon rank-sum test was used for two-group comparisons, and the Kruskal–Wallis test for three or more groups.

For categorical variables, the Pearson's Chi-square test was applied when the expected cell counts were adequate (i.e., ≥5 per cell). In cases with small sample sizes or low expected frequencies, the Fisher's exact test was used. A two-tailed p-value of less than 0.05 was considered statistically significant in all analyses.

3. Results

In this study, a total of 117 patients diagnosed with brucellosis were included, of whom 79 were classified as non-bacteremic and 38 as bacteremic based on blood culture results. The overall proportion of female patients was 39.32%, and males constituted 60.68% of the cohort. There was no statistically significant difference in sex distribution between the groups ($p = 0.324$). The median age of the study population was 144 months (range: 23–216), and no significant difference was observed between the non-bacteremic and bacteremic groups ($p = 0.731$).

Regarding residence, 63.25% of the patients lived in rural areas, with a higher proportion among bacteremic patients (76.32%) compared to non-bacteremic ones (56.96%), although this difference did not reach statistical significance ($p = 0.067$). Hospitalization was significantly more common among bacteremic patients (39.47%) than non-bacteremic patients (11.39%) ($p = 0.001$). The median hospital stay was 14 days across all groups; however, the distribution differed significantly, with bacteremic patients showing a narrower range (7–21 days) compared to non-bacteremic patients (12–47 days) ($p = 0.035$).

Clinically, the most common symptoms were arthralgia (90.60%), followed by fever (33.33%) and sweating (34.19%). There were no statistically significant differences in the presence of fever, arthralgia, weight loss, or sweating between bacteremic and non-bacteremic groups (all $p > 0.05$). A family history of brucellosis was reported by 45.30% of patients, and raw milk consumption was prevalent in 93.16% of the cohort. Neither family history nor livestock ownership nor raw milk consumption showed significant associations with bacteremia ($p = 0.610$, $p = 0.113$, and $p = 0.713$, respectively).

On physical examination, fever and hepatomegaly were observed in 62.39% and 9.40% of the patients, respectively, without significant group differences. Sacroiliitis was rare (5.13%) and also not significantly different between groups. However, splenomegaly was significantly more frequent in non-bacteremic patients (36.71%) compared to bacteremic ones (10.53%) ($p = 0.004$). Similarly, arthritis was more commonly detected in the non-bacteremic group (51.90%) than in the bacteremic group (18.42%) ($p = 0.001$). The distribution of arthritis location also differed significantly ($p < 0.001$), with knee involvement being predominant in the non-bacteremic group.

Relapse was observed in 11.97% of the patients, with no statistically significant difference between groups ($p = 0.562$). Neurobrucellosis was rare and occurred only in one patient from the non-bacteremic group (Table 1).

Table 1: Comparison of Clinical Characteristics Between Bacteremic and Non-Bacteremic Patients

	Overall (n = 117)	**Non-Bacteremic (n = 79)**	**Bacteremic (n = 38)**	**p**
Sex				0.324
Female	46 (39.32%)	34 (43.04%)	12 (31.58%)	
Male	71 (60.68%)	45 (56.96%)	26 (68.42%)	
Age (Months)	144 (23 - 216)	140 (23 - 216)	147 (52 - 214)	0.731
Residence Area				0.067
Urban	43 (36.75%)	34 (43.04%)	9 (23.68%)	
Rural	74 (63.25%)	45 (56.96%)	29 (76.32%)	
Hospitalization	24 (20.51%)	9 (11.39%)	15 (39.47%)	0.001
Hospital Stay (Days)	14 (7 - 47)	14 (12 - 47)	14 (7 - 21)	0.035

Symptoms				
Fever	39 (33.33%)	27 (34.18%)	12 (31.58%)	0.944
Arthralgia	106 (90.60%)	71 (89.87%)	35 (92.11%)	>0.999
Weight Loss	13 (11.11%)	7 (8.86%)	6 (15.79%)	0.422
Sweating	40 (34.19%)	28 (35.44%)	12 (31.58%)	0.838
Family History				
Brucellosis History	53 (45.30%)	34 (43.04%)	19 (50.00%)	0.610
Livestock Ownership	57 (48.72%)	43 (54.43%)	14 (36.84%)	0.113
Raw Milk Consumption	109 (93.16%)	74 (93.67%)	35 (92.11%)	0.713
Physical Examination				
Fever	73 (62.39%)	51 (64.56%)	22 (57.89%)	0.622
Hepatomegaly	11 (9.40%)	10 (12.66%)	1 (2.63%)	0.100
Splenomegaly	33 (28.21%)	29 (36.71%)	4 (10.53%)	0.004
Arthritis	48 (41.03%)	41 (51.90%)	7 (18.42%)	0.001
Arthritis Location				<0.001
None	69 (58.97%)	38 (48.10%)	31 (81.58%)	
Knee	26 (22.22%)	25 (31.65%)	1 (2.63%)	
Ankle	15 (12.82%)	12 (15.19%)	3 (7.89%)	
Hip	7 (5.98%)	4 (5.06%)	3 (7.89%)	
Sacroiliitis	6 (5.13%)	3 (3.80%)	3 (7.89%)	0.388
Relapse	14 (11.97%)	8 (10.13%)	6 (15.79%)	0.562
Neurobrucellosis	1 (0.85%)	1 (1.27%)	0 (0.00%)	>0.999

Data are presented as median (range) for continuous variables and n (%) for categorical variables. Statistical comparisons were made using the Wilcoxon rank-sum test for continuous variables and the Pearson Chi-square or Fisher's exact test for categorical variables, depending on distribution and cell size. A p-value of <0.05 was

In the comparative analysis of laboratory findings between bacteremic and non-bacteremic patients, several hematological and biochemical parameters were assessed. The median hemoglobin level in the overall cohort was 12.4 g/dL. Patients in the non-bacteremic group had a slightly higher median hemoglobin level of 12.5 g/dL (range: 8.5 to 16.7), compared to 11.9 g/dL (range: 9.8 to 13.5) in the bacteremic group, and this difference reached statistical significance (p = 0.037).WBC count was 6980 per cubic millimeter across all patients. There was no statistically significant difference between the non-bacteremic group, which had a median WBC count of 7230, and the bacteremic group, with a median of 6625 (p = 0.297). Similarly, neutrophil counts did not differ significantly between groups, with medians of 3130 and 2875 per cubic millimeter for the non-bacteremic and bacteremic groups, respectively (p = 0.250). Lymphocyte counts were also comparable, with a median of 3170 in the non-bacteremic group and 2780 in the bacteremic group (p = 0.126).

Platelet counts were slightly lower in the bacteremic group, with a median of 265 thousand per cubic millimeter, compared to 282 thousand in the non-bacteremic group; however, this difference was not statistically significant (p = 0.490). In contrast, mean platelet volume (MPV) showed a borderline significant difference, being lower in the bacteremic group (7.65 fL) than in the non-bacteremic group (8.0 fL) (p = 0.048).ESR was similar between groups, with median values of 18 mm/h in the non-bacteremic group and 19 mm/h in the bacteremic group (p = 0.420). CRP levels were also comparable, with a median of 1.17 mg/dL in the non-bacteremic group and 0.62 mg/dL in the bacteremic group (p = 0.195).

Regarding liver function markers, elevated AST levels (greater than 40 U/L) were observed in 34.19% of the total sample, with no significant difference between groups (p = 0.530). Similarly, elevated ALT levels were found in 35.90% of patients, again with no significant group difference (p = 0.444).

Serological titers assessed by the Wright agglutination test did not show significant differences at any dilution threshold between the two groups. The proportions of patients with titers of 1 in 80, 1 in 160, 1 in 320, 1 in 640, 1 in 1280, and 1 in 2560 were comparable, with all p-values greater than 0.05. Although titers at or above 1 in 2560 were more frequently observed in the bacteremic group (5.26%) compared to the non-bacteremic group (1.27%), this difference was not statistically significant.

Table 2: Comparison of Laboratory Parameters and Serological Test Results Between Bacteremic and Non-Bacteremic Patients With Brucellosis

	Overall (n = 117)	**Non-Bacteremic (n = 79)**	**Bacteremic (n = 38)**	**p**
Hemoglobin (g/dL)	12.4 (8.5 - 16.7)	12.5 (8.5 - 16.7)	11.9 (9.8 - 13.5)	0.037
WBC (mm³)	6980 (1800 - 18400)	7230 (3200 - 18400)	6625 (1800 - 11420)	0.297
Neutrophil (mm³)	3040 (830 - 9530)	3130 (1200 - 9530)	2875 (830 - 5520)	0.250
Lymphocyte (mm³)	2980 (710 - 9470)	3170 (1000 - 9470)	2780 (710 - 5290)	0.126
Platelet (x10³/mm³)	280(69 - 675)	282 (89 - 675)	265 (69 - 413)	0.490
MPV (fL)	7.9 (6.2 - 12.1)	8 (6.2 - 12.1)	7.65 (6.2 - 9)	0.048
ESR (mm/h)	18 (2 - 93)	18 (2 - 93)	19 (3 - 72)	0.420
CRP (mg/dL)	0.9 (0.29 - 35)	1.17 (0.29 - 35)	0.62 (0.3 - 28)	0.195
AST (U/L)				0.530
Normal	77 (65.81%)	54 (68.35%)	23 (60.53%)	
>40	40 (34.19%)	25 (31.65%)	15 (39.47%)	
ALT (U/L)				0.444
Normal	75 (64.10%)	53 (67.09%)	22 (57.89%)	
>40	42 (35.90%)	26 (32.91%)	16 (42.11%)	
Serological Titers				
≥ 1/80	9 (7.69%)	5 (6.33%)	4 (10.53%)	0.469
≥ 1/160	36 (30.77%)	28 (35.44%)	8 (21.05%)	0.172
≥ 1/320	25 (21.37%)	16 (20.25%)	9 (23.68%)	0.855
≥ 1/640	30 (25.64%)	20 (25.32%)	10 (26.32%)	>0.999
≥ 1/1280	14 (11.97%)	9 (11.39%)	5 (13.16%)	>0.999
≥ 1/2560	3 (2.56%)	1 (1.27%)	2 (5.26%)	0.246

Data are presented as median (range) for continuous variables and n (%) for categorical variables. Comparisons were performed using the Wilcoxon rank-sum test for continuous variables and the Pearson Chi-square or Fisher's exact test for categorical variables, as appropriate. A p-value < 0.05 was considered statistically significant.

Abbreviations:

ALT (Alanine Aminotransferase), AST (Aspartate Aminotransferase), CRP (C-Reactive Protein), ESR (Erythrocyte Sedimentation Rate), MPV (Mean Platelet Volume), WBC (White Blood Cell Count).

4. Discussion

This study evaluated and compared the clinical and laboratory features of bacteremic and non-bacteremic pediatric brucellosis cases over a 7-year period in an endemic region. Our findings indicate that brucellosis continues to be a significant public health concern in rural pediatric populations, largely due to the ongoing consumption of unpasteurized dairy products.Unlike previous studies, this research analyzed pediatric brucellosis cases comparatively based on blood culture results and identified statistically significant clinical and laboratory differences between the groups, offering new perspectives on the disease's clinical spectrum. The demographic features observed in our study are consistent with the literature, with male predominance, rural residency, animal contact, and particularly raw milk consumption emerging as prominent risk factors [10,11]. Over 93% of the cases reported consuming unpasteurized dairy products, supporting the central role of oral transmission in pediatric brucellosis [12].The most frequently reported clinical symptoms were arthralgia, fever, and sweating, which are consistent with findings from other large pediatric series in endemic areas [13,14]. Arthritis was observed in 41% of patients, most commonly involving the knee and ankle joints. When analyzed according to blood culture status, arthritis was significantly more common in non-bacteremic patients (51.9%) than in bacteremic patients (18.4%) ($p = 0.001$). Similarly, splenomegaly was more frequent in non-bacteremic cases (36.7%) compared to bacteremic cases (10.5%) ($p = 0.004$). These differences may reflect variations in immune response or timing of presentation. In addition, the distribution of arthritis localization differed significantly between the groups ($p < 0.001$), with knee involvement predominating among non-bacteremic patients. Osteoarticular involvement is one of the most common complications of pediatric brucellosis and may lead to permanent sequelae if diagnosis is delayed [15,16]. Although hepatosplenomegaly and sacroiliitis were observed less frequently, they should always be considered in clinical evaluation.Regarding laboratory findings, there were no statistically significant differences in CRP and ESR levels between the groups. These results are consistent with the subacute inflammatory nature of

brucellosis and the mild to moderate acute phase response reported in previous studies [17]. Approximately one-third of patients exhibited elevated transaminases, reflecting hepatic involvement that is common but often subclinical in pediatric brucellosis [18,19]. No significant difference was found between groups in terms of transaminase levels.In our study, a STA titer of ≥1/160 was considered diagnostic; however, 7.7% of patients with a titer of 1/80 were also included due to strong clinical and epidemiological compatibility. No significant differences in clinical or laboratory parameters were found between patients with titers of 1/80 and those with ≥1/160 ($p > 0.05$). These findings support previous literature suggesting that lower titers may be acceptable in symptomatic children in endemic regions [20,21]. Confirmatory testing and careful clinical correlation are essential in such cases.Brucella melitensis was isolated in 32.5% of blood cultures, a rate that, while within the 20–40% range reported in the literature, may be considered relatively low. This could be related to empirical antibiotic use prior to hospital admission or reduced culture sensitivity in subacute presentations [22]. Hospitalization rates were significantly higher in bacteremic cases ($p = 0.001$), and the length of hospital stay differed significantly between groups ($p = 0.035$). Hemoglobin ($p = 0.037$) and MPV ($p = 0.048$) levels were significantly lower in bacteremic patients. Low MPV has been associated with worse outcomes in systemic infections. These findings suggest that bacteremia may be associated with more severe clinical presentations, consistent with previous reports [23,24].The relapse rate was 12%, consistent with previous pediatric brucellosis studies reporting rates between 5–15% [25]. Most relapsed patients had a history of poor treatment adherence or early discontinuation of therapy. These results reinforce the importance of adequate duration of combination antibiotic treatment and the need for regular follow-up and patient education [26].Neurobrucellosis was identified in only one patient (0.85%), a rate consistent with the 1–5% prevalence reported in pediatric brucellosis [27,28]. Although rare, neurobrucellosis is a serious complication that should always be considered in children presenting with persistent fever, headache, or neurological symptoms.This study contributes to the existing literature by presenting data from an endemic region over a 7-year period. Its strengths include a relatively large sample size and a detailed comparison between bacteremic and non-bacteremic cases. However, the retrospective design and the limited number of culture-positive cases restricted the ability to perform more advanced statistical analyses.

5. Conclusion

Pediatric brucellosis continues to pose a significant public health burden in endemic areas, particularly among rural populations. Our findings emphasize the importance of early and accurate diagnosis, sufficient duration of combination antibiotic therapy, and close follow-up to prevent relapse. Public awareness campaigns focusing on the risks of consuming unpasteurized dairy products are essential. Furthermore, the comparison of bacteremic and non-bacteremic cases in this study highlights the clinical variability of the disease. Future prospective and multicenter studies are warranted to better elucidate risk factors for complications such as neurobrucellosis and to guide more standardized diagnostic and treatment approaches.

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Incidence and Risk Factors of Contrast-Induced Nephropathy in Emergency Department Patients Undergoing Contrast-Enhanced CT

Acil Servise Başvuran Hastalarda Kontrastlı Bilgisayar Tomografi Sonrası Opak Nefropatisi İnsidansı ve Risk Faktörleri

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Abstract: Contrast-induced nephropathy (CIN) is a serious complication following the administration of iodinated contrast media, contributing significantly to hospital-acquired acute kidney injury. Contrast-induced nephropathy is defined as either a ≥25% increase from baseline creatinine levels or an absolute increase >0.5 mg/dL, within 48–72 hours after contrast media administration. This study evaluated CIN incidence and associated risk factors in emergency department (ED) patients undergoing contrast-enhanced CT. A prospective observational study was conducted at a tertiary-care ED (June 2013–September 2014). Adults (≥18 years) undergoing CT were enrolled, excluding those with baseline creatinine >1.2 mg/dL, acute kidney injury, or hemodynamic instability. Of the contrast-enhanced CT group (n=171), 14 patients (8.1%) developed CIN, whereas in the non-contrast CT group (n=171), 12 patients (7.0%) developed nephropathy. Hospitalization (p=0.030), advanced age (p=0.026), anemia (p=0.045), leukocytosis (p=0.005), and reduced GFR (p=0.028) were identified as risk factors for contrast-induced nephropathy. In the non-contrast group, anemia (p=0.003), hospitalization (n=9; p=0.039), and leukocytosis (p=0.007) were identified as risk factors for nephropathy. No cases of nephropathy was observed in patients discharged from the ED in either group. Contrast media did not significantly increase nephropathy risk in ED patients with normal renal function. However, older age, anemia, and hospitalization identified high-risk subgroups. Prophylactic measures showed no clear benefit, possibly due to ED time constraints. Vigilance is recommended for elderly and hospitalized patients, with renal monitoring following contrast administration.
Keywords: Contrast-induced nephropathy, emergency department, CT, risk factors, prophylaxis.

Özet: Kontrast kaynaklı nefropati (CIN), iyotlu kontrast madde uygulanmasını takiben gelişen ciddi bir komplikasyon olup, hastane kökenli akut böbrek hasarına (AKI) önemli ölçüde katkıda bulunur. CIN, kontrast madde uygulamasından 48–72 saat sonra bazal kreatinin değerine göre %25'lik bir artış veya ≥0.5 mg/dL'lik mutlak bir artış olarak tanımlanır. Bu çalışma, acil serviste (AS) kontrastlı BT uygulanan hastalarda CIN insidansını ve ilişkili risk faktörlerini değerlendirmiştir. Haziran 2013 – Eylül 2014 tarihleri arasında üçüncü basamak bir AS'te prospektif gözlemsel çalışma yürütülmüştür. BT çekilen ≥18 yaş erişkin hastalar çalışmaya dahil edilmiştir. Başlangıç kreatinin değeri >1.2 mg/dL olanlar, akut böbrek yetmezliği veya hemodinamik instabilitesi olanlar hariç tutulmuştur. Kontrastlı BT yapılan grupta (n=171), 14 hasta (%8.1) CIN geliştirmiş; kontrastsız BT grubunda (n=171) ise 12 hasta (%7.0) nefropati geliştirmiştir. Hastaneye yatış (n=11, p=0.030), ileri yaş (p=0.026), anemi (p=0.045), lökositoz (p=0.005) ve düşük GFR (p=0.028), kontrast maddeye bağlı nefropati gelişimiyle ilişkili risk faktörleri olarak belirlenmiştir. Kontrastsız BT grubunda ise anemi (p=0.003), hastaneye yatış (n=9; p=0.039) ve lökositoz (p=0.007) nefropati için anlamlı risk faktörleri olarak bulunmuştur. Her iki grupta da acil servisten taburcu edilen hastalarda nefropati tespit edilmemiştir. Normal böbrek fonksiyonlarına sahip AS hastalarında kontrast maddesi nefropati riskini anlamlı ölçüde artırmamıştır. Bununla birlikte, ileri yaş, anemi ve hastaneye yatış, yüksek riskli alt grupları tanımlamıştır. Zaman kısıtlılığı nedeniyle profilaktik önlemlerin belirgin bir yararı gözlenmemiştir. Özellikle yaşlı ve hospitalize hastalarda kontrast maruziyeti sonrası böbrek fonksiyonlarının yakından izlenmesi önerilmektedir.
Anahtar Kelimeler: Kontrast kaynaklı nefropati, acil servis, BT, risk faktörleri, profilaksi.

Ethics Committee Approval: . The study protocol was approved by the Research Ethics Committee of Eskişehir Osmangazi University Faculty of Medicine (Protocol No: 17.06.2014-06).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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1. Introduction

The expanding use of interventional procedures for diagnostic and therapeutic purposes has led to a significant increase in the use of iodinated contrast agents. As a result, a spectrum of adverse effects, ranging from immediate reactions to delayed complications including mortality cases, has been reported. Among these, contrast-induced nephropathy (CIN) is one of the most clinically significant and potentially preventable complications.

CIN is defined as an acute impairment of renal function, characterized by either a ≥25% relative increase in serum creatinine from baseline or an absolute rise of ≥0.5 mg/dL within 48 to 72 hours following contrast exposure, in the absence of alternative causes (1).

As a major contributor to hospital-acquired acute kidney injury (AKI), CIN has been identified as the third most common cause of iatrogenic acute kidney injury, with reported incidence rates varying from 11% to 14.5% in high-risk populations (2). In the general population, the estimated incidence is approximately 1–2%; however, discrepancies in AKI definitions and variations in patient comorbidities have led to a wide range of reported rates, ranging from 3.3-31% (3).

The incidence of CIN has been reported to reach as high as 50% in the presence of multiple predisposing risk factors, including hypotension, the use of an intra-aortic balloon pump, congestive heart failure, advanced age (≥75 years), anemia, and diabetes mellitus (4).

This study aims to evaluate the incidence of CIN following contrast-enhanced computed tomography (CT) in the emergency department (ED) setting. By improving risk stratification prior to contrast administration, our findings aim to guide clinical decision-making and support the implementation of targeted preventive strategies, ultimately helping to reduce the burden of this preventable complication.

2.Materials and Methods

2.1 Ethical Approval and Study Design

This prospective observational study was conducted in the emergency department (ED) of Eskisehir Osmangazi University Hospital, a tertiary care center, between June 1, 2013, and September 30, 2014. The study protocol was approved by the Research Ethics Committee of Eskisehir Osmangazi University Faculty of Medicine (Approval No: 17.06.2014-06).

The study population comprised adult patients (≥18 years) who underwent CT in the ED. Based on a power analysis ($\beta = 0.95$), a minimum sample size of 160 participants per group was required, with one group receiving contrast-enhanced CT and a control group undergoing non-contrast CT.

2.2 Hospital Capacity

This study was conducted in a high-volume tertiary care center.

2.3 Imaging Protocols

All CT scans were performed using a multidetector Siemens Somatom Perspective scanner. For contrast-enhanced imaging, non-ionic iopromide (Ultravist™, Bayer Schering Pharma, 370 mg/mL) was administered intravenously in a standard dose of 100 mL.

2.4 Study population

Eligible participants included adults aged 18 years or older who underwent CT imaging in the ED. Patients were excluded if they had acute kidney injury, baseline serum creatinine levels exceeding 1.2 mg/dl, multiple trauma, stage 3 or 4 heart failure (NYHA classification), hemodynamic shock, sepsis, pregnancy, or if they died within 48 hours following contrast administration or did not return for follow-up evaluation.

2.5 Data Collection

Data collection included patients' demographic characteristics and detailed medical history. Renal function was assessed through serial measurements of serum creatinine and electrolytes at baseline (0 hours), 24 hours, and 48 hours post-imaging. Procedural details such as the administered contrast volume (in mL) were also recorded. The study also documented whether patients received any nephroprotective interventions before or after imaging to prevent CIN. Finally, clinical outcomes at discharge and total hospital length of stay were systematically recorded for all participants.

2.6 Statistical Analysis

Continuous data were presented as mean ± standard deviation. Categorical data were expressed as percentages (%). The normality of the data was

assessed using the Shapiro-Wilk test. For comparisons of normally distributed groups, independent t-tests were used for two-group comparisons. For groups that did not follow a normal distribution, the Mann-Whitney U test was applied for two-group comparisons. Pearson's Chi-square, Pearson's Exact Chi-square, and Fisher's Exact Chi-square tests were used for the analysis of cross-tabulations. Odds ratios were calculated. All analyses were performed using IBM SPSS Statistics version 21.0. A p-value of <0.05 was considered statistically significant.

2.7 Assessment of Contrast-Induced Nephropathy

In this study, CIN was defined as either a ≥ 25% increase in serum creatinine or an absolute increase of ≥ 0.5 mg/dl (44.2 μmol/l) from baseline (0 hours) to 48-hour post-procedure measurements. This biochemical definition was uniformly applied across both study groups in order to allow for standardized comparison. However, the classification of nephropathy was group-specific: patients in the contrast-enhanced CT group who met the criteria were diagnosed with contrast-induced nephropathy (CIN), whereas in the non-contrast CT group, similar biochemical changes were classified as hospital-acquired acute kidney injury (AKI), not CIN. This terminology distinction was maintained throughout the analysis to preserve conceptual accuracy.

2.8 Evaluation of Patients Receiving Preventive Treatment for CIN

1. Administration of intravenous saline (0.9%) at a rate of ≥100 mL/hour for at least 1 hour before contrast administration and thereafter.

2. Administration of sodium bicarbonate infusion before and/or after contrast administration.

3. Administration of 600 mg oral N-acetylcysteine before and after contrast administration.

Patients who met any of the above criteria were considered to have received preventive (prophylactic) treatment for CIN

3.Results

A total of 342 patients, including 168 females (49.1%) with a mean age (±SD) of 62.01 (±17.59, min: 18-max: 98), were included in the study (the flowchart is presented in Figure 1). Among the patients whose comorbidities are outlined in Table 1, 102 (29.8%) had no comorbidities recorded in their medical history.

Table 1. Comorbidities

Comorbidities	**n**	**%**
HT	113	33.0
DM	70	20.5
COPD/Asthma	22	6.4
CAD/CABG	41	12.0
CHF (Stage 1-2)	17	5.0
Malignancy	45	13.1
Other	54	17.2

HT: Hypertension, DM: Diabetes Mellitus, CAD: Coronary Artery Disease, CABG: Coronary Artery Bypass Graft, COPD: Chronic Obstructive Pulmonary Disease, CHF: Congestive Heart Failure

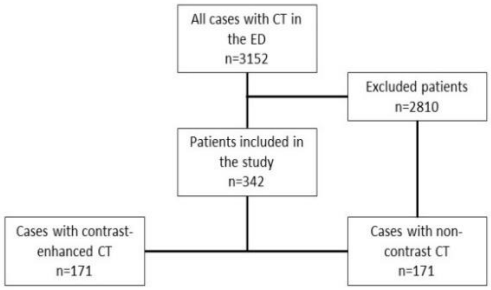

Figure 1. Flowchart of the patient selection process.

The distribution of CT examinations was as follows: abdominal CT in 18% of cases (n=61), chest CT in 15% (n=52), neuro CT angiography in 16% (n=53), brain CT in 37% (n=125), and other CT scans in 14% (n=51).

CIN was observed in a total of 14 patients (8.1%) who underwent contrast-enhanced CT, with a mean age (±SD) of 70.57 (±16.09), 9 of whom were female. In the non-contrast CT group, nephropathy developed in 12 patients, with a mean age (±SD) of 65.75 (±19.42), 6 of whom were female. No significant differences were found between the two groups in terms of gender or age (p=0.481 and p=0.498, respectively).

Among the CIN patients, 78.6% (n=11) were admitted to the intensive care unit (ICU), while 21.4% (n=3) were hospitalized in the general ward. ICU admission was found to be significantly associated with CIN (p=0.030). Of the patients with CIN, 35% (n=5) died during hospitalization. The mean hospital stay for the 14 patients who developed CIN was 14.36 ± 13.72 days, compared to 8.84 ± 9.01 days for the remaining 157 patients who underwent contrast-enhanced CT. However, no significant difference in hospital stay duration was observed in relation to CIN development (p=0.190).

Analysis of the 26 patients who developed nephropathy following non-contrast CT revealed that 76.9% (n=20) required intensive care unit admission, with a mortality rate of 34.6% (n=9) among these cases. ICU admission demonstrated a significant association with nephropathy development (p=0.030). The mean duration of hospitalization was 11.38±11.08 days (mean±SD), though hospital length of stay did not reach statistical significance in relation to nephropathy occurrence (p=0.116). Table 2A and table 2B present a comparison of the two groups in terms of demographics, comorbidities, admission, locations, length of hospital stay, and laboratory parameters.

Table 2A. Comparison of Patients Undergoing Contrast-Enhanced CT: CIN (+) vs CIN (–)

Variable	CIN (+) (Contrast CT) (n=14)	CIN (–) (Contrast CT) (n=157)	p-value
Age (years) ± SD	70.57 ± 16.09	60.62 ± 16.30	0.026
Female (n)	9	-	0.236
DM (n)	4	66	0.678
HT (n)	12	101	0.207
CHF (n)	1	16	1.000
COPD/Asthma (n)	3	19	0.228
CAD / CABG (n)	2	39	0.753
ICU Admission	11	67	0.030
Length of Stay (days)	14.36 ± 13.72	8.84 ± 9.01	0.190
eGFR (mL/min/1.73m²)	74.99 ± 34.53	96.54 ± 32.23	0.028
Hemoglobin (g/dL)	12.08 ± 1.87	14.01 ± 9.61	0.045
Leukocyte (×10³/µL)	16.8 ± 8.91	10.53 ± 5.28	0.005
Lactate (mmol/L)	2.16 ± 1.70	1.63 ± 0.99	0.373

Table 2B. Comparison of Patients Undergoing Non-Contrast CT: AKI (+) vs AKI (–)

Variable	AKI (+) (Non-Contrast CT) (n=12)	AKI (-) (Non-Contrast CT) (n=159)	p-value
Age (years) ± SD	65.75 ± 19.42	62.34 ± 17.77	0.498
Female (n)	6	-	0.481
DM (n)	3	37	0.891
HT (n)	8	106	0.999
CHF (n)	0	8	1.000
COPD/Asthma (n)	1	5	0.358
CAD / CABG (n)	0	20	0.364
ICU Admission	9	39	0.039
Length of Stay (days)	7.92 ± 5.66	7.53 ± 10.41	0.340
eGFR (mL/min/1.73m²)	91.53 ± 34.31	94.34 ± 39.00	0.918
Hemoglobin (g/dL)	12.26 ± 1.62	14.16 ± 10.68	0.003
Leukocyte (×10³/µL)	14.69 ± 8.31	10.22 ± 6.64	0.007
Lactate (mmol/L)	1.90 ± 0.90	2.05 ± 1.70	0.430

Among patients who underwent contrast-enhanced CT, 42.7% (n=73) were identified as low-risk for CIN and did not receive prophylactic treatment before or after contrast administration. Hydration therapy was administered to 48.5% (n=83), while 3.5% (n=6) received N-acetylcysteine (NAC) and 5.3% (n=9) received sodium bicarbonate. No prophylactic measures were implemented for patients undergoing non-contrast CT. The incidence of CIN in patients receiving various prophylactic regimens is presented in Table 3. No significant difference in CIN development was observed among the different prophylactic approaches (p=0.066). Similarly, comparative analysis between patients who received prophylaxis and those who did not revealed no statistically significant difference in CIN incidence (p=0.051).

Table 3. Prophylactic Treatments

	CIN (+)	CIN (-)	Total
IV Fluids	10 (%83.3)	73 (%84.8)	83 (%84.7)
NaHCO3	2 (%16.7)	7 (%8.6)	9 (%9.1)
NAC	0 (% 0)	6 (%6.6)	6 (%6.2)

NAC: N-Acetylcysteine, NaHCO3: Sodium bicarbonate.

In CIN patients, hemoglobin (Hb) levels were significantly lower compared to the remaining 157 patients (p=0.045). Similarly, nephropathy patients also showed significantly lower Hb values compared to others (p=0.003). Leukocyte count analysis in CIN patients showed a significant difference compared with non-CIN patients (p=0.005. No significant associations were found regarding mean arterial pressure between CIN patients and control group (p=0.728), nor between nephropathy patients and others. Additionally, comorbidity analysis revealed no association between underlying diseases and CIN development (p=0.711). Blood lactate levels showed no significant difference between groups (p=0.373).

Among the 14 patients who developed CIN, none required hemodialysis. Fifty percent (n=7) of these patients returned to their baseline creatinine levels. The mortality rate attributed to contrast-induced nephropathy was 35% (n=5). No significant difference in nephropathy risk was observed between patients who received contrast media and those who did not (p=0.838). Hospital admission rates showed statistical significance in both groups.

4.Discussion

Current literature reports significant variability in CIN incidence, ranging from 3.1% to 31% across different study populations (5). Notably, this rate may escalate to 50% in high-risk patients with multiple predisposing factors. Nash et al. identified CIN as the third most common cause of acute kidney injury (AKI) in hospitalized patients (4). However, few studies have specifically examined the incidence of CIN related to diagnostic imaging and contrast use in ED settings, with most existing research focusing on patients undergoing percutaneous coronary interventions. While Mitchell et al. reported 11% CIN incidence in emergency department patients undergoing contrast-enhanced CT (6), Kim et al. observed 4.5% following abdominal CT (7), and a retrospective stroke study found just 2.9% among 198 angiography cases (8), although some studies showing no significant differences (9). Our study revealed an 8.1% incidence of CIN, predominantly observed in critically ill patients requiring ICU management.

Multiple studies have consistently identified advanced age (>75 years) as a significant risk factor for CIN development (10,11). Our findings corroborate this association, with CIN-positive cases demonstrating a mean age of 70.57±16.09 years, which showed statistical significance (p=0.026). The observed increase in CIN incidence with advancing age likely reflects the physiological decline in glomerular filtration rate (GFR), representing an expected pathophysiological consequence.

Several studies have identified female sex as a potential risk factor for CIN, possibly due to age, baseline renal dysfunction, and comorbidities such as hypertension and diabetes mellitus. Although previous studies suggested increased susceptibility in female patients, in our study, sex was not significantly associated with CIN (12,13). baseline renal dysfunction, and higher prevalence of comorbid conditions such as hypertension and diabetes mellitus. However, in our study cohort, we found no statistically significant difference in CIN incidence between male and female patients. Previous research by Durukan et al. (14) involving 114 ED patients undergoing CT imaging demonstrated that contrast volumes under 100 mL

did not increase CIN risk. Notably, this study differed from our investigation by exclusively enrolling patients with baseline creatinine levels under 1.5 mg/dL. In our current study, all patients received contrast volumes below 100 mL; therefore, we cannot draw definitive conclusions about the dose-dependent effects of contrast media. These collective findings suggest that reducing contrast volume for CT imaging may not be necessary for CIN prevention.

Current evidence demonstrates that low-osmolar contrast media (LOCM) are associated with significantly lower CIN incidence compared to high-osmolar agents (15). Studies utilizing intravenous LOCM administration have reported a CIN incidence of approximately 12% (16).

In our study, we exclusively used a single type of non-ionic, low-osmolar contrast medium administered solely via the intravenous route. Consequently, our study design did not permit comparative analysis between different types of contrast media.

Multiple studies have established cardiac failure as a significant risk factor for CIN development (10,12). Particular emphasis has been placed on left ventricular ejection fraction (LVEF) <40% as a predisposing factor for CIN in several investigations (17). It should be noted that these findings primarily derive from studies conducted on patients undergoing percutaneous coronary interventions (PCI). In our current study, we did not observe a statistically significant increase in CIN risk among patients with congestive heart failure (p=1.00). However, this finding must be interpreted with caution, as our study cohort excluded patients with Stage 3-4 heart failure, thereby limiting our ability to analyze this specific high-risk population.

Various treatment approaches have been investigated for the prevention of CIN. Studies have demonstrated that administering IV fluids at a rate of 100-150 mL/hour for 12 hours before and after PCI significantly reduces the incidence of CIN. The European Society of Urogenital Radiology (ESUR) similarly recommends normal saline infusion at 100 mL/hour, starting 4 hours before the procedure and continuing for 24 hours afterward (18).

In our study, no significant difference in CIN development was observed between patients who received preventive treatment and those who did not. Due to the constraints of the ED setting, it was not feasible to implement the 12-hour pre-procedure fluid regimen as it would delay necessary diagnostic tests and treatments. Instead, fluid administration was initiated only 1 hour prior to contrast-enhanced CT. Additionally, as our hospital is a stroke center, preventive treatment was not administered to thrombolytic therapy candidates prior to cerebral CT angiography to avoid time delays. Fluid therapy was subsequently provided to patients as clinically indicated. According to the European Society of Urogenital Radiology (ESUR) guidelines, optimal prophylaxis against CIN includes intravenous isotonic saline at 100 mL/h for 6–12 hours before and after contrast exposure, and in some high-risk cases, oral N-acetylcysteine (NAC) or intravenous sodium bicarbonate may be added. Similarly, KDIGO guidelines emphasize periprocedural volume expansion as the main preventive measure. However, these recommendations are challenging to implement in emergency department settings, where time constraints and the need for rapid imaging often preclude prolonged pre-hydration protocols. This limited implementation window may explain the lack of statistically significant benefit observed with prophylactic strategies in our cohort..

The reported incidence of dialysis requirement following CIN varies considerably across studies. Nikolsky and colleagues documented a 3.1% dialysis rate among affected patients (19). More severe outcomes have been reported elsewhere, with 14% of CIN patients requiring emergent dialysis and 2% progressing to chronic hemodialysis dependence (15). Notably, Gruberg et al. observed dialysis requirements reaching 35% in their patient cohort (20). In contrast, our study population demonstrated a remarkably favorable course, with no cases requiring renal replacement therapy. This discrepancy likely reflects our exclusion criteria, which intentionally omitted patients with baseline serum creatinine exceeding 1.2 mg/dL, thereby selecting for lower-risk individuals.

Regarding hospitalization metrics, while multiple investigations have identified CIN as a significant predictor of prolonged inpatient stays (10), our analysis failed to demonstrate such an association. This finding may relate to our study's unique patient demographics or the exclusion criteria affecting disease severity in our cohort.

A recent study comparing patients undergoing contrast-enhanced versus non-contrast CT examinations found no significant difference in nephropathy rates (21), a finding consistent with our results. However, unlike our investigation which excluded patients with serum creatinine levels >1.2

mg/dL, this study specifically included a higher-risk population. These findings raise an important conceptual issue: whether contrast media itself is the primary cause of acute kidney injury (AKI) or merely a coincidental factor in high-risk patients. In our study, we applied the same biochemical criteria (≥25% or ≥0.5 mg/dL increase in creatinine) to both contrast and non-contrast groups; however, we strictly classified only contrast-exposed patients were classified as having contrast-induced nephropathy (CIN). In the non-contrast group, similar renal impairment was referred to as hospital-acquired AKI. This distinction aligns with recent literature questioning the existence of CIN as a distinct clinical entity (1). The comparable incidence of nephropathy in both groups (8.1% vs. 7.0%) supports the hypothesis that other clinical factors—rather than contrast itself—may play a dominant role in the development of AKI in emergency department settings.

Numerous studies have investigated the association between CIN and both short- and long-term mortality rates. In a retrospective analysis of 7,586 patients undergoing PCI, in-hospital mortality rate was 22% in patients who developed CIN compared to just 1.4% in those without CIN (10). Another study following 1,826 PCI patients reported an overall CIN incidence of 14.5%, with 0.7% requiring dialysis. In-hospital mortality rates were 35.7% in CIN patients requiring dialysis, 7.1% in non-dialysis requiring CIN cases, and 1.1% in patients without CIN (22). Freeman et al.'s analysis of 16,592 patients found that 0.44% developed dialysis-requiring acute kidney injury post-PCI, with a 39% in-hospital mortality rate in this subgroup (23).

In our study, the mortality rate among CIN patients was 35%, with deaths attributed to underlying comorbidities. Among patients undergoing non-contrast CT, 12 cases developed nephropathy with a subsequent mortality rate of 34%, thus demonstrating comparable outcomes.

