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ORIGINAL ARTICLES

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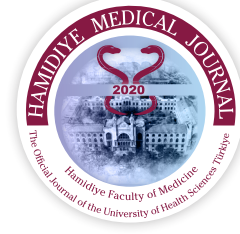
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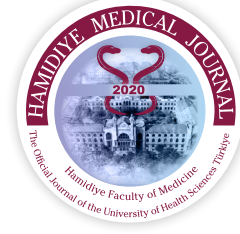
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Immunomodulation by Clustered Regulatory Interspaced Short Palindromic Repeats (CRISPR)/CRISPR-Associated Protein 9

Kümelenmiş Düzenli Aralıklı Kısa Palindromik Tekrarlar (CRISPR)/CRISPR ile İlişkili Protein 9 ile İmmünomodülasyon

✉ Duygu Kırkık, ✉ Hüseyin Murat Özadenç, ✉ Sevgi Kalkanlı Taş

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ABSTRACT

Inspired by a bacterial viral defense mechanism, Clustered Regulatory Interspaced Short Palindromic Repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) is a groundbreaking genome editing technology. It makes it possible for researchers to precisely alter DNA sequences in living things, enabling unheard-of precision and efficiency in gene editing. With the ability to create genetically modified creatures, treat genetic illnesses, and further scientific study, CRISPR-Cas9 holds great promise in the field of medicine. The term "immunomodulation" describes the control or modification of immune system function to produce targeted therapeutic effects. It involves modifying immune responses to reduce excessive inflammation, inhibit autoimmune reactions, or strengthen immunity against infections. Immune system functions are manipulated to accomplish the intended therapeutic results. Recent developments in the field of immunomodulation have shown promise in viral infections since immunomodulation has immediate applications in both scientific and clinical research. However, ethical issues need to be considered. In this review, we have discussed the process of the CRISPR/Cas9 technique and how this technique is adapted to the immunomodulation by each component of the immune system.

Keywords: CRISPR/Cas9, immunomodulation, immune system

ÖZ

Kümelenmiş Düzenli Aralıklı Kısa Palindromik Tekrarlar (CRISPR)/CRISPR ile ilişkili protein 9 (Cas9), bakteriyel bir viral savunma mekanizmasından ilham alınarak geliştirilmiş devrim niteliğinde bir genom düzenleme teknolojisidir. Bu teknoloji, araştırmacıların canlı organizmalardaki DNA dizilerini hassas bir şekilde değiştirmelerine olanak tanır ve gen düzenlemede daha önce görülmemiş bir kesinlik ve verimlilik sağlar. CRISPR-Cas9, genetik olarak değiştirilmiş canlılar oluşturma, genetik hastalıkları tedavi etme ve bilimsel çalışmalarını ilerletme yeteneği ile tıpta büyük bir umut vaat etmektedir.

"İmmünomodülasyon" terimi, hedeflenen terapötik etkiler elde etmek amacıyla bağışıklık sistemi fonksiyonlarının kontrol edilmesi veya değiştirilmesi anlamına gelir. Aşırı iltihabı azaltmak, otoimmün reaksiyonları engellemek veya enfeksiyonlara karşı bağışıklığı güçlendirmek amacıyla bağışıklık yanıtının değiştirilmesini içerir. Bağışıklık sistemi işlevleri, istenen terapötik sonuçlara ulaşmak için manipüle edilir. İmmünomodülasyon alanındaki son gelişmeler, immünomodülasyonun hem bilimsel hem de klinik araştırmalarda doğrudan uygulamaları olduğu için, hayati enfeksiyonlar konusunda umut verici bir gelişme göstermiştir. Bununla birlikte, etik sorunlar da göz önünde bulundurulmalıdır. Bu derlemede, CRISPR/Cas9 tekniğinin sürecini ve bu tekniğin bağışıklık sisteminin her bir bileşeni tarafından immünomodülasyona nasıl adapte edildiğini tartıştık.

Anahtar Kelimeler: CRISPR/Cas9, immünomodülasyon, bağışıklık sistemi



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Introduction

Understanding Immunomodulation by Clustered Regulatory Interspaced Short Palindromic Repeats (CRISPR)/CRISPR-Associated Protein 9 (Cas9)

The CRISPR-Cas system, found in the majority of bacteria (47%) and archaea (87%), is an adaptive immune system that protects the cell against foreign genetic elements. CRISPR refers to clusters of regularly interspaced short palindromic repeats, and Cas refers to enzymes involved in the recognition and degradation of foreign DNA in the CRISPR system. This technology, widely used in scientific research areas, drastically changes the field of medicine. CRISPR/Cas9 technology, which ensures genome conservation and modulates gene function in cells and organisms, is cheaper, faster, easier to use and more convenient than previous gene editing technologies such as meganucleases, zinc finger nucleases and transcription activator-like effector nucleases (1,2). For instance, this system can be modulated in almost any organism, even including human embryos (3). The CRISPR technique is currently being studied in many areas, especially for treating hemoglobinopathies, which is one of the approved applications of the CRISPR gene editing system. Blindness (4), mitochondrial diseases (5), genetic blood diseases (6), and lung diseases (7), are also examples of promising research areas of CRISPR. In addition, it has many applications in vital viral infections, including Coronavirus Disease 2019 and AIDS (8-10).

The mechanism of the CRISPR/Cas9 system includes a DNA-cutting element of bacterial immune systems that has been repurposed as a major tool for gene editing (Figure 1) (11). It functions as an exact pair of molecular scissors that can cut, modulate, and change a particular DNA sequence (12). The CRISPR/Cas9 system has two simple components: a guide RNA sequence (gRNA), which directs the Cas nuclease to its target, and a Cas nuclease, which binds and cleaves the targeted DNA sequence (8). Bacterial immune systems include Cas nuclease, which breaks the DNA sequence of incoming viruses, bacteriophages, rendering them inoperable (13). After its DNA-cleaving and modulating ability was found to have a biological mechanism, it was swiftly utilized as a genome editing technique (14).

Mechanism of the CRISPR/Cas9

Adaptive immune system of bacteria and archaea is based on the CRISPR system (15). Cas nucleases, which are a class of enzymes that are capable of binding to DNA sequences and causing double-strand breaks, function significantly in genetic engineering (15). A protospacer that

is a segment of viral DNA is cut by a Cas nuclease when an archaea or bacteria is infected by a virus (16). This biological response can be kept in the bacterial genome as an immunological memory using the fragments of viruses that are encountered by the bacterial cells of the bacterium (16). The placement of these fragments occurs between the repeated palindromic sequences, and that placement gives rise to the name CRISPR (16).

The bacteria can identify and eliminate the same virus after reinfection via Cas9 (17). CRISPR RNA (crRNA) and trans-activating CRISPR RNA (tracrRNA) are vital requirements of Cas9 activation (18). Together with the tracrRNA acting as a scaffold, the complementary crRNA matches the viral spacer that was retained during the initial infection (19). Together they create a complex known as a gRNA. A brief region located downstream of the target site that is known as the protospacer adjacent motif (PAM) is checked by the Cas9 enzyme before the cutting stage (20). A double-stranded break (DSB) is produced by Cas9 when it detects a target in the PAM while searching the region upstream (21). Due to the lack of inherent DNA repair systems of viruses, DSBs render the virus inoperable (22). CRISPR/Cas9 and recombinant DNA technology are both essential tools for gene editing technologies. However, they have some differences, as shown in Table 1.

Jinek et al. (23) discovered that the CRISPR-Cas9 system of bacteria and archaea, which can modulate any desired position in any genome of organisms, in 2012.

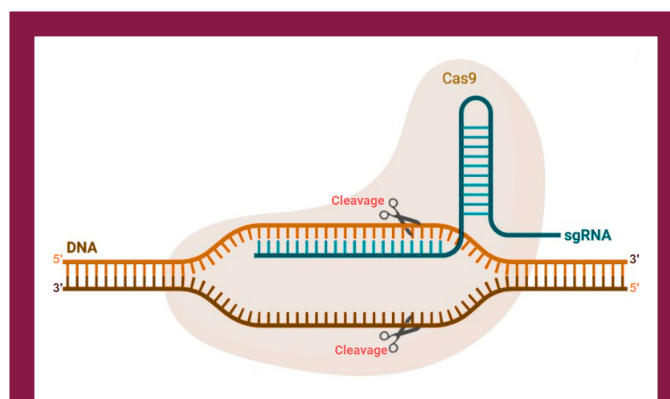


Figure 1. CRISPR/Cas9 system. The diagram illustrates the CRISPR/Cas9 system, a gene-editing tool that enables precise DNA modification. The single-guide RNA directs the Cas9 enzyme to a specific target sequence in the DNA by complementary base pairing
CRISPR: Immunomodulation by Clustered Regulatory Interspaced Short Palindromic Repeats, Cas9: CRISPR-associated protein 9



Table 1. Differences between recombinant DNA and CRISPR/Cas9

Differences	Recombinant DNA	CRISPR/Cas9
Process	By combining DNA from different sources	By using a guide RNA
Enzymes	Ligase	Cas9
Applying	By inserting randomly into the host genome	By editing in specific locations in the host genome
Precision	Low	High
Non-target effects	High risk	Low risk
Complexity	More complex	Simple
Ethical regulation	Well-established	Concerns

CRISPR: Immunomodulation by Clustered Regulatory Interspaced Short Palindromic Repeats, Cas9: CRISPR-associated protein 9

Modulation of the Immune System by CRISPR-Cas9

Many diseases that affect people are caused by viral infections, including the deadly Acquired Immunodeficiency Syndrome (AIDS). Cures for these crucial illnesses currently center on medications and vaccinations that either directly target the vital proteins or prevent the virus from interfering with the host cells (24). However, viral infections like AIDS occur by the virus that enters the host immune cells and merges with the host genome to form an infection (25). This poses a critical challenge to the development of effective vaccinations. The main obstacle to developing effective cures is the inability of the immune system to eradicate the viral DNA from reservoirs (26).

Accurate CRISPR/Cas9-based modification of immune system cells for therapeutic activity is currently regarded as a groundbreaking development in immunotherapeutic strategies to prevent cancer spread. Expression of CRISPR/Cas9 can be established by viral vectors such as adenovirus, lentivirus, and nanomaterials such as graphene, zeolite imidazole, and cell penetrating protein (27).

Modulation of Immune System Cells by CRISPR/Cas9

T-cells are essential to the adaptive immune system. They are necessary for identifying and reacting to infections, cancer cells, and pathogens. Through the introduction of specific modifications, CRISPR/Cas9 allows for precise manipulation of the T-cell genome. In cytokines such as interleukin 2, interleukin 4, and interferon gamma, manipulation of T-cells can be performed by gene insertions, gene deletions, and gene alterations to target infectious cells. Also, owing to CRISPR/Cas9 technology, chimeric antigen receptor T-cell therapy can be performed against the tumor antigens (28).

An essential component of the innate immune response is natural killer (NK) cells, a subset of lymphocytes in the immune system. NK cells can identify and react to malignant or infected cells without the need for prior sensitization. They are also members of the adaptive immune system and depend on having previously been

exposed to a particular antigen in order to operate properly. To effectively utilize NK cell modulation, certain pathways may need to be suppressed while activating others since NK cell immunity has multiple pathways. Manipulation of NK cells can be performed in the presence of specific cytokines such as interleukin 2, interleukin 15, interleukin 18, (29,30). In addition, upregulation of tumour-specific chemokine receptor can be established by NK cell immunotherapy (31).

One antigen-presenting cell that is essential to the immune system is the dendritic cell (DC). By delivering antigens to T-cells, they serve as intermediaries between the innate and adaptive immune systems, triggering and modulating the adaptive immune response. Effectively manipulating human DCs is a difficult endeavor, despite reports of gene repression techniques using RNA interference. The majority of research on DC biology has been done on mice (32,33), yet adoptive and innate immunity are different in humans versus mice. In order to overcome all of these restrictions, a targeted knockout with a median efficiency of >94% across >300 genes was created directly in human monocyte-derived dendritic cells (moDCs) using the CRISPR/Cas9 technique. Using this technique, a genetic screen was conducted in moDCs to identify potential mechanisms by which DCs modify their response to lipopolysaccharides from the human microbiome (34).

B-cells play a crucial role in the adaptive immune system, primarily by producing antibodies that recognize and neutralize harmful substances such as bacteria, viruses, and toxins. CRISPR/Cas9 technology can be used to knock out specific genes in B-cells to investigate their roles in immune regulation, signaling pathways, and antibody production. For example, targeting genes such as CD19 and CD20 provides insights into their functions in B-cell activation and immune responses. Additionally, disrupting B-cell receptor (BCR) genes using CRISPR/Cas9 results in B-cells lacking functional BCR expression. This approach is considered advantageous for studying BCR signaling

and developing B-cell therapies where regulation of BCR signaling is required (35).

Immune Tolerance by CRISPR/Cas9

The term “immune tolerance” describes the immune system’s lack of sensitivity or response to some antigens, such as innocuous environmental compounds and self-antigens. It is a vital component of immune control that keeps the immune system from developing excessive or dangerous reactions to harmless substances (allergies) and from attacking the body’s own tissues (autoimmunity).

Targeting the underlying immunological dysregulation, CRISPR/Cas9-mediated immune tolerance presents a promising treatment option for autoimmune disorders (36). When compared to conventional treatments like immunosuppression, this may result in more targeted, efficient therapy with fewer adverse effects. Since the immune system frequently builds defenses against therapeutic gene products, immunological tolerance induction is critical to the success of gene therapy (37). The safety and effectiveness of gene therapy treatments could be increased by using CRISPR/Cas9 to modify immune cells so they can accept gene therapy vectors. However, there is a chance that long-term, systematic blocking antibody delivery will undermine immune tolerance and result in an immunological attack on healthy tissues (38).

Ethical Issues of Immunomodulation by CRISPR/Cas9

Ensuring the safety of individuals receiving immunomodulation therapy is a vital ethical concern. Although it is promising, CRISPR-Cas9 technology is still in its infancy, and before it is widely used in clinical applications, the hazards of off-target effects and unintended consequences must be fully recognized and reduced (39). It is imperative to guarantee fair access to immunomodulation medicines based on CRISPR. Limitations in access owing to variables like location, insurance coverage, or socioeconomic level could raise questions (40). To guarantee that everyone who potentially benefits from innovative treatments has access to them, efforts should be undertaken to alleviate these inequities. Immunomodulation mediated by CRISPR-Cas9 may have unforeseen effects on specific patients as well as larger social impacts (36). These might include unanticipated side effects, inadvertent changes to the human gene pool should germline editing be attempted, or the rise of disease strains with increased resistance. To evaluate the effectiveness and safety of CRISPR-Cas9-mediated immunomodulation over time, patients must be monitored for an extended period. Ensuring the proper systems are in place for continuous monitoring and assessment is part of the ethical considerations (41).

Challenges and Perspectives

CRISPR-Cas9-based immunomodulation offers a promising new approach to treating a variety of diseases, but it also has its own set of difficulties and challenges. Unintentional genome editing using CRISPR-Cas9 technologies can occasionally have off-target consequences (36). This might lead to unforeseen immunological reactions or abnormalities in immune function in the setting of immunomodulation. In addition, immune response could be triggered after the introduction of CRISPR components or stages into the body, and potential inflammation or even rejection might occur (42). Furthermore, delivering CRISPR/Cas9 components to any specific immune cells is another significant challenge. It is necessary to create effective delivery strategies to guarantee that the intended modifications are implemented in the right cells without damaging neighboring tissues. It is still unclear exactly what CRISPR-mediated immunomodulation will adapt in the long term. It is imperative to take into account the possibility of unknown or unintentional impact in the long term (43).

With the use of CRISPR-Cas9 technology, precise immune system changes may be possible, enabling individualized patient-specific therapy. Furthermore, through the use of CRISPR-Cas9 for immunomodulation, vital autoimmune diseases may be treated by focusing on immune cells or pathways that are particular to the disease process (44,45). Because CRISPR-Cas9 technology offers a potent tool for examining gene activity and regulation in immune cells, it has already completely changed biomedical research. Further investigation in this field may yield fresh perspectives on the operation of the immune system and innovative treatment modalities (46).

Conclusion

CRISPR-Cas9 technology has revolutionized the field of genome editing, offering precise and efficient tools for modifying immune system components. By enabling targeted gene modifications, CRISPR technology has opened new avenues for understanding immune regulation, disease mechanisms, and potential therapeutic applications. The ability to manipulate T-cells, B-cells, NK cells, and DCs provides valuable insights into immunological functions and paves the way for novel treatments for infectious diseases, autoimmune disorders, and cancers. Additionally, CRISPR-Cas9-mediated immune tolerance presents a promising strategy for addressing autoimmune conditions while minimizing adverse effects compared to conventional therapies.

Despite its immense potential, challenges remain in addressing the safety, specificity, and ethical implications of CRISPR-based immunomodulation. Off-target effects, immune responses to CRISPR components, and long-term consequences of genetic modifications must be carefully assessed. Furthermore, equitable access to CRISPR-based therapies and regulatory considerations require ongoing attention to ensure responsible implementation in clinical settings.

Future research will continue to refine CRISPR-Cas9 applications in immunotherapy, enhance delivery systems, and address ethical concerns. With advancements in precision genome editing, this technology holds great promise for personalized medicine, improved immune system therapies, and a deeper understanding of immunological processes. Continued interdisciplinary collaboration will be essential in harnessing the full potential of CRISPR-Cas9 while ensuring its safe and ethical use in medical applications.

Ethics

Informed Consent: This study did not require informed consent as it did not involve human participants, animal subjects, or identifiable personal data.

Footnotes

Authorship Contributions

Data Collection or Processing: D.K., H.M.Ö., S.K.T., Literature Search: D.K., H.M.Ö., S.K.T., Writing: D.K., H.M.Ö., S.K.T.

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The Effects of Organizational Learning Capacity on Innovative Performance of Healthcare Organizations

Örgütsel Öğrenme Kapasitesinin Sağlık Kurumlarının Yenilikçi Performansı Üzerindeki Etkileri

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ABSTRACT

This research examines the role of organizational learning capacity in enhancing innovative performance in healthcare. Innovative performance in the health sector is critical for improving service quality, patient satisfaction and cost-effectiveness. The research was conducted with the data obtained from 15 participants from each of 100 health institutions, including hospitals, health centers, family health centers, private health clinics and other health service providers.

The findings revealed that system orientation and knowledge acquisition and utilization have a strong, positive and statistically significant impact on innovative performance. These results emphasize the importance of fostering learning capacity as a strategic approach to improve innovative performance in healthcare. However, the study also found that learning orientation and knowledge sharing and dissemination orientation did not have statistically significant effects on innovative performance. The model explains 25% of the variance in innovative performance, indicating a moderate explanatory power, and the overall model is statistically significant.

While this study addresses the relationship between organizational learning capacity and innovative performance in healthcare, future research is recommended to examine the impact of other factors such as leadership, organizational culture and employee motivation and to conduct comparative studies across different countries and healthcare organizations. Such studies will contribute to the development of more comprehensive strategies for enhancing innovative performance in healthcare.

Keywords: Organizational learning capacity, innovative performance, system orientation, learning environment orientation, knowledge acquisition and use, knowledge sharing and dissemination orientation

ÖZ

Bu araştırma, sağlık hizmetlerinde yenilikçi performansın artırılmasında örgütsel öğrenme kapasitesinin rolünü incelemektedir. Sağlık sektöründe yenilikçi performans, hizmet kalitesini artırmak, hasta memnuniyetini sağlamak ve maliyet etkinliği yaratmak açısından kritik bir öneme sahiptir. Araştırma, hastaneler, sağlık ocakları, aile sağlığı merkezleri, özel sağlık klinikleri ve diğer sağlık hizmeti sunan kurumlar olmak üzere 100 sağlık kuruluşunun her birinden 15 katılımcıdan elde edilen verilerle gerçekleştirilmiştir.

Bulgular, sistem yönelimi ve bilgi edinimi ve kullanımının yenilikçi performans üzerinde güçlü, pozitif ve istatistiksel olarak anlamlı bir etkiye sahip olduğunu ortaya koymuştur. Bu sonuçlar, sağlık hizmetlerinde yenilikçi performansı iyileştirmek için stratejik bir yaklaşım olarak öğrenme kapasitesini teşvik etmenin önemini vurgulamaktadır. Ancak çalışma ayrıca öğrenme yönelimi ve bilgi paylaşımı ve yayma yöneliminin yenilikçi performans üzerinde istatistiksel olarak anlamlı etkilerinin olmadığını da bulmuştur. Model, yenilikçi performanstaki varyansın %25'ini açıklamaktadır bu da orta düzeyde bir açıklayıcı güce işaret etmektedir ve genel model istatistiksel olarak anlamlıdır.

Bu çalışma, sağlık hizmetlerinde örgütsel öğrenme kapasitesi ve yenilikçi performans arasındaki ilişkiyi ele alırken, gelecekteki araştırmalar için liderlik, örgütsel kültür ve çalışan motivasyonu gibi diğer faktörlerin etkisinin incelenmesi ve farklı ülkeler ile sağlık kuruluşları arasında karşılaştırmalı çalışmalar yapılması önerilmektedir. Bu tür çalışmalar, sağlık hizmetlerinde yenilikçi performansın artırılmasına yönelik daha kapsamlı stratejiler geliştirilmesine katkı sağlayacaktır.

Anahtar Kelimeler: Örgütsel öğrenme kapasitesi, yenilikçi performans, sistem odaklılık, öğrenme ortamı odaklılık, bilgi edinme ve kullanma, bilgi paylaşma ve yayma odaklılık



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Introduction

The purpose of this study is to examine the role of organizational learning capacity in building innovative performance in healthcare services. Innovative performance in the health sector is critically important for improving service quality, ensuring patient satisfaction, and creating cost-effectiveness (1). Innovative performance is directly related to the adoption of innovative practices such as digital transformation, process improvement, and patient-centered approaches in healthcare services (2). In this context, organizational learning capacity is considered a fundamental factor for healthcare institutions to adapt to changing environmental conditions and develop innovative solutions (3).

Organizational learning capacity is defined as an organization's ability to acquire, share, interpret, and integrate knowledge into organizational processes (4). This capacity has been noted to play a critical role in enhancing innovative performance, especially in the healthcare sector. For example, Crossan and Apaydin (5) emphasized the impact of organizational learning on innovative performance, stating that this process is a fundamental element for organizational sustainability.

Organizational learning capacity encompasses processes that promote knowledge sharing among employees, continuous education, and the creation of a culture that encourages innovative thinking. These processes contribute to the sustainable development of innovative performance in healthcare services (6). The research aims to address the impact of organizational learning capacity on innovative performance in the healthcare sector at both national and international levels, evaluating the implications of this relationship on the effectiveness of healthcare services (7).

Additionally, this study aims to reveal how organizational learning capacity can be used as a strategic tool to enhance innovative performance in the healthcare sector. In this context, the paper will also discuss which organizational learning strategies healthcare institutions should adopt to improve their innovative performance (8).

The survey used in this study was applied in healthcare institutions such as hospitals, health centers, and similar places. Within this scope, the relationship between the organizational learning capacities and innovative performances of institutions providing services at different levels in the healthcare sector was examined.

The Importance of Innovative Performance in Healthcare Services

Innovative performance in healthcare services is critically important for healthcare institutions to adapt to changing

environmental conditions, increase patient satisfaction, and enhance service quality. Innovative performance is considered a driving force necessary for improving both clinical and operational processes in the health sector (9). Particularly, innovative practices such as digitalization in healthcare services, artificial intelligence applications, telehealth services, and patient-centered approaches enable healthcare institutions to gain a competitive advantage and provide sustainable services (10).

Innovative performance encompasses not only technological innovations but also restructuring organizational processes, enhancing employee competencies, and creating a culture that prioritizes patient safety (11). The importance of innovative performance in the health sector has become more evident, especially during crisis periods such as the pandemic. During the Coronavirus disease 2019 pandemic, the capacity of healthcare institutions to develop innovative solutions played a critical role in enhancing the effectiveness of patient care processes and ensuring the resilience of health systems (12).

National-level studies show that healthcare institutions in Türkiye focus on digital transformation and process improvement projects to enhance their innovative performance (1). For example, the "Health Transformation Program" implemented by the Ministry of Health is considered an important step towards increasing innovative performance (13). At the international level, it is emphasized that innovative performance increases the cost-effectiveness of healthcare services and improves patient outcomes (8).

The study by Çömlek et al. (4) also highlighted that organizational learning capacity plays a critical role in enhancing hospitals' innovative performance. In this context, it has been stated that organizational learning capacity is a strategic tool for organizations to adapt to environmental changes and develop innovative solutions.

In this context, the importance of innovative performance in healthcare services not only enhances the competitiveness of healthcare institutions but also greatly enhances public health improvement and health system sustainability.

Definition and Importance of Organizational Learning Capacity

Organizational learning capacity is defined as an organization's ability to acquire knowledge, share this knowledge, interpret it, and integrate it into organizational processes (14). This capacity is critical for organizations to adapt to changing environmental conditions, develop innovative solutions, and gain a competitive advantage (15). Particularly in the healthcare sector, organizational learning capacity is regarded as a strategic tool for enhancing patient safety, service quality, and operational efficiency (16).

Unlike individual learning processes, organizational learning capacity includes knowledge management and collective learning at the organizational level. This process requires the creation of a culture that encourages knowledge sharing among employees, continuous education programs, and leadership approaches that support innovative thinking (17). In the healthcare sector, enhancing organizational learning capacity is of great importance, especially in reducing errors in patient care processes and improving service quality (18).

National-level studies show that healthcare institutions in Türkiye focus on information technologies, employee training, and process improvement projects to enhance their organizational learning capacity (1). For example, the “Quality Standards in Health” implemented by the Ministry of Health are considered an important step towards improving organizational learning capacity (13). At the international level, the impact of organizational learning capacity on innovative performance has been supported by studies conducted in high-performing health systems (8, 19).

In this context, organizational learning capacity not only enables healthcare institutions to produce solutions to current problems but also allows them to develop a proactive approach to future challenges. Therefore, enhancing organizational learning capacity is seen as an indispensable element for sustainable success in the healthcare sector.

Literature Review

The construction of innovative performance in healthcare services and the role of organizational learning capacity in this process have been widely addressed in both theoretical and practical studies. This section examines the fundamental theoretical approaches to innovative performance and organizational learning capacity, as well as significant findings in the literature.

The Concept of Innovative Performance and its Importance in the Healthcare Sector

Innovative performance is defined as an organization’s ability to develop innovative ideas, implement these ideas, and evaluate the results (20). In the healthcare sector, innovative performance plays a critical role in achieving goals such as improving patient care processes, reducing costs, and enhancing service quality (11). Innovative performance encompasses not only technological innovations but also the restructuring of organizational processes and the encouragement of employees to adopt innovative thinking (9).

