HAMIDIYE MEDICAL JOURNAL
The Official Journal of University of Health Sciences Türkiye, Hamidiye Faculty of Medicine
E-ISSN: 2718-0956
June - 2025
Volume - 6
Issue - 2



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Phone: +90 (530) 177 30 97 / +90 (539) 307 32 03 **E-mail:** info@galenos.com.tr
Web: www.galenos.com.tr **Publisher Certificate Number:** 14521
Online Publication Date: July 2025 **E-ISSN:** 2718-0956
International periodical journal published three times in a year.

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Issue 2

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MEDICAL JOURNAL

2025
Volume 6
Issue 2

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2025
Volume 6
Issue 2

Please refer to the journal's webpage (**https://www.hamidiyemedj.com/**) for "Aims and Scope", "Instructions to Authors" and "Ethical Policy".

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Hamidiye Medical Journal is indexed in **Ulakbim TR Index, EBSCO Host, Embase, Gale, Turk Medline** and **J-Gate**.

The journal is published online.

Owner: Ayşe BATIREL on Behalf of University of Health Sciences Türkiye, Hamidiye Faculty of Medicine

Responsible Manager: Ebru KALE

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DOI: 10.4274/hamidiyemedj.galenos.2025.98700

Hamidiye Med J 2025;6(2):67-77

The Role of Microbiota in Ovarian Cancer: Implications for Diagnosis, Prognosis, and Treatment

Yumurtalık Kanserinde Mikrobiyotanın Rolü: Teşhis, Prognoz ve Tedaviye Etkileri

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ABSTRACT

Ovarian cancer remains one of the most lethal gynaecological malignancies due to late diagnosis and poor prognosis. Recent studies highlight the potential role of microbiota in the development, progression, and management of ovarian cancer. The female reproductive tract hosts diverse microbial communities, with the lower tract dominated by Lactobacillus species and the upper tract containing a low-biomass microbiome. Dysbiosis in these microbial populations has been linked to chronic inflammation, immune dysregulation, and tumour progression. Notably, altered levels of specific taxa, such as elevated *Fusobacterium* and decreased *Lactobacillus*, have been associated with ovarian cancer. Advances in microbial profiling, particularly 16S rRNA sequencing, and machine learning offer novel approaches for improving ovarian cancer diagnosis and prognosis by identifying microbial biomarkers. Furthermore, microbiota may influence treatment outcomes through its interaction with chemotherapeutic agents and immune responses. This growing body of evidence suggests that targeting the microbiome could provide innovative strategies for ovarian cancer management, including personalized therapies aimed at restoring microbial balance. Further research is essential to fully clarify the role of microbiota in ovarian cancer and harness its potential for early detection and effective treatment.

Keywords: Microbiome, microbiota, ovarian cancer, biomarkers, therapeutics

ÖZ

Yumurtalık kanseri, geç teşhis ve kötü prognoz nedeniyle en ölümcül jinekolojik malignitelerden biri olmaya devam etmektedir. Son çalışmalar, mikrobiyotanın yumurtalık kanserinin gelişimi, ilerlemesi ve yönetimindeki potansiyel rolünü vurgulamaktadır. Kadın üreme yolu, Lactobacillus türlerinin baskın olduğu alt yol ve düşük biyokütleli bir mikrobiyom içeren üst yol ile çeşitli mikrobiyal topluluklara ev sahipliği yapar. Bu mikrobiyal popülasyonlardaki disbiyoz kronik enflamasyon, immün düzensizlik ve tümör progresyonu ile ilişkilendirilmiştir. Özellikle, yüksek *Fusobacterium* ve azalmış *Lactobacillus* gibi belirli taksonların değişen seviyeleri yumurtalık kanseri ile ilişkilendirilmiştir. Mikrobiyal profilleme, özellikle 16S rRNA dizileme ve makine öğrenimindeki gelişmeler, mikrobiyal biyobelirteçleri tanımlayarak yumurtalık kanseri teşhisini ve prognozunu iyileştirmek için yeni yaklaşımlar sunmaktadır. Ayrıca mikrobiyota, kemoterapötik ajanlar ve immün yanıtlarla etkileşimi yoluyla tedavi sonuçlarını etkileyebilir. Giderek artan bu kanıtlar, mikrobiyomun hedeflenmesinin, mikrobiyal dengeyi yeniden sağlamayı amaçlayan kişiselleştirilmiş tedaviler de dahil olmak üzere yumurtalık kanseri yönetimi için yenilikçi stratejiler sağlayabileceğini göstermektedir. Mikrobiyotanın yumurtalık kanserindeki rolünü tam olarak açıklığa kavuşturmak ve erken teşhis ve etkili tedavi potansiyelinden yararlanmak için daha fazla araştırma yapılması gerekmektedir.

Anahtar Kelimeler: Mikrobiyom, mikrobiyota, yumurtalık kanseri, biyobelirteçler, terapötikler

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Received: 07.02.2025 **Accepted:** 12.06.2025 **Publication Date:** 04.07.2025

Cite this article as: Akçeşme B, Berilo A, Islam N. The role of microbiota in ovarian cancer: implications for diagnosis, prognosis, and treatment. Hamidiye Med J. 2025;6(2):67-77

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Introduction

The Role of Microbiota in Ovarian Cancer: Implications for Diagnosis, Prognosis, and Treatment

Ovarian cancer is a significant concern for women's health worldwide, primarily because it often goes undetected until reaching an advanced stage. This asymptomatic progression leads to approximately 75% of ovarian cancer cases being diagnosed only in later stages of the disease, critically impacting survival rates (1). Globally, ovarian cancer ranks as the eighth most common cancer among women and is the eighth leading cause of cancer-related deaths, with an incidence rate of about 6.6 per 100,000 women annually (2). In Türkiye, the situation mirrors global trends, with ovarian cancer accounting for a substantial portion of gynecological cancer diagnoses. According to Ugurlu et al. (3), ovarian cancer ranks as the third most common gynecological cancer in Türkiye, with 12,186 women diagnosed with gynecological cancer that year. This is reflected in advanced-stage diagnoses and high mortality rates, underscoring the need for increased awareness and early detection efforts.

Ovarian tumours are broadly classified into three major categories according to cell of origin: epithelial tumours, germ cell tumours, and sex cord-stromal tumours. The World Health Organization 2020 classification further refines the categorization of epithelial tumours, which account for over 90% of malignant ovarian neoplasms (4). Epithelial tumours are subdivided based on cell type into high-grade serous, low-grade serous, endometrioid, clear cell, and mucinous carcinoma (MC). There are also less common types such as seromucinous and Brenner tumours, with a rare category of mixed carcinomas, now reintroduced (5).

Epithelial ovarian cancers are the most frequently diagnosed subtype and the leading cause of gynaecological cancer death worldwide, accounting for roughly 3.7% of all new female cancer cases and 4.7% of cancer deaths in 2020 (6). Globally, 313,959 new cases and 207,252 deaths from ovarian cancer are estimated to occur each year (7). Most cases present at an advanced stage, with overall survival rates remaining low at approximately 40% for stage III disease and 20% for stage IV disease (8).

Ovarian cancer encompasses five principal histological subtypes: high-grade serous carcinoma (HGSC), low-grade serous carcinoma, endometrioid carcinoma, clear cell carcinoma (CCC), and MC, each considered distinct diseases with specific cells of origin, molecular alterations, and clinical behaviors (9). For instance, HGSC, the most common subtype, is primarily associated with BRCA1 and BRCA2 mutations (10), while CCC may be linked to endometriosis (11).

The pathogenesis of ovarian cancer, despite extensive research, remains partially understood, with gaps in understanding the precise origins of some subtypes and the heterogeneous nature of tumours, which make prevention and treatment challenging. The human microbiome is now emerging as a potential key in unraveling this complexity, as recent studies suggest it may play a role in cancer development and progression by modulating immune responses, influencing inflammation, and interacting with host and microbial metabolites (12-14). The trillions of microorganisms that inhabit the different parts of the human body form intricate, habitat-specific ecosystems uniquely adapted to the host's dynamic and ever-changing physiology. Changes in the microbiome composition, known as dysbiosis, have been linked to a wide range of diseases, including cancer (15). The rapid pace of global transformations significantly affects individuals' physiological and psychological well-being, disrupting the homeostasis of the microbiota (16). The human microbiome exhibits a high level of complexity due to its intricate interactions with other microorganisms and its surrounding environment. Several factors, including host genetics, gender, age, diet, lifestyle, and antibiotic exposure, influence it (17).

Recent studies have demonstrated a link between estrogenic metabolism and host recognition receptors in microorganisms, which influence changes in the gut and pelvic microbiomes. Understanding the composition of the microbiota involved in the progression of ovarian cancer could provide valuable insights for developing diagnostic and prognostic methods, as well as effective treatments (18). In this review, we aimed to summarize the research conducted on microbiota associated with ovarian cancer. The alterations in microbial species associated with ovarian cancer, highlighting both increased and decreased abundance, as well as etiological factors and mechanistic roles, in ovarian cancer are illustrated in Figure 1.

The aim of this paper is to comprehensively review current research regarding the relationship between human microbiota and ovarian cancer, with a focus on the potential impact of microbiome alterations in the development, progression, and management of epithelial ovarian cancer. By examining key studies and presenting current evidence, this review seeks to highlight both the clinical significance and future therapeutic implications of microbiome research in the context of ovarian cancer.

Bacterial Composition in Female Reproductive Tract

The female reproductive tract (FRT), plays a critical role in fertility, pregnancy, sexual activity, and childbirth. Its interconnected anatomy facilitates the migration of various

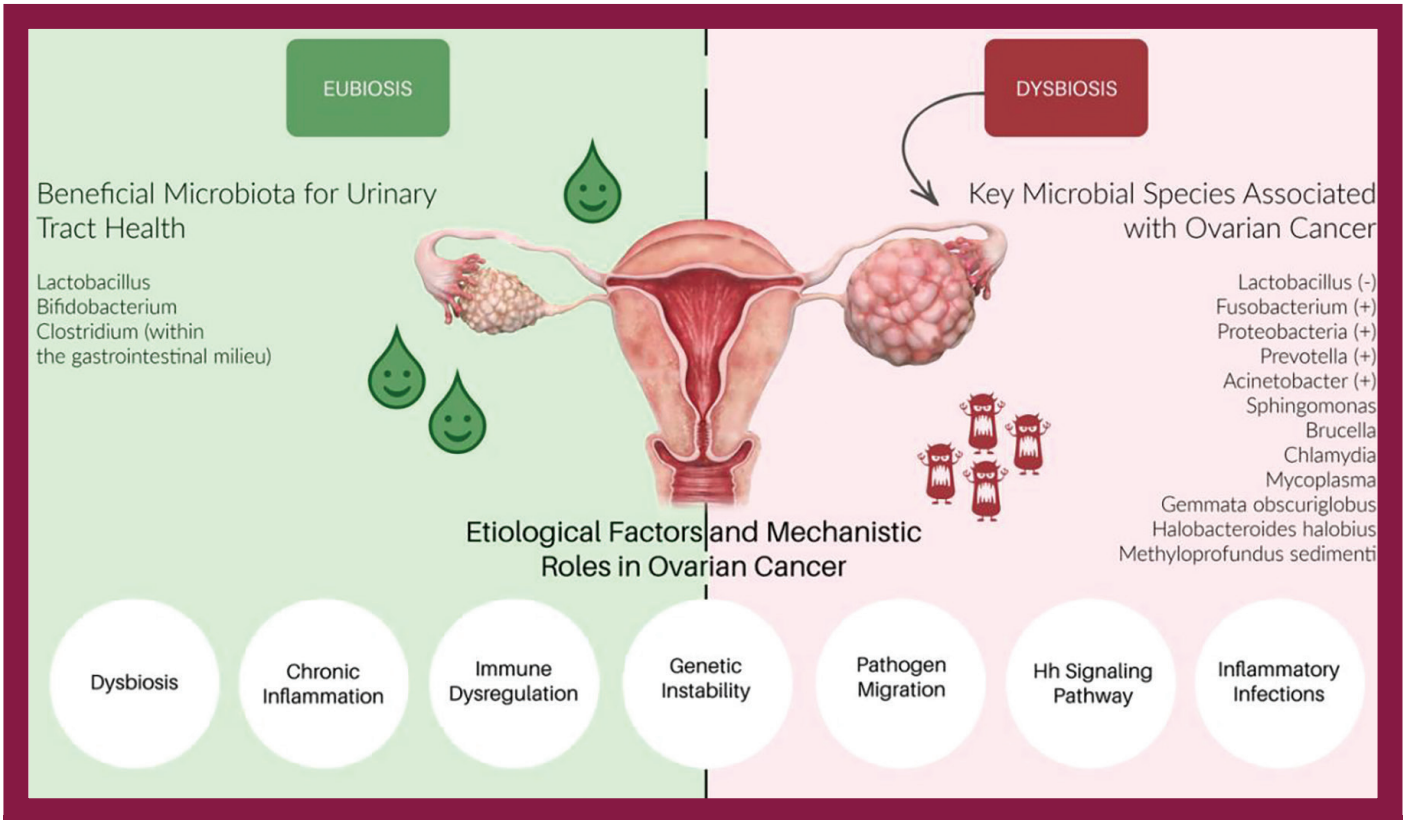


Figure 1. Microbial alterations in ovarian cancer and their implications for urinary tract health; the symbol (-) indicates a decrease in abundance in ovarian cancer, while the symbol (+) indicates an increase in abundance in ovarian cancer

substances between the lower and upper reproductive tracts (URTs). For instance, the dynamic nature of this system is highlighted by the passage of menstrual fluid, bacterial infections, and sperm through the vagina. Contrary to previous beliefs, the ovaries and fallopian tubes are not sterile structures, which makes them more susceptible to certain diseases, including infections and cancers (19). This susceptibility necessitates a deeper understanding of the microbiome's impact on reproductive health.

Bacteria are not inherently harmful to the human body, and certain bacterial species play a crucial role in maintaining health. The majority of the microbiota contributes to regulating the pH and acidity of the vagina, which is essential for maintaining reproductive health (20). Among these beneficial bacteria, *Lactobacillus* stands out as the predominant species in healthy ovaries. *Lactobacillus* is particularly significant as it prevents the invasion of pathogenic bacteria, thereby reducing the risk of reproductive tract infections (21). This protective role underscores the importance of maintaining a healthy microbiome.