5.Study Limitations

Our study has several limitations that should be acknowledged. First, as a single-center study, our findings require further validation through multicenter research. Second, the absence of follow-up data from ED patients who did not return for evaluation, as well as the exclusion of hospitalized patients whose 48-hour BUN and creatinine values were unavailable, may have influenced our results.

Another limitation is the absence of multivariate logistic regression analysis to control for potential confounders. While univariate analysis identified several statistically significant associations, multivariate modeling was not feasible due to the limited number of CIN and AKI cases (n=14 and n=12, respectively). Performing regression on such a small number of outcome events would have introduced model instability and increased the risk of overfitting. Therefore, we chose to report univariate associations transparently and interpret the findings with caution.

Additionally, due to our hospital's designation as a stroke center, thrombolytic candidates requiring urgent neuro CT angiography could not receive prophylactic treatment prior to imaging, as time-sensitive diagnostic intervention took precedence. However, appropriate post-procedural therapy was initiated for these patients.

6.Conclusions

Our study found no significant difference in nephropathy incidence between patients undergoing contrast-enhanced and non-contrast CT, suggesting that iodinated contrast media can be safely used in ED patients with normal baseline renal function. However, advanced age, anemia, and inpatient status were associated with increased risk of acute kidney injury. While no prophylactic strategy demonstrated benefit in our setting, vigilant monitoring remains essential. Close post-procedural renal monitoring is recommended, particularly for elderly patients and those admitted to intensive care units.

One limitation of this study is that the manuscript was originally written in a non-native language. Therefore, language editing tools were used to improve clarity and grammar.

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Clinical Outcomes of Parenteral Antibiotics Used in Staphylococcus aureus-Related Skin and Soft Tissue Infections in Pediatric Hospitalized Patients

Çocuk Hastalarda Staphylococcus aureus'a Bağlı Deri ve Yumuşak Doku Enfeksiyonlarında Kullanılan Parenteral Antibiyotiklerin Klinik Sonuçları

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Abstract: This study aimed to determine the clinical and laboratory characteristics of hospitalized pediatric patients with skin and soft tissue infections (SSTIs) associated with Staphylococcus aureus and to compare parenteral antibiotic therapies in terms of clinical outcomes. This single-center retrospective study analyzed patients aged 1 month to 18 years who were treated for S. aureus-associated SSTIs at Ankara Bilkent City Children's Hospital between September 2019 and September 2022. A total of 89 patients were included. Infections were caused by methicillin-susceptible (S. aureus, MSSA; n=54, 60.7%) and methicillin-resistant (S. aureus, MRSA; n=35, 39.3%). Compared to the MSSA group, the MRSA group had significantly higher rates of central venous catheter-related infections, prior hospitalizations, and complications (34.1% vs. 11.1%, 62.9% vs. 24.1%, and 28.6% vs. 5.6%, respectively; p=0.010, p=0.010, p=0.003). No significant difference in clinical outcomes was observed between patients treated with vancomycin or teicoplanin in the MRSA group. In the MSSA group, clinical outcomes were similar between patients who received beta-lactam/beta-lactamase inhibitors and third-generation cephalosporins. However, those treated with ampicillin-sulbactam had lower recurrence and complication rates compared to those treated with piperacillin-tazobactam (0% and 0% vs. 25% and 25%, respectively; p=0.029). Teicoplanin may be a reasonable option for treating MRSA-related SSTIs due to comparable clinical outcomes to vancomycin. For MSSA-related SSTIs, beta-lactam/beta-lactamase inhibitors such as ampicillin-sulbactam, piperacillin-tazobactam, and third-generation cephalosporins may also be appropriate treatment options with satisfactory results.
Keywords: Staphylococcus aureus, skin and soft tissue infections (SSTIs), parenteral antibiotics, clinical outcomes, children

Özet: Bu çalışmanın amacı, hastanede yatan çocuk hastalarda Staphylococcus aureus'a bağlı deri ve yumuşak doku enfeksiyonlarının klinik ve laboratuvar özelliklerini belirlemek ve parenteral antibiyotiklere göre klinik sonuçları karşılaştırmaktır. Bu tek merkezli retrospektif çalışmada, Eylül 2019 – Eylül 2022 tarihleri arasında Ankara Bilkent Şehir Hastanesi Çocuk Hastanesi'nde S. aureus ilişkili deri ve yumuşak doku enfeksiyonu tanısı alarak tedavi edilen 1 ay–18 yaş arası hastalar analiz edilmiştir. Çalışmaya toplam 89 hasta dahil edilmiştir. Enfeksiyonların %60,7'si metisiline duyarlı (MSSA; n=54), %39,3'ü metisiline dirençli (MRSA; n=35) S. aureus kaynaklıydı. MRSA grubunda santral kateter ilişkili enfeksiyon, önceki hastaneye yatış ve komplikasyon oranları MSSA grubuna göre anlamlı olarak daha yüksekti (%34,1 vs. %11,1; %62,9 vs. %24,1; %28,6 vs. %5,6; p=0,010; p=0,010; p=0,003). MRSA grubunda vankomisin ve teikoplanin tedavisi arasında klinik sonuçlar açısından fark izlenmedi. MSSA grubunda ise beta-laktam/beta-laktamaz inhibitörü ve üçüncü kuşak sefalosporin alan hastalarda klinik sonuçlar benzerdir. Ancak ampisilin-sulbaktam alan hastalarda nüks ve komplikasyon oranları piperasilin-tazobaktam alanlara göre anlamlı şekilde daha düşüktü (%0, %0 vs. %25, %25; p=0,029). MRSA ilişkili deri ve yumuşak doku enfeksiyonlarının tedavisinde teikoplanin, vankomisine benzer klinik sonuçları nedeniyle makul bir seçenek olabilir. MSSA ilişkili enfeksiyonların tedavisinde ise ampisilin-sulbaktam, piperasilin-tazobaktam ve üçüncü kuşak sefalosporinler tatmin edici sonuçları nedeniyle uygun tedavi seçenekleri olabilir..
Anahtar Kelimeler: Staphylococcus aureus, deri ve yumuşak doku enfeksiyonları (DYDE), parenteral antibiyotikler, klinik sonuçlar, çocuklar

Ethics Committee Approval: The study was approved Ankara City Hospital Clinical Research Ethics Committee (Decision no: E2-22-2008 Date:22.06.2022

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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1. Introduction

Pediatric patients often face skin and soft tissue infections (SSTIs) that may necessitate hospitalization. *Staphylococcus aureus* is the most commonly isolated pathogen from cutaneous abscesses and infected wounds among hospitalized children (1). The rising prevalence of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) is a major concern in *S. aureus*-associated SSTIs (1,2). However, hospital-acquired MRSA (HA-MRSA) and methicillin-susceptible *S. aureus* (HA-MSSA) infections remain clinically significant, especially in hospitalized children with underlying comorbidities (3,4). Established risk factors for MRSA-associated SSTIs include the presence of an indwelling central venous catheter (5), underlying medical conditions (5), and a recent history of hospitalization within the past 12 months (6). If left untreated or in severe cases, *S. aureus*-associated SSTIs may lead to complications such as bacteremia, sepsis, septic arthritis, osteomyelitis, and toxic shock syndrome (7). The standard management of SSTIs includes incision and drainage of abscesses, debridement of necrotic tissue, removal of infected foreign material, and administration of antimicrobial therapy, either empirically or based on antibiotic susceptibility testing (8). Antimicrobial treatment prevents recurrence and secondary spread following drainage procedures (9). Antibiotic selection may vary depending on the local microbiological flora, antimicrobial resistance profiles, and the patient's clinical condition. Other factors such as drug availability, institutional resources, and physician preferences may also influence therapeutic decisions. Despite the clinical importance of this issue, data on the outcomes of parenteral antibiotics used to treat *S. aureus*-associated SSTIs in hospitalized pediatric patients remain limited (10,11). This study aimed to fill these knowledge gaps and provide a comprehensive comparison of the clinical outcomes of various antistaphylococcal parenteral antibiotics in pediatric patients hospitalized with purulent skin and soft tissue infections (SSTIs) caused by *Staphylococcus aureus*, thereby enlightening the medical community on the most effective treatment strategies.

2. Materials and-Methods

2.1 Study design and study population

This single-center retrospective cohort study, conducted at Ankara City Children's Hospital between September 2019 and September 2022, included a comprehensive sample of pediatric inpatients diagnosed with *S. aureus*-associated skin and soft tissue infections (SA-SSTIs). The thoroughness of our study design and the depth of our data collection process ensure the reliability and validity of our findings.

2.2 Data collection

Demographic data, laboratory results, treatment characteristics, and clinical outcomes were retrieved from the hospital information system. Patients aged between 1 month and 18 years were eligible if they had complete data, mono-microbial culture results confirming *S. aureus* infection, and received appropriate parenteral antibiotic therapy for at least five days after pathogen identification. This rigorous selection process ensured that our study included a homogenous group of pediatric patients with SSTIs caused by *S. aureus*, allowing for more reliable and applicable results.

2.3 Microbiological methods

Pathogen identification and antimicrobial susceptibility testing were performed using VITEK MS v3.2.0 (bioMérieux, Marcy-l'Étoile, France) and matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS). Breakpoint values established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) were applied for susceptibility interpretation (12). Methicillin resistance was determined via cefoxitin screening, with strains exhibiting minimum inhibitory concentrations (MICs) >4 mg/L classified as methicillin-resistant (12).

2.4 Definitions

SA-SSTI was defined as a culture-confirmed *S. aureus* infection from an abscess or wound site accompanied by clinical signs of infection. Hospital-acquired SSTI (HA-SSTI) was an infection occurring ≥48 hours after hospital admission or in patients with inpatient hospitalization within the previous year. Cases not meeting these criteria were classified as community-acquired SSTIs (CA-SSTIs) (13,14). SSTIs were categorized as either abscesses or infected wounds (15). Length of stay (LOS) due to infection was defined as the time between the first culture-confirmed detection of *S. aureus* and the completion of antimicrobial therapy and management of complications. Recurrence was defined as the re-detection of SA-SSTI between 14 days and 12 months after the initial culture positivity

(16,17). Definitive treatment duration was the interval from the first dose of culture-guided antibiotic therapy to the final dose. The primary outcome was the comparison of clinical outcomes between MRSA- and MSSA-associated skin and soft tissue infections (SSTIs). The secondary outcome was the comparison of clinical outcomes based on the specific antistaphylococcal agents administered.

2.5 Statistical analysis

All analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was applied to assess normality. Non-normally distributed variables were compared using the Mann-Whitney U test. If applicable, comparisons of multiple antibiotic groups in MRSA cases were performed using the Kruskal-Wallis H test and Dunn's post hoc test. Results were expressed as medians (minimum–maximum). Categorical variables were analyzed using the Pearson chi-square test, Likelihood Ratio test, or Fisher's exact test, as appropriate, and reported as counts and percentages. A p-value <0.05 was considered statistically significant.

2.6 Ethical approval

The study protocol was approved by the xxx Hospital Clinical Research Ethics Committee (Decision No: E2-2022-2008; Date: June 22, 2022).

3. Results

3.1 Demographic, clinical and laboratory characteristics

A total of 89 pediatric patients with culture-confirmed *S. aureus*-associated skin and soft tissue infections (SA-SSTIs) were included in the study. The cohort consisted of 48.3% male patients, with a median age of 41.4 months (2–213 months). Methicillin-resistant *S. aureus* (MRSA) was identified in 39.3% of cases (n = 35), and hospital-acquired infections (HAIs) were observed in 76.4% (n = 68). Detailed demographic, clinical, laboratory, and treatment outcome data are presented in Table 1. The most common anatomical site for specimen collection was the head and neck region (42.6%). Risk factors such as indwelling central venous catheter (20.2%), trauma (40.4%), neurological disorders (18.0%), and hospitalization within the previous 12 months (39.3%) were more frequently observed in the MRSA group compared to the MSSA group, with statistically significant differences ($p = 0.012$, $p < 0.001$, and $p < 0.001$, respectively). No significant differences were found between the two groups for other epidemiological variables (Table 1). Overall, complications occurred in 14.6% of patients, with a higher incidence in the MRSA group (28.6%) compared to the MSSA group (5.6%) ($p = 0.003$). No significant differences were noted between the groups regarding other clinical outcome measures ($p > 0.05$).

Table 1. Comparison of the patients in terms of their demographic, clinical and laboratory characteristics

	TOTAL n=89 (%)	**MSSA-SSTI n=54 (60.7%)**	**MRSA-SSTI n=35 (39.3%)**	**p-value**
Demographic and Clinical Characteristics				
Age, months median (range)	41.4 (2-213)	34 (2-210)	72 (2-213)	0.133 ʊ
Gender, n, (%)				
Male	43 (48.3)	26 (48.1)	17 (48.6)	0.969 ʊ
Female	46 (51.7)	28 (51.9)	18 (51.4)	
Source of infection, n, (%)				
Community-acquired (CA)	21 (23.6)	16 (29.6)	5 (14.3)	0.096 ʊ
Hospital-acquired (HA)	68 (76.4)	38 (70.4)	30 (85.7)	
Source of bacterial growth, n (%)				
Abscess aspirate culture	44 (49.4)	28 (51.9)	16 (45.7)	0.571 ʊ
Wound swap culture	45 (50.6)	26 (48.1)	19 (54.3)	
Region of bacterial growth, n, (%)				**0.015 ɸ, a**
Cranium	5 (5.6)	1 (1.9)	4 (11.4)	
Face	10 (11.2)	6 (11.6)	4 (11.4)	
Neck	23 (25.8)	21 (38.9)	2 (5.7)	
Chest	14 (15.7)	5 (9.3)	9 (25.7)	
Abdomen	8 (9.0)	5 (9.3)	3 (8.6)	
Perineum	2 (2.2)	1 (1.9)	1 (2.9)	
back	1 (1.1)	0 (0.0)	1 (2.9)	
Upper extremity	8 (9.0)	5 (9.3)	3 (8.6)	
Lower extremity	15 (16.9)	8 (14.8)	7 (20.0)	
Multiple regions	3 (3.4)	2 (3.7)	1 (2.9)	
Invasive medical devices, n, (%)				
Central venous catheter	18 (20.2)	6 (11.1)	12 (34.3)	**0.010 ɸ**
Non-tunnelled CVC	5 (5.6)	2 (3.7)	3 (8.6)	**0.013 ɸ**
Tunnelled CVC	3 (3.4)	2 (3.7)	1 (2.9)	0.321 ɸ
Implantable port	10 (11.2)	2 (3.7)	8 (22.9)	0.012 ɸ
Ventriculoperitoneal shunt	4 (4.5)	1 (1.9)	3 (8.6)	0.207 ɸ
Implant	1 (1.1)	1 (1.9)	0 (0.0)	0.326 ɸ
Comorbidities, n (%)				**<0.001 φ,b**
Trauma	36 (40.4)	30 (55.6)	6 (17.1)	
Burns	10 (11.2)	6 (11.1)	4 (11.4)	

Hematologic-oncologic disorders	6 (6.7)	4 (7.4)	2 (5.7)	
Neurological disorders	16 (18.0)	4 (7.4)	12 (34.3)	
Immunological disorders	9 (10.1)	5 (9.3)	4 (11.4)	
Rheumatic diseases	2 (2.2)	2 (3.7)	0 (0.0)	
Surgical disorders	2 (2.2)	2 (3.7)	0 (0.0)	
Gastroenterological disorders	1 (1.1)	1 (1.9)	0 (0.0)	
Congenital heart disease	4 (4.5)	0 (0.0)	4 (11.4)	
Kidney diseases	2 (2.2)	0 (0.0)	2 (5.7)	
Prematurity, n, (%)	7 (7.9)	4 (7.4)	3 (8.6)	0.843 $^{\phi}$
Hospital stay within the previous 12 months, n (%)	35 (39.3)	13 (24.1)	22 (62.9)	**<0.001** $^{\circlearrowleft}$
Hospital stay up to bacterial growth, median days (range)	4 (1-46)	3.5 (1-24)	6 (1-46)	**0.045** $^{\tau}$
LABORATORY FINDINGS				
White blood cell count, /mm^3 median (range)	11000 (550-33000)	9590 (550-20700)	11990 (1280-33000)	**0.021** $^{\tau}$
Total neutrophil count, /mm^3 median (range)	6620 (30-26000)	5040 (30-14470)	7315 (350-26000)	**0.027** $^{\tau}$
CRP, mg/dL median (range)	27.5 (5-295)	24.50 (11-295)	48 (5-198)	0.190 $^{\tau}$
OUTCOMES				
Total length of hospital stay, days, median (range)	18 (7-184)	16.5 (7-184)	28 (8-157)	**0.002** $^{\tau}$
Infection-associated length of hospital stay, median days (range)	10 (5-35)	10 (5-35)	12 (7-35)	0.726 $^{\tau}$
PICU admission (n, %)	11 (12.4)	7 (13.0)	4 (11.4)	0.829 $^{\circlearrowleft}$
Need for surgery, n (%)	52 (58.4)	32 (59.3)	20 (57.1)	0.843 $^{\circlearrowleft}$
Time to CRP-negativity, days median (range)	7 (2-21)	6 (2-21)	7 (3-14)	0.829 $^{\tau}$
Recurrence, n (%)	9 (10.1)	3 (5.6)	6 (17.1)	0.077 $^{\circlearrowleft}$
Development of complication(s), n (%)	13 (14.6)	3 (5.6)	10 (28.6)	**0.003** $^{\circlearrowleft}$
Complications developed, n (%)				
Bacteremia	6 (6.7)	1 (1.9)	5 (14.3)	**0.022** $^{\phi}$
Septic arthritis	3 (3.4)	2 (3.7)	1 (2.9)	**0.826** $^{\phi}$
Osteomyelitis	4 (4.5)	0 (0.0)	4 (11.4)	**0.024** $^{\phi}$

Abbreviations: *MRSA: Methicillin-resistant Staphylococcus aureus; MSSA: Methicillin-susceptible Staphylococcus aureus: SSTI: Skin and soft tissue infection; $^{\phi}$: Likelihood Ratio Test; $^{\circlearrowleft}$: Pearson Chi Square test; $^{\Theta}$: Kruskal Wallis H test; $^{\tau}$: Mann- Whitney U Test*

a: In the MSSA group, high rates of bacterial growth were observed in culture materials obtained from patients with SSTIs of the neck region (38.9%), whereas in the MRSA group, high rates of bacterial growth were observed in the patients with SSTIs of the cranial region (11.4%), chest and lower extremities. b: In the MSSA group, traumatic lesions were observed, while in the MRSA group, neurological disorders and congenital heart disease were observed at a higher rate.

3.2 Antibiotic Susceptibility Profile

Antibiotic susceptibility testing revealed that all isolates (100%) were susceptible to glycopeptides (vancomycin, teicoplanin), linezolid, daptomycin, fosfomycin, and tigecycline. Clindamycin susceptibility was 74.1% in MSSA and 60.0% in MRSA isolates. Inducible clindamycin resistance (IRC) was identified in 25.9% of MSSA and 40.0% of MRSA isolates. No statistically significant difference was found between the two groups for clindamycin susceptibility or IRC rates.

Erythromycin resistance was 70.4% in MSSA and 82.4% in MRSA isolates, while tetracycline resistance was 62.9% in MSSA and 60.0% in MRSA isolates. Trimethoprim-sulfamethoxazole susceptibility remained high in both groups—94.4% for MSSA and 88.6% for MRSA isolates. Fluoroquinolone resistance (ciprofloxacin and levofloxacin) was more frequent in MRSA isolates ($p = 0.005$ for both agents). These data indicate a higher antimicrobial resistance profile in MRSA compared to MSSA isolates. Antibiotic susceptibility patterns and inducible clindamycin resistance rates are summarized in Figure 1 below.

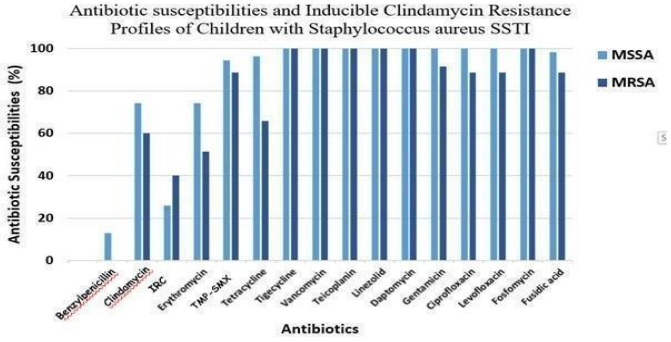

Figure 1. *Antibiotic susceptibilities and inducible clindamycin resistance rates of the isolates*
Abbreviations: *SSTI: skin and soft tissue infection, IRC: Inducible clindamycin resistance, TMP-SMX: Trimethoprim-sulfamethoxazole*

3.3. Comparison of Clinical Outcomes According to Parenteral Antibiotics Used for MRSA-SSTIs

No significant differences were found in clinical outcomes between patients treated with vancomycin and those treated with teicoplanin. However, patients who received clindamycin had a significantly shorter median infection-related hospital stay (7 days) compared to those treated with vancomycin (21 days) and teicoplanin (12 days) (p = 0.002). No statistically significant differences were observed between the three treatment groups regarding other clinical outcome parameters. The comparison of parenteral antibiotics used in MRSA-SSTIs in terms of clinical outcomes is summarized in Table 2.

Table 2. Comparison of parenteral antibiotics used in MRSA-SSTIs in terms of clinical outcomes

	All antibiotics used				Glycopeptide subgroup antibiotics		
	Clindamycin (n=7)	Vancomycin (n=14)	Teicoplanin (n=14)	p-value	Vancomycin (n=14, %)	Teicoplanin (n=14)	p-value
Infection-related length of hospital stay, median days (range)	7[c] (7-10)	21[a] (7-35)	12[b] (7-28)	0.002 $^{\Theta}$	21 (7-35)	12 (7-28)	0.125 $^{\tau}$
PICU admission n (%)	0 (0.0)	3 (21.4)	1 (7.1)	0.210 $^{\sigma}$	3 (21.4)	1 (7.1)	0.596 $^{\varphi}$
Recurrence, n (%)	0 (0.0)	4 (28.6)	2 (14.3)	0.147 $^{\phi}$	4 (28.6)	2 (14.3)	0.648 $^{\varphi}$
Development of complication(s), n (%)	0 (0.0)	5 (35.7)	5 (35.7)	0.068 $^{\phi}$	5 (35.7)	5 (35.7)	1.00 $^{\varphi}$

$^{\Theta}$: Kruskal Wallis H test ^{abc}: Different letters written as superscripts indicate differences between columns (Dunn's test for intergroup analysis);
$^{\varphi}$: Fisher Exact Test; $^{\sigma}$: Pearson Chi-Square test; $^{\tau}$: Mann-Whitney U Test; $^{\phi}$: Likelihood Ratio Test.
***Abbreviations:** PICU: pediatric intensive care unit; MRSA: Methicillin-resistant Staphylococcus aureus; SSTI: Skin and soft tissue infection*

3.4. Clinical Outcomes of Parenteral Antibiotics Used for MSSA-SSTIs

In the MSSA group, clinical outcomes were assessed through two distinct analyses. The first analysis, presented in Table 3, compared outcomes between patients who received clindamycin in combination and those who did not. The second analysis, detailed in Table 4, focused on a subgroup of MSSA-SSTI patients who did not receive clindamycin and compared those treated with β-lactam/β-lactamase inhibitor combinations to those treated with third-generation cephalosporins. Both analyses revealed no significant difference in clinical outcomes across the compared treatment groups. Supplementary material includes detailed data on SSTI-related complications as presented in Table S1, surgical interventions in Table S2, PICU admissions in Table S3, clindamycin combination therapy in MSSA-SSTIs in Table S4, piperacillin-tazobactam use in MSSA cases in Table S5, and antibiotic regimens used in the MRSA group in Table S6

Table 3. Comparison of different empirical antibiotic regimens used in MSSA-SSTIs, including clindamycin combinations, in terms of clinical outcomes

	MSSA group			Not combined with clindamycin (n=30)			Combined with clindamycin (n=24)		
	Not combined with clindamycin (n=30)	Combined with clindamycin (n=24)	P value	BL-BLİ** (n=24)	3. generation CS* (n=6)	P value	BL-BLİ (n=21)	3. generation CS (n=3)	P value
Infection-related length of hospital stay, median days (range)	10 (5-35)	10 (5-21)	0.768 $^{\tau}$	10 (5-21)	8.5 (5-14)	0.273 $^{\tau}$	10 (5-21)	10 (5-14)	1.00 $^{\tau}$
PICU admission, n (%)	4 (13.33)	2 (8.33)	0.682 $^{\varphi}$	4 (16.7)	1 (16.7)	1.00 $^{\varphi}$	1 (4.8)	1 (4.8)	0.239 $^{\varphi}$
Recurrence, n, (%)	2 (6.7)	1 (4.2)	1.00 $^{\varphi}$	2 (8.3)	0 (0.0)	1.00 $^{\varphi}$	1 (4.8)	0 (0.0)	1.00 $^{\varphi}$
Development of complications	3 (10.00)	0 (0.0)	0.245 $^{\varphi}$	2 (8.3)	0 (0.0)	1.00 $^{\varphi}$	1 (4.8)	0 (0.0)	1.00 $^{\varphi}$

$^{\tau}$: Mann-Whitney U Test, $^{\varphi}$: Fisher Exact Test;
**3rd generation cephalosporins: ceftriaxone, cefotaxime*
***Abbreviations.** PICU, pediatric intensive care unit; BL, beta-lactam; BL-BLI, beta-lactam/beta-lactamase inhibitor combination; CS, cephalosporin; MSSA, methicillin-susceptible Staphylococcus aureus*

This table includes all MSSA-SSTI cases regardless of clindamycin use. Clindamycin combination therapies are also included and compared to monotherapies.

Table 4. Subgroup analysis of MSSA-SSTI patients treated without clindamycin: comparison of BL-BLI combinations versus third-generation cephalosporins in terms of clinical outcomes

	BL+BLİ subgroup (n=24)			**3rd generation cephalosporin subgroup (n=6)**		
	Ampicillin-sulbactam (n=16)	**Piperacillin-tazobactam (n=8)**	**p**	**Ceftriaxone (n=3)**	**Cefotaxime (n=3)**	**p**
Infection-associated hospital stay (days: median (range)	10 (5-14)	11 (10-21)	0.320 [τ]	7 (5-10)	14 (7-14)	0.200 [τ]
PICU admission, n (%)	3 (18,8)	1 (12,5)	0.333 [φ]	1 (33,3)	0 (0,0)	1.00 [φ]
Recurrence, n (%)	0 (0,0)	2 (25,0)	0.101 [φ]	0 (0.0)	0 (0.0)	N/A
Development of complications, n (%)	0 (0,0)	2 (25,0)	0.101 [φ]	0 (0.0)	0 (0.0)	N/A

[φ]: Fisher Exact Test; [τ]: Mann Whitney U Test;
**Third-generation cephalosporins: ceftriaxone, cefotaxime*
Abbreviations: *PICU, pediatric intensive care unit; BL-BLI, beta-lactam/beta-lactamase inhibitor combination; N/A, not applicable*

This analysis only includes MSSA-SSTI patients who were not treated with clindamycin. The aim is to compare clinical outcomes between patients treated with β-lactam/β-lactamase inhibitor combinations and those receiving third-generation cephalosporins.

4. Discussion

This study presents detailed findings on the clinical outcomes of parenteral antibiotics used to treat *Staphylococcus aureus*-associated skin and soft tissue infections (SA-SSTIs) in hospitalized pediatric patients. These findings contribute valuable insights to the limited pediatric literature addressing this topic.

4.1. Demographic, Clinical, and Laboratory Characteristics

The epidemiological and clinical characteristics of pediatric patients with SA-SSTIs can vary depending on multiple factors. The high incidence of SSTIs in children aged 6 months to 5 years has been associated with factors such as increased exposure to communal environments (e.g., daycare), close physical contact, suboptimal hygiene, and a decline in maternally acquired passive immunity after infancy (10,11). Although MSSA is classically considered less virulent, hospital-acquired MSSA (HA-MSSA) strains may act as nosocomial pathogens in pediatric SSTIs (18,19). The severity of SSTIs has been linked to the presence of Panton-Valentine leukocidin (PVL) genes, detected in 8.4–49% of MSSA strains (6,18,20) and 31–73% of MRSA strains (2,21), suggesting a potential genetic overlap and shared virulence between MRSA and MSSA isolates (13). In line with previous pediatric studies, most infections in our cohort originated from abscesses or infected wounds, particularly in the head and neck region and lower extremities (10,11). Known risk factors, such as central venous catheters, comorbidities, previous hospitalizations, and *S. aureus* colonization, were also observed in our study population (5,6,9). Unlike previous studies (2,20,21) where community-acquired MRSA (CA-MRSA) was predominant, most of our cases were hospital-acquired and MSSA-associated. These previous studies were predominantly conducted in community settings and in pediatric populations, particularly in regions with high CA-MRSA prevalence (2,20,21). The observed difference in our cohort may reflect regional variations in hospital microbiota, as well as the fact that our study focused on hospitalized children, many of whom had comorbidities or recent healthcare exposure. This shift in epidemiology raises the possibility of PVL-positive methicillin-susceptible *Staphylococcus aureus* (MSSA) strains, warranting future molecular analysis. Median hospital stay durations of approximately 10 days, as reported in the literature (11,22), were consistent with our findings, although they were prolonged in patients with complications or comorbidities. Rates of recurrence (19–63%), complications (4–16%), and bacteremia (2.1–12.5%) reported previously (5,10,11,16,23) were also reflected in our cohort. Among patients requiring PICU admission, nearly all had significant comorbidities, and a notable proportion required surgical intervention, especially abscess drainage. Although PVL testing was not conducted, the severity of clinical presentation supports the need for further molecular studies.

4.2 Antibiotic Susceptibility Profile

Clindamycin susceptibility, including inducible resistance, remains a key consideration in empirical treatment decisions (24). In pediatric studies, nearly all isolates have been reported to be susceptible to glycopeptides, linezolid, daptomycin, and tigecycline (17,46,47). In our cohort, all *S. aureus* isolates demonstrated full susceptibility (100%) to glycopeptides (vancomycin and teicoplanin), linezolid, daptomycin, fosfomycin, and tigecycline, aligning well with previous literature. However, high resistance rates have previously been reported for trimethoprim-sulfamethoxazole (78.4–98.6%), clindamycin (34.2–88.1%), inducible clindamycin (4.5–26.5%), and tetracycline (80.8–89.7%) (17,46,47). In our study, clindamycin resistance was detected in 40.0% of MRSA and 25.9% of MSSA isolates, while inducible clindamycin resistance was observed in 40.0% and 25.9% respectively, indicating higher resistance rates than typically reported for inducible forms. MRSA isolates are generally more resistant to clindamycin and tetracycline than MSSA (25,26). Consistent with this, we observed higher erythromycin and tetracycline resistance among MRSA isolates (82.4% and 60.0%) compared to MSSA isolates (70.4% and 62.9%). Trimethoprim-sulfamethoxazole susceptibility remained relatively high, at 88.6% for MRSA and 94.4% for MSSA isolates, suggesting it may be a viable option in selected MRSA-SSTI cases. Among fluoroquinolones, ciprofloxacin and levofloxacin resistance was more common in MRSA isolates in our study, again consistent with previous findings of broader resistance in this group. These findings emphasize the higher antimicrobial resistance profile of MRSA isolates and support the continued necessity of local susceptibility data to guide empirical antibiotic choices in pediatric SSTIs. While clindamycin and doxycycline may still be considered for targeted therapy, their empirical use should be approached with caution in settings where resistance is common. When glycopeptides are contraindicated, linezolid and daptomycin represent valuable alternatives. However, further prospective studies are needed to confirm their safety and effectiveness in pediatric *S. aureus*-related SSTIs.

4.3 Clinical outcomes of parenteral antibiotics used for MRSA-SSTIs

The potential for resistance development during clindamycin treatment should be considered, especially in the presence of inducible or erythromycin resistance (27). Vancomycin remains the standard of care for complicated methicillin-resistant *Staphylococcus aureus* (MRSA) skin and soft tissue infections (SSTIs) (8). Pediatric studies comparing clindamycin and glycopeptides are lacking; however, adult studies suggest comparable outcomes (28). Teicoplanin, which offers the advantages of once-daily intramuscular dosing, reduced toxicity, and no need for therapeutic drug monitoring, may be a viable alternative to vancomycin (29,30). In our study, clindamycin was mainly preferred in uncomplicated or CA-MRSA infections, while glycopeptides were reserved for more severe, hospital-acquired, or clindamycin-resistant cases. Although hospital stay was longer in patients treated with glycopeptides, clinical outcomes were similar between teicoplanin and vancomycin, consistent with the literature. Furthermore, Turkey's lack of a liquid clindamycin suspension may contribute to the preference for parenteral formulations in hospitalized children.

4.4 Clinical outcomes of parenteral antibiotics used for MSSA-SSTIs

Ampicillin-sulbactam is widely accepted as a first-line agent for MSSA-SSTIs, with efficacy comparable to cefazolin (31–33). Pediatric studies directly comparing ampicillin-sulbactam with piperacillin-tazobactam or cephalosporins are lacking. Adult studies have shown no differences in clinical outcomes among ampicillin-sulbactam, antistaphylococcal penicillins, and cephalosporins (34–37). Some reports suggest a shorter hospital stay with ampicillin-sulbactam than piperacillin-tazobactam (38), though this finding is inconsistent (39). Piperacillin-tazobactam remains a recommended empirical choice for more complicated SSTIs (40). No pediatric studies have assessed the effect of clindamycin combination therapy in MSSA-SSTIs. Studies in adults have shown no added benefit of combining clindamycin with standard agents (41–43), and such combinations may increase adverse events such as diarrhea (43). Our cohort utilized clindamycin combinations in complicated methicillin-susceptible *Staphylococcus aureus* (MSSA) cases involving large abscesses or wounds. However, no significant differences in outcomes were observed between the combination and monotherapy groups. Similarly, no outcome differences were found between beta-lactamase inhibitors and third-generation cephalosporins. Piperacillin-tazobactam was more frequently used in patients with complicated MSSA-SSTIs.

This study has several limitations. Its retrospective, single-center design and modest sample size limit the generalizability of the findings. Molecular

testing for virulence genes such as PVL was not performed. Additionally, adverse effects related to antibiotic treatment were not recorded, and culture results from wound swabs may be subject to contamination bias. Despite these limitations, the study has several strengths. It includes a well-characterized pediatric cohort with a high proportion of hospital-acquired infections. Importantly, the study provides comparative outcome data for different antistaphylococcal antibiotics in managing pediatric SA-SSTIs, an area that remains understudied.

Although susceptibility differences were observed between MRSA and MSSA isolates, particularly for clindamycin, inducible clindamycin resistance (IRC), erythromycin, and tetracycline, these differences did not translate into meaningful differences in clinical outcomes such as recurrence, complication, or PICU admission rates. In the MRSA group, clinical outcomes were comparable between patients treated with vancomycin and teicoplanin, despite variable susceptibility patterns. Similarly, in the MSSA group, clinical outcomes did not significantly differ between patients treated with beta-lactam/beta-lactamase inhibitors and third-generation cephalosporins, even though resistance profiles slightly varied. These findings suggest that while resistance patterns are critical for guiding empirical therapy, they may not always predict clinical progression, especially when definitive treatment is guided by susceptibility results.

5. Conclusion

Given the comparable clinical outcomes, Teicoplanin is a reasonable alternative to vancomycin in treating MRSA-associated skin and soft tissue infections (MRSA-SSTIs). For MSSA-SSTIs, ampicillin-sulbactam and third-generation cephalosporins demonstrated satisfactory efficacy and may serve as appropriate therapeutic options. Additionally, combining clindamycin with other antibiotics did not improve clinical outcomes in cases of MSSA, suggesting that routine combination therapy may not be necessary for these infections. Considering this study's retrospective and single-center design, further prospective, multicenter investigations are warranted to validate these findings and provide stronger evidence for treatment recommendations in pediatric SA-SSTIs.

Abbreviations

CA: Community-acquired

HA: Hospital-acquired

MSSA: Methicillin-susceptible *Staphylococcus aureus*

MRSA: Methicillin-resistant *Staphylococcus aureus*

SSTI: Skin and soft tissue infection

SA-SSTI: *Staphylococcus aureus*-associated skin and soft tissue infection

LOS: Length of stay

MIC: Minimum inhibitory concentration

PVL: Panton-Valentine leukocidin

PICU: Pediatric intensive care unit

SPSS: Statistical Package for the Social Sciences

BL-BLI: Beta-lactam/beta-lactamase inhibitor

EUCAST: European Committee on Antimicrobial Susceptibility Testing

MALDI-TOF MS: Matrix-assisted laser desorption ionization-time of flight mass spectrometry

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Sağlık Hizmetlerine Erişim Engellerinin Zaman İçindeki Değişimi ve Tedavi Edilebilir Ölüm Oranları Üzerindeki Etkisi: Avrupa Birliği Ülkeleri Üzerine Bir Panel Veri Yaklaşımı

Changes in Barriers to Accessing Health Care Services Over Time and Their Effects on Treatable Mortality Rates: A Panel Data Approach on European Union Countries

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Abstract: Unmet healthcare needs often degrade individuals' health status and can lead to death due to the inability to address health needs. The purpose of the current study is to reveal the impact of unmet healthcare needs on treatable deaths. This study is a longitudinal study conducted with data from 27 European Union member countries between 2011 and 2021. The data in the study were extracted from individual declaration reports on unmet healthcare needs published on the Eurostat website. Treatable deaths were included in the model as the dependent variable, while cost, waiting time, and distance were included as independent variables. Analyses were performed using Jamovi Version 2.4. The findings indicate that, in the model constructed without including the time unit, cost and waiting time statistically significantly and positively affect deaths from treatable causes, whereas distance shows no statistically significant effect. With the inclusion of the time unit, it was found that only waiting time significantly and positively affects treatable deaths, while other variables have no significant effect. Furthermore, the time variable itself was observed to positively affect treatable deaths in all other years compared to 2011. This study sheds light on critical issues in the healthcare system by examining the impact of barriers to healthcare access on treatable deaths. The analysis results show that, especially long waiting times, have a significant and consistent positive effect on treatable deaths. This is consistent with the literature suggesting that delays in accessing healthcare negatively affect the treatment of diseases requiring timely intervention and increase the risk of mortality.
Keywords: Unmet Healthcare Needs, Treatable Deaths, Mixed Effects Model

Özet: Karşılanamayan sağlık hizmetleri çoğu zaman bireylerin hem sağlık statüsünü düşürmekte hem de sağlık ihtiyacının giderilmemesi sebebi ile ölümle sonuçlanabilmektedir. Mevcut çalışmanın amacı karşılanamayan sağlık hizmetlerinin tedavi edilebilir ölümler üzerindeki etkisini ortaya koymaktır. Bu çalışma Avrupa Birliği üyesi 27 ülkenin 2011-2021 yılları arasındaki verisi ile yürütülmüş bir boylamsal çalışmadır. Çalışmadaki veriler Eurostat web sitesinde yayınlanan karşılanamayan sağlık ihtiyaçlarına yönelik bireysel beyan raporundan çekilmiştir. Tedavi edilebilir ölümler, bağımlı değişken, pahalılık, bekleme süresi ve uzaklık ise bağımsız değişken olarak modele dahil edilmiştir. Analizler Jamovi Sürüm 2.4 ile gerçekleştirilmiştir. Elde edilen bulgular zaman biriminin dahil edilmeden kurulan modele göre pahalılık ve bekleme süresinin tedavi edilebilir nedenlerden kaynaklanan ölümleri istatistiksel olarak anlamlı pozitif yönde etkilemekte, buna karşın uzaklığın istatistiksel olarak anlamlı bir etki göstermediği görülmektedir. Zaman biriminin dahil edilmesi ile birlikte sadece bekleme süresinin tedavi edilebilir ölümleri anlamlı pozitif yönde etkilediği buna karşın diğer değişkenlerin anlamlı bir etkiye sahip olmadığı tespit edilmiştir. Bununla birlikte zaman değişkeninin de 2011 yılı ile kıyas edildiğinde tüm diğer yıllarda tedavi edilebilir ölümleri pozitif yönde etkilediği görülmüştür. Bu çalışma, sağlık hizmetlerine erişimde yaşanan engellerin, tedavi edilebilir ölümler üzerindeki etkisini inceleyerek, sağlık sistemindeki kritik sorunlara ışık tutmaktadır. Analiz sonuçları, özellikle uzun bekleme sürelerinin, tedavi edilebilir ölümler üzerinde anlamlı ve istikrarlı bir etkisi olduğunu göstermektedir. Bu durum, sağlık hizmetlerine erişimde yaşanan gecikmelerin, zamanında müdahale gerektiren hastalıkların tedavisini olumsuz etkilediği ve ölüm riskini artırdığı yönündeki literatürle tutarlılık göstermektedir.
Anahtar Kelimeler: Karşılanamayan Sağlık Hizmetleri, Tedavi Edilebilir Ölümler, Karma Etkiler Modeli

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1. Giriş

Bireylerin fiziksel, ruhsal ve sosyal yönden iyilik hallerini korumak için sahip oldukları önemli temel haklardan birisi de sağlıktır. Çünkü sağlık, toplumsal gelişmenin de önemli bir göstergesidir. Sağlığın bu önemine karşın birçok ülkede karşılanamayan sağlık hizmetleri sebebi ile bireyler bu temel hakka erişim sağlayamamaktadır. Karşılanamayan sağlık hizmetleri, bireylerin finansal yetersizlikler, coğrafi uzaklık, bilgi eksikliği, kültürel veya sosyal bariyerler gibi nedenlerle ihtiyaç duydukları sağlık hizmetlerine ulaşamaması durumudur (1,2). Bu durum, bireylerin sağlık statülerinde kötüleşmeye, kronik hastalıkların ilerlemesine ve hatta ölümlerin artmasına yol açabilmektedir. Özellikle, zamanında ve uygun tedavi ile önlenebilecek veya tedavi edilebilecek durumların göz ardı edilmesi, tedavi edilebilir ölümler olarak tanımlanan istenmeyen sonuçları beraberinde getirmektedir.