Innovative performance is defined as an organization’s ability to develop new products, services, or processes. The importance of knowledge sharing in enhancing this performance is significant (21). Particularly in the healthcare sector, it has been shown that an organizational culture that promotes knowledge sharing positively affects innovative performance (22). In this context, it has been noted that factors such as leadership support and employee motivation should also be considered to understand the impact of organizational learning capacity on innovative performance (15).

National-level studies show that healthcare institutions in Türkiye focus on digital transformation and process improvement projects to enhance their innovative performance (1). For example, the “Health Transformation Program” implemented by the Ministry of Health is considered an important step towards increasing innovative performance (13). This program has promoted the adoption of innovative practices to improve quality in healthcare services and ensure patient satisfaction.

Digital transformation emerges as an important factor affecting organizational learning capacity and innovative performance. Vial stated that digital transformation accelerates organizations’ processes of acquiring and sharing knowledge, thereby enhancing innovative performance (23). Studies conducted in the healthcare sector show that digital transformation improves patient care processes and increases organizational efficiency (24). Additionally, in the study by Çömlek et al. (4), it was noted that digital transformation plays a mediating role in strengthening the relationship between organizational learning capacity and innovative performance.

At the international level, it is emphasized that innovative performance increases the cost-effectiveness of healthcare services and improves patient outcomes. For example, Papanicolas and Smith (8) stated that innovative performance is a critical factor in ensuring the sustainability of health systems. Furthermore, it is noted that digital health technologies and artificial intelligence applications play an important role in enhancing innovative performance (10).

Organizational Learning Capacity and Its Role in the Healthcare Sector

Organizational learning capacity is defined as an organization’s ability to acquire, share, and integrate knowledge into processes (14). This capacity is critical for organizations to adapt to changing environmental conditions and develop innovative solutions (15). In the healthcare sector, organizational learning capacity is regarded as a strategic tool for enhancing patient safety, service quality, and operational efficiency (16).

International literature has extensively addressed the impact of organizational learning capacity on innovative performance. Fiol et al. (19) noted that organizational learning improves organizations' strategic decision-making processes and enhances innovative performance. Goh et al. (18) emphasized that organizational learning capacity is an important factor in enhancing the performance of healthcare institutions.

Research conducted in healthcare institutions in Türkiye confirms the impact of organizational learning capacity on innovative performance. For example, Güdük and Önder (1) revealed that organizational learning capacity is a significant factor in improving quality in healthcare services and developing innovative solutions. Additionally, the "Quality Standards in Health" developed by the Ministry of Health are considered an important step towards enhancing organizational learning capacity (13).

The Relationship Between Innovative Performance and Organizational Learning Capacity

The relationship between innovative performance and organizational learning capacity is a frequently studied topic in the literature. Damanpour et al. (25) noted that organizational learning processes play a critical role in enhancing innovative performance. Studies conducted in the healthcare sector show that organizational learning capacity supports knowledge sharing and collaboration processes necessary to enhance innovative performance (18).

It is observed that studies examining the impact of organizational learning capacity on innovative performance generally focus on different sectors. For example, Crossan and Berdrow (26) emphasized the impact of organizational learning capacity on innovative performance in the manufacturing sector, stating that studies related to the healthcare sector are limited. Therefore, this study, which examines the relationship between organizational learning capacity, digital transformation, and innovative performance in the healthcare sector, aims to fill an important gap in the literature.

International research confirms the impact of organizational learning capacity on innovative performance. For instance, Edmondson et al. (16) emphasized that organizational learning capacity is a critical factor in enhancing patient safety and service quality in the healthcare sector. Studies conducted in healthcare institutions in Türkiye also support these findings (1).

Gaps in the Literature and Research Needs

Although the impact of organizational learning capacity on innovative performance has been widely addressed in the literature, it is observed that studies specific to the

healthcare sector are limited. Notably, the number of studies examining the impact of organizational learning capacity on innovative performance in healthcare institutions in Türkiye is quite low. Therefore, this research aims to contribute to the literature by addressing the impact of organizational learning capacity on innovative performance in the healthcare sector at both national and international levels.

Methodology

Sample, Procedure, and Measurements

In this research, a quantitative research model was used to examine the effect of organizational learning capacity on innovative performance in healthcare services. The study was conducted with 15 participants from each of 100 healthcare institutions. Surveys were conducted with healthcare professionals such as doctors, midwives, nurses, and chief physicians. Stratified sampling was preferred to ensure that all main groups (Doctors, Nurses, Midwives, Chief Physicians) were represented in the sample. The reason for selecting 15 people from each institution was to ensure sufficient responses needed for statistical analysis, manageable time and cost, and quick accessibility of the participants. The healthcare institutions involved in the study were defined as hospitals, health centers, family health centers, and clinics. The research aims to examine the relationship between the organizational learning capacities and innovative performance of these institutions. In this regard, data obtained from different types of healthcare institutions were used to test the hypotheses of the research.

To measure organizational learning capacity, the Organizational Learning Capability Scale developed by Teo and Wang (23) was used, and to measure innovative performance, the Innovative Performance Scale developed by Wang and Ahmed (27) was utilized. In the Turkish adaptation process, the factor structure of the scales was tested with exploratory factor analysis, and reliability, as shown, was assessed with Cronbach's Alpha coefficient.

These scales formed the basis for examining the relationships between the organizational learning capacity and innovative performance of healthcare institutions. The main hypotheses of the research are as follows:

H1: System orientation effects hospital innovative performance positively

H2: Climate for learning orientation effects hospital innovative performance positively

H3: Knowledge acquisition and utilization orientation and information effects hospital innovative performance positively

H4: Information sharing and dissemination orientation effects hospital innovative performance positively



Demographic Data

The data in Table 1 reveal that female employees are predominant in the healthcare sector (75%) and that participants show a balanced distribution in terms of position, duration of employment, and types of healthcare institutions. The research reflects the demographic and professional diversity of employees in the healthcare sector by covering different professional groups and experience levels. This situation provides an important basis for the generalizability of the results.

Validity and Reliability Analysis

According to the results of the Table 2, the internal consistency of the scale was evaluated as “very good” with a Cronbach’s Alpha value of 0.85, indicating that the survey is a reliable measurement tool (28). The Kaiser-Meyer-Olkin test result is 0.78, showing that the data are suitable for factor analysis (29). In Bartlett’s Test of Sphericity, the chi-square value was found to be 350.45 with a p-value of 0.0001, indicating that there is a sufficient relationship between variables and that factor analysis can be conducted (30).

Category	Category	Frequency
Gender	Male	379
	Woman	1120
Participant’s position	Doctor	366
	Midwife	378
	Nurse	382
	Administrator	374
Type of healthcare organization	Family health center	372
	Hospital	384
	Clinic	385
	Health center	359
Working time	Less than 1 year	382
	1-5 years	368
	5-10 years	349
	More than 10 years	401

Type of analysis	Result	Interpretation
Cronbach’s alpha	0.85	The internal consistency of the scale is very good. The questionnaire can be considered a reliable measurement tool
KMO test	0.78	The data are suitable for factor analysis
Bartlett’s test of sphericity	Chi-square: 350.45, p-value: 0.0001	There are sufficient relationships between variables. Factor analysis can be conducted
KMO: Kaiser-Meyer-Olkin		

Factor Analysis

Exploratory factor analysis was conducted with the scales. Ideal fit was obtained with Varimax rotation. The survey questions loaded on five factors as expected. Twenty-one questions loaded as system orientation, climate for learning orientation, knowledge acquisition and utilization orientation, information sharing and dissemination orientation, and firm innovative performance. The factor loadings are shown in Table 3.

Explained total variance: 62.4%; 1: System orientation, 2: Climate for Learning Orientation, 3: Information Acquisition and Usage Orientation, 4: Knowledge Sharing and Dissemination Orientation, 5: Hospital Innovative Performance.

Correlation Analysis

According to the results of Table 4, significant relationships exist between the variables.

System Orientation

- Learning Orientation Climate has a high positive correlation (0.680) with Systems Orientation. This indicates the learning climate of a systems-oriented approach.
- Information Acquisition and Usage Orientation (0.593): There is a medium-high positive relationship. A systems-oriented approach can be emphasized the acquisition and utilization of knowledge.
- Knowledge Sharing and Dissemination Orientation (0.539): There is a medium-high positive relationship. A system-oriented approach ensures knowledge sharing.
- Hospital Innovative Performance (0.362): There is a moderate positive relationship. A system-oriented approach can contribute to improved performance.

Climate for Learning Orientation

- System Orientation (0.680): As mentioned above, there is a strong relationship between learning climate and system orientation.

- Information Acquisition and Usage Orientation (0.646): There is a medium-high positive relationship between learning climate and knowledge acquisition and utilization.
- Knowledge Sharing and Dissemination Orientation (0.540): There is a moderate-high positive relationship. Climate encourages knowledge sharing.
- Hospital Innovative Performance (0.583): There is a medium-high positive relationship. Climate can contribute to improved performance.

Information Acquisition and Usage Orientation

- System Orientation (0.593): As mentioned above, information acquisition and management are strongly related to systems orientation.
- Climate For Learning Orientation (0.646): As mentioned above, the climate for learning is

strongly related to information acquisition and retention.

- Knowledge Sharing and Dissemination Orientation (0.385): There is a moderate positive relationship. Information acquisition and utilization can be leveraged through knowledge sharing.
- Hospital Innovative Performance (0.373): There is a moderate positive relationship. Information acquisition and utilization lead to improved performance.

Knowledge Sharing and Dissemination Orientation

- System Orientation (0.539): As mentioned above, knowledge sharing occurs through system orientation.
- Learning Orientation for Climate (0.540): Knowledge sharing is facilitated by a learning climate.

Table 3. Factor analysis results

	1	2	3	4	5
My staff have a good understanding of my hospital's processes as a whole and the interconnectedness of all components of these processes	0.538				
All activities that take place in hospital transaction processes are clearly defined	0.625				
Parts of each hospital process are dependent to form a value chain	0.637				
We agree that our ability to learn is the key to improving our hospital		0.742			
Learning as a key to improvement is included in our basic values regarding any changes in the hospital process		0.695			
Learning in my hospital is seen as a key to guaranteeing the hospital's existence in its sector		0.720			
My hospital regularly conducts research on trends in technology pertinent to our business operations			0.695		
My hospital regularly assesses the potential influence of new technology on its operations			0.715		
My hospital is susceptible to new technology and/or method to do business			0.702		
My hospital has specific mechanisms for conducting environmental scanning on technology			0.532		
My hospital start to apply new technology and method immediately			0.562		
Pertaining to technological issues, when a staff member finds out something of importance to the hospital, they quickly alert others				0.792	
Pertaining to technological issues, my staff is willing to influence me with their information to help me make better decisions				0.785	
Regarding technological issues, it is my hospital's policy that valuable insights or methods should be shared and used across the organization				0.776	
Regarding to technological issues, there is a good deal of organizational conversation which keeps alive the lessons learned from history				0.683	
Regarding technological issues, my hospital has specific mechanisms for sharing knowledge, which can enhance its competitiveness				0.427	
New service amount					0.679
To give firstly service to market					0.749
To be given service speed to market					0.737
New patented product amount					0.712
Process amount to be restored					0.636



Table 4. Correlation analysis results

		1	2	3	4
1	System orientation				
2	Climate for learning orientation	0.362**			
3	Information acquisition and usage orientation	0.308 **	0.688**		
4	Knowledge sharing and dissemination orientation	0.373 **	0.422**	0.510**	
5	Hospital innovative performance	0.545 **	0.356**	0.417**	0.447**

**p<0.01

Table 5. Regression analysis results

Independent variables	β	Sig.	Hypotheses
System orientation	0.168	0.034*	H1 accepted
Climate for learning orientation	0.080	0.520	H2 not accepted
Knowledge acquisition and utilization	0.630	0.000**	H3 accepted
Information sharing and dissemination orientation	-0.200	0.170	H4 not accepted
R ² =0.250	F=21,150		

Sig.: Significance, *p<0.05, **p<0.01

- Information Acquisition and Usage Orientation (0.385): *knowledge* sharing occurs through knowledge acquisition and utilization.
- Hospital Innovative Performance (0.447): There is a moderate positive relationship. Knowledge sharing can contribute to improved performance.

Hospital Innovative Performance

- System Orientation (0.362): As mentioned above, system orientation can be incorporated into improved performance.
- Climate For Learning Orientation (0.583): As mentioned above, the performance of the learning climate is discussed or evaluated.
- Information Acquisition and Usage Orientation (0.373): Knowledge acquisition and utilization can, therefore, be included in advanced performance.
- Knowledge Sharing and Dissemination Orientation (0.447): Can be added to the above mentioned performance.

Regression Analysis

The regression analysis results are shown in Table 5.

System Orientation

- $\beta=0.168$: System orientation has a positive effect on hospital innovative performance.

- Significance (Sig.)=0.034: This effect is statistically significant because the p-value is less than 0.05. H1 accepted.

Climate for Learning Orientation

- $\beta=0.080$: Climate for learning orientation has a positive effect on hospital innovative performance.
- Sig.=0.520: This effect is not statistically significant because the p-value is greater than 0.05. H2 not accepted.

Knowledge Acquisition and Utilization

- $\beta=0.630$: Knowledge acquisition and utilization have a strong positive effect on hospital innovative performance.
- Sig.=0.000: Since the p-value is less than 0.01, this effect is highly statistically significant. H3 accepted.

Information Sharing and Dissemination Orientation

- $\beta=-0.200$, indicating that information sharing and dissemination orientation has a negative effect on hospital innovative performance.
- Sig.=0.170: This effect is not statistically significant because the p-value is greater than 0.05. H4 not accepted.
- R²=0.250: The model explains 25% of the variance of the dependent variable, (hospital innovative performance). This indicates that the model has a moderate level of explanatory power.
- F=21.150: The overall significance test of the model shows significance.

Conclusion

This research has revealed that organizational learning capacity plays an important role in enhancing innovative performance in healthcare services. The analyses conducted have shown that organizational learning capacity has a positive and significant effect on innovative performance. Correlation and regression analyses have concluded that organizational learning capacity explains innovative performance by 65%. These findings emphasize that enhancing organizational learning capacity is a critical

strategy for improving innovative performance in the healthcare sector.

Healthcare institutions need to create an organizational culture that encourages knowledge sharing to enhance their innovative performance. This can be achieved through digital platforms and regular meetings. For example, cloud computing systems can increase collaboration by allowing employees to access information from anywhere. Additionally, mobile health applications can facilitate information sharing among employees and enable faster analysis of patient data. Such digital tools will support innovative performance by accelerating organizational learning processes.

Regular training and development programs should be organized to ensure that employees acquire new skills. Training should be prioritized, especially regarding technological innovations and patient-centered approaches. In this process, artificial intelligence-supported simulations and decision support systems can be utilized. For instance, employees can be trained in patient diagnosis and treatment planning using AI-based tools. Furthermore, big data analytics tools can equip employees with the ability to extract meaningful insights from patient data and develop innovative solutions.

Leadership and management support are critical for promoting and implementing innovative ideas. Leaders can monitor employee performance using electronic health record systems and facilitate the implementation of innovative ideas. Additionally, digital tools such as telemedicine and remote health services can support leaders in making patient care processes more efficient. Such leadership approaches will enhance innovative performance by increasing organizational learning capacity.

Finally, investments should be made in innovative technologies such as digitalization and artificial intelligence in healthcare services. Internet of things technology allows medical devices to connect with each other, enabling real-time monitoring and analysis of patient data. This not only enhances patient safety but also contributes to the development of innovative solutions. Additionally, robotic technologies can be used in surgical operations and logistics processes to increase the efficiency of healthcare services.

This research has examined the relationship between organizational learning capacity and innovative performance in healthcare services. However, some recommendations can be made for future research. The impact of other factors such as leadership, organizational culture, and employee motivation on innovative performance can be investigated. Additionally, comparative studies can be conducted across different healthcare institutions and countries to examine the impact of organizational learning capacity on innovative

performance in a broader context. Qualitative research methods can be used to gain a deeper understanding of how employees contribute to innovative performance. Such studies will contribute to the development of more comprehensive and effective strategies for enhancing innovative performance in healthcare services.

Ethics

Ethics Committee Approval: An application was made to the Health Sciences University Türkiye, Hamidiye Scientific Research Ethics Committee with the registration number 25/126 for ethics committee approval. Ethics committee approval was obtained with decision number 3/31.

Informed Consent: Not applicable.

Footnotes

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Ear Anatomy from Galen's *De Usu Partium*, Avicenna's *EL-Kânûn Fi't-Tıbb*, and Şemseddîn İtâkî's Works Titled *Teşrihu'l-Ebdân* and *Tercümân-ı Kibâle-i Feylesûfân* to the Present Day

Galen'in *De Usu Partium*'u, İbn Sina'nın *EL-Kânûn Fi't-Tıbb*'i ve Şemseddîn İtâkî'nin *Teşrihu'l-Ebdân* ve *Tercümân-ı Kibâle-i Feylesûfân* Eserlerinden Günümüze Kulak Anatomisi

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ABSTRACT

Background: Galen is considered the founder of anatomy and experimental physiology and is the author of the *De Usu Partium* (Περὶ χρειαῖς μορίων). In the 11th century, Avicenna wrote *EL-Kânûn Fi't-Tıbb* (*Kânûn*), one of the fundamental books of medicine, inspired by Galen's teachings. *Teşrihu'l-Ebdân* ve *Tercümân-ı Kibâle-i Feylesûfân* (*Teşrihu'l-Ebdân*), an anatomy book written by physician Şemseddîn İtâkî in the 17th century. The primary purpose of our study was to compare the ear anatomy of works written in different centuries with each other and current anatomy information.

Materials and Methods: The Greek edition of *De Usu Partium* (Περὶ χρειαῖς μορίων) and the Arabic edition of the *Kânûn* were obtained. Translations of the works into Turkish have been completed. One of the illustrated copies of *Teşrihu'l-Ebdân* has been accessed. In this study, ear anatomy information obtained from three studies was compared with each other and with current anatomy. Additionally, the data in his *Kânûn* were compared with his first Turkish commentary, *Tahbüzü'l-Mathûn*.

Results: Some information familiar to all three physicians was obtained, such as the fifth cranial nerve providing hearing, second cervical spinal nerve reaching the outer ear layer, and carotid artery providing blood supply to the ear. However, no information was found regarding the middle ear ossicles, middle ear muscles, inner ear structures, or the function of the ear to maintain balance in the narratives of the three physicians.

Conclusion: Although some incorrect and incomplete information has been presented in the studies, the information given by the three physicians regarding ear anatomy is mainly similar to current ear anatomy. Our study shows that although they lived in different centuries, they were influenced by each other in terms of anatomy.

Keywords: Ear anatomy, Galen, Avicenna, Şemseddîn İtâkî, Tokadî Mustafa Efendi

ÖZ

Amaç: Galen, anatomi ve deneysel fizyolojinin kurucusu olarak kabul edilir ve *De Usu Partium* (Περὶ χρειαῖς μορίων) adlı eserin yazarıdır. On birinci yüzyılda İbn Sînâ, Galen'in öğretilerinden ilham alarak tıbbın temel kitaplarından biri olan *EL-Kânûn Fi't-Tıbb* (*Kânûn*) adlı eseri yazmıştır. *Teşrihu'l-Ebdân* ve *Tercümân-ı Kibâle-i Feylesûfân* (*Teşrihu'l-Ebdân*), 17. yüzyılda hekim Şemseddîn İtâkî tarafından yazılmış bir anatomi kitabıdır. Çalışmamızın ana amacı, farklı yüzyıllarda yazılmış bu eserlerin kulak anatomisini birbirleriyle ve günümüz anatomisiyle karşılaştırmaktır.

Gereç ve Yöntemler: *De Usu Partium* (Περὶ χρειαῖς μορίων) eserinin Yunanca baskısı ve *Kânûn* eserinin Arapça baskısına ulaşılmıştır. Eserlerin Türkçeye çevirileri tamamlanmıştır. *Teşrihu'l-Ebdân* adlı eserin bir illüstrasyonlu kopyasına erişilmiştir. Çalışmada, üç



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eserden elde edilen kulak anatomisi bilgileri birbiriyle ve günümüz anatomisiyle karşılaştırılmıştır. Ayrıca, Kânûn eserindeki veriler, ilk Türkçe şerhi olan Tahbîzü'l-Mathûn ile karşılaştırılmıştır.

Bulgular: Üç hekimin de bildiği bazı bilgiler elde edilmiştir, örneğin beşinci kranial sinirin işitmeye katkı sağlaması, ikinci servikal spinal sinirin dış kulak katmanına ulaşması ve karotis arterinin kulağa kan sağlaması gibi. Ancak, üç hekimin anlatılarında orta kulak kemikçikleri, orta kulak kasları, iç kulak yapıları veya kulak dengeyi sağlama fonksiyonu hakkında bilgi bulunmamaktadır.

Sonuç: Eserlerde bazı yanlış ve eksik bilgiler olsa da, üç hekimin kulak anatomisi hakkındaki verdikleri bilgiler genel olarak günümüz kulak anatomisiyle benzerlik göstermektedir. Çalışmamız, farklı yüzyıllarda yaşamış olmalarına rağmen, bu hekimlerin anatomi alanında birbirlerinden etkilendiklerini göstermektedir.

Anahtar Kelimeler: Kulak anatomisi, Galen, İbn Sînâ, Şemseddîn İtâkî, Tokadî Mustafa Efendi

Introduction

The knowledge of mummification before writing illustrates the ancient origins of anatomy (1). The Ebers Papyrus (1550 BC) contains prescriptions for ear diseases (1,2). Hippocrates first described the eardrum as “a dry, finely woven network” and linked it to hearing (2). Although Aristotle (384-322 BC) did not add new insights into ear anatomy, he contributed to the field by defining animal dissection, coining the term “anatomy,” and founding comparative anatomy (1,3,4).

Dissection freedom at the Alexandria Medical School advanced anatomy significantly, training famous anatomists like Galen (129-216 AD) (1). Galen, the father of anatomy and experimental physiology, wrote nearly 400 treatises, making him one of the most influential surgeons and philosophers of his time (5,6). His *De Usu Partium* was crucial for understanding his anatomical and physiological concepts (7). Ibn Sînâ quoted Galen over 300 times in his *EL-Kânun fit-Tıbb* (the Canon of Medicine) (8).

Ibn Sînâ (980-1037), also known as Avicenna, was regarded as the “prince of physicians” and the author of the most influential medical texts ever written (8,9). He wrote 273 works, 43 of which focused on medicine (10). The Canon was written over ten years, starting in 1012, and it became the most printed book after the Bible (11-13). It comprises approximately one million Arabic words and is divided into five sections covering various medical topics (8,12,13).

Teşrihu'l-Ebdân ve Tercümân-ı Kibâle-i Feylesûfân (*Teşrihu'l-Ebdân*), the first illustrated anatomy book in Ottoman Turkish, was written by Şemseddîn İtâkî in the 17th century, around 1632, and dedicated to Sultan Murad IV (14-17).

Comparing medical texts across time periods is valuable for understanding medical history. Few comparative anatomy studies have examined changes across four periods, including the present. Our study uniquely compares ear anatomy between Galen, Ibn Sînâ, İtâkî and modern knowledge, illustrating how medical knowledge evolves and

influences practitioners. The aim of this study was to show how physicians influence each other and how information changes.

Materials and Methods

In this study, Galen's *De Usu Partium* was accessed through the Greek works of Georgius Helmreich via an open-source platform (Internet Archive) (18). The Greek texts served as the primary source for the study, and information about the ear sensory organ was translated from Greek to Turkish (19,20). The Canon was based on two volumes of the four-volume Arabic Kânûn available at the Islamic Research Center (21,22). Access was also provided to the illustrated copy of *Teşrihu'l-Ebdân* from the Süleymaniye Manuscripts Library, Vehbi Efendi (Baghdad) Collection. This work, written in Ottoman Turkish, was translated into modern Turkish by the authors. *Tahbîzü'l-Mathûn*, the first Turkish commentary on the Canon in the 18th century, was examined.

Tokadî Mustafa Efendi prepared this commentary under the order of Sultan Mustafa III, referencing prior excellent Kânûn commentaries when necessary. The modern Turkish transcription of this work was accessed through an e-book application from the Turkish Manuscripts Institution (23,24). In this study, *Tahbîzü'l-Mathûn* was compared with the Arabic Kânûn, and any differences in ear anatomy within the Kânûn's particular commentary tradition were also examined.

Statistical Analysis

All the information is qualitative and obtained from ancient texts. Therefore, statistical analysis is unnecessary and should not be performed.

Results

Galen and Ear Anatomy

In *De Usu Partium* (Chapter 7, Volume 2, 750-755), Galen explains that the skull is made of multiple bones to prevent

fractures from spreading in case of impact. The petrous bone, described as “stone-hard” (τὸ λιθώδης ὀστέον), contains the auditory nerve. However, his descriptions do not mention the middle ear bones. In Chapter 7, Volume 1 (622-623), Galen states that the encephalon originates from nerves, which transmit sensations from sensory organs. The encephalon is softer than the nerves it generates, facilitating sensory processing. Sensory nerves are smoother and shorter to reduce the risk of external damage, which is why sensory organs are close to the encephalon.

Chapter 7, Volume 2 (270-271) further differentiates soft nerves for sensation and hard nerves for voluntary movement. Sensory organs, such as the eye, ear (οὖς), and tongue, contain both types of nerves.

Galen identified seven cranial nerves, with the fifth pair being responsible for hearing. This pair passes through a petrous bone and divides into two branches: one leads to the ear canal. At the same time, the other opens into the stylomastoid foramen, which he clarifies is curved and not “blind,” as previously thought. The fifth pair also has a temporal branch from the stylomastoid foramen.

Finally, according to Chapter 7, Volume 2 (295-297), animals with large temporal muscles and ears have larger nerves and can move their ears, whereas smaller animals like humans and monkeys cannot. Galen described the fifth cranial pair as being relatively soft and protected as it enters the ears near the meninges. To facilitate hearing, the nerve is shielded from external factors by being housed in a rigid bone and passing through curved spirals, which lengthen its path, protect it from cold, and reduce humidity, thus hardening the nerve. According to Galen, sensory organs typically exist in pairs to ensure proper functioning even in the presence of damage. Nature also protects exposed organs such as ears to prevent injury. The auricle's cartilage (χονδρῶδης) structure prevents it from being too brittle or too soft, with its convex outer and concave inner shapes protecting the ear canal from damage. Galen emphasized that the ear's design is not rough or disproportionate but an elegant natural ornament for humans. (19,20).