Ravel et al. (22) discovered that the vaginal microbiota in reproductive-aged women can be divided into five distinct community state types (CSTs). CSTs I, II, III, and V are primarily characterized by relatively simplistic microbial communities dominated by various Lactobacillus species, specifically, *Lactobacillus crispatus, Lactobacillus gasseri*, *Lactobacillus iners*, and *Lactobacillus jensenii*, respectively. In contrast, CST IV is marked by increased microbial diversity and includes a range of bacterial species aside from *Lactobacillus*. This group largely consists of anaerobic bacteria, including *Prevotella*, *Dialister*, *Atopobium*, and *Gardnerella*. A thorough understanding of these differences is crucial for developing targeted interventions for microbiome-related health issues. Brewster et al. (19) examined microbiota variations within different regions such as the ovary, fallopian tube, and fimbriae, in healthy individuals. They found significant differences in the abundance of certain bacterial species between these sites. For instance, species like *Actinoplanes*, *Arthrobacter*, *Bradyrhizobium*, *Gemmatimonas*, *Limnobacter*, *Roseobacter*, *Saccharopolyspora*, and *Mycobacterium* were more prevalent in the ovary, compared to the fallopian tube. Additionally, comparisons between the fallopian tube and the fimbriae revealed significant differences in the abundance of *Acidovorax*, *Bradyrhizobium*, *Mesorhizobium*, *Mycobacterium*, and *Ralstonia*.

Previous research has largely focused on gynaecological tumours, often linking microbiome alterations to disease progression (23). This focus reflects the potential for microbiome analysis to serve as a diagnostic tool or therapeutic target. However, there remains a significant knowledge gap regarding the microbiome of healthy ovaries, primarily due to the limited availability of samples for study. This gap presents an opportunity for future research to enhance our understanding of reproductive health.

Bacterial Composition Changes in Ovarian Cancer

In women of reproductive age, the lower FRT, encompassing the vagina and cervix, is mainly dominated by *Lactobacillu*s species. These bacteria engage in mutually beneficial interactions that support the host. Conversely, the upper FRT, including the uterus, fallopian tubes, and ovaries, houses a low-biomass microbiome characterized by a diverse range of microorganisms. An imbalance in this area, known as dysbiosis, can interfere with immune and metabolic signaling pathways, affecting crucial cancer-related mechanisms such as chronic inflammation, epithelial barrier breaches, changes in cellular growth and death, genetic instability, angiogenesis, and metabolic disruptions. Such pathological alterations may play a role in the onset of gynecological cancers (24). A study comparing healthy women with women with ovarian cancer identified notable differences in microbial populations. Specifically, there was a rise in Aquificae and Planctomycetes, and a reduction in Crenarchaeota among the ovarian cancer groups (18). At the species level, Zhao et al. (25) reported that in healthy individuals, the predominant bacteria in the ovarian microbiome were *Halobacteroides sediment* at 14.53%, followed by *Gemmata obscuriglobus* at 11.07%, and *Methyloprofundus sediment* at 10.69%. In contrast, among those with cancer, *Gemmata obscuriglobus* was most prevalent at 13.89%, with *Halobacteroides sediment* at 11.99% and *Methyloprofundus sediment* at 11.12%. Importantly, *Lactobacilli*, typically abundant in healthy ovaries, were significantly reduced in cancer patients, suggesting a decreased ability to prevent bacterial invasion and emphasizing the protective function of *Lactobacilli*. Additionally, bacterial genera like *Prevotella* and *Proteobacteria*, typically associated with healthy ovaries, were found to be elevated in ovarian cancer cases (26). According to Brewster et al. (19), a noticeable reduction in the abundance of certain microbial taxa was observed in the URT tissues of ovarian cancer patients compared to healthy controls. Specifically, in cancer patients, species such as *Acidovorax*, *Acinetobacter*, *Aeromonas*, Cloacibacterium, *Conexibacter*, *Mariomonas*, *Methylobacterium*, *Propionibacterium*, *Pseudoalteromonas*, *Vibrio*, and *Xanthomonas* were significantly less common in URT tissues. In contrast, species like *Bosea*, *Mesorhizobium*, *Mycobacterium*, *Ralstonia*, and *Variovorax* showed increased prevalence in these tissues. Researchers found a significant increase in the ratio of *Proteobacteria* to *Firmicutes* in ovarian cancer, indicating that changes in microbial composition might be associated with the disease's development. Notably there was an increase of *Proteobacteria*, *Acinetobacter*, *Sphingomonas*, and *Methylobacterium species* in samples derived from normal distal fallopian tube tissues in ovarian cancer patients. In contrast, the composition of firmicutes, *Acidobacteria, Lactococcus* spp., *Acinetobacter lwoffii*, and *Lactococcus piscium* was decreased. They suggested that microbial dysbiosis might influence the onset or advancement of ovarian cancer by dampening the host's inflammatory and immune reactions, effectively forming an immunosuppressive microenvironment around the tumour (27).

The Role of Bacterial Metabolites in Ovarian Cancer

In a comprehensive study, researchers examined a unique collection of viral, bacterial, fungal, and parasitic markers that have a strong association with ovarian cancer. This research identified the presence of *Brucella*, *Chlamydia*, and *Mycoplasma* in 76%, 60%, and 74% of ovarian cancer samples, respectively (28). The potential involvement of lipopolysaccharides (LPS), lysophosphatidic acid, and tryptophan metabolites in the development of ovarian cancer through bacterial metabolism was reviewed (29). LPS, lipoglycans, and endotoxins are components that are found in Gram-negative bacteria which protect them from toxins, antibiotics, and bile acids.

In ovarian cancerous tissues, a notable shift occurs in the balance of Gram-negative bacteria, resulting in increased levels of LPS in the tissue (30). LPS is crucial in driving inflammation related to ovarian cancer, as it stimulates cancer cells and tumour-associated macrophages, thus facilitating disease progression. According to Zheng et al. (31), lysophospholipids, metabolic by-products of bacterial membrane homeostasis abundant in Gram-negative bacteria, are produced both by these bacteria and the host. These molecules are important for various physiological processes, including reproduction, vascular development, cancer, and nervous system functions. Lysophospholipids activate G protein-coupled receptors, which are essential for the binding of water-soluble hormones. Unfortunately, ovarian cancer patients exhibit significantly higher lysophospholipid levels in their plasma compared to individuals with benign ovarian conditions. The levels of lysophospholipids align with the expression of metastasis-promoting factors critical to ovarian cancer progression. Additionally, Ness et

al. (32) found that women with *Chlamydia* infections face a 90% increased risk of developing ovarian cancer. This association is explained by the inflammation hypothesis, which posits that inflammation or infection is responsible for one in four cancer cases. Factors such as cytokines, free radicals, prostaglandins, and growth factors contribute to inflammation by inducing point mutations and DNA methylation and posttranslational modifications (33,34).

In another comprehensive investigation into ovarian cancer, researchers employed Mendelian randomization to explore causal relationships between gut microbiota and their influence on ovarian cancer risk. The analysis identified 24 gut bacteria involved in the pathogenesis of ovarian cancer, categorized into 10 risk factors such as *Dorea phocaeense* and *Pseudomonas aeruginosa*, and 14 protective factors, such as Enorma massiliensis and *Turicibacter sp001543345*. These bacteria demonstrated causal links to lipoproteins, lipids, and amino acids, impacting ovarian cancer risk by modulating cholesterol and fatty acid ratios within various lipoprotein subtypes. Specifically, *Enorma massiliensis* and *Turicibacter sp001543345* showed potential protective roles by adjusting lipid profiles, thereby influencing ovarian cancer risk. This research highlights the genetic and metabolic interplay mediating the role of the gut microbiota in ovarian cancer, enhancing our understanding of its pathogenesis (35).

In exploring the potential role of metabolites from the vaginal microbiome in ovarian cancer, a cross-sectional study investigated how these compounds might contribute to racial disparities in cancer progression. Researchers found significant differences in the concentration of certain metabolites in vaginal fluids from Black and White patients, highlighting the biological role these metabolites may play in cancer-related inflammation. Among 99 metabolites analyzed, arachidonoylcarnitine, a derivative of arachidonic acid known for its inflammation-inducing properties, consistently appeared at lower levels in Black patients compared to their White counterparts. This metabolite, involved in eicosanoid signaling pathways, plays a critical role in inflammatory responses that may facilitate ovarian cancer progression (36). This study also revealed that more than one-third of the vaginal metabolites analysed were correlated with systemic inflammation markers, suggesting that bacterial metabolites might influence inflammatory processes relevant to cancer development. The research pointed to the involvement of pathways related to mitochondrial dysfunction and sphingolipid metabolism, which can affect the proliferation and apoptosis of cancer cells. Specifically, sphingolipids and their metabolites, such as ceramides and sphingomyelins, were found to interact with inflammatory pathways, indicating potential roles in either promoting or inhibiting tumour growth.

Building on this understanding, recent research further supports the emerging role of the gut microbiome and its metabolites in shaping the tumour microenvironment in ovarian cancer. Metabolites such as lactic acid, produced by certain bacterial species like *Ruminococcus* and *Leuconostoc mesenteroides*, have been found in greater abundance in patients who respond well to immunotherapy. Lactic acid is known to enhance the effectiveness of T-cell responses by boosting cytokine production, which can improve both chemotherapy and immunotherapy outcomes. Additionally, metabolic pathways involving tryptophan, amino acids, and glycerophospholipids are increasingly recognized for their contribution to immune modulation. Furthermore, metabolites such as trimethylamine N-oxide, associated with bacteria like *Desulfovibrio fastidiosa*, have shown potential in modulating immune responses within the tumour microenvironment, offering insights into dietary interventions that could enhance immunotherapy effectiveness (37). These bacterial metabolites not only interact with immune cells but also have a direct impact on cellular metabolism and the tumour's ability to grow and metastasize. For instance, changes in lipid and amino acid metabolism, potentially mediated by gut microbiota, can support cell survival and proliferation, or conversely, promote cancer cell apoptosis.

Influence of Gut Microbiota on Ovarian Cancer Development

Several studies have indicated that the microbiota present in both the FRT and other body regions may play a significant role in ovarian cancer. Since the most diverse microorganisms are found in the abdomen, we have focused on examining the gut microbiota in this review. Some of the research mentions that the following bacteria interact with the human intestinal tract: *Bacteroides, Clostridium*, *Bifidobacterium*, and *Lactobacillus*. The mention of all these bacteria indicates that *Lactobacillu*s is present in the ovaries, demonstrating a strong connection. One of the studies reveals that the gynaecologic malignancies have changes in their intestinal flora proving another connection (38).

In studies, it is often mentioned that Hedgehog (Hh) signalling pathways play an important role in the occurrence of ovarian cancer. This pathway and gut microbiota play a crucial role in maintaining the homeostasis of physiological processes (39).

Abnormally active Hh signaling pathway raises the risk of cancer by promoting cell proliferation, invasion, and migration. The pathway indicating activation in ovarian cancer patients can be decreased by introducing Gli antagonist v61 in vitro or in vivo, or insulin-like growth

factor 1 as an epidermal growth factor. All of these agents can be regulated by the gut microbiota. In addition, this can be a potential biomarker for ovarian cancer (40). Dysbiosis is a bacterial infection of the gut or the gastrointestinal tract, which is observed in cancers related to the female population such as breast, cervical, and ovarian cancer (41).

The connection of gut microbiota is still being studied in a variety of diseases because the gut microbiota is very complex, and the healthy gut microbiome composition is not yet known due to inter-individual variation. It is only known that gastrointestinal microbiota is connected to many diseases like obesity, diabetes, cardiovascular disorder, cancer, hypertension, and inflammatory bowel disease. Microbiome alterations in gut, cervicovaginal, and different compartments from patients with ovarian cancer are summarized in Table 1.

The Impact of Environmental Factors on Microbiota Linked to Ovarian Cancer

The investigation into the role of environmental factors in microbiota associated with ovarian cancer, illustrates a significant interface between the human microbiome and cancer. Current research predominantly focuses on the gut microbiome and its connection to gastrointestinal cancers, yet the influence of the vaginal microbiome on ovarian cancer remains inadequately explored beyond the established link between human papillomavirus and cervical cancer. The retrospective study delves into the relationship between ovarian cancer, platinum-free interval durations, and both vaginal and gut microbiomes (42). Findings indicate that *Lactobacillus*-dominated vaginal communities are less prevalent among women with ovarian cancer compared to similarly aged women without cancer. Notably, the absence of *Lactobacillus* and presence of *Escherichia*, in

Table 1. Microbiome alterations in ovarian cancer tissues

Location	Microbiome/Relative abundance		References
Ovarian cancer tissues	*Brucella*	+	(28)
	Chlamydia	+	
	Mycoplasma	+	
	Proteobacteria/Firmicutes	+	(18,27)
	Fusobacteria/Bacteroides	+	(59)
	Acinetobacter	+	(28)
	Lactococcus	_	
	Gram-negative bacteria	+ (high LPS)	(18)
Gut	*Bacteroides*	-	(60)
	Prevotella	+	(26)
	Proteobacteria	+	
	Ruminococcus	-	
	Actinobacteria	-	
	Gram-positive bacteria	+	(60)
Cervicovagina	*Mobiluncus curtisii*	+ → -	(61)
	Eubacterium rectale	+ → -	
	Fusobacterium nucleatum	+ → -	
	Porphyromonas	+ → -	
	Lactobacilli	- (protective)	(17,62)
Other compartments	Gram-negative bacteria in the peritoneal microbiome	+	(54)
	No α/β diversity interference observed in serum	0 (no interference observed in diversity)	(63)
	Increased risk related to genital pathogens like Neisseria gonorrhoeae and Chlamydia trachomatis	+	(32,64)

LPS: Lipopolysaccharide. The plus (+) denotes greater abundance, while the minus (-) signifies reduced abundance in ovarian cancer patients or ovarian cancer cells compared to the control group

the vaginal microbiome correlates with platinum-resistant ovarian cancer, where patients show higher rates of disease recurrence and reduced survivability. Women with platinum-resistant tumours display lower phylogenetic diversity than their platinum-sensitive counterparts. This reduced diversity aligns with trends observed in other inflammatory conditions, suggesting that unique environmental exposures impacting the gut microbiota may influence cancer progression and treatment resistance. The presence of *Escherichia*-dominated profiles in these patients could be linked to immune system modulation, which affects the effectiveness of platinum-based chemotherapies, potentially through alterations in reactive oxygen species production.

Diet, a fundamental environmental factor, plays a crucial role in determining gut microbiota composition. Diets high in processed foods, red meats, and sugars can lead to dysbiosis, characterized by a loss of beneficial microbes and an increase in potentially pathogenic bacteria. Conversely, diets rich in fibre, fruits, and vegetables promote the growth of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*, which can produce short-chain fatty acids with anti-inflammatory and anti-carcinogenic properties (43). The Western diet, characterized by high-fat and low-fibre intake, has been linked to an increased risk of various cancers, including ovarian cancer, through mechanisms involving chronic inflammation and immune modulation. Obesity, a condition often resulting from dietary choices and sedentary lifestyles, is another critical environmental factor affecting gut microbiota composition (44). Obesity is associated with reduced microbial diversity and a higher prevalence of pro-inflammatory bacteria, which can lead to systemic inflammation a known contributor to cancer progression. Increased adipose tissue in obese individuals can alter hormone levels, further affecting cancer risk (45). Additionally, changes in gut microbiota can influence the metabolism of oestrogens and other hormones, potentially impacting ovarian cancer development (46).