Tedavi edilebilir ölümler, sağlık sisteminin etkinliğini ve erişilebilirliğini değerlendirmede önemli bir göstergedir (3). Genellikle kaçınılabilir ölümlerin iki ana kategorisinden biri olarak ele alınan tedavi edilebilir ölümler, ikinci kategoride yer alan önlenebilir ölümlerle de ilişki içindedir (4). Önlenebilir ölümler, hastalıkların ortaya çıkmasını engelleyen kamu sağlığı girişimleri (örneğin, aşılar, sağlıklı yaşam teşvikleri) ile engellenebilecek ölümler iken, tedavi edilebilir ölümler, bireysel düzeyde verilen tıbbi bakımın kalitesi ve zamanında erişilebilirliği ile doğrudan ilişkilidir. Yani, mevcut tıbbi bilgi ve teknoloji ile başarılı bir şekilde tedavi edilebilecek hastalıklardan veya durumlardan kaynaklanan ölümler, tedavi edilebilir ölümleri yansıtmaktadır.

Karşılanamayan sağlık hizmetleri ile tedavi edilebilir ölümler arasında doğrudan ve güçlü bir ilişki bulunmaktadır. Sağlık hizmetlerine erişimde yaşanan engeller, teşhisin gecikmesine, tedavinin aksamasına veya hiç başlamamasına neden olarak tedavi edilebilir durumların ölümcül sonuçlara yol açmasına zemin hazırlamaktadır. Örneğin, diyabet, hipertansiyon, bazı kanser türleri veya enfeksiyonlar gibi erken teşhis ve uygun tedavi ile yönetilebilecek hastalıklar, sağlık hizmeti erişimi eksikliği nedeniyle ilerleyerek ölümlere neden olabilmektedir (5).

Her ne kadar sağlık, çoğu ülkenin anayasasında yer alan evrensel bir hak (6) olarak görülse de gerek gelişmiş gerekse de gelişmekte olan ülkelerde bazı sağlık eşitsizliklerinin olduğu görülmektedir (2,7). Bu eşitsizliklerin sebepleri çeşitli ve karmaşıktır. Zira meslek, gelir düzeyi, eğitim seviyesi, istihdam, çoğrafi konum ve fiziksel çevre kaynaklı kır veya kent yaşamı ile sağlık sisteminin yapısı, kültürel ve dil bariyerleri ile toplumun sağlık okuryazarlığı durumu gibi faktörlerin tamamı sağlık eşitsizliklerinin birer belirleyicisidir. Ancak bu çalışmanın odak noktası giren Eurostat'ın belirttiği en önemli sağlık eşitsizliklerinin sağlık hizmetlerinin pahalı oluşundan, bekleme sürelerinin uzun olmasından ve sağlık hizmet sunucularının yaşanılan yere gereğinden fazla uzak olmasından kaynaklandığı görülmektedir (8–12). Bu sebepler sağlık sistemlerinin güçlendirilmesi ile ortadan kaldırılabilir sebeplerdir (13). Ancak yirmi birinci yüzyılın ilk çeyreğine girdiğimiz bu günlerde bile halen bu sebepler ile dünyanın farklı yerlerinde sağlık hizmetini alamayan insanlar olduğu görülmektedir. Bu sebepler, tedavi edilebilir nedenlerden kaynaklanan ölümlerin artmasına yol açmaktadır (14,15). Artan bu ölümler ise küresel sağlık sistemlerini derinden etkilemektedir (16–18). Bu durum sağlık politikacıları tarafından değerlendirilmekte ve buna yönelik çözüm önerileri geliştirilmektedir. Ancak bu politikaların geliştirilmesi için gerekli olan kanıtların olmaması politikacıların etkin olmayan kararlar almasına yol açmaktadır (17,19).

Dünya Sağlık Örgütü (DSÖ) tedavi edilebilir nedenlerden kaynaklanan ölümleri sağlıkta eşitsizlik olarak rapor etmektedir. DSÖ'ne göre sağlıktaki eşitsizliklerin nedenleri, sosyal-ekonomik, çevresel ve davranışsal faktör kaynaklı olduğunu ifade etmektedir (2,20). Bu faktörler de sağlık hizmetlerinin pahalılığına, bekleme sürelerinin uzun olmasına ve sağlık kurum ve kuruluşlarının yerleşim yerlerine olması gerekenden daha uzak olmasına bağlanmaktadır (8–12).

Sağlık sistemlerinin sahip olduğu alt yapı eksiklikleri, sağlık insan gücünün farklı bölgeler arasında dengesiz bir şekilde dağılımı, bazı sağlık teknolojilerinin eksikliği, sosyo-ekonomik ve coğrafik eşitsizlikler gibi nedenlerden yaşanan ölümlere tedavi edilebilir ölümler denmektedir. Bu ölümler ilgili nedenler ortadan kaldırıldığında yaşanmayacak olan ölümlerdir (11,21). Normalde düşük ve orta gelirli ülkelerde daha sık yaşanan tedavi edilebilir nedenlerden kaynaklı ölümlerin son yıllarda sağlık sistemleri üzerindeki finansal yükler oluşturmakta ve yanlış politikalar nedeniyle Avrupa Birliği üyesi ülkelerde dahi yaşanmaktadır. Bu durum küresel bir sağlık sorunu olarak gündemdeki yerini korumaya devam etmektedir (22–24).

Gelişmekte olan ülkelerin bir sağlık sorunu olan tedavi edilebilir ölümler, son yıllarda Birleşmiş

Milletler'e üye ülkelerin de gündemini meşgul eden bir halk sağlığı sorunu haline gelmiştir (25). Zira sağlık sistemlerinin üzerindeki finansal yüklerin artması ile birlikte bazı sağlık hizmetlerine ekonomik erişimin kısıtlandığı görülmektedir (11,26). Bazı ülkelerde sağlık sisteminin tıkanması ile geç verilen randevular sağlık hizmetine erişim için çok uzun bekleme sürelerine yol açmaktadır (27–29). Bunlara ek olarak bazı ülkelerdeki sağlık hizmet sunucularının ülkenin her tarafına yeterli düzeyde konumlandırılmamış olması uzaklık açısından sağlık hizmetine erişimi engellemektedir. Bu durum ise özellikle de köy ve kasaba gibi kırsal alanda yaşayan bireylerin, sosyo ekonomik olarak dezavantajlı olan bireylerin ve mülteci gibi topluma entegre olamayan normalin dışında kalan bireylerin istediği zaman istediği şekilde sağlık hizmetini almasını engellemektedir (30,31).

Karşılanamayan sağlık hizmetleri çoğu zaman bireylerin hem sağlık statüsünü düşürmekte hem de sağlık ihtiyacının giderilmemesi sebebi ile ölümcül olabilmektedir (17,32). Ölümle sonuçlanacak kadar ciddi olan karşılanamayan sağlık hizmetlerinin yol açtığı tedavi edilebilir ölümlerle ilişkilendirilmesi ve buna yönelik çalışmaların yapılması henüz yeni sayılabilir. Bununla beraber bu konuda yapılmış pek çok çalışma da mevcuttur (3,33–35). Ancak bu çalışmanın odak noktası tedavi edilebilir ölümler ile ilgili politikacıların yapacağı politika ve kararlar için güncel ve sağlam kanıtlar ortaya koymaktır. Zira kanıt olmadan alınan kararlar ve yapılan politikaların çoğu zaman etkili olmamaktadır. Bu eksikliğin giderilmesi ve konuya ilişkin kanıtların oluşturulması bu çalışmanın yapılmasındaki en önemli motivasyon unsurudur. Bu sayede güncel veriler ile kanıta dayalı kanıtlar ortaya konularak yapılan kararlar pratik yaşamda daha etkili olabilecektir.

Bu bilgiler ışığında mevcut çalışmanın amacı karşılanamayan sağlık hizmetlerinin tedavi edilebilir ölümler üzerindeki etkisini ortaya koymaktır. Bu amaçla pahalılık, uzun bekleme süreleri ve uzaklık gibi önemli nedenlerin tedavi edilebilir ölümlere olan etkisi araştırılarak bu konuda çözüm önerileri rapor edilecektir. Bu sayede politika yapıcılara ve karar vericilere yapacakları politikalar ve verecekleri kararlar için yol haritası sunulacaktır.

2. Gereç ve Yöntem

2.1. Araştırmanın Tip ve Modeli

Bu araştırma belli bir zaman diliminde (2011-2021 yılları) farklı ülkeler için ikincil verileri kapsadığından boylamsal çalışmalardan biri olan panel veri tipinde dizayn edilmiştir. Araştırmanın istatistiksel modeli ise nedensel karşılaştırma alt türünden biri olan nicel araştırma modelidir.

2.2. Araştırmanın Evren ve Örneklemi

Mevcut araştırmanın evreni Avrupa Birliği üyesi 27 ülkedir. Bu ülkelerin evren olarak seçilmesinin nedeni modelde yer alan değişkenlere ait verilerin eksiksiz bulunması ve bu ülkelerdeki bireylerin son yıllarda sağlık hizmeti almak için sağlık turizmi gibi alternatiflere yönelmiş olmasıdır. Çünkü bu ülkelerdeki vatandaşların birçoğu pahalılık, uzun bekleme süresi ve uzaklık için alternatif sağlık hizmeti sunan destinasyonlara yönelmektedir. İlgili bağımlı ve bağımsız değişkenlere ait evreni oluşturan 27 ülkenin eksiksiz verisi olduğunda örneklem seçim yoluna gidilmemiştir. Dolayısıyla evrenin tamamına ilişkin veriler ile gerekli analizler yürütülmüştür.

2.3. Araştırmaya Ait Veri Kaynakları ve Modeldeki Değişkenler

Bu çalışmada kullanılan ikincil veriler, Eurostat tarafından web sitesinde yayınlanan karşılanamayan sağlık ihtiyaçlarına yönelik bireysel beyan raporundan çekilmiştir. Raporlanan veri seti 2011-2021 yıllarını kapsamaktadır (36).

Mevcut çalışmanın dört değişkeni bulunmaktadır. Bu değişkenlerden birisi bağımlı diğer üçü ise bağımsız değişkenlerdir. Bağımlı değişken tedavi edilebilir ölümler olarak, bağımsız değişkenler ise pahalılık, bekleme süresi ve uzaklık olarak belirlenmiştir. Ayrıca modele sabit bir değişken olarak zaman kukla değişkeni de eklenmiştir. Araştırmadaki bağımlı ve bağımsız değişkenlere logaritmik dönüşüm uygulanmıştır. Modele dahil edilen değişkenlerin dağılımını normalleştirmek, heteroskedastisiteyi azaltmak, katsayıların yorumunu kolaylaştırmak ve değişkenler arasındaki ilişkinin doğrusallığını sağlamak için logaritmik dönüşüm uygulanmıştır (37).

Bağımlı değişken olan "tedavi edilebilir ölümler" tedavi edilebilir nedenlerden kaynaklanan ölüm oranını göstermektedir. Bu oranın bir standardı yoktur. Her ülkenin tedavi edilebilir nedenlerden kaynaklanan ölüm oranları birbirinden farklılık göstermektedir. Zira çalışmanın bağımlı değişkeni olan "tedavi edilebilir ölüm oranı" tedavi edilebilir nedenlere bağlı ölümleri göstermektedir. Yani eğer bireyler pahalılık, uzun bekleme süresi ve uzaklık sebebi ile alamadığı sağlık ihtiyaçlarını karşılamış olsalardı bu ölümler gerçekleşmeyecekti. Dolayısı tedavi edilebilir ölümler aslında uygun zaman, mekân ve uygun ücretler ile desteklenir ise gerekli tıbbi tedavi verilmiş olur ve ilgili ölümler

engellenebilir. Standart Avrupa nüfusuna göre ayarlanmış olan tedavi edilebilir ölüm oranları, yaşa, cinsiyete ve diğer değişkenlere göre standardize edilmiş verilerdir. Bu durum ülke birimleri ile zaman birimleri açısından kıyaslamayı mümkün kılmaktadır.

Araştırma modeline dahil edilmiş olan bağımsız değişkenler pahalılık, uzun bekleme süresi ve uzaklıktır. Özellikle sadece bu değişkenlerin analize dahil edilmesinin sebebi verinin alındığı ülkelere ait sadece ilgili değişkenlerin eksiksiz olması ve bu değişkenlerin daha önceki çalışmalarla tedavi edilebilir nedenlerden kaynaklanan ölümün belirleyicileri olarak rapor edilmesinden kaynaklanmaktadır. Öte yandan bu değişkenlerin tedavi edilebilir ölümlerin en önemli faktörleri olması modele sadece bu değişkenlerin etkisinin incelenmeye değer olduğunu düşündürmüştür. Zira bu değişkenler, bireylerin ihtiyaç duyduğu gerekli sağlık hizmetlerinin karşılanmasını engellemektedir.

Sağlık hizmetlerinin pahalı olması bazı bireylerin ihtiyaç duyduğu sağlık hizmetini alamamasına sebebiyet verildiğinden zengin ile fakir arasında bazı eşitsizliklere yol açmaktadır.

Sağlık hizmetlerinin kullanımı için bireylerin uzun bekleme sürelerine maruz kalması da bireylerin tedavi almasını engellemektedir. Bu durum ise bireyin tedavi edilebilir nedenden kaynaklanan ölüm ile karşı karşıya kalmasına yol açabilmektedir.

Modele dahil edilen bir diğer bağımsız değişken ise sağlık hizmet sunucularına olan uzaklıktır. Sağlık hizmeti ihtiyacı doğduğunda bireylerin makul bir uzaklıkta olmayan sağlık hizmet sunucularına erişimde problem yaşaması onların gerektiği zamanda tedavi alamamasına ve tedavi edilebilir bir nedenden kaynaklanan ölüme maruz kalabilmesine yol açmaktadır.

Modele dahil edilen bir diğer değişken ise zaman birimidir. Zaman değişkeni 11 yıllık dönemi kapsadığından 11 kategorisi olan bir birimdir.

2.4. Araştırmanın Tahmin Modeli ve İstatistiksel Analizleri

Araştırmada kurulan tahmin modeli ve bu tahmin modeline ilişkin fonksiyon aşağıdaki gibidir:

$$Y_{it} = \beta_0+\beta_1 X_{it}+\beta_2 X_{it}+\beta_3 X_{it} + \beta_{ti}+\upsilon_{it}+\varepsilon_{it} \quad (1)$$

$$Y_{it} = \beta_{\_0}+\beta_{\_1} X_{it}+\beta_{\_2} X_{it}+\beta_{\_3} X_{it} + \beta\_T_i+\upsilon_i+\varepsilon_{it} \quad (2)$$

Modelde yer alan ifadeler:

Y_{it}: (t) zamanında birim (i) için bağımlı değişken

β: Katsayılar

X_{it}: Her birim içi farklı seviyelerdeki bağımsız değişken

T_i: Birim (i) ile ilişkili rastgele etkiler

u_i: Birimler arası rastgele etkilerin temsilcisi

ε_{it}: Hata terimi

Zaman değişkeni hariç diğer değişkenlerin dahil edildiği denklem:

$$lnTM_{it} = \beta + \beta lnTE_{it} + \beta lnWL_{it} + \beta lnTFT_{it} + \upsilon_{it} + \varepsilon_{it} \quad (3)$$

Modelde yer alan bağımlı ve bağımsız değişkenler:

lnTM: Tedavi edilebilir ölümler (bağımlı değişken)

lnTE: Pahalılık (bağımsız değişken)

lnWL: Bekleme süresi (bağımsız değişken)

lnTFT: Uzaklık (bağımsız değişken)

Zaman değişkeni dahil değişkenlerin yer aldığı denklem:

$$lnTM_{it} = \beta + \beta lnTE_{it} + \beta lnWL_{it} + \beta lnTFT_{it} + \beta\_T_i + \upsilon_i + \varepsilon_{it} \quad (4)$$

Modelde yer alan bağımlı ve bağımsız değişkenler:

lnTM: Tedavi edilebilir ölümler (bağımlı değişken)

lnTE: Pahalılık (bağımsız değişken)

lnWL: Bekleme süresi (bağımsız değişken)

lnTFT: Uzaklık (bağımsız değişken)

ln: Logaritma

T_i: time/zaman (bağımsız değişken)

Bu araştırmada zaman değişkeni hariç kullanılan tüm değişkenler sürekli değişkenlerdir. Dolayısıyla bu sürekli değişkenlerin ortalama ve standart sapmaları tanımlayıcı bulgular için rapor edilmiştir. Normallik varsayımlarının incelenmesi için çarpıklık ve basıklık değerleri ile Shapiro-Wilk testi rapor edilmiştir. Bunlara ek olarak değişkenler arası korelasyon için Pearson korelasyon katsayısı kullanılmıştır. Boylamsal veri setindeki sabit ve

rastgele etkileri ortaya koymak için Doğrusal Karma Etkiler Modeli yürütülmüştür. Kurulan modelin uyumu için Akaike Bilgi Kriteri (AIC), Bayes Bilgi Kriteri (BIC) değerleri rapor edilmiştir (38). Artık değerler ile bağımsız değişkenler arasındaki korelasyon varsayımı raporlanmıştır. Modele ilişkin doğrusal varsayım için Ramsey RESET testi F (3, 296) = 4.73 ve p=0.083 olarak tespit edildi. Bu değerler modelin doğrusallık varsayımını karşıladığını göstermektedir (39). Değişkenler arası çoklu bağlantı ortaya konulması için VIF ve Tolerance değerleri rapor edilmiş olup Tablo 4 ve Tablo 5'in altında dip not olarak verilmiştir. VIF değerlerinin istenildiği gibi 5'ten küçük ve Tolerans değerinin ise 0,40'tan büyük olduğu tespit edilmiştir (40). Dolayısı ile bağımsız değişkenler arasında çoklu bağlantı sorununun olmadığı ifade edilebilir. Ayrıca otokorelasyon için yürütülen Durbin-Watson test sonucunun (D-W Statistic=1.94) istatistiksel olarak anlamlı olmaması (p>0,05) modelde otokorelasyon sorununun da olmadığını göstermektedir (41). Analizler Jamovi Sürüm 2.4 ile gerçekleştirilmiştir (42,43).

2.5. Araştırmanın Etik Beyanı

Bu araştırmanın verileri kamuya açık veri setlerinden çekildiğinden araştırmanın yapılması için etik kurul onayı gerekmemektedir.

3. Bulgular

Tablo 1. Bağımlı ve Bağımsız Değişkenlere İlişkin Tanımlayıcı Bulgular

Değerler	Tedavi edilebilir ölüm	Pahalılık	Bekleme süresi	Uzaklık
Ort.	1.981	0.144	0.349	0.770
SS	0.185	0.487	0.539	0.251
Min.	1.66	1.00	1.00	1.00
Max.	2.41	0.964	1.15	0.0969
Çarpıklık	0.737	0.210	0.475	0.738
Çarpıklık standart hatası	0.141	0.152	0.157	0.234
Basıklık	0.786	0.834	0.570	0.382
Basıklık standart hatası	0.282	0.302	0.314	0.463

Ort.=Ortalama, SS=Standart sapma

Tablo 1 incelendiğinde tedavi edilebilir ölüm oranı değişkeninin ortalama 1.981±0.185, pahalılık değişkeninin ortalama 0.144±0.487, Bekleme süresi değişkeninin ortalama 0.349±0.539 ve Uzaklık değişkeninin ortalama 0.770±0.251 olduğu tespit edilmiştir. Tüm değişkenlere ilişkin normallik varsayımı için rapor edilen çarpıklık ve basıklık değerlerinin eşik değer olan -1.5 ile +1.5 arasında olduğu ve Shapiro-Wilk normallik test sonucunun da istatistiksel olarak anlamlı olmadığı (p=0,093) görülmüştür (44).

Tablo 2. Bağımlı ve Bağımsız Değişkenlere İlişkin Pearson Korelasyon Bulguları

Değişkenler	Tedavi edilebilir ölüm	Pahalılık	Bekleme süresi	Uzaklık
Tedavi edilebilir ölüm	—			
Pahalılık	0.163**	—		
Bekleme süresi	0.139**	0.116*	—	
Uzaklık	0.255***	0.122*	0.435***	—

** p < .05, ** p < .01, *** p < .001.*

Modeldeki bağımlı ve bağımsız değişkenler arasındaki korelasyon bulguları Tablo 2'de rapor edilmiştir. Bu bulgulara göre bağımlı değişken olan tedavi edilebilir nedenlerden kaynaklanan ölüm ile bağımsız değişkenler olan pahalılık, bekleme süresi ve uzaklık arasında istatistiksel olarak anlamlı düşük düzeyde pozitif korelasyon bulunmuştur (p<0.05).

Tablo 3. Karma Etkiler Modellerine İlişkin Tahmin Bilgileri

Zaman Değişkeninin Dahil Edilmediği Model	
Tahmin	Doğrusal Karma Etkiler Modeli
Model	lnTedavi edilebilir ölüm ~ 1 + lnPahalılık + lnBekleme süresi + lnUzaklık+(1 | Ülke)
AIC	-1009.3353
BIC	-956.9072
Log. Olasılığı	495.5348
Marjinal R^2	0.0162
Koşullu R^2	0.9688
Birleşik	**evet**
Optimizer	bobyqa
Zaman Değişkeninin Dahil Edildiği Model	
Tahmin	Doğrusal Karma Etkiler Modeli
Model	lnTedavi edilebilir ölüm ~ 1 + lnPahalılık + lnBekleme süresi + lnUzaklık + Zaman+(1 | Ülke)
AIC	-1199.8390
BIC	-1020.5991
Log. Olasılığı	555.8494
Marjinal R^2	0.0200
Koşullu R^2	0.9847
Birleşik	evet
Optimizer	bobyqa

Tablo 3, hem zaman değişkeninin dahil edildiği hem de zaman değişkeninin dahil edilmediği modellere ilişkin bilgileri göstermektedir. Buna göre zaman değişkeni olmadan kurulan model bilgilerine bakıldığında marjinal R^2 değerinin 0.016 olduğu görülmektedir. Bu değer bağımsız değişkenlerin bağımlı değişkeni açıklama gücünün düşük olduğunu göstermektedir. Ancak, panel veri analizinde sabit etkili modellerin temel amacı, birimler arası varyasyonu kontrol ederek zaman içindeki değişimleri modellemek olduğundan koşullu R^2 değerlerinin modelin birim içi varyasyonu açıklama gücünü daha iyi yansıttığı ifade edilmektedir. Araştırmada koşullu R^2 değeri yaklaşık olarak %97 çıkmıştır. Bu değer araştırmadaki bağımsız değişkenlerin birim içi varyasyonun önemli bir kısmını açıkladığını göstermektedir. Ayrıca, panel verilerinde R^2 değerlerinin tek başına modelin uygunluğunu belirlemede yetersiz kalabileceği ve modelin teorik temelleri, değişkenlerin anlamlılığı ve varsayım testlerinin de göz önünde bulundurulması gerektiği ifade edilmektedir (45,46). Bu bağlamda bakıldığında modelin teorik olarak değişkenler ile uyumlu olması düşük marjinal R^2 değerinin önemsiz olduğu çıkarımı yapılabilmektedir. Modelde rapor edilen bir diğer değer ise koşullu R^2 değeridir. Bu değer ise modelin açıklanan varyansına rastgele etkilerin de katkı sunduğunu göstermektedir. Zaman değişkeninin dahil edilerek kurulan modele ilişkin AIC ve BIC değerleri, zaman değişkeninin dahil edilmeden kurulan modele göre daha iyi hale geldiği bu sebeple değişkenlerin modelde iyi bir uyum gösterdiği ifade edilebilir. Zaman değişkeninin dahil edildiği ve dahil edilmediği modellerdeki birleşik "evet" olarak rapor edildiğinden ilgili modellerin başarılı olduğu söylenebilir.

Tablo 4. Sabit Etkili Omnibus Test Sonuçları

Zaman Değişkeni Hariç	**F**	**p**
Pahalılık	4.96	0.027**
Bekleme süresi	22.54	< .001***
Uzaklık	2.20e-4	0.988
Zaman Değişkeni Dahil	**F**	**p**
Pahalılık	0.00142	0.970
Bekleme süresi	5.00685	0.026**
Uzaklık	1.77500	0.184
Zaman	30.30728	< .001***

** p < .05, ** p < .01, *** p < .001.*

Zaman değişkeninin dahil edilmeden kurulan sabit etkiler model bulgularına göre pahalılık ve bekleme süresinin tedavi edilebilir ölümler üzerinde istatistiksel olarak anlamlı bir etkiye sahip olduğu ($p<0.05$) buna karşın uzaklığın anlamlı bir etkiye sahip olmadığı tespit edilmiştir ($p>0.05$) (Tablo 4).

Zaman değişkeninin sabit etkiler modeline dahil edilmesi ile elde edilen bulgular pahalılığın anlamlı etkisinin kalmadığı ve bekleme süresinin de anlamlı kaldığı ancak etkisinin düştüğü görülmüştür. Zaman değişkenin de istatistiksel olarak anlamlı olduğu ancak halen uzaklığın anlamlı bir etki göstermediği tespit edilmiştir. Bu bulgular ilgili bağımsız değişkenlerin tedavi edilebilir ölümler üzerindeki etkisinin zamana bağlı değiştiğini göstermektedir (Tablo 4).

Tablo 5. Sabit Etkiler Modeline İlişkin Tahmin Bulguları

			% 95 Güven Aralığı			
Zaman Değişkeni Hariç	**Tahmin**	**Sh**	**Düşük**	**Yüksek**	**t**	**p**
(Sabit)	1.977	0.035	1.907	2.047	55.449	< .001***
Pahalılık	0.007	0.003	7.89e-4	0.012	2.227	0.027*
Bekleme süresi	0.013	0.003	0.007	0.018	4.748	< .001***
Uzaklık	3.68e-4	0.025	-0.048	0.049	0.015	0.988
			% 95 Güven Aralığı			
Zaman Değişkeni Dahil	**Tahmin**	**Sh**	**Düşük**	**Yüksek**	**t**	**p**
(Sabit)	1.977	0.035	1.908	2.046	55.805	< .001***
Pahalılık	-7.94e	0.002	-0.004	0.004	-0.048	0.970
Bekleme süresi	0.014	0.001	5.29e-4	0.008	2.238	0.026*
Uzaklık	0.023	0.017	-0.010	0.057	1.332	0.184
Zaman1 (2012 – 2011)	-0.008	0.006	-0.019	0.004	-1.172	0.242
Zaman2 (2013 – 2011)	-0.023	0.006	-0.034	-0.009	-3.514	< .001***
Zaman3 (2014 – 2011)	-0.038	0.006	-0.050	-0.025	-5.997	< .001***
Zaman4 (2015 – 2011)	-0.034	0.006	-0.046	-0.021	-5.349	< .001***
Zaman5 (2016 – 2011)	-0.048	0.006	-0.060	-0.035	-7.561	< .001***
Zaman6 (2017 – 2011)	-0.055	0.006	-0.068	-0.043	-8.736	< .001***
Zaman7 (2018 – 2011)	-0.057	0.006	-0.070	-0.045	-9.061	< .001***
Zaman8 (2019 – 2011)	-0.075	0.006	-0.087	-0.062	-11.721	< .001***
Zaman9 (2020 – 2011)	-0.074	0.006	-0.086	-0.060	-11.427	< .001***
Zaman10 (2021 – 2011)	-0.068	0.006	-0.080	-0.054	-10.427	< .001***
			% 95 Güven Aralığı			
Bağımsız Değişkenler ile Zaman Etkileşimleri	**Tahmin**	**Sh**	**Düşük**	**Yüksek**	**t**	**p**
(Sabit)	1.977	0.033	1.990	2.090	53.723	< .001***
Pahalılık	0.010	0.001	-0.001	0.001	4.341	0.013*
Bekleme süresi	0.014	0.001	0.006	0.008	3.212	0.019*
Uzaklık	0.023	0.017	-0.010	-0.008	2.980	0.027*
Pahalılık ✻ Time	0.079	0.003	-0.003	0.004	15.048	< .001***
Bekleme süresi ✻ Time	0.097	0.004	-0.002	0.005	11.134	< .001***
Uzaklık ✻ Time	0.068	0.001	-0.030	0.029	9.005	< .001***

** p < .05, ** p < .01, *** p < .001.*

Zaman biriminin dahil edilmeden kurulan sabit etkiler model bulguları, pahalılık ve bekleme süresinin tedavi edilebilir nedenlerden kaynaklanan ölümleri istatistiksel olarak anlamlı pozitif yönde etkilediğini ($p<0.05$), buna karşın uzaklığın istatistiksel olarak anlamlı bir etki göstermediğini göstermiştir ($p>0,05$) (Tablo 5).

Sabit etkiler modeline zaman biriminin dahil edilmesi ile birlikte sadece bekleme süresinin tedavi edilebilir ölümleri anlamlı pozitif yönde etkilediği buna karşın diğer değişkenlerin anlamlı bir etkiye sahip olmadığı gözlemlenmiştir. Bununla birlikte zaman değişkeninin de 2011 yılı ile kıyas edildiğinde tüm diğer yıllarda tedavi edilebilir ölümleri pozitif yönde etkilediği görülmüştür (Tablo 5).

Tablo 6. Rastgele Bileşenler Modeline İlişkin Bulgular

Gruplar (Zaman hariç)	**İsim**	**SD**	**Varyans**	**ICC**
Ülke	(Sabit)	0.185	0.034	0.968
Artık		0.034	0.001	
Gruplar (Zaman dahil)	**İsim**	**SD**	**Varyans**	**ICC**
Ülke	(Sabit)	0.184	0.033	0.984
Artık		0.023	5.360	
Gruplar (Bağımsız Değişken ve Zaman Etkileşimleri Dahil)	**İsim**	**SD**	**Varyans**	**ICC**
Ülke	(Sabit)	0.163	0.021	0.991
Artık		0.041	2.123	

Not: Gözlem sayısı: 297, Grup sayısı (ülke sayısı): 27

Zaman değişkeni hariç oluşturulan modelin rastgele bileşenleri, kesme için yüksek bir standart hata ve varyans değerini rapor etmiştir. Buna ek olarak her ülke varyansının toplam ülke varyansına oranını gösteren ICC (ülkeler arası korelasyon) değerinin oldukça yüksek olduğu görülmüştür. Böylesi bir bulgunun çıkması ülkeler arasındaki farkın bir sonucudur. Bu sonuç birimler (ülkeler) arasındaki rastgele etkilerin önemini göstermektedir (Tablo 6).

Zaman değişkeninin rastgele etkiler modeline dahil edilmesi ile elde edilen bulgulara göre standart hata, varyans değeri ve kesme için ICC değeri yüksek görünse de zaman değişkeninin dahil edilmesiyle varyans ve standart hatada bir miktar düşüş yaşanmıştır. Bu durum, zaman değişkeninin modele eklenmesiyle ülkeler arası farklılıkların bir miktar daha az önemli hale geldiğini, zamanın etkisi de hesaba katıldığında modelin ülkeler arası daha az varyansa dayandığını göstermektedir. Zaman değişkeninin modele dahil edilmesiyle artık SD'nin de azaldığı ve dolayısıyla modelin açıklayıcı gücünün arttığı görülmektedir (Tablo 6).

4. Tartışma

Bu çalışma ile sağlık hizmetlerinin pahalılığı, uzun bekleme süreleri ve sağlık kuruluşlarına olan uzaklığın tedavi edilebilir nedenlerden kaynaklanan ölümler üzerindeki etkisi ortaya konulmuştur. Bu sayede sağlık hizmetlerinde meydana gelen erişim ve ödeme gücü ile ilgili yaşanan sorunlara ışık tutulmuştur.

Yapılan analizlere ilişkin bulgular sağlık hizmetlerine erişim için uzun bekleme sürelerinin tedavi edilebilir nedenlerden kaynaklanan ölümleri istatistiksel olarak anlamlı bir şekilde arttırdığını göstermektedir. Bu tespit özellikle de sağlık hizmetlerine erişimde yaşanan uzun bekleme sürelerinin zamanında yapılması gereken teşhis ve tedaviyi geciktirdiği ve bu sebeple acil müdahale gerektiren durumlarda tedaviyi olumsuz etkilediği dolayısıyla buna bağlı olarak tedavi edilebilir nedenlerden kaynaklanan ölümleri arttırdığı yönündeki alan yazınla da tutarlılık göstermektedir (35,47–53). Özellikle de acil tedavi gerektiren akut enfeksiyon kaynaklı hastalıklar, kalp ve damar hastalıkları ile kanserler gibi zamanında müdahale ve tedavinin önemli olduğu hastalıklar için meydana gelen tıbbi gecikmeler hastaların yaşama şansını azaltmakta hatta bazen ölümlere yol açabilmektedir. Bu tarz problemlerin yaşanmaması için sağlık hizmet sunucuları, karar vericiler ile hasta, hasta yakınları veya hasta temsilcileri ile ödemeyi yapan kurumların iş birliği yapması gerekmektedir.

Çalışma bulgularının ortaya koyduğu diğer bir önemli tespit ise sağlık hizmetleri pahalılığın tedavi edilebilir nedenlerden kaynaklanan ölümleri arttırdığı gerçeğidir. Bu bulgu, sağlık hizmetlerinin pahalı oluşunun bazı kesimler için bir bariyer olduğunu göstermektedir. Bir diğer deyişle sağlık hizmetlerinin ödeme gücü olmayanlar tarafından alınamaması riski bazı insanların sağlık hizmetlerine erişimini engellediğinden tedavi edilebilir ölümlere yol açtığını göstermektedir. Bu bulgunun alan yazındaki başka çalışmalarla da ortaya konulduğu görülmektedir (33,54–57). Sağlık hizmetlerinin kendi özgü özellikleri nedeniyle sağlık hizmetleri piyasasını aksak bir piyasa haline getirmektedir. Bu kapsamda piyasa başarısızlığı ile ilgili bilgi aktarımının yapılması gerekmektedir. Öyle ki pahalılık yüzünden sağlık hizmetinin alınamaması ve buna bağlı ölümlerin ortaya çıkması iyi bir sosyal sistemin olmadığını göstermektedir. Zira bu konudaki sorumluluğun bir kısmı yanlış kaynak dağılımı yapan ve sağlık hizmetlerinde öncelikleri yanlış veya eksik bir şekilde belirleyen karar vericiler ve politika belirleyicilerindir. Bu sorumluluğun bir diğer kısmı da sağlık sektörünün dinamizmi, sağlık hizmetlerinin kendine has özellikleri ve paydaşların sorumluluklarını kısmen veya tam olarak yerine getirememesinden kaynaklanmaktadır. Çünkü sağlık eşitsizliklerinin ortaya çıktığı durumlarda sağlık hizmeti piyasasına

müdahale edilmesi kaçınılmazdır. Ancak bu sayede herkes ihtiyaç duyduğu sağlık hizmetine ödenebilir bir ücret ile erişim sağlayabilir. Aksi halde bu serbest piyasa mantığı ile başarılabilir bir hedef değildir.

Sağlık hizmet sunucularına olan uzaklığın tedavi edilebilir nedenlerden kaynaklanan ölümleri etkilemediği tespit edilmiştir. Bu sonuç alan yazındaki çalışma bulgularından farklı bir şekilde ortaya çıkmıştır. Böyle bir sonucun çıkması modeldeki değişkenlerden kaynaklanabileceği düşünülmektedir. Buna bağlı olarak Avrupa Birliği ülkeleri için pahalılık ve bekleme sürelerinin sağlık hizmetlerine erişimde daha önemli birer faktör olduğu söylenebilir. Zira farklı çalışmalarda ortaya konular bulgulara göre sağlık hizmet sunucularına olan uzaklık artınca daha fazla ölümlerin meydana geldiği rapor edilmiştir (17,33,52,58).

Zaman değişkeninin modele dahil edilmesi ile birlikte istatistiksel olarak anlamlı etkisi olan pahalılığın da tıpkı uzaklık gibi anlamsız bir etki gösterdiği tespit edildi. Ancak bekleme sürelerinin halen istatistiksel olarak anlamlı bir etkisi olduğu ve bu etkinin tedavi edilebilir nedenlerden kaynaklanan ölümleri arttırdığı görülmektedir. Bu sonuç zamanla sağlık hizmetleri ihtiyaçlarının giderilmesi için bekleme sürelerinin arttığını ve bu bekleme sürelerinin de tedavi edilebilir ölümleri arttırdığını göstermektedir. Zamanla sağlık hizmetlerine erişim için bekleme sürelerinin istikrarlı bir şekilde tedavi edilebilir nedenlerden kaynaklanan ölümleri arttırdığı tespit edilmiştir. Bu durum, uzun bekleme sürelerinin tedavi edilebilir ölümler üzerindeki etkisinin, zaman içinde artışa yol açacak şekilde değişmediğini veya diğer faktörlerden bağımsız olduğunu göstermektedir. Sağlık sistemindeki yapısal sorunlar, kaynak yetersizlikleri ve yönetimsel engeller, uzun bekleme sürelerine neden olarak, tedavi edilebilir ölümler üzerinde kalıcı bir etki yaratmaktadır (59–61).