In Chapter 7, Volume 2 (97-99), Galen explains that the cervical spinal nerves innervate the neck muscles and control head movement. The second pair of spinal nerves extend to the area around the ears, the top of the head, and the front of the head (bregma). In Chapter 7, Volume 2 (266-267), he describes the artery leaving the heart, which divides into two branches: the larger branch descends to the lower body, while the smaller branch supplies the upper body. In Chapter 7, Volume 2 (332-336), Galen details the carotid artery (καρωτιδής), which divides into two branches—one going toward the back and the other toward the front,

each branching again. The front branch supplies the tongue and inner muscles of the lower jaw, while the other branches supply the temporal muscle near the ear. Galen states that there are no veins reaching the ear.

Avicenna and Ear Anatomy

In the title of Bone Anatomy of the Lower Side of the Skull in the first volume of the Canon, it is explained that two of the skull bones serve as walls on the right and left, that the two bones are called temporal bones (الحجرتين) because they are as hard as a stone, and that they contain the ears.

In the Canon, Avicenna described the temporal bones as walls for the skull containing the ears, but provided no details about the middle ear bones (21). The cheek muscles, which have four fibers, involve a fiber that extends from the cervical vertebrae to the cheeks and, in some individuals, allows ear movement (21). Regarding the cerebral nerves, Avicenna explains that the fifth cranial nerve, which is responsible for hearing, passes through the temporal bone, which curves and merges with the third cranial nerve to reach the temporal muscles (21).

Avicenna identified eight pairs of cervical spinal nerves, with the second pair reaching the ears and supplying the sensory feedback. He also discussed arterial pathways, noting that the vein leaving the heart splits, with the giant branch forming the carotid artery, which supplies blood to the neck, head, and ears. In vein anatomy, the external jugular vein is mentioned, which branches into two parts and serves areas near the head and ears (21).

In the third volume of the Canon, Avicenna details the ear's anatomy, describing its shell-like structure, auditory canal, and role in sound vibration. The ear's design, with its long, curved canal, regulates the temperature and protects the auditory nerve. The cartilage auricle maintains its shape and is protected from impacts. He noted the strategic positioning of the ears for optimal hearing and vision and noted that ear diseases can cause severe pain and fever (22).

Avicenna's descriptions align with Tokadî's *Tahbîzû'l-Mathûn* in terms of ear anatomy. However, Tokadî only mentioned the auditory nerve entering the area near the ear canal without referencing the involvement of the seventh cranial nerve.

Şemseddin Itâkî and Ear Anatomy

Itâkî mentions skull bones in the title of the Lower Side of the Skull Bone Anatomy Section. In this section, the ears' bones are called *haceriyân* (temporal bone) because they are as solid as stone. (25).

In the Cheek Muscle Anatomy section, it is seen that the muscles in the lower jaw, lip, and each cheek achieve the

movement of the cheek. The cheek muscles consist of four fibers. The fourth fiber comes to the cheek. In some people, this fiber passes through the immediate area of the ear and allows ear movement. No information about middle ear muscles was detected in other muscle descriptions. (25).

In the Anatomy of Nerves Section title, Itâkî states that seven pairs of nerves emerge from the brain, supporting this narrative through drawings. According to Itâkî, the fifth pair of heads emerges from both sides of the brain and is found in multiple pairs within itself. A branch of the pair distributes to the membrane inside the ear, and the sensation of hearing occurs with this branch (see Figure 1). The other branch of the pair leaves the blind hole in the temporal bone and joins the third pair of nerves. Most of it reaches the face and flat muscles, while some reaches the temporal muscles (25).

Under the Cervical Nerves and Tracts Anatomy Section heading, eight pairs of nerves emerge from the cervical vertebrae. The second pair of these nerves emerges from the hole between the first and second vertebrae and reaches the head. From this area, it turns toward the front and distributes to the outer skin of the ear and its surroundings (see Figure 2) (25).

Itâkî provides information about non-beating veins. In the section explaining the superior vena cava, one of these veins, Itâkî states that the superior vena cava, which reaches the neck circle, is divided into two branches, and the outer branch is called vidâc-ı zâhir (external jugular vein). The

vein divides into two branches again in this region, and one branch of the separated branches is distributed around the ear and head (25).

The last information shared about the vein is the carotid artery. According to this information, the arteries leaving the heart consist of ascending and descending sections. The vein ascending from the heart is divided into large and small. The more prominent vein came to the chest and split into three branches, two of which formed the carotid artery. When the carotid artery reaches the neck region, it is divided into two parts, one going to the front and the other to the back of the head. The vein coming to the front again divides into two branches. The second branch of these branches reaches the outer region and reaches the front of the ear and temple muscles, while the remaining branches reach the head region (25).

In the Ear Anatomy Section, the ear of each birthing animal is visible, but the ear of the egg-laying animal is not visible, and fish are against this rule. The ear has a shell structure like a sail made of cartilage, nerves, and flesh. This region is where a force activates the air, gathers in the sheath, and vibrates. The ear hole bends obliquely inside the temporal bone. This structure extends the path when hot and cold winds enter the ear. Thus, the hot and cold effects of the wind are broken and become moderate. A tree-like bone is in front of the ear hole, which opens into it. The air remains in this bone, and the auditory nerve is located there. The nerve is resistant to exposure to air and sound. The importance of this nerve in the ear is similar to the crystalline humor in the eye. Just as all other parts of the eye exist to protect and serve this structure, so does the duty of other ear parts on the auditory nerve. The benefit of the ear hole is likened to the iris layer in the eye (25).

Discussion

When all the information obtained from the investigations is evaluated, although the works of Galen,

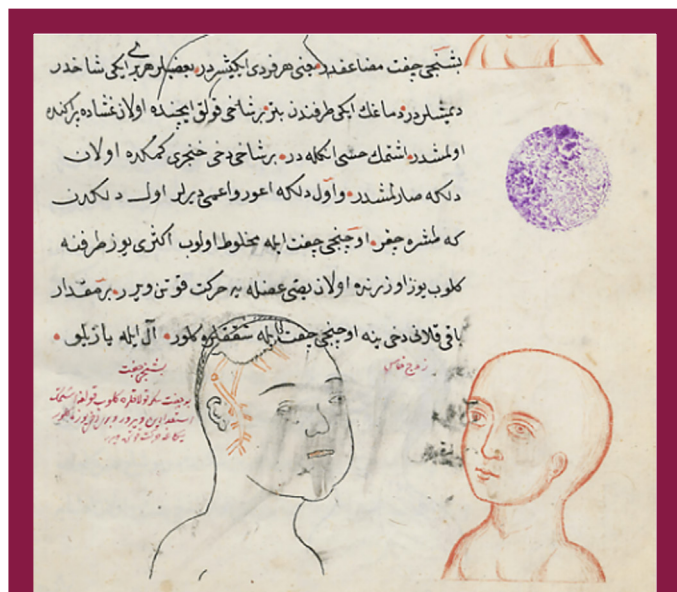


Figure 1. Drawing of the fifth pair of heads in the work of Şemseddin-i Itâkî [Taken from the Süleymaniye Manuscript Library, Vehbi Efendi (from the Baghdad) Collection, copy number 1476]

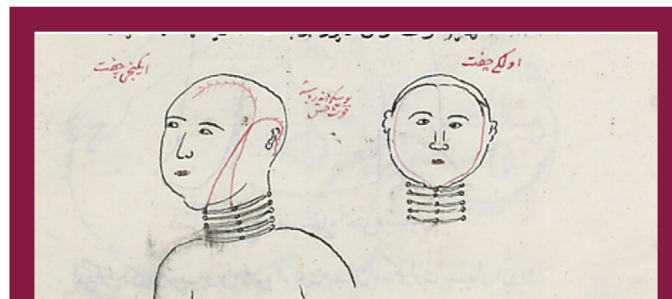


Figure 2. Drawing about the second cervical nerve in the work of Şemseddin-i Itâkî [Taken from the Süleymaniye Manuscript Library, Vehbi Efendi (from the Baghdad) Collection, copy number 1476]

Table 1. Ear anatomy

	Galen (<i>De Usu Partium</i>) (Περί χρείας μορίων)	Ibn Sîna (<i>Al-Kânûn fi't-Tıbb</i>)	Şemseddin İtâkî (<i>Teşrîhu'l-Ebdân ve Tercümân-ı Kibâle-i Feylesûfân</i>)	Modern anatomy
The bone at which the sensory organ is located	Hard bone as a stone “τὸ λιθώδης ὀστέον”	A “harten” bone is a wall on the right and left side, with an ear sensory organ inside	The one on the right and left is a bone called “haceryân” that contains ears	Temporal bone
Total number of cranial nerves emerging from the brain	Seven pairs	Seven pairs	Seven pairs	Twelve pairs
The cranial nerve provides hearing	Fifth cranial nerve	Fifth cranial nerve	Fifth cranial nerve	The eighth cranial nerve
The course of the auditory nerve	After the nerve progresses through the petrous bone, it comes to a crossroads. Some of it entered the ear canal, and some entered the blind hole section	After the nerve progresses through the petrous bone, it comes to a crossroads. Some of it entered the ear canal, and some entered the blind hole section	After the nerve progresses through the petrous bone, it comes to a crossroads. Some of it entered the ear canal, and some entered the blind hole section.	After nerve progression through the petrous bone, the transverse crest is located within the Internal acoustic canal, where the fundus of the internal acoustic meatus is located. Known as the auditory nerve, the cochlear nerve reaches the cochlea by passing through the canal in the lower front of the crest
Number of cervical spinal nerve pairs	Eight pairs	Eight pairs	Eight pairs	Eight pairs
The cervical spinal nerve reaches the outer layer of the ear	The second spinal nerve	The second spinal nerve	The second spinal nerve	Greater auricular nerve (C2-C3), lower occipital nerve (C2)
The artery that reached the ear	Carotid artery	Carotid artery	Carotid artery	Carotid artery
The vein accessing the ear	No direct ear vein was detected.	External jugular vein	External jugular vein	Posterior auricular vein à External jugular vein
Middle ear bones	Not detected	Not detected	Not detected	There are three bones in the middle ear: the malleus, incus, and stapes
Middle ear muscles	Not detected	Not detected	Not detected	There are tensor tympani and stapedius muscles in the middle ear
Hearing mechanism	The fifth cranial nerve, which has both hard and soft nerve types, reaches the ear next to the membranes and provides a sense of hearing. No information was provided regarding the inner ear	The sound penetrates the hole in the temporal bone and hits the complex fifth cranial nerve, and the nerve perceives that sound. No information was provided regarding the inner ear	The air reaches the ear, where the branch of the fifth head pair, located in one eardrum, detects the vibration. No information was provided regarding the inner ear	The cochlea structure in the inner ear transforms sound waves into electrochemical stimuli through inner and outer hair cells
The inner ear's relationship with balance	Not detected	Not detected	Not detected	The inner ear contains the otolith and semicircular organs, which are part of the peripheral vestibular system
Structure of the Auricula	Cartilage	Cartilage	Cartilage	Cartilage
Do you have an eardrum?	Yes	Yes	Yes	Yes

Avicenna, and Itâkî seem to have progressed in parallel, they contain some differences from today's modern medicine. The primary among these differences is the number of head pairs, as stated by Avicenna and Itâkî, inspired by Galen, which is seven. However, modern medicine has the opposite. It is observed that the current version of the cranial nerves was created by Samuel Sömmering (1755-1830 AD) in the 18th century (26,27).

Depending on the field of study, ear innervation is provided by many cranial nerves. While hearing and balance occur with the innervation of the eighth cranial pair (vestibulocochlear nerve), as defined today, many cranial nerves are involved in the section from the muscles in the middle ear to the external auditory canal and auricula (28). In the descriptions of Galen, Avicenna, and Şemsettin Itâkî, the fifth cranial nerve includes its modern counterparts, the facial nerve (7th cranial pair), and the vestibulocochlear nerve (8th cranial pair). Since these two nerves emerge with the same course and enter the same place (meatus acusticus internus) in the pons section of the brainstem, they were considered a single nerve by Galen and many subsequent scientists. They are referred to as the 5th cranial pair (26). Differences in the exact exit locations of the mentioned nerves in the brainstem and the nuclei where their fibers originate, as well as differences in their course and branching after the meatus acoustics internet, have shown that they are different nerves and have enabled them to be referred to as two separate skull pairs as used today. While Galen defined the two cranial nerves as a single nerve, he stated that they were divided into two branches after entering the inner ear canal. It states that while the auditory nerve moves from the larger side, the other branch enters another canal called the blind hole. By definition, this canal is thought to represent the facial canal where the facial nerve enters, and it can be said that these definitions are roughly similar to today's information based on the distribution of the vestibulocochlear and facial nerve within the internal acoustic meatus (29).

The descriptions of the ear by Galen, Avicenna, and Itâkî closely align with modern anatomical knowledge. Galen and Avicenna, who referred to the ear as made of cartilage, likely meant the auricula, which is the outer, curved part of the ear. Ibn Sîna also noted that the auditory nerve (5th cranial pair), which enters the inner ear, is structurally rigid to protect it from damage due to air and impact. Sound perception occurs when sound waves stimulate a nerve (22). The first statement contradicts current anatomical knowledge. The auditory nerve, one of the eight cranial nerves, is the only nerve that does not emerge from the skull; thus, it cannot be

influenced by weather or external factors. While the second statement was a logical explanation based on knowledge of the time, modern understanding of hearing involves sound waves reaching the eardrum. The eardrum's vibrations are transmitted to the inner ear *via* the ossicles (malleus, incus, stapes), and the vibration is then passed to the cochlea. The fluid movement stimulates the outer hair cells, activating the auditory nerve (30,31).

Galen and Avicenna stated that it would be more appropriate to separate the visual part of the front portion of the brain from hearing to another part (22). Although a precise localization is not given regarding hearing, the hypothesis regarding the visual aspect does not coincide with current knowledge of brain anatomy. The visual center of the brain is generally located in the posterior portion of the brain (occipital lobe) (28,32). Based on Galen's texts, the issue of hard and soft motor and sensory nerves cannot be clarified with today's knowledge. The most necessary observations in this context are that while motor neurons have a multipolar structure, their axons are long, and they must form a motor unit, sensory neurons have a unipolar structure, and their axons are shorter.

In Teşrîhu'l-Ebdân, Itâkî mentions a group of muscle fibers that enable the movement of the cheek and the lips coming together and provides information that these fibers also pass close to the ear in humans and allow the movement of the ear (25). If the variations in facial muscles are ignored, then the structure is unknown. Although the internal and external muscles that move the ear and the muscles that enable cheek and lip movement are generally considered mimic muscles, they can affect each other through the fascial system due to the layer in which they are located. From another perspective, the fact that a movement starting from the cheek area extends to the ear and its surroundings indicates the possibility of a connection between the buccinator and superior constrictor muscles, which have common attachment points in this region. Some studies have demonstrated the existence of this connection by revealing the possibility of two muscles acting as a single muscle (33). It is predicted that the fiber group mentioned above is based on these connections.

In all three works, the descriptions of the course and branching of arteries and veins although they lack detailed information, align with modern anatomical knowledge. The "tree-like bone" near the ear, described in different sources, is the temporal bone, which contains the ear's bony structures. The definitions of sensory branches from spinal nerves to the auricula and veins that drain the region are accurate despite the changes in modern nomenclature. These structures

include the greater auricular nerve (C2-C3), lesser occipital nerve (C2), and posterior auricular vein (34).

The dissection of the ear, including the inner and middle ear, was likely incomplete in earlier anatomical studies, as the petrous bone's delicate structure required foresight and proper tools for detailed examination. The facial canal curve highlights challenges in understanding the region. The comparison of the Canon commentary with the original Arabic text revealed similar descriptions of ear anatomy. Tokadî's version, however, states that only the auditory nerve enters the medial surface of the ear region. In contrast, the Arabic text indicates that both the auditory nerve and the fiber of the seventh cranial nerve are present. This differs from modern understanding because the seventh cranial nerve is the facial nerve, which has no direct relation to the ear during its course.

Conclusion

In our study, we tried to understand the interaction and change of the science of anatomy through the sensory organ of the ear by referencing the works of three different physicians who lived to varying dates for approximately 15 centuries, starting from the 2nd century. Subsequently, classical medical anatomy information was analyzed in light of contemporary modern anatomy information. The findings and inferences presented are expected to guide further medical history research on comparative anatomy.

Ethics

Ethics Committee Approval: Not applicable.

Informed Consent: Not applicable.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.K., İ.T., Concept: B.K., İ.T., Design: B.K., İ.T., Data Collection or Processing: B.K., İ.T., Z.S., F.C., Analysis or Interpretation: B.K., İ.T., Z.S., F.C., Literature Search: B.K., İ.T., Z.S., Writing: B.K., İ.T., Z.S., F.C.

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Calreticulin and GRP78 as Bioindicators for the Diagnosis of COVID-19 Pneumonia

COVID-19 Pnömonisi Tanısında Biyoindikatör Olarak Calreticulin ve GRP78

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ABSTRACT

Background: Coronavirus Disease 2019 (COVID-19) has been reported by the World Health Organization as a global health issue, leading to severe respiratory infections in humans. Recent studies have shown that endoplasmic reticulum stress can contribute to both the development and increased severity of many diseases, such as viral infections. In our study, we evaluated the diagnostic adequacy of the ER stress markers glucose-regulated protein 78 (GRP78) and calreticulin for diagnosing COVID-19 pneumonia and predicting mortality.

Materials and Methods: Our study included patients who presented to the emergency department, were over 18 years of age, had at least two clinical symptoms compatible with COVID-19 pneumonia, and whose diagnosis was confirmed by polymerase chain reaction testing, and had typical findings compatible with COVID-19 pneumonia on radiological imaging. GRP78 and calreticulin levels were statistically compared between patient (n=44) and control (n=44) groups, and between patient groups (survivors and non-survivors).

Results: GRP78 levels were found to be significantly greater in patients with COVID-19 pneumonia than in controls. The calreticulin levels were significantly lower. However, no significant difference was observed between the two groups in terms of survival. The sensitivity and specificity of GRP78 were 52.27% and 93.18%, respectively, when the cut-off value for GRP78 was >1.61 [area under the curve (AUC): 0.697, p<0.001]. The sensitivity and specificity were 81.82% and 72.73%, respectively, when the calreticulin cut-off was <3.96 (AUC: 0.816, p<0.001).

Conclusion: Our results showed that both GRP78 and calreticulin may be good bioindicators for COVID-19 pneumonia.

Keywords: COVID-19, pneumonia, endoplasmic reticulum stress, calreticulin, GRP78

ÖZ

Amaç: Koronavirüs Hastalığı 2019 (COVID-19), Dünya Sağlık Örgütü tarafından insanlarda ciddi solunum yolu enfeksiyonlarına yol açan küresel bir sağlık sorunu olarak bildirmiştir. Son çalışmalar endoplazmik retikulum stresinin, enflamatuvar bozukluklar ve viral enfeksiyonlar da dahil olmak üzere çeşitli hastalıkların patogeneze katkıda bulunduğunu ve bu olayların şiddetini artırabileceğini göstermektedir. Çalışmamızda endoplazmik retikulum stres belirteçlerinden glukoz düzenleyici protein 78 (GRP78) ve kalretikulinin COVID-19 pnömonisinin teşhisi ve mortaliteyi öngörmede tanılabilirliğini değerlendirmeyi planladık.

Gereç ve Yöntemler: Çalışmamızda acil tıp kliniğine başvuran 18 yaş üzeri ve COVID-19 pnömonisi ile uyumlu en az iki klinik semptomu bulunan gerçek zamanlı ters transkriptaz polimeraz zincir reaksiyonu testi ile tanısı doğrulanan ve radyolojik görüntüleme COVID-19 pnömonisi ile uyumlu tipik bulguları olan hastalar dahil edildi. GRP78 ve kalretikulin düzeyleri hem hasta (n=44) hem de kontrol (n=44) gruplarında istatistiksel olarak karşılaştırıldı.

Bulgular: GRP78 düzeylerinin COVID-19 pnömonisi saptanan hastalarda kontrol grubuna göre anlamlı olarak yüksek olduğu tespit edildi. Kalretikulin seviyeleri ise anlamlı olarak düşüktü. Ancak sağkalım açısından değerlendirildiğinde her iki grup arasında anlamlı bir fark görülmedi. GRP78'in kesim değeri >1,61 [eğri altındaki alan (AUC): 0,697, p<0,001] olduğunda duyarlılığı %52,27, özgüllüğü %93,18 olarak tespit edilmiştir. Kalretikulinin kesim değeri <3,96 (AUC: 0,816, p<0,001) olduğunda duyarlılığı %81,82, özgüllüğü %72,73 olarak tespit edilmiştir.

Sonuç: Sonuçlarımız, hem GRP78 hem de kalretikulinin COVID-19 pnömonisi için iyi biyoindikatörler olabileceğini göstermiştir.

Anahtar Kelimeler: COVID-19, pnömoni, endoplazmik retikulum stresi, kalretikulin, GRP78



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Introduction

Coronavirus Disease 2019 (COVID-19) is a multisystemic disease with a clinical presentation ranging from mild flu-like symptoms to severe pneumonia. Understanding the pathogenesis of this disease is necessary to reduce hospitalization and mortality rates, predict the development of pneumonia, and identify patients at risk (1).

Endoplasmic reticulum (ER) stress has been implicated in the pathogenesis of many respiratory diseases (2). Excessive accumulation of unfolded proteins in the lumen of the ER leads to activation of the signaling pathway known as the unfolded protein response (UPR). Protein kinase R-like ER kinase (PERK), activating transcription factor 6 (ATF6), and inositol-requiring enzyme 1 alpha (IRE1 α) are transmembrane proteins that mediate the UPR (3). The UPR is part of the cellular stress response that can be exploited by respiratory viruses to fight against the host's immune system. In coronavirus (CoV) infection, it has been suggested that the possible mechanism responsible for the induction of the UPR may involve excessive synthesis, modification, and folding of viral proteins (4). Although PERK is most commonly associated with CoV infections, there is evidence that IRE1 and ATF6 are also involved (5).

Glucose-regulated protein 78 (GRP78) is the major chaperone protein of the UPR in the ER. GRP78, a member of the heat shock protein 70 (HSP70) family, is localized to the ER membrane of all eukaryotic cells. Forces cause unfolded proteins to undergo refolding or degradation via cellular degradation mechanisms (6). The amino-terminal region of the GRP78 protein is known as the ATP binding domain, and the carboxy-terminal region is known as the substrate binding domain. GRP78 normally binds PERK, IRE1 α , and ATF6 and keeps these proteins inactive. When the UPR is increased and the folding capacity of the ER is exceeded, these proteins dissociate from GRP78 and become activated (7). In this case, the cell may resort to protein refolding or inhibition of protein synthesis. In studies, GRP78 has been associated with viral infections. It is thought to be involved in the synthesis of envelope proteins in some viruses. GRP78 may be one of the proteins that mediates the entry of some viruses into the cell by binding to cell surface proteins. Overexpression of GRP78 may cause its translocation from the ER to the cell membrane and mediate the entry of some viruses into the cell through its substrate binding site (7,8).

Calreticulin is an ER chaperone protein that plays an important role in regulating intracellular calcium homeostasis and proper protein folding in the ER. It binds, stores, and translocates Ca²⁺ ions in the lumen of the ER (9). Calreticulin consists of three parts: an N domain, a P domain, and a C domain (10). The N-domain is a spherical

structure with internal folding, a highly conserved amino acid sequence, and the ability to bind Zn²⁺. It can interact with other chaperone molecules (11). The P domain has a high affinity for Ca²⁺ but a low Ca²⁺-binding capacity. The C-domain binds Ca²⁺ with low affinity and high capacity due to its acidic structure and thus plays a role in Ca²⁺ storage and homeostasis in the ER lumen (12). Loss of calreticulin function in cells may cause the onset of ER stress (9,13). The UPR has been shown to increase in viral infections. Therefore, it is important to evaluate the function of calreticulin in viral infections. However, to our knowledge, there are little data in the literature on the role of calreticulin, an ER stress indicator, in COVID-19 pneumonia.

Biomarkers are becoming increasingly important in areas such as predicting disease progression and monitoring treatment. They also help to better understand the pathogenesis of the disease. In this study, we evaluated the diagnostic adequacy of GRP78 and calreticulin as biomarkers for the diagnosis of COVID-19 pneumonia and the prediction of mortality.

Materials and Methods

Study Design

Our study was conducted between March 2021 and June 2021. Patients who presented to the emergency medicine clinic were over 18 years of age, had at least two clinical symptoms compatible with COVID-19 pneumonia (shortness of breath, cough, sputum, pleuritic chest pain, fever of 38 °C and above), had a diagnosis confirmed by real-time reverse transcriptase polymerase chain reaction test, and had typical findings compatible with COVID-19 pneumonia on radiological imaging (unilateral or bilateral ground-glass appearance, subpleural consolidation, paving stone appearance). These patients were included in our study. People who did not have clinical, laboratory, or radiological suspicion of COVID-19 infection and who were informed about the study and agreed to participate were included in the control group. Written informed consent was obtained from patients without consciousness disorder who were mentally healthy enough to sign, and from the first-degree relatives of patients with a consciousness disorder or who were not mentally healthy enough to sign. Patients under 18 years of age, pregnant women, cancer patients, immunosuppressed patients, those with impaired consciousness, sepsis, multiorgan failure, respiratory failure, and hemodynamically unstable conditions for any reason other than COVID-19 pneumonia were excluded from the study.

All patients included in the study were grouped into survivors and non-survivors. GRP78 and calreticulin levels

were statistically compared between the patient (n=44) and control (n=44) groups, and within the patient group (survivors and non-survivors). Approval was received from the Ethics Committee of Kocaeli University Non-interventional Clinical Trials (KÜ GOKAEK-2021/7.01, dated: 01.04.2021).

Biochemical Analyses

Blood samples collected at enrollment were analyzed for white blood cell count, neutrophil count, lymphocyte count, D-dimer level, and C-reactive protein (CRP) level. Blood samples from the patient and control groups were centrifuged at 1500 g for at least 15 minutes. The serum obtained was stored at -80 °C until analysis of GRP78 and calreticulin levels. GRP78 and calreticulin levels in these samples were analyzed by sandwich enzyme-linked immunosorbent assay (ELABSCIENCE-E-EL-H5586 and ELABSCIENCE-E-EL-H0627, respectively). The sensitivities of these assays were 0.38 ng/mL and 0.10 ng/mL, respectively. The intra-assay and inter-assay coefficients of variation (%) of both assays were less than 10%. Within 24 hours of diagnosis, 10 mL of venous blood was collected in EDTA tubes for hematological analysis. Complete blood count was performed on a Sysmex XN-1000 automated hematology analyzer (Sysmex Europe SE, Norderstedt, Germany).