Lifestyle factors such as physical activity also play a role in modulating the gut microbiome. Regular exercise has been shown to increase microbial diversity and promote the abundance of beneficial bacteria, potentially enhancing immune function and reducing cancer risk. Conversely, sedentary behaviour is associated with dysbiosis and a higher risk of inflammatory diseases (47). Alcohol consumption can lead to dysbiosis by selectively increasing harmful bacteria and reducing beneficial species. It can impair gut barrier function, allowing microbial endotoxins such as LPS to enter circulation and promote systemic inflammation. This inflammatory state is linked to an increased cancer risk (48).

Antibiotic use is another significant environmental factor affecting gut microbiota. While antibiotics can be lifesaving, overuse or misuse can lead to a drastic reduction in microbial diversity and the proliferation of antibiotic-resistant bacteria. This alteration can result in a disrupted gut ecosystem and an inflammatory environment conducive to cancer development (49). The impact of probiotics and prebiotics as potential interventions to restore microbial balance and mitigate cancer risk is an area of ongoing research. Probiotics may enhance the gut's barrier function, promote anti-inflammatory pathways, and modulate immune responses. Emerging evidence suggests that specific strains of probiotics could exert protective effects against cancer progression.

Smoking is recognized as an environmental risk factor that significantly affects the composition of the gut microbiome. Exposure to cigarette smoke is associated with decreased microbial diversity and an increase in harmful bacteria, creating a pro-inflammatory state that may facilitate carcinogenesis. The toxic substances found in cigarette smoke, such as polycyclic aromatic hydrocarbons and heavy metals, can modify the gut environment, leading to dysbiosis, a condition of microbial imbalance (50). This imbalance in the gut microbiome can trigger systemic inflammation and oxidative stress, processes that are closely linked to cancer development, including ovarian cancer. While smoking's negative impact on ovarian function and menopause is well established, its effect on the gut microbiome represents an additional pathway through which it may influence cancer risk. Altered microbial composition can impact the metabolism of oestrogens and other hormones, potentially affecting cancer susceptibility. Specifically, the pro-inflammatory environment caused by smoking can activate pathways that promote tumour growth and progression. In a study using two-sample Mendelian randomization analysis, researchers showed that environmental factors like smoking can incite changes in the gut microbiome that may contribute to ovarian cancer risk, highlighting the necessity for further investigation into these complex interactions. The environmental factors contributing to microbiota disruption and their potential link to ovarian cancer are summarized in Figure 2.

Microbiome as Biomarker and Therapeutic in Ovarian Cancer

The use of microbiomes as a biomarker for the diagnosis and prognosis of ovarian cancer holds significant importance due to their potential to address critical challenges in the management of this deadly disease. Ovarian cancer is often diagnosed at advanced stages due to the lack of specific early symptoms and reliable biomarkers. The microbiome, particularly the changes in microbial diversity and composition, could serve as a non-invasive biomarker for early detection. Specific

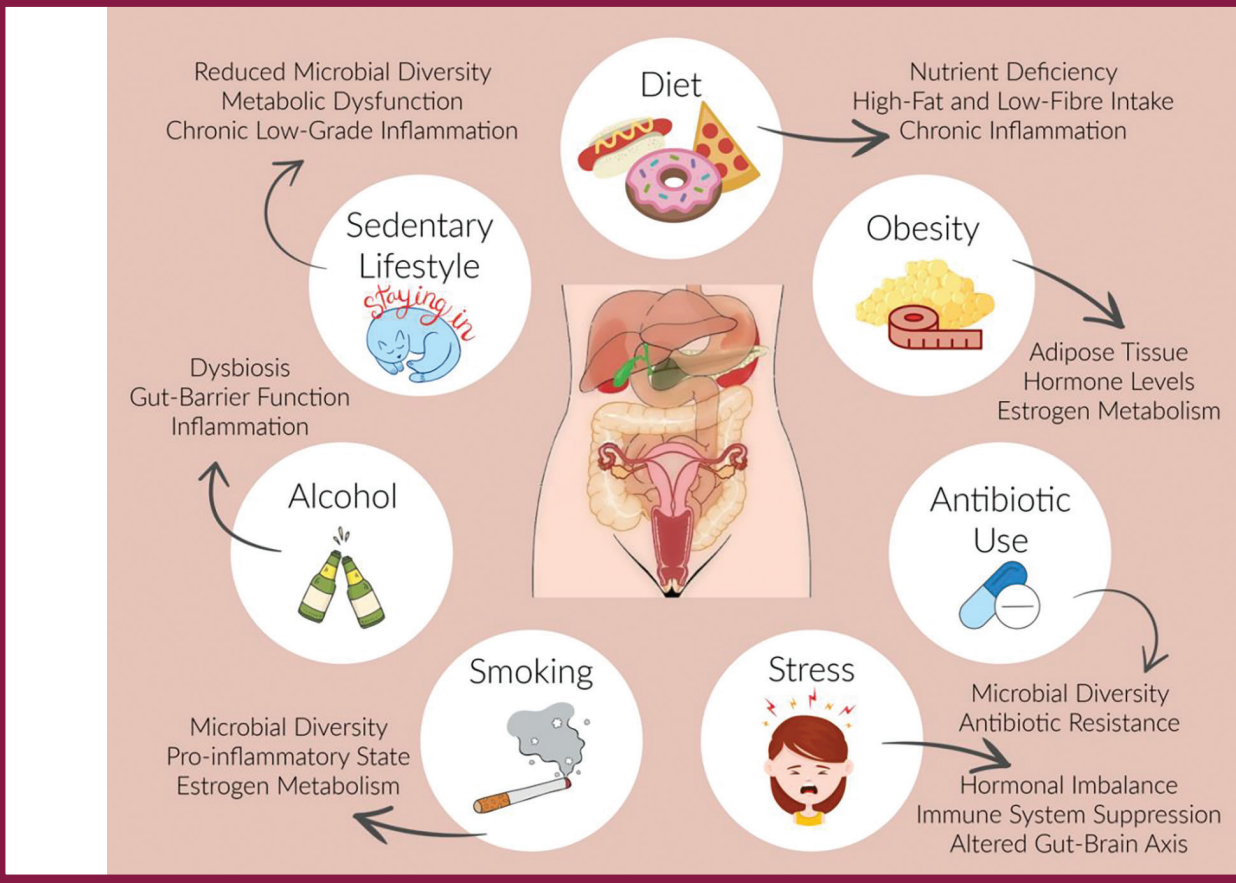


Figure 2. Environmental factors contributing to microbiota disruption and their potential link to ovarian cancer (Drawing of abdominal organs taken from Shutterstock©)

microbial signatures in the reproductive tract, gut, or blood may indicate disease development before conventional clinical symptoms appear (51). As mentioned above, this study revealed an increase in *Bacteroides*, *Prevotella*, and *Proteobacteria*, along with a decrease in *Ruminococcus* and *Actinobacteria,* in gut samples from patients with ovarian cancer (26). Research has consistently shown reduced levels of *Lactobacilli* in the cervicovaginal microbiome of ovarian cancer patients (26,52). The composition of *Proteobacteria* and *Firmicutes* and *Acinetobacter* was observed to increase, whereas *Lactococcus* decreased in ovarian cancer tissues. A decrease in *Lactococcus* in ovarian cancer likely contributes to microbial dysbiosis, inflammation, immune dysregulation, and the loss of protective antimicrobial activity. These changes collectively create an environment that facilitates tumour initiation, progression, and immune escape, emphasizing the importance of maintaining a balanced microbiome for ovarian health.

Another phenomenon that may serve as a potential biomarker is the predominant origin of microorganisms within the reproductive tract. The connection between the upper and lower reproductive tracts enables the migration of pathogens from the lower to the upper regions. This complicates the identification of a specific target for potential biomarkers. However, the upper genital tract in women with ovarian cancer differs significantly from that of healthy women, a finding supported by the observed increase in *Fusobacterium* levels in affected individuals (53). In a study, they combined microbial analysis with machine learning techniques that represent a promising and powerful approach for the diagnosis and prognosis of ovarian cancer. They revealed 18 microbial features that were unique for ovarian cancer by performing ensemble modeling and machine learning pathways method (54).

The microbiome is increasingly recognized as a critical target for cancer therapies due to its impact on cancer initiation, progression, and the effectiveness of treatments. Researchers highlight the microbiome's therapeutic importance in various areas: modulation of the tumour microenvironment, enhancement of responses

to immunotherapy, chemotherapy, and radiotherapy, and the development of probiotics and microbiome engineering strategies (55). Researchers also found that *Lactobacillus reuteri* engineered to secrete IL-22 (LR-IL-22) can safeguard intestinal tissues during whole abdomen irradiation in mouse models of ovarian cancer, indicating its potential as an intestinal radioprotector that could be used in future treatment protocols (56). In a later study, researchers showed that this genetically modified probiotic could transform the tumour microenvironment, which may improve irradiation outcomes in ovarian cancer (57). Meanwhile, Qin et al. (58) observed that changes in the microbiota, caused by ovarian cancer, enhance their potential as a biotherapeutic option not only for ovarian cancer but possibly for other malignancies and conditions as well. They suggest that the microbiota could be analysed and harnessed within a predictive, preventive, and personalized medicine framework for treating ovarian cancer (58). Additionally, it was noted that restoring the disrupted gut microbiota following surgery and chemotherapy can lead to improved survival rates in ovarian cancer patients. A summary of these findings and their implications can be found in Table 2, which outlines the role of the microbiome as both a biomarker and therapeutic in ovarian cancer.

Conclusion

The human body is a highly interconnected system, including the microorganisms that reside within. These microorganisms are dynamic and can adapt to various factors such as lifestyle, diet, environment, gender, age, ethnicity, and stress exposure. However, the alteration of the microbiota may sometimes lead to severe diseases, including ovarian cancer. The high diversity of microorganisms in the female body poses challenges for the treatment of reproductive diseases. Researchers have investigated the microbiota present in diseased individuals and compared it to that of healthy individuals to explore the molecular and genetic mechanisms underlying the connection between microorganisms and the host. This review has highlighted the complex relationship between human microbiota and ovarian cancer, summarizing recent findings that alterations in microbial communities may contribute to the development, progression, and prognosis of ovarian malignancy. Studies comparing the microbiota of healthy individuals and ovarian cancer patients have revealed distinctive microbial signatures, and suggest that dysbiosis may play a significant role in tumour biology.

Looking forward, understanding these microbial patterns opens promising avenues for early diagnosis, prognostic assessment, and the development of novel microbiome-based therapies. Future clinical studies investigating targeted modulation of microbiota may provide new strategies to improve outcomes and reduce treatment-related side effects for ovarian cancer patients.

Table 2. Role of microbiome as a biomarker and therapeutic in ovarian cancer

Aspect	Findings	References
Early detection	Changes in microbial diversity in reproductive tract, gut and blood as potential biomarkers for early detection	(26,51)
Microbial signatures	Increase in *Bacteroides Prevotella Proteobacteria* decrease in *Ruminococcus* and *Actinobacteria* in ovarian cancer patients	(26)
Reproductive tract microbiota	Increase in *Fusobacterium* in the upper genital tract of ovarian cancer patients	(53)
Machine learning for diagnosis/ Prognosis	18 unique microbial features for ovarian cancer identified through machine learning	(54)
Therapeutic impact	Modulation of tumour microenvironment enhancement of responses to immunotherapy chemotherapy and radiotherapy	(55)
Probiotics and microbiome engineering	Lactobacillus reuteri engineered to secrete IL-22 to protect intestinal tissues during irradiation	(56,57)
Predictive and personalized medicine	Potential of microbiota as a biotherapeutic option and within personalized treatment frameworks	(58)
Post-treatment microbiota restoration	Restoring gut microbiota post-surgery and chemotherapy can improve survival rates	(24)

Ethics

Informed Consent: The retrospective study delves into the relationship between ovarian cancer, platinum-free interval durations, and both vaginal and gut microbiomes.

Footnotes

Authorship Contributions

Concept: B.A., A.B., N.I., Design: B.A., A.B., N.I., Literature Search: B.A., A.B., N.I., Writing: B.A., A.B., N.I.

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

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

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ORIGINAL ARTICLE

DOI: 10.4274/hamidiyemedj.galenos.2025.38233

Hamidiye Med J 2025;6(2):78-84

A Retrospective Evaluation of Cases of Necrotizing Fasciitis Presenting to the Emergency Department

Acil Servise Başvuran Nekrotizan Fasiit Olgularının Retrospektif Değerlendirmesi

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ABSTRACT

Background: This study set out to identify parameters of potential use in distinguishing soft tissue infections from necrotizing fasciitis (NF) and in predicting mortality during presentation to the emergency department.

Materials and Methods: Twenty-six patients presenting to the emergency department and diagnosed with NF were included in the study. Vital findings at presentation, laboratory, radiological, and microbiological tests, Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score, Shock Index (SI), Systemic Inflammation Response Index (SIRI), and Systemic Immune-Inflammation Index (SII) values were calculated and recorded.

Results: Diabetes and immobilization were the principal risk factors in the 26 patients with NF, and the in-hospital mortality rate was 15.4%. Heart rate (p=0.030) and respiration rate (p<0.001) were significantly higher in the emergency department in this patient group than in the survivors, while systolic blood pressure (p=0.030) and fingertip pulse (p=0.001) oximetry values were significantly lower. The laboratory parameters of urea (p=0.030) and lactate (p=0.050) were higher in the mortal cases, while hemoglobin (p=0.030) and albumin (p=0.001) were lower. Additionally, SI values were significantly greater in the mortal group (p=0.040).

Conclusion: Personalized strategies in which predisposing factors and comorbid conditions are evaluated during admission need to be developed for early diagnosis and to prevent repeat presentations. A higher LRINEC score, low albumin, and elevated lactate are associated with increased mortality, and these clinical characteristics must be considered in patients diagnosed with NF.

Keywords: Necrotizing fasciitis, systemic inflammation response index, systemic immune-inflammation index, laboratory risk indicator for necrotizing fasciitis

ÖZ

Amaç: Bu çalışma, yumuşak doku enfeksiyonlarını, nekrotizan fasiitten (NF) ayırt etmede ve acil servise başvuru sırasında mortaliteyi öngörmede potansiyel olarak kullanılabilecek parametreleri tanımlamayı amaçlamaktadır.

Gereç ve Yöntemler: Acil servise başvuran ve NF tanısı alan 26 hasta çalışmaya dahil edildi. Başvuru anındaki vital bulgular, laboratuvar, radyolojik ve mikrobiyolojik testler, NF için Laboratuvar Risk Göstergesi (LRINEC) skoru, Şok İndeksi (SI), Sistemik İnflamasyon Yanıt İndeksi (SIRI) ve Sistemik İmmün-İnflamasyon İndeksi (SII) değerleri hesaplandı ve kaydedildi.