Bu çalışmanın bazı sınırlılıkları bulunmaktadır. Öncelikle, çalışma, belirli bir zaman dilimindeki verileri kapsamaktadır ve zaman içindeki değişiklikleri tam olarak yansıtmamaktadır. İkinci olarak, çalışmada kullanılan değişkenler, sağlık hizmetlerine erişimdeki tüm engelleri kapsamamaktadır. Örneğin, sağlık okuryazarlığı, kültürel farklılıklar ve dil engelleri gibi faktörler çalışmada ele alınmamıştır. Ayrıca, sağlık hizmetlerinin kalitesi ve hasta memnuniyeti gibi faktörlerin, tedavi edilebilir ölümler üzerindeki etkisi de incelenmemiştir.

Gelecekteki araştırmalar, sağlık hizmetlerine erişimdeki engellerin tedavi edilebilir ölümler üzerindeki etkisini daha kapsamlı bir şekilde incelemelidir. Özellikle, farklı sosyoekonomik gruplar, coğrafi bölgeler ve hastalık türleri arasındaki farklılıklar araştırılmalıdır. Ayrıca, sağlık politikalarının ve müdahalelerin, tedavi edilebilir ölümler üzerindeki etkisi değerlendirilmelidir. Sağlık sistemindeki yapısal sorunların çözülmesi, kaynakların etkin kullanımı ve hasta odaklı politikaların geliştirilmesi, bu konuda atılacak önemli adımlar olabilir.

5. Sonuçlar ve Öneriler

Bu çalışma, sağlık hizmetlerine erişimde yaşanan engellerin, tedavi edilebilir ölümler üzerindeki etkisini inceleyerek, sağlık sistemindeki kritik sorunlara ışık tutmaktadır. Analiz sonuçları, özellikle uzun bekleme sürelerinin, tedavi edilebilir ölümler üzerinde anlamlı ve istikrarlı bir etkisi olduğunu göstermektedir. Bu durum, sağlık hizmetlerine erişimde yaşanan gecikmelerin, zamanında müdahale gerektiren hastalıkların tedavisini olumsuz etkilediği ve ölüm riskini artırdığı yönündeki literatürle tutarlılık göstermektedir.

Çalışmada, uzaklık değişkeninin tedavi edilebilir ölümler üzerinde anlamlı bir etkisinin bulunmaması, sağlık hizmetlerine erişimin karmaşık doğasını ve modele dahil edilen ülkelerin sağlık sisteminin özgün yapılarını yansıtmaktadır. Ancak, uzun bekleme sürelerinin etkisi, sağlık sistemindeki yapısal sorunların ve kaynak yetersizliklerinin, tedavi edilebilir ölümler üzerinde kalıcı bir etki yarattığını göstermektedir. Sonuçta elde edilen bulgulara dayalı olarak bazı öneriler sunulabilir. Bu önerilerin birincisi, sağlık hizmetlerine erişimde yaşanan gecikmelerin uzaktan sağlık hizmetleri ile azaltılması, sistemdeki sorunların tespit edilerek kanıta dayalı politikaların geliştirilmesi için öncelikle gereksiz sağlık hizmeti kullanımının önlenmesi için sağlık okuryazarlığı eğitimlerin verilmesi önerilmektedir. Bu kapsamda sağlık sistemindeki randevu ve bekleme süreçlerinin optimize edilmesi, acil müdahale gerektiren hastaların önceliklendirilmesi ve tele-tıp gibi alternatif hizmet modellerinin sağlık sistemine entegre edilmesi gerekmektedir. Ayrıca evde sağlık hizmetlerinin yaygınlaştırılarak hastanelere düşen iş yükünün düşürülmesi gerekmektedir. İkinci öneri ise sağlık hizmeti altyapısının güçlendirilmesine yöneliktir. Bunun için sağlık kuruluşlarının sayısının artırılması, ülkenin farklı sosyo-ekonomik bölgelerinde optimum bir şekilde dağıtılması, sağlık çalışanlarının dağılımındaki dengesizliklerin

giderilmesi ve tıbbi malzeme eksikliklerinin önlenmesi tedavi edilebilir ölümlerin azaltılmasına katkı sağlayacaktır. Üçüncü bir diğer öneri ise sağlık okuryazarlığının artırılmasına yöneliktir. Bireylerin sağlık hizmetlerine erişimini kolaylaştırmak ve zamanında müdahale edilmesini sağlamak için, sağlık okuryazarlığı düzeyinin artırılmasına yönelik eğitim programlarının düzenlenmesi gereklidir. Son olarak dezavantajlı popülasyonlara yönelik özel politikalar geliştirilmelidir. Örneğin engelli bireylerin öncelikle tele-tıp hizmetleri ile teşhis edilmesi ve mümkün ise evde bakım hizmetleri ile tıbbi tedavinin verilmesi. Mülteciler, yaşlılar ve engelliler gibi dezavantajlı grupların sağlık hizmetlerine erişimini kolaylaştırmak için, özel politikalar ve müdahaleler geliştirilmelidir. Dezavantajlı gruplar için ayrı bir randevu sistemi yapılandırılması mümkün olabilir. Bunun için esnek hastane bilgi sistemleri kullanılarak daha önce bir engeli olan veya dezavantajı olan bu konuda rapor alan kişiler bu sayede daha hızlı bir şekilde sağlık hizmeti alınabilir.

Özetle bu çalışma, sağlık hizmetlerine erişimde yaşanan engellerin, tedavi edilebilir ölümler üzerindeki etkisini ortaya koyarak, sağlık sistemindeki iyileştirme alanlarına dikkat çekmektedir. Ancak sağlık politikalarının ve müdahalelerin, tedavi edilebilir ölümler üzerindeki etkisini değerlendiren daha fazla araştırmaya ihtiyaç vardır. Dolayısıyla gelecekte daha fazla çalışmanın yapılması gerektiği ortadadır.

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The Effect of Femoral Nerve Block on the Neutrophil-to-Lymphocyte Ratio in Total Knee Arthroplasty

Total Diz Artroplastilerinde Femoral Sinir Bloğunun Nötrofil Lenfosit Oranı Üzerine Etkisi

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Ethics Committee Approval: The study was approved by KTO Karatay University Ethics Committee for Research Excluding Drugs and Medical Devices (Decision no: 12, Date: 26.12.2024).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

Authorship Contributions: Study Design: NAE, EK, Data Collection: NAE, EK, Data Analysis and Interpretation: MST, Drafting the Manuscript: EK; NAE Critical Review and Final Approval: AY, NAE.

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Abstract: This study investigated whether femoral nerve block (FNB) reduces postoperative systemic inflammation, as measured by the neutrophil-to-lymphocyte ratio (NLR), in patients undergoing total knee arthroplasty (TKA) under spinal anesthesia. It was hypothesized that FNB would mitigate the inflammatory response by alleviating pain and surgical stress. In this retrospective cohort study, data from 199 patients who underwent unilateral TKA between January 1 and December 1, 2024, were analyzed. Patients were divided into two groups: Group F (n=97), who received spinal anesthesia combined with femoral nerve block (FNB), and Group C (n=102), who received spinal anesthesia with standard analgesia only. Preoperative and 24-hour postoperative NLR values were obtained from complete blood counts. Statistical analysis was performed using IBM SPSS Statistics 26.0. The independent samples t-test or Mann-Whitney U test was used, depending on data distribution. Baseline NLR values were similar between groups (Group C: 1.85, Group F: 2.08; p=0.255). Postoperatively, NLR increased significantly in both groups; however, the increase was significantly lower in Group F (Group C: 9.15 vs. Group F: 5.58; p<0.001). The percentage increase in NLR was 356.58% in Group C and 170.99% in Group F (p<0.001), indicating a markedly attenuated inflammatory response in patients receiving FNB. FNB significantly reduces the postoperative rise in NLR in patients undergoing TKA under spinal anesthesia. This effect may result from both superior pain control and the anti-inflammatory properties of local anesthetics. These findings suggest that FNB may enhance recovery beyond analgesia by modulating the surgical stress response.
Keywords: Total knee arthroplasty, femoral nerve block, neutrophil-to-lymphocyte ratio, inflammation, spinal anesthesia.

Özet: Bu çalışma, spinal anestezi altında total diz artroplastisi (TDA) uygulanan hastalarda femoral sinir bloğunun (FSB) nötrofil lenfosit oranı (NLR) üzerindeki etkisini incelemeyi hedeflemiştir. NLR, cerrahi sonrası sistemik inflamasyonun bir göstergesi olarak kullanılmıştır. FSB'nin postoperatif ağrı ve stres yanıtını azaltarak inflamasyonu hafifleteceği ve NLR'de düşüş sağlayacağı iddia edilmektedir. Yöntemler: Retrospektif kohort analizi, 1 Ocak 2024 - 1 Aralık 2024 tarihleri arasında tek taraflı TDA geçiren 199 hasta. Grup F (n=97): Spinal anestezi + FSB uygulanan hastalar, Grup K (n=102): Sadece spinal anestezi ile standart analjezi alan hastalar. Preoperatif ve postoperatif 24. saatte NLR değerleri tam kan sayımından hesaplandı. İstatistiksel analizler için IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, ABD) yazılımı kullanıldı. Grupların karşılaştırılmasında; verilerin dağılımına göre bağımsız örneklem t testi veya Mann-Whitney U testi kullanıldı. Preoperatif NLR gruplar arasında benzerdi (Grup K: 1.85, Grup F: 2.08, p=0.255). Postoperatif NLR: Grup K'da 9.15'e yükselirken Grup F'de 5.58 olarak kaldı (p<o,001).NLR artış oranı Grup K'da %356.58 iken Grup F'de %170.99 (p<0.001) olarak bulundu. FSB uygulanan hastalarda NLR artışı anlamlı derecede daha azdı, bu da inflamasyonun baskılandığını göstermektedir. Femoral sinir bloğu, TDA sonrası cerrahi stres ve inflamasyonu azaltarak NLR'de belirgin bir düşüş sağlayabilir. Bu etki, FSB'nin etkili ağrı kontrolü ile stres yanıtını sınırlaması ve lokal anesteziklerin antienflamatuar özelliklerinden kaynaklanabilir. Bulgular, FSB'nin analjezik faydasının ötesinde iyileşme sürecini olumlu etkileyebileceğini düşündürmektedir.
Anahtar Kelimeler: Total diz artroplastisi, femoral sinir bloğu, nötrofil lenfosit oranı, inflamasyon, spinal anestezi

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1. Introduction

Total knee arthroplasty (TKA) is a widely performed surgical intervention used to restore joint function and alleviate pain when severe knee joint damage cannot be managed with conservative treatments. Despite its effectiveness, patients often experience moderate to severe pain in the early postoperative period, which can negatively impact rehabilitation, patient satisfaction, and overall surgical outcomes. Although opioids have long been a mainstay in perioperative pain management due to their strong analgesic properties, their use is linked to several side effects, including nausea, respiratory depression, urinary retention, and the risk of dependency. As a result, multimodal analgesia—an approach that integrates multiple techniques and medications to optimize pain control— has become the preferred strategy for managing perioperative pain in TKA (1,2). This approach includes preemptive analgesia, central neuraxial blocks (such as spinal anesthesia), peripheral nerve blocks, patient-controlled analgesia, local infiltration, and combinations of opioid and non-opioid medications. Together, these methods aim to enhance pain relief, support faster recovery, and minimize opioid requirements (1).

A key component of multimodal analgesia, femoral nerve block (FNB), is a regional anesthesia technique frequently employed in knee surgeries. Temporary blockade of the femoral nerve using local anesthetics effectively reduces surgical pain, particularly in the anterior knee region, thereby decreasing opioid requirements and their associated side effects (3,4). In recent years, regional anesthesia techniques have gained attention not only for their analgesic effects but also for their influence on surgical stress and inflammation. Some experimental and clinical studies suggest that peripheral nerve blocks may modulate the inflammatory response to surgery. For instance, in an animal model, peripheral nerve block was shown to enhance acute inflammatory responses to surgical incision (5). Conversely, continuous peripheral block techniques have been reported to reduce inflammatory markers (6,7), highlighting the potential of peripheral nerve blocks to influence inflammation and immune response.

The neutrophil-to-lymphocyte ratio (NLR), a simple and widely available laboratory marker, is calculated from complete blood count data and reflects the ratio of neutrophils to lymphocytes. First described by Zahorec in 2001, NLR is considered an indicator of systemic inflammation and stress, reflecting the balance between neutrophilia and lymphopenia (8). In response to major surgery, trauma, sepsis, or shock, neutrophil counts typically increase while lymphocyte counts decrease, resulting in an elevated NLR. NLR has demonstrated prognostic and predictive value in various clinical contexts, including cardiovascular risk assessment, tumor burden and prognosis in cancer, and diagnosis and prognosis in sepsis and infections (9-14). In healthy adults, the average NLR has been reported to be approximately 1.65, with a 95% confidence interval ranging from 0.78 to 3.53 (15).

Postoperative pain is closely associated with tissue injury and inflammation. Experimental studies have shown that systemic inflammation increases pain sensitivity and lowers the pain threshold in humans (16). Moreover, severe acute pain can exacerbate stress responses and suppress immune function, negatively impacting recovery (7). Therefore, effective control of postoperative pain is essential for both patient comfort and reduction of the surgical stress response. In this context, the femoral nerve block administered after TKA may not only relieve pain but also attenuate the inflammatory response induced by surgery.

The present study aimed to investigate the effect of femoral nerve block on NLR as a marker of postoperative inflammation in patients undergoing TKA. We compared postoperative NLR values between patients who received femoral nerve block and those who did not, all of whom underwent spinal anesthesia. Our hypothesis was that femoral nerve block would reduce systemic inflammatory response by mitigating postoperative pain and stress, leading to a significant decrease in NLR values.

2. Materials and Methods

Study Design and Sample: This retrospective study was based on data collected from patients who underwent unilateral total knee arthroplasty (TKA) in the Orthopedics Department of our hospital between January 1 and December 1, 2024. Ethical approval from the institutional review board and necessary institutional permissions were obtained (Decision No:

2024/012). The inclusion criteria consisted of patients aged between 18 and 80 years who underwent elective primary TKA under spinal anesthesia. Patients were excluded if they had malignancy, sepsis, underwent emergency surgery, experienced thromboembolic events, had multiple trauma, severe respiratory failure, or a history of pneumonia. A total of 199 patients who met the inclusion criteria were enrolled in the study.

Data Collection

Demographic data, anesthesia and surgical records, and laboratory findings were retrospectively reviewed from the hospital's electronic medical records. For each patient, preoperative neutrophil and lymphocyte counts, along with NLR values, were recorded based on blood tests performed at hospital admission. Similarly, neutrophil, lymphocyte, and NLR values within the first 24 postoperative hours were noted. In accordance with the institutional protocol, all patients who received spinal anesthesia as the primary anesthetic technique had been administered hyperbaric bupivacaine. In patients who underwent a single-shot femoral nerve block, the procedure had also been performed in line with the institutional protocol—immediately after the completion of surgery, while the patient was still on the operating table, under sterile conditions and with ultrasound guidance, using 20 mL of 0.25% bupivacaine. Based on the analgesic method, patients were divided into two groups: those who received a femoral nerve block after spinal anesthesia (Group F) and those who received standard analgesia without a femoral block (Group C).

Statistical Analysis

Sample size was determined based on a power analysis targeting 80% power and 5% alpha error to detect a significant difference. Statistical analysis was performed using IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA). Normality of distribution for continuous variables was assessed with the Kolmogorov-Smirnov test. Data were expressed as mean ± standard deviation for normally distributed variables and as median (25th-75th percentile) for non-normally distributed variables. Categorical variables were presented as frequencies and percentages. The independent samples t-test or Mann-Whitney U test was used for between-group comparisons of continuous variables, depending on distribution. Categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test. A p-value <0.05 was considered statistically significant.

3. Results

In this retrospective study, a total of 218 patients were evaluated. Nineteen patients who did not meet the eligibility criteria or had incomplete data were excluded from the study. The remaining 199 patients were included and divided into two groups based on the anesthesia technique used: 102 patients who received spinal anesthesia alone were assigned to Group C, while 97 patients who received spinal anesthesia combined with a femoral nerve block were assigned to Group F (Figure 1).

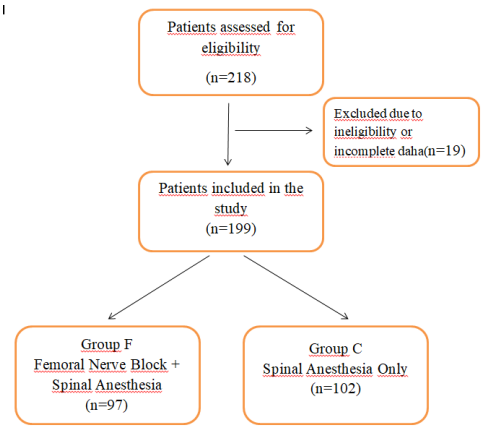

Figure 1. Study flowchart

The average age of the patients was around 65 years, and 74% of the study population were female. There were no statistically significant differences between Group F (n = 97) and Group C (n = 102) regarding age, gender distribution, ASA classification, or comorbid conditions such as diabetes and hypertension (all p-values > 0.05; Table 1).

Table 1. Demographic Characteristics of the Patients

Characteristic	Group C (n=102)	Group F (n=97)	p value
Age (years)	64 ± 7	65 ± 8	0.717ǂ
Sex			0.780*
Female	75 (73.5%)	73 (75.3%)	
Male	27 (26.5%)	24 (24.7%)	
ASA Classification			0.111*
ASA I	16 (15.7%)	24 (24.7%)	
ASA II	86 (84.3%)	73 (75.3%)	
Coronary artery disease	4 (3.9%)	5 (5.2%)	0.743**
Respiratory disease	8 (7.8%)	11 (11.3%)	0.401*
Hypertension	54 (52.9%)	39 (40.2%)	0.072*
Diabetes mellitus	29 (28.4%)	19 (19.6%)	0.145*

Data are presented as mean ± standard deviation or n (%). ASA: American Society of Anesthesiologists physical status classification.
ǂ *Independent samples t-test*
* *Chi-square test*
** *Fisher's exact test*

Preoperative and postoperative NLR values are presented in Table 2. There was no significant difference in preoperative NLR values between the groups (p=0.255). However, at 24 hours postoperatively, the median NLR in Group C increased markedly to 9.15 (5.99–13.12), while in Group F it remained lower at 5.58 (3.89–7.58), a statistically significant difference (p<0.001).

Table 2. Neutrophil-to-Lymphocyte Parameters of the Patients

Neutrophil/Lymphocyte Ratio	Group C (n=102)	Group F (n=97)	p value
Preoperative	1.85 (1.5–2.66)	2.08 (1.58–2.67)	0.255
Postoperative (24th hr)	9.15 (5.99–13.12)	5.58 (3.89–7.58)	<0.001
Percentage Change (%)	356.58 (190.57–626.23)	170.99 (59.47–300.27)	<0.001

Data are presented as median (25th–75th percentile). Mann-Whitney U test was used. Percentage change = 100 × (Postoperative – Preoperative) / Preoperative Although both groups exhibited increased NLR values postoperatively compared to baseline, the rate of increase was significantly higher in the control group. The median percentage increase in NLR was 356.6% (190.6–626.2) in Group C and 171.0% (59.5–300.3) in Group F ($p<0.001$). These findings suggest that patients who did not receive FNB experienced approximately twice the increase in NLR compared to those who did (Figure 2).

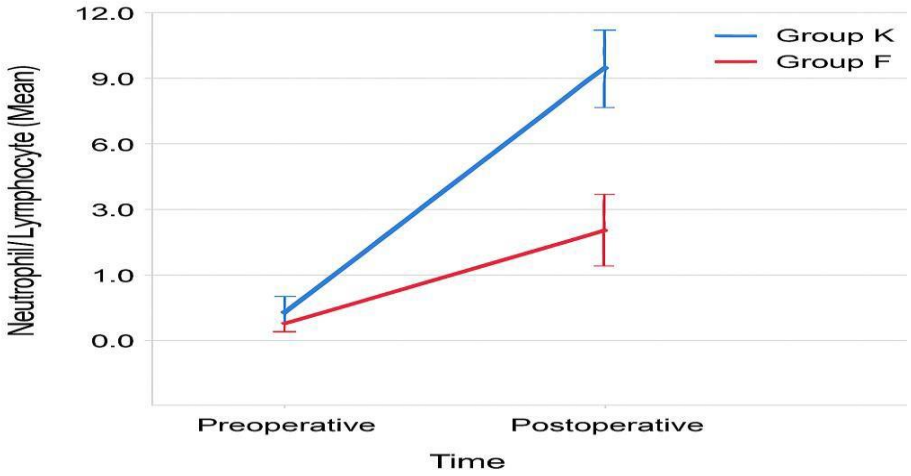

Figure 2. Neutrophil-to-Lymphocyte Parameters Over Time.

4. Discussion

This study demonstrated that the addition of femoral nerve block in patients undergoing TKA under spinal anesthesia significantly reduced postoperative NLR values, a marker of systemic inflammation. Patients who received FNB had notably lower postoperative NLR compared to those who did not, indicating that while spinal anesthesia alone partially suppresses surgical stress, additional peripheral nerve block further limits NLR elevation. Our findings suggest that femoral nerve block, in addition to its analgesic effect, may help mitigate the inflammatory response to surgery.

Surgical trauma triggers a cascade of immunological changes. Neutrophil counts increase rapidly due to lysosomal enzyme release, bone marrow mobilization, and delayed apoptosis, while lymphocyte counts decline due to migration to peripheral tissues and apoptosis (8). This concurrent neutrophilia and lymphopenia lead to a marked rise in NLR within the first 24 hours postoperatively. In major surgeries, neutrophil percentages may exceed 80% and lymphocytes drop below 10% (8). Elevated NLR correlates with the severity of surgical stress and clinical outcomes. HigherNLR values areassociated with more severe surgical trauma or sepsis, reflecting the intensity of the stress response (8,17). In our study, the control group exhibited nearly a four-fold increase in NLR following TKA, confirming a substantial systemic inflammatory response. In contrast, the FNB group had only a two-fold increase, suggesting reduced surgical stress.

The preoperative NLR values observed in both groups (Group C: ~1.85, Group F: ~2.08) were consistent with reference ranges reported in the literature. In a study by Forget et al., the normal NLR range in healthy adults was reported as 0.78–3.53, with an average of approximately 1.65 (15). Both groups in our study were within this normal range preoperatively, indicating comparable baseline inflammatory status. Postoperatively, while NLR increased in both groups, Group C exceeded the normal range substantially, reaching a median value of 9, whereas Group F showed a more moderate increase with a median of 5.6. NLR values above 5 are generally considered indicative of significant systemic inflammation (13, 14). Thus, patients in the control group appeared to experience a higher inflammatory burden compared to those who received FNB.

Anesthetic technique is known to influence surgical stress and inflammatory responses. General anesthesia (GA) may provoke a strong neuroendocrine stress response due to intubation,

surgical awareness, and systemic drug effects, whereas regional techniques like spinal anesthesia (SA) may attenuate inflammatory responses by limiting afferent signaling to the medulla and reducing sympathetic activity (18). In a study by Hadimoğlu et al. on cesarean deliveries, patients under GA exhibited significantly higher levels of IL-6 and NLR compared to those under SA (16). Similarly, a recent retrospective study by Bengü Köksal et al. showed that patients undergoing upper extremity surgery under general anesthesia had significantly higher postoperative NLR values (mean 6.12) than those who received infraclavicular peripheral nerve block (mean 3.82) (7). The authors emphasized that better analgesia and reduced opioid use in the nerve block group may positively influence immune response. They proposed that the superior pain control and anti-inflammatory effects of local anesthetics help suppress excessive inflammatory responses to surgery (7). These findings support the notion that regional anesthesia techniques, whether central or peripheral, can help reduce systemic inflammation.

Our study adds a novel perspective to the existing literature by demonstrating the additional anti-inflammatory benefit of peripheral nerve block when used in conjunction with spinal anesthesia. Previous studies comparing GA with SA or GA with peripheral nerve block had shown reduced NLR with regional techniques (7,16,18). In our study, all patients received SA, which already limits surgical stress, yet the addition of FNB further reduced NLR. This finding underscores the value of combining effective analgesic methods such as FNB with regional anesthesia to attenuate the inflammatory response. Lower pain scores and reduced intraoperative/postoperative opioid requirements in the FNB group may have contributed to lower stress hormone and pro-inflammatory cytokine levels. Moreover, local anesthetics are known to have anti-inflammatory effects by modulating neutrophil and macrophage activity in addition to blocking nerve conduction. These mechanisms likely underlie the reduced neutrophilic response and lymphopenia observed in patients who received FNB.

Limitations

Our study had some limitations. Firstly, inflammation was assessed solely using the neutrophil-to-lymphocyte ratio (NLR); other inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), were not included in the evaluation. Incorporating these additional markers might have offered a more comprehensive view of the inflammatory response. However, there is substantial evidence in the literature supporting the link between NLR and systemic inflammation, and our results were interpreted within this framework. Secondly, due to the retrospective nature of the study, precise documentation of sensory block durations related to spinal and femoral blocks, as well as quantitative pain scores (e.g, VAS), was not consistently available. However, the analgesic effect of the femoral nerve block was evaluated based on clinical observations, institutional standards, and supported by findings from previous literature.

5. Conclusion

In patients undergoing total knee arthroplasty under spinal anesthesia, the addition of femoral nerve block was associated with a significant reduction in postoperative NLR levels, a hematological marker of surgical stress. Through effective pain control and attenuation of the inflammatory response, peripheral nerve blocks may contribute positively to recovery in patients undergoing major orthopedic surgery.

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A Bibliometric Analysis of Botulinum Toxin in Cerebral Palsy from 2005 to 2024

2005-2024 Yılları Arasında Serebral Palsi'de Botulinum Toksinin Bibliyometrik Analizi

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Abstract: This study presents a comprehensive bibliometric analysis of the literature on botulinum toxin A (BoNT-A) applications in cerebral palsy (CP) between 2005 and 2024. A search conducted in the Web of Science Core Collection identified 690 publications (550 original research articles and 140 reviews). An overall increase in publication output was observed over the years, peaking in 2018, with a temporary decline noted in 2020–2021. The United States, Australia, and Italy were the leading contributors, with Australia achieving the highest average citation rate. Desloovere K was identified as the most productive author, while Graham HK received the highest number of citations. Keyword analysis revealed that "cerebral palsy," "botulinum toxin," and "spasticity" were central themes, while concepts such as "rehabilitation," "gait analysis," and "quality of life" also stood out. In recent years, the use of technological terms such as "ultrasound" and "electromyography" has increased. In addition, intraglandular BoNT-A applications for the treatment of "sialorrhea" have been highlighted. The study also noted that BoNT-A in the upper limb is recommended to be combined with rehabilitation in order to achieve functional gains. The literature emphasizes that data on long-term efficacy remain limited and that there is a need for multicenter, prospective studies.
Keywords: Bibliometric analysis, botulinum toxin, cerebral palsy, spasticity

Özet: Bu çalışma, 2005–2024 yılları arasında serebral palside (SP) botulinum toksin A (BoNT-A) uygulamalarıyla ilgili literatürü değerlendiren kapsamlı bir bibliyometrik analiz sunmaktadır. Web of Science Core Collection veri tabanında yapılan tarama sonucunda 690 yayın (550 araştırma makalesi, 140 derleme) incelenmiştir. Yayın sayısında yıllar içinde genel bir artış gözlenmiş, 2018'de en yüksek üretim gerçekleşmiş, 2020–2021'de geçici bir düşüş yaşanmıştır. Araştırmalara en fazla katkı sağlayan ülkeler ABD, Avustralya ve İtalya olurken, Avustralya en yüksek ortalama atıf oranına ulaşmıştır. En üretken yazar Desloovere K, en çok atıf alan yazar ise Graham HK olarak belirlenmiştir. Anahtar kelime analizinde "cerebral palsy", "botulinum toxin", "spasticity" merkezde yer almış; "rehabilitation", "gait analysis" ve "quality of life" gibi kavramlar ön plana çıkmıştır. Son yıllarda "ultrasound" ve "electromyography" gibi teknolojik kavramların kullanımı artmıştır. Ayrıca "sialorrhea" tedavisine yönelik intraglandüler BoNT-A uygulamaları vurgulanmıştır. Çalışmada, üst ekstremitede BoNT-A'nın fonksiyonel kazanımlar için rehabilitasyonla birlikte uygulanmasının önerildiği belirtilmiştir. Literatürde uzun dönem etkinlik verilerinin sınırlı olduğu ve çok merkezli, prospektif çalışmalara ihtiyaç duyulduğu vurgulanmıştır.
Anahtar Kelimeler: Bibliyometrik analiz, botulinum toksin, serebral palsi, spastisite

Ethics Committee Approval: Since the data in this study were derived from previous studies, ethics committee approval was waived.
Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.
Authorship Contributions: Concept: GS, Design: GS, Data Collection or Processing: GS, AMÇ, Analysis or Interpretation: GS, AMÇ, Literature Search: GS, AMÇ, Writing: GS, AMÇ.
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1. Introduction

Cerebral palsy (CP) is a neurological disorder that affects muscle tone, movement, and posture, primarily resulting from abnormal brain development or damage during early development (1). Spasticity is part of a condition known as the upper motor neuron syndrome, characterized by a velocity-dependent increase in muscle tone and reflex activity (2). Spasticity is considered the most common cause of motor impairment in children with CP, affecting approximately 80% of patients. In addition to impaired mobility, it can lead to serious complications such as contractures and pressure sores (3,4).

Intramuscular administration of botulinum toxin type A (BoNT-A) is a widely preferred treatment modality for focal or segmental spasticity (4). By targeting specific muscles, BoNT-A can temporarily reduce spasticity, enhance functional abilities, relieve pain, and contribute to the rehabilitation process. There is no single standardized treatment strategy for BoNT-A administration in CP, and the dosages used have varied over the years (5–7).

The continuous increase in the number of scientific publications and the increasingly fragmented nature of studies make it challenging to organize the existing body of knowledge. Bibliometrics is an important method for systematically evaluating and quantifying the literature. It enables us to assess various indicators of scientific publications by transforming them into numerical data (8,9). Furthermore, it assists researchers in identifying areas that require attention (10–12). In this way, aspects such as scientific productivity, collaboration networks, research impact, and emerging trends become objective and measurable. The Web of Science Core Collection (WOSCC) is one of the most frequently used and user-friendly databases for bibliometric analyses, providing key information for researchers aiming to measure scientific output and impact (13). Tools such as VOSviewer and Bibliometrix, an R-based package, are commonly employed in bibliometric analyses (14). These tools enhance the effectiveness of bibliometric studies through features such as citation network analysis, mapping of collaborative relationships, and visualization of key concepts in the literature.

Bibliometric analyses of studies on BoNT-A administration in CP are valuable for understanding the role of this treatment in clinical practice and evaluating its development over time. These analyses can provide insights into the efforts aimed at developing improved therapeutic strategies. This study aims to present a comprehensive bibliometric analysis of research on BoNT-A injections in CP, providing an overview of the evolution and impact of global research in this field and summarizing emerging trends in the application of BoNT-A in CP.

2. Materials and Methods

On December 24, 2024, the WoSCC was used to search for published articles on BoNT-A applications in CP. The search strategy was: AB = (“cerebral palsy” OR “spastic cerebral palsy” OR “spasticity in cerebral palsy”) AND AB = (“Botulinum toxin” OR “Botox” OR “botulinum neurotoxin” OR “BoNT” OR “Botulinum”). The results were refined by publication year (2005–2024), English language, and document type (articles, review articles, and proceeding papers). The remaining 690 results were sorted by citation count, with the most cited article listed first. As the data in this study were obtained from previously published studies, ethical approval was not required.

For each article, the following data were recorded: title, total number of authors and their names (corresponding author and first author), publication year, citation count and citation index, journal name, h-index, impact factor, authors’ countries, article type, and funding sources. When authors were from different countries, the country of the first listed author was recorded. To perform comprehensive bibliometric analyses, the open-source Bibliometrix R package (http://www.bibliometrix.org/) and VOSviewer software (version 1.6.20, Leiden University, Leiden, the Netherlands) were used. Bibliometrix is an R-based software used for bibliometric analysis and visualization (15). Subsequently, VOSviewer was employed to perform co-occurrence analysis of abstracts and keywords to identify the most frequently associated terms in this field. The citation index was calculated as the total number of citations a paper received divided by the number of years since its publication.

3. Results

a. Publication Outputs

In this study, a total of 690 publications meeting the inclusion criteria (550 research articles and 140 review articles) were analysed (Figure 1). The total number of citations for these publications was 15.734, with an average of 22.7 citations per article.

Figure 2 shows the distribution of publications by year, revealing a general upward trend in publication output between 2005 and 2024. The year 2018 saw the highest number of publications, with a total of 44 articles released. A temporary decline in publication numbers was observed in 2021–2022; however, this was followed by a recovery in 2023 and 2024. The annual growth rate was calculated as 5.01%.

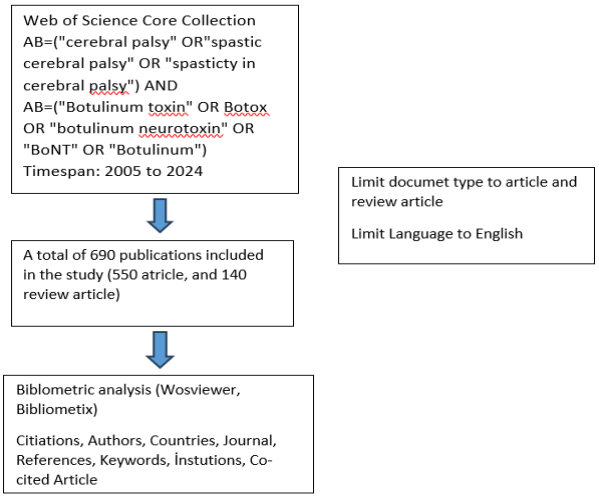

Figure 1. A flowchart of searching literature and analysis process

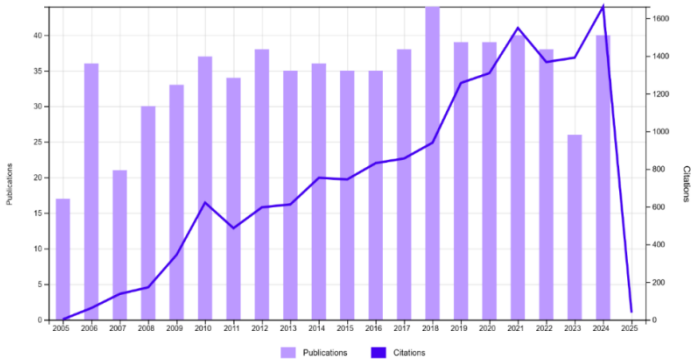

Figure 2. Annual scientific production

b. Countries/Regions

Based on the results of the bibliometric analysis, scientific publications were contributed by a total of 66 countries from 2005 to 2024. The United States (USA) ranked first in publication count with 115 publications, followed by Australia with 86 publications and Italy with 54 publications. In terms of average citation counts, Australia demonstrated the highest citation performance (Table 1). Regarding international collaboration, the most significant contributions were made by the USA, France, and the United Kingdom (UK) (Figure 3).

Table 1. Top 10 Countries by Number of Publications (2005–2024)

Ranking	Countries/ Regions	Publications (P)	TC	AAC	H-index
1	USA	115	3244	28.1	29
2	Australia	86	4639	53.9	37
3	Italy	54	1238	22.8	19
4	South Korea	47	704	14.9	16
5	UK	47	1478	31.4	25
6	Turkey	45	723	16.0	13
7	France	44	1213	27.5	18
8	The Netherlands	44	1364	31	20
9	Belgium	41	1392	33.9	18
10	Canada	38	1089	26.6	14

USA: The United States of America, UK: The United Kingdom TC: Times Cited, AAC: Avarage Article Citation

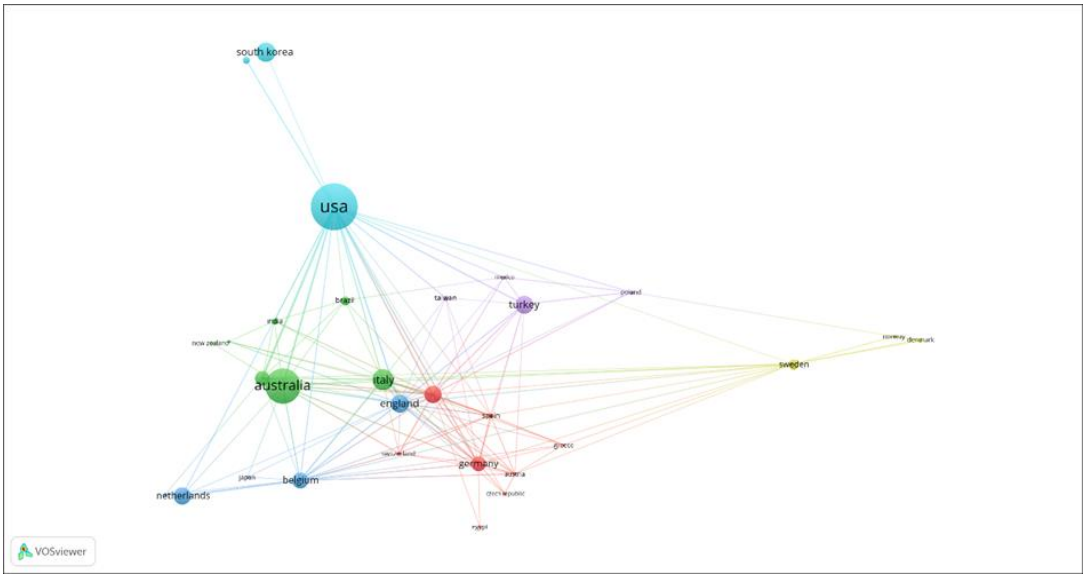

Figure 3. *International collaboration network generated by VOSviewer. Node size is proportional to the number of publications from each country, while link thickness represents the intensity of collaboration between countries. Colors indicate clusters of countries with strong collaborative relationships.*

c. Institute

This article identifies a total of 1,164 institutions based on author affiliations from publications between 2005 and 2024. Table 2 presents the ten most active institutions and their countries of origin, ranked by the number of publications related to BoNT-A research in CP. Katholieke Universiteit (KU Leuven) in Belgium ranks first with 68 publications, followed by leading research institutions from Australia, South Korea, the Netherlands, Taiwan, and the USA. The table emphasizes the global scope of research in this field, particularly noting that Australia boasts several prominent institutions.