Statistical Analysis

The IBM SPSS 29.0 (IBM Corp., Armonk, NY, USA) program was used for statistical analysis. The Shapiro-Wilk test was used to assess the normality of the data. Continuous variables were expressed as mean \pm standard deviation or median and interquartile range. Categorical variables are presented as numbers and percentages. Independent sample t-tests were used for normally distributed variables and Mann-Whitney U tests were used for non-normally distributed variables. The chi-square test was used to investigate the relationships between categorical variables. Receiver operating characteristic (ROC) analysis was used to determine the area under the curve (AUC), sensitivity, specificity, and cut-off values. A p-value <0.05 was considered statistically significant. According to the power analysis result, the minimum sample size required to find a significant difference using this test was determined to be 84 in total, 42 in each group; the type 1 error amount (alpha) was 0.001; the power of the test (1-beta) was 0.90; the effect size was 0.76; and the alternative hypothesis (H1) was two-sided.

Results

There were 88 participants in the study, 44 in the control group and 44 in the patient group. The patients were divided into survivors (n=32) and non-survivors (n=12).

The mean age of the patients was 65 years (male, 63.6%; female, 36.4%) and the mean age of the controls was 65.5 years (male, 52.3%; female, 47.7%). Oxygen saturation was significantly lower in the non-survivor group ($p=0.011$). However, no significant difference was observed between the two groups in terms of temperature, heart rate, or systolic or diastolic blood pressure. CRP was also significantly lower in the survivor groups than in the non-survivor groups (46.7, 108.4; mg/L $p=0.015$). GRP78 and calreticulin levels were not significantly different between the survivors and non-survivors groups (1.49, 2.15; 1.90, 3.23, ng/mL, respectively). Table 1 shows the data for the groups.

Table 2 shows the comparison of GRP78 and calreticulin levels, as well as age and sex, between the patient group and the control group. GRP78 levels were significantly greater ($p=0.001$) and calreticulin levels were significantly lower ($p<0.001$) in the patient group than in the control group.

ROC analysis of GRP78 and calreticulin levels in the patient and control groups is shown in Figures 1 and 2. The cut-off and AUC values of GRP78 and calreticulin are given in Table 3. When the cut-off value of GRP78 was >1.61 (AUC: 0.697, 95% CI: 0.590-0.791, $p<0.001$), the sensitivity was 52.27%, and the specificity was 93.18%. When the cut-off value of calreticulin was <3.96 (AUC: 0.816, 95% CI: 0.719-0.890, $p<0.001$), the sensitivity was 81.82%, and the specificity was 72.73%.

Discussion

In viral infections, especially during the replication cycle, a high level of viral protein accumulates in the ER and exceeds its folding capacity. This situation therefore triggers the UPR (14). CoV infections are also among the infections that can activate the UPR (15). Understanding the relationship between COVID-19 and ER stress is important for comprehending the pathogenesis of COVID-19. In our study, the level of GRP78, an ER chaperone protein, was significantly greater in patients with COVID-19 pneumonia than in the controls ($p=0.001$). There was significantly less calreticulin in the patient group than in the control group ($p<0.001$). In addition, when ROC analysis of GRP78 and calreticulin was performed, the AUC values calculated for both indicators were 0.697 for the patient group and 0.816 for the control group.

GRP78 functions as a major chaperone that maintains protein homeostasis within the ER. It has also been shown in many studies to participate in various processes, such as cellular signaling, the inflammatory response, apoptosis, and the development of viral infection (16,17). In autopsies of COVID-19 patients, increased expression of GRP78 was found in both pneumocytes and lung macrophages (18). Overexpression of GRP78 may increase the likelihood of

Table 1. Basic characteristics of the patients

Variables	All Patients (n=44)	Survivors (n=32)	Non-survivors (n=12)	p-value
Age ^a	65.00 (50.75-70.75)	65 (50.75-71.75)	65 (49.75-69.75)	0.711
Gender, n (%) ^b				
Male	28 (63.6)	20 (62.5)	8 (66.7)	1.00
Female	16 (36.4)	12 (37.5)	4 (33.3)	
Fever ^a	36.7(36.5-37.2)	36.7 (36.5-37.4)	36.7 (36.5-37.1)	0.886
Heart rate (min.) ^c	94.25±17.3	92.97±16.9	97.6±18.6	0.431
Systolic pressure ^a	120 (110-130)	120 (110-130)	120 (100-140)	0.745
Diastolic pressure ^a	70 (62.5-80)	70 (70-80)	80 (60-80)	0.507
Saturation, (%) ^a	96 (9.5-97)	96 (93-97.75)	89 (81.75-96.50)	0.011
WBC, (10 ³ /mL) ^a	5.1 (3.95-7.05)	5.1 (4.12-6.82)	5.65 (3.4-10)	0.726
Neutrophil, (10 ³ /mL) ^a	3.40 (2.60-4.57)	3.35 (2.60-4.20)	3.90 (2.40-7.32)	0.474
Lymphocyte, (10 ³ /mL) ^a	1.20 (0.80-1.40)	1.30 (0.82-1.47)	1 (0.80-1.37)	0.507
CRP, (mg/L) ^a	2.70 (2.20-4.40)	46.7 (11.10-81.10)	108.4 (54.12-173.15)	0.015
D-dimer, (ug/mL) ^a	0.62 (0.44-1.43)	0.57 (0.41-1.18)	0.97 (0.57-2.13)	0.112
GRP78, (ng/mL) ^a	1.66 (1.01-2.82)	1.49 (0.98-2.28)	2.15 (1.01-3.27)	0.397
Calreticulin, (ng/mL) ^a	2.33 (1.35-3.76)	1.90 (1.32-3.51)	3.23 (1.76-5.38)	0.089
Length of stay in hospital, (day) ^a	9 (5.75-14)	9 (6-12)	10 (2-17)	0.504

^aData are presented as the median (IQR), ^bData are presented as the n (%), ^cData are presented as the mean ± standard deviation, IQR: Interquartile range, WBC: White blood cell, CRP: C-reactive protein, GRP78: Glucose-regulated protein 78

Table 2. Comparison of GRP78 and calreticulin levels between the patient and control groups

	Patient (n=44)	Control (n=44)	p-value
Age ^a	65 (50.75-70.75)	65.50 (46.25-72.50)	0.917
Gender ^b			
Male	28 (63.6)	23 (52.3)	0.388
Female	16 (36.4)	21 (47.7)	
GRP78 (ng/mL) ^a	1.66 (1.01-2.82)	1.11 (0.79-1.29)	0.001
Calreticulin (ng/mL) ^a	2.33 (1.35-3.76)	6.23 (3.63- 8.32)	<0.001

^aData are presented as the median (IQR), ^bData are presented as the n (%), IQR: Interquartile range, GRP78: Glucose-regulated protein 78

Table 3. Predictive value of GRP78 and calreticulin for the patient and control groups

	AUC	95% CI Lower/Upper limit	Cut-off	Sensitivity (%)	Specificity (%)	p-value
GRP78 (ng/mL)	0.697	0.590/0.791	>1.61	52.27	93.18	<0.001
Calreticulin (ng/mL)	0.816	0.719/0.890	<3.96	81.82	72.73	<0.001

AUC: Area under the ROC curve, ROC: Receiver operating characteristic, CI: Confidence interval, GRP78: Glucose-regulated protein 78

GRP78 translocation from the ER to the cell membrane. Once GRP78 is translocated to the cell membrane, the cell becomes more susceptible and can mediate virus entry (7). The frequency of CD45+GRP78+ cells increased significantly in patients with severe COVID-19 (17). In their prospective case-control study, Sabirli et al. (19) reported that the level of GRP78 in serum samples from COVID-19 (+) patients was significantly greater than that in both the control group and the COVID-19 (-) pneumonia

group. They suggested that the high level of GRP78 in patients with computed tomography-negative COVID-19 infection may increase ER stress and cause upregulation of GRP78 expression even before Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) triggers pneumonia. Our study results support these findings. In our study, we found that the serum GRP78 level was greater in patients with COVID-19 pneumonia than in controls ($p < 0.001$). In addition, when the cut-off value of GRP78 exceeded

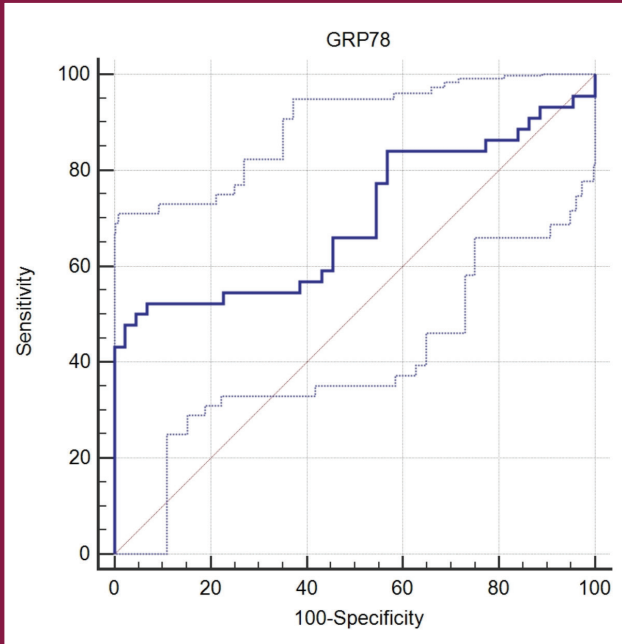


Figure 1. Receiver operating characteristic analysis of the best cut-off values for GRP78 levels in the patient and control groups
 GRP78: Glucose-regulated protein 78

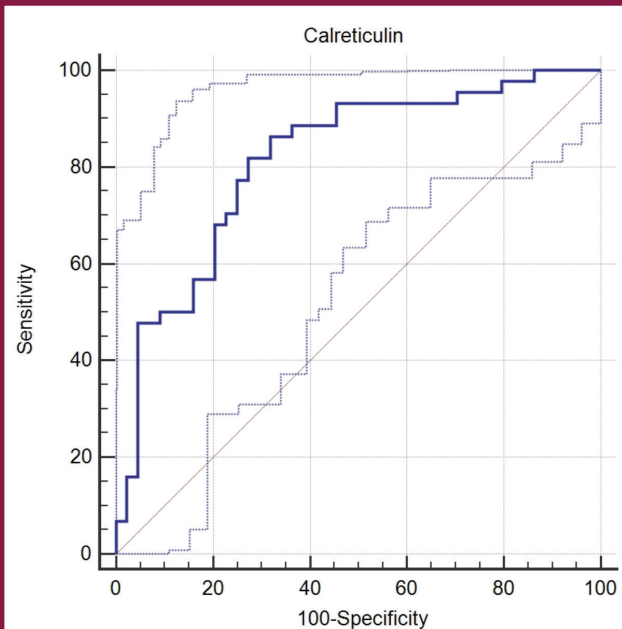


Figure 2. Receiver operating characteristic analysis of the best cut-off values for calreticulin levels in the patient and control groups

1.61 (AUC: 0.697, 95% CI: 0.590-0.710), its sensitivity and specificity were 52.27% and 93.18%, respectively. Our statistical analyses revealed that it was not a significant predictor of mortality.

Loss of calreticulin function in cells may cause the onset of ER stress (9). Calreticulin gene deletion has been found to cause the accumulation of unfolded proteins (20). The UPR is activated by a significant increase in GRP78, Ire1 α , and PERK levels (9). Rahimi et al. (21) also reported that the absence of calreticulin in SARS-CoV-2-infected cells causes the spike protein to escape lysosome-mediated degradation. Therefore, they emphasized that shRNA-mediated knockdown of calreticulin may increase the severity of SARS-CoV-2 infection. In our study, serum calreticulin levels were significantly lower in the COVID-19 patient group than in the control group ($p < 0.001$). However, no significant difference was found between the survivor and non-survivor groups.

Decreased calreticulin levels in COVID-19 patients may impair Ca²⁺ homeostasis in the ER. It can also induce ER stress by causing the UPR to increase. Our data confirm this finding. In addition, calreticulin was used as an indicator of COVID-19, with a sensitivity of 81.82% and specificity of 72.73% when the calreticulin cut-off was < 3.96 ng/mL (AUC: 0.816, 95% CI: 0.719-0.890, $p < 0.001$).

Increases in CRP and D-dimer during COVID-19 pneumonia are indicators of an increased inflammatory response. These parameters were also correlated with the severity of the disease (22,23). In addition, parameters such as interleukin-6, ferritin, and the neutrophil-to-lymphocyte ratio have been shown to be effective in predicting mortality. However, D-dimer did not show similar results in the same study (24).

Study Limitations

Our study is the first to investigate the diagnostic value of GRP78 and calreticulin in COVID-19 pneumonia, informed by our open-source literature searches. The limitation of this study was the insufficient data and limited sample size regarding GRP78 and calreticulin's ability to predict mortality. In addition, many factors, such as existing diseases, medications used by patients before hospitalization, and biodiversity, may have influenced the measurement results.

Conclusion

ROC curve analysis revealed that both GRP78 and calreticulin may be good indicators of COVID-19 pneumonia. Calreticulin appears to be more accurate and sensitive than GRP78 for detecting COVID-19 pneumonia. However, using both parameters together may be more promising.

Ethics

Ethics Committee Approval: Approval was received from the Ethics Committee of Kocaeli University Non-interventional Clinical Trials (KÜ GOKAEK-2021/7.01, dated: 01.04.2021).

Informed Consent: Written informed consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ş.K., Concept: B.Ö., Design: B.Ö., Ş.K., Data Collection or Processing: Ş.K., Analysis or Interpretation: B.Ö., Literature Search: Ş.K., Writing: B.Ö.

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

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Socio-demographic Properties of Children Affected by the 2023 Kahramanmaraş-Centered (Türkiye) Earthquake in a Tertiary Hospital 1000 km Away

2023 Kahramanmaraş Merkezli Depremden 1000 km Uzaklıktaki Üçüncü Basamak Bir Hastanede Depremden Etkilenen Çocukların Sosyodemografik Özellikleri

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ABSTRACT

Background: The earthquake on February 6, 2023, significantly impacted Türkiye, affecting 13.5 million individuals and resulting in substantial damage and loss of life, including among children. Due to the high number of cases, earthquake-affected children who received initial medical intervention were transferred to various hospitals for further treatment. In our study, we aimed to evaluate the socio-demographic and clinical characteristics of earthquake-affected children who received treatment in our hospital.

Materials and Methods: The study included children admitted to our hospital either through referral or outpatient assessment. Socio-demographic data on age, gender, place of residence, reason for admission, duration of entrapment, rescue method, loss of first-degree relatives, presence of a companion, and discharge status were collected. Descriptive statistical methods were used for analysis.

Results: Between February 9 and March 2, 2023, 42 pediatric patients were hospitalized at a tertiary care center in İzmir. The mean age was 8.3±4 years, with 23 (54.8%) being male. The average duration under the wreckage was 28.60±26.87 hours (range: 1-105 hours). Among 33 children trapped, 17 (51.5%) were rescued by official teams, while 16 (48.5%) were extricated by civilians or relatives. Seventeen children (40.4%) who had no accompanying relatives were cared for by hospital staff. First-degree relative loss was reported in 24 (29.16%) cases. Fasciotomy was required in 14 (42.4%) children, and six (18%) underwent amputation. No significant correlation was found between entrapment duration and the need for amputation, fasciotomy, or dialysis. The mean hospitalization period was 33 days (range: 6-84). Following discharge, 29 (70.7%) children were unable to return home.

Conclusion: Although the study represents a limited sample, the displacement of many children highlights significant social challenges. Beyond medical treatment, long-term housing solutions and psychological support remain critical components of post-disaster care for pediatric patients.

Keywords: Disaster, earthquake, children, wreckage



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Amaç: Yaklaşık 13,5 milyon kişinin etkilendiği Türkiye’de 6 Şubat 2023’te meydana gelen deprem, çocuklar da dahil olmak üzere önemli hasarlara ve can kayıplarına neden oldu. Vaka sayısının yüksek olması nedeniyle ilk müdahaleleri yapılan depremde çocuklar tedavilerinin devamı için Türkiye genelindeki çeşitli hastanelere sevk edildi. Çalışmamızda hastanemizde tedavi gören depremde çocukların sosyodemografik ve klinik özelliklerinin değerlendirilmesini amaçladık.

Gereç ve Yöntemler: Çalışmaya, hastanemize sevk edilen veya poliklinik başvurusu sonrası yatırılan çocuk hastalar dâhil edildi. Yaş, cinsiyet, ikamet yeri hastaneye başvuru nedeni, enkazda kalma durumu ve süresi, kurtarıma şekli, birinci derece yakını kaybı, refakatçi durumu ve taburculuk sonrası yerleşim durumu gibi sosyodemografik veriler toplandı ve tanımlayıcı istatistik yöntemleri kullanılarak analiz edilmiştir.

Bulgular: 9 Şubat-2 Mart 2023 tarihleri arasında, üçüncü basamak bir hastanede 42 çocuk hasta takip edilmiştir. Çocukların yaş ortalaması 8,3±4 yıl olup, 23’ü (%54,8) erkekti. Enkaz altında kalma süresi ortalama 28,60±26,87 saat (1-105 saat) olarak belirlenmiştir. Enkaz altında kalan 33 çocuktan 17’si (%51,5) resmi kurtarma ekipleri, 16’sı (%48,5) ise yakınları veya siviller tarafından çıkarılmıştır. Refakatçisi olmayan 17 (%40,4) çocuk, hastane yönetimi tarafından görevlendirilen personel eşliğinde takip edilmiştir. Birinci derece yakını kaybeden çocuk sayısı 24 (%29,16) olarak belirlenmiştir. Dört ekstremiteden en az birinde fasyotomi gereksinimi 14 (%42,4) hastada görülürken, 6 (%18) çocuk amputasyon geçirmiştir. Enkaz altında kalma süresi ile amputasyon, fasyotomi veya diyaliz ihtiyacı arasında anlamlı bir ilişki saptanmamıştır. Ortalama yatış süresi 33 gün (6-84 saat) olarak hesaplanmıştır. Taburculuk sonrası 29 (%70,7) çocuk, önceki ikametgahlarına dönememiştir.

Sonuç: Çalışmamızdaki olgular depremden ciddi şekilde etkilenen kesimin çok az bir kısmını yansıtsa da özellikle çocukların büyük bir kısmının yaşadığı yerden farklı bir bölgede ikamet etmek zorunda kalması önemli bir sosyal soruna işaret etmektedir. Bu nedenle doğal afetler sonrası medikal tedavileri tamamlansa bile çocuk olguların için barınma ve psikososyal destek gibi uzun vadeli ihtiyaçların karşılanması büyük önem taşımaktadır.

Anahtar Kelimeler: Afet, deprem, çocuk, enkaz

Introduction

Natural disasters are ecological events that disrupt the normal living conditions in society, resulting in an urgent and great need for foreign aid (1). Disasters are natural or man-made events that cause physical, economic, and social losses, stop human activities, and negatively affect society. Earthquakes are natural disasters that cause more loss of life and property (2). Disaster exposure varies among individuals. Those with a low socioeconomic and cultural level, minority groups, women, children, elderly people, and disabled persons are at greater risk of social harm. Children are one of the vulnerable groups affected by disasters (3). The child’s gender, age, education, previous exposure to disasters, the degree of damage caused, and loss of family members and loved ones, are essential factors that determine the effects of disasters on children and adolescents (4,5). In addition, while some of the children rescued from the wreckage after the earthquake are taken to the nearest health institutions, others are transferred to other centers without having been registered, which causes difficulties in identification. In disaster situations, obstacles such as the age of children, the degree of trauma, and the state of consciousness cause the recording process to become more difficult (6).

Between 1900 and 2023, Türkiye experienced 269 earthquakes that resulted in damage or loss of life. The most devastating earthquakes were the 2023 Kahramanmaraş, 1939 Erzincan, and 1999 Gölcük-

centered Marmara Earthquakes. On February 6th, 2023, two earthquakes with magnitudes of 7.7 and 7.6, and focal depths of 8.6 km and 7 km, respectively, occurred in the Pazarcık and Elbistan districts of Kahramanmaraş at 04:17 am and 01:24 pm, respectively, causing significant damage in Syria also (7). The earthquakes triggered a level 4 alarm in Türkiye, and the Director General of the World Health Organization declared a level 3 emergency (8). The earthquakes resulted in more than 50,000 reported deaths, destruction, or severe damage to over half a million buildings, and significant losses. About 13.5 million people were affected by these earthquakes, which destroyed over 35,000 buildings in 11 provinces and left many homeless. The affected provinces contained 12.5% of secondary and tertiary healthcare facilities and 17.5% of primary healthcare facilities, which makes providing access to healthcare services, including those in destroyed hospitals, challenging. The earthquakes affected 21.3% of the child population under 18 years old (4,805,937) in Türkiye, causing adverse effects including injuries from wreckage, and chronic diseases (7).

Due to the high number of cases, earthquake-affected children who received first aid were referred to various hospitals across Türkiye for further treatment. We evaluated the socio-demographic and clinical characteristics of earthquake-affected children who were referred to our hospital for treatment in pediatric services.

Materials and Methods

In this article, we explained the characteristics of children who were admitted to our hospital from earthquake-affected cities. Age and gender of the cases, time of admission, location of residence, duration of stay in the wreckage, the individual who extricated the patient, type and reason of hospitalization, presence of fasciotomy, amputation, crush, dialysis, and hyperbaric treatment were recorded. The loss of parents and siblings was questioned. The presence and proximity of the companion was recorded. The companion was defined as a close family member after the identity of the incoming persons was confirmed by the police. Assigned officers attended to children who did not have any relatives or companions. The same child and adolescent psychiatrist conducted a psychiatric evaluation. The province and place of settlement after discharge were noted.

Patient Consent Information

Since this study involved retrospective data collection from hospital records, formal patient consent was not required. However, ethical approval was obtained from University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital Non-interventional Research Ethics Committee (approval number: 2023/02-31, dated: 08.03.2023), and all patient data were anonymized to ensure confidentiality.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences for Windows (version 22.0; IBM Inc., Armonk, NY, USA). Descriptive statistics were used to summarize the data. Continuous variables were expressed as mean \pm standard deviation (SD), while categorical variables were expressed as frequencies and percentages. The chi-square test was used for categorical data comparisons, and a p-value of <0.05 was considered statistically significant.

Results

Socio-demographic and clinical data of 42 children who were victims of an earthquake were evaluated. The mean age of the children was 8.3 ± 4 years (mean and SD), and 23 (54.8%) were boys. The referral date was between February 9 and March 2. Earthquake victims were sent to our hospital in three groups by air ambulance.

The first group of patients arrived on February 9th at the 69th hour of the earthquake. Thirty patients were transferred from Kahramanmaraş, and nine children were referred to our hospital (Table 1). Eight of these children had trauma injuries, and the other 9-year-old boy who had type 1

diabetes mellitus was diagnosed with diabetic ketoacidosis due to a lack of insulin therapy. Two earthquake victims who had crush syndrome needed hemodialysis. On the same day, two earthquake survivors from Adana who were intubated due to crush syndrome and needed dialysis were admitted to the pediatric intensive care unit.

On March 10th, the second group of patients, including nine earthquake patients, was brought by air ambulance from Adiyaman. The mother of the patients aged 8 and 14, who were siblings, was also sent to another hospital in İzmir by the same ambulance. During this process, their father was missing, and we later learned that he was injured and being treated in a hospital in Ankara.

On February 11th, two patients who had relatives in İzmir and came from the region using their own means were admitted to our pediatric emergency department. Two patients with a history of staying in the wreckage for one hour were hospitalized at our facility on the fifth day of the earthquake, due to trauma.

Another six earthquake victims were transferred by air ambulance from Mersin on February 12th, 2023. These patients used to live in Hatay. Three children, aged 4, 11, and 13, were siblings. All the patients had at least one fasciotomy on the extremities. Two of them, (3- and 6-year-old boys), with multiple traumas were transferred to the pediatric intensive care unit. On the same day, a 9-year-old girl, who was not affected by the earthquake, hospitalized in the pediatric intensive care unit from Mersin due to a history of chronic disease, including pneumonia. She was referred to our hospital because of required pediatric intensive care in the earthquake area.

On February 16th, three child patients with multiple traumas were brought to our emergency department by air ambulance. On the same day, a 9-month-old male patient with hydrocephalus and a ventriculoperitoneal shunt, who had been under the wreckage for one hour, was admitted to our emergency department and subsequently hospitalized in the service department.

While 35 earthquake-affected children (83.3%) were transferred to our hospital by air ambulance, seven patients (16.7%) were admitted to the emergency service by their own means. Thirty-four (81.0%) patients were hospitalized because of trauma, and the remaining eight (19.0%) patients were hospitalized for other indications (one patient with diabetic ketoacidosis, five patients with lower respiratory tract infection, and two patients with status epilepticus). Of the 42 children who suffered from earthquakes, 19 (45.2%) were girls 23 (54.8%) were boys. The mean age of the patients was 8.3 ± 4.47 years. The list of cities they lived in before the earthquake is shown in Table 1.



Rescue times of 33 (78.6%) patients who remained in the wreckage ranged from the shortest one hour to the longest 105 hours. The mean stay in the wreckage was 28.60 ± 26.87 hours. It was learned that 17 (51.5%) of the 33 patients who were left in the wreckage were rescued by the rescue teams and by their relatives and the civilian population (Table 1). Crush syndrome was present in thirteen of the patients (39.3%) who remained under the wreckage, while dialysis treatment was needed for six patients (46.15%). There was no significant difference between patients with and without crush syndrome in terms of age, gender, and time spent under the wreckage. Six of the 33 patients (18%) who remained under the wreckage had an amputation. Amputation was already performed on four of the patients who were referred. During the follow-up, the demarcation line developed despite hyperbaric oxygen therapy, and the pulses could not be palpated due to the circulatory disorder development. Two patients underwent amputation performed by teams from the orthopedics and cardiovascular surgery clinics during their hospitalization in our service. There were fasciotomies on at least one extremity in 14 (42.4%) cases. Two of them had bilateral lower extremity fasciotomy, while one had bilateral upper extremity fasciotomy.