Bulgular: Diyabet ve immobilizasyon, NF'li 26 hastada başlıca risk faktörleriydi ve hastane içi mortalite oranı %15,4 idi. Bu hasta grubunda acil serviste kalp hızı (p=0.030) ve solunum hızı (p<0.001) sağ kalanlara göre anlamlı derecede yüksek, sistolik kan basıncı (p=0.030) ve parmak ucu nabız (p=0.001) oksimetre değerleri ise anlamlı derecede düşüktü. Laboratuvar parametrelerinden üre (p=0.030) ve laktat (p=0.050) ölümcül vakalarda daha yüksek, hemoglobin (p=0.030) ve albümin (p=0.001) ise daha düşüktü. Ek olarak, SI değerleri mortal grupta anlamlı olarak daha yüksekti (p=0.040).

Sonuç: Erken tanı ve tekrarlayan başvuruların önlenmesi için, yatış sırasında predispozan faktörlerin ve komorbid durumların değerlendirildiği kişiselleştirilmiş stratejilerin geliştirilmesi gerekmektedir. Yüksek LRINEC skoru, düşük albümin ve yüksek laktat artmış mortalite ile ilişkilidir ve bu klinik özellikler NF tanısı alan hastalarda göz önünde bulundurulmalıdır

Anahtar Kelimeler: Nekrotizan fasiit, sistemik inflamasyon yanıt indeksi, sistemik immün-inflamasyon indeksi, nekrotizan fasiit için laboratuvar risk göstergesi

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Received: 09.09.2024 **Accepted:** 13.05.2025 **Publication Date:** 04.07.2025

Cite this article as: Altuntaş G, Yazıcı MM, Ataş İ, Kaçan M, Bilir Ö. A retrospective evaluation of cases of necrotizing fasciitis presenting to the emergency department. Hamidiye Med J. 2025;6(2):78-84

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Introduction

Necrotizing fasciitis (NF) is a rare but potentially fatal disease characterized by widespread necrosis of subcutaneous tissue extending along the fascia. Mortality rates exhibit societal variations but can be as high as 100% if left untreated, despite advances in medical care services (1). A traumatic lesion on the surface of the body or a complicated intra-abdominal infection is frequently involved in the etiology. The spread of infection and necrosis depends on the specific characteristics of the host and pathogenic bacteria. NF is classified into four types depending on microbiological findings. The most common form is the polymicrobial type (Type 1) seen in individuals with comorbid diseases, such as diabetes. Two or more pathogens are involved in this manifestation, and the most common sites are the perineum and the trunk (2). Early diagnosis is essential if mortality is to be prevented. The most frequent symptoms are local pain, swelling, and edema associated with the development of infection. However, critical manifestations such as sepsis and multiorgan failure can also be encountered following rapid progression of necrosis. Pain is particularly disproportionate to clinical findings. Patients require rapid and aggressive treatments, including antibiotherapy, surgical debridement, and intensive care management (3).

The clinical manifestation is the most important factor in diagnosis (4). Although laboratory results are not specific, the use of various scoring systems and biomarkers is recommended for early diagnosis and for classifying the disease according to risk categories (5-7). Based on the conclusion that oxidative stress and inflammation cause changes in erythrocyte and platelet functions, laboratory parameters such as red blood cell distribution width (RDW), platelet count (PC), and mean platelet volume have been employed in diagnosis (8-10). The Systemic Inflammation Response Index (SIRI) and Systemic Immune-Inflammation Index (SII), indicators of systemic inflammation and cellular immunity, can also serve as useful guides. However, studies involving biochemical markers and scoring systems, employed in differential diagnosis, have largely focused on indications for surgery and for predicting admission to the intensive care unit (ICU), rather than for diagnosis. The purpose of the present study was to identify effective parameters in the evaluation of early diagnosis and prognosis, capable of distinguishing NF from soft tissue infections, by determining characteristics of the process commencing from admission to the emergency department.

Materials and Methods

Study Design

This study represents a retrospective examination of patients diagnosed with NF in the emergency department of a tertiary hospital between January 2019 and December 2023. Local ethical approval was obtained from the Recep Tayyip Erdoğan University Non-Interventional Clinical Research Ethics Committee prior to commencement (approval number: 2024/216, dated: 15.08.2024).

The local computer-based Hospital Information Management System (HIMS), in which patients' records are kept, was used during the collection of clinical and radiological data. Patients younger than 18 years of age, those with a history of chronic kidney disease, known pressure ulcers due to compression or immobilization, or incomplete clinical or radiological data were excluded. The study included twenty-six patients diagnosed with NF in the emergency department and admitted, depending on their clinical condition, to any clinic or to the ICU for follow-up and treatment.

Clinical Parameters

The medical records of the patients diagnosed with NF in the emergency department were examined retrospectively. Using a standardized data collection page, clinical data (age, sex, comorbid diseases, systolic/diastolic blood pressures, heart rate, body temperature, presentation symptoms, examination findings, and treatments administered), laboratory data (complete blood count, biochemistry, and blood gas parameters), radiological findings, pathological and microbiological parameters, and hospital outcome were recorded. The HMIS was used to determine any emergency department or clinic presentation due to a symptom that might be associated with NF prior to diagnosis. The laboratory risk indicator for necrotizing fasciitis (LRINEC) score (11), Shock Index (SI), Modified SI (MSI), SIRI, and SII values were calculated and recorded. The cut-off value of parameters such as SII and SIRI, which have recently been frequently evaluated as predictors of mortality in many diseases, could not be calculated due to data limitations. However, the values obtained in the living and deceased patients' groups were compared.

Patients receive fluid resuscitation depending on their clinical conditions, during presentation to the emergency department. However, vasopressor therapy is applied in case of presentation with septic shock and/or lack of response to the fluid administered. Broad-spectrum antibiotherapy is initiated while awaiting the culture sensitivity test results.

Patients are treated and followed up in the ICU or other clinics, depending on their clinical condition. In addition, a stoma is created to prevent fecal wound contamination in conjunction with wide surgical debridement of necrotic tissue. The treatment received by patients with NF in the emergency department, the areas in the hospital where they were followed up as inpatients, whether or not surgical treatment was applied, and the length of hospital stay were also recorded. In addition, 6-month, and 1-year mortality rates of the patients were recorded. For this purpose, the status of the patients was inquired by calling the patients' telephone numbers registered on the HIS, and in case of death, the information about when the patient died was confirmed from his/her relatives.

Statistical Analysis

All statistical analyses were performed using Jamovi v.1.6 software (Jamovi Project Computer Software, version 1.6. Sydney, Australia). A 5% significance level for Type 1 errors was used in all analyses. Depending on the normality status, continuous variables were expressed as mean and standard deviation (SD) or median and interquartile ranges (IQR). The Shapiro-Wilk test and Q-Q plots were applied to evaluate whether data were normally distributed. Categorical data were presented as frequency (n) and percentage (%). Comparisons of continuous variables were performed using the Mann-Whitney U test for non-normally distributed groups.

Results

Twenty-six patients diagnosed with NF in the emergency department between January 2019 and December 2023 were included in the data analysis. All the patients' are shown in Table 1. The patients' mean age was 62.5±13.8 (37-92) years, and 69.2% (n=18) were men. Primary infection

Table 1. The patients' demographic data and baseline characteristics

Characteristics, n=26	Value
Gender (male), n (%)	18 (69.2)
Age (years), mean ± SD (minimum-maximum)	62.5±13.8 (37-92)
Comorbidities	
Hypertension, n (%)	14 (53.8)
diabetes, n (%)	20 (76.9)
stroke, n (%)	3 (11.5)
neoplasia, n (%)	6 (23.1)
Predisposing factor	
Immobility, n (%)	7 (26.9)
operation, n (%)	6 (23.1)
obesity, n (%)	3 (11.5)
Presentation symptom	
Testicular pain-swelling, n (%)	7 (26.9)
lesion in the gluteal region, n (%)	6 (23.1)
rash-pain in the suprapubic region, n (%)	4 (15.4)
rash-pain in the lower extremity, n (%)	3 (11.5)
Lesion site	
Gluteal region, n (%)	7 (26.9)
scrotum-perineum, n (%)	4 (15.4)
suprapubic region, n (%)	4 (15.4)
lower extremity, n (%)	4 (15.4)
Lesion appearance	
Erythema, n (%)	15 (57.7)
necrosis, n (%)	8 (30.8)
Physical examination findings	
Rash-tenderness in the gluteal region, n (%)	7 (26.9)
rash-tenderness in the scrotum t, n (%)	6 (23.1)
rash-edema in the suprapubic region, n (%)	5 (19.2)
rash-crepitation-tenderness in the leg, n (%)	4 (15.4)
Vital Signs	
Systolic blood pressure (mmHg), median (IQR)	120 (116-130)
diastolic blood pressure (mmHg), median (IQR)	70 (60.3-80)
pulse rate (min), median (IQR)	95.5 (83.3-104)
temperature (0C), median (IQR)	36.6 (36.4-37.2)
Length of stay in the ED (minute), median (IQR)	194 (138-347)
Time from Hospitalisation to Surgery (hour), median (IQR)	2.3 (1.0-32.8)
Blood culture positivity, n (%)	4 (15.4)

IQR: Interquartile range (25p, 75p), SD: Standard deviation, ED: Emergency department

was commonly located in the gluteal region (26.9%), and immobilization was the most frequent predisposing factor in these patients.

The results of laboratory tests during presentation to the emergency department are given in Table 2. Median values for disease risk indicators and their association with mortality are shown in Table 3. Statistical analyses of vital signs are presented in Table 4. All patients with preliminary diagnoses of NF on the basis of history, physical examination, and laboratory tests were started on prophylactic antibiotics in the emergency department, and two received vasopressor therapy due to instability. Edema and swelling in the scrotum, were observed at bedside ultrasound (USG) in three patients (11.5%). Edema and gas were observed in 65.3% (n=17) of the patients between soft tissues in the scrotum, gluteal region, and abdominal anterior wall at the computed tomography.

A total of 80.8% of the patients were transferred from the emergency department to the clinic for surgical procedures, and 19.2% were admitted to the ICU. The median length of hospital stay was 22 days (IQR: 15.3-33.8). Repeated presentations to hospital due to soft tissue infection occurred in all cases, and all patients underwent surgical debridement after admission. Pathological evaluation of the lesion site revealed suppurative inflammation and necrosis in 46.2% of the samples. The most common agent at microbiological analysis was *Escherichia coli* at 23.1% and coagulase-negative Staphylococcus infection at 19.2%.

The in-hospital mortality rate was 15.4% (n=4), six-month mortality was 23.1% (n=6), and one-year mortality was 34.6% (n=9). Heart rate (survivor group median value 88 (IQR: 78-97), non-survivor group median value 99 (IQR: 93-110), p=0.030) and respiration rate (survivor group median value 16 (IQR: 16-20), non-survivor group median value 20 (IQR: 19-25), p<0.001) in the emergency department were significantly higher in this patient group than in the survivors; while SBP (survivor group median value 120 (IQR: 120-130), non-survivor group median value 110 (IQR: 100-120), p=0.030) and fingertip pulse oximetry values (survivor group median value 95 (IQR: 93-96), non-survivor group median value 90 (IQR: 89-93), p=0.001) were significantly lower in the non-survivor group. Statistical analyses of vital signs are presented in Table 4. Urea (survivor group median value 41 (IQR: 29.8-85.3), non-survivor group median value 111 (IQR: 86.8-133), p=0.030) and lactate (survivor group median value 1.9 (IQR: 1.4-2.5), non-survivor group median value 3.0 (IQR: 2.6-3.9), p=0.050) values were higher in the mortal cases, while hemoglobin (survivor group median

Table 2. The patients' laboratory findings

Parameter	Value
Hemoglobin (g/dL), median (IQR)	11.3 (9.3-12.6)
Leukocyte (10^3/μL), median (IQR)	15.5 (13.8-18.5)
Neutrophil (10^3/μL), median (IQR)	13.6 (11.1-16.5)
Lymphocyte (10^3/μL), median (IQR)	1.10 (0.8-1.66)
Platelet (10^3/μL), median (IQR)	335 (224-386)
RDW (fL), median (IQR)	44.7 (41.2-47.8)
MPV (fL), median (IQR)	9.30 (8.70-10.4)
PDW (fL), median (IQR)	16.1 (15.8-16.3)
Urea (mg/dL), median (IQR)	53 (32-90)
Albumin, (g/dL), median (IQR)	27 (23.9-30.5)
Sodium (mmol/L), median (IQR)	133 (127-135)
Lactate (mmol/L), median (IQR)	1.95 (1.52-2.75)

IQR: Interquartile Range (25p, 75p), RDW: Red blood cell distribution width, MPV: Mean platelet volume, PDW: Platelet distribution width

Table 3. Factors associated with mortality

Factors	Surviving group	Non-surviving group*	p
LRINEC, median (IQR)	7.50 (6-9)	7.50 (7-8)	0.970
SI, median (IQR)	0.7 (0.6-0.8)	0.85 (0.8-1.1)	**0.040**
MSI, median (IQR)	1.0 (0.9-1.2)	1.3 (1.3-1.6)	0.100
SIRI, median (IQR)	7.3 (4.5-13.2)	6.4 (5.4-10.8)	0.970
SII, median (IQR)	2565 (1581-4449)	4996 (3918-8493)	0.130
Urea (mg/dL), median (IQR)	41.0 (29.8-85.3)	111 (86.8-133)	**0.030**
Albumin, (g/mL), median (IQR)	27.5 (25.3-32.5)	21.0 (21.0-22.3)	**0.008**
Lactate (mmol/L), median (IQR)	1.9 (1.4-2.5)	3.0 (2.6-3.9)	0.050
Hemoglobin (g/dL), median (IQR)	11.7 (9.9-12.8)	9.0 (8.0-10.1)	**0.030**

*: In hospital. The Mann-Whitney U test was used for statistical analysis.
IQR: Interquartile Range (25p, 75p), LRINEC: Laboratory risk indicator for necrotizing fasciitis, SI: Shock Index, MSI: Modified Shock Index, SIRI: Systemic Inflammation Response Index, SII: Systemic Immune-Inflammation Index

Table 4. Relationship of vital signs between surviving and non-surviving groups

Vital signs	Surviving group	Non-surviving group*	p
SBP (mmHg), median (IQR)	120 (120-130)	110 (100-120)	**0.030**
DBP (mmHg), median (IQR)	75 (70-80)	70 (60-70)	0.135
Heart Rate (/min), median (IQR)	88 (78-97)	99 (93-110)	**0.030**
RR (min), median (IQR)	16 (16-20)	20 (19-25)	**0.001**
Fingertip pulse (%), median (IQR)	95 (93-96)	90 (89-93)	**0.001**
Fever (0C), median (IQR)	36.6 (36.5-36.9)	36.8 (36.4-37.3)	0.773

*: In hospital. The Mann-Whitney U test was used for statistical analysis.
IQR: Interquartile Range (25p, 75p), SBP: Systolic blood pressure, DBP: Diastolic blood pressure, RR: Respiratory rate

value 11.7 (IQR: 9.9-12.8), non-survivor group median value 9.0 (IQR: 8.0-10.1), p=0.030) and albumin (survivor group median value 27.5 (IQR: 25.3-32.5), non-survivor group median value 21.0 (IQR: 21.0-22.3), p=0.001) were lower. The SI was also significantly higher in this patient group (survivor group: median value 0.7, IQR: 0.6-0.8; non-survivor group: median value 0.85, IQR: 0.8-1.1; p=0.040) (Table 3).