Table 2. Top 10 Institutions by Number of Publications

Ranking	Institute	P	Country
1	Katholieke Universiteit Leuven	68	Belgium
2	Royal Childrens Hospital	57	Australia
3	Radboud University Nijmegen	51	Holland
4	Yonsei Univ	50	South Korea
5	University Hospitals Leuven	38	Belgium
6	National Cheng Kung University	30	Taiwan
7	University Western Australia	27	Australia
8	University Queensland	26	Australia
9	Shriners Hospital Children	25	The USA
10	University Melbourne	25	Australia

d. Funding Sources

Of the articles reviewed, 360 received funding from various agencies. The most common funding sources were AbbVie (27 publications), Allergan (26 publications), and IPSEN (21 publications). Details of the top 10 funding sources are presented in Table 3.

Table 3. The top 10 funding sources

Ranking	Funding Sources	Countries	Frequency
1	ABBVIE	USA	27
2	ALLERGAN	USA	26
3	IPSEN	France	21
4	National Institutes of Health (NIH)	USA	15
5	United States Department of Health Human Services	USA	15
6	National Health Medical Research Council (NHMRC)	Australia	12
7	FWO	Belgium	9
8	Medytox INC.	South Korea	6
9	National Institutes Of Health Research (NIHR)	UK	6
10	Netherlands Government	Holland	6

e. Journals

The journals with the highest number of publications were Developmental Medicine and Child Neurology, which had 83 articles, and Toxins, which had 32 articles. In terms of impact factor (IF), Toxins had the highest value at 3.9, followed closely by Developmental Medicine and Child Neurology, which had an IF of 3.8 **(Table 4)**. In the citation analysis, Developmental Medicine and Child Neurology was the most cited journal, with 616 co-citations. It was followed by the European Journal of Neurology, which had 100 co-citations, and the Journal of Pediatric Orthopedics, with 92 co-citations. Among the top 10 co-cited journals, Pediatrics had the highest impact factor at 8 (Table 4).

Table 4. The top 10 journals by number of publications and co-citations from 2005 to 2024.

Journals	P	IF	Co-cited Jornals	Cit	IF
Developmental Medicine and Child Neurology	83	3.8	Developmental Medicine and Child Neurology	616	3.8
Toxins	32	3.9	Europan Journal of Neurology	100	4.5
American Journal of Physical Medicine & Rehabilitation	23	2.2	Journal of Pediatric Ortopedics	92	1.4

Journal of Child Neurology	21	2.0	European Journal of Paediatric Neurology	68	2.3
European Journal of Paediatric Neurology	20	2.3	Archives Physical Medicine and Rehabilitation	66	3.6
Archives of Physical Medicine and Rehabilitation	14	3.6	Journal Child Neurology	52	2.0
European Journal of Physıcal and Rehabılıtatıon Medıcıne	11	3.3	Clınıcal Rehabilitation	35	2.6
Frontiers in Neurology	11	2.7	Pediatrics	46	8.0
Gait & Posture	11	2.2	Physical Theraphy	40	3.5
BMC Pediatrıcs	10	2.0	Disability Rehabilitation	34	2.1

f. Citations

When examining the average annual citation counts, an increase was noted during the periods of 2009–2011 and 2012–2014. The most significant growth occurred between 2017 and 2020. However, after 2020, there was a noticeable decline in citation rates (Figure 1). Table 5 lists the ten most cited articles on CP and the applications of BoNT-A, all of which have significantly contributed to the literature. The studies by Novak I, published in 2013 and 2020, focused on evidence-based treatment approaches in CP and ranked at the top of the list with 878 and 541 total citations, respectively (16,17). Similarly, the studies by Simpson DM and Sadowska M have established a significant presence in the literature by outlining the efficacy and safety profile of BoNT-A in treating spasticity (18,19). Heinen F and Delgado MR provided an in-depth discussion of the clinical applications of botulinum toxin in pediatric neurology (21,22). These studies stand out with their high annual citation rates and emphasise the importance of BoNT-A in the treatment of CP. The fact that most of these articles were published after 2010 indicates a growing research interest in BoNT-A during this period.

Table 5. Top 10 Most Cited Articles (2005-2024)

Title	First Author	Source Title	Total Citations	Average Citiations
A systematic review of interventions for children with cerebral palsy: state of the evidence (16)	Novak I	Developmental Medicine and Child Neurology	878	64.5
State of the Evidence Traffic Lights 2019: Systematic Review of Interventions for Preventing and Treating Children with Cerebral Palsy (17)	Novak I	Current Neurology and Neuroscience Reports	541	90.17
Assessment: Botulinum neurotoxin for the treatment of spasticity (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (18)	Simpson DM	Neurology	270	15
Cerebral Palsy: Current Opinions on Definition, Epidemiology, Risk Factors, Classification and Treatment Options (19)	Sadowska, M	Neuropsychiatric Disease and Treatment	248	41.33
Efficacy of upper limb therapies for unilateral cerebral palsy: a meta-analysis (20)	Sakzewski, L	Pediatrics	213	17.75
The updated European Consensus 2009 on the use of Botulinum toxin for children with cerebral palsy (21)	Heinen F	European Journal of Paediatric Neurology	193	12.06

Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (22)	Delgado, MR	Neurology	175	10.94
Botulinum toxin A as an adjunct to treatment in the management of the upper limb in children with spastic cerebral palsy (23)	Hoare, BJ	Cochrane Database of Systematic Reviews	140	8.75
Botulinum toxin assessment, intervention and after-care for lower limb spasticity in children with cerebral palsy: international consensus statement (24)	Love, SC	The European Journal of Neurology	132	8,25
Medial gastrocnemius muscle volume and fascicle length in children aged 2 to 5 years with cerebral palsy (25)	Barber, L	Developmental Medicine & Child Neurology	130	8.67

g. Authors

The authors with the most publications include Desloovere K with 29 publications, and both Molenaers G and Van Campenhout A, each with 23 publications **(Table 6)**. Among these ten authors, Graham HK and Molenaers G are notable for having the highest citation impact. When considering the H-index, which reflects influence in academia, Graham HK and Desloovere K stand out as the most influential authors **(Table 6)**. **Figure 4** examines the types of collaborations in academic publications based on the countries of the corresponding authors. The USA is prominent in academic leadership, having the highest number of corresponding authors. However, the majority of its work falls into the category of Single Country Publications (SCP), indicating that much of the research output is produced at the national level. In contrast, European countries show a comparatively more balanced distribution between Multiple Country Publications (MCP) and SCP, highlighting their greater involvement in international collaborations.

Table 6. Top 10 Authors by Number of Publications

Authors	**P**	**Institution**	**Countries**	**Citiations**	**Avarage citiation**	**h-index**
DESLOOVERE, K	29	KU Leuven	Belgium	1050	36.2	45
MOLENAERS, G	23	KU Leuven	Belgium	1149	49.9	41
VAN CAMPENHOUT, TA	21	KU Leuven	Belgium	717	34.1	28
GRAHAM, HK	20	Royal Children's Hospital Melbourne	Australıa	1133	56.6	63
VAN HULST, K	14	Radboud University Nijmegen Medical Center	Netherlands	358	25.5	19
PARK, ES	13	Yonsei University	South Korea	256	19.6	26
BAR-ON, L	11	Amsterdam UMC location Vrije Universiteit	Netherlands	259	23.5	21
VAN DEN HOOGEN, FJA	12	Radboud University Nijmegen Medical Center	Netherlands	216	18.0	32
JONGERIUS, PH	11	Sint Maartens Clinicdept Rehabilnıjmegen, Netherlands	Netherlands	515	46.8	21
RHA, DW	11	Yonsei University	South Korea	224	20.3	23

P: Number of publications

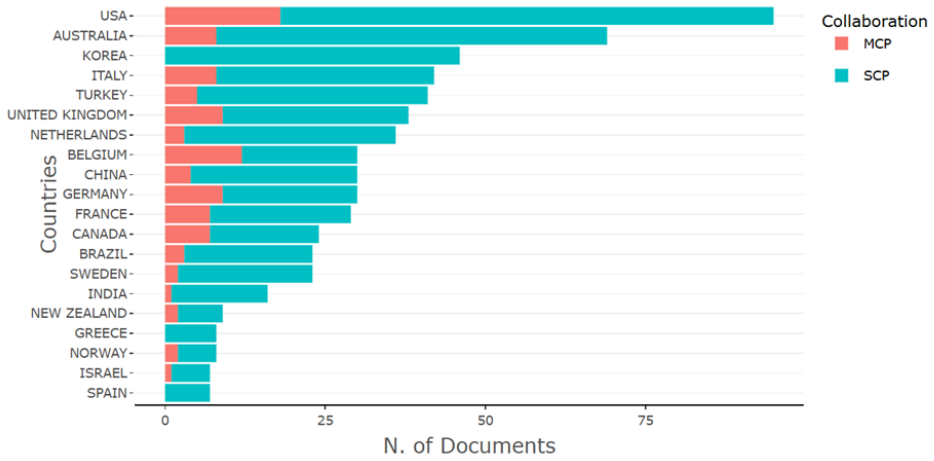

Figure 4. Corresponding author's countries. MCP: Multiple Country Publications, SCP: Single Country Publications.

h. Analysis of Keywords

Keyword analysis provides valuable insights into research trends and areas of focus. Terms like "cerebral palsy," "botulinum toxin," and "spasticity" highlight central themes in this field. Additionally, the frequent use of words such as "rehabilitation," "gait analysis," and "quality of life" indicates a thorough examination of treatment strategies. In recent years, there has also been an increase in the use of technological innovations, including "ultrasound" and "electromyography" (Figure 5).

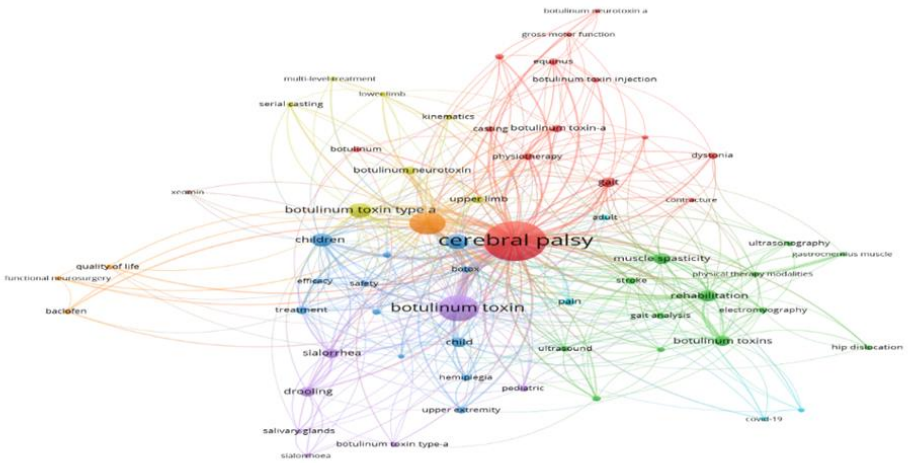

Figure 5. *Keywords analysis. The co-occurrence network of keywords was generated using VOSviewer. In this network, the size of each node reflects the frequency of keyword occurrence, while the thickness of the links represents the strength of co-occurrence between keywords. Different colors indicate clusters of keywords that frequently appear together.*

i. References

Table 7 lists the most frequently cited references in the literature regarding CP and the use of botulinum toxin. The study by Palisano et al. from 1997 ranks first, having received 121 citations for its significant contribution to classifying the motor functions of individuals with CP (26). Following closely are Bohannon's 1987 study on assessing spasticity with 110 citations, and Graham's 2000 research on the effects of botulinum toxin on gait and posture, which has garnered 100 citations (27,28). The majority of these studies address key issues related to motor skills and spasticity management in CP, and they have been published in prestigious journals such as Developmental Medicine and Child Neurology.

Table 7. The Top 10 Most Local Cited References

Cited References	Citations	First Author	Journal	Publication year
Development and reliability of a system to classify gross motor function in children with cerebral palsy (26)	121	Palisano, R	Developmental Medicine and Child Neurology	1997
Interrater reliability of a modified Ashworth scale of muscle spasticity (27)	110	Bohannon, RW	Physical Therapy & Rehabilitation Journal	1897
Recommendations for the use of botulinum toxin type A in the management of cerebral palsy (28)	100	Graham, HK	Gait & Posture	2000
A report: the definition and classification of cerebral palsy April 2006 (29)	93	Rosenbaum, P	Developmental Medicine and Child Neurology	2007
Botulinum toxin type A neuromuscular blockade in the treatment of lower extremity spasticity in cerebral palsy: a randomized, double-blind, placebo-controlled trial. BOTOX Study Group (30)	88	Koman, LA	Journal of Pediatric Orthopaedics	2000
The updated European Consensus 2009 on the use of Botulinum toxin for children with cerebral palsy (31)	84	Heinen, F	European Journal of Paediatric Neurology	2010
Randomised double blind placebo controlled trial of the effect of botulinum toxin on walking in cerebral palsy (32)	76	Ubhi,T	Archives of Disease in Childhood	200
Botulinum toxin assessment, intervention and after-care for lower limb spasticity in children with cerebral palsy: international consensus statement (33)	74	Love, SC	Europan Journal of Neurology	2010
Management of cerebral palsy with botulinum-A toxin: preliminary investigation (34)	69	Koman, LA	Journal of Pediatric Orthopaedics	1993
Botulinum toxin in the management of the lower limb in cerebral palsy (35)	67	Cosgrove, AP	Developmental Medicine and Child Neurology	1994

4. Discussion

In this study, we conducted a bibliometric analysis of publications on CP and BoNT applications at WOSCC between 2005 and 2024. We used R, Bibliometrix, and VOSviewer for this analysis. This study makes a significant contribution by comprehensively examining general CP bibliometric data and, in particular, the usage trends of BoNT-A applications within CP.

According to our findings, although the number of publications fluctuated over the years, there was an overall upward trend. Similar increases in research articles have also been reported in other bibliometric studies on CP (36). As highlighted in the literature, since the 1980s intramuscular BoNT-A injections have been increasingly used to modulate spasticity in CP, particularly contributing to improved functional outcomes in the pediatric population (22, 37). Although 2020 was the year in which the FDA approved BoNT-A for the treatment of spasticity in pediatric CP, the graph shows a decrease in publications in 2020 and 2021 (Figure 2). This is most likely related to the COVID-19 pandemic. The slowdown in research activities and interruptions in clinical studies during the pandemic may explain this decline. With the easing of pandemic effects, publication numbers gained momentum again in 2023 and 2024.

Studies on BoNT-A applications in CP were distributed across 247 journals and books, reflecting the interest of multiple medical disciplines. Developmental Medicine and Child Neurology was the journal with the highest number of publications

in this specific field, with 83 articles. Graham HK was the most cited author with 1,133 citations, while Desloovere K was the most productive author with 29 publications. When countries' research productivity is evaluated, as shown in Table 1, the USA leads with 115 publications. This leadership can be attributed to its robust academic infrastructure, substantial research funding, large population, and interest in innovative treatments. The USA also leads in publications on BoNT-A applications for spasticity across all conditions, not only in CP (38). Australia ranks second in the total number of publications but leads in average citation count (AAC) with 53.9, suggesting that studies from Australia have a significant impact. Turkey ranks fourth with 41 publications; however, its AAC of 8.90 is considerably lower than that of other countries. Turkey's international cooperation level (MCP: 5) shows the need for further development to enhance its impact in this area. Examination of the international collaboration network also highlights the contributions of European countries, particularly in terms of multi-country publications and global cooperation.

The analyses showed that the terms "cerebral palsy," "botulinum toxin," and "spasticity" occupy a central position in the literature, while concepts such as "rehabilitation," "gait analysis," and "quality of life" were also among the most frequently used keywords. This indicates that research in this field is not limited to improving motor functions but also focuses on enhancing quality of life and supporting functional gains. Terms specific to BoNT-A applications, such as "dysport," "xeomin," "efficacy," and "safety," were noted, reflecting a strong emphasis on drug efficacy and safety. Keywords such as "gait analysis," "rehabilitation," and "muscle spasticity" remain classical themes consistently present in the literature, indicating their long-term status as key research focuses. Since 2016, there has been a significant increase in the use of keywords such as "ultrasound" and "electromyography," highlighting the ongoing advancements in this field due to technological innovations. The important role of ultrasound guidance in BoNT-A applications has been emphasized (39, 40). Ultrasound accurately identifies the target muscle during injection, enhancing procedural precision. Additionally, it offers valuable insights for predicting treatment responses and monitoring structural changes in the muscle (41–43).

In recent years, "sialorrhea" has emerged as a significant theme. The literature emphasizes that sialorrhea is common in children with CP and greatly impacts their quality of life (44). Intraglandular BoNT-A injections have been reported to significantly reduce saliva production, typically administered at an average dose of 2 U/kg/gland into the parotid and submandibular glands under ultrasound guidance (44,45). Suskind et al. reported doses of 10–30 U per gland (45).

We found that 52% of the total publications received external funding. As shown in Table 3, the list of top funding organizations reveals that U.S.-based institutions (ABBVIE, ALLERGAN, NIH, HHS) supported a total of 83 studies. This suggests that the geographical distribution of research may be unbalanced, with global funding sources concentrated in certain regions.

European (21) and international (24) consensus statements emphasise that BoNT-A is safe and effective, particularly for lower-limb spasticity, but should always be implemented within a multidisciplinary approach. These guidelines recommend setting treatment goals collaboratively with the family and the care team, taking GMFCS levels into account, and evaluating effectiveness using multidimensional measures. The trends identified in our bibliometric analysis are consistent with the framework outlined in these guidelines. In the study by Novak et al., in 2013, BoNT-A was listed among the strongly recommended interventions for managing spasticity in children with CP (16). The study highlighted that BoNT-A not only reduces hypertonia but also contributes to functional improvement. It was further noted that targeted rehabilitation approaches, such as physiotherapy and occupational therapy, applied after BoNT-A administration significantly enhance treatment effectiveness. These findings support the importance of multidisciplinary approaches in integrating BoNT-A into clinical practice. Novak et al.'s updated systematic review, published in 2019, changed the status of using serial casting after BoNT-A injection for contracture management at week four from "emerging" to "recommended" (17). Additionally, there is low-level evidence suggesting some benefits of incorporating electrical stimulation with BoNT-A. However, a previous evidence-based review from 2008 indicated that combining serial casting with BoNT-A did not offer any additional advantage for treating equinus deformity (18). BoNT-A is effective for pain management in children with CP, particularly for equinus gait, adductor spasticity, and after adductor lengthening surgery. However, evidence regarding its effects on hamstring spasticity remains limited (18).

Research indicates that injecting BoNT-A into the upper limbs of individuals with spasticity can aid in facilitating passive movements. When these injections are paired with task-oriented and goal-directed rehabilitation approaches, as shown in a 2014 meta-analysis, they may offer modest but meaningful additional functional benefits (20). However, further research is necessary to better understand their effects on active functional improvements (18, 20). Nevertheless, there are also opposing findings in the literature. For example, the systematic review by Farag et al. reported that BoNT-A reduces upper-limb spasticity in the short term but found no evidence of long-term improvements in function or quality of life (46). Similarly, another study demonstrated that adding BoNT-A injections did not provide any additional benefit compared with rehabilitation alone (47). A 2010 Cochrane review also emphasised that BoNT-A alone has limited effectiveness in the upper limb, but when combined with goal-oriented occupational therapy, it provides meaningful additional benefits in reducing spasticity and achieving functional goals (23). Future studies should investigate the effects of repeated injections at various doses and frequencies on upper limb spasticity (23).

Considering the current evidence, there is a need for more comprehensive and prospective studies evaluating the long-term efficacy and safety outcomes of BoNT-A treatments. Furthermore, increasing the number of studies on upper limb function, which is less represented in the literature, would strengthen the evidence base for clinical practice. Finally, enhancing multicenter and interdisciplinary collaborations between countries and institutions would contribute to improving the quality and global impact of scientific output in this field.

This study has certain limitations. First, the analysis was based solely on the WOSCC database and English-language publications; therefore, studies indexed in other databases or published in other languages were excluded. Furthermore, the data analyzed were limited to the period from 2005 to 2024, and studies outside this timeframe were not considered. Since the bibliometric methods used rely on quantitative indicators, they do not directly assess the methodological quality or clinical impact of the publications. Moreover, country, institution, and author information was recorded based on the first author, which may not fully reflect the contributions of co-authors. On the other hand, this study also has strengths. We comprehensively examined research trends and collaborations in BoNT-A applications for CP using a large and up-to-date dataset. The combined use of powerful analytical and visualization tools such as Bibliometrix and VOSviewer enabled a detailed representation of both the quantitative and network structures of the literature. In this respect, the study provides a comprehensive overview that may guide future research in this field.

In conclusion, this bibliometric analysis highlights the growing global importance of BoNT-A applications in CP and demonstrates the need for research to become more multidisciplinary, internationally collaborative, and technology-integrated.

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Predictors of Severe Nicotine Dependence in Patients with Chronic Pain

Kronik Ağrı Hastalarında Şiddetli Nikotin Bağımlılığının Öngördürücüleri

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Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

Authorship Contributions: Conceptualization: İGYK, GG, MSG,Methodology: İGYK, GG, MSG,Data curation: EG, HK, HU,Formal analysis: İGYK,Writing – original draft: HU, EG, HK, Writing – review & editing: HU, İGYK,Supervision: İGYK, GG, MSG

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Abstract: The combined presence of chronic pain and nicotine dependence has been shown to elevate the risk of both physical and mental illnesses. Consequently, understanding the interconnected relationship between chronic pain, smoking, and nicotine dependence is crucial for developing effective interventions and improving patient outcomes. The present study aimed to reveal if pain intensity, symptoms of anxiety and depression, anxiety sensitivity, and distress tolerance serve as predictive factors of severe nicotine dependence risk among patients with chronic pain. Seventy-six smokers with chronic pain were recruited (mean age = 50.28±12.37, 63.2% female). The study utilized self-reported measures to assess pain intensity, distress tolerance, anxiety sensitivity, nicotine dependence, and symptoms of anxiety and depression. Univariate binary logistic regression was performed to find the predictors of severe nicotine dependence risk. Among the patients, 34.2% reported anxiety (n=26), and 56.6% reported depression (n=43). The anxiety subscale scores of the HADS (odds ratio = 1.125 [1.016–1.245]) and the total scores of the ASI-3 (odds ratio = 1.038 [1.005–1.073]) significantly predicted severe nicotine dependence risk (p = 0.023 and p = 0.025, respectively), as well as pain intensity over the past week (odds ratio = 1.331[1.030–1.720]; p = 0.029). This study highlights the need to address smoking behavior and mental health in patients with chronic pain and emphasizes the importance of pain management, anxiety symptoms, and anxiety sensitivity as potential targets for intervention in smoking cessation efforts within this population.
Keywords: Anxiety sensitivity; Nicotine Dependence; Chronic Pain; Smoking; Tobacco.

Özet: Kronik ağrı ve nikotin bağımlılığı birlikteliği, fiziksel ve ruhsal hastalıkların riskini arttırmaktadır. Bu nedenle kronik ağrı, sigara kullanımı ve nikotin bağımlılığı arasındaki ilişkinin anlaşılması, etkili müdahaleler geliştirmek için kritik öneme sahiptir. Bu çalışma, kronik ağrısı olan hastalarda şiddetli nikotin bağımlılığı riskinin öngördürücüleri olarak ağrı şiddeti, anksiyete ve depresyon semptomları, anksiyete duyarlılığı ve sıkıntıya dayanma düzeylerini ortaya koymayı amaçlamıştır. Çalışmaya, kronik ağrısı olan, ağrı yönetimi için tedavi gören ve sigara içen 76 kişi katılmıştır (ortalama yaş = 50.28 ± 12.37, %63.2 kadın). Çalışmada; ağrı şiddeti, anksiyete ve depresyon semptomları, anksiyete duyarlılığı ve sıkıntıya dayanma düzeyleri ile nikotin bağımlılığı riskini değerlendirmek için öz-bildirim ölçekleri kullanılmıştır. Şiddetli nikotin bağımlılığı riskinin belirleyicilerini saptamak amacıyla tek değişkenli lojistik regresyon analizi yapılmıştır. Hastane Anksiyete ve Depresyon Ölçeği (HADÖ) kesme değerlerine göre, hastaların %34.2'si anksiyete (n=26) ve %56.6'sı depresyon (n=43) bildirmiştir. HADÖ'nün anksiyete alt ölçek puanları (odds oranı = 1.125 [1.016–1.245]), Anksiyete Duyarlılığı Ölçeği-3 toplam puanları (odds oranı = 1.038 [1.005–1.073]) ve ağrı şiddeti (odds oranı = 1.331[1.030–1.720]) şiddetli nikotin bağımlılığı riskini anlamlı şekilde öngörmüştür (sırasıyla p=0.023, p=0.025, p=0.029). Bu çalışma, kronik ağrı hastalarında sigara kullanımı ve ruh sağlığının ele alınmasının gerekliliğine dikkat çekmekte ve bu hasta grubunda sigara bırakma sürecinde potansiyel müdahale alanları olarak ağrı yönetimi, anksiyete semptomları ve anksiyete duyarlılığının önemini vurgulamaktadır.
Anahtar Kelimeler: Anksiyete Duyarlılığı; Nikotin Bağımlılığı; Kronik Ağrı; Sigara Kullanımı; Tütün.

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1. Introduction

Addiction is a chronic medical condition involving complex interactions among biological systems, genetics, and environmental factors. It is characterized by the compulsive use of substances despite their mental, physical, and social consequences. Tobacco use, as a form of addiction, is one of the most significant public health challenges, contributing to over 8 million tobacco-related deaths annually (1). According to World Health Organization statistics, 22.3% of the global population used tobacco in 2020, including 7.8% of women and 36.7% of men (2). Tobacco use is linked to numerous health issues affecting almost every organ system, including cancer (3). While nicotine itself does not directly cause cancer, tobacco smoke contains at least 69 carcinogenic chemicals (3).

People with certain medical conditions, such as mental disorders, substance use disorders, and chronic obstructive pulmonary disease, are known to smoke at higher rates (4,5). From this perspective, there are studies investigating the relationship between smoking and chronic medical conditions such as chronic pain. Chronic pain refers to pain that persists or recurs for more than three months. It is associated with low quality of life, disability, and mental symptoms like depressed mood or anxiety (6). Chronic pain and tobacco use are both highly prevalent and often co-occur (3). Research indicates that individuals with chronic pain are more likely to smoke than the general population (7), with these patients being twice as likely to smoke compared to those without chronic pain (8). Chronic pain is associated not only with current smoking status but also with nicotine dependence, smoking severity, and challenges in the quitting process (9). Additionally, smokers with chronic pain report higher pain intensity, greater functional impairment, and an increased need for analgesics compared to non-smokers (10). In terms of nicotine dependence, it is known that higher nicotine dependence is related to an increased risk of persistent smoking (11). The combined presence of chronic pain and nicotine dependence has been shown to elevate the risk of both physical and mental illnesses (12). Consequently, understanding the interconnected relationship between chronic pain, smoking, and nicotine dependence is crucial for developing effective interventions and improving patient outcomes.

Chronic pain is related to mental disorders. Patients suffering from chronic pain report high rates of depression and anxiety symptoms (13). Regarding the relationship between depression, anxiety, and smoking, past studies have documented that smoking is more prevalent among individuals with depression and anxiety disorders (14, 15). Since both chronic pain and symptoms of anxiety and depression are associated with increased cigarette use, chronic pain patients with anxiety and depression may be at an elevated risk for smoking.

The concept of anxiety sensitivity (AS) was introduced by Reiss and McNally in 1985 as part of their expectancy model of fear. It was defined as the fear of bodily sensations associated with anxiety (16). AS reflects the fear that anxiety symptoms may lead to harmful physical, mental, or social consequences. AS has three dimensions: physical, cognitive, and social. The physical dimension involves fear of physical symptoms of anxiety, such as palpitations. The cognitive dimension pertains to the fear of losing control, while the social dimension involves the fear of others noticing one's anxiety symptoms. AS is considered a risk factor for anxiety disorders, and it is typically elevated in individuals with panic disorder and other anxiety disorders (17). Regarding the relationship between smoking and AS, a study found patterns similar to those observed in chronic pain studies. AS was significantly related to the severity of tobacco dependence, perceived barriers to quitting, and problems during quit attempts (18).

The relationship between AS, chronic pain, and smoking is a relatively new and emerging area of research. A review of the literature reveals notable findings. In a study involving participants who used electronic cigarettes, Zvolensky et al. (2019b) reported that the interaction between AS and pain severity was significantly associated with increased e-cigarette dependence (19). Similarly, Rauven et al. (2021) found that among adult smokers experiencing homelessness, participants with higher AS demonstrated heavier smoking (based on the Heaviness of Smoking Index) (20) as past month pain increased (21).

Distress tolerance (DT) refers to an individual's perceived capacity to endure negative emotional and physical states, such as pain, as well as the behavioral effort to resist distressing internal experiences triggered by stressors (22). Evidence suggests that low DT is associated with an increased vulnerability to various addictions and poorer treatment outcomes (22, 23). While earlier research primarily focused on alcohol and substance use (24,

25), smoking has also emerged as an area of interest. Recent studies have placed greater emphasis on how DT relates to smoking persistence, motives for smoking, and early lapses during cessation attempts (26, 27). Redmond et al. (2024) highlighted that DT is associated with smoking motives related to addiction, alleviation of negative emotions, and stimulation-seeking (27). Moreover, DT has been shown to indirectly influence nicotine dependence through smoking motives, such as tension reduction and habitual smoking (28). In terms of chronic pain, Trepanier et al. (2022) stated that DT may influence the pain experience of patients suffering from chronic pain (29).

The present study aimed to reveal if symptoms of anxiety and depression, anxiety sensitivity, and distress tolerance were predictive factors of severe nicotine dependence risk among smoking patients with chronic pain.

2. Materials and Method

The present study has a cross-sectional design.

Inclusion criteria included being between 18 and 65 years old, experiencing pain for at least 3 months, currently smoking at least one cigarette per day, volunteering to participate in the study, and being literate enough to complete the forms independently. Exclusion criteria included having psychosis or severe depression, cognitive impairment or intellectual disability, and substance abuse or severe alcoholism. The study criteria were monitored and managed by trained psychiatry residents during patient recruitment.

2.1. Procedure

The study recruited patients with chronic pain from the Algology Unit of the Eskişehir Osmangazi University Hospital. The patients were either inpatients or outpatients. Data recruitment took place between April 1, 2021, and March 1, 2022.

2.2. Measurements

Sociodemographic and clinical data form: The form included age, sex, marital status, employment status, educational level, and the clinical characteristics of the pain.

Visual Analog Scale (VAS): The patients' pain intensity over the last week and the discomfort associated with it were evaluated using the VAS. Having a single-item measurement with VAS is commonly used in healthcare settings. The VAS scores range from 0 to 10 (30). Regarding pain intensity, 0 indicated no pain, and 10 represented the worst possible pain. For discomfort, 0 indicated no discomfort, and 10 referred to the highest level of discomfort.

Hospital Anxiety and Depression Scale (HAD): It is a self-assessment scale designed to assess the risk of anxiety and depression, as well as to measure the severity and changes in these conditions in patients with physical illnesses and those seeking primary care (31). It was translated into Turkish, and a validity and reliability study was conducted (32). There are subscales for anxiety (HAD-A) and depression (HAD-D). It contains a total of 14 questions. Seven of them (odd numbers) measure anxiety, and the other seven (even numbers) measure depression. Provides a four-point measurement using the Likert scale. The cut-off score for the anxiety subscale was 10/11 and for the depression subscale 7/8 among the Turkish population (32). The lowest score that patients can achieve on both subscales is 0, the highest 21. Considering that our study included patients hospitalized due to pain, the HAD was preferred because it does not contain any items related to physical symptoms, which helped us obtain more accurate results (33). Since the present study evaluated anxiety and depression using self-report measures, the variables are referred to as probable anxiety and probable depression.

The Anxiety Sensitivity Index-3 (ASI-3): It is the most commonly used scale for assessing anxiety sensitivity, developed by Reiss et al. in 1986 (34). The scale consists of three subscales (physical, cognitive, and social) and a total of 16 items. The physical subscale measures the “fear of physical symptoms” caused by anxiety, such as fear of palpitations or shortness of breath. The cognitive subscale measures the "fear of losing cognitive control" dimension, which assesses situations such as the fear of not being able to concentrate on a topic or the fear of feeling strange or empty. The social subscale assesses situations defined as "fear of one's anxiety symptoms being noticed" by others in society, like being noticed that one is shaking. After several revisions, ASI-3 was developed (35). ASI-3 consisted of 18 items and three subscales (physical, cognitive and social). The Turkish validity and reliability study was conducted (36).

The Fagerström Nicotine Dependence Test (FNDT): It is a six-question questionnaire created by revising the Fagerström Tolerance Questionnaire (FTQ) (37). The FNDT is a short, practical test for smoking dependence. The Turkish version of the test is valid and reliable (38). In the FNDT scoring system, a score of 0–2 indicates very low

dependence, 3–4 indicates low dependence, 5 indicates moderate dependence, 6–7 indicates high dependence, and 8–10 indicates very high dependence. FNDT scores ≥6 reflect severe nicotine dependence (39). The study evaluated severe nicotine dependence psychometrically; thus, the variable used was probable severe nicotine dependence, defined based on an FNDT score of 6 or higher.

Distress Tolerance Scale (DTS): The DTS, developed by Simons and Gaher (2005), is a self-assessment scale consisting of 16 items (40). The items are rated on a Likert scale ranging from 1 to 5. The scale options range from (5) 'strongly disagree' to (1) 'strongly agree,' with higher scores reflecting a greater ability to tolerate stress. The DTS comprises four subscales designed to measure the ability to tolerate emotional stress: 1) Tolerance to emotional stress (Tolerance), 2) Subjective appraisal of stress (Appraisal), 3) Distraction from distressing emotions (Attention Distraction), and 4) Regulatory efforts to reduce stress (Regulation). The DTS was valid and reliable among the Turkish population (41).

2.3. Ethics

The study was approved by the Non-invasive Clinical Studies Ethics Committee of Eskişehir Osmangazi University on 30.03.2021 with decision number 29. Written informed consent was obtained from all partipants. The study adheres to the principles outlined in the Declaration of Helsinki.

2.4. Statistical Analysis

SPSS version 25 was utilized for the statistical analysis. Categorical variables were presented as frequencies and percentages, while continuous variables were presented as means and standard deviations, or medians and interquartile ranges. The normality of the data was evaluated based on skewness and kurtosis values. The associations between continuous variables were tested by utilizing the Pearson correlation test. Binary logistical regression analysis was performed to identify predictors of severe nicotine dependence. A statistically significant p-value was set at 0.05.

A post-hoc power analysis was conducted for the Pearson correlation test of FNDT and ASI-3 ($r = 0.297$, $p = 0.009$, $n = 76$), yielding an estimated statistical power of 72.4% ($\alpha = 0.05$, two-tailed). That indicates a moderate probability of correctly detecting the observed effect size.

3. Results

Among the participants, 63.2% were female (n=48), and 36.8% were male (n=28). The mean age of the participants was 50.28 ± 12.37 years. Most participants were married (80.3%, n=61). Regarding employment status, 23.7% were retired, 36.8% were employed full-time, and 28.9% were unpaid domestic workers, also known as homemakers. The sociodemographic characteristics of the participants are presented in Table 1.

Table 1. Sociodemographic characteristics of the participants (n=76)

		Mean	Standard deviation
Age		50.28	12.37
		Frequency (n)	Percentage (%)
Sex	Female	48	63.2
	Male	28	36.8
Civil status	Single	15	19.7
	Married	61	80.3
Employment	Full-time	28	36.8
	Part-time	1	1.3
	Retired	18	23.7
	Unpaid domestic worker	22	28.9
	Unemployed	7	9.2
Education	Primary school	45	44.1
	Secondary school	11	10.8
	High school	23	22.5
	Graduate or post-graduate	23	22.5

3.1. Smoking Characteristics

The daily cigarette consumption was as follows: 42.1% smoked 10 or fewer cigarettes per day (n=32), 46.1% smoked 11 to 20 cigarettes (n=35), 10.5% smoked 21 to 30 cigarettes (n=8), and 1.3% smoked more than 30 cigarettes (n=1). The mean duration of smoking was 24.65 ± 13.09 years. Table 2 summarizes the severity of the nicotine dependence. Based on the FNDT scores, ≥6 points reflecting severe nicotine dependence; 25% of the participants (n = 19) met the criteria for severe dependence (See Table 2).

Table 2. Nicotine dependence levels of the participants based on FNDT scores

	Frequency (n)	**Percent (%)**
Very low dependence	32	42.1
Low dependence	16	21.1
Moderate dependence	9	11.8
High dependence	11	14.5
Very high dependence	8	10.5

3.2. Pain Characteristics

Table 3 demonstrates the pain characteristics of the patients.

Table 3. Pain characteristics of the patients (n=76)

		Frequency (n)	Percentage (%)
Pain localization*	Lumbar	42	55.26
	Extremities	8	10.53
	Hip	8	10.53
	Other	8	10.53
	Shoulder	7	9.21
	Neck	7	9.21
	Head	4	5.26
Treatment*	Surgical	51	67.1
	Medical	43	56.6
		Median	Q1-Q3
Pain duration (months)		60	24- 120
		Mean	Standard deviation
Pain intensity over the past week		7.18	± 2.73
Discomfort due to pain		7.82	± 2.25

**: Some patients had more than one.*

3.3. Evaluation of Measurements

Based on the HADS cut-off scores, 34.2% of patients reported anxiety (n=26), and 56.6% reported depression (n=43). Among the participants, 25% (n=19) had Fagerström Nicotine Dependence Test (FNDT) scores ≥6, indicating severe dependency (39). The mean values and standard deviations are presented in Table 3.

Table 4. Mean values and standard deviations of the scales utilized (n=76)

		Mean	Standard deviation
Hospital Anxiety Depression Scale	Anxiety	8.57	5.34
	Depression	8.17	3.87
Anxiety Sensitivity Index-3	Total	19.71	15.80
Distress Tolerance Scale	Total	47.83	12.65
Fagerström Nicotine Dependence Test		3.63	2.85

Spearman correlation analysis was used to examine the relationships between variables. There was a significant positive correlation between FNDT scores and ASI-3 total scores (r=0.297, *p=0.009*), indicating that higher anxiety sensitivity is associated with greater nicotine dependence. FNDT scores were also positively and significantly correlated with both HADS-Anxiety (r=0.284, *p=0.013*) and HADS-Depression scores (r=0.262, *p*=0.022), indicating that higher levels of anxiety and depression symptoms are associated with increased nicotine dependence scores. Additionally, a positive correlation was found between FNDT scores and pain intensity over the past week (r=0.287, *p*=0.012), suggesting that increased pain severity is related to higher nicotine dependence. Relevant results are presented in Table 5.

Table 5. Correlation analysis of the study variables

Measures	**(1)**	**(2)**	**(3)**	**(4)**	**(5)**	**(6)**
FNDT (1)	-					
DTS (2)	-.191	-				
ASI-3 (3)	.297**	-.636**	-			
HADS-Anxiety (4)	.284*	-.388**	.552**	-		
HADS-Depression (5)	.262*	-.288*	.484**	.543**	-	
Pain intensity over the past week (6)	.287*	-.264*	.341**	.399**	.419**	-

***: Correlation is significant at the 0.01 level (2-tailed)*

**: Correlation is significant at the 0.05 level (2-tailed)*

FNDT: Fagerström Nicotine Dependence Test

DTS: Distress Tolerance Scale

ASI-3: Anxiety Sensitivity Index-3

HADS: Hospital Anxiety Depression Scale

3.4. Predictors of Severe Nicotine Dependence

Univariate binary logistic regression was performed to find the predictors of severe nicotine dependence (See Table 6). Age and sex did not show a statistically significant prediction.