In contrast, the remaining nine patients had single extremity fasciotomy, in 7 cases in one lower extremity, and in two instances in one upper extremity. Hyperbaric oxygen therapy was applied to 14 patients with fasciotomies. During the follow-up, all patients' fasciotomies were closed primarily. The indications for hyperbaric oxygen therapy included wound healing of fasciotomies (14 patients), foot drop (4 patients), and retinal hemorrhage (1 patient). No correlation was observed between the duration of stay in the wreckage and the history of amputation, fasciotomy, and dialysis. Twelve of 42 patients were followed up in the ward after first being treated in the intensive care unit. Five patients with crush syndrome were followed up in the intensive care unit. A significant relationship was found between crush syndrome and intensive care admission ($p=0.032$).

Seventeen patients (40.4%) with no relatives were accompanied by the staff assigned by the hospital administration (Table 1). The relatives of all patients were reached in the following days. The relatives of the patients were accepted as companions after the police confirmation. For six patients, the staff continued as a companion until discharge because their first-degree relatives were in other hospitals or the patients had lost their parents. It was reported that 24 patients were missing from their families. Eight patients (19%) with familial loss experienced a single-parent loss. Three siblings, aged 3,

11, and 14 years old, lost their parents. There was loss of a single parent and sibling in nine patients (21.4%), loss of two parents and siblings in 3 patients (7.1%), and loss of siblings in one patient (2.4%). Seven of 24 children (29.16%) who lost their 1st-degree relative were told about their loss by their relatives under the supervision of a child psychiatrist. A child psychiatrist started the administration of melatonin and hydroxyzine dihydrochloride on seven earthquake patients due to sleep problems. In the follow-up, antidepressant treatment was added to two patients who had losses in their families.

The discharge time ranged from 6-84 days, with a mean of 33 days. Forty-one patients hospitalized were discharged after their treatment was completed. Twelve of the discharged patients (29.3%) returned to their residences. Five of these patients were sent to stay in tents because their houses were destroyed, after the necessary arrangements were made. One of our patients returned to the container in the earthquake area, where he lived. The remaining 29 patients (70.7%) who were discharged were sent in to the surrounding provinces where their relatives lived (Table 1).

Table 1. Socio-demographic features of the patients

	n (%)
Age (year)	8.3 \pm 4.47
Gender	
Boy	23 (54.8)
Girl	19 (45.2)
City of residence	
Kahramanmaraş	11 (26.2)
Hatay	16 (38.1)
Adiyaman	10 (23.8)
Gaziantep	3 (7.1)
Adana	2 (4.8)
Hospital admission	
Air ambulance	35 (83.3)
Other	7 (16.7)
Hospitalization indication	
Trauma	34 (81.0)
Others	8 (19.0)
Being trapped in the wreckage	
Yes	33 (78.6)
No	9 (21.4)
Time of being trapped in the wreckage (hours)	30.35 \pm 26.80
Companion (at first arrival)	
Parent	15 (35.6)
Relative	10 (24 %)
Hospital staff	17(40.4)
Destination after discharge	
Their place of residence	12 (29.3)
Others	29 (70.7)

Discussion

The Kahramanmaraş-centered earthquake, affected an area of 110,000 square kilometers, causing significant damage and a high loss of life. The winter conditions destroyed transportation routes, including airports. Individuals and teams dedicated critical hours to rescue efforts. After the first interventions, the injured were rescued from the wreckage and transferred to hospitals nearby in the big city. Patients with moderate but stable general conditions were referred to our hospital, which is 1,000 km away from the earthquake zone.

The most important causes of death in earthquakes include significant trauma. Earlier reports stated that most patients hospitalized after the Marmara earthquake, Van earthquake, and the most recent Aegean earthquake had trauma-related orthopedic causes (9-12). Rescue team members and the medical team should work together to coordinate effectively with timely and skilled management in removing the patient from the wreckage (13). Half of the cases were not removed from the rubble by professional teams. Due to the magnitude of the destruction in the Kahramanmaraş-centered earthquake, traumas from being under the debris were common. Since untrained people also carry out post-earthquake rescue work, we believe it is essential for all people living in earthquake areas to receive training on contributing to the rescue so that the trauma does not aggravate the effects.

One of the most critical problems seen after the earthquake is crush syndrome resulting from being trapped under the wreckage (14,15). Iskit et al. (16) reported the clinical features of pediatric patients after the Marmara earthquake. It was recommended that children be followed more closely for the development of acute renal failure due to crush syndrome. In the study conducted in our hospital after the 2020 İzmir earthquake, it was reported that no crush syndrome or death was observed in pediatric age group patients (17). We did not observe any relationship between the duration spent under the wreckage and the occurrence of fatal crush syndrome in patients.

The time spent under the wreckage, the number of limbs exposed to trauma, and the fasciotomy performed are correlated with the likelihood of amputation (18,19). In the early period (first 6-12 hours), surgical fasciotomy should be performed with appropriate indication, wound debridement carried out, and antibiotic treatment started (20-22). No relationship was found between the duration that earthquake victim children stayed under the wreckage and the amputation rates. Still, we think that this relationship will be more accurately evaluated in a large-scale study to be conducted with all pediatric patients.

Another health problem that emerged after the earthquake is the increased demand for intensive care. It was stated that 39 (13%) of 301 patients needed intensive care after the Marmara earthquake, while 10 (10.5%) of 95 patients needed intensive care after the Van earthquake (18,23). The need for intensive care was high due to the severe injury rates in the Kahramanmaraş-centered earthquake, which caused great destruction the area it affected. Pediatric patients hospitalized in intensive care units in the provinces affected by the earthquake for non-earthquake reasons, were also admitted to our intensive care unit to meet the intensive care needs of the cases injured in the earthquake. No deaths occurred in any cases brought to our hospital after the earthquake. After the 1999 Marmara earthquake, intensive care patients were reported to have crush syndrome (n=110, 21%), extremity fractures (16.8%), and pelvic and spinal injuries (16.1%) (18). The absence of lower abdominal and chest trauma in our patients had a positive effect on survival. We believe that earthquake survivors who come to our hospital, despite it being 1000 km away from the earthquake area, are usually referred to closer centers after the first interventions are made. Those with moderately stable general conditions are sent to our hospital.

Unaccompanied minors in an earthquake zone should not be handed over to any third party other than an official social worker or law enforcement agency. If they can express themselves about the child, all kinds of information about the child and their family should be recorded in detail. If they have a sibling, they should be kept together, but records should be maintained separately for each child. Children whose relatives cannot be found should be placed in official social service institutions. Children who were extracted from the wreckage in the earthquake area, transported to hospitals, and whose treatments were completed should be taken into care in official institutions as soon as possible after they are registered. Only official institutions should contact families who could not reach their children or hear from them after they were removed from the wreckage (24). In this context, the Ministry of Family and Social Services has established an official registration system for unaccompanied children whose families and relatives cannot be reached in earthquake zones. In our hospital, the hospital police confirmed the relatives of the patients, if any, and hospital staff were arranged to accompany children without relatives. However, the severe impacts of this great earthquake will become more apparent as many damaged and destroyed buildings are exposed in future earthquakes. Most of our earthquake victims went to their relatives' homes because their houses were destroyed or their buildings were severely damaged. Some of our patients who returned to

the earthquake area settled into tents because their homes were destroyed. One of the patients who returned to the tent was a patient with type 1 diabetes mellitus who had to be followed closely. We think that living conditions should be regulated, especially in tents, so that patients with chronic diseases do not experience problems in the supply and monitoring of medications. Being hungry, vulnerable, and without shelter in the middle of an unsafe environment is a traumatic process for children. In addition, being under the wreckage, witnessing deaths and disappearances, and having traumatic experiences also have negative effects on children. Children who need physical therapy due to orthopedic problems, or who will have to live with a new orthosis/prosthesis due to the loss of a limb, will feel the effects of the earthquake for life. The basis of psychosocial assistance for children is to meet their needs and to provide a safe environment. It is crucial to maintain psychosocial support for children following the earthquake, which had a significant impact on the area, and whose effects we will feel for a long time.

Study Limitations

There are various limitations to this study. First, as only those with moderately stable conditions were transported to our facility, the number of pediatric patients referred to our hospital may not accurately reflect the full extent of trauma and medical needs following the earthquake that occurred in Kahramanmaraş, moreover, the lack of a control group of pediatric patients from the seismic zone restricts the applicability of our results. Finally, because of resource limitations, it was not possible to follow up with the afflicted children over an extended period, especially for those who had psychosocial difficulties and chronic health problems.

Conclusion

In conclusion, the findings of this study highlight the needs of vulnerable groups, such as children, for immediate and efficient access to healthcare services, especially in the aftermath of natural disasters. The fact that people went outside of the area where they resided, and that those who returned to their houses did so in communal areas, indicates that we must face a significant social problem. However, the cases in our investigation represent a very small percentage of the population that suffered damage from the earthquake. Consequently, after disasters, social and psychological support needs, such as shelter-one of the most difficult issues affecting pediatric patients-should not be neglected, even after medical treatment has been completed.

Ethics

Ethics Committee Approval: This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval was obtained from the University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital Non-interventional Research Ethics Committee (approval number: 2023/02-31, dated: 08.03.2023).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: G.T., Concept: G.T., G.Ö., C.B., F.M., S.A.Ç., Design: G.T., G.Ö., S.A.Ç., Data Collection or Processing: G.T., C.B., F.M., B.K.D., D.A., G.G., A.B.A., S.A.Ç., Analysis or Interpretation: G.T., G.Ö., C.B., F.M., B.K.D., D.A., G.G., M.Z.K., N.O.D., A.B.A., S.A.Ç., Literature Search: G.T., G.Ö., C.B., F.M., B.K.D., D.A., G.G., M.Z.K., N.O.D., A.B.A., S.A.Ç., Writing: G.T., G.Ö., S.A.Ç.

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Rare Parasitic Causes of Acute Appendicitis: Enterobius Vermicularis in Focus

Akut Apandisitinin Nadir Paraziter Nedenleri: Enterobius Vermicularis Üzerine Bir İnceleme

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ABSTRACT

Background: Acute appendicitis is one of the most common causes of emergency surgery. Usually, it occurs due to luminal obstruction. However, enterobius vermicularis (EV) infections can also contribute to appendiceal pathology. EV may mimic symptoms of appendicitis, complicating diagnosis. Anthelmintic therapy emerges as a potential alternative to surgery in cases without inflammation.

Materials and Methods: Appendectomy cases from May 2020 to April 2024 were retrospectively analyzed. EV-positive patients were compared with age- and gender-matched controls. Parameters such as white blood cell count (WBC), appendix diameter, and imaging findings were examined using blood tests and computed tomography (CT) imaging.

Results: Among 2,599 cases, 13 were EV-positive (0.5%). WBC levels ($10.6 \pm 1.8 \times 10^3/\text{mm}^3$) and appendix diameter (10.1 ± 1.0 mm) were significantly lower in the EV group compared to controls. No significant differences were observed in neutrophil count, C-reactive protein levels, or signs of inflammation. The appendix diameter on CT has shown high sensitivity in excluding EV cases, but its specificity is low.

Conclusion: EV infestation often presents symptoms like appendicitis without causing histological inflammation, potentially leading to unnecessary surgeries. Anthelmintic therapy is a promising alternative. Retrospective analysis limits this study and underlines the need for prospective research, which should include symptoms like pruritus ani, to enhance diagnostic accuracy. Differentiating EV-related appendiceal symptoms from acute appendicitis is crucial to avoid unnecessary surgeries. Developing diagnostic tools and clinical algorithms could allow for non-operative management with targeted anthelmintic therapy, providing a promising alternative for EV-positive cases.

Keywords: Acute appendicitis, enterobius vermicularis, appendectomy

ÖZ

Amaç: Akut apandisit, cerrahi müdahale gerektiren yaygın bir acil durumdur ve genellikle lümen obstrüksiyonu ile ilişkilendirilir. Ancak enterobius vermicularis (EV) enfeksiyonları, daha az rastlanan bir neden olarak apendiks patolojilerinde önemli bir rol oynayabilir. EV, apandisit belirtilerini taklit edebilir ve tanıda zorluklara yol açabilir. Parazitin tedavi edilmesi, enflamasyon olmadığında cerrahiye alternatif bir yaklaşım sunabilir.

Gereç ve Yöntemler: Mayıs 2020-Nisan 2024 arasında yapılan apendektomi olguları retrospektif olarak incelenmiştir. EV pozitif hastalar ve benzer yaş-cinsiyet özelliklerine sahip kontrol grubu karşılaştırılmıştır. Kan testleri ve bilgisayarlı tomografi görüntüleme ile beyaz kan hücresi (WBC), apendiks çapı gibi parametreler analiz edilmiştir.



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Bulgular: Toplam 2.599 olgudan 13'ü EV pozitif bulunmuştur (%0,5). EV grubunda WBC düzeyi ($10,6\pm 1,8\times 10^3/\text{mm}^3$) ve apandiks çapı ($10,1\pm 1,0$ mm), kontrol grubuna göre anlamlı derecede düşüktür. Ancak, nötrofil, C-reaktif protein ve enflamasyon gibi diğer parametrelerde fark saptanmamıştır. BT'deki apandiks çapı, EV olgularını dışlamakta yüksek hassasiyet göstermiştir ancak özgüllüğü düşüktür.

Sonuç: EV enfestasyonları, apandisit belirtilerini taklit eder ve sıklıkla enflamasyon görülmez. Bu durum, gereksiz cerrahi müdahalelere yol açabilir. Antelmintik tedavi, cerrahiye alternatif bir yaklaşım olarak değerlendirilebilir. Ancak, mevcut çalışma retrospektif olduğundan, ileriye yönelik çalışmalarda pruritus ani gibi semptomların dahil edilmesi önerilmektedir. EV ile ilişkili apandiks belirtilerini akut apandisitten ayırmak, gereksiz cerrahiden kaçınmak için önemlidir. Uygun tanısal araçlar ve klinik algoritmalar geliştirildiğinde, birçok hasta cerrahiden kurtarılabilir. Non-operatif izlem ve hedefe yönelik antelmintik tedavi, umut vadeden bir alternatif olarak dikkat çekmektedir.

Anahtar Kelimeler: Akut apandisit, enterobius vermicularis, appendektomi

Introduction

Acute appendicitis remains a predominant cause of surgical emergencies globally, with individuals facing a 7% to 8% lifetime risk (1). Traditionally, the etiology has been attributed to luminal obstruction resulting from fecalith, lymphoid hyperplasia, or neoplasms, which leads to increased intraluminal pressure, bacterial proliferation, and subsequent inflammation (2). However, parasitic infections, particularly those caused by enterobius vermicularis (EV), represent a less frequent but clinically significant contributor to appendiceal pathology.

EV, commonly referred to as pinworm, is the most widespread human helminth infection worldwide, predominantly affecting children and populations of lower socioeconomic status (3,4). Although typically inhabiting the cecum and proximal colon, EV can migrate to the appendix, potentially inducing appendiceal colic or mimicking symptoms of acute appendicitis (5,6). It is noteworthy that multiple studies have indicated a correlation between EV infestation and negative appendectomies, as histological evidence of acute inflammation may be lacking in these instances (7-9).

Cases associated with EV may exhibit clinical presentations indistinguishable from acute appendicitis. This similarity in symptomatology presents diagnostic challenges and may result in unnecessary surgical procedures. Elevated eosinophil levels have been observed in patients undergoing appendectomy due to EV-related complications (10). While preoperative imaging techniques such as ultrasound or computed tomography may provide valuable insights in certain cases, the definitive diagnosis is typically established through pathological examination (11).

As conservative management of uncomplicated appendicitis gains traction, EV-related appendiceal inflammation may similarly benefit from anti-helminthic

therapy (12). Consequently, the ability to establish a preoperative diagnosis of EV-related acute appendicitis-like presentation is of paramount importance.

Our retrospective investigation sought to enhance preoperative diagnostic accuracy by analyzing imaging and laboratory findings in cases of EV-related appendicitis. The Neutrophil to lymphocyte ratio (NLR) and systemic immune-inflammatory (SII) Index were employed to assess the inflammatory response in EV-related appendicitis compared to conventional acute appendicitis. We propose that EV-associated appendicitis may be amenable to medical management, contingent upon accurate preoperative evaluation that considers EV as a potential etiological factor.

Materials and Methods

Patients who had undergone appendectomy in our clinic between May 2020 and April 2024 were retrospectively reviewed. Patients older than 18 years of age and those who had undergone appendectomy for acute abdomen or had a prediagnosis of acute appendicitis were included in the study. Patients under 18 years of age and those who underwent appendectomy for unrelated conditions were excluded.

Demographic data and pathology results of the patients were analyzed. For each patient whose pathology slides indicated EV, four control group patients were selected who met similar age and gender criteria. The matching was conducted using the propensity score matching method. Neutrophil (Neu), lymphocyte (Lym), NLR, platelet (Plt), platelet-to-lymphocyte ratio (PLR), C-reactive protein (CRP), and white blood cell (WBC) levels, as well as appendix diameter and periappendicular inflammation, were examined in preoperative blood tests and computed tomography images of the EV positive and control groups. The widest diameter of the appendix was measured on computed tomography scans. Periappendicular inflammation was recorded categorically.

Approval for this study was obtained from the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Local Ethics Committee (approval number: 28, date: 06.11.2024).

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics (version 24) and R software (version 4.3.2). The Shapiro-Wilk test was applied to assess the normality of continuous variables. For non-normally distributed data, the Mann-Whitney U test was employed, while the Pearson chi-square test was used to analyze categorical variables. Matched logistic regression analysis was applied to determine the factors predicting the EV positive group. In this analysis, the effect of each parameter on the EV positive group was reported using odds ratios (ORs) and 95% confidence intervals (CIs). The accuracy of the model was measured by concordance. The predictive power of the model was evaluated by receiver operating characteristic (ROC) analysis. Cut-off points for appendix diameter and WBC were determined, and sensitivity and specificity of both variables were calculated. Parameters with an area under the curve (AUC) value greater than 0.600 were considered significant in terms of diagnostic accuracy. The results of the analyses were presented as mean and standard deviation for quantitative data and as frequency (n) and percentage for categorical data. The statistical analyses were conducted with a significance level set at $p < 0.05$.

Results

A total of 2,599 appendectomy cases were retrospectively analyzed, and 13 EV-positive cases were identified according to pathology reports. The EV rate in our case series was determined to be 0.5%. One patient was excluded from the EV group due to missing data. For each patient with EV, four age- and sex-matched patients were selected as the control group. Sixty cases were included in the analyses in total.

WBC levels were significantly elevated in the control group compared to the EV-positive group (13.2 ± 2.1 vs. 10.6 ± 1.8 , $p = 0.039$). The control group exhibited a significantly larger appendix diameter (12.5 ± 1.3 mm) compared to the study group (10.1 ± 1.0 mm, $p = 0.009$). Whereas no significant difference was detected between the groups in terms of Neu, Lym, eosinophils, CRP, Plt, NLR, PLR, and SII. There was no statistically significant variation in eosinophil percentage between the two groups ($p = 0.853$, Table 1).

There was no significant difference between the EV-positive and EV-negative groups in the presence of periappendiceal inflammation as assessed by computed tomography (CT) imaging ($p = 0.764$).

Analysis with conditional logistic regression was conducted to evaluate the predictive power of WBC and appendix diameter for EV-positive cases. The OR for WBC was 0.930 (95% CI: 0.740-1.168) and was not statistically significant ($p = 0.531$). Similarly, the OR for appendix diameter was 0.803 (95% CI: 0.592-1.090), and this association was also not statistically significant ($p = 0.160$). The overall predictive accuracy of the model was assessed using the Concordance Index, and was calculated as 0.604 (standard error: 0.111), indicating limited predictive power (Table 2).

ROC analysis was performed to evaluate the diagnostic accuracy of WBC count and appendix diameter. The AUC value for WBC was calculated as 0.568 (95% CI: 0.357-0.779), with an optimal cut-off value determined to be 12,785, providing 58.3% sensitivity and 64.6% specificity. The AUC for appendix diameter on CT imaging was 0.632 (95% CI: 0.469-0.795), with an optimal cut-off value of 12.15 mm, which provided 100% sensitivity and 29.2% specificity. Although appendix diameter demonstrated high sensitivity in detecting positive conditions, its low specificity suggests a potential for high false-positive rates (Table 3, Figures 1, 2).

Table 1. Comparison of laboratory and clinical data between study and control groups

Parameter	EV + group (mean ± SD)	Control group (mean ± SD)	p-value
WBC ($\times 10^3/\text{mm}^3$)	11.25±3,306	13.83±3.88	0.039*
Neutrophil ($\times 10^3/\text{mm}^3$)	6.60±4.79	7.35±4.89	0.605**
Lymphocyte ($\times 10^3/\text{mm}^3$)	1.75±0.866	1.94±0.81	0.622**
CRP (mg/dL)	46.50±51,856	28,71±49,279	0.168**
Appendix diameter (mm)	8.08±1,730	10.10±2,425	0.009*
Platelet ($\times 10^3/\text{mm}^3$)	259.58±74,650	258.08±51,820	0.935*
PLR	193.85±149.99	163.20±78.92	0.712**
SII	1577.17±930.08	1868.08±1352.65	0.606**

*: Pearson chi-square test was used for categorical variables, **: Mann-Whitney U test or t-test was used for continuous variables. EV: Enterobius vermicularis, SD: Standard deviation, WBC: White blood cell count, CRP: C-reactive protein, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammatory

Table 2. Conditional logistic regression analysis of WBC and appendix diameter

Parameter	Coefficient (β)	OR (95% CI)	z-value	p-value
WBC ($\times 10^3/\mu\text{L}$)	-0.073	0.930 (0.740-1.168)	-6.26	0.531
Appendix diameter (mm)	-0.219	0.803 (0.592-1.090)	-1.405	0.160

Model statistics
 Concordance Index (C-index): 0.604 (S.E.: 0.111)
 Likelihood ratio test: $\chi^2=2.79$, p=0.2
 Wald test: $\chi^2=2.29$, p=0.3
 Score (log-rank) test: $\chi^2=2.5$, p=0.3

WBC: White blood cell count, OR: Odds ratio, CI: Confidence interval, S.E.: Standard error

Table 3. Receiver operating characteristic analysis of WBC and appendix diameter for diagnostic accuracy

Parameter	Optimal cut-off	Sensitivity, (%)	Specificity, (%)	AUC	95% CI for AUC	Youden index
WBC ($\times 10^3/\mu\text{L}$)	12,785	58.3	64.6	0.568	0.357-0.779	0.229
Appendix diameter (mm)	12.15	100	29.2	0.632	0.469-0.795	1.292

Sensitivity: True positive rate (%), Specificity: True negative rate (%), AUC: Area under the curve, CI: Confidence interval

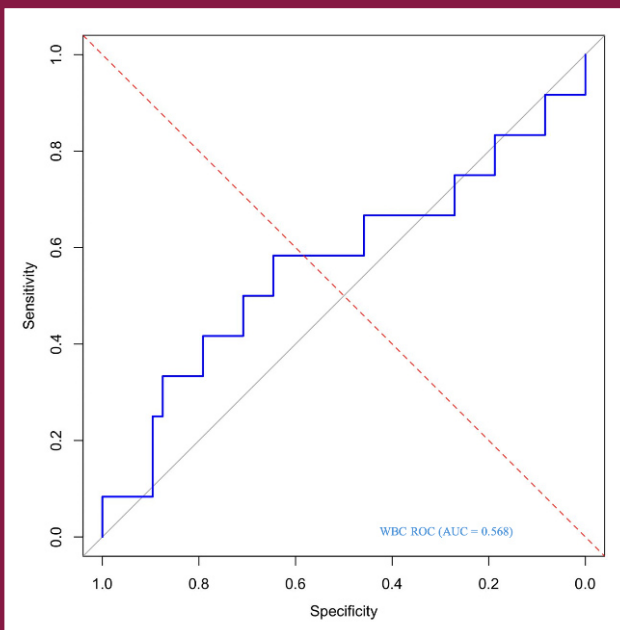


Figure 1. ROC curve for WBC
 ROC: Receiver operating characteristic, WBC: White blood cell count

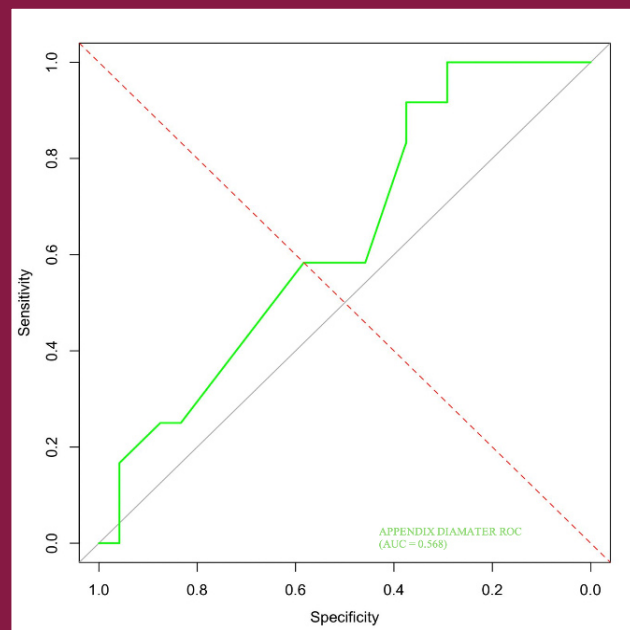


Figure 2. ROC curve for appendix diameter
 ROC: Receiver operating characteristic

Discussion

This study elucidates the clinical and diagnostic challenges associated with EV-related appendiceal symptoms, particularly in differentiating them from acute appendicitis requiring surgical intervention (13,14). Among the 2,599 appendectomy cases reviewed, EV infestation was identified in 13 patients, constituting a small but clinically significant subset. These findings raise important

considerations regarding the necessity of surgery in these cases and the potential for targeted non-operative management.

In the literature, EV was found in appendectomy specimens with a rate ranging between 2 to 9% (3). Its frequency increases in young patients and low socioeconomic regions. In our study, the rate of patients found to be EV positive was 0.5%. These rates also suggest which patients, targeted for our study, might benefit from potential medical treatments.

There are reports in the literature that eosinophil values may be higher in patients who underwent EV-related appendectomy (5). Nevertheless, no significant difference was found between the groups in terms of eosinophil values in our study.

In accordance with the literature, we found that WBC values were higher in the acute appendicitis control group (15,16). Although the mean CRP values were lower in EV cases mimicking acute appendicitis compared to other cases, no significant difference was found. Moreover, no difference significantly was observed in NLR and SII between the groups.