Discussion

In this Retrospective study of 26 cases of community-acquired NF, low albumin and elevation in lactate values were more closely associated with mortality than the other laboratory data. In their multicenter study from 2019, Madsen et al. (12) also observed that an increased lactate value was correlated with mortality. In addition, while high SI on admission was associated with mortality, fever, one of the classic symptoms of infection, was not present in the majority of patients, in agreement with most studies in the literature (13,14).

NF is a life-threatening condition that is frequently diagnosed late or incorrectly due to the absence of typical symptoms. It is important to distinguish NF from soft tissue infection by determining patients' debridement needs and addressing potential poor outcomes in the emergency department (4). All our patients presented to the hospital repeatedly due to current symptoms, but superficial infections were also observed to have progressed to NF due to inappropriate treatment. To evaluate predisposing factors and comorbid conditions, in particular, the development of personalized strategies is necessary. While the incidence of NF in immobile and diabetic individuals was noteworthy in this research, this is inconsistent with some previous studies (12,15) and may derive from societal variations. Considering all these reasons, it is important to plan frequent visits, and follow-up through home care services for patients with predisposing factors such as immobility and comorbid diseases. These patients often present to the emergency department due to soft tissue infection. In addition, patients who apply as outpatients should be followed up closely.

Although pain and rash in the lesion site are common characteristics, these are not specific. Scoring systems such as LRINEC and changes in laboratory parameters caused by inflammation are therefore modalities capable of assisting early diagnosis and predicting outcomes (5,10,16). Similarly, in the present study, LRINEC scores of 6 or above during emergency department presentations were found to be predictive, and all cases were started on antibiotic therapy. SIRI and SII, which have become important inflammatory indicators in recent years (17), also increased in this patient group. However, due to the limited nature of the data, we were unable to evaluate whether they can be employed as a prognostic factor. Mean Platelet Volume (MPV), platelet distribution width (PDW), RDW, neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR) employed as markers of oxidative stress and inflammation were of no significance in terms of diagnosis or outcomes compared with the previous literature (10,18,19).

Imaging techniques used in combination with clinical suspicion can serve as a useful guide in the differentiation of soft tissue infections. Appearances of gas at CT, in addition to USG which is frequently employed in the emergency department since it can be used at the bedside, can prevent delays in treatment and false diagnoses. The visualization of gas between soft tissues in 65.3% of the present cases was a useful guide. Although all patients received surgical treatment, suppurative inflammation and necrosis were encountered in only 46.2% at pathological investigation. In agreement with the previous literature, the most common agents at microbiological analysis were *Escherichia coli* and coagulase-negative Staphylococci (12,20).

General mortality rates for the disease vary in the literature. This has been attributed to variations in age, underlying comorbid diseases, and the timing of antibiotherapy and surgical intervention (21,22). Consistent with a previous study, the mortality rate in the present study was 15.4%.

If NF is suspected or diagnosed, surgical debridement and exfoliation of the affected tissue should be performed

immediately (23). Especially in terms of survival, continuing debridement in the early period until healthy tissue is reached, broad-spectrum antibiotic treatment, aggressive fluid resuscitation, and follow-up in the ICU are important factors (24). In our study, the median hospitalisation time was 194 minutes and the median time from hospitalisation to surgery was 2.3 hours. These durations are valuable for NF, where speed in diagnosis and treatment is important. In studies with a larger number of cases, comparison of these times may be valuable, for determining the importance of time in the follow-up and treatment of NF.

There are several limitations of this study. Firstly, the retrospective study design makes it impossible to access much data. Another important limitation is that no sample calculation was made for the study. This may have been because the study was planned as a single-centre study with a limited sample, and this may have prevented obtaining definite findings. Due to the limited sample, cut-off values were not determined for scores that previously lacked a cut-off value. Furthermore, extensive studies are now needed on the subject.

Conclusion

In conclusion, due to the absence of typical symptoms and the risk of false diagnoses, determining risk factors is critical for managing this disease with high mortality rates. The use of laboratory parameters such as albumin and lactate, together with primary markers of infection and predisposing factors, should be considered in diagnosis in the emergency department and mortality.

Ethics

Ethics Committee Approval: Local ethical approval was obtained from the Recep Tayyip Erdoğan University Non-Interventional Clinical Research Ethics Committee prior to commencement (approval number: 2024/216, dated: 15.08.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: İ.A., M.K., Ö.B., Design: G.A., M.M.Y., Data Collection or Processing: G.A., M.M.Y., Ö.B., Analysis or Interpretation: M.M.Y., Literature Search: İ.A., M.K., Ö.B., Writing: G.A., Ö.B.

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

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

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ORIGINAL ARTICLE

DOI: 10.4274/hamidiyemedj.galenos.2025.43434

Hamidiye Med J 2025;6(2):85-91

Investigating Impostor Syndrome Among Postgraduate Anatomy Students

Lisansüstü Anatomi Öğrencileri Arasında İmpostor Sendromunun Araştırılması

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ABSTRACT

Background: Impostor syndrome (IS) is marked by persistent self-doubt and the fear of being perceived as a fraud, even in the presence of clear accomplishments, and it notably affects high-achieving individuals. This study examined IS prevalence and associated factors among postgraduate anatomy students in Türkiye.

Materials and Methods: Using the Clance Impostor Phenomenon Scale, 79 participants were surveyed to assess IS levels alongside demographic and psychiatric variables.

Results: The results revealed that 39.2% of participants exhibited frequent impostor feelings (FIF) or intense impostor experiences (IIE). Notably, individuals with psychiatric conditions had significantly higher IS levels, with 64.7% classified in the FIF category and 17.6% in IIE, compared to those without psychiatric issues, who predominantly fell into lower IS categories ($p<0.05$). No statistically significant associations were observed between IS and demographic variables, including gender, marital status, or education level. However, individuals with no income were overrepresented in the IIE category, aligning with findings from studies suggesting a link between socioeconomic status and heightened IS levels.

Conclusion: This study underscores the prevalence of IS in postgraduate students within a demanding academic discipline and highlights its association with psychiatric conditions. Increasing awareness of IS, particularly in high-stress, perfectionist professions such as academia, is critical. Such efforts can improve recognition, provide targeted interventions, and mitigate IS's impact on individual well-being and professional performance.

Keywords: Impostor syndrome, impostor phenomenon, postgraduate anatomy education

ÖZ

Amaç: İmpostor sendromu (IS), belirgin başarılara rağmen sürekli kendinden şüphe duyma ve başkaları tarafından bir sahtekar olarak algılanma korkusuyla karakterizedir ve özellikle yüksek başarı gösteren bireyleri etkiler. Bu çalışma, Türkiye'deki lisansüstü anatomi öğrencileri arasında IS yaygınlığını ve ilişkili faktörleri incelemeyi amaçlamaktadır.

Gereç ve Yöntemler: Clance Sahtekar Fenomeni Ölçeği kullanılarak 79 katılımcı üzerinde bir anket uygulanmış, SS düzeyleri ile demografik ve psikiyatrik değişkenler değerlendirilmiştir.

Bulgular: Sonuçlar, katılımcıların %39,2'sinin sık sahtekâr duyguları (FIF) veya yoğun sahtekâr deneyimleri (IIE) sergilediğini ortaya koydu. Özellikle psikiyatrik rahatsızlığı olan bireylerde IS düzeyleri anlamlı derecede yüksek bulundu; bu grubun %64,7'si FIF kategorisinde, %17,6'sı ise IIE kategorisinde yer aldı. Buna karşılık, psikiyatrik sorunu olmayan bireylerin büyük çoğunluğu daha düşük IS kategorilerinde sınıflandırıldı ($p<0,05$). IS ile cinsiyet, medeni durum veya eğitim düzeyi gibi demografik değişkenler arasında

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Received: 12.03.2025 **Accepted:** 13.05.2025 **Publication Date:** 04.07.2025

Cite this article as: Ok F, Karip B, Chatzioglou GN, Temizsoy Korkmaz F, Yiğit M. Investigating impostor syndrome among postgraduate anatomy students. Hamidiye Med J. 2025;6(2):85-91

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ÖZ

istatistiksel olarak anlamlı bir ilişki saptanmadı. Ancak, geliri olmayan bireylerin IIE kategorisinde daha yüksek oranda temsil edildiği görüldü ve bu durum, sosyoekonomik durum ile yüksek IS düzeyleri arasındaki bağlantıyı öne süren çalışmalarla tutarlılık gösterdi.

Sonuç: Bu çalışma, zorlu bir akademik disiplin içinde yer alan lisansüstü öğrenciler arasında IS'nin yaygınlığını ve psikiyatrik durumlarla ilişkisini vurgulamaktadır. IS'nin farkındalığını artırmak, özellikle akademi gibi yüksek stres ve mükemmeliyetçilik gerektiren mesleklerde kritik öneme sahiptir. Bu tür farkındalık çalışmaları, IS'nin tanınmasını kolaylaştırabilir, hedefe yönelik müdahaleler sunabilir ve bireylerin iyi oluşu ile mesleki performansları üzerindeki etkisini azaltmaya yardımcı olabilir.

Anahtar Kelimeler: İmpostor sendromu, impostor fenomeni, mezuniyet sonrası anatomi eğitimi

Introduction

Impostor syndrome (IS), impostor phenomenon, or IS is a condition in which individuals working in highly qualified positions do not feel qualified enough, despite evidence to the contrary, and are afraid that others will discover that they are an intellectual fraud. Individuals with IS believe they achieved their success entirely by chance, and if rewarded, they fear they will unknowingly damage their positive image. Individuals with IS believe that their success is not the result of their inherent abilities or talent but is instead attributed to external factors such as luck, excessive effort, or the manipulation of others' perceptions (1-3).

This syndrome was first defined by Clance and Imes in 1978. Clance and Imes (1) five-year clinical study was conducted with more than 150 successful women between the ages of 20 and 45 who had doctorates in various specialties such as law, nursing, medicine, social work, and teaching. They were respected professionals in their fields or successful students.Studies have found that despite these women's successes, academic degrees, high scores on standardized tests, and praise from colleagues and respected authorities, they do not experience an inner sense of success and see themselves as "impostors". As a result of the observations, it was seen that many female graduate students thought that they were accepted to graduate programs by mistake or stated that their high exam scores were due to luck, incorrect grading, or faulty evaluations by professors. Female professionals commonly feel that they are overly evaluated by their colleagues and managers. Another characteristic observed about these women is that they tend to deny objective evidence that they are intelligent. They also struggle with accepting compliments or positive feedback. However, when they receive negative feedback, they hide it and view it as a reminder of their shortcomings (4). It has also been revealed that these women experience anxiety due to their constant fear of not being able to continue their success and their inadequacies being revealed (5).

The concept of IS describes individuals who are successful according to external criteria but experience the illusion that they are inadequate. People naturally present a social self that is different from the self they present in their close relationships because they are forced to do so by society. However, individuals who experience the IS experience greater feelings of inauthenticity and loneliness. This situation is a burden for them (6). Recently, with the influence of positive psychology, studies have been conducted that draw attention to the "bright" aspects of employees. On the other hand, there are individuals who have not internalized their success, doubt their intelligence, and continue to live with the fear that their failures will be discovered one day (7). These individuals, who constantly try to cope with feelings of inadequacy, cannot accept no matter how much objective evidence there is about their success, and continue to experience the fear of being exposed.

Although many characteristics have been attributed to people who feel impostors, Leary et al. (8) stated that these people generally have three defining characteristics. The primary characteristic of IS is the persistent feeling of being an impostor, accompanied by the belief that others perceive them more positively than their actual abilities warrant. The other fear is being exposed as a fraud and others finding out they failed. The third defining characteristic is that they have difficulty internalizing their success, and behave in ways that perpetuate their feelings of fraudulence (8). These emotions cause people with IS to approach the tasks assigned to them in a perfectionist way and to exert more effort than average in the projects they need to do. Individuals with IS tend to set goals that are almost impossible to achieve. If these goals are not achieved, individuals may experience feelings of inadequacy. This extraordinary effort often leads to positive feedback from superiors and colleagues and reinforces this behavioral pattern (9). However, this pattern of behavior can lead to burnout. Medical students, graduate students, residents, and faculty are prime candidates for this burnout syndrome (10).

The literature review revealed that no studies have been reported investigating IS among individuals pursuing postgraduate education in the field of anatomy in Türkiye.

The aim of this study was to identify factors that may be associated with IS, including age, gender, income status, psychiatric conditions and marital status. and to examine the syndrome prevelance in individuals pursuing postgraduate education who were considered potential targets for this phenomenon. Although IS affects many high-achieving individuals across various professions and countries, such as academics, graduate students, and medical doctors, many experience it without recognizing or knowing its name (11-14). Increasing awareness of the syndrome and its associated symptoms can be highly beneficial for these individuals.

Given the increasing recognition of IS as a psychological barrier that impairs performance and well-being in high-achieving individuals, it becomes essential to explore its prevalence in specific academic domains where perfectionism and intellectual rigor are emphasized. Postgraduate anatomy education represents one such environment where IS may occur, yet studies examining IS within this population remain scarce, particularly in Türkiye. The primary aim of this study was to investigate the prevalence and severity of IS among postgraduate students enrolled in anatomy programs. Additionally, the study aimed to examine potential associations between IS and various demographic and psychosocial variables, including age, gender, income level, marital status, and psychiatric history. By identifying subgroups more susceptible to impostor feelings, this study seeks to contribute to the broader understanding of how IS manifests within advanced medical education and inform future interventions aimed at enhancing academic and emotional resilience.

Material and Methods

This study was reviewed and approved for ethical compliance by the Scientific Research and Publication Ethics Committee of İstanbul Health and Technology University (decision number: 2025/03-01, date: 05.02.2025). This cross-sectional, anonymous online survey was conducted among randomly selected postgraduate anatomy students from various faculties across Türkiye. Participants were invited to participate via email. A web-based (Google form,) survey was conducted among postgraduate anatomy students (master's, doctoral, and medical specialization) in Türkiye in February 2025. There was no need to use a patient consent form.

Clance IP Scale

The survey, developed by Clance in 1985, is a unidimensional, 5-point Likert-type (1: Not at all true, 5: Definitely true) data collection tool consisting of 20 questions designed to assess individuals' tendencies toward the Impostor Phenomenon. Total scores on the CIPS range from 20 to 100, with a score of 60 or above signifying a strong experience of impostor feelings.The scores obtained as a result of the answers given to the scale were examined in 4 categories: scores less than 40 points show limited few impostor characteristics (FIC), scores between 41-60 show moderate impostor experiences (MIE), scores between 61-80 show frequently impostor feelings (FIF), and scores above 80 points show intense impostor experiences (IIE). According to the results of reliability analyses conducted in a doctoral thesis, the reliability coefficient of the Clance Impostor Phenomenon Scale (n=148) was found to be 0.84 (15). This value supports the previous research showing that the scale is a reliable data collection tool (16).