The anxiety subscale scores of the HADS (B=0.118, p=0.023) significantly predicted severe nicotine dependence. According to the univariate binary logistic regression analysis, a 1-point increase in the anxiety subscale increased the probability of severe nicotine dependence 1.125 times. Anxiety sensitivity was one of the predictors; the total scores of the ASI-3 (B=0.038, p=0.025) significantly predicted severe nicotine dependence. Lastly, pain intensity over the past week (B=0.286, p=0.029) was associated with an increased probability of severe nicotine dependence. Specifically, each 1-point increase in VAS was related to a 1.331 times higher probability of severe nicotine dependence.

Table 6. Predictors of Severe Nicotine Dependence (n=76)

Predictor	B	p	Exp(B)	95% CI	
				Lower	Upper
Anxiety- HADS	0.118	0.023*	1.125	1.016	1.245
Depression- HADS	0.122	0.082	1.130	0.984	1.298
Anxiety Sensitivity Index	0.038	0.025*	1.038	1.005	1.073
VAS- Last week	0.286	0.029*	1.331	1.030	1.720

**Statistically significant predictor of severe nicotine dependence ($p<0.05$)*

4. Discussion

The present study focused on patients with chronic pain to identify mental health-related predictive factors of severe nicotine dependence (FNDT scores ≥6). One key finding was high psychological distress among the participants: 34.2% reported anxiety, and 56.6% reported depression, based on psychometric assessments. Anxiety symptoms, anxiety sensitivity, and the pain intensity reported over the past week were found to predict severe nicotine dependence risk among patients with chronic pain.

The predominance of women in the sample and the mean age being over 50 are consistent with the literature, indicating that the prevalence of chronic pain is higher among women and older age groups (42).

It is widely recognized that the rate of comorbid chronic conditions, both mental and physical, is elevated in patients with chronic pain (43). As previously mentioned, anxiety disorders and depression, in particular, are more prevalent among adults suffering from chronic pain (44). In our study, 34.2% of participants reported anxiety, and 56.6% reported depression, based on the scales administered to participants. The relationship between depression, anxiety, and chronic pain is clinically significant, as these mental health conditions are associated with worse outcomes in individuals with chronic pain (45).

The strong association between depression and chronic pain is well established, yet the exact prevalence of this comorbidity remains unclear. Epidemiological studies on chronic pain and depression report that depression affects 20–50% of individuals with chronic pain (43, 46). Recent findings further support this link, with 42.4% of individuals with chronic pain reporting mild, moderate, or severe depressive symptoms (44). In the present study, 56.6% of participants reported depression, consistent with previous findings. Given the common overlap between chronic pain and depression, as well as the adverse effects of depression on pain-related disability (47), it is important to emphasize the need to treat depression in this population.

The link between smoking and depression is also well-documented, with estimates indicating that 50–60% of individuals with major depression experience nicotine dependence, compared to approximately 25% in the general population (48). As previously noted, individuals with chronic pain report higher rates of both depressive symptoms and smoking compared to the general population. This overlap suggests a potential relationship between depression and smoking within this group. In this context, depression may serve as a predictor of nicotine dependence in chronic pain patients who smoke. However, a review of the literature reveals that data on this relationship remain limited. In our study, depressive symptoms did not predict severe nicotine dependence risk in patients with chronic pain. This finding may be attributed to certain limitations of the study, including its single-center design, small sample size, and the fact that depression was self-reported rather than assessed through clinical interviews with a physician.

In the context of chronic pain and anxiety comorbidity, numerous studies have demonstrated that individuals with chronic low back pain exhibit a higher prevalence of anxiety disorders compared to the general population, with rates ranging from 19% to 31% (49, 50). In a recent nationally representative study in the United States, 43.6% of respondents with chronic pain reported elevated levels of anxiety (44). In our study, symptoms of anxiety were reported by 34.2% of participants.

Individuals with anxiety disorders tend to smoke at higher rates, consume more cigarettes per smoker, and quit smoking at lower rates compared to those without anxiety disorders (51). While smoking prevalence is elevated among individuals with anxiety disorders, the evidence regarding nicotine

dependence remains inconsistent. In a systematic review of population-based epidemiological studies, Moylan et al. (2012) found that certain baseline anxiety disorders serve as risk factors for the initiation of smoking and nicotine dependence (52). However, the literature provides more substantial evidence for the relationship between anxiety and smoking rather than nicotine dependence.

When examining the role of anxiety in smoking dependence among chronic pain patients, Ditre et al. (2014) highlighted the influence of pain-related anxiety (53). They suggested that smokers with comorbid chronic pain may be at heightened risk of sustaining or worsening their nicotine dependence, possibly due to individual variations in pain-related anxiety. Another study involving electronic cigarette users found that pain intensity was positively associated with past failed cessations and negative abstinence expectancies among participants with high levels of pain-related anxiety, but not among those with moderate or low levels (54). Although pain-related anxiety was not measured in our study, this concept may be particularly relevant for patients hospitalized for pain management. In this regard, specifying anxiety symptoms in a domain-specific manner among patients hospitalized due to pain may be important for future research. In the present study, symptoms of anxiety were identified as a predictor of severe nicotine dependence risk in patients with chronic pain. This finding highlights the potential role of emotional distress in maintaining or exacerbating nicotine use in this population. Individuals with heightened anxiety levels may engage in smoking as a maladaptive coping strategy to reduce psychological discomfort (55).

As mentioned earlier, anxiety sensitivity is simply the fear of anxiety symptoms (16). AS has been linked to smoking dependence and persistence (18, 56). In this regard, Zvolensky et al. (2019a) reported that, based on their study using the Fagerström Nicotine Dependence Test, AS was significantly related to the severity of nicotine dependence among Latinx smokers and that the physical dimension of AS also showed a significant association with cigarette dependence (18). A recent study showed that anxiety was associated with tobacco dependence in individuals highly anxiety sensitive, but not in those with lower levels of anxiety sensitivity (57). This outcome indicates that the interconnection between anxiety and anxiety sensitivity is important for a better understanding of tobacco dependence. In terms of cessation, smokers with high levels of AS tend to experience more difficulties during the quitting process (18). The literature also notes more intense withdrawal symptoms in these individuals during the early phases of quitting (58). This finding, when considered alongside the study of Zvolensky et al. (2019a), which emphasized the impact of the physical subdimension of AS on dependence, may help explain the underlying mechanism (18).

Research examining the relationship between AS and nicotine dependence among chronic pain patients is limited. One important study by Zvolensky et al. (2020) examined the role of anxiety sensitivity concerning pain intensity among chronic pain patients who smoke (12). They stated that the ASI-3 total score was significantly positively associated with smoking problems (measured by the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) tobacco problems score) among chronic pain patients. Another important finding was the significant indirect effect of pain intensity on smoking problems through AS. This finding suggests that individuals with higher pain intensity may develop smoking-related problems more strongly if they also have high AS. From this point of view, targeting AS could help in reducing the impact of pain on smoking behaviors. In the present study, AS and higher pain intensity over the past week positively predicted severe nicotine dependence risk in patients with chronic pain. In this respect, our findings are consistent with the existing literature. Furthermore, understanding the interconnected relationship between anxiety sensitivity, pain intensity, and severe nicotine dependence seems important in order to better support this patient group.

Distress tolerance (DT) is simply the capacity to endure distress, as previously noted. Individuals with low levels of DT are thought to be more prone to addictive behavior, such as smoking. Previous research has demonstrated that low DT is linked to a higher risk of smoking maintenance, greater nicotine dependence, and complications of cessation (59, 60). More recently, Niezabitowska et al. (2022) also emphasized that individuals with low DT are especially likely to develop nicotine dependence (28). Schlam et al. (2020) stated that higher DT was associated with higher quitting success and predicted abstinence over a year after quitting (61). Contrary to the findings mentioned above, a systematic review by Veilleux (2019) reported inconsistent evidence on the relationship between distress tolerance and smoking (62). The review also noted

that lower DT does not appear to be associated with higher smoking frequency or longer smoking duration. Furthermore, treatments targeting DT show promise; however, additional research is needed to gain a better understanding of this relationship.

Studies investigating the relationship between pain, smoking dependence, and DT are limited. An important study on this topic found that smokers who experienced pain in the past month had lower scores on the distress tolerance test compared to those without pain (63). Based on this finding, DT among smokers suffering from pain may be one mechanism by which pain contributes to the continuation of tobacco use. In the present study, DT did not predict severe nicotine dependence among chronic pain patients. When the literature is collectively evaluated, although data on the relationship between DT and nicotine dependence show variability, we would have expected DT to be a predictor of severe nicotine dependence in patients with chronic pain. This outcome may be related to several limitations of the study: a small sample size, its single-center design, and the focus on severe nicotine dependence (FNDT score ≥6) rather than nicotine dependence in general. Nonetheless, our findings may contribute to the diverse literature on this topic.

Chronic pain is associated with nicotine dependence, as mentioned earlier. In the coexistence of chronic pain and nicotine dependence, pain intensity appears to play a significant role as well. Bakhshaie et al. (2016) found that smoking severity variables—such as years of daily smoking, current cigarettes per day, cigarettes per day during the heaviest lifetime smoking period, and current nicotine dependence levels—were significantly linked to higher pain intensity (64). Similarly, in the present study, higher pain intensity reported over the past week was found to predict the risk of severe nicotine dependence. Several mechanisms may underlie this relationship. One possibility is the reinforcement of the conditioned use of nicotine through its acute analgesic, arousing, and mildly euphoric effects (65). Besides increasing pain thresholds and tolerance to painful stimuli, the effects of nicotine have been shown (66). Building on this, nicotine use may serve as a coping strategy for patients with higher pain intensity. However, this behavior may reinforce dependence in the long term and perpetuate the pain-nicotine cycle. From this point of view, pain can be considered not only a physical symptom but also a factor associated with addictive behavior. When the literature is examined from this perspective, Ditre et al. (2011) suggest that nicotine use may be adopted as a coping mechanism for pain, a perspective further supported by Zale et al. (2016) (67, 68). Our current finding supports this assumption. Mechanisms stated below may help explain the increased prevalence of smoking and nicotine dependence among individuals with chronic pain, but evidence suggests a bidirectional interaction. According to that, pain increases smoking, and smoking, in turn, increases pain (10). It is not entirely evident how chronic tobacco use contributes to increased pain. In this manner, a recent study showed that chronic exposure to nicotine can induce hypersensitivity to pain by activating dopaminergic projections to the anterior cingulate cortex (7).

Several limitations of the present study should be acknowledged. First, the cross-sectional design restricts the ability to infer causal relationships between anxiety, anxiety sensitivity, pain intensity, and severe nicotine dependence. As a result, the findings only reflect associations rather than directional effects. To address this limitation, future research should have longitudinal study designs. Second, the study was conducted at a single center, which limits the generalizability of the findings to broader populations. Third, the findings rely on self-reported psychometric scales, and the diagnosis of depression and anxiety was not validated through clinical interviews conducted by a mental health professional. Finally, the analyses were not specified for subgroups of chronic pain but were instead based on the general condition of experiencing any chronic pain.

The strengths of this study include its contribution to the limited literature on this topic and its emphasis on smoking and mental health among patients with chronic pain.

5. Conclusion

The present study focused on patients with chronic pain to identify mental health–related predictors of severe nicotine dependence (FNDT scores ≥6). One key finding was the high level of psychological distress among participants: 34.2% reported anxiety symptoms and 56.6% reported depressive symptoms, based on psychometric assessments. Anxiety symptoms, higher anxiety sensitivity scores, and greater pain intensity experienced in the past week were found to predict the risk of severe nicotine dependence among patients with chronic pain.

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Case Report
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Cases of Anti-NMDAR Encephalitis Caused by HSV Encephalitis: Two Different Clinical Courses and Prognosis

HSV Ensefalitinin Neden Olduğu Anti-NMDAR Ensefaliti Olguları: İki Farklı Klinik Seyir ve Prognoz

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Abstract: The recurrence of symptoms or the emergence of new clinical findings following herpes simplex virus encephalitis (HSVE) can result due to the relapse of the same viral agent, development of a new infectious encephalitis or autoimmune encephalitis. Differences in the presentation, clinical course, and electrophysiological findings of cases may be associated with variations in prognosis. In the first case of anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDARE) following HSVE that we presented here, the patient exhibited epileptic seizures, and electroencephalography (EEG) revealed lateralized periodic discharges (LPDs) with plus modifiers. During the follow-up, status epilepticus developed and the patient did not respond to treatment and died. In contrast, the second case of anti-NMDARE following HSVE presented with psychiatric symptoms. EEG revealed LPDs in the form of a monomorphic blunt delta pattern. This patient responded rapidly to first-line treatments and achieved recovery with mild cognitive impairment. The pathogenic processes underlying the differences in clinical course and outcomes remain unclear, emphasizing the need for further research. Early initiation of immunotherapy is critical in patients with poor prognostic indicators after excluding HSVE relapse via polymerase chain reaction testing of cerebrospinal fluid.

Keywords: Herpes simplex virüs encephalitis; autoimmune encephalitis; lateralized periodic discharges; anti-NMDAR encephalitis

Özet: Herpes simpleks virüs ensefaliti (HSVE) sonrası semptomların tekrarlaması veya yeni klinik bulguların ortaya çıkması, aynı viral etkenin nüksü, yeni bir enfeksiyöz ensefalit ya da otoimmün ensefalit gelişimine bağlı olabilir. Olguların başvuru semptomlarındaki, klinik seyirlerindeki ve elektrofizyolojik bulgularındaki farklılıklar, prognozlarındaki değişikliklerle ilişkili olabilir. Burada sunduğumuz HSVE sonrası gelişen anti-N-metil-D-aspartat reseptör ensefaliti (anti-NMDARE) tanılı ilk olgu, epileptik nöbetler ile başvurmuş ve elektroensefalografisinde (EEG) artı modifikatörleri olan lateralize periyodik deşarjlar (LPD) tespit edilmiştir. Takibinde status epileptikus gelişmiş, hasta tedavilere yanıt vermeyerek eksitus olmuştur. Buna karşılık, HSVE sonrası gelişen ikinci anti-NMDARE olgusu psikiyatrik semptomlarla başvurmuş, EEG'sinde monomorfik künt delta paterninde LPD'ler gözlemlenmiştir. Bu hasta birinci basamak tedavilere hızla yanıt vermiş ve hafif bilişsel bozukluk ile iyileşme sağlamıştır. Klinik seyir ve sonuçlardaki farklılıkların altında yatan patogenetik süreçler henüz net değildir ve daha fazla araştırmaya ihtiyaç duyulmaktadır. Beyin omurilik sıvısında polimeraz zincir reaksiyonu testi ile HSVE nüksü dışlandıktan sonra, kötü prognostik göstergelere sahip hastalarda erken immünoterapinin başlatılması kritik öneme sahiptir.

Anahtar Kelimeler: Herpes simpleks virüs ensefaliti; otoimmün ensefalit; lateralize periyodik deşarjlar; anti-NMDAR ensefaliti

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1. Introduction

Anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDARE) is an autoimmune encephalitis (AE) characterized by an acute or subacute onset of prodromal symptoms such as headache, nausea, vomiting, and fever, followed by psychiatric manifestations, seizures, memory impairment, speech disturbances, central hypoventilation, altered consciousness, autonomic dysfunction, and movement disorders primarily involving the face and oral region, but also affecting the limbs and trunk [1,2]. While predominantly affecting children and young women, it can also present in males and older individuals, with age-related variations in presenting symptoms. In middle-aged and older adults, initial symptoms often include altered consciousness, memory problems, paranoia, grandiose delusions, hallucinations, mania, anxiety, and insomnia. In contrast, children and young adults typically present with neurological symptoms such as movement disorders, including choreoathetosis, and epileptic seizures [1-3].

The clinical manifestation is attributed to antibodies targeting heteromers of the NR1 and NR2 subunits of the NMDA receptor [1,2]. Since it frequently has a paraneoplastic etiology, malignancy screening is important following diagnosis. Particularly in young women over the age of 18, up to 45% of cases are associated with bilateral or unilateral ovarian teratomas. However, AEs can also be triggered by infections caused by viruses, parasites, bacteria, or even Borrelia [1-4]. Among these, herpes simplex virus (HSV) is a common trigger [4]. It has been reported that 7–25% of patients develop NMDAR antibodies following HSV encephalitis (HSVE), typically within the first three months. The time to development of anti-NMDARE after HSVE is longer in adults but shorter in children [5].

Here, we aim to present two cases diagnosed with anti-NMDARE following HSVE, highlighting their different presentations, clinical courses, and prognoses in the context of the current literature.

2. Case Report

Case 1

A 37-year-old male admitted to the emergency department with fever, nausea, vomiting, speech disturbances, and epileptic seizures characterized by loss of awareness and convulsions in the right arm and leg, which had begun three weeks prior. He had no history of chronic illnesses or medication use. Neurological examination revealed the patient was conscious and globally aphasic but intact muscle strength and no evidence of meningeal irritation. Cranial magnetic resonance imaging (MRI) demonstrated an asymmetric hyperintense lesion in the left medial temporal lobe, hippocampal region, and insular cortex on T2-weighted sequences. Electroencephalography (EEG) showed lateralized periodic discharges with sharp and spike-wave activities of high amplitude in the left temporoparietal region (Figure 1). Cerebrospinal fluid (CSF) analysis confirmed HSV positivity. The patient was diagnosed with HSVE and started on acyclovir (2250 mg/day) for 21 days, after which his neurological symptoms fully resolved. On the 28th day of follow-up, the patient experienced a recurrence of fever and developed altered consciousness. Neurological examination revealed somnolence; the patient opened his eyes in response to verbal stimuli but could not establish cooperation or orientation to time and place, though he localized painful stimuli. Neuroimaging showed slight progression of the previously noted lesion. Repeated CSF analysis revealed 260 leukocytes/mm³ and elevated protein (136 mg/dL). A repeated viral encephalitis panel was negative. Autoimmune and paraneoplastic antibody panel was requested. Repeated EEG findings were consistent with nonconvulsive status epilepticus (NCSE), as the observed patterns were suppressed with diazepam and did not exhibit clinical seizures (Figure 2).

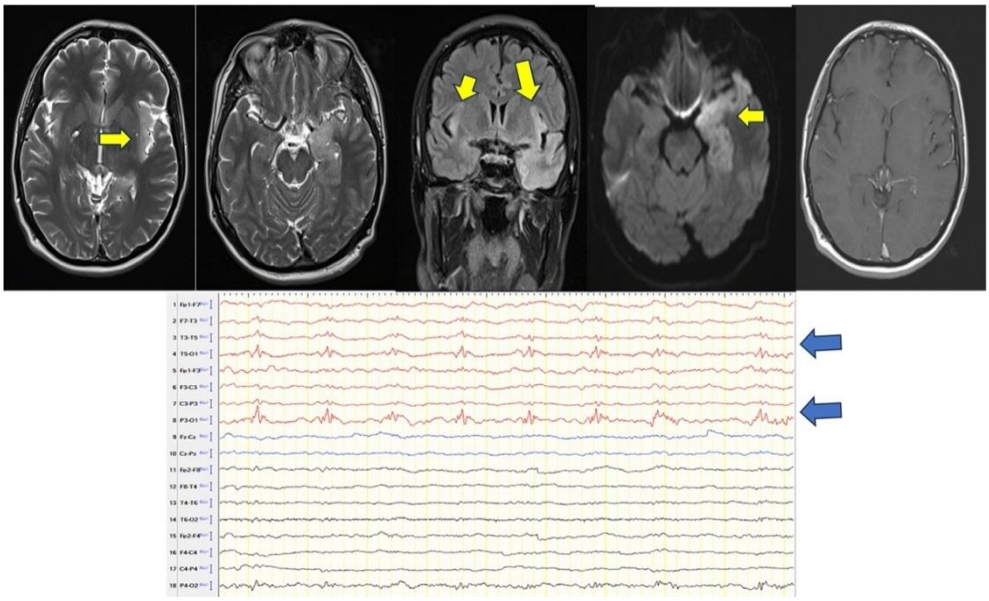

Figure 1. Cranial MRI and EEG examinations of the first case at the time of presentation. MRI demonstrated an asymmetric hyperintense lesion in the left medial temporal lobe, hippocampal region, and insular cortex (yellow arrows). EEG showed lateralized periodic discharges with sharp and spike-wave activities of high amplitude in the left temporoparietal region (blue arrows).

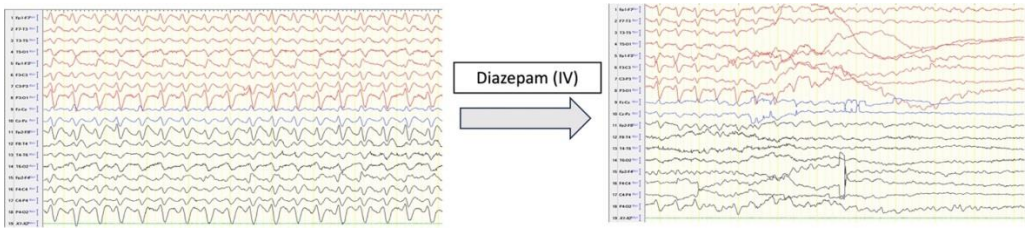

Figure 2. EEG findings were compatible with NCSE in the follow-up of the first case. Epileptiform discharges supressed after diazepam.

Due to lack of consciousness and continued EEG findings levetiracetam (3000 mg/day), phenytoin (300 mg/day), and lacosamide (400 mg/day) were started respectively. He was admitted to the neurology intensive care unit (ICU) for monitoring. Subsequent EEG revealed suppression of epileptic activity in the right hemisphere, with decreased amplitude of discharges in the left hemisphere, although prominent discharges persisted in the frontotemporal regions. His CSF was found to be positive for anti-NMDAR antibodies and we diagnosed his as having anti-NMDARE. The patient received 1000 mg/day of intravenous methylprednisolone (IVMP) for 10 days. Due to persistent altered consciousness, the patient was treated with intravenous immunoglobulin (IVIG) at 0.4 g/kg/day for five days. Malignancy screening was unremarkable. On the 40th day of follow-up, the patient's clinical condition deteriorated, with worsening consciousness. A new EEG revealed generalized slow-wave activity in the delta frequency range without epileptic discharges. The patient underwent seven cycles of plasmapheresis and than was treated with rituximab. Despite these interventions, focal seizures accompanied by oral automatisms recurred. EEG showed a re-emergence of periodic discharges and interictal fast rhythmic activity (plus modifiers). The patient was intubated and managed with midazolam, followed by thiopental infusion. Burst suppression patterns were

observed on EEG. The patient's condition continued to detoriate and sepsis developed during follow-up, and he died on the 67th day of hospitalization.

Case 2

A 35-year-old female admitted to our clinic with nonsensical speech, somnolence, paranoid thoughts of harmed by her relatives, inability to recognize her husband and children, and suspicious behaviors. Her medical history revealed that she had been admitted to another hospital four weeks ago due to altered consciousness and seizures. At that time, her EEG showed high-amplitude sharp-wave discharges in the left temporal regions, and cranial MRI revealed an edematous lesion involving the cortex and subcortical areas of the left temporofrontal lobe, including the insular cortex and hippocampus, without contrast enhancement. CSF analysis confirmed HSVE, for which she was treated with 21 days of acyclovir (750 mg/day) and levetiracetam (1000 mg/day). She was discharged with normal EEG findings and full resolution of her neurological symptoms. However, psychotic symptoms emerged eight days after discharge, the patient was taken to a psychiatry outpatient clinic by her family, where antipsychotic treatment was recommended. Due to her persistent symptoms, she admitted to our clinic. In our neurological examination she was conscious, sensorily aphasic, and exhibited full muscle strength but had persecutory delusions and referential ideation. Cranial MRI showed that the lesion had developed mild hemorrhagic characteristics and exhibited contrast enhancement. EEG demonstrated lateralized periodic discharges with a monomorphic blunt delta wave pattern in the left temporoparietal region (Figure 3). CSF analysis revealed elevated protein levels (71 mg/dL), the viral encephalitis panel was negative and anti-NMDAR antibodies was found to be positive therefore the patient was diagnosed as anti-NMDARE. Levetiracetam was discontinued and valproic acid (1000 mg/day) and olanzapine (5 mg/day) were started. Her agitation and persecutory delusions subsequently diminished. She received 1000 mg/day of IVMP for five days. Due to incomplete resolution of her clinical symptoms, she was additionally treated with IVIG at 0.4 g/kg/day for five days. Malignancy screening revealed no abnormalities. The patient's psychotic symptoms and EEG findings were resolved, and she was discharged. At her follow-up one month later, she demonstrated full recovery except for mild cognitive impairment.

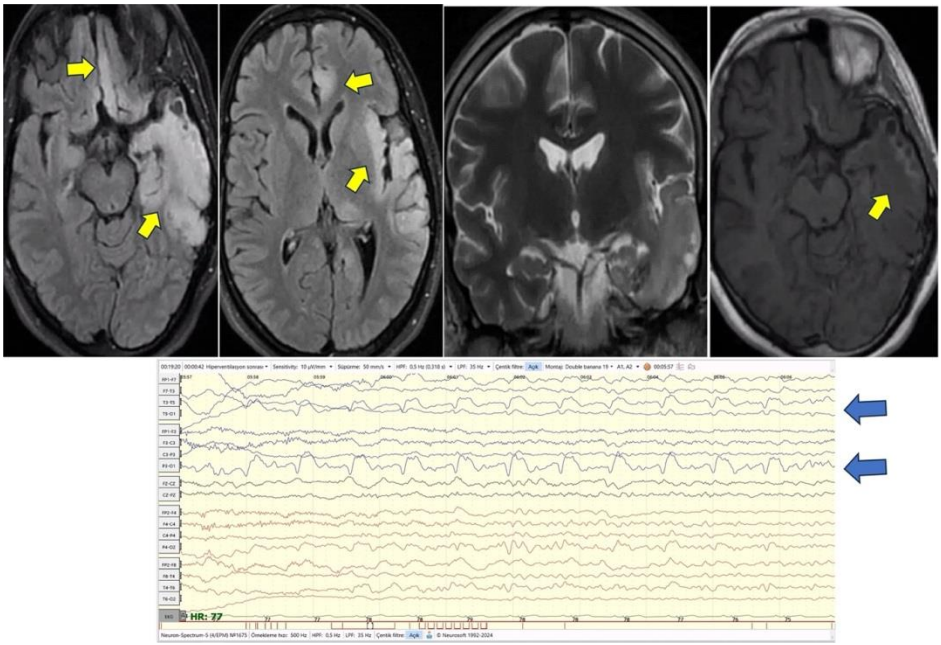

Figure 3. Cranial MRI and EEG examination of the second case at 6 weeks after HSVE. MRI showed that the lesion had developed mild hemorrhagic characteristics and exhibited contrast enhancement (yellow arrows). EEG demonstrated lateralized periodic discharges with a monomorphic blunt delta pattern in the left temporoparietal region (blue arrows).

3. Discussion

Despite the similarity in age between two cases, their clinical courses and outcomes were strikingly different. While the first patient presenting with altered consciousness and refractory epileptic seizures, did not respond to treatment and had a fatal outcome, the second patient, whom characterized by psychiatric symptoms, demonstrated a rapid recovery. These disparities in presentation, clinical progression, and therapeutic response may reflect the influence of distinct antibody profiles and underlying pathogenic mechanisms.

The pathogenesis of anti-NMDARE following HSVE remains unclear. Potential mechanisms include molecular mimicry, neuronal damage leading to expose the NMDA receptors to the immune system, altered NMDA expression post-HSV infection, immune system modulation by HSV, and misrecognition of NMDA receptors [6]. In a retrospective cohort study conducted in 2012 by Prüss et al. [7] NMDAR antibodies detected approximately 30% of HSVE patients. Leypoldt et al. [8] first reported anti-NMDARE following HSVE in an adult after it was identified in a pediatric patient in 2013.

Symptom recurrence or emergencing of new clinical findings after HSVE often complicate the diagnosis. The presence of new hemorrhagic or necrotic lesions on neuroimaging, detection of HSV deoxyribonucleic acid (DNA) by polymerase chain reaction in CSF, and response to acyclovir treatment may help to suggest HSVE relapse. In contrast, stable MRI findings or lesion enlargement as observed in our first case, negative viral encephalitis panel, and unresponsiveness to antiviral treatment indicates AE [9]. Contrast enhancement of lesions may occur in HSVE due to blood-brain barrier disruption [10]. In the second case, the emergence of mild contrast enhancement and hemorrhagic features on repeated MRI, were suggested that HSE relapse. However, the detection of anti-NMDAR antibodies and the absence of HSV DNA in CSF supported the diagnosis of anti-NMDARE in both cases.

Autoimmune encephalitis presents with diverse clinical manifestations, which are largely dependent on the different neuronal antigens and specific brain regions targeted by the autoimmune process [11]. In children and young adults, anti-NMDARE following HSVE commonly manifests as movement disorders and seizures, while adult patients frequently present with psychiatric symptoms and cognitive dysfunction. Due to the nature of initial symptoms, up to 70–77% of adult female patients are misdiagnosed with psychiatric disorders after being evaluated by psychiatrists [1,2]. Similarly, our second case presented with psychotic symptoms and was misdiagnosed with a psychiatric disorder.

Seizures occur nearly half of anti-NMDARE cases, either as an initial symptom or during the disease course. Generalized tonic-clonic seizures are most common, but focal seizures with or without impaired awareness may also occur [12,13] As in our first case, SE has been reported to be significantly associated with morbidity and mortality in anti-NMDARE. In a study of 109 cases by Liu X et al. [13] seizures occurred in 80.7% during the acute phase, with 25% experiencing non-refractory SE, 14.8% refractory SE, and 10.2% super-refractory SE. Certain EEG features, such as lateralized periodic discharges (LPDs) expecially with plus modifers (LPDs with rhythmic delta activity, fast activity, superimposed rapid sharp, spike waves) are linked to higher seizure and mortality risk. Both of our cases exhibited LPDs on their EEGs. Literature indicates that 58–100% of patients with LPDs experience clinical seizures [14]. LPDs of our first case was exhibiting plus modifiers, he presented with seizures and progressed to SE with a fatal outcome. In contrast, the second case, whom with monomorphic blunt delta patterned LPDs, did not experience seizures during follow-up and recovered fully except for mild cognitive symptoms.

Anti-NMDARE following HSVE typically responds well to immunotherapy in children older than four years [2]. Except HSVE, corticosteroids are the first-line treatment for autoimmune encephalitis. The treatment of post-HSVE anti-NMDARE remains debated. The literature suggests combining corticosteroids with antiviral therapy. IVIG is another acute-phase treatment, often administered as 0.4 g/kg/day for five days, with a repeat course if symptoms persist. Plasma exchange may also be used. Refractory cases may also require cyclophosphamide or rituximab [1-3]. All treatment steps were implemented in our first case but no success was achieved, whereas the

second case improved with corticosteroids and IVIG.

The prognosis of anti-NMDARE following HSVE is less satisfactory than isolated AE. Prolonged ICU stays, recurrent seizures, and development of SE significantly increase morbidity and mortality. In long-term follow-up may reveal persistent seizures or cognitive impairments [2,3,7]. Our first patient, who developed refractory seizures and SE, died during ICU follow-up, while the second patient achieved full recovery except for mild cognitive deficits.

It is essential to recognize that anti-NMDARE can occur following HSVE. The prognosis of patients varies significantly depending on clinical presentation, course, electrophysiological features, and treatment response. Future studies which will investigate the clinical significance and mechanisms of intracellular and neuronal surface antibody production may provide further insights into these differences.

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Case Report
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In A Patient with Parathyroid Adenoma Who Has Wound Healing Problems: Endoscopic Gasless Trans-Axillary Parathyroidectomy

Yara Yeri İyileşme Sorunu Olan Paratiroid Adenomlu Hastada Endoskopik Gazsız Trans-Aksiller Paratiroidektomi

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Abstract: Primary hyperparathyroidism is a common endocrinological disease in the society. The disease can be detected symptomatically or non-symptomatically. The basic treatment of this disease is surgical excision of the adenoma. With the increase in imaging methods, localizations are determined more accurately. The fact that the patients are usually women and do not want incisions in the neck region has helped the development of new techniques such as moving the incisions to invisible areas (axillary region, under the breast) and leaving them inside the body (transoral approach). In our case, Endoscopic Gasless Trans-Axillary Parathyroidectomy, which moves the incision to the axilla, was preferred in a 55-year-old female patient with persistent scars due to previous surgeries.
Keywords: Hyperparathyroidism, Endoscopic, Axilla

Özet: Primer hiperparatriodizim toplumda sık görülen endokrinolojik bir hastalıktır. Hastalık semptomatik veya non-semptomatik tedadüfen saptanabilir. Bu hastalığın temel tedavisi cerrahi olarak adenomun ekzisyonudur. Görüntüleme yöntemlerinin artması ile lokalizasyonları daha doğru saptanmaktadır. Hastaların genellikle kadın olması ve boyun bölgesinde insizyon istememesi hastalarda insizyonların görünmeyen bölgelere taşınmasına (aksillar bölge, meme altı) ve vücut içinde bırakılması (transoral yaklaşım) gibi yeni tekniklerin geliştirilmesine yardımcı olmuştur.Olgumuz 55 yaşında geçirilmiş cerrahilere bağlı geçmeyen skarları olan kadın hastada insizyonu aksillaya taşıyan endoskopik gazsız trans-aksiller paratiroidektomi tercih edildi.

Anahtar Kelimeler: Hiperparatiroidizm, Endoskopik, Aksilla

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1. Introduction

Primary hyperparathyroidism (PHPT) is seen in the body with high calcium and increased parathyroid hormone levels at a rate of 28/100,000 (1). Patients may present with nephrolithiasis, bone resorption, peptic ulcer fractures, or may be detected as non-s in blood values. In 70-95% of cases, parathyroid hormone secretion is due to a parathyroid adenoma. However, the probability of multiple parathyroid adenomas is 15% and the probability of carcinoma is 1% (2,3). The current treatment and most effective method for PHPT treatment is surgery. Minimally invasive methods are replacing traditional methods. The fact that patients are women and do not want incisions in the neck area has helped new methods such as separating the incisions into invisible areas (axillary region, under the breast) and hiding them inside the body (transoral approach). In particular, surgeries performed without incisions in the neck, where wounds are healing, are current treatments. In our case, neck incision was not preferred by the patient due to keloid formation and bad scar development in the wound area due to old incisions. Since the patient's oral mucosa and teeth were not good, the surgery was planned as an endoscopic gasless trans-axillary approach.

2. Case Report

A 55-year-old female patient presented to us with an incisional hernia in the abdominal region. She was admitted to our service for detailed evaluation after the calcium value was found to be 12.4 (8.8-10.2) mg/dl in routine blood tests taken during preoperative preparation. Since the parathyroid hormone (pth) level was found to be 160 pg/dl (10-65 pg/dl), neck ultrasound (USG) and parathyroid scintigraphy were requested with suspicion of PHPT. The USG showed a hypoechoic solid nodule with internal vascularization in the left thyroid gland, approximately 12x8 mm in size. However, the distinction between thyroid nodule and parathyroid adenoma could not be clearly evaluated in the differential diagnosis. On scintigraphy, findings suggestive of parathyroid adenoma with low-level activity uptake in the inferior left thyroid lobe were detected (Figure 1). The patient was then consulted by the endocrinology department. After additional tests and evaluation, the patient was diagnosed with primary hyperparathyroidism and a surgical excision decision was made. No additional features were detected in the contrast-enhanced neck tomography taken due to the close organ proximity (Figure 1).

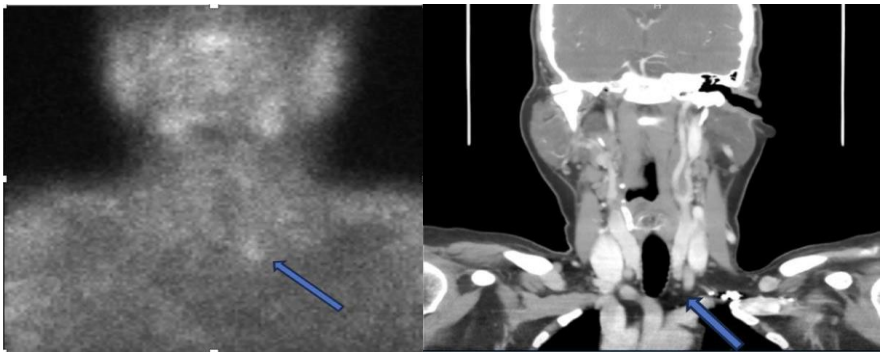


Figure 1. Left Parathyroid adenoma marked with blue arrow

(scintigraphy and computed tomography image)

Due to the known history of keloids and possible cosmetic problems in the neck area, the patient was planned to undergo endoscopic gasless transaxillary parathyroidectomy (Figure 2).

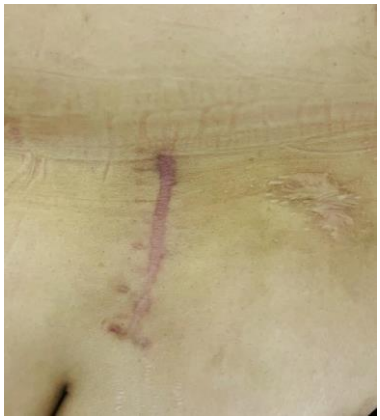


Figure 2. Old supra-umbilical incisions

After obtaining informed consent, the patient was taken to surgery. After general anesthesia, the patient was positioned in the supine position by placing an elevation on the left axillary region and the back of the neck. The neck was lateralized to the right sideat a 15-degree angle. Then, the probable parathyroid localization, the area where the flap would be shifted, and the sternal and clavicular notches of the sternocleoiomastoid (SCM) muscle were marked with a non-sterile pen (Figure 3).

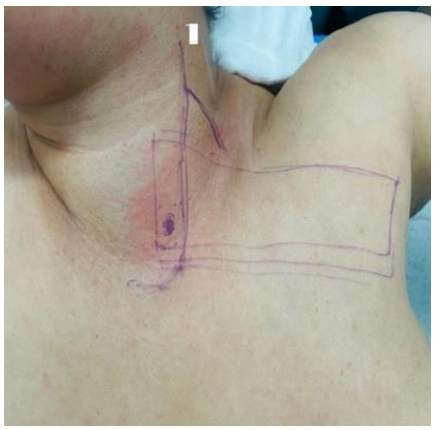


Figure 3. Surgical position, drawing of SCM muscle and dissection area

After sterile staining and draping, a 5 cm incision was made from the left anterior axillary line, through which the skin slit was passed, and a Farabeuf retractor was used to reach the fascia of the pectoralis major muscle. A subcutaneous flap was created from this region to between the two notches of the SCM muscle. Since there was no Kuppersmith retractor, a Thompson retractor was inserted. The liver retractor was used to elevate the subcutaneous tissue (Figure 4).