There are reports that preoperative imaging of patients who underwent EV-related appendectomy showed no or fewer signs of classical acute appendicitis inflammation (11,15). In the CT images analyzed, the appendix diameter in the EV group was significantly smaller than that in the control group. This finding supports the literature and suggests that inflammation is less severe in comparison to previous reports. However, while we hypothesized that the findings of periappendicular inflammation on CT images would be less pronounced in the EV group, we could not significantly detect a difference between the two groups.

The potential for non-operative management in EV-related cases is an emerging area of interest. The use of anthelmintic therapy (e.g., albendazole or mebendazole) has been shown to resolve symptoms effectively in similar cases, suggesting that surgery may not be necessary for all patients with EV infestation (7). In our cohort, the absence of gangrenous or perforated appendices in EV-positive patients further supports the feasibility of a conservative approach.

By incorporating clinical indicators such as pruritus ani, eosinophilia, and imaging findings, a diagnostic algorithm could be developed to identify patients who may benefit from medical therapy. Such a framework could reduce unnecessary surgeries, particularly in pediatric populations where EV prevalence is higher (10). As our study was retrospective, complaints such as pruritus ani were not recorded. It should be analyzed as an additional symptom in prospective studies.

Our findings are consistent with Budd and Armstrong (2), who observed that EV is rarely associated with histological acute appendicitis and is more frequently found in appendices removed for non-specific abdominal pain. Similarly, Dahlstrom and Macarthur (1) reported that most EV-related cases present with clinical features of appendicitis but lack histological inflammation, supporting the role of EV in mimicking appendicitis rather than causing it.

Study Limitations

This study has a few limitations. The retrospective nature of the investigation imposed certain constraints. Furthermore, the detection of fewer EV-related appendicitis cases than anticipated could be considered a limitation of the study. Considering our results, such as low WBC and smaller appendix diameter, in patients with an appendicitis-like clinical presentation, the possibility of EV should be considered. Prospective studies incorporating different biomarkers or findings in addition to our research are necessary. If new diagnostic methods are developed and diagnosis is facilitated, non-operative follow-up and medical treatment, particularly anti-helminthic therapy, may be recommended for this patient group. Consequently, the risk associated with surgery could be potentially mitigated, and the burden on the healthcare system potentially reduced.

Conclusion

The objective of our study was to develop parameters to aid in the diagnosis of patients with EV-associated appendicitis, who present with clinical features similar to acute appendicitis, and to provide these patients with an opportunity for medical treatment. EV-associated appendicitis should be considered in patients with low WBC values on preoperative evaluation and small appendix diameter on imaging.

Ethics

Ethics Committee Approval: This study was ethically approved by the Local Ethics Committee of the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital (approval number: 28, date: 06.11.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.Y.K., Concept: Y.Y.K., Design: Y.Y.K., M.Ş.K., Data Collection or Processing: Y.Y.K., M.Ş.K., Analysis or Interpretation: F.T.K., Literature Search: Y.Y.K., F.B.S.K., Writing: Y.Y.K., F.T.K., F.B.S.K.

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Postnatal Management and Outcomes of Hydrocephalus in Patients with Myelomeningocele: a Retrospective Study from a Single Institution

Miyelomeningoselli Hastalarda Hidrosefalinin Doğum Sonrası Yönetimi ve Sonuçları: Tek Bir Kurumdan Retrospektif Bir Çalışma

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ABSTRACT

Background: This study aims to analyze retrospectively the incidence and management of hydrocephalus in patients with myelomeningocele (MMC) treated at the Gülhane Training and Research Hospital between 2017 and 2022. The study focuses on patients diagnosed with both MMC and hydrocephalus, either prenatally or postnatally.

Materials and Methods: We retrospectively reviewed the medical records of 30 patients diagnosed with MMC and hydrocephalus. Variables such as gender, birth weight, localization of the MMC sac, timing of MMC repair surgery, and the onset and management of hydrocephalus were documented. Exclusion criteria included patients operated on alone for either MMC or hydrocephalus, patients with diastematomyelia, myelocoele, or lipomyelomeningocele, as well as cases with incomplete records.

Results: Of the 30 patients included in the study, 13 (43.3%) were male, and 17 (56.7%) were female. Hydrocephalus was detected at birth in 10 patients (33.3%), while it developed postoperatively in 20 patients (66.7%). MMC lesions were observed in the thoracic region (4 patients, 13.3%); the lumbar region (6 patients, 20%); the sacral region (5 patients, 16.7%); the thoracolumbar region (6 patients, 20%); and the lumbosacral region (9 patients, 30%). Ventriculoperitoneal shunt (VPS) placement was performed in 12 (60%) of the 20 patients who developed hydrocephalus postoperatively; while endoscopic third ventriculostomy (ETV) was performed in 8 patients (40%). Among the 10 patients who presented with hydrocephalus at birth, VPS was performed after initial placement of an Ommaya reservoir.

Conclusion: Hydrocephalus remains a significant and challenging complication in MMC patients, often requiring surgical intervention. The timing and approach to the treatment of hydrocephalus, particularly in the context of MMC, demand careful consideration to minimize the risk of infection and surgical complications. Our findings suggest that while ETV combined with VPS can be effective, close monitoring and timely intervention are crucial to managing hydrocephalus in these patients.

Keywords: Hydrocephalus, myelomeningocele, ETV, Ommaya reservoir

ÖZ

Amaç: Bu çalışma, myelomeningosel (MMC) hastalarında hidrosefalinin insidansını ve yönetimini retrospektif olarak analiz etmeyi amaçlamaktadır. Çalışma, 2017 ve 2023 yılları arasında Gülhane Eğitim ve Araştırma Hastanesi'nde tedavi edilen MMC tanılı hastaları kapsamaktadır. Çalışma, hem MMC hem de hidrosefalisi olan hastalara odaklanmaktadır ve bu hastaların hidrosefalisi ya doğuştan ya da doğum sonrası gelişmiştir.

Gereç ve Yöntemler: MMC tanısı konmuş ve hidrosefalisi olan 30 hastanın tıbbi kayıtları retrospektif olarak incelenmiştir. Cinsiyet, doğum ağırlığı, MMC'nin yeri ve hidrosefalinin yönetimi gibi değişkenler analiz edilmiştir. Çalışmaya dahil edilen hastalar arasında diğer nöral tüp defekti türleriyle (ensefalosel, lipomiyelomeningosel, myelosele, lipomyelosele) ameliyat edilenler yer almamaktadır.



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Bulgular: Çalışmaya dahil edilen 30 hastanın 13'ü (%43,3) erkek, 17'si (%56,7) kız idi. Hidrosefali doğumda 10 hastada (%33,3) saptanırken, 20 hastada (%66,7) doğumdan sonra gelişti. MMC lezyonları, torasik bölgede 4 hastada (%13,3), lomber bölgede 6 hastada (%20), sakral bölgede 5 hastada (%16,7), torakolomber bölgede 6 hastada (%20) ve lumbosakral bölgede 9 hastada (%30) gözlemlendi. Ventriküloperitoneal şant (VPS) yerleştirme işlemi, hidrosefalisi olan 20 hastanın 12'sinde (%60) uygulandı. Endoskopik üçüncü ventrikülostomi (ETV) 8 hastada (%40) uygulandı. Hidrosefali ile başvuran ve ameliyat edilen 10 hasta arasında, VPS yerleştirilmeden önce Ommaya rezervuarı takıldı.

Sonuç: Hidrosefali, MMC'de önemli ve zorlu bir komplikasyon olarak kalmaya devam etmektedir ve çoğu zaman cerrahi müdahale gerektirmektedir. MMC bağlamında tedaviye yaklaşımda zamanlama ve yöntem, enfeksiyon riskini ve cerrahi komplikasyonları minimize etmek için büyük önem taşır. Bulgularımız, ETV ve VPS'nin her ikisinin de etkili olduğunu, ancak yakından izleme ve zamanında müdahalenin tedavi başarısı için kritik olduğunu göstermektedir.

Anahtar Kelimeler: Hidrosefali, miyelomeningocele, ETV, Ommaya rezervuarı

Introduction

Cranial defects, encompassing a spectrum of congenital anomalies known as neural tube defects (NTDs) that include open or closed spinal dysraphism, are among the most common severe central nervous system anomalies and rank second only to cardiovascular anomalies in causing congenital morbidity and mortality (1). Myelomeningocele (MMC), which occurs due to the incomplete closure of the spinal neural tube during the first month of embryonic development, is the most severe form of spinal dysraphism and is characterized by the protrusion of the spinal cord and meninges through a defect in the vertebral column (2). The incidence of MMC varies between 0.2 and 2 per 1000 live births, and depending on the affected vertebral region, it can result in devastating clinical manifestations such as Chiari II malformation, genitourinary dysfunction, sensory and motor deficits, and hydrocephalus. Therefore, if not diagnosed early or left untreated, the prognosis generally worsens (3). Historically, the relationship between MMC and hydrocephalus was first suspected by Morgagni as early as 1769, with the hypothesis that excess fluid was responsible for both the spinal cyst and hydrocephalus (4). The exact pathophysiology of hydrocephalus associated with MMC remains unclear; however, one theory suggests that inappropriate intrauterine cerebrospinal fluid (CSF) leakage through the MMC defect leads to the underdevelopment of normal CSF drainage pathways, while another theory posits that meningeal irritation caused by amniotic fluid during the intrauterine period contributes to this condition (5,6). These theories provided the scientific basis for early animal studies and pilot human studies evaluating prenatal MMC closure, with the hope that early defect closure would lead to milder neurological deficits and reduced postnatal hydrocephalus (7).

Symptomatic hydrocephalus usually occurs in the first month after MMC repair, and more than half of the patients require surgical treatment (8). Initially, a CSF shunt was the only treatment for MMC-associated hydrocephalus,

but nowadays endoscopic third ventriculostomy (ETV) and choroid plexus cauterization (CPC) may be preferred (9,10). Additionally, there is still no consensus in the literature regarding the timing of treatment for these patients; some are treated for hydrocephalus simultaneously with the initial closure, while others are monitored post-closure to determine whether they will require intervention for hydrocephalus (11).

Although managing hydrocephalus associated with MMC is challenging, if patients are well-managed, particularly with the prevention of infections, a favorable cognitive outcome can be achieved in these children. In this study, we retrospectively reviewed the postnatal management of patients with hydrocephalus associated with MMC who were operated on in our clinic.

Materials and Methods

Ethical approval of the project was obtained from the Gülhane Faculty of Medicine Clinical Research Ethics Committee (approval number: 2023-159, dated: 05.07.2023). Patient consent was not required as the study was retrospective, based on computer records, and did not include figures showing the patient's face. In this study, patients with hydrocephalus who underwent surgery between 2017 and 2022 were retrospectively analyzed, with a specific focus on those with hydrocephalus associated with MMC. Patients included in the study were those who had intrauterine detection of MMC and hydrocephalus and were born alive, those who presented with both MMC and hydrocephalus postnatally, and those who developed hydrocephalus during follow-up after MMC surgery, and required treatment. Patients who were operated on solely for MMC or hydrocephalus, those with diastematomyelia, myelocoele, and lipomyelomeningocele, and those whose medical records were incomplete, were excluded from the study. A total of 30 patients met these criteria and were included in the study.

The patients' files were retrospectively reviewed. The recorded data included gender, birth weight, location of the MMC sac, timing of MMC repair surgery, timing of the first detection and treatment of hydrocephalus, type of treatment, and the need for and timing of revision surgery in patients treated for hydrocephalus.

Statistical Analysis

IBM SPSS Statistics software version 29.0.2.0 (20) (IBM, SPSS, Chicago, Illinois, USA) was used for the statistical analysis of the data for this study. Categorized variables were reported using descriptive statistics as the number of patients (n) and percentage (%). The distribution properties of numerical variables were evaluated with the Shapiro-Wilk test. The homogeneity of the variances was analyzed by Levene's test. Differences at the $p < 0.05$ level were considered statistically significant.

Results

Of the 30 patients who met the inclusion criteria, 13 (43.3%) were male, and 17 (56.7%) were female. The average birth weight of the patients was 3305 grams. MMC surgery was performed on 15 patients (50%) on the first day after birth, on 10 patients (33.3%) on the second day, on 2 patients (6.7%) on the third day, on 2 patients (6.7%) on the fourth day, and on 1 patient (3.3%) in the first month due to late presentation by the family (Table 1).

The MMC lesion was located in the thoracic region in 4 patients (13.3%), the lumbar region in 6 patients (20%), the sacral region in 5 patients (16.7%), the thoracolumbar

region in 6 patients (20%), and the lumbosacral region in 9 patients (30%) (Figure 1 and Table 2).

Of the 30 patients included in the study, 20 (66.7%) initially underwent MMC surgery and were monitored for hydrocephalus. Among the 20 patients who developed hydrocephalus during follow-up, ventriculoperitoneal shunt (VPS) placement was performed in 12 patients (60%) between one week and five months after MMC surgery. ETV was performed in 8 patients (40%) with hydrocephalus, and simultaneous VPS placement was performed in 6 of these patients, which is 75%. An Ommaya reservoir were placed in 2 patients (25%) who weighed less than 3000 grams, and VPS placement surgery was performed once they reached an appropriate weight within 2 months. VPS dysfunction

Table 1. Demographic and surgical timing data

Variable	Number of patients (n=30)	Percentage (%)
Gender		
Male	13	43.3%
Female	17	56.7%
Average birth weight	3305 grams	
Timing of MMC surgery		
First day	15	50%
Second day	10	33.3%
Third day	2	6.7%
Fourth day	2	6.7%
Within 1 month (late presentation)	1	3.3%
MMC: Myelomeningocele		



Figure 1. Preoperative images of (a) sacral, (b) thoracolumbar, and (c) thoracic myemomeningocele patients

requiring revision occurred in 17 patients (85%) between 3 and 18 months postoperatively. Three patients (15%) did not need revision surgery (Table 3).

Hydrocephalus was observed at birth in 10 patients alongside MMC. An Ommaya reservoir was placed simultaneously with MMC closure surgery in 6 of these 10 patients (60%), and a VPS was placed once they reached an appropriate weight within 2 months. In 4 patients (40%), ETV was performed simultaneously with MMC closure surgery, followed by the placement of an Ommaya reservoir, and VPS placement was performed within 1 month. VPS dysfunction requiring revision occurred in 8 patients (80%), between 1 and 6 months during follow-up. Two patients (20%) did not need revision surgery (Table 3).

Table 2. Location of MMC lesion

Location	Number of patients (n=30)	Percentage (%)
Thoracic region	4	13.3%
Lumbar region	6	20%
Sacral region	5	16.7%
Thoracolumbar region	6	20%
Lumbosacral region	9	30%

MMC: Myelomeningocele

Table 3. Hydrocephalus management and outcomes

Variable	Number of patients	Percentage (%)
Hydrocephalus following MMC surgery (n=20)		
VPS placement	12	60%
ETV	8	40%
Simultaneous VPS placement	6	75%
• Ommaya reservoir placement	2	25%
• VPS dysfunction (requiring revision)	17	85%
No revision required	3	15%
Hydrocephalus present at birth (n=10)		
Ommaya reservoir placement simultaneous with MMC closure	6	60%
ETV	4	40%
VPS dysfunction (requiring revision)	8	80%
No revision required	2	20%

MMC: Myelomeningocele, VPS: Ventriculoperitoneal shunt, ETV: Endoscopic third ventriculostomy

Discussion

Hydrocephalus is a clinical and neuroradiographic diagnosis characterized by abnormal CSF accumulation within the brain ventricles, leading to ventricular enlargement, and is often associated with increased intracranial pressure (12). Hydrocephalus complicates 35-91% of MMCs, and while it may be evident at birth, it can also develop following MMC repair (13). Among the 30 MMC patients included in our study, 10 (33.3%) had evident hydrocephalus at birth, while 20 (66.7%) developed hydrocephalus after MMC repair (Table 3).

It has been observed that the likelihood of developing hydrocephalus requiring treatment in patients with MMC varied according to the anatomical level of the lesion, and hydrocephalus developed in 60.7% in sacral lesions, 82.4% in lumbar lesions, and 92.2% in thoracic lesions (14). Among the MMC patients requiring surgery for hydrocephalus in our study, the lesion levels were distributed as follows: thoracic in 4 patients (13.3%), lumbar in 6 patients (20%), sacral in 5 patients (16.7%), thoracolumbar in 6 patients (20%), and lumbosacral in 9 patients (30%) (Table 2).

The primary principle of MMC surgical repair is to identify and carefully handle neural tissues to minimize the risk of damage to remaining functional neural tissue. A secondary principle involves preserving and reconstructing the covering structures to re-establish CSF circulation and prevent CSF leakage. Lastly, correct timing of surgical repair and the prevention of perioperative complications ensure proper MMC management (15). Surgery within the first 48 hours of life is crucial to reduce the risk of infection (e.g., reducing the incidence of ventriculitis from 37% to 7% if surgery is performed within 48 hours) and to decrease the likelihood of neurological deterioration due to dehydration or stretching of the placode (16). In our center, we aim to perform MMC repair within 24 hours of birth for all newborns with MMC. However, surgeries were delayed for patients referred from other hospitals. On the first day, in 15 patients (50%), MMC surgery was performed; on the first day in 15 patients (50%), on the second day, in 10 patients (33.3%); on the second day in 10 patients (33.3%), on the third day in 2 patients (6.7%), on the fourth day, in 2 patients (6.7%); on the fourth day in 2 patients (6.7%), and, in 1 patient (3.3%), surgery was performed at 1 month due to delayed referral by the family (Table 1).

Several factors contribute to hydrocephalus in MMC patients. McLone and Knepper (5) reported that permanent CSF leakage due to NTDs disrupts the development of the brain and CSF pathways, leading to crowding of the posterior fossa, which results in downward displacement of the brain stem and hydrocephalus (17).

Prenatal diagnosis of hydrocephalus in MMC can be achieved using ultrasound and magnetic resonance imaging (MRI). High-resolution fetal ultrasound is a non-invasive, sensitive, affordable, and widely available examination, but it is dependent on the observer. Fetal MRI is more accurate and non-invasive but is expensive and more difficult to access (18). In our study, of the 10 patients with concurrent MMC and hydrocephalus at birth, the condition was detected by fetal ultrasound during obstetric follow-ups in 7 patients. The families were informed about the process.

In addition to ultrasound and MRI, computed tomography (CT) can also be used in the postnatal diagnosis of hydrocephalus. Ultrasonography, which has the advantages of being cost-effective and non-invasive, is one of the most commonly used methods for the diagnosis of hydrocephalus in newborns (Figure 2a). CT remains one of the most sensitive and widely used modalities to confirm hydrocephalus and aid in treatment planning, although there are increasing concerns about the radiation effects of CT on the developing brain, particularly regarding cognitive development and tumor induction (Figure 2b) (19). In our clinical practice, patients undergoing surgery for MMC are closely monitored for head circumference and fontanel tension, and in cases of suspicious increases, they are evaluated for hydrocephalus with ultrasonography and MRI (Figure 2c). In cases of acute neurological deterioration, urgent CT imaging is performed.

The two main accepted procedures for hydrocephalus treatment in MMC patients are CSF shunt placement and ETV (20,21). Although VPS surgery is the gold standard and most commonly used CSF shunt procedure in hydrocephalus treatment, other alternatives include ventriculopleural and ventriculoatrial shunts (22). In our routine clinical practice, VPS surgery is the first choice, provided there are no contraindications.

While many authors believe that placement of VPS at the same time as MMC surgery, increases the risk of shunt infection, others believe that there is no association, which shows that there is still controversy about the timing of surgery (23-26). MMC may increase the risk of shunt infection by causing CSF contamination through the defect (27,28). Therefore, it is recommended that VPS placement be performed meticulously, with particular attention to preventing infection. At our center, we adopt a cautious approach to VPS placement while closely monitoring for hydrocephalus development. Ventricular tapping, external ventricular drainage, and Ommaya reservoir placement are preferred treatment alternatives until VPS surgery, especially if there is evidence or suspicion of MMC repair breakdown or infection. Of the 30 patients included in this study, we initially performed MMC repair surgery without prophylactic hydrocephalus surgery in 20 (66.7%) patients who did not have evident hydrocephalus at birth, while closely monitoring them for hydrocephalus. In the 10 (33.3%) patients with hydrocephalus at birth, we opted for simultaneous placement of an Ommaya reservoir during MMC surgery and delayed VPS surgery.

In recent years, ETV has become an important treatment option, especially for obstructive hydrocephalus because of its lower risk of infection and the fact that it does not rely on extracranial mechanical drainage (29). Although the success rate of ETV in patients with MMC-associated hydrocephalus is known to be as low as 35%, the success rate is 76%, in combination with CPC (30). We prefer not to perform ETV in newborns with hydrocephalus associated with MMC due to the low success rate in this age group. In this study, among the 10 patients diagnosed with MMC and hydrocephalus at birth and operated on during the neonatal period, 6 received an Ommaya reservoir, while 4 underwent ETV along with the placement of an Ommaya reservoir. Of the 20 patients

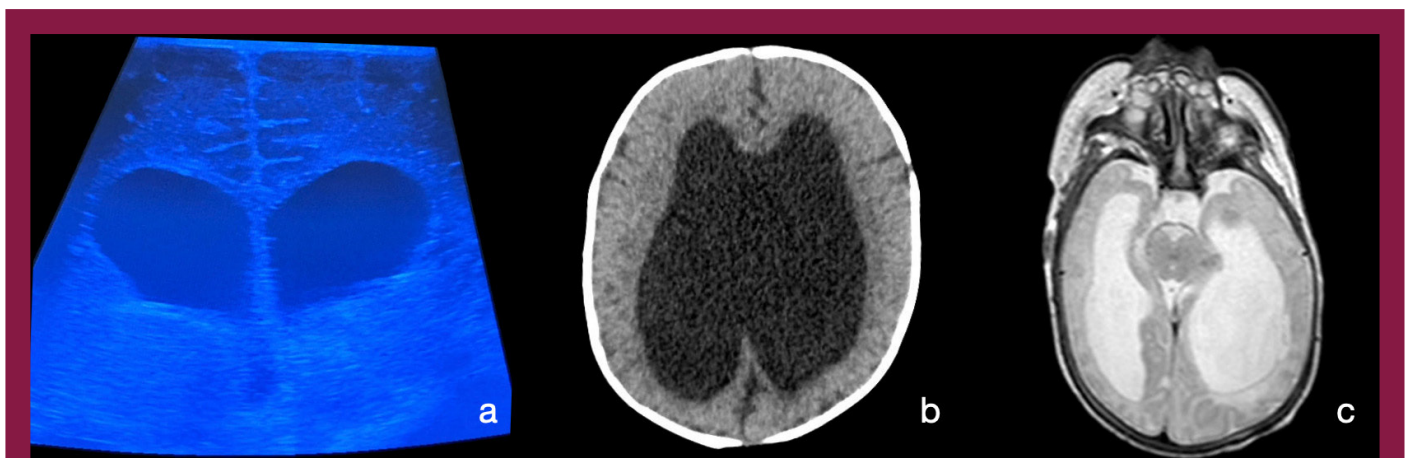


Figure 2. (a) Ultrasonography, (b) computed tomography and (c) magnetic resonance imaging in the diagnosis of hydrocephalus in patients with myelomeningocele

who developed hydrocephalus during follow-up, 8 (40%) underwent ETV, but 6 of these also received concurrent VPS placement, and 2 received an Ommaya reservoir. None of our patients underwent the CPC procedure.

In these patients, it is very important to remain vigilant regardless of the treatment modality, which makes close follow-up necessary. Initially, a follow-up every three months is recommended. Once patients have stabilized, annual follow-up is preferred.

Conclusion

This study provides valuable insights into the management of hydrocephalus in patients with MMC and highlights the importance of individualized treatment strategies. Our findings indicate that while the incidence of hydrocephalus remains significant, the timing and choice of surgical interventions, particularly the use of VPS and ETV, play a critical role in patient outcomes. The decision to delay VPS placement in favor of vigilant monitoring and the selective use of Ommaya reservoirs or ETV has been shown to be effective in reducing the risk of infection and other complications associated with premature shunt insertion.

Furthermore, the data underscore the need for careful consideration of anatomical factors, such as an abnormal base of the third ventricle and the presence of communicating hydrocephalus, when determining the suitability of ETV in neonates. The success rate of ETV in neonates with MMC remains limited, and alternative or adjunctive approaches are required.

The study also highlights the necessity for close postoperative follow-up to promptly detect and address potential shunt failures or other complications, thereby ensuring better long-term neurological outcomes. As the field of pediatric neurosurgery continues to evolve, our experience suggests that a cautious, tailored approach to the management of MMC-associated hydrocephalus, informed by ongoing clinical assessment and the latest surgical techniques, will likely yield the best results for this vulnerable patient population.

Future research should focus on further refining these treatment protocols, exploring the potential of newer technologies and minimally invasive procedures, and developing long-term follow-up strategies to enhance the quality of life for patients with MMC and hydrocephalus.

Ethics

Ethics Committee Approval: Ethical approval of the project was obtained from the Gülhane Faculty of Medicine Clinical Research Ethics Committee (approval number: 2023-159, dated: 05.07.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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Development of a Blended Clinical Education Faculty Development Program in Postgraduate Medical Education and Evaluation with the Kirkpatrick Model

Mezuniyet Sonrası Tıp Eğitiminde Karma Klinik Eğitici Gelişim Programı Geliştirilmesi ve Kirkpatrick Modeliyle Değerlendirme

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ABSTRACT

Background: The structure of postgraduate medical education differs as it is mostly a competency-based education focused on opportunity-based learning. The content of faculty development programs (FDPs) is mostly intended to help enhance knowledge and skills and to adapt to the developing and changing educator roles by responding to the needs of educators. The aim of this study was to develop a blended FDP for postgraduate medical educators implement the program evaluate it using the Kirkpatrick model.

Materials and Methods: Clinical educators of internal medicine and obstetrics and gynecology were included in the study. The program was carried out with asynchronous training through an online learning management system, and face-to-face training with 5 modules. The program was evaluated with the Kirkpatrick model.

Results: The Likert scale scores were: achievement of session objectives 4.74, training techniques-methods 4.75, program content 4.77, performance of trainers 4.72, duration-methods of sessions 4.89, and satisfaction 4.85. The pre-test and post-test results were found to be statistically significant ($p<0.001$ and $p=0.001$). When the educational activities carried out in the clinics before and after the training were compared, journal club activity at the end of the program increased statistically ($p<0.001$), while a statistically significant increase was detected in the appointment of educational consultants to residents after the training ($p=0.001$).

Conclusion: This study is the first blended clinical FDP developed, implemented and evaluated with the Kirkpatrick model for postgraduate medical education. According to the results, the program was found to be successful at every stage of its evaluation.