The survey also consisted of psychiatric conditions and demographic questions, including age, gender, income status, education status, and marital status.

Statistical Analysis

The statistical methods employed in this study included Crosstabulation Analysis, the chi-square test, the Monte Carlo simulation, and the Fisher's exact test. Crosstabulation was used to examine the distribution of categorical variables, such as age, gender, marital status, income level, educational status, and psychiatric diagnosis, in relation to IS levels. The chi-square test was applied to identify associations between these variables and impostor levels. However, due to the presence of small expected cell frequencies that violated the assumptions of the chi-square test, Monte Carlo simulations, and Fisher's exact test were utilized as alternative methods to ensure the robustness of the results. Monte Carlo simulation generated p-values and confidence intervals through iterative computations, enhancing the reliability of the statistical analysis. Fisher's exact test provided additional support, particularly in cases where sample sizes were small.

In this study, the process of creating graphs and tables from the dataset was supported by utilizing Chat GPT-4, an advanced AI tool.

Results

Demographic and IS Characteristics

The study included 79 postgraduate students: IS levels were distributed as FIC (21.5%, n=17), MIE (39.2%, n=31), FIF (32.9%, n=26), and IIE (6.3%, n=5). Gender distribution was nearly balanced, with 50.6% (n=40) male and 49.4% (n=39) female participants. Regarding income status, the majority of participants were state university or government

employees (60.8%, n=48), followed by individuals in private employment (19.0%, n=15), those with no income (11.4%, n=9), participants receiving scholarships (3.8%, n=3), and others with different income sources (5.1%, n=4). Educational status showed that 22.8% (n=18) were master's students, 30.4% (n=24) were PhD students, and 46.8% (n=37) were medical specialization students. Psychiatric status data indicated that most participants had no psychiatric issues (78.5%, n=62), while 21.5% (n=17) reported having psychiatric conditions. The age distribution highlighted the largest group as those aged 26–30 years (48.1%, n=38), followed by 18-25 years (17.7%, n=14), over 35 years (17.7%, n=14), and 31–35 years (16.5%, n=13). In terms of marital status, 54.4% (n=43) were single, while 45.6% (n=36) were married (Table 1).

The Relationship Between IS and Psychiatric Diagnosis

The crosstabulation analysis revealed notable differences in the distribution of IS levels between participants with and without psychiatric issues. Among those without psychiatric issues, the proportions were FIC (25.8%), MIE (46.8%), FIF (24.2%), and IIE (3.2%). In contrast, participants with psychiatric issues exhibited distributions of FIC (5.9%), MIE (11.8%), FIF (64.7%), and IIE (17.6%). Statistical analyses confirmed a significant association between psychiatric status and IS levels ($p<0.05$) (Figure 1).

Variables such as age, gender, marital status, income level, and educational attainment were not found to have a significant effect on impostor level ($p>0.05$). However, individuals with no income demonstrated a higher representation in the IIE category (22.2%).

Discussion

IS, also referred to as the impostor phenomenon, is not a recent concept. Still, it has attracted the attention of researchers in recent years, as it greatly reduces the working performance of individuals and the efficiency of departments and institutions (9,17). In this study, we

Table 1. Descriptive statistics for participant demographics and characteristics

Variable	Group	Valid (n)	Percentage (%)
Income status	State university/government employee	48	60.8
	Private	15	19.0
	No income	9	11.4
	Receiving scholarship	3	3.8
	Other	4	5.1
Impostor level	FIC	17	21.5
	MIE	31	39.2
	FIF	26	32.9
	IE	5	6.3
Education status	Master's student	18	22.8
	PhD student	24	30.4
	Medical specialization student	37	46.8
Psychiatric status	No psychiatric issue	62	78.5
	Has psychiatric issue	17	21.5
Age group	18-25	14	17.7
	26-30	38	48.1
	31-35	13	16.5
	Over 35	14	17.7
Gender	Male	40	50.6
	Female	39	49.4
Marital status	Single	43	54.4
	Married	36	45.6

FIC: Few impostor characteristics, MIE: Moderate impostor experiences, FIF: Frequently impostor feelings, IIE: Intense impostor experiences

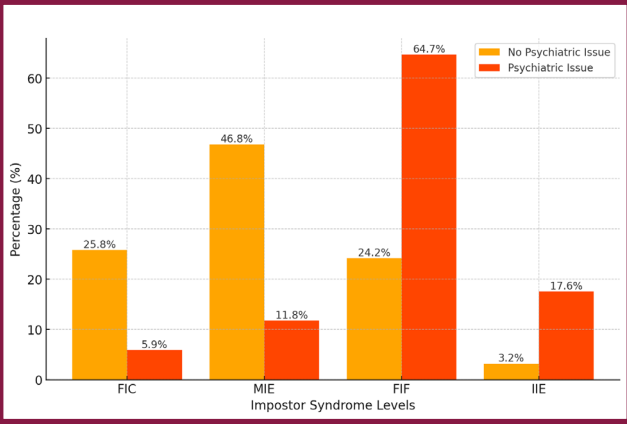


Figure 1. Distribution of impostor syndrome levels by psychiatric status ($p<0.05$)
FIC: Few Impostor characteristics; MIE: Moderate Impostor experiences; FIF: Frequently Impostor feelings; IIE: Intense impostor experiences

reported, for the first time, the prevalence of IS in students receiving postgraduate anatomy education in Türkiye. The number of studies on the prevalence of IS in individuals who teach and receive academic training is limited.

According to the results of this study, 39.2% of participants exhibited frequent impostor feelings and IEE. No previous study conducted among postgraduate students on anatomy that has contributed to the worldwide literature. Therefore, there is no comparable data. However, its prevalence has been reported in various countries among physicians who perform work and among medical, dental, and pharmacy students who undergo intensive training. In the study of Paladugu et al. (18) on hospitalists, the prevalence of IS was reported as 34 percent. In the study conducted by Beckman (19) the prevalence of frequent and intense IS experience among physicians was reported as 23 percent. Studies of U.S. medical students show that 20% to 50% of them have significant experience with IS (10,20,21). In a study conducted among postgraduate medical and surgical doctors in Sri Lanka, the proportion of individuals exhibiting frequent impostor feelings and IEE was reported to be 39.3% (22). Considering the impostor scale score results, the number of students receiving postgraduate anatomy education who show frequently impostor feelings and IEE is aligned with the data reported in global literature.

The study conducted by Shanafelt et al. (23) reported that physicians have a higher rate of disappointment because they require high intellectual knowledge. Since academics who receive postgraduate education also have a high intellectual knowledge requirement, they can be evaluated among similar groups. Since the academic community is a field that requires serious knowledge and skills in addition to professionalism, it is not surprising that these people are perfectionists and have unrealistic expectations. As a result of this condition, individuals often become trapped in a self-reinforcing behavioral pattern known as the impostor cycle. Within this cycle, perfectionist individuals tend to overwork and prepare excessively for tasks. Despite achieving success, they experience only a fleeting sense of confidence, which quickly dissipates as they attribute their accomplishments not to their abilities but to their hard work and effort. Consequently, they come to believe that they are frauds and live in fear that this will eventually be exposed. This fear compels them to maintain their perfectionistic tendencies and overwork patterns in an effort to avoid such perceived exposure. This cycle persists and perpetuates itself, reinforcing the feelings of inadequacy characteristic of IS (24).

The current study revealed a statistically significant relationship, indicating that individuals with psychiatric disorders exhibited higher levels of impostor feelings, with 64.7% classified in the FIF category and 17.6% in the IIE category. In contrast, individuals without psychiatric disorders predominantly demonstrated lower levels of impostor feelings, categorized as FIC and MIE. These findings suggest a strong association between psychiatric conditions and the severity of impostor experiences. In line with these findings, Shanafelt et al. (23) reported that impostor phenomenon scores correlated with burnout syndrome's emotional and depersonalization domains but were inversely correlated with professional satisfaction. Numerous studies have identified a significant correlation between IS and various psychological and emotional challenges, including anxiety, depression, burnout, and related forms of distress (10,25,26).

When examined in terms of demographic characteristics, no significant relationship was established between the IS and gender in this study. This finding is inconsistent with studies showing that women are more likely to suffer from the IS (21,27,28) and supports previous studies in which the gender variable was insignificant (29,30). Although some past studies have reported that women are more prone to IS, this finding has not been consistent across all professions and settings. A recent systematic review found that comparing genders IS, 16 reported a predisposition in women, while 17 reported no susceptibility (9). This result indicates that the IS is not an individual tendency based on biological sex, that women will be more prone to. Although women have a more active, constructive approach based on social support, men have a less constructive and avoidant approach (31,32). The influence of IS and the associated adaptation strategies on gender differences requires further investigation.

In contrast to our initial hypothesis, the analysis revealed no statistically significant associations between the IS and general demographic characteristics. However, it is noteworthy that individuals with no income exhibited a higher representation in the IIE category. A study by MacInnis et al. (33) offers corroborative evidence, demonstrating that individuals from lower socioeconomic backgrounds exhibit significantly elevated levels of impostor feelings. This finding warrants further investigation and suggests that studies conducted with larger sample sizes may yield more accurate and reliable results.

Study Limitations

The present study has several limitations, including a limited sample size. However, the study group in our research is limited to postgraduate students specializing in anatomy, resulting in a relatively small sample size. In addition, administering the Clance IP scale to participants once instead of twice may reduce test reliability. Furthermore,while the present study focused on the categorical classification of IS levels, we acknowledge that analyzing mean total CIPS scores across subgroups (such as income or educational status) might have offered further insights. Future studies with larger and more diverse samples could explore such score-based comparisons using parametric or non-parametric methods to enhance the depth of analysis. Despite its limitations, this study offers an initial insight into the prevalence and severity of IS and the sociodemographic characteristics associated with it among graduate students in the anatomy field in Türkiye.

Conclusion

According to the data obtained in this study and findings from similar studies conducted on comparable professional groups worldwide, IS appears to be highly prevalent. Furthermore, as this syndrome frequently co-occurs with various psychiatric issues, it is imperative to raise awareness, particularly in highly demanding, perfectionism-oriented professions such as academia. Increased attention to IS in such high-stress fields can foster better recognition and address its impact more effectively.

Ethics

Ethics Committee Approval: This study was reviewed and approved for ethical compliance by the Scientific Research and Publication Ethics Committee of İstanbul Health and Technology University (decision number: 2025/03-01, date: 05.02.2025).

Informed Consent: There was no need to use a patient consent form.

Footnotes

Authorship Contributions

Concept: F.O., Design: F.O., G.N.C., Data Collection or Processing: F.O., F.T.K., M.Y., Analysis or Interpretation: F.T.K., Literature Search: F.O., Writing: F.O., B.K.

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

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

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ORIGINAL ARTICLE

DOI: 10.4274/hamidiyemedj.galenos.2025.32559

Hamidiye Med J 2025;6(2):92-101

Investigation of the Number of International Passengers at Türkiye Airports During the First Year of the COVID-19 Pandemic from a Public Health Perspective

COVID-19 Pandemisinin İlk Yılında Türkiye Havalimanlarındaki Dış Hat Yolcu Sayısının Halk Sağlığı Bakış Açısıyla İncelenmesi

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ABSTRACT

Background: Our study aims to contribute to the literature by examining the change in the number of coronavirus disease-2019 (COVID-19) cases between 1 January 2020 and 31 December 2020 and the reflection of the health measures taken by and health and aviation authorities on the number of international passengers at Türkiye airports from a public health perspective.

Materials and Methods: This cross-sectional study was conducted using secondary data obtained from national health and aviation authorities. The data were analyzed using time series analysis methods with the SPSS 25 software package, along with descriptive statistics in Excel 2013. The findings were presented in tables and figures.

Results: In 2020, the total number of international passengers at 56 airports open to civil air traffic in Türkiye decreased by 71% compared to 2019, with the sharpest decline, nearly 100%, occurring in the second quarter of the year. The time series analysis did not identify any evidence of a trend effect in the data. Monthly variations in international passenger numbers were determined to be non-random. Additionally, the breakpoints observed in the time series graph aligned with the implementation dates of international travel measures introduced in response to the COVID-19 pandemic.

Conclusion: It was found that the increase in the number of cases in the early stages of the COVID-19 pandemic directly increased the public health measures taken at airports in the context of international travel and caused a significant decrease in the number of international passengers. It is recommended that public health measures and travel restrictions taken in prolonged epidemic situations implemented by conducting a multidimensional risk assessment.

Keywords: Airport, COVID-19, international passengers, international travel restrictions, public health, Türkiye

ÖZ

Amaç: Çalışmamız, 1 Ocak 2020 ile 31 Aralık 2020 tarihleri arasında koronavirüs hastalığı-2019 (COVID-19) olgu sayılarındaki değişimi ve sağlık ve havacılık otoriteleri tarafından alınan sağlık tedbirlerinin Türkiye havalimanlarındaki dış hat yolcu sayılarına yansımasını halk sağlığı perspektifinden inceleyerek literatüre katkı sağlamayı amaçlamaktadır.

Gereç ve Yöntemler: Bu araştırma kesitsel tipte yapılmıştır. Araştırmada, ulusal sağlık ve havacılık yetkili otoritelerinden elde edilen ikincil veri kaynaklarından yararlanılmıştır. Veriler, SPSS 25 paket programı kullanılarak zaman serisi analizi yöntemleri ve Excel 2013 programında tanımlayıcı istatistik düzeyinde değerlendirilerek tablo ve şekillerle gösterilmiştir.

Bulgular: Türkiye'de sivil hava trafiğine açık 56 havalimanının 2020 yılındaki toplam dış hat yolcu sayısı 2019 yılına göre %71 azalış göstermiş olup, en keskin düşüş %100'e yakın seyreden yılın ikinci çeyreğinde yaşanmıştır. Zaman serisi analizinde seride trend etkisine ilişkin bir kanıt elde edilememiştir. Aylık dış hat yolcu sayılarındaki değişimin rassal olmadığı tespit edilmiştir. Zaman

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Received: 28.01.2025 **Accepted:** 04.06.2025 **Publication Date:** 04.07.2025

Cite this article as: Tekin Z, Bektemür G. Investigation of the number of international passengers at Türkiye airports during the first year of the COVID-19 pandemic from a public health perspective. Hamidiye Med J. 2025;6(2):92-101

***This article is produced from the Master's thesis titled "INVESTIGATION OF HEALTH MEASURES TAKEN AGAINST The COVID-19 PANDEMIC AT AIRPORTS IN TURKEY IN 2020" prepared by researcher Züleyha TEKİN under the supervision of Prof. Dr. Güven BEKTEMÜR.**

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ÖZ

serisi grafiğindeki kırılma noktalarının, COVID-19 pandemisi sebebiyle uluslararası seyahate yönelik getirilen tedbirlerin tarihleriyle uyumlu olduğu bulgusuna ulaşıldı.