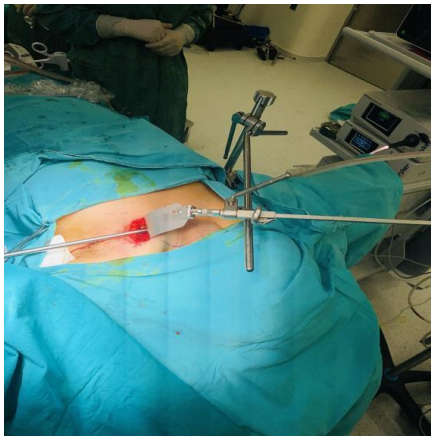
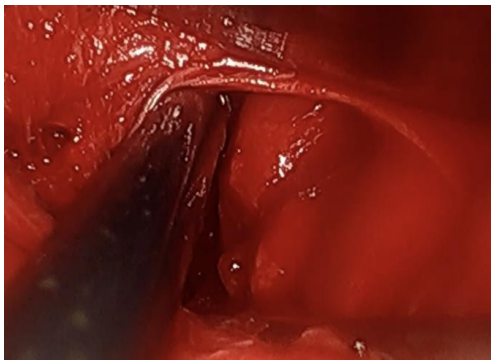


Figure 5. Placement of the retractor

The camera was inserted under the skin with the help of a trocar and the neck cavity was entered between the clavicular and sternal notches of the SCM muscle with the help of two holding tools. After reaching the thyroid lodge, the thyroid tissue and internal jugular vein were seen. During exploration, tissue that could be compatible with parathyroid adenoma adjacent to these structures was reached. Then, an attempt was made to reveal the laryngeal recurrence nerve. After the nerve was verified with nerve monitoring, the parathyroid adenoma was



grasped from above and removed (Figure 5).

Figure 5. PA Endoscopic image

Frozen examination was performed on the removed tissue and blood was sent for

intraoperative PTH measurement at 5 minutes after excision. Pathological frozen examination showed that the removed tissue was compatible with parathyroid adenoma. The intraoperative Pth value was measured as 30 pg/dl. Thereupon, a minivac drain was placed under the skin, the layers were closed appropriately and the operation was terminated. After the postoperative follow-ups were unremarkable and he tolerated oral intake, the patient was discharged with recovery on the 2nd postoperative day. The patient was called for a check-up on the 7th postoperative day and it was observed that the wound was unremarkable (Figure 6)

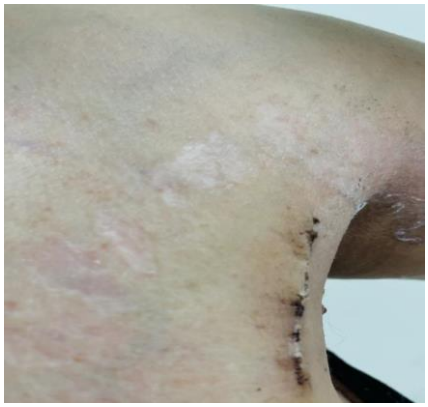


Figure 6. Postoperative 7th day wound site

3. Discussion

Today, minimally invasive approaches are increasingly being used in parathyroid surgery, as in many other diseases. The American Association of Endocrine Surgeons recommended the use of endoscopic procedures in patients with solitary parathyroid adenomas in a consensus report published in 2016 (1). The reasons for this are shown as small incisions, better cosmetic results, and faster return to work. However, being able to perform surgery with a minimally invasive approach depends on good preoperative imaging. In particular, neck ultrasonography and thyroid scintigraphy or 3D tomography performed by an experienced radiologist greatly increase the chance of adenoma excision with a minimally invasive approach, as the size and location of the lesion are well demonstrated (1-3).

In order to minimize cosmetic problems, many methods have been described for endoscopic parathyroidectomy, especially in China. The most common of these are Transoral endoscopic parathyroidectomy (TOEPVA) with a vestibular approach, gasless endoscopic parathyroidectomy with a transaxillary approach, and total endoscopic parathyroidectomy (EPA) with an areola approach. There is not enough information and studies on which method to choose in patients with parathyroid adenoma. However, in the study conducted by Makay Ö. et al. on 27 TOEPVA cases, the inclusion criteria were all patients with pHPT with a single adenoma, while the exclusion criteria were a historyof significant thyroiditis, previous neck surgery or neck radiation, lithium use, and the possibility of malignancy (7)

A possible complication of submental endoscopic parathyroidectomy is the transection of the marginal mandibular branch of the facial nerve or the mental nerve (8). In young women who undergo EPA, there are discussions about whether placement under the areola changes the structure of the breast tissue and causes loss of sensation at the edge of the areola. Although Zhan L. et al. showed in their study on 40 patients in 2024 that this did not cause any mammographic changes, the fact that the surgery is a new technique and long-term mammographic results have not yet been obtained is not reassuring (9). In addition, the use of this method in patients with a high risk of breast cancer is controversial.

Each method has its own advantages and limitations. For example, oral hygiene is very important in the TOEPVA method. These patients should use mouthwash for oral hygiene before surgery and the dentist should evaluate the patient's suitability in a multidisciplinary manner. If this issue is not taken into consideration, it can lead to repeated surgical drainage procedures (6). In our patient, we planned a gasless endoscopic parathyroidectomy with a trans-axillary approach due to oral problems.

Gasless transaxillary approaches were first tried in thyroid surgery in 2005 and were first performed in China in 2017 for parathyroidectomy (10). In a study comparing the classical method with the gasless endoscopic transaxillary approach, no significant difference was found in terms of bleeding amount, drainage procedures and hospital stay. The gasless endoscopic transaxillary approach was found to be cosmetically and psychologically significant

(10). An important advantage of the gasless technique is that gas insufflation does not cause possible complications such as subcutaneous emphysema, pneumothorax and pneumomediastinum. (11) The disadvantage of this method is the difficulties in contralateral dissections in patients with multiple adenomas. (12) Therefore, it is predicted to be more suitable for use in unilateral inferior parathyroid adenomas.

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Case Report
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Delayed Anastomotic Leakage After Bevacizumab Therapy in Rectal Cancer Patient: A Case Report

Rektal Kanserli Hastada Bevacizumab Tedavisi Sonrası Gecikmiş Anastomoz Kaçağı: Olgu Sunumu

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Abstract: Surgery, chemotherapy, and targeted agents play crucial roles in the treatment of colorectal cancer (CRC). Bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor used in metastatic CRC, has been associated with delayed wound healing, potentially increasing the risk of anastomotic leakage. In this case, a 71-year-old patient who underwent low anterior resection for rectal cancer developed delayed anastomotic leakage 26 months after surgery. Imaging revealed a presacral abscess and a collection communicating with the intestinal lumen, and surgical exploration confirmed anastomotic dehiscence. A diverting colostomy was performed, and the patient remained stable in the postoperative period. This case highlights that bevacizumab therapy can impact anastomotic integrity even in the late postoperative period, emphasizing the need for prolonged and careful follow-up in such patients.
Keywords: Colorectal cancer, anastomotic leak, bevacizumab

Özet: Kolorektal kanser (KRK) tedavisinde cerrahi, kemoterapi ve hedefe yönelik ajanlar önemli rol oynar. Bevacizumab, metastatik KRK'de kullanılan bir VEGF inhibitörüdür ancak yara iyileşmesini geciktirerek anastomoz kaçağı riskini artırabilir. Bu olguda, rektum kanseri nedeniyle düşük anterior rezeksiyon yapılan 71 yaşındaki bir hastada, ameliyattan 26 ay sonra gecikmiş anastomoz kaçağı gelişmiştir. Görüntülemelerde presakral apse ve bağırsak lümeni ile bağlantılı koleksiyon saptanmış, cerrahi eksplorasyonda anastomoz ayrışması görülmüştür. Hastaya saptırıcı kolostomi açılmış ve postoperatif dönemde stabil seyretmiştir. Bu vaka, bevacizumab tedavisinin geç dönemde bile anastomoz bütünlüğünü etkileyebileceğini göstermekte ve bu hastaların uzun süreli dikkatli takibinin gerekliliğini vurgulamaktadır.
Anahtar Kelimeler: Kolorektal kanser, anastomoz kaçağı, bevacizumab

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Author Contribution Yilmaz AS: conceptualization (lead), ınvestigation (lead), resources (lead), writing – original draft (lead); Ulfanov O: data curation (equal), methodology (lead), project administration (lead), writing – review & editing (lead); Yasar NF: ınvestigation (lead), methodology (supporting), software (equal), writing – original draft (supporting) All authors reviewed and approved the final version submitted for publication
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1. Introduction

Colorectal cancer (CRC) is the third most frequently diagnosed malignancy worldwide in both men and women. The rising incidence of colorectal malignancies remains a significant public health concern, as CRC continues to be a leading cause of cancer-related mortality globally (1). For localized disease, preoperative radiotherapy is recommended for stage II/III rectal cancers. However, in approximately 20% of cases, synchronous metastases are present at diagnosis, necessitating primary tumor resection followed by first-line chemotherapy. Moreover, even after curative surgical resection of the primary tumor, metastatic recurrence occurs in approximately 40% of cases, at which point systemic chemotherapy followed by possible surgical resection is advised (2).

Despite advancements in surgical techniques and perioperative rehabilitation, anastomotic leakage remains a rare but feared surgical complication with potentially catastrophic consequences for the patient (3). Anastomotic leakage is defined as a disruption of intestinal wall integrity at the colorectal or coloanal anastomotic site, leading to a pathological communication between the intraluminal and extraluminal compartments (4). The incidence of anastomotic leakage and dehiscence in colorectal surgery varies, reaching up to 35% in some cases. Factors such as surgical technique, bowel integrity, anastomotic tension, comorbid conditions, and the use of medications that impair healing significantly contribute to the risk of anastomotic leakage (5).

Over the past decade, survival rates for unresectable and recurrent CRC have improved significantly due to the development of cytotoxic agents such as fluorouracil (5-FU), irinotecan, and oxaliplatin, as well as molecularly targeted therapies, including VEGF and epidermal growth factor receptor (EGFR) inhibitors (6). Despite their promising benefits, these treatments require thorough investigation of their impact on postoperative complications, particularly anastomotic leakage after colectomy (7).

Bevacizumab has been reported to cause adverse events such as arterial thrombosis, bleeding, and gastrointestinal perforation. Additionally, limited studies have suggested that bevacizumab therapy increases the risk of anastomotic leakage in rectal cancer patients undergoing low anterior resection (8). Here, we present a case of delayed anastomotic leakage occurring approximately 26 months after low anterior resection in a rectal cancer patient.

2. Case Presentation

A 71-year-old male patient presented with complaints of abdominal distension, pain, constipation, and hematochezia. The patient had no known chronic illnesses, and laboratory tests revealed no abnormalities. To investigate the etiology, thoracic and abdominal computed tomography (CT) was performed, revealing circumferential, irregular, mass-like thickening of the rectal wall. Additionally, mesorectal fascia showed infiltration with fatty tissue stranding and pathologically enlarged lymph nodes, the largest measuring approximately 9 mm.

Colonoscopy identified a broad-based polypoid lesion in the cecum and an ulcerovegetative mass completely encircling the lumen at the 3 cm level of the rectum. Biopsies confirmed adenomatous changes with low-grade dysplasia in the cecal polyp and adenocarcinoma in the rectal lesion. Pelvic magnetic resonance imaging (MRI) showed a circumferential tumor affecting a 5-5.5 cm segment of the distal rectum, beginning approximately 1 cm from the anorectal angle. The tumor was protruding into the intraluminal space and extended into the perirectal fat tissue, particularly at the 2 to 6 o'clock position. The deepest invasion was measured at approximately 4 mm, classifying the lesion as T3. The patient was subsequently planned for neoadjuvant therapy, receiving 50.4 Gy (1.8 Gy x 28 fractions) of radiotherapy, followed by surgery.

After obtaining informed consent, the patient underwent low anterior resection, hand-sewn coloanal anastomosis at approximately 3 cm from the anal verge, using non-absorbable monofilament sutures, and ileocecal resection with ileocolonic anastomosis for the cecal lesion. Intraoperatively, the anastomotic site appeared well vascularized, with no evidence of tension or ischemia. A protective loop ileostomy was created proximal to the ileocolonic anastomosis. The patient had an uneventful postoperative course, tolerated oral intake, and was discharged in good condition. Final pathology confirmed a moderately differentiated adenocarcinoma, staged

as pT3N0, located below the peritoneal reflection, and the patient was referred to medical oncology for adjuvant treatment.

Follow-up imaging and colonoscopy revealed no abnormalities, and the ileostomy was closed at 16 months postoperatively. This extended interval was due to the patient undergoing prolonged adjuvant chemotherapy and close surveillance imaging, which delayed surgical candidacy. However, approximately nine months after ileostomy closure, the patient presented to the emergency department with a deteriorated general condition. CT revealed a presacral collection, surrounding the anorectal level by more than 180 degrees and containing fluid, air, and fecaloid material, which was suggestive of anastomotic leakage (Figure 1).

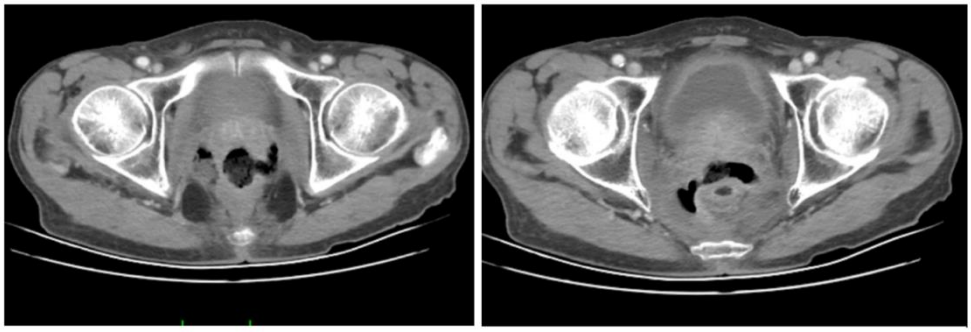

Figure 1. CT imaging showing anastomotic dehiscence

Subsequent colonoscopy confirmed a 3-4 cm opening in the perirectal area at the anastomotic site, located 3 cm proximal to the anal verge. The proximal colonic anastomosis in the ascending colon was intact (Figure 2).

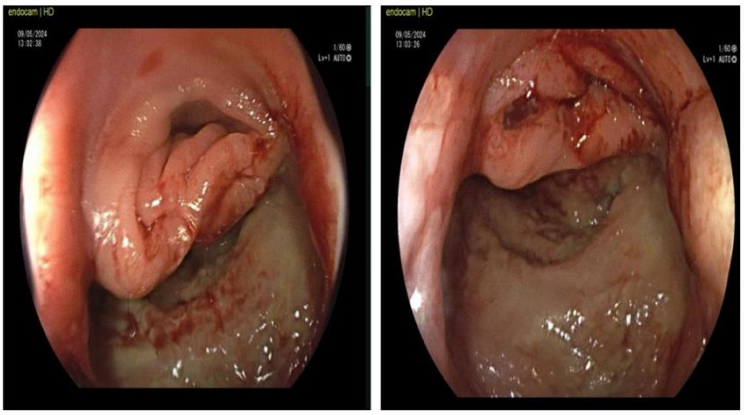

Figure 2. Colonoscopic view of the defect with granulation tissue

The patient was taken to surgery, where intra-abdominal contamination, a presacral abscess, and intestinal contents at the anastomotic site were observed. The anastomotic line was found to be partially dehiscent in a crescent-shaped pattern. After extensive peritoneal lavage, a diverting colostomy was created from the left colonic segment, and the operation was completed. The patient had an uneventful postoperative recovery,

tolerated oral intake, and was discharged. His follow-up is ongoing.

3. Discussion

Bevacizumab is a humanized monoclonal antibody targeting VEGF, which inhibits tumor neovascularization and enhances chemotherapy efficacy by modifying tumor vasculature permeability and Starling forces. Although not effective as a single agent, clinical studies have demonstrated that bevacizumab enhances the effectiveness of chemotherapy in metastatic CRC (9, 10).

Serious adverse events associated with bevacizumab include intestinal ischemia, gastrointestinal perforation, impaired wound healing, bleeding, and arterial thromboembolic events (11, 12). The exact pathophysiological mechanism leading to intestinal perforation is not well understood. One hypothesis is that tumor-related necrosis caused by bevacizumab predisposes patients to perforation (13). Another theory suggests that bevacizumab-induced thrombosis impairs microvascularization, disrupting tissue perfusion and leading to ischemia and perforation (14).

Bevacizumab has also been associated with delayed anastomotic leakage due to impaired wound healing (13). Patients who have undergone previous pelvic radiotherapy and multiple surgeries are at particularly high risk for anastomotic leakage (8). Current guidelines recommend a minimum interval of six weeks between bevacizumab therapy and surgery (9, 15). However, in this case, anastomotic failure occurred despite an extended interval after receiving 5-FU and panitumumab prior to bevacizumab, suggesting an increased risk of delayed anastomotic leakage.

While antiangiogenic agents prolong survival in metastatic CRC, their negative impact on postoperative healing should not be overlooked. This case is particularly unique due to the exceptionally delayed onset (26 months postoperatively) of anastomotic leakage, a complication rarely described in current literature. In most reported cases, anastomotic dehiscence associated with bevacizumab occurs within weeks to months postoperatively, often in the early treatment phase.

Our case stands out in that the patient had completed adjuvant therapy, underwent late ileostomy closure, and had a clinically silent course for over two years before presenting with leakage. This suggests that delayed vascular compromise or microenvironmental changes due to anti-VEGF therapy may have contributed to progressive anastomotic weakening long after initial healing.

Before initiating bevacizumab therapy, anastomotic integrity should be assessed via endoscopic and imaging techniques. Additionally, surgical interventions should be scheduled at least 6-8 weeks after bevacizumab therapy, with close postoperative monitoring.

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Case Report
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Morel-Lavallée Lesion of the Knee: A Case Report

Dizde Morel-Lavallée Lezyonu: Bir Olgu Sunumu

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Abstract: Morel-Lavallée lesions are closed soft tissue injuries caused by a shearing force that separates the skin and superficial fascia from the deep fascia, creating a potential space where hemolymphatic fluid accumulates. These lesions are often misdiagnosed due to their variable clinical presentation and heterogeneous morphology, which can lead to confusion with conditions such as hematoma, fat necrosis, and sarcoma. The typical localization of the lesion is the trochanteric region. This case report presents the clinical and radiological findings, along with the diagnosis and treatment process, of a 56-year-old female patient who developed a Morel-Lavallée lesion in the prepatellar region following a fall. In the first stage, no bone abnormality was seen in computed tomography (CT) imaging. Magnetic resonance imaging (MRI) and ultrasonography (USG) performed as a result of her ongoing complaints revealed a well-defined fluid accumulation in the prepatellar region, consistent with a Morel Lavallée lesion. Clinical examination and patient history are essential for diagnosis. However, MRI and USG play an important role in confirming the diagnosis and monitoring the course of the disease. A classification has been proposed for Morel-Lavallée lesions, which are divided into six subtypes based on MRI features. USG is particularly practical and useful modality both for initial diagnosis and follow-up evaluation. Some lesions may resolve spontaneously. If not recognized and treated appropriately, they may become chronic or complicated, requiring more invasive interventions. Recognizing the lesion's characteristics and implementing a personalized treatment strategy are essential for achieving optimal patient outcomes.
Keywords: Morel-Lavallée lesion, knee, degloving injury, ultrasound

Özet: Morel-Lavallée lezyonları, deri ve yüzeysel fasya ile derin fasyayı ayıran ve hemolenfatik sıvının biriktiği potansiyel bir boşluk yaratan bir kesme kuvvetinin neden olduğu kapalı yumuşak doku yaralanmalarıdır. Bu lezyonlar, değişken klinik sunumları ve hematom, yağ nekrozu ve sarkom gibi durumlarla karıştırılmasına yol açabilen heterojen morfolojileri nedeniyle sıklıkla yanlış teşhis edilir. Lezyonun tipik lokalizasyonu trokanterik bölgedir. Bu olgu sunumunda ise, düşme sonrası prepatellar bölgede Morel-Lavallée lezyonu gelişen 56 yaşında bir kadın hastanın klinik ve radyolojik bulguları ile beraber tanı ve tedavi süreci sunulmaktadır. İlk aşamada, bilgisayarlı tomografi (BT) görüntülemesinde kemik anormalliği görülmemiştir. Devam eden şikayetleri sonucunda yapılan manyetik rezonans görüntüleme (MRG) ve ultrasonografi (USG), Morel Lavallée lezyonuyla uyumlu, prepatellar bölgede iyi tanımlanmış bir sıvı birikimi ortaya koymuştur. Tanı için klinik muayene ve hastanın öyküsü esastır. Ancak tanıyı doğrulamak ve hastalığın seyrini izlemek için MR ve USG önemli rol oynar. Morel Lavallée lezyonları için MRI özelliklerine dayanan altı alt tipe ayrıldığı bir sınıflandırma önerilmiştir. USG de hem ilk tanı aşamasında hem de takip değerlendirmesi için oldukça pratik ve kullanışlı bir yöntemdir. Bazı lezyonlar kendiliğinden çözülebilir. Uygun şekilde tanınmaz ve tedavi edilmezse kronikleşebilir veya komplike hale gelebilir ve daha invaziv müdahaleler gerektirebilir. Lezyonun özelliklerini tanımak ve kişiselleştirilmiş bir tedavi stratejisi uygulamak, optimum hasta sonuçlarına ulaşmak için esastır.

Anahtar Kelimeler: Morel-Lavallée lezyonu, diz, soyulma yaralanması, ultrason

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1. Introduction

The Morel-Lavallée lesion was first described by Maurice Morel-Lavallée and is characterized by the sudden separation of soft tissue from the deep fascial layer (1). This shearing force leads to damage of perforating vessels and lymphatics, resulting in the accumulation of hemolymphatic fluid and necrotic fat within a potential space (2). While Morel-Lavallée lesions are commonly associated with high-energy trauma such as motor vehicle accidents and sports injuries, they may also result from low-energy trauma and iatrogenic causes (3,4). While they are most frequently observed in the pelvic region, thigh, and hip, they can also develop in other parts of the body (5,6).

Untreated or overlooked lesions may become chronic, making their management more complex. In chronic cases, surgical interventions such as debridement, sclerotherapy, percutaneous drainage, and skin grafting may be required (6-8). Early diagnosis and appropriate treatment are crucial in preventing such complications. This case report presents an example of a Morel-Lavallée lesion and outlines the diagnostic process and clinical approach. The importance of early diagnosis and proper management in such lesions is emphasized.

2. Case Report

A 56-year-old female patient with no significant medical history presented with right knee pain. The pain began after she fell onto her knee on a slippery surface, and she subsequently noticed swelling in the affected area. The patient initially visited the emergency department, where a computed tomography (CT) scan was performed, revealing normal bone contours and structures. Due to persistent symptoms, she later consulted the orthopedics and traumatology department, where the orthopedic specialist ordered a magnetic resonance imaging (MRI) scan (Fig. 1). The patient was prescribed nonsteroidal anti-inflammatory drugs (NSAIDs), rest, and cold therapy.

However, the patient, whose complaints persisted, presented to the physical medicine and rehabilitation clinic 14 days after the injury for additional opinions. The patient walked with an antalgic gait, keeping the right knee slightly flexed. Physical examination revealed swelling in the right knee without warmth or erythema. On palpation, there was significant tenderness and a fluctuant swelling extending across the anterior knee. The patient reported intense pain with quadriceps contraction and stretching.

An ultrasonographic (USG) evaluation was performed, revealing a well-defined anechoic fluid collection localized between the subcutaneous tissue and deep fascial planes, extending superiorly and inferiorly from the prepatellar region. The lesion was compatible with fascial separation, had an internal structure containing minimal echogenic residue. No intra-articular effusion was detected, and the muscle anatomy was intact (Fig. 2A).

Aspiration of the lesion yielded serohemorrhagic, low-viscosity fluid without clot formation. Based on clinical findings and imaging, and in conjunction with the radiologist's evaluation, the diagnosis of a Morel-Lavallée lesion was confirmed. The patient was prescribed cold therapy, compression bandaging, and a combination of codeine-paracetamol for symptomatic relief. One week later, the swelling recurred, prompting the patient to return for evaluation. A repeat USG showed a fluid collection similar in volume to the previous aspiration. A second aspiration was performed, and the aspirated fluid had the same characteristics as before (Fig. 2B). Due to recurrent fluid accumulation, the patient was referred to the orthopedic clinic for further intervention evaluation. After evaluation by the orthopedic specialist, non-surgical management was recommended, with ongoing clinical and radiological follow-up planned. The patient's follow-up care included the addition of range of motion exercises to her existing treatment plan. After two weeks of follow-up, the patient's pain decreased, and an improvement in range of motion was observed, so conservative management was continued.

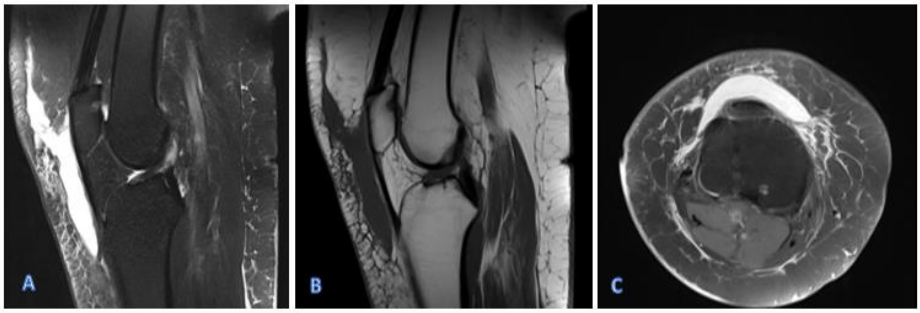

Fig 1. In the sagittal plane (A, B), a 14x3 cm fusiform/ovoid-shaped fluid collection is observed in the prepatellar region, located within the deep subcutaneous fat tissue with an epifascial distribution. The lesion appears hyperintense on T2-weighted sequences (A), hypointense on T1-weighted sequences (B), and hyperintense on PD-weighted images (C). No effusion is detected in the adjacent knee joint. Musculo-tendinous structures were intact.

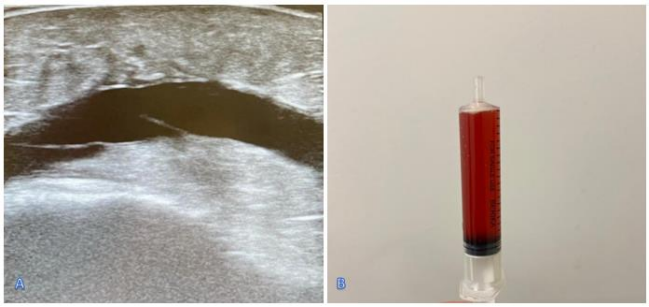

Fig 2. (A) High-frequency ultrasound shows a hypoechoic fluid collection with septations in the distal upper leg. (B) Sero-hemorrhagic aspirated fluid from the prepatellar fluid collection.

Table 1. Mellado & Bencardino's MRI classification of Morel-Lavallee lesions.

Lesion Type	Morphology	T1W	T2W	Capsule
Type 1 *Seroma*	Laminar	Hypointense	Hyperintense	Occasional
Type 2 *Subacute hematoma*	Oval	Hyperintense	Hyperintense	Thin
Type 3 *Chronic organizing hematoma*	Oval	Intermediate	Heterogeneous	Thick
Type 4 *Closed laceration*	Linear	Hypointense	Hyperintense	Absent
Type 5 *Pseudonodular*	Round	Variable	Variable	Thin/thick
Type 6 *Infected*	Variable sinus tract	Variable	Variable	Thick

3. Discussion

Morel-Lavallée lesion is a soft tissue injury that can be easily overlooked in the early period and may be misdiagnosed. However, a history of trauma, typical localization, and MRI characteristics can aid in confirming the diagnosis. In the literature, the most common localization has been reported as the lateral aspect of the greater trochanter (2). However, in one case series, 64.3% of cases were detected in the knee region (9). Tejwani et al. identified the most common mechanism of Morel-Lavallée lesion in football players as a shearing blow to the playing

surface, with the most frequent movement restriction being a loss of active flexion (10). Similarly, in our case, the patient developed a lesion in the prepatellar region following a shearing injury caused by a slip and fall. In our case, there was also a restriction in active flexion; however, at the time of the initial presentation, the patient had difficulty achieving full knee extension. In another study, four cases of prepatellar MLL, similar to our case, showed cranio-caudal lengths of the lesions ranging from 10.5 cm to 13.6 cm (11).

MRI plays a crucial role in the diagnosis and classification of Morel-Lavallée lesions. Mellado and Bencardino, after a comprehensive evaluation, classified Morel-Lavallée lesion into six subtypes based on MRI patterns (Table 1) (12). Although CT is considered the first-line imaging modality in acute trauma cases, Morel-Lavallée lesions are not well-defined in the acute phase. Three-dimensional reconstructions may assist in detecting the lesion in the interfascial plane. In Morel-Lavallée lesions, while USG is helpful in confirming the location of the lesion and detecting anechoic or hypoechoic, non-specific fluid collections, MRI is the preferred method for characterizing the lesion and determining its type and chronicity (2, 8). In MRI, chronic lesions typically exhibit a fibrotic capsule formed by hemosiderin accumulation. Additionally, the detection of features such as fluid-fluid levels, fatty globule, internal debris, and septations provides a more detailed insight into the lesion's content and structure. The presence of blood products within the fluid can create a heterogeneous appearance depending on whether the lesion is in the acute, subacute, or chronic phase (13-16). The additional contribution of USG is providing imaging guidance for interventional procedures.

Morel-Lavallée lesions can be mistaken for various other clinical conditions (2,17). The primary differential diagnoses include sarcomas, subcutaneous hematomas, bursitis, and fat necrosis. Hematomas typically resolve spontaneously within a few weeks and exhibit clot organization, whereas Morel-Lavallée lesions often contain serosanguinous fluid, present with a fluctuant mass, and tend to become chronic. In rare cases, chronic, slowly expanding hematomas may also be observed. These lesions can also mimic hemorrhagic neoplasms, in which case contrast-enhanced MRI or biopsy may be required for differentiation (18,19). Bursitis may sometimes be confused with Morel-Lavallée lesions, but bursitis remains confined within bursa boundaries, presents as a well-localized fluid collection, and may demonstrate synovial hypertrophy. Chronic hemorrhagic bursitis can resemble Type 3 Morel-Lavallée lesions, although management of both conditions is often similar (9,20).

If Morel-Lavallée lesions are not adequately treated in the early stage, they may become encapsulated and firm due to repeated bleeding and inflammation (2). This can create an atypical soft tissue mass appearance, leading to diagnostic confusion with malignant soft tissue tumors, particularly sarcomas. Internal contrast enhancement of the lesion and a history of previous trauma can serve as important clues in the differential diagnosis. However, biopsy is required for definitive diagnosis, and histopathological examination is necessary to rule out malignancy (21,22).

The management of Morel-Lavallée lesions should be individualized based on the lesion’s phase, size, and risk of complications (8). Compression bandages and symptomatic treatment may suffice for acute and small lesions, whereas ultrasound-guided drainage is recommended for larger fluid collections (12). In our case, which was evaluated in the subacute phase, two sessions of aspiration were performed. Follow-up with compression bandaging and symptomatic treatment revealed a marked reduction in the fluid collection. Although corticosteroid injections have been attempted as part of conservative treatment in some cases of Morel-Lavallée lesions, they have generally resulted in recurrence and demonstrated lower success rates compared to sclerotherapy (23). The most commonly used sclerosing agents reported in studies include doxycycline, talc, ethanol, and bleomycin (2,23-25). According to the Mayo Clinic experience, lesions requiring fluid aspiration exceeding 50 mL carry a high risk of recurrence and are more likely to necessitate surgical intervention (26). Surgical intervention is considered an effective treatment option for Morel-Lavallée lesions that are large, recurrent, infected, associated with overlying skin necrosis, significant soft tissue loss, or chronic encapsulation (8). In such cases, open surgical debridement, along with skin grafting or flap reconstruction when necessary, may be performed to remove necrotic tissue and minimize the risk of reinfection and fluid reaccumulation (8,27).

However, in cases where skin viability is preserved, less invasive approaches may be preferred. Li et al. reported favorable clinical outcomes and low recurrence rates using a minimally invasive incision and loop drainage technique (28). Additionally, in cases with compromised skin viability or infection, negative pressure wound therapy can be applied either as a preparatory step prior to surgery or as an adjunct to surgical intervention (26).

In conclusion, Morel-Lavallée lesions require careful evaluation in the diagnostic and treatment process due to their evolving morphological characteristics over time. While these lesions can be managed with conservative methods in the early stage, they may become encapsulated and chronic, eventually necessitating surgical intervention. Therefore, in cases of large and recurrent fluid collections, determining the appropriate treatment approach early on is crucial for the patient's prognosis. The treatment strategy should be individualized based on the lesion's stage and the patient's clinical condition.

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Paraganglioma Tanılı Hastada Postoperatif ARDS: Olgu Sunumu

Postoperative ARDS in a Patient with Paraganglioma: A Case Report

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Abstract: Paraganglioma is a rare neuroendocrine tumor that typically originates from chromaffin cells and is most commonly located in the retroperitoneal region. Similar to pheochromocytoma, it can secrete catecholamines and cause significant cardiovascular effects. Surgical intervention, trauma, or anesthesia may act as stressors, triggering a pheochromocytoma crisis through sudden and excessive catecholamine release. This clinical condition may lead not only to cardiovascular instability but also to a rare yet life-threatening complication: acute respiratory distress syndrome (ARDS). ARDS is characterized by widespread pulmonary edema due to disruption of the alveolar-capillary barrier and may become fatal if not managed promptly.In this case report, we present a rare case of ARDS secondary to a pheochromocytoma crisis in the postoperative period following paraganglioma surgery. A 53-year-old female patient with a history of hypertension, diabetes mellitus, and pancreatitis was evaluated for sudden hypertensive episodes. Advanced imaging revealed a retroperitoneal paraganglioma. Despite preoperative treatment with alpha- and beta-blockers, the patient developed hemodynamic instability and hypoxemic respiratory failure in the early postoperative period. The diagnosis of ARDS was confirmed by thoracic computed tomography. The patient was managed in the intensive care unit with invasive mechanical ventilation and was successfully extubated and discharged following clinical improvement.In conclusion, potentially life-threatening complications such as pheochromocytoma crisis and ARDS should be considered before paraganglioma surgery. A multidisciplinary approach plays a crucial role in the effective management of diagnosis and treatment processes.
Keywords: Paraganglioma, pheochromocytoma crisis, ARDS

Özet: Paraganglioma, genellikle retroperitoneal yerleşimli ve kromaffin hücrelerden köken alan nadir bir nöroendokrin tümördür. Feokromositoma gibi katekolamin salgılayarak kardiyovasküler sistem üzerinde ciddi etkiler oluşturabilir. Özellikle cerrahi girişim, travma veya anestezi gibi stres faktörleri, ani ve yoğun katekolamin salınımını tetikleyerek feokromositoma krizine yol açabilir. Bu klinik tablo, kardiyovasküler instabiliteye ek olarak nadir ancak ciddi bir komplikasyon olan akut respiratuvar distres sendromu (ARDS) ile birlikte seyredebilir. ARDS, alveol-kapiller bariyerin bozulması sonucu gelişen yaygın pulmoner ödemle karakterize olup, zamanında müdahale edilmediğinde mortal seyredebilir. Bu olgu sunumunda, paraganglioma nedeniyle opere edilen ve postoperatif dönemde feokromositoma krizine sekonder olarak ARDS gelişen nadir bir vaka sunulmuştur. 53 yaşındaki kadın hasta, mevcut hipertansiyon, diyabetes mellitus ve pankreatit öyküsüne ek olarak ani gelişen hipertansif ataklar nedeniyle ileri tetkiklerle değerlendirilmiş ve retroperitoneal yerleşimli paraganglioma tanısı almıştır. Preoperatif dönemde uygulanan alfa ve beta bloker tedaviye rağmen cerrahi sonrası erken dönemde hemodinamik instabilite ve hipoksemik solunum yetmezliği gelişmiş; toraks bilgisayarlı tomografi (BT) ile ARDS tanısı doğrulanmıştır. Yoğun bakım ünitesinde invaziv mekanik ventilasyon desteğiyle takip edilen hasta, klinik iyileşme sonrası ekstübe edilerek şifa ile taburcu edilmiştir. Sonuç olarak, paraganglioma cerrahisi öncesinde feokromositoma krizi ve ARDS gibi hayatı tehdit eden komplikasyonların öngörülmesi büyük önem taşımaktadır. Tanı ve tedavi sürecinde multidisipliner yaklaşımın etkinliği kritik rol oynamaktadır.
Anahtar Kelimeler: Presakral tümör, schwannoma, kolon kanseri, lenf nodu metastazı

Informed Consent: It was declared that the patient signed an informed consent form.

Copyright Transfer Form: Copyright Transfer Form was signed by all authors.

Author Contribution Rates: Medical Practices: M. Kılıç,, Concept: O. Ulfanov, M. Kılıç,Design: O. Ulfanov, Y.S. Angın, Data Collection or Processing: O. Ulfanov, Analysis or Interpretation: M. Kılıç, Literature Search: Y.S. Angın, Writing: O. Ulfanov, Y.S. Angın

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1. Giriş

Adrenal medulladan köken alan ve katekolamin salgılayan tümörler feokromositoma olarak adlandırılır. Bu tümörler adrenal bez dışında yerleştiğinde ise paraganglioma (PGL) olarak isimlendirilir (1,2). PGL'ler, tüm kromaffin hücre kökenli tümörlerin yaklaşık %10–18'ini oluşturan nadir endokrin tümörlerdir. Nöral krest kaynaklı hücrelerden gelişen bu tümörler, sempatik veya parasempatik paragangliyonlardan köken alır. Çoğunlukla diyaframın alt kısmında lokalizedir ve tanıda metanefrin ile metoksitiramin düzeylerinin ölçülmesi önemlidir (3-5).

Cerrahi işlem, travma, stres, enfeksiyon ve anestezi gibi durumlar, katekolamin salınımını tetikleyerek feokromositoma krizine yol açabilir (6). Bu nedenle, bu tür tetikleyicilere maruz kalan hastalarda kriz riski artar (7). Feokromositoma krizi genellikle hipertansif ataklar ve kardiyomiyopati ile kendini gösterir; ancak nadiren akut pulmoner ödem ya da ARDS ilk bulgu olabilir (8).

ARDS, ciddi akciğer hasarına bağlı olarak gelişen, oksijenlenmede bozulmaya yol açan ve yaşamı tehdit eden bir klinik tablodur. Genellikle sepsis, ciddi travma veya pnömoni gibi altta yatan nedenlerle ortaya çıkar (9,10). Patofizyolojisinde, alveoler-kapiller bariyerin geçirgenliğinde artış sonucu oluşan yaygın alveoler ödem temel rol oynar (11). Feokromositoma krizine eşlik eden ARDS'nin gelişim mekanizması tam olarak aydınlatılamamış olsa da katekolaminlerin pulmoner kapiller venüller ve lenfatik damarlar üzerinde vazokonstriktif etki göstererek kapiller geçirgenliği ve hidrostatik basıncı artırdığı düşünülmektedir (12).