Keywords: Faculty development program, Kirkpatrick model, postgraduate medical education

ÖZ

Amaç: Mezuniyet sonrası tıp eğitiminin yapısı klinik ortamda, çoğunlukla fırsatta dayalı öğrenmeye odaklı yeterlilik temelli bir eğitim olması nedeniyle farklılık göstermektedir. Eğitici gelişim programlarının içeriği çoğunlukla eğitimcilerin ihtiyaçlarına cevap verecek bilgi ve becerilerin geliştirilmesine yardımcı olmak, gelişen ve değişen eğitimci rollerine uyum sağlamaya yöneliktir. Bu çalışmanın amacı mezuniyet sonrası tıp eğitimcilerine yönelik karma eğitici gelişim programı geliştirmek, programı uygulamak ve Kirkpatrick modeliyle değerlendirmektir.

Gereç ve Yöntemler: Çalışmaya dahiliye ve kadın hastalıkları ve doğum klinik eğitimcileri dahil edildi. Program, çevrimiçi eğitim öğrenme yönetim sistemi üzerinden 5 modülden oluşan asenkron ve yüz yüze eğitimlerle gerçekleştirildi. Program Kirkpatrick modeliyle değerlendirildi.

Bulgular: Beşli Likert memnuniyet anketine göre; oturum hedeflerine ulaşma 4,74, eğitim teknik-yöntemleri 4,75, program içeriği 4,77, eğitimcilerin performansı 4,72, oturumların süre-yöntemleri 4,89, memnuniyet 4,85 olarak puanlanmıştır. Çevrimiçi ve yüz yüze eğitimler ön test-son test sonucu istatistiksel olarak anlamlı saptanmıştır ($p<0,001$ ve $p=0,001$). Kliniklerde eğitim öncesi ve sonrası gerçekleştirilen eğitim faaliyetleri karşılaştırıldığında program sonunda makale saati etkinliği istatistiksel olarak artarken ($p<0,001$),



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eğitim sonrası asistanlara eğitim danışmanı atanmasında ise istatistiksel olarak anlamlı bir artış tespit edildi ($p=0,001$).

Sonuç: Bu çalışma mezuniyet sonrası tıp eğitimi için geliştirilen, uygulanan ve Kirkpatrick modeliyle değerlendirmesi yapılan ilk karma klinik eğitici gelişim programı olması özelliği taşımaktadır. Sonuçlara göre eğitici gelişim programı, değerlendirmesinin her aşamasında başarılı bulunmuştur.

Anahtar Kelimeler: Eğitici gelişim programı, Kirkpatrick model, mezuniyet sonrası tıp eğitimi

Introduction

To increase training motivation in trainers, adequate faculty development programs (FDPs) should be implemented to train them in the required competencies according to institutional policies and the desired academic excellence (1). It has been reported that the goal of quality education can only be achieved after the trainers' skills are enhanced (2). Khan et al. (3) emphasized that being an expert in medicine and a successful surgeon is not enough to be a successful educator and that additional FDPs are needed. Attention was drawn to the training of trainers, particularly on effective surgical training in surgical branches, focusing on residents' evaluation and feedback, coaching in the role of a trainer, and training skills during surgery (4).

Trainers working in training and research hospitals (TRHs) in our country are responsible for training residents, conducting research, and managing an intense clinical workload. To this end, educators are trying to become involved in FDPs to improve their academic and professional skills. There is no regular and compulsory FDP for clinical trainer training in TRHs, but trainers receive this training based on opportunities available and through their personal efforts. FDPs existing in our country are designed for undergraduate medical education, though postgraduate education may differ in method and content. To this end, the following research questions were asked:

- What are the needs of clinical educators involved in postgraduate medical education regarding "training the trainer"?
- If the FDP is developed and implemented;
- What is the satisfaction level of the participants at the end of the training?
- What are the participation and success rates in the training event?
- What is the level of participants' usage of the training content given in the clinic after the training?
- How is the applied training reflected in clinical education?

Materials and Methods

Approval for the study was obtained from the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (approval number: KAEK-569, dated: 02.09.2021), and the participants were informed and consent was received.

An internal medicine (IM) department and a surgical department, both with the highest number of residents at Health Sciences University Türkiye, Antalya Training and Research Hospital, were selected for the program. Seventeen trainers from IM and all trainers from obstetrics and gynecology (OG) agreed to participate in the study. The demographic characteristics of the participants are shown in Table 1.

Program Development

The blended clinical FDP was developed by taking into consideration the Kern program development steps (5).

Table 1. Demographic characteristics of blended clinical FDP participants

Variables	Mean \pm SD	Median (min-max.)
Age (years)	45.5 \pm 6.39	45 (30-62)
	N	%
Female	9	37.5
Male	15	62.5
Participant's section		
Internal medicine	17	70.8
Obstetrics and gynecology	7	29.2
Participant's title		
Professor (MD)	6	25.0
Associate professor (MD)	12	50.0
Dr. lecturer (MD)	6	25.0
Previous trainer training certificate		
There is certificate	4	16.7
None	20	83.3

None; No certificate. FDP: Faculty development program, SD: Standard deviation, min-max.: Minimum-maximum, MD: Medical doctor

Determining the Current Situation

Before starting the FDP, an online survey was administered to a total of 50 residents in IM (26) and OG clinics (24) to evaluate the educational activities of residents in the clinics.

Needs Assessment

To develop the training program, it is extremely important to first determine the need for postgraduate medical education. For this purpose, a structured focus group meeting was held with IM and OG educators who agreed to participate in the study to analyze needs. A structured focus interview form consisting of ten basic questions, each with opening questions, was used for the focus group interview. During the interview, the researcher first introduced himself and the project, shared information about the purpose of the research and how long the interview would last, and obtained verbal approval for recording. The interviews were held with 19 out of 24 educators in 3 groups of 5-7 people, for an average of 30-45 minutes.

While creating the training program, in addition to these interviews, all articles containing FDPs published to date in the electronic databases of PubMed, Science Direct, and Google Scholar were transcribed. However, no FDPs specifically developed for postgraduate medical education could be found. The content of the training program was created in line with the data obtained.

This study aimed to develop a blended FDP by combining the advantages of online education with the strengths of face-to-face education.

Educational Strategies

The Canvas learning management system was chosen in this study because its web-based interface is suitable for small groups and it provides opportunities such as a mobile application, exams, video uploading, and feedback to discussions. The training videos were prepared by medical education experts in the field who determined the learning goals and objectives. Online courses consist of 5 modules, which can be entered and repeated at any time: Module 1: National Core Education Program (NCEP), Competence-Competency, Learning Goal Writing, Medical Specialization Board Curriculum Creation and Standards Determination System; Module 2: Adult Learning Principles; Module 3: Educational Roles and Feedback in the Clinic; Module 4: Educational Methods in Clinical Education; Module 5: Assessment and Evaluation in the Clinic.

Program Implementation

In order to implement the educational development training, internal support from the Department of Medical Education Faculty Members and external support from

Computer Engineering and the administrative dimension of the program from the Chief Physician's Office were included at every stage. To foresee the problems that may be encountered during the implementation of the program, a pilot application was carried out with 2 participants to obtain information about the content of the program and the evaluation methods used, and any problems in the program were eliminated.

The educator development program started with online training. Twenty-four participants were monitored through the system logs by ensuring that they entered the system with their username and password. When the participant moved on to the course content, he/she started the program with the pre-test before starting the training. In line with the video learning goal, the pre-test questions consisted of 15 multiple choice questions prepared by the trainers working in the online training. The participants were given 30 minutes to answer; the pre-test answers were kept confidential. After all training modules were completed, participants answered the post-test. When the participants answered the post-test questions, they were able to see their exam results, their answers to the questions, and the correct answers in the system. Online courses were kept open for active participants for 3 months.

Face-to-face training was organized three months later for the participants who completed the online training. A pre-test consisting of 15 questions, in line with the aims and objectives of the face-to-face education content, was conducted before the session, and a post-test was conducted after the program. Sixteen participants (12 in IM, 4 in OG) completed the face-to-face training (Face-to-face Training Content; Assessment and Evaluation in the Clinic, Use of Audiovisual Tools, Effective Presentation Planning, Interactive Training Techniques, Body Language).

Program Evaluation

Using the Kirkpatrick program evaluation model, for the first level evaluation, a 5-point Likert online satisfaction survey was administered at the end of the training program to all participants who attended both the face-to-face and online meetings. For the second level evaluation, pre-test and post-test results in online and face-to-face training were compared. For the third level evaluation, residents who received the training were asked 4 months later to fill out the same online survey forms that we applied to obtain their opinions on the educational activities implemented in their clinics.

Statistical Analysis

For the qualitative evaluation of the research, the video recordings of the structured focus group interviews



were watched and the conversations were transcribed. The researchers first coded the data, then codes and subcategories were organized, and the findings were defined and interpreted. In addition to the researcher, the opinions of two lecturers, who are experts in their field, were obtained. Expressions with common meanings were combined, themes were formed. The accuracy of these themes was confirmed by evaluating the opinions of the trainers.

Categorical variables were analyzed with Pearson's chi-square and Fisher's exact test. The suitability of the data for normal distribution was checked with the Shapiro-Wilk test. The Mann-Whitney U test and Kruskal-Wallis test, were used to analyze the difference between continuous variables in independent groups. Bonferroni correction was performed in post-hoc tests. The pre-test and post-test results of the trainers, in online and face-to-face training, were compared with the Wilcoxon signed-rank test. The IBM SPSS 23.0 software package (IBM Corp., Armonk, NY) was used to analyze the data, and p-values less than 0.05 were considered statistically significant.

Results

Participant Focus Group Interview Results

The video and audio-recorded interviews were then transcribed, and transcript codes, categories, and sub-themes were determined through descriptive analysis. The coding done within this framework was grouped into four main themes: educational roles, educational methods, program scope, and assessment-evaluation. Quotations from the participants' opinions are stated to conceal the identity of the participant. To facilitate interpretation of the quote, the group in which the interview was held, the participant code, and the time period in which the statement was made are provided for each participant.

Educational Roles

Although it was not expressed conceptually, the participants stated that the trainer should be less of a lecturer and more of a guide and role model. Regarding the educational role;

Group 3 (P17, 21:05); Residents struggle with preparing presentations. I think it is our duty as educators to guide the residents on these issues, such as how to write an article, how to read it, and where to publish it, before reaching the thesis stage.

Program Scope

Participants generally stated that they prepared a training program compatible with the NCEP for residents.

They reported that they were able to prepare the content, but did not know how to write a purpose or objective.

Group 1 (P4, 34:04): I think the real problem is that the educator does not know what, how much, and how to teach.

Educational Methods

In the interviews with the participants, they stated that they mostly used lectures, seminars, journal clubs, and multidisciplinary case presentations as training methods. They reported that bedside training and rounds were held regularly.

Group 1 (P5, 27:04): As a young educator, I sometimes cannot control the back rows while teaching. The residents are already so tired, and they start falling asleep at the fifth minute. I need to engage them in the lesson, but I do not know how to achieve that.

Assessment and Evaluation

Multiple-choice midterm exams are frequently administered as assessments in clinical evaluations. It was observed that the participants were not knowledgeable about how to conduct the structured exam.

Group 1 (P5, 08:49): Assessment and evaluation are the areas where we are completely lacking. I learned numerous checklists in assessment and evaluation in my previous training, but I cannot apply them. Today, I have difficulty when someone asks me to prepare a question.

Program Evaluation Results Based on Kirkpatrick Model

First Level (Reaction); Participants' Satisfaction Evaluation Results

At the end of the training program, all participants were asked to evaluate the program in all aspects according to the propositions (Table 2).

Participants' opinions regarding the FDP are included based on the propositions.

"Unlike the trainer training I had previously received, topics related to resident training were explained. This made it very useful, and the fact that some of the courses were online made our job easier."

"The asynchronous online training eliminated the time constraint, and I had the chance to watch the videos over and over again."

Second Level (Learning); Test Results of Participants

For the second level evaluation, the change in knowledge among the FDP participants before and after the training was evaluated (Table 3). It was determined that there was a significant increase in the post-test scores of the participants in both online and face-to-face training ($p < 0.001$ and $p = 0.001$). No significant relationship was observed between

the participants' pre-test and post-test scores in terms of their gender, title and department ($p>0.05$), ($p=0.018$).

Third Level (Transfer); Opinions of Residents on Educational Activities Implemented in Clinics

Forty-two of the residents (participation rate: 84%) responded to the survey. When the educational activities implemented in the clinics before and after the FDP were compared (Table 4), journal club activity was seen to have increased significantly ($p<0.001$).

Likert scale scores were compared to evaluate the clinical training of the resident before and after the FDP (Table 5). Score increases were observed in statistically significant findings.

Discussion

This study covers the development of a blended educator development program for postgraduate medical education, and the implementation and the evaluation of the program based on the Kirkpatrick model. In the study, the program was evaluated from multiple perspectives by collecting and analyzing quantitative and qualitative data in the same time period.

The structure of postgraduate medical education differs in the clinical environment as it is mostly a competency-based education focused on opportunity-based learning (6,7). Therefore, instructors need to be actively involved. While FDPs of medical faculties are becoming widespread in our country, access to these trainings is left to individual

Table 2. Participants' responses to propositions related to program evaluation at the end of the training program

Propositions	Average	SD
Achieve session goals		
1. Targets are clearly explained	4.88	0.34
2. The content of the courses met my learning objectives	4.88	0.34
3. The content was understandable	4.75	0.45
4. There was an effective communication environment	4.56	0.63
5. Course duration was sufficient to achieve learning objectives	4.63	0.62
Educational techniques and methods		
6. The training method was consistent with the goal of the session	4.81	0.4
7. Our interest was constantly kept high in the face-to-face program	4.75	0.45
8. Technological infrastructure was sufficient for application in online courses	4.75	0.45
9. I did not have any technical problems in online courses	4.69	0.48
Program content		
10. The topics included in the program, addressed the areas I needed in the clinic.	5	0
11. The time allocated was sufficient for the program content.	4.44	0.81
12. Lessons were taught according to the program given at the beginning of the course	4.88	0.34
13. The topics covered in the program met my needs	4.75	0.45
Trainers' performance		
14. Training was provided by instructors who are competent in their field	4.94	0.25
15. I was able to communicate effectively with the trainers throughout the program	4.69	0.48
16. Trainers took into account participants' different learning styles	4.25	0.93
17. Trainers had sufficient knowledge and skills about online education applications	5	0
Duration and method of sessions		
18. The course content was appropriate for the education method (face-to-face/online)	4.75	0.45
19. Lessons started and finished at the scheduled time	4.81	0.4
20. Online courses were more advantageous in terms of time usage	5	0
21. The course was well organized	5	0
Satisfaction		
22. The mixed trainer training, which I attended, contributed to my development as a trainer	5	0
23. I plan to apply what I have learned in clinical training	4.75	0.45
24. The training were of a quality that would improve my professional knowledge and skills	4.81	0.4
SD: Standard deviation		



preferences. This is especially true for clinicians who take part in post-graduate training, and work very hard, as it poses certain cost, time, and accessibility obstacles. The majority of

the trainers in our study (83.3%) had not participated in an FDP before and were trained as trainers with the traditional master-apprentice model.

The content of FDPs is mostly intended to support the development of knowledge and skills and to adapt to the developing and changing educator roles by responding to the needs of educators in parallel with the developments in medical education (8). In a study that analyzed the literature on FDPs for clinicians, it was reported that educational development programs focused only on teaching skills covering topics such as training methods, training curriculum development, implementation and evaluation, research methodology, presentation skills, evidence-based medical teaching and quality improvement, as well as using technology tools, communication skills, and

Table 3. Participants' pre-test and post-test results in online and face-to-face training

Trainings	Mean ± SD	Median (min.-max.)	p-value
Online (n=24)			
Pre-test	3.33±1.46	3.5 (1-6)	<0.001
Post-test	7.54±1.86	7 (5-11)	
Face to face (n=16)			
Pre-test	9.88±1.26	10 (8-12)	0.001
Post-test	11.87±1.09	12 (9-13)	

SD: Standard deviation, min.-max.: Minimum-maximum

Table 4. Evaluation of educational activities in clinics before and after clinical education faculty development program

Variables, n (%)	Before training (n=42)	After training (n=42)	p-value
Does our clinic have a structured training program for resident training?			
No	5 (11.9)	2 (4.8)	0.433
Yes	37 (88.1)	40 (95.2)	
Do you have an education advisor assigned to you other than your thesis advisor?			
No	28 (66.7)	21 (50)	0.001
Yes	3 (7.1)	17 (40.5)	
I don't know	11 (26.2)	4 (9.5)	
Educational activities carried out in the clinic			
Seminar hours	37 (88.1)	38 (90.5)	0.999
Journal club	9 (21.4)	30 (71.4)	<0.001
Councils	22 (52.4)	21 (50)	0.827
Fact discussions	7 (16.7)	10 (23.8)	0.415
Mortality/Morbitide	1 (2.4)	3 (7.1)	0.616
Other	4 (9.5)	4 (9.5)	0.999
Is there anything other than the final exam in your clinic?			
No	7 (16.7)	6 (14.3)	0.763
Yes	35 (83.3)	36 (85.7)	
Exam methods used in the clinic			
Traditional oral exam	28 (66.7)	25 (59.5)	0.498
Multiple choice questions	18 (42.9)	29 (69)	0.016
Mini clinical evaluation exercise (mini-cex)	3 (7.1)	2 (4.8)	0.999
Structured oral examination	6 (14.3)	3 (7.1)	0.483
Case discussion	4 (9.5)	5 (11.9)	0.999
Report	6 (14.3)	13 (31)	0.068
Multiple choice based on clinical case	2 (4.8)	8 (19)	0.088
360 degree evaluation	1 (2.4)	0 (0)	0.999
Assessment scale of surgical skills	4 (9.5)	3 (7.1)	0.999

role modeling (9). In 2007, Stanford University Department of Anesthesiology reported the development of a program for faculty members in the department to improve and strengthen the training of residents, contributing to the education of residents in the program (10).

When planning an FDP, the diversity of trainers should be recognized, attention paid to the responsibilities of participants. Organizing and categorizing faculty members by their titles will help ensure that each faculty member receives the best benefit from the program and will help faculty members work effectively as a group. Additionally, in line with the FDP, activities should have different content for different levels of trainers in order to ensure maximum satisfaction (11). This is important, as the content that is appropriate for a junior faculty member, just starting out in academic life, is likely to be different from that for a senior faculty member. For this reason, we included participants with different academic titles in our study. While creating the content, literature analysis, review of FDPs conducted in our

country, focus group interview data with IM, obstetrics, and gynecology clinic trainers, who constitute the population of our study, contributed greatly to the creation of the training program.

The time and location requirements of face-to-face training can be a barrier when participants and instructors have busy schedules and heavy workloads. Online learning provides a ubiquitous and self-paced learning experience, whereas face-to-face learning encourages adherence to pre-planned formal instruction. Online learning not only eliminates the time and space logistics problems of face-to-face education; it also reduces costs and increases the effectiveness of education by increasing participation (12). In our study, we found that while online courses were 100% completed, the participation rate in face-to-face training was 66.6%. In their study, Yılmaz et al. (13) aimed to determine how junior and senior faculty members of medical departments at a Turkish university perceived the facilitators and barriers in a new blended educator

Table 5. Evaluation of satisfaction levels regarding the clinical education process as scores before and after training

Questions	Before training (n=42)	After training (n=42)	p-value
In our clinic, bedside training is provided regularly by trainers			
Mean ± SD	3.17±1.23	3.26±1.21	0.699
Median (min.-max.)	3 (1-5)	3.5 (1-5)	
Resident midterm exams are held regularly in our clinic			
Mean ± SD	3.69±1.3	3.95±1.03	0.446
Median (min.-max.)	4 (1-5)	4 (1-5)	
In our clinic, bedside patient visits are made regularly			
Mean ± SD	4.19±0.97	4.5±0.94	0.028
Median (min.-max.)	4 (1-5)	5 (1-5)	
Learning objectives are achieved in clinical and non-clinical rotations			
Mean ± SD	2.79±1.12	3.24±0.98	0.065
Median (min.-max.)	3 (1-5)	3 (1-5)	
Trainers support my participation in the course and congress			
Mean ± SD	2.4±1.19	3.14±1.3	0.009
Median (min.-max.)	2 (1-5)	3 (1-5)	
In our clinic, residents are included in scientific research projects			
Mean ± SD	3.1±1.03	3.74±0.91	0.003
Median (min.-max.)	3 (1-5)	4 (1-5)	
The trainer regularly gives me feedback			
Mean ± SD	2.52±1.19	2.98±1.16	0.075
Median (min.-max.)	2.5 (1-5)	3 (1-5)	
I regularly provide feedback to trainers during their training			
Mean ± SD	2.38±1.15	3.17±1.02	0.001
Median (min.-max.)	2 (1-5)	3 (1-5)	

SD: Standard deviation, min.max.: Minimum-maximum

development program. Lack of time was seen as the most critical barrier to participation in the program, while setting goals for personal development and gaining skills in teaching were presented as key enabling factors in the blended program (13).

Program developers devote significant effort to program design and implementation, but less effort to evaluation (14). A significant gap that exists in the academic literature is the lack of discussion and analysis of how FDPs can be implemented to help medical educators improve their skills in all areas of performance. In this context, it has been stated that the Kirkpatrick model can be used not only to evaluate a health program, but also to evaluate a comprehensive FDP (14,15). When creating a new FDP, the target group and method for measuring the results of Kirkpatrick's four levels should be determined in advance for each stage. Attention is drawn to the importance of establishing goals and measurable performance criteria in program development early in the planning process (16). In our study, while developing the program as suggested by the literature, we determined the program evaluation model (Kirkpatrick) and identified measurable criteria, such as the satisfaction survey, pre-test, and post-test. In the first stage, we evaluated the program. As a result of the satisfaction survey, consisting of 24 questions that questioned every aspect of the program, we determined that the participants were generally satisfied with the program. In addition, the statements left by the participants at the end of the program, which indicate that the program was very useful, they wanted to participate again, and they watched the videos repeatedly, show that the program was successful for the first level evaluation. In the second phase, we found that there was a significant increase in the post-test scores of the trainers in both online and face-to-face training ($p < 0.001$ and $p = 0.001$). Turning the knowledge, skills, and attitudes gained after the training into behavior and transferring it to real life constitutes the third stage of the Kirkpatrick program evaluation. This stage must be evaluated, and a certain period of time must pass for behavioral change to develop. In our study, a survey was conducted on residents to determine to what extent the training activities and achievements of FDP participants were transferred to their work areas, 4 months after the end of the program. When the survey results before and after the FDP were compared, it was seen that there were significant gains in certain educational activities. However, we think that long-term evaluations are needed to understand why there was no obvious methodological change in assessment and evaluation.

Studies conducted considering the Kirkpatrick model to evaluate FDPs were evaluated in a systematic review article (17). These studies used the Kirkpatrick model of program evaluation. Researchers found that participants reported a positive change in their attitudes after participating in such educator development activities, and demonstrated greater knowledge of their teaching skills. However, few studies have evaluated FDPs in relation to their outcomes addressing changes at the highest level of Kirkpatrick's model (18). Most studies in the literature have examined changes in small groups of educators rather than on a large scale, revealing only short-term changes in behavior (19). Additionally, most of the data collected in these studies were based on feedback; thus, they did not contain conclusive evidence about the impact of FDPs on student performance or instructors' teaching skills (16). The results of the FDP according to the Kirkpatrick program evaluation model are considered to be the most important limitation of the study, since our longest data includes the 4th month after the program. The long-term results are unknown, and the results could not be directly observed on the job.

Conclusion

This study is the first blended clinical FDP developed, implemented, and evaluated using the Kirkpatrick program evaluation model for postgraduate medical education. According to the research data, we determined that the program was successful, achieving statistically significant results at every stage of the Kirkpatrick program evaluation of educator training programs. In order to maintain clinical teaching skills in the long term, the training must be repeatable and its reflections on the field must be closely monitored.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (approval number: KAEK-569, dated: 02.09.2021).

Informed Consent: The participants were informed and consent was received.

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Footnotes

Authorship Contributions

Concept: H.E., E.G., Design: H.E., E.G., Data Collection or Processing: H.E., Analysis or Interpretation: H.E., Literature Search: H.E., E.G., Writing: H.E.

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Correlation of Human Epididymis Protein 4 Expression with Clinicopathologic Parameters in Gastric Carcinomas

Mide Karsinomlarında İnsan Epididim Proteini 4 Ekspresyonunun Klinikopatolojik Parametrelerle İlişkisi

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ABSTRACT

Background: Human epididymis protein 4 (HE4) was discovered in 1991 as a glycoprotein secreted from the cells of the human epididymal epithelium and associated with sperm development and immunity. Subsequent studies have shown that HE4 is also expressed in many normal tissues such as reproductive, respiratory, and digestive tract epithelia. Although the mechanism of action of HE4 in cancers is still unknown, its increased expression has been reported in many tumors, especially gynecologic malignancies. In our study, we have investigated the relationship between gastric carcinomas and increased HE4 expression.

Materials and Methods: HE4 expression was studied in 114 formalin-fixed paraffin-embedded gastric carcinoma specimens and its association with different clinicopathologic parameters was evaluated.

Results: Immunohistochemical HE4 expression was strong in 88 patients and weak in 26 of 114 patients. A significant correlation was found between HE4 staining intensities and five-year survival rates ($p=0.002$). There was no significant correlation between HE4 staining intensity and human epidermal growth factor 2 (HER2)/neu amplification, as well as other clinicopathologic data.

Conclusion: This study has demonstrated the association of HE4 expression with 5-year survival in gastric tumors. In addition, although no significant correlation was found between HE4 staining intensity and HER2/neu amplification in our study, a significant correlation between these parameters has been reported in the literature. In conclusion, HE4, which we have found to be associated with long-term survival in our study, can be used as a prognostic marker in gastric cancers.

Keywords: Gastric cancer, HE4, HER2/neu

ÖZ

Amaç: İnsan epididim proteini 4 (HE4), 1991 yılında insan epididim hücrelerinden salgılanan sperm gelişimi ve immüniteyle ilişkili bir glikoprotein olarak keşfedilmiştir. Daha sonraki çalışmalarda HE4, reproduktif, solunum ve sindirim yollarının epiteli gibi birçok normal dokularda da eksprese edildiği görülmüştür. HE4'ün kanserlerdeki mekanizması halen kesin olarak bilinmemesine rağmen, başta jinekolojik maligniteler olmak üzere birçok tümörde ekspresyonun arttığı bildirilmiştir. Araştırmamızda mide karsinomları ile HE4 ekspresyon artışı arasındaki ilişkiyi inceledik.