Sonuç: COVID-19 pandemisinin erken dönemlerinde olgu sayısı artışının uluslararası seyahat bağlamında havalimanlarında alınan halk sağlığı tedbirlerini direkt olarak artırdığı ve dış hat yolcu sayısında ciddi düşüşlere neden olduğu saptanmıştır. Uzamış salgın durumlarında alınan halk sağlığı tedbirlerinin ve seyahat kısıtlamalarının çok boyutlu risk değerlendirmesi yapılarak uygulanması önerilir.

Anahtar Kelimeler: Havalimanı, COVID-19, uluslararası yolcular, uluslararası seyahat kısıtlamaları, halk sağlığı, Türkiye

Introduction

Throughout human history, epidemics such as, plague, measles, smallpox, and others that caused mass deaths have caused serious material and moral losses in various fields, especially social, economic, cultural, and political, to civilizations. Today, epidemics have the potential to move and spread much faster with the development of air transportation, the increase in global passenger-freight transportation, and extraordinary human mobility (1,2). In other words, the international air transportation network, which is an important component of globalization, may also have the effect of accelerating the development and spread of potential epidemics.

On December 31, 2019, cases of pneumonia of unknown cause were reported in Wuhan, Hubei province, of China. On January 7, 2020, the causative agent was identified as a new coronavirus (2019-nCoV) that had not been detected in humans before, and the disease was later named coronavirus disease-2019 (COVID-19). The virus with close similarities to severe acute respiratory syndrome-coronavirus (SARS-CoV) was named SARS-CoV-2. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic (3).

While the risk of the spread of epidemics through air transportation and the threat this risk poses to global health is known, the COVID-19 pandemic in 2020 has once again underscored this threat by amplifying its global impact. The COVID-19 pandemic has been the most vivid example of how air transportation affects epidemics and epidemics affect air transportation, bidirectionally.

In the early days of 2020, many countries took the first measures against the pandemic in the aviation sector because the COVID-19 disease, which contains many unknowns, is transmitted by droplet and that many passengers are together in airports and aircraft cabins (4). To prevent the entry of the virus into the country and/or to reduce its spread, measures that started in the aviation sector, where human mobility is the highest, sometimes aligning with the WHO's recommendations and sometimes not, have rapidly spread to cover all public areas. Countries have implemented a series of health measures for travelers both domestically and in the context of international travel, including air transportation (5-7). The main public health measures taken, such as reciprocal or non-reciprocal border closures, flight suspension, travel restrictions, entry-exit health screenings, health declarations, quarantine and isolation practices, testing practices such as polymerase chain reaction (PCR)/antigen testing, contact tracing, mask, social distancing, hygiene, have been adjusted according to additional measures in line with the course of the outbreak (5,8). As of January 7, 2021, within the first year of SARS-CoV-2 identification, a total of 87,198,403 confirmed cases and 1,953,783 deaths were reported worldwide (9).

The International Health Regulations (10), to which Türkiye is also a party, require each state party to develop basic public health capacities for both routine operations and public health emergencies at designated points of entry (PoE) (airports, ports, land crossings), using existing national structures and resources. In Türkiye, five international airports have been designated as PoE that fulfill the required capacities. These airports, where the specified capacity requirements are implemented and maintained, include Adnan Menderes, Antalya, Esenboğa, İstanbul, and Sabiha Gökçen Airports (11).

In the context of international travels, airports, which are the windows of countries to the outside world by allowing people from many continents and countries who prefer air transportation to share the same environment for a certain period of time, are special areas that can directly affect global health in terms of the spread and control of infectious diseases. However, the successful continuation of preventive health services provided to the public within the country is undoubtedly closely related to the health conditions and health measures taken at airports where international passenger mobility is most intense.

The literature review reveals that studies on COVID-19 pandemic measures at Türkiye, airports are primarily focused on the social, economic, and management aspects within the aviation sector. However, there is a notable gap in addressing

the issue from a public health perspective. Our study aims to contribute to the literature by examining the change in the number of COVID-19 cases between 1 January 2020, and 31 December 2020; and the reflection of the health measures taken by health and aviation authorities on the number of international passengers (arrivals and departures) at Türkiye airports, from a public health perspective.

Materials and Methods

The research is a cross-sectional study as it deals with a certain period of time and a descriptive study because it endeavours to explain the existence of a certain phenomenon. Our study focuses on the number of international passengers (arrival and departure) at 56 airports open to civil air traffic in Türkiye and the national number of COVID-19 cases between 1 January 2020 and 31 December 2020.

The study excludes data on direct transit passengers and domestic passengers. The aim here is to see the change in international passenger numbers in relation to travel restrictions imposed as part of national public health interventions during pandemic periods in 2020, including international passenger numbers in 2018-2019.

Data Sources

The data used in this study include international passenger numbers obtained from the website of the General Directorate of State Airports Authority and confirmed COVID-19 case numbers published by the Ministry of Health on its COVID-19 information platform.

Furthermore, NOTAMs related to COVID-19, issued by the Directorate General of Civil Aviation, were obtained from the relevant institution, reviewed, and utilized as a data source. Notice to Airmen (NOTAM) is defined as "a broadcast made to promptly inform flight operations personnel about any aviation facility, service, method, or the presence, conditions, or changes of a hazard." NOTAMs were reviewed for health measures for passengers, and international travel restriction information during the COVID-19 pandemic.

The necessary approvals for conducting the research were obtained from the Non-Interventional Research Ethics Committee of Hamidiye University of Health Sciences (approval number: 2021/29, dated: 17/09/2021).

Statistical Analysis

Descriptive statistics were used to summarize monthly international passenger volumes and COVID-19 case numbers. Time series analysis was conducted using Kwiatkowski Phillips Schmidt and Shin test (KPSS) and Augmented Dickey Fuller (ADF) unit root tests to assess stationarity. Autocorrelation and partial autocorrelation functions were plotted to evaluate temporal dependency. These data were transferred to the Microsoft Office Excel 2013 program, analyzed using descriptive statistics, and presented in tables and figures. Additionally, international passenger numbers were analyzed using time series analysis methods after being imported into the Statistical Package for the Social Sciences (SPSS) for Windows (version: 25.0; Armonk, NY: IBM Corp., USA), with the analysis results presented in detail through tables and figures.

Results

Descriptive Findings on Total the Number of International Passengers at Airports

The international passenger numbers for the pre-COVID-19 period (2018-2019) and the COVID-19 pandemic period (2020) has been compiled based on data publicly shared by the General Directorate of State Airports Authority on a monthly basis. Monthly and yearly variations in the total number of international passengers at Türkiye airports are presented in Table 1, while the total number of international passengers specific to individual Türkiye airports is shown in Table 2.

Table 1 shows that the total number of international passengers was 97,587,056 in 2018 and 108,427,124 in 2019, while in 2020, it dropped to 31,875,837. In 2020, the total number of international passengers carried decreased by 71% compared to 2019. The highest decline occurred in the second quarter of 2020, with a nearly 100% reduction. In 2018 and 2019, the international passenger numbers decreased by 55% and 57%, respectively, in December compared to August, the month with the highest number of international passengers. In 2020, international passenger numbers decreased by 56% in December compared to the peak month of September.

Table 2 shows that in 2020, İstanbul Airport represented 50% of the total percentage of international passengers, followed by Antalya Airport with 21%, İstanbul Sabiha Gökçen Airport with 16%, İzmir Adnan Menderes Airport with 3%, Muğla Dalaman Airport with 3%, and other airports, accounting for 7%.

In 2020, 54% of the total number of international passengers at designated PoE (comprising five airports) were at İstanbul Airport, followed by Antalya Airport with 22%, İstanbul Sabiha Gökçen Airport with 18%, İzmir Adnan Menderes Airport with 3%, and Ankara Esenboğa Airport with 3%.

Findings on Time Series of Total International Passenger Numbers at Airports

As a result of KPSS and ADF unit root tests conducted to examine the stationarity of the series in time series, it was found that the series was not stationary (pKPSS: 0.016;

pADF: 0.456; p<0.05). Additionally, in the time series graph in Figure 1, there is no evidence of a trend effect. The lack of stationarity suggests a high degree of correlation. Table 3 shows the autocorrelation results between the lag values of the series; Figure 2 shows the autocorrelation graph and Figure 3 shows the partial autocorrelation graph. It was found that the changes in monthly international passenger numbers are not random.

In the time series graph of international passenger numbers for the year 2020 shown in Figure 4, several breakpoints are worth noting. Based on the NOTAM reviews published during the COVID-19 pandemic (Table 4), the breakpoints in the time series graph align with the dates when international travel measures were introduced.

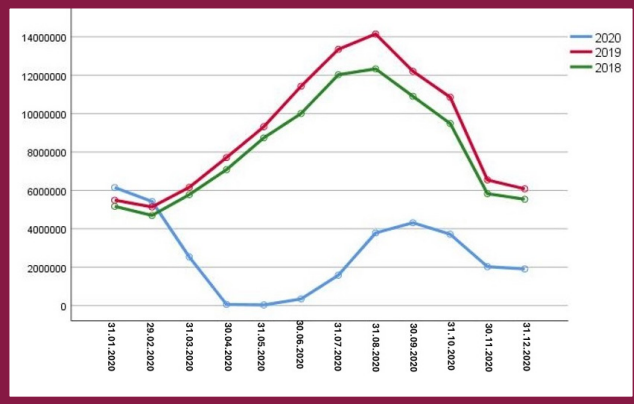


Figure 1. Time series graph of the number of international passengers for the years (2018, 2019 and 2020)

Table 1. Monthly and yearly changes in the total number of international passengers at Türkiye airports

Months	Years				Years			
	2018	2019	Change	Change (%)	2019	2020	Change	Change (%)
January	5.169.937	5.489.751	319.814	6,19%	5.489.751	6.150.060	660.309	12.03%
February	4.695.638	5.137.969	442.331	9,42%	5.137.969	5.424.274	286.305	5.57%
March	5.778.644	6.160.367	381.723	6,61%	6.160.367	2.535.235	-3.625.132	-58.85%
April	7.083.650	7.711.442	627.792	8,86%	7.711.442	60.163	-7.651.279	-99.22%
May	8.737.437	9.316.809	579.372	6,63%	9.316.809	32.782	-9.284.027	-99.65%
June	10.007.807	11.427.985	1.420.178	14,19%	11.427.985	344.152	-11.083.833	-96.99%
July	12.026.182	13.349.825	1.323.643	11,01%	13.349.825	1.582.720	-11.767.105	-88.14%
August	12.332.042	14.150.587	1.818.545	14,75%	14.150.587	3.783.054	-10.367.533	-73.27%
September	10.903.327	12.204.381	1.301.054	11,93%	12.204.381	4.313.672	-7.890.709	-64.65%
October	9.487.068	10.855.875	1.368.807	14,43%	10.855.875	3.717.626	-7.138.249	-65.75%
November	5.828.225	6.544.396	716.171	12,29%	6.544.396	2.024.275	-4.520.121	-69.07%
December	5.537.099	6.077.737	540.638	9,76%	6.077.737	1.907.824	-4.169.913	-68.61%
Total	**97.587.056**	**108.427.124**	**10.840.068**	**11,11%**	**108.427.124**	**31.875.837**	**-76.551.287**	**-70,60%**

Table 2. Number of international passengers by year for Türkiye airports

No.	Airport name	2018		2019		2020	
		Number of passengers (n)	Percent (%)	Number of passengers (n)	Percent (%)	Number of passengers (n)	Percent (%)
1	Atatürk	49.130.261	50.35	11.876.601	10.95	0	0
2	İstanbul	30.199	0.03	39.434.579	36.37	15.936.505	50
3	Sabiha Gökçen	11.619.569	11.91	14.055.522	12.96	5.263.612	16.51
4	Esenboğa	2.241.901	2.3	2.277.395	2.1	746.764	2.34
5	Adnan Menderes	2.730.772	2.8	3.333.332	3.07	995.334	3.12
6	Antalya	24.127.993	24.72	28.720.491	26.49	6.584.984	20.66
7	Dalaman	2.935.900	3.01	3.321.930	3.06	830.652	2.61
8	Others (49 airports)	4.770.461	4.88	5.407.274	5	1.499.986	4.76
Total (56 airports)		**97.587.056**	**100**	**108.427.124**	**100**	**31.875.837**	**100**

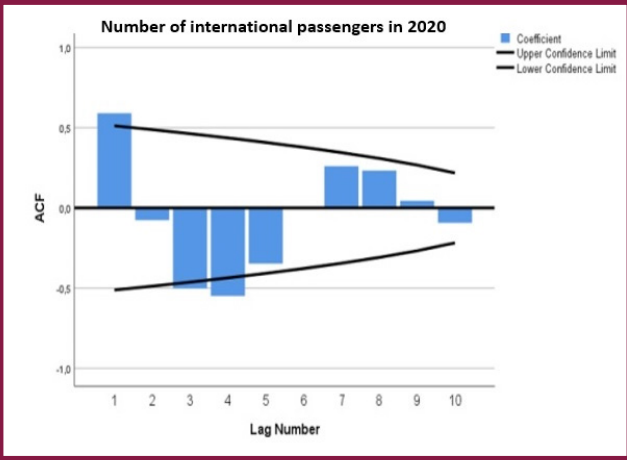


Figure 2. Autocorrelation graph

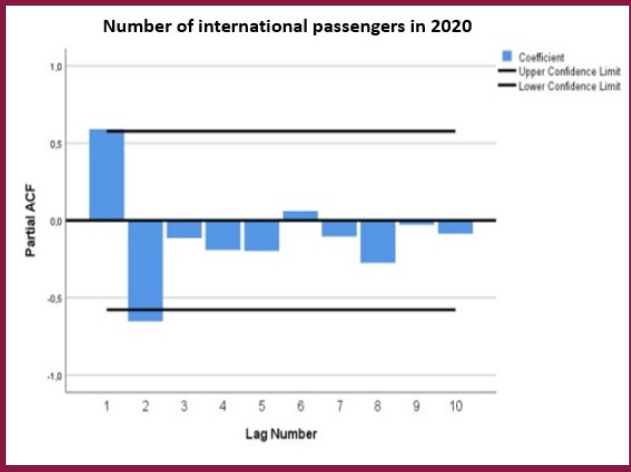


Figure 3. Partial autocorrelation graph

Table 3. Autocorrelation results

Lag	Autocorrelation	Standard error
1	0.591	0.256
2	-0.076	0.244
3	-0.502	0.231
4	-0.549	0.218
5	-0.347	0.204
6	-0.004	0.189
7	0.26	0.173
8	0,233	0.154
9	0.044	0.134
10	-0.093	0.109

International Travel Restrictions and Related Health Measures in Airline Transport

A total of 36 NOTAMs related to COVID-19 were analyzed. Travel restrictions began on February 3, 2020, with the suspension of flights with China, and they changed throughout the year in response to the progression of the pandemic. In our research, these measures were categorized into five distinct time periods: "first flight restrictions to risky countries (February 3)", "complete suspension of international flights (March 27)", "gradual reopening of international flights (June 11)", "new flight restrictions to risky countries (December 21)", and 'PCR test requirement for passengers from all countries (December 30)'. These time periods are shown in Table 4.