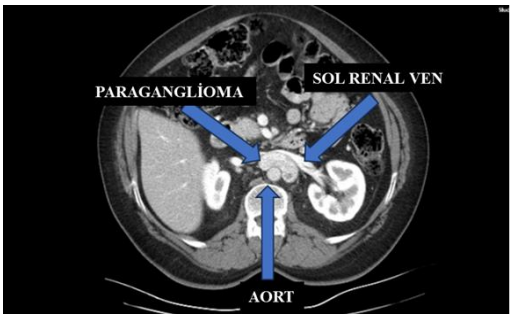
Bu olgu sunumunda, retroperitoneal yerleşimli paraganglioma nedeniyle cerrahi müdahale uygulanan ve postoperatif dönemde hipotansiyon ile ARDS gelişen 53 yaşında bir kadın hastanın tanı süreci, klinik seyri ve tedavi yaklaşımı ele alınmıştır.

2. Olgu Sunumu

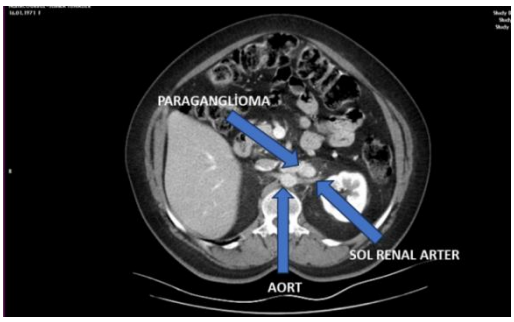
Diyabetes mellitus ve hipertansiyon tanısı bulunan, pankreatit öyküsü olan ve 20 yıldır sigara kullanan 53 yaşındaki kadın hasta, tekrarlayan ani hipertansif ataklar nedeniyle değerlendirilmiştir. Abdominal ultrasonografide paraaortik bölgede, 40×13 mm boyutlarında, vasküler yapı içermeyen solid bir kitle tespit edilmiştir. Lezyon, lenf nodu ya da nörojenik kökenli olasılıklarla değerlendirilmiştir.

Laboratuvar incelemelerinde 24 saatlik idrarda; hidroksiindol asetik asit 12,79 µg/24 sa (referans: 0–7,9), vanilmandelik asit 12,36 µg/24 sa (1,4–6,5), homovanilik asit 6,58 µg/24 sa (2–8 µg/mg kreatinin), metanefrin 244 µg/24 sa (30–180) ve normetanefrin 3627 µg/24 sa (128–484) olarak ölçülmüştür. Ayrıca bazal ACTH düzeyi 60,3 pg/mL (7,2–63,3) ve kortizol düzeyi 13,9 µg/dL (6,24–18) bulunmuştur.

Abdomen bilgisayarlı tomografide, portokaval alanda 47×26 mm boyutlarında, paraganglioma ile uyumlu yumuşak doku dansitesinde bir lezyon saptanmıştır. Dinamik pankreas manyetik rezonans görüntülemesinde, renal ven düzeyinde, paraaortik alandan interaortakaval alana uzanan 48×20 mm boyutlarında bir kitle izlenmiştir. Lezyonun iç yapısı düzensiz, çevre dokularla benzer yoğunlukta ve kontrast madde sonrası belirgin kanlanma göstermiştir. Doku içi sıvı hareketliliği belirgin şekilde azalmıştır. Bulgular, kitlenin solid ve vasküler yapıda olabileceğini düşündürmüştür. Görüntüleme bulguları, konglomere lenfadenopati veya paraganglioma ile uyumlu olarak değerlendirilmiştir.



Şekil 1a: Kitlenin Bilgisayarlı Tomografik görüntüsü

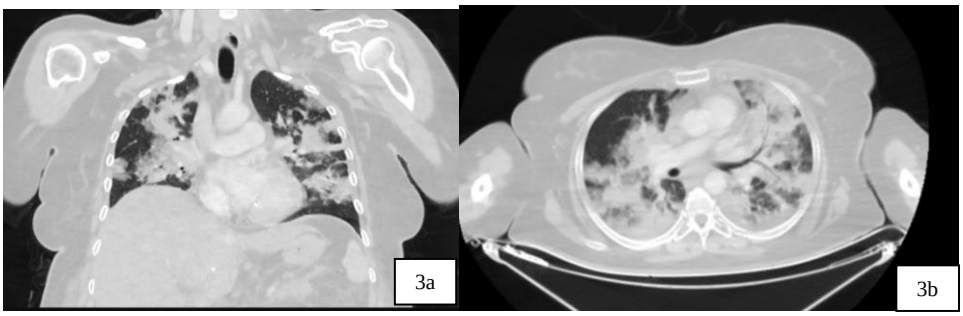


Şekil 1b: Kitlenin Bilgisayarlı Tomografik görüntüsü

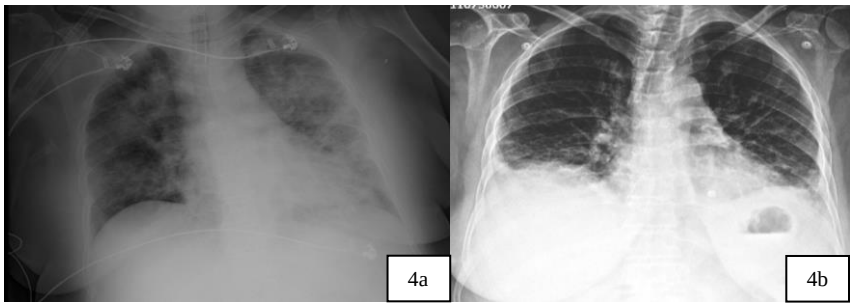
Boyun ultrasonografisinde, sol lob-istmus bileşkesinde 15×10×16 mm boyutlarında birkaç nodül, sağ lob orta kesiminde ise 20×17×25 mm boyutlarında, periferik kalsifikasyon ve kistik alan içeren izoekoik bir nodül tespit edilmiştir. Multipl endokrin neoplazi tip II B sendromu şüphesi ile medüller tiroid kanseri açısından biyopsi alınmış ve kalsitonin boyası uygulanmıştır. Sağ lobdan alınan biyopsi nondiagnostik, istmustan alınan örnek ise benign olarak değerlendirilmiş ve kalsitonin boyasında spesifik bir boyanma saptanmamıştır.

Hastaya tarafımızca paraganglioma tanısı ile cerrahi tedavi planlandı. Operasyon öncesinde, endokrinoloji kliniğinin önerisi doğrultusunda alfa ve beta bloker tedavisine başlandı; hasta intravenöz sıvı replasmanı ile üç gün boyunca hastanede takip edildi. Aydınlatılmış onam alındıktan sonra hasta ameliyata alındı. Genel anestezi altında yapılan laparotomi sırasında, sol renal venin posteriorunda ve aorta komşu yerleşimde bulunan yaklaşık 5×3 cm boyutundaki kitle dikkatli bir diseksiyonla eksize edildi.

Ameliyat sonrası hasta ekstübe edilerek uyanma ünitesine alındı. Sistolik kan basıncı 80 mmHg olarak ölçüldü, inotrop tedavi başlandı. Oksijen satürasyonu %85 olarak saptandı ve hastaya maske ile oksijen desteği verildi. Postoperatif birinci saatte, 7 L/dk oksijen desteğine rağmen satürasyon düşük seyretmeye devam etti. Arter kan gazında PO_2: 55 mmHg ve oksijen satürasyonu %88 olarak ölçüldü. Bunun üzerine göğüs hastalıkları kliniğine konsülte edildi. Hastaya solunum fizyoterapisi, inhale bronkodilatör tedavi, düşük molekül ağırlıklı heparin ve aralıklı non-invaziv mekanik ventilasyon başlandı. Ancak mevcut tedaviye yanıt alınamayınca, hasta pulmoner emboli ve aspirasyon pnömonisi açısından yoğun bakım ünitesine alınarak ileri tetkikler planlandı.



Şekil 3a: *Operasyon sonrası post op 2. günde ARDS ile uyumlu torasik BT görüntüsü*
Şekil 3b: *Operasyon sonrası post op 2. günde ARDS ile uyumlu torasik BT görüntüsü*



Şekil 4a: *Post op 2. günde ARDS ile uyumlu Akciğer grafisi görüntüsü*
Şekil 4b: *Postop 15. günde tedavi sonrası Akciğer grafisi*

Takip ve Tedavi Süreci

Yoğun bakım ünitesine alınan hasta, hiperglisemi nedeniyle endokrinoloji kliniği tarafından değerlendirildi ve intravenöz insülin infüzyonuna başlandı. Postoperatif ikinci günde çekilen toraks BT görüntülemesinde bilateral infiltratif alanlar ve diffüz opasiteler izlendi. Bu bulgular doğrultusunda hastaya ARDS tanısı konuldu. Klinik ve radyolojik bulgularla tanı netleştirildikten sonra hasta entübe edilerek invaziv mekanik ventilasyon desteğine alındı ve yoğun bakım koşullarında ARDS yönetim protokolü uygulandı.

Hemodinamik olarak instabil seyreden hasta, kardiyojenik kaynaklı solunum yetmezliği açısından kardiyoloji kliniğine danışıldı. Yapılan değerlendirmede pro-BNP düzeyi 74 pg/mL olarak ölçüldü ve yatak başı gerçekleştirilen ekokardiyografide patolojik bir bulguya rastlanmadı. Üçüncü postoperatif günde yapılan laboratuvar incelemelerinde hemoglobin düzeyi 8,3 g/dL, lökosit sayısı 15,13×10⁹/L ve C-reaktif protein düzeyi 255,7 mg/L olarak saptandı. Diğer hemogram ve biyokimya parametreleri normal sınırlarda izlendi. Enfeksiyon hastalıkları kliniği ile konsültasyon sağlanarak uygun intravenöz antibiyotik tedavisine başlandı.

Kırk sekiz saatlik entübe takibin ardından hastanın solunum parametrelerinde anlamlı düzelme gözlendi ve alınan arter kan gazında parsiyel oksijen basıncı 106 mmHg ve oksijen satürasyonu %99,6 olarak sonuçlandı. Bu gelişmeler üzerine hasta ekstübe edilerek non-invaziv mekanik ventilasyon desteğine alındı. Takip sürecinde inotrop tedavisi kademeli olarak azaltıldı ve sonlandırıldı. Yirmi dört saatlik non-invaziv mekanik ventilasyon sonrasında hasta, maske aracılığıyla dakikada 2 litre oksijen desteğiyle takip edildi. Oksijen satürasyonu %93 düzeyinde stabil seyreden hastanın vital bulguları normal sınırlarda idi.

Postoperatif 15. günde yapılan laboratuvar değerlendirmelerinde hemoglobin düzeyi 11,1 g/dL, lökosit sayısı 11,26×10⁹/L ve C-reaktif protein düzeyi 9 mg/L olarak ölçüldü. Klinik ve laboratuvar bulgularının stabil seyretmesi üzerine, postoperatif 16. günde hasta şifa ile taburcu edildi. Patoloji sonucunda eksize edilen kitlenin paraganglioma ile uyumlu olduğu, tümör dokusu içerisinde nekroz alanlarının bulunduğu ve mitotik aktivitenin 2 mitoz/mm² olduğu bildirildi.

3. Tartışma

Bu çalışmada, paraganglioma cerrahisi sonrası gelişen feokromositoma krizi nedeniyle solunum ve hemodinamik yetmezlik gelişen bir kadın hasta sunulmuştur. Katekolamin salgılayan tümörler için erken tarama önemlidir. Klasik semptomları veya düzensiz hipertansiyonu olan hastalar mutlaka değerlendirilmelidir. Adrenal insidentaloma, aile öyküsü, çocuk yaş grubu ve MEN 2A, MEN 2B, von Hippel-Lindau gibi genetik sendromlar yüksek risk faktörleri arasında yer almaktadır (4,13).

Yirmi dört saatlik idrarda metanefrin ölçümü, fonksiyonel paragangliomaların tanısında en güvenilir test olarak kabul edilmektedir. Bu testin duyarlılığı %87–90, özgüllüğü ise %99 veya daha fazladır. Ayrıca testin doğruluğunu değerlendirmek amacıyla kreatinin düzeyi de ölçülmelidir (4,13).

Feokromositomaların preoperatif lokalizasyonu, cerrahi planlama açısından kritik öneme sahiptir. Görüntüleme teknikleri, çoğu vakada tümörü doğru şekilde lokalize edebilmektedir. BT, 1 cm veya daha büyük adrenal feokromositomaların %95'ini, 2 cm'den büyük ekstra-adrenal

tümörlerin ise %90'ını tespit edebilmektedir (14). Manyetik rezonans görüntüleme (MRG) ve fonksiyonel görüntüleme tekniklerindeki gelişmeler, tümörlerin lokalizasyonunu ve metastatik hastalığın belirlenmesini kolaylaştırmaktadır. 123I-MIBG sintigrafisi, 68Ga-DOTATATE PET/BT ve 18F-Fluorodopa PET/BT, feokromositoma ve paragangliomaların tanısında değerli yöntemlerdir (15).

Paragangliomanın ana tedavisi cerrahidir ve kür ya da remisyon sağlanmasında büyük önem taşımaktadır. Cerrahi planlama; biyokimyasal testler, genetik analizler ile anatomik ve fonksiyonel görüntüleme sonuçlarına göre kişiye özel olarak yapılmalıdır (16).

Feokromositoma veya PGL tanısı alan hastalarda preoperatif değerlendirme kritik öneme sahiptir. Scholten ve arkadaşlarının yaptığı çalışmada, yetersiz preoperatif hazırlığın cerrahi sonrası ciddi morbidite ve mortaliteye yol açabileceği gösterilmiştir (17). Hormonal olarak aktif PGL'si olan tüm hastalar, perioperatif kardiyovasküler komplikasyonları önlemek amacıyla preoperatif dönemde α-adrenerjik reseptör blokerleri ile tedavi edilmelidir. Kan basıncını ve kalp atım hızını normalleştirmek için ameliyat öncesinde 7 ila 14 gün boyunca tıbbi tedavi uygulanmalıdır. Ayrıca, postoperatif hipotansiyon riskini azaltmak için ameliyat öncesinde yüksek sodyum içerikli diyet ve yeterli sıvı alımı önerilmektedir. Cerrahi sonrası dönemde ise kan basıncı, kalp hızı ve kan şekeri dikkatle izlenmeli; gerekli tedaviler hızla düzenlenmelidir (18).

Feokromositoma krizi, nadir görülen ancak erken tanı konulmaz ve uygun şekilde tedavi edilmezse ölümcül seyredebilme potansiyeline sahip bir klinik tablodur (12). Tümör teması, travma ve bazı ilaçlar (glukokortikoidler, β-blokerler, metoklopramid ve anestezikler vb.) krizi tetikleyebilmektedir (8).

Feokromositoma hastalarında, miyokard enfarktüsü, kardiyomiyopati ve şiddetli aritmilere bağlı kardiyojenik pulmoner ödem gelişebilir. Özellikle normal kan basıncına sahip ya da hipotansif hastalarda ortaya çıkan pulmoner ödem, feokromositomanın nadir klinik bulgularındandır. Bu vakada feokromositoma krizi, tümör teması sonrası gelişmiştir.

Kardiyojenik olmayan pulmoner ödem ise oldukça nadirdir ve katekolamin fazlalığına bağlı olarak pulmoner kapiller basınç artışı ile nötrofil birikiminin artması sonucunda geliştiği düşünülmektedir (19).

4. Sonuç

Paraganglioma cerrahisi öncesinde, olası feokromositoma krizi ve akut solunum sıkıntısı sendromu gibi komplikasyonların öngörülerek, kapsamlı bir preoperatif hazırlık sürecinin yürütülmesi büyük önem arz etmektedir. Bu olguda olduğu gibi, uygun preoperatif medikal tedavi uygulanmasına rağmen akut solunum sıkıntısı sendromu gelişebilmektedir. Bu durum, bu tür kompleks vakalarda yakın takip ve hızlı müdahalenin ne kadar hayati olduğunu ortaya koymaktadır.

Yoğun bakım, göğüs hastalıkları, endokrinoloji, kardiyoloji ve cerrahi branşlarının bir arada yer aldığı multidisipliner ekip yaklaşımı, bu tür karmaşık vakalarda tanı ve tedavi süreçlerinin etkin şekilde yönetilmesini sağlamakta ve olumlu klinik sonuçların elde edilmesine katkıda bulunmaktadır (20).

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Eating Disorders and Low Energy Availability in Female Athletes: Prevalence, Risk, and Impact on Athletic Performance

Kadın Sporcularda Yeme Bozuklukları ve Düşük Enerji Kullanılabilirliği: Prevelans, Risk ve Sportif Performansa Etkisi

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Abstract: Adequate nutrition is essential for meeting athletes' energy demands and maintaining physiological functions. Restrictive diets, eating disorders, or excessive energy expenditure can result in low energy availability (LEA), which disrupts multiple systems, causing hormonal imbalances, reduced bone density, and psychological issues. The literature indicates that female athletes competing in sports emphasizing aesthetics or weight categories are at greater risk of these conditions. This review evaluates studies published between 2010 and 2024 on the relationship between eating disorders and LEA in female athletes, synthesizing findings from databases including PubMed, Scopus, and Web of Science. The aim is to integrate epidemiological data with performance outcomes, addressing a gap in the literature by combining health and performance perspectives to guide sports health professionals. Findings indicate a higher prevalence of both eating disorders and LEA in aesthetic and weight-class sports compared to other disciplines. LEA is associated with reduced endurance, impaired coordination, diminished training responsiveness, and increased injury risk. Early detection and targeted nutritional strategies can improve both health and performance outcomes.
Keywords: Sports nutrition, eating disorder, low energy availability, athletic performance

Özet: Sporcularda yeterli beslenme, enerji gereksiniminin karşılanması ve fizyolojik işlevlerin sürdürülmesi açısından kritik öneme sahiptir. Kısıtlayıcı diyetler, yeme bozuklukları veya aşırı enerji harcaması, düşük enerji kullanılabilirliği (LEA) ile sonuçlanabilir. Mevcut literatürde, kadın sporcuların özellikle estetik kaygının veya sıkletin ön planda olduğu branşlarda bu durumlar açısından daha yüksek risk altında olduğu bildirilmektedir. Bu derleme, 2010–2024 yılları arasında yayımlanan kadın sporcularda yeme bozukluğu ve LEA ilişkisini inceleyen çalışmaları değerlendirmekte olup, PubMed, Scopus ve Web of Science veri tabanlarından elde edilen bulguları sentezlemektedir. Amaç, epidemiyolojik veriler ile performans sonuçlarını birleştirerek literatürdeki boşluğu doldurmak ve spor sağlığı profesyonellerine yol göstermektir. Bulgular, estetik ve sıklet sporlarında yeme bozukluğu ve LEA prevalansının diğer branşlara kıyasla daha yüksek olduğunu göstermektedir. LEA; dayanıklılıkta azalma, koordinasyon kaybı, antrenman yanıtının düşmesi ve sakatlık riskinde artış ile ilişkilidir. Erken tanı ve uygun beslenme stratejileri, hem sağlık hem performans açısından iyileşme sağlayabilir.
Anahtar Kelimeler: Sporcu beslenmesi, yeme bozukluğu, düşük enerji kullanılabilirliği, sportif performans

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1. Introduction

Adequate nutrition is essential for sustaining the physiological and performance needs of athletes. Ensuring sufficient intake of energy and nutrients allows the body to maintain training adaptations, prevent injuries, and support recovery. While all athletes require balanced nutrition, the needs may vary considerably based on factors like age, sex, the type of sport, and the intensity of training (1). However, in female athletes, these requirements may be more challenging to meet due to factors such as high energy demands, body image concerns, and sport-specific pressures (2). Inadequate energy intake relative to expenditure can lead to low energy availability (LEA), a condition that disrupts multiple physiological systems and can lead to suboptimal performance (3). LEA can develop for various reasons, and one of the most common is disordered eating (DE). DE includes a range of unhealthy eating habits, from mild dieting and strict food rules to clinically diagnosed eating disorders (EDs) (4). This progression often begins with prolonged caloric restriction or rapid weight-loss practices—sometimes reducing energy intake below ~30 kcal per kilogram of fat-free mass per day—combined with high training loads. Over time, such behaviors can result in hormonal disturbances, menstrual dysfunction, reduced bone mineral density, psychological stress, and diminished training responsiveness (3, 5).

This review presents current evidence on the prevalence, risk factors, and performance consequences of EDs and LEA in female athletes and highlights key strategies for early recognition, prevention, and management.

2. Eating Disorders

Eating disorders are characterized by marked changes in eating habits that compromise both physical health and psychosocial well-being. These disorders are distinct clinical conditions, not merely symptoms of other psychiatric or medical disorders such as depression or neurological disease (6). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), published by the American Psychiatric Association in 2013, classifies eating disorders into several categories, including pica, rumination disorder, avoidant/restrictive food intake disorder (ARFID), anorexia nervosa (AN), bulimia nervosa (BN), and binge-eating disorder (BED). Among these, AN, BN, and BED are the most studied and are considered the primary focus in diagnosis and treatment.

Anorexia nervosa is marked by severe energy restriction leading to significantly low body weight, intense fear of gaining weight, and a distorted body image. Bulimia nervosa involves recurrent episodes of binge eating followed by compensatory behaviors such as self-induced vomiting, laxative misuse, or excessive exercise, with body weight typically remaining in the normal range. Binge-eating disorder is characterized by recurrent binge episodes without compensatory behaviors, often accompanied by feelings of loss of control and distress. ARFID, in contrast, features severe food avoidance or restriction without body image disturbance, often due to sensory sensitivities, fear of adverse consequences, or lack of interest in eating (7, 8). Although these conditions occur in the general population, evidence shows that female athletes—particularly in aesthetic, endurance, and weight-class sports—face a higher risk due to weight-related performance pressures, frequent body composition monitoring, and sociocultural ideals of leanness (9, 10).

2.1. Diagnostic Criteria

Table 1. Comparison of Core Diagnostic Features of Major Eating Disorders (Based on DSM-5)

Diagnostic Feature	Anorexia Nervosa (AN)	Bulimia Nervosa (BN)	Binge-Eating Disorder (BED)	Avoidant/Restrictive Food Intake Disorder (ARFID)
Restriction of Energy Intake	Persistent restriction → significantly low body weight	Not persistent; occurs with binge–purge cycles	Not persistent; occurs with binge episodes	Significant restriction → weight loss, nutritional deficiency

Body Weight	Significantly below normal	Usually normal or above	Usually normal or above	Underweight or normal; nutritional deficiency
Fear/Concern About Weight or Shape	Intense fear of weight gain; distorted body image	High concern with body weight/shape	May be present but not required	Absent — absence is a key diagnostic feature
Binge-Eating Episodes	May occur, but not required	At least once/week for 3 months	At least once/week for 3 months	Absent
Compensatory Behaviors	Present in binge–purge subtype	Present at least once/week for 3 months	Absent	Absent
Other Key Features	Denial of seriousness of low weight	Self-evaluation overly influenced by body weight/shape	Eating rapidly, until uncomfortably full, when not hungry, or with guilt/distress	Avoidance due to sensory sensitivity, fear, or disinterest in eating

Driven by severe weight control practices, anorexia nervosa (AN) and bulimia nervosa (BN) are eating disorders often shaped by the internalization of a thin body ideal. Both share excessive preoccupation with body weight and shape as a central feature. AN typically presents with dangerously low body weight resulting from strict self-imposed dietary restriction, often accompanied by a distorted body image. BN, in contrast, is defined by recurrent episodes of overeating followed by compensatory behaviors such as self-induced vomiting, laxative misuse, or excessive exercise, while body weight usually remains within the normal range (6).

Binge-eating disorder (BED) and avoidant/restrictive food intake disorder (ARFID) are generally associated with factors other than body image concerns. BED involves recurrent binge-eating episodes without compensatory behaviors, often accompanied by feelings of loss of control and distress. ARFID is characterized by persistent food avoidance or restriction without body image disturbance, most often due to sensory sensitivities, fear of adverse consequences, or lack of interest in eating (6).

2.2. Prevalence in Athletes

Although eating disorders can occur in various populations, numerous studies have shown that elite athletes experience them at significantly higher rates than the general population (11-14). Female athletes and those competing in weight-categorized, aesthetic, or precision sports (e.g., gymnastics, weightlifting) are particularly at risk. According to Torstveit and Sundgot-Borgen (2004), approximately 20% of elite female athletes and 8% of elite male athletes meet the diagnostic criteria for eating disorders. Among non-athletes, the prevalence drops to about 9% in women and 0.5% in men (11). Similar patterns have been reported in adolescent populations: one study found a prevalence of 14% among female athletes and 3.2% among male athletes, whereas the overall prevalence for non-athletes was 2.3% (13). In a study of 590 competitive athletes, irregular eating behaviors—particularly in weight-class athletes—were strongly linked to a higher risk of developing eating disorders (14). Several studies have further confirmed that female athletes are at greater risk of developing eating disorders compared to their male peers (15). Another study focusing on young athletes reported that the incidence of ED varied between 0-19% in males and 6-45% in females (7). When researchers analyzed prevalence based on sport type, one study revealed that aesthetic sports—such as rhythmic gymnastics, ballet, and figure skating—had the highest rates of eating disorders at around 40%. This was followed by weight-class sports, where the prevalence reached 30%, and team sports, which showed a lower rate of about 15% (16).

2.3. Risk Factors

Eating disorders and associated risk factors are generally divided into two main categories. The first group consists of general risk factors seen in both athletes and non-athletes, while the second group includes factors specific to athletes (17).

2.3.1. General Risk Factors

General risk factors can be categorized as biological, psychological, and sociocultural factors. Biological factors include age, genetic predisposition, puberty, and body mass index (BMI). Psychological factors include low emotional intelligence (difficulty recognizing, understanding, and managing emotions), insecure attachment (inconsistent or inadequate emotional connection with parents), dissatisfaction with body image, depressed or stressed mood, low self-esteem, and perfectionistic tendencies. Sociocultural factors include pressure to achieve unrealistic body ideals, a family history of eating disorders, bullying on sports teams, at school, or within the family, and critical comments about body shape or weight. These factors, especially when combined with the need for approval from significant others, can negatively influence eating behaviors (17).

2.3.2. Risk Factors in Athletes

Sport-specific risk factors include various challenges inherent in the sporting environment. These include frequent weight-control practices in some sports (e.g., weight-categorized and aesthetic sports), irregular eating behaviors, inadequate nutritional knowledge, inadequate energy and fluid intake, and limited time to prepare nutritious meals. Additionally, overly intense training, coach-driven personality expectations (e.g., perfectionism, high achievement orientation, over-compliance), early focus on sport-specific training, and injury-related weight gain are also risk factors. The desire to maintain a slimmer body to improve performance and the influence of coaching behaviors are also included in this group (15, 18). Current research indicates that athletes often lack sufficient nutritional knowledge, which may increase their susceptibility to unhealthy eating behaviors (18).

Studies focusing on athlete-specific risk factors consistently highlight certain variables that are associated with a higher likelihood of developing eating disorders. For example, a prospective study of 677 Norwegian athletes and 421 non-athletes found that those athletes who engaged in dieting and pursued thinness to enhance performance had a significantly higher likelihood of developing eating disorders (13). Another study of 122 British athletes examined how interpersonal difficulties can be used to monitor eating problems. The results showed that interactions between athletes and their coaches or team members were strongly associated with the amount they ate. Interestingly, coaching experiences emerged as an independent predictor of eating psychopathology, sometimes exerting greater influence than family members as young athletes specialize in their careers (19). A separate study looking at the effects of coaching style found that performance- and weight-focused coaching increased dieting behaviors, body image concerns, and fear of gaining weight, while a more supportive and empathetic coaching approach decreased the risk of eating disorders. These findings indicate that coaching style plays an significant role in shaping athletes' sensitivity to body image and eating concerns (20). Additional studies have shown that international-level gymnasts score higher than national-level athletes on measures of restrictive eating behavior (21), and female athletes generally report more dietary restrictions than their male peers (22).

Athletes at the most at risk of developing eating disorders are those for whom optimizing body weight is often considered essential to gaining an advantage in their sport. These high-risk groups include athletes in weight-class sports (such as boxing, taekwondo, and judo), aesthetic sports (such as gymnastics, and figure skating), endurance events (such as long-distance running, swimming, and cycling), and sports that involve defying gravity (such as high jump and ski jumping) (23). Elite athletes who participate in sports classified by weight class, 94% report engaging in dieting and using extreme weight management methods to meet specific weight targets before competition (8). Female athletes, especially during adolescence, often express concern about the natural fat mass gains that occur during puberty, which they fear could negatively impact their performance. Research shows that about one-third of the weight gained during puberty in women is made up of fat tissue (24). In response, some young female athletes may resort to unhealthy eating behaviors to compensate for these natural bodily changes (17). Overall, these findings suggest that sport requirements interact with developmental factors, particularly during adolescence, to increase the risk of eating disorders, highlighting the need for targeted nutrition education and preventive interventions in high-risk sports.

3. Low Energy Availability (LEA)

3.1. Definition of Energy Availability

The concept of energy availability (EA) is fundamental in the field of sports nutrition. It refers to the amount of energy remaining from the diet to support the body's basic physiological functions

after the energy used during exercise has been calculated (25). In athletes, EA is expressed in kilocalories (kcal) per kilogram of fat-free mass (FFM) rather than total body weight. This is because FFM—specifically muscle tissue—is the primary determinant of resting energy expenditure. This approach provides a more accurate assessment of the available energy to maintain health, recovery, and daily functioning beyond the demands of training (26). Available (usable) energy is expressed in calories (kcal) per kg of fat free mass (FFM):

EA= [Daily energy intake (kcal) – Energy expended during exercise (kcal)] / FFM (kg)

When energy intake is too low to fully support all normal physiological functions of the body, the limited energy available is diverted to prioritize vital, life-sustaining processes. This situation, in which caloric intake does not meet the demands of energy expenditure, is called low energy availability (LEA) (27). LEA can have a variety of harmful effects on the body; most notably, when energy availability falls below 30 kcal per kilogram of lean mass (FFM) per day, impairments in reproductive health and bone metabolism are frequently observed (28).

3.2. Prevalence of Low Energy Availability in Female Athletes

Recent studies report that the prevalence of low energy availability (LEA) in athletes ranges from 22% to 58% (9). A systematic review published in 2024, analyzing 59 studies covering different sports and levels of competition, aimed to investigate the prevalence of LEA and REDs in athletes and examine their effects on sports performance and injury risk. This review found an overall prevalence of LEA of 44.7% (10). Of the 4,134 female athletes included in the studies, 44.2% had LEA. The review revealed that LEA is more common in endurance and aesthetic sports, where body composition is closely linked to performance.

Measurable decreases in performance parameters have been observed in athletes with LEA. Decreases in running performance, endurance, and explosive strength, as well as declines in physiological adaptations such as increased aerobic capacity, have been reported. Coordination, agility, and cognitive functions have also been negatively affected. These limitations not only reduce competitive performance but also increase the likelihood of missing training due to illness (10). This highlights the importance of early diagnosis and targeted interventions in female athlete populations, where energy availability plays a critical role in maintaining health and performance.

3.3. Relative Energy Deficiency in Sport (RED-S)

The Female Athlete Triad (FAT) and Relative Energy Deficiency in Sport (RED-S) are two interrelated concepts based on low energy availability (LEA) and are critical for understanding this condition. For many years, FAT has described the relationship between energy availability, bone health, and menstrual function in female athletes (29). Recent studies have shown that LEA affects all athlete groups and has broader physiological consequences. Following these findings, the International Olympic Committee (IOC) introduced the RED-S concept in 2014, emphasizing both short- and long-term health and performance effects (30). RED-S reflects chronic low energy availability, in which energy intake persistently falls short of the combined demands of daily living and training. Furthermore, dangerous weight-control methods. Furthermore, dangerous weight control methods—such as rapid weight cycling, dehydration through sauna use or fluid restriction, and the misuse of laxatives or diuretics—(31) and obsessive eating or exercise behaviors driven by body image concerns can also trigger this condition (25).

In athletes who remain undernourished for extended periods, reductions in body fat percentage are accompanied by significant neuroendocrine changes: leptin, a satiety hormone, decreases; ghrelin, the “hunger hormone,” increases; and elevated peptide YY can blunt ghrelin’s orexigenic effects. Insulin levels fall while insulin sensitivity increases, and elevated cortisol suppresses GnRH secretion. This suppression disrupts the hypothalamic–pituitary–ovarian (HPO) axis, leading to functional hypothalamic amenorrhea, delayed menarche, or secondary amenorrhea (12, 32). Given the high prevalence of LEA among young female athletes, menstrual disturbances are particularly common in this population (33). Reduced GnRH also lowers estrogen production. Estradiol helps maintain bone health by inhibiting bone resorption and promoting bone formation—partly via osteoprotegerin (OPG)—so estrogen deficiency disrupts bone turnover and increases stress-fracture risk (34).

In addition to these physiological and hormonal consequences, athletes with RED-S may also experience psychological symptoms such as fatigue,

irritability, anxiety, and depression (35). The Low Energy Availability in Females Questionnaire (LEAF-Q) is a screening tool designed to identify athletes at risk for LEA and RED-S. It collects information about the athlete's lifestyle and symptoms, including reduced athletic performance, menstrual irregularities, and a history of bone stress injuries (36).

3.4. Impact on Athletic Performance

A significant amount of research has investigated the effects of LEA on athletic performance, examining various dimensions of how athletes respond to inadequate fueling. One study focused on female distance runners and found that athletes who did not adjust their energy intake to match a 130% increase in training volume over four weeks experienced a measurable decline in performance, at least 1.8% below baseline levels. Strikingly, this decline persisted not only at the end of the training period, but also after a two-week recovery phase. Regression analysis of the study confirmed a significant correlation between energy intake and running performance ($r = 0.61$, $p = 0.017$), reinforcing the idea that appropriate dietary adjustments are key to maintaining performance. Importantly, athletes who met their increased energy needs showed significant improvements, while those who did not were left behind (37). Similarly, another study has shown that LEA negatively impacts both physical and mental performance in athletes (38). These findings are consistent with other studies demonstrating that insufficient energy availability negatively affects performance across various sports and athlete populations.

In a large-scale investigation involving 1,000 female athletes aged 15–30 years, those with LEA were significantly more likely to experience reduced responsiveness to training, decreased endurance, coordination difficulties, and impaired concentration compared with athletes who maintained normal energy levels (2). These findings suggest that LEA can hinder both neuromuscular and cognitive adaptations, ultimately compromising training quality and competitive outcomes

Similarly, a study conducted with 833 athletes in Ireland found that those with LEA were significantly more likely to miss extended training periods—specifically 22 or more days in the past year—due to illness, compared with athletes who maintained adequate energy intake. This prolonged absence not only reduced athletes' readiness for competition but also slowed their long-term progression, highlighting the cumulative performance cost of chronic under-fueling (39).

Taken together, these studies demonstrate that inadequate energy intake not only impairs short-term performance but can also slow training adaptation, potentially disrupting intra-season and inter-season development. This necessitates monitoring energy balance as a critical component of training program planning.

4. Treatment of Eating Disorders and Low Energy Availability

4.1. Early Diagnosis and Screening

Early detection and management of low energy intake and disordered eating are of utmost importance in athletic programs (40). Physical examinations and questionnaires meant to find early warning indicators of LEA and EDs are among usual screening techniques. These evaluations should address important topics including body image, bone density, menstrual health, and dietary practices; for female athletes especially, these issues are quite pertinent. Tools such as food frequency surveys also help to draw attention to dietary group exclusion, low calorie intake, or nutrient deficits. Among the many well-known screening tools available to identify eating disorders are the Eating Disorder Examination Questionnaire (EDE-Q), the SCOFF Questionnaire, and the Primary Care Eating Disorder Screening (PCE-ESP).

Coaches and health professionals should actively track athletes' daily habits and behaviors outside of formal questionnaires and clinical interviews since subtle behavioral changes can sometimes indicate early signs of disordered eating. This emphasizes the need of continuous education—not only for medical teams but also for athletes themselves—to increase awareness and assist prevent the development of EDs and LEA (16). In support of this, a recent systematic review found that nutrition education interventions—often delivered through focused sessions by nutrition professionals—consistently improved sports nutrition knowledge, dietary behaviors, and factors affecting energy availability. This underscores the protective value of such education in reducing LEA risk and supporting performance recovery (41).

4.2. Preventive Strategies

Preventive Techniques Prominent groups like the American Academy of Pediatrics, the IOC Medical Commission, and the American College of Sports

Medicine (ACSM) have vigorously pushed national and international sports organizations to create policies limiting harmful weight loss behaviors. While the details of these policies vary by sport, key strategies include creating educational programs that discourage athletes from excessive dieting, providing serious attention to athletes who express concerns about weight loss or body composition changes, and revising sport-specific guidelines when necessary to protect athlete health.

The primary focus should be on athletes who attempt to change their weight and eating patterns in the belief that this will improve performance. Preventive measures center around education and awareness campaigns aimed at discouraging very low-calorie diets and reducing the risk of developing EDs. It is also important to create protective environments that minimize exposure to factors that may promote disordered eating behaviors (16). Beyond these measures, interventions that reduce the emphasis on leanness in coaching and media, and that increase nutrition education, have shown promise in lowering the risk of disordered eating in athletic populations. For example, studies conducted in school and university settings indicate that programs designed to reduce thin-ideal internalization and improve media literacy can effectively mitigate eating disorder risk factors (42).

4.3. Multidisciplinary Treatment

Early detection of ED is vital to improving prognosis and supporting the recovery journey. It is vital that athletes diagnosed with ED are seen as patients and receive a comprehensive care plan that includes medical nutrition therapy, psychological/psychiatric support, and regular medical follow-up. Nutritional interventions generally focus on restoring adequate energy availability, addressing nutrient deficiencies, and establishing sustainable eating habits appropriate for the athlete's training load. Among psychological interventions, cognitive behavioral therapy (CBT), family-based therapy (FBT) for young athletes, and motivational interviewing techniques are effective methods for addressing negative eating attitudes and body image issues. In severe cases of medical instability, inpatient or day hospital programs may be necessary for security and structured refeeding (43).

ACSM advocates a multidisciplinary treatment approach and emphasizes that training for athletes with eating disorders should be tailored to both the intensity and quality of their training. Restrictions implemented within this framework—such as reducing training load, limiting competition participation, or temporarily suspending the athlete—are primarily aimed at protecting the athlete's physical health. Furthermore, the psychological and performance-related impacts on teammates and the overall team environment are also considered (44).

Continuous education and follow-up following initial treatment are essential to prevent relapse and support the athlete's return to optimal performance. Coordinated communication between the sports medicine physician, dietitian, psychologist/psychiatrist, coach, and, if necessary, the athlete's family, along with consistent messaging and support, is crucial during this process (43).

5. Conclusion

In many sports, low body weight and low fat content are seen as performance-driven, and some athletes implement weight-loss strategies to achieve this goal without fully assessing the potential risks. However, low energy availability (LEA) and eating disorders (ED) can lead to numerous negative deteriorations in both health and performance. These include muscle loss, increased fatigue, impaired performance, increased risk of injury, impaired flexibility function, and impaired recovery.

These conditions can negatively impact training adaptations and competition preparation rather than leading to the intended performance enhancement. Therefore, supporting athletes to maintain healthy bodies through individualized nutrition education, adequate energy intake, and multidisciplinary monitoring is crucial. Early intervention, ongoing training, and personalized performance strategies play a critical role in protecting athletes' performance in both the short and long term.

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