Gereç ve Yöntemler: Formalinle fikse edilmiş parafine gömülü 114 mide karsinomu örneğinde HE4 ekspresyonu çalışıldı ve farklı klinikopatolojik parametrelerle ilişkisi değerlendirildi.

Bulgular: İmmünohistokimyasal HE4 ekspresyonu 114 olgumuzun 88'inde güçlü, 26'sında zayıf olarak izlendi. Beş yıllık sağkalım süresi ile HE4 boyanma şiddetleri arasında anlamlı ilişki bulundu ($p=0,002$). HE4 boyanma şiddeti ile insan epidermal büyüme faktörü 2 (HER2)/neu amplifikasyon ve diğer klinikopatolojik veriler arasında anlamlı ilişki saptanmadı.

Sonuç: Bu çalışma mide tümörlerinde HE4 ekspresyonunun 5 yıllık sağkalım ile ilişkisini göstermiştir. Ayrıca çalışmamızda HE4 boyanma şiddeti ile HER2/neu amplifikasyon arasında anlamlı ilişki bulunmamış olsa da literatürde anlamlı ilişki bulunduğu



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bildirilmektedir. Sonuç olarak, çalışmamızda uzun süreli sağlıklılıkla ilişkili bulduğumuz HE4, mide kanserlerinde prognostik bir belirteç olarak kullanılabilir.

Anahtar Kelimeler: Mide kanseri, HE4, HER2/neu

Introduction

Gastric cancer is the fourth most common cancer in the world and is still the second leading cause of cancer-related mortality despite the decline in its incidence in recent years (1). Gastric cancer is a multifactorial disease. Environmental factors contributing to carcinogenesis include *Helicobacter pylori* (*H. pylori*) infection, low socioeconomic status, and the consumption of smoked and low-fiber foods (1-3). Genetic processes play more prominent roles in diffuse-type adenocarcinomas (1-3). Gastric cancer is 2-3 times more common in men than in women. The incidence of gastric cancer also varies between geographical regions. In countries with a low incidence of gastric adenocarcinomas, diffuse type and proximal location are more common, while in countries with a high incidence, intestinal type and distal location are more common (1-3). Mostly, acquired genetic alterations are involved in gastric carcinogenesis. Mutations in the K-ras oncogene and *adenomatous polyposis coli* gene are seen in adenoma, intestinal metaplasia, and intestinal-type gastric cancer, but not in diffuse gastric cancer. Instead, allelic loss of the *TP53* gene is seen in 60% of cases, and it is the most common genetic alteration detected in gastric cancer (4). Amplification of c-erbB-2, a transmembrane tyrosine kinase receptor oncogene, encoded by the *human epidermal growth factor 2 (HER2)* gene, is reported in 10-30% of mainly intestinal type gastric carcinomas in different series and indicates poor prognosis (5-7). The incidence of gastric cancer increases with age and is extremely rare before the age of 30. These young patients are mainly females with diffuse-type cancer. Intestinal-type adenocarcinomas, on the other hand, are common in older male patients. While the five-year survival rate was 15% in the past years, this rate has reached 30% today (1,6,7).

Human epididymis secretory protein 4 (HE4) was first identified in 1991 as a glycoprotein secreted by human epididymal epithelial cells and associated with sperm development and immunity. In subsequent studies, HE4 has been demonstrated in a wide variety of epithelial cells including reproductive epithelium, respiratory epithelium, salivary gland mucus cells, mammary ductal epithelium, and lung epithelium (8). It is expressed at a lower rate in kidney, prostate, pituitary, and thyroid cells, particularly in the distal tubule of kidney. HE4 belongs to the whey acidic proteins (WAP) family. WAP-like proteins belong to a small

group of heterogeneous, acidic, heat-stable proteins with diverse biological functions. The basis of their biological function lies in their binding capacity to membrane receptors. A significant number of them also show protease-inhibitory activity (8,9). HE4 expression has been shown to be increased in gynecologic malignancies, lung, and breast cancers (10-12).

HE4 was approved as a serum tumor marker in ovarian carcinomas by the US Food and Drug Administration in 2003. Although increased HE4 expression has been shown in many malignancies, the role of this protein in gastric cancer is not yet clearly known (13,14).

The objective of this study is to investigate the correlations between HE4 expression and different clinicopathologic variables of gastric carcinomas, with a focus on HER2 expression status.

Materials and Methods

A total of 114 gastrectomized gastric carcinoma patients, diagnosed in the Pathology Laboratory of University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital between 2011 and 2014, with sufficient archival material were included in the study. Informed consent was obtained for this study. This study was ethically approved by the Local Ethics Committee of the University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital (approval number: 1-11, date: 26.01.2017). Age, gender, tumor location, tumor diameter, TNM stage, and overall survival data were obtained from pathology records. Hematoxylin-eosin (H&E) stained slides of all cases were re-evaluated according to the 2019 World Health Organization classification system (6). The staging system most often used for stomach cancer is the American Joint Committee on Cancer (AJCC) TNM system, which was last updated in 2018 (7). Clinical prognostic factors such as tumor type, grade, stage, lymphovascular, and perineural invasion, and lymph node involvement were evaluated. In addition, c-erbB2 immunohistochemical (IHC) expressions and HER2 amplification have been re-assessed according to the American Society of Clinical Oncology/College of American Pathologists 2013 guidelines on the archived slides.

Among the paraffin blocks of the cases, the one that best reflected the tumor tissue for IHC staining was selected.

The area to be analyzed was marked first on the slide and then on the block. Tissue samples with a diameter of 2 mm were taken from the labeled areas on donor paraffin blocks and transferred to microarray blocks by a manual mapping-addressing technique using a microarray device. H&E sections were first taken from the prepared multiple blocks, and the presence of tumors in the sampled areas was confirmed. Then, 4-micrometer-thick sections were taken onto polylysine-coated slides and manually stained with the anti-HE4 antibody. The sections were kept in an oven at 60 °C overnight. Antigen retrieval was performed by heating prepared slides in citrate buffer (pH: 6.0) in a microwave oven at 400 Watt for 20 minutes in plastic chalices with closed lids. Primary antibody anti-HE4 (1:20 dilution; Signet Laboratories Inc., Dedham, MA, USA) was applied for 1 hour. Manual staining was performed using the streptavidin-biotin method. All cases demonstrated cytoplasmic staining for HE4. Therefore, a quantitative evaluation could not be made. HE4 cytoplasmic staining intensities were considered weak or strong.

Statistical Analysis

The SPSS 22.0 program (IBM Corporation, Armonk, NY, USA) was used to statistically analyze the variables. Quantitative variables are shown as mean \pm standard deviation and categorical variables as percentages (%). A Student's t-test was used in independent two-group comparisons in which quantitative data were evaluated. Pearson chi-square, linear-by-linear association, and Fisher's exact test were used in the comparisons of categorical variables in which qualitative data were evaluated. The results of analyses were considered statistically significant at $p < 0.05$ within a 95% confidence interval. The Kaplan-Meier methods and the log-rank (Mantel-Cox) test were used to test the effects of HE4 staining status on survival.

Results

Demographic and histopathologic data were obtained by evaluating the information available in the pathology laboratory records of 114 patients, including 36 (31.6%) female and 78 (68.4%) male cases. The mean age at diagnosis was 63.6 ± 12.3 years (range: 36-89 years). During a mean follow-up period of 29.7 ± 20.6 (0-89) months, 37 (32.5%) patients survived, and 77 (67.5%) patients died. Tumors were located in the corpus ($n=57$; 50%), pylorus ($n=36$; 31.6%), and cardia ($n=21$; 18.4%). The mean tumor diameter was 6.2 ± 2.9 cm (1-15 cm). In our study, diffuse type adenocarcinoma ($n=46$; 31.6%), intestinal type adenocarcinoma ($n=71$; 62.3%), and mixed type adenocarcinoma ($n=7$; 6.1%) were detected in the indicated number of cases. The tumors diagnosed were poorly ($n=60$; 52.7%) and moderately differentiated

($n=54$; 47.3%). Only 5 cases (4.9%) had neuroendocrine differentiation. Tumor necrosis was observed in 6 (5.3%), lymphovascular invasion in 74 (64.9%), and perineural invasion in 69 (60.5%) cases. Lymph node metastasis was present in 90 (78.9%) cases. The pT distribution of our cases according to the 2018 AJCC TNM staging system is as follows: pT1b ($n=7$; 6.1%), pT2 ($n=6$; 5.3%), pT3 ($n=68$; 59.6%), and pT4 ($n=33$; 28.9%). Our patients were in the early ($n=13$; 11.4%) and advanced ($n=101$; 88.6%) stages of the disease. Distant organ metastases were present in 33 (28.9%) cases. Most frequently, liver ($n=15$; 13.2%) and then pulmonary ($n=11$; 9.6%), peritoneal ($n=5$; 4.4%), and ovarian ($n=2$; 1.8%) metastases were seen.

Immunohistochemically, c-erbB2 expression status was investigated in all 114 cases. HER2/neu amplification was also evaluated at a molecular level by FISH test in cases. Immunocytochemically, 2+ or 3+ positive c-erbB2 expression was detected in 28 cases (24.6%). However combined evaluation of both immune histochemical c-erbB2 expression and HER2 amplification, only 21 cases (18.4%) were evaluated as positive. The HE4 staining results were evaluated in terms of staining intensity in indicated percentages of cells as follows: 0, negative: 0-10%; 1+, weak: 11-30%; 2+, moderate: 31-60%, and 3+, strong: 61-100%. However, since all 114 cases, showed 61-100% staining intensities, a proportional evaluation could not be made. Due to the small number of cases and the insufficient number of cases in the groups, HE4 cytoplasmic staining intensities 0 and 1+ were considered as weak while 2+ and 3+ staining intensities as strong staining and all parameters were compared according to cytoplasmic staining intensity. According to this evaluation, all cases demonstrated cytoplasmic staining. Among 114 patients, 26 (22.8%) cases demonstrated weak and 88 (77.24%) cases strong staining intensities for HE4 (Figures 1-3).

We investigated the relationship between IHC HE4 staining intensities and clinicopathologic parameters of diagnostic, therapeutic, and prognostic importance, in 114 patients who underwent gastrectomy for gastric cancer patients (Table 1). HE4 staining intensities were not associated with gender ($p=0.919$), mean age at diagnosis ($p=0.420$), localization ($p=0.916$), diameter ($p=0.551$), histological type of tumors ($p=0.498$), and degree of tumor differentiation ($p=0.402$), no statistically significant correlation was found between the presence of neuroendocrine differentiation ($p=0.680$), tumor necrosis, lymphovascular invasion ($p=0.682$), perineural invasion ($p=0.136$), and lymph node metastasis ($p=0.167$). There was no statistically significant correlation between tumor stage and HE4 staining intensity according to the 2018 AJCC TNM staging system ($p=0.686$). Also, no statistically significant

correlation was detected between distant organ metastasis ($p=0.816$), the organ of metastasis ($p=0.586$), HE4 staining intensity. No statistically significant correlation was found between IHC c-erbB2 staining, which is used to evaluate HER2/neu amplification, and HE4 staining intensity ($p=0.848$). Any statistically significant difference was not observed in terms of HE4 staining intensity between the group of patients with positive, and negative HER2/neu amplification detected by FISH test ($p=0.179$). No statistically significant correlation was noted between survival times and HE4 staining intensities ($p=0.190$). However, the mean 5-year survival times of the patient groups demonstrating

weak and strong staining intensities were 54.7 and 64.03 months, respectively. Accordingly, a statistically significant correlation was detected between survival times and HE4 staining intensities ($p=0.028$) (Figure 4).

Discussion

Diet, genetics, *H. pylori* infection, chronic gastritis, gastric dysplasia, intestinal metaplasia, and surgical damage are known risk factors involved in the complex etiology

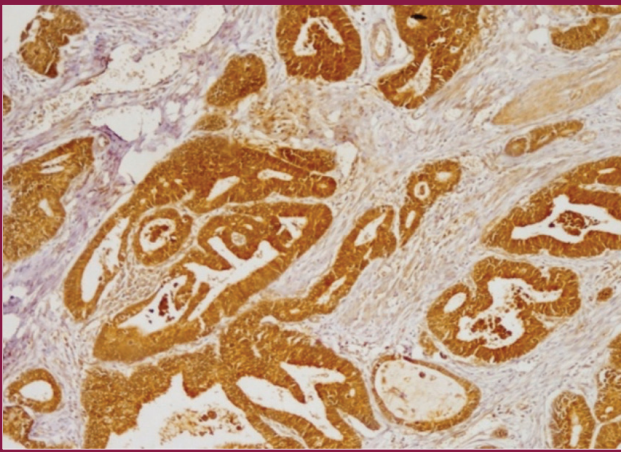


Figure 1. Immunohistochemically detected strong cytoplasmic HE4 staining in a case with intestinal type adenocarcinoma (DAB, x200)
 HE4: Human epididymis protein 4

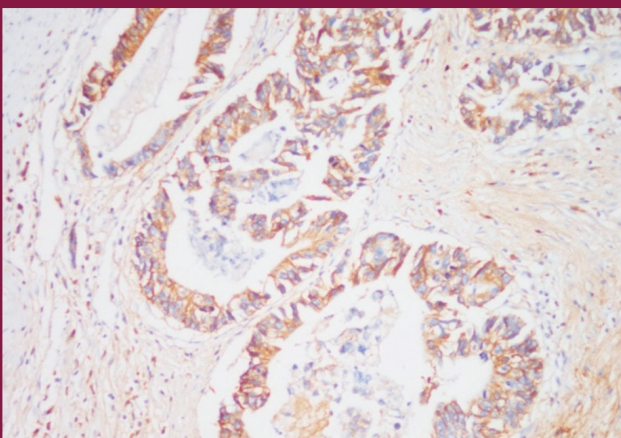


Figure 2. Immunohistochemically detected weak cytoplasmic HE4 staining in a case with intestinal-type adenocarcinoma (DAB, x200)
 HE4: Human epididymis protein 4

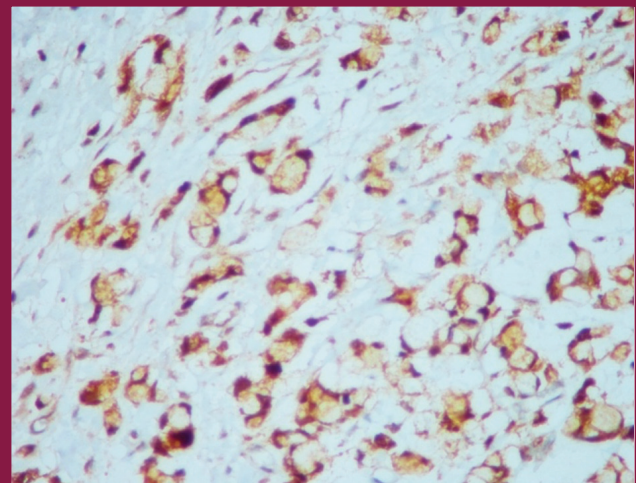


Figure 3. Immunohistochemically detected strong cytoplasmic HE4 staining in a case with diffuse-type adenocarcinoma (DAB, x200)
 HE4: Human epididymis protein 4

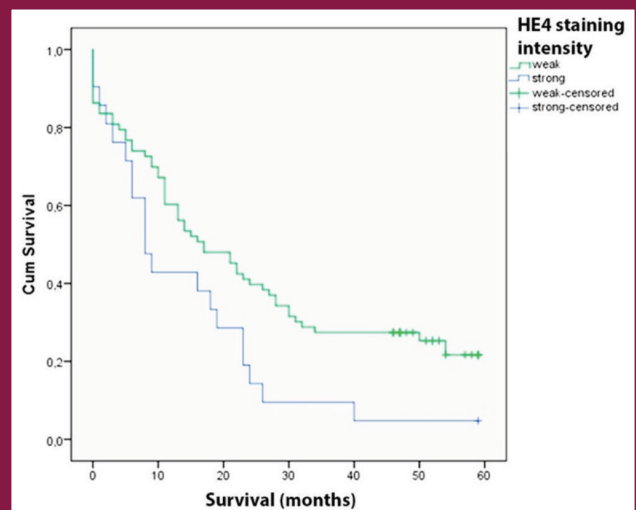


Figure 4. Differences in 5-year survival rates according to HE4 staining intensities (log-rank test, $p=0.028$)
 HE4: Human epididymis protein 4



and pathogenesis of gastric cancers, but the significance of these parameters has not been fully elucidated (1-4). Gastric cancer is one of the most common cancers with fatal outcomes in the world. The survival rate is quite low, as 90% of the cases are in the advanced stage at the time of diagnosis. Due to the lack of simple and sensitive markers for early diagnosis, the optimal treatment window is often overlooked (1).

Recent studies have focused on identifying new molecular markers both to predict survival and recurrence in gastric cancer and to develop relevant active treatment methods (13,14). HE4 is a marker of proven prognostic importance in many malignancies, especially gynecologic cancers (15-20). There are few studies in the literature on the prognostic importance of HE4 in gastric carcinoma (13,14). In our study, the statistically significant prolonged

survival time in patients with poor HE4 expression suggests that HE4 expression is a marker that may have prognostic significance in gastric cancer.

Many of the biological functions of proteins encoded by the *HE4* gene are linked to their capacity to bind to membrane receptors. A significant number of them also exhibit protease inhibitor activity. IHC studies have shown that this protein is located in the cytoplasm of cells (8,9). In addition, *HE4* gene expression has been shown to be increased in tumors compared to normal ovarian tissue, particularly in ovarian tumors (12). Although the precise functional mechanism of HE4 involved in cancers is still unknown, its increased expression and secretion have been described in a wide variety of epithelial tumors including epithelial ovarian carcinomas, bronchial adenocarcinomas, and breast tumors. Apart from these carcinomas, increased

Table 1. Findings of patients according to the HE4 expression

Severity of HE4 expression		Strong; n, % (88: 77.2%)	Weak; n, % (26: 22.8%)	p-value
Gender	Male	60/68.2	18/69.2	0.919
	Female	28/31.8	8/30.8	
Tumor location	Cardia	16/18.2	5/19.2	0.633
	Corpus	46/52.3	11/42.3	
	Pylor	26/29.5	10/38.5	
Survival status	Deceased	57/64.8	20/76.9	0.245
	Survived	31/35.2	6/23.1	
Lymph node metastases	Absent	16/18.2	8/30.8	0.167
	Present	72/81.8	18/69.2	
Location of distant metastases	Absent	63/71.6	18/69.2	0.816
	Liver	12/13.6	3/11.5	
	Lung	9/10.2	2/7.7	
	Periton	3/3.4	2/7.7	
	Ovary	1/1.1	1/3.8	
Tumor stage	Early	11/12.5	2/7.7	0.391
	Late	77/87.5	26/92.3	
Histology	Intestinal-type	53/60.2	18/69.2	0.498
	Poorly adhesive/mixed	35/39.8	8/30.8	
Lymphovascular invasion	Present	58/65.9	16/61.5	0.682
Perinueral invasion	Present	50/56.8	19/73.1	0.136
HER2 simple (according to ASCO/CAP 2013 criteria)	Negative	71/80.7	22/84.6	0.179
	Positive	17/19.3	4/15.4	
Age (year)	Mean ± SD	62.3±12.1	67.8±12.4	0.420
Tumor diameter (cm)	Mean ± SD	6.2±3	5.9±2.9	0.551
Survival (months)	Mean ± SD	26.6±20.8	22.7±20.3	0.190
Patients with longer survival	5 years and over	54.6±11.5	64±4.7	0.028

HE4: Human epididymis protein 4, HER2: Human epidermal growth factor 2, ASCO/CAP: American Society of Clinical Oncology/College of American Pathologists, SD: Standard deviation

expression of the *HE4* gene has also been reported in mesothelioma, gastrointestinal tumors, and melanoma (21-24). HE4 is also used as a biomarker in the differentiation between benign and malignant ovarian neoplasms and the determination of their types. Indeed, its expression is increased in epithelial ovarian cancers, but not in non-epithelial ovarian tumors. Currently, HE4 is used as a tumor biomarker in epithelial ovarian carcinomas in combination with cancer antigen-125 (25). High serum HE4 levels are associated with the development of ascites, chemoresistance, and decreased survival in ovarian malignancies. It is known that HE4 elevation in ascites fluid, as well as in serum, has significant implications (26). Similarly, in our study, gastric carcinoma patients with strong HE4 expression in tumor cells had shorter survival times.

There is increasing evidence that HE4 may be an effective biomarker not only in ovarian carcinomas but also in other gynecologic cancers. For example, although HE4 expression is present in normal endometrial tissues, HE4 protein levels are also increased in endometrial cancer. Expression levels of HE4 in endometrial carcinoma are associated with poor prognosis. Significantly higher HE4 expression levels have been detected in atypical hyperplasia, which is one of the precursor lesions of the endometrial tumor, compared with the healthy control group. Accordingly, it has been claimed that serum HE4 concentration in endometrial cancer patients may give an idea about the diameter of the primary tumor and depth of myometrial invasion (18). Studies examining the association of HE4 with neoplasms of the cervix have found increased HE4 expression levels in normal cervical epithelium and invasive tumors, in contrast to lower expression levels in intraepithelial carcinoma (19). All these studies suggest that HE4 is an implicated gene in the development of gynecologic cancers (18-20).

The relationship between breast cancer and HE4 has been investigated in recent years. A study published in 2016 showed that serum HE4 levels were higher in breast cancer patients compared with healthy individuals (23,27). Aköz et al. (17) found a significant correlation between cytoplasmic HE4 staining intensity and c-erbB2 staining status, HER2/neu amplification, as well as an inverse relationship with tumor grade. HER2/neu amplification is an indicator of poor prognosis in gastric cancer. The presence or absence of amplification changes the treatment protocol. Therefore, evaluation of HER2/neu amplification, which is an indicator of poor prognosis and leads to the creation of new treatment targets, is recommended in all gastric cancer cases. No case reports on the relationship between HER2/neu amplification and HE4 expression have been cited in the literature so far. Similarly, we couldn't find any statistically significant relationship between HE4 staining intensity

and the presence or absence of HER2/neu amplification using both c-erbB2 expression by immunohistochemistry and HER2 amplifications by in situ hybridization. Studies suggest that HE4, whose biological function has not yet been clarified, is a gene involved in the process of carcinogenesis. HE4 expression has been effectively used in the diagnosis and therapy of gynecological cancers. Especially, in cancers of the digestive system, HE4 expression has been overlooked in the English literature. Therefore, the current articles have mentioned the HE4 expression, in terms of differential diagnosis (12). A limited number of studies have investigated HE4 expression in gastric cancer (13,14). O'Neal et al. (13) reported that normal gastric mucosa could not be immunohistochemically stained for HE4, but HE4 expression was detected in epithelium with intestinal metaplasia which indicates a step toward malignant progression. When gastric cancer patients were compared with the healthy group, it was found that both the intensity and percentage of IHC HE4 staining increased in cancer patients. According to Lauren's classification of gastric tumors, diffuse-type gastric cancer is stained more strongly than intestinal-type gastric cancer. Diffuse-type cancers have a worse prognosis than intestinal-type cancers. In light of this information, it has been suggested that HE4 may be an indicator of poor prognosis (13). In our study, no significant correlation was found between Lauren's classification of gastric tumors and increased HE4 expression. Since 77.8% of diffuse-type cancers stained strongly for HE4, further studies with larger case series would likely confirm these findings to be consistent with the literature. O'Neal et al. (13) found a negative correlation between increased HE4 expression, and survival in the second group consisting of patients in Western countries. Similarly, increased HE4 expression was inversely correlated with 5-year survival in our study.

A study by Guo et al. (14) in 2014 evaluated the relationship between increased HE4 expression and clinicopathologic parameters of gastric cancer, as presented in the literature. In this study, increased HE4 expression was observed in gastric cancer patients in accordance with the literature. Among the prognostic markers, age, gender, stage of the disease, lymph node metastasis, and tumor invasion (pT) were not found to be significantly associated with HE4 staining intensities (14). In our study, no correlation was found between the above-mentioned parameters and HE4 staining intensities. However, they found that overall survival time decreased as HE4 staining intensity increased, and strong HE4 staining and overall survival time were inversely correlated with each other. In our study, no correlation was found among Lauren's classification of tumors, tumor size, and increased HE4 expression. In the survival analysis of our study, 70%

of our patients were not alive when the statistical analyses were performed, and the median follow-up period was 29.2 months. The survival analysis of the patients according to HE4 staining intensities could not reveal any significant difference between the median survival times. However, we examined the relationship between 5-year survival times and HE4 staining intensities and found that the 5-year survival times of strongly stained cases were significantly decreased compared to weakly stained cases, consistent with the literature findings. As the HE4 staining intensities or HE4 expression levels increased, 5-year survival times decreased significantly.

HE4 expression has been more effectively used in the diagnosis and therapy of gynecological cancers. Especially in the cancer of the digestive system, HE4 expression was seen to be overlooked in the English literature. Therefore, current articles have mentioned the HE4 expression in terms of differential diagnosis.

Study Limitations

The most important limitation of this study is that HE4 immunostaining was applied only in microarray blocks prepared from small tumor samples. For this reason, staining intensity could not be compared with the surrounding tissue, and no comment could be made as to whether the expression detected in the tumor was also present in the normal mucosa.

Conclusion

Although the functional mechanism involved has not been fully elucidated, all these studies have shown that the *HE4* gene is effective in the processes of carcinogenesis. The absence of HE4 expression in healthy gastric epithelial cells and its increased expression during the progression of gastric cancer, suggest that the use of this parameter may shed light on early diagnosis and treatment protocols in gastric cancer. The inverse correlation between HE4 expression and 5-year survival in our study suggests that HE4 may be a marker for the diagnosis, prognosis, and treatment of gastric cancer patients. Therefore, studies on HE4 expression in gastric cancer should be conducted in large series.

Ethics

Ethics Committee Approval: This study was ethically approved by the Local Ethics Committee of the University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital (approval number: 1-11, dated: 26.01.2017).

Informed Consent: Informed consent was obtained for this study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: P.Ö., G.D., T.A., Y.K., D.A., Concept: P.Ö., G.D., D.A., Design: P.Ö., G.D., D.A., Data Collection or Processing: P.Ö., G.D., T.A., Y.K., D.A., Analysis or Interpretation: P.Ö., G.D., Literature Search: P.Ö., G.D., T.A., Y.K., D.A., Writing: P.Ö., G.D., T.A., Y.K., D.A.

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