Descriptive Findings on the Total Number of International Passengers and COVID-19 Cases at Airports

The changes in Türkiye's number of international air passengers and the number of COVID-19 cases in 2020, organized based on publicly available data shared by the General Directorate of State Airports Authority and the Ministry of Health (12,13) are shown in Figure 5.

Discussion

In Türkiye, during the COVID-19 pandemic, the majority of international passengers (93%) traveled through international airports where core capacity requirements are met during routine and internationally important public health events within the scope of The International Health Regulations (2005).

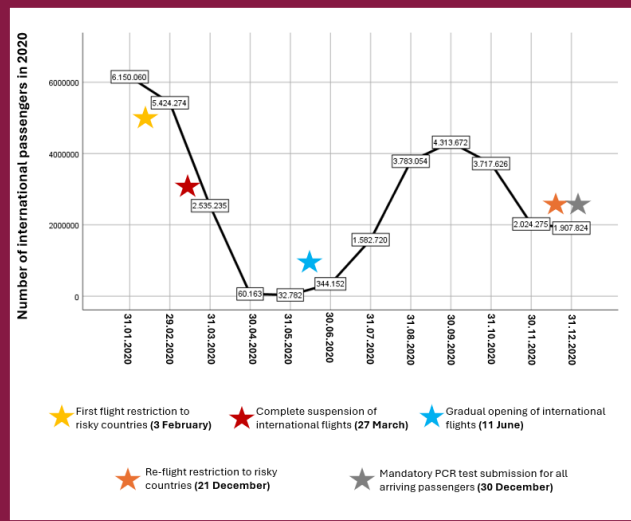


Figure 4. Time series graph of the number of international passengers in 2020

Table 4. International travel restrictions and related health measures in airline transport at Türkiye	
3 February 2020	**All flights from China have been stopped**
27 March 2020	**All flights from the airports of all countries to airports in Türkiye and from Türkiye to airports in all countries (except for the flights specified) are prohibited:** 1. Flights to repatriate Turkish citizens from restricted countries are subject to special authorization. All Turkish citizens on board the flight are quarantined for 14 days 2. The ban on flights to and from restricted countries does not apply to the following situations: 1) Cargo flights, 2) Government flights, 3) Emergency medicine flights, 4) Emergency landings for technical reasons
11 June 2020	**All flights to and from Türkiye airports are authorized and are subject to the following rules:** 1. All passengers must wear masks at airports and on aircraft 2. All passengers are required to fill in the passenger information form upon arrival on flights 3. All arriving passengers will be examined and those showing symptoms will be tested. This procedure will be announced to passengers by the airline before and during the flight 4. Passengers with positive test results will not be deported but will be treated 5. Flight permits for destination countries will be coordinated with the Ministry of Health 6. On all flights, airlines will comply with the rules outlined in the airline and airport pandemic guide published by the Directorate General of Civil Aviation
21 December 2020	**Flights from the United Kingdom, Denmark, and South Africa to Türkiye airports have been canceled. It is stated that the following conditions are valid:** 1. Unless special authorisation is granted for the carriage of Turkish citizens and persons residing in Türkiye, operators of the restricted countries may operate only transport flights from Türkiye carrying their own citizens of the operating country's nationality. 2. Turkish operators may carry only Turkish citizens, foreigners with residence permits, state officials and diplomatic personnel to Türkiye 3. Evacuation flights will be exempt from this restriction. All arriving passengers will undergo PCR testing upon arrival 4. Passengers who have been to the three countries mentioned above will be tested using PCR upon arrival. These passengers will be quarantined for 7 days starting from the date of arrival from these countries. On the 7th day, a second PCR test will be performed, and if the test result is negative, the quarantine will end 5. General aviation and business flights may be authorized, provided that they are coordinated with the Ministry of Health 6. Ambulance, humanitarian aid, and all cargo flights are exempt from these restrictions 7. There is no PCR test and quarantine requirement for the crew
30 December 2020	**It is stated that the following conditions are valid for flights to Türkiye:** 1. Passengers aged 6 years and older who will enter Türkiye by air from abroad are required to present negative SARS-CoV-2 PCR test results taken within 72 hours prior to departure of the aircraft 2. Those who do not submit a negative SARS-CoV-2 PCR test result will not be accepted for boarding. This requirement does not apply to transit and transfer passengers 3. This application will continue until March 1, 2021 4. There is no PCR test and quarantine requirement for crew members **Flights from the United Kingdom, Denmark and South Africa to Türkiye airports have been canceled. It is stated that the following conditions are valid:** 1. Unless special authorization is granted for the carriage of Turkish citizens and persons residing in Türkiye, operators of the restricted countries may only operate transport flights from Türkiye carrying their own citizens 2. Turkish operators may only carry Turkish citizens, foreigners with residence permits, government officials, diplomatic personnel, and transit/transfer passengers to Türkiye 3. Evacuation flights will be exempted from this restriction and passengers aged 6 years and older must present negative SARS-CoV-2 PCR test results taken within the last 72 hours prior to departure before boarding the aircraft. These passengers will be quarantined for 7 days. On the 7th day, the PCR test will be performed, and if the test result is negative, the quarantine will end 4. Passengers aged 6 years and older who have been in the three countries mentioned in the last 10 days must submit negative SARS-CoV-2 PCR test results which were performed within the last 72 hours before the departure of the aircraft, before boarding the aircraft. These passengers will be quarantined for 7 days. On the 7th day, the PCR test will be performed and if the test result is negative, the quarantine will end 5. General aviation and business flights may be permitted provided that coordination with the Ministry of Health 6. Ambulance, humanitarian aid and all cargo flights are exempt from these restrictions 7. There are no PCR test and quarantine requirement for the crew
PCR: Polymerase chain reaction, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus	

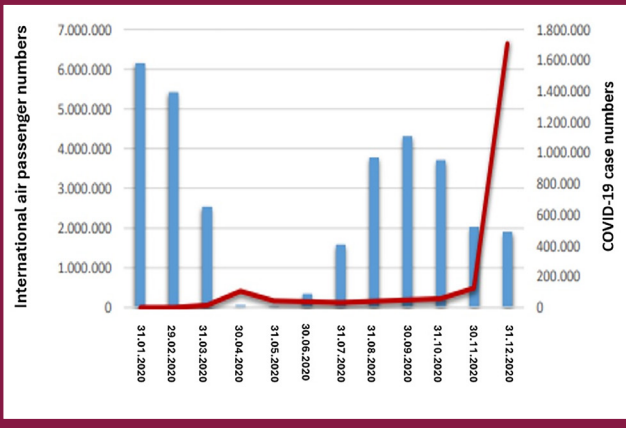


Figure 5. Changes in Türkiye's international air passenger numbers and COVID-19 case numbers in 2020
COVID-19: Coronavirus disease-2019

When comparing the international passenger numbers of these airports in 2020 to those in 2019, Antalya, Adnan Menderes, Esenboğa, Sabiha Gökçen, and İstanbul Airport saw decreases of 77%, 70%, 67%, 63%, and 60%, respectively (Table 2). Despite these declines, İstanbul Airport remained the busiest Türkiye airport for international passengers during the first year of the COVID-19 pandemic, as it was in 2019.

In 2020, the total number of international passengers decreased by 70.6% compared to 2019, while domestic passengers declined by 50.2%. Overall, the combined total of international and domestic passengers dropped by 60.8%. In Türkiye, the decline in passenger numbers in air transportation was significant throughout 2020, with international passenger numbers experiencing an almost complete drop-nearly 100%-in April, May, and June (Table 1). This decline is attributed to the COVID-19 measures, beginning with the cancellation of all flights from China on February 3, 2020 (14), followed by flight restrictions on other high-risk countries in March, and the suspension of all international flights on March 27, 2020, to curb the spread of the virus. The months of April and May, during which only evacuation flights were operated, marked the periods of the most significant decline (Figure 4 and Table 4). When the number of daily new cases during the same period is examined, the peak of the pandemic in this wave occurred on April 11, with 5,138 cases. A downward trend began thereafter, and on May 20, the number of cases dropped to triple digits for the first time, reaching 972 cases (14).

Following the announcement of the normalization roadmap in Türkiye on May 3, 2020, studies on the "new normal" steps began. The Coronavirus Scientific Advisory Board provided recommendations for the normalization plan and prepared guidelines for various sectors (14). As part of the "Controlled Social Life" steps initiated by Türkiye on June 1, 2020, and reflecting the gradual resumption of international flights on June 11, 2020 (15), the number of international passengers began to rise in the second half of the year and continued to increase until the end of the third quarter. The international passenger movement, driven by the revival of summer tourism activities in Türkiye, reflects this trend, with the number of international passengers exceeding 1.5 million in July. In August, the number of international passengers more than doubled compared to July, reaching 3,783,054. In the fourth quarter of the year, the decline in the number of international passengers, which had resumed, continued until year-end. This period, marked by growing concerns worldwide about the global spread of SARS-CoV-2 variants (16,17), coincided with a further decrease in the number of international passengers in Türkiye. As seen in the number of international passengers in 2018-2019 (Figure 1), the decline that began after August, and continued throughout the fourth quarter of the year, can be attributed to the end of the summer season and the decrease in tourism activities. In other words, the decrease observed in the fourth quarter of 2020 can be considered a seasonal decline, as expected (Table 1). Starting from the end of December, in this new period, when the number of cases both globally and nationally increased again, Türkiye introduced new regulations for all passengers coming from all countries, including those with observed variants, via airline transport (Table 4).

On January 10, 2020, when the WHO issued its first recommendations for international travel and trade (18), the first death due to the disease was reported in China (19). Before this announcement, the Coronavirus Scientific Advisory Board established by the Türkiye Ministry of Health and comprising 26 experts and academicians from various medical disciplines (14) played a crucial role in guiding the implementation of COVID-19 measures at airports. The airport pandemic certification circular (20), prepared based on the recommendations of the Scientific Advisory Board and implemented prior to the gradual reopening of flights, serves as the most concrete example of this particular emphasis. Similarly, when the International Health Regulations (2005) Emergency Committee first convened on January 22, 2020 (21), the Coronavirus Scientific Advisory Board of the Ministry of Health, which also convened on the same date, made recommendations for airport measures based on a risk assessment (22). In this context, it can be said that the decisions to implement infectious disease control measures for all flights arriving from China to screen passengers with thermal cameras upon arrival,

to require passenger information forms, and to inform ground personnel (22) contributed relatively positively to preventing or delaying the entry of the epidemic into the country. The lack of academic studies on the effects, results, and evaluations of health screenings and public health measures taken at Türkiye airports during past epidemics and pandemics, including the COVID-19 pandemic, does not allow for sufficient scientific clarification and discussion on the subject. More research is needed on these issues.

The range of health measures taken in the country was further expanded following the detection of the first COVID-19 case in Türkiye on 11 March 2020 and the WHO's declaration of a pandemic on that day (14,23). With the first COVID-19 case known to have acquired the virus through European contact, the number of new cases detected from people with international travel history and their contacts increased rapidly, and by March 18, 2020, the total number of confirmed cases in Türkiye had reached 191 (24). Following the declaration of a pandemic and the rapid increase in cases, various time-limited restrictions and measures were implemented to protect public health and manage social life. These measures included national and international travel restrictions, the suspension of in-person education with a shift to distance learning, bans on mass gatherings, curfews, and lockdowns, all aimed at preventing the local spread of the virus and reducing case numbers (14,23).

Bakırcı (25) assessed the "impact of the COVID-19 pandemic on Türkiye air transportation" by analyzing changes in airline passenger and cargo volumes between January and August 2020. In his study, he also highlighted the changes in passenger and cargo volumes during the SARS and Swine Flu outbreaks in the recent past. He concluded that the COVID-19 pandemic followed a significantly different trajectory compared to those of these epidemics, with far more drastic decline rates (25).

The travels of millions of people via national and international transportation networks due to the Lunar New Year holiday in China coincided with the beginning of the COVID-19 outbreak (26). This played a role in the increase in imported cases and the spread of the disease around the world, as predicted by the WHO in its travel advisories dated January 10 and January 24 (18,27). Considering that approximately 415 million people travelled during the Lunar New Year in 2019 (28), that Wuhan, identified as the origin of the outbreak serves as a major air and rail transportation hub in central China (26), that 13.5% of all outbound flights in Wuhan are international outbound flights (26), and that the disease is caused by a novel coronavirus previously undetected in humans (29) which raises many uncertainties, the significance of the outbreak in terms of the risk of international spread was clear from the outset.

Wu et al. (26) conducted a modeling study to estimate the potential local and international spread of the 2019-nCoV outbreak, which originated in Wuhan, China. Given that Beijing, Shanghai, Guangzhou, and Shenzhen account for 53% of all international air travel from China, the study indicated that a significant outbreak in these cities would contribute to the spread of 2019-nCoV both within and beyond mainland China. It also projected that countries outside China would be at risk of experiencing 2019-nCoV outbreaks during the first half of 2020 (26). The predominance of air travel as the primary mode of international transportation within mainland China has been a key factor in facilitating the global spread of COVID-19 (30).

The disease continued to spread rapidly worldwide, with the global cumulative number of cases reaching 798,396 in March and 3,110,429 in April (9). The flight restrictions imposed by countries one after another as part of international travel measures (8) indicate that health measures implemented in air transportation continue to intensify. Although countries that began implementing different policies regarding public health measures on international travel and social life in the second half of the year attempted to ease various strict measures introduced after the declaration of the pandemic, the ongoing increase in the number of global cases generally led to these measures being tightened again throughout the year (5,8,9). The B.1.1.7 variant (Alpha), which emerged in the UK in December, was reported to have first appeared in the second half of September and spread rapidly despite strict lockdown measures (16). Similarly, the B.1.351 variant (Beta), which became dominant in South Africa in early December, drew attention due to its increased transmission rate. SARS-CoV-2 variants have heightened concerns about global public health by accelerating the pandemic and altering the current epidemiological situation (16,17). In particular, the rapid increase in cases from November to December, resembling a snowball in growth, led countries to introduce new regulations for international travel, especially to countries where the variant had been detected (5,8,9,16). During the 2020 COVID-19 pandemic, the number of global airline passengers experienced significant declines due to international travel restrictions (31), while the number of global COVID-19 cases continued to rise (9). In other words, travel restrictions alone were not effective in reducing the number of COVID-19 cases. This situation highlights the importance of adopting a risk-based and multi-layered approach to public health measures in aviation as a key strategy in combating epidemics (32).

Lau et al. (30) in their study on "the association between international and domestic air traffic and the COVID-19 outbreak", found that there was a direct relationship between the number of passengers between mainland China and international destinations and the number of COVID-19 cases diagnosed outside China (30). Additionally, it was stated that the number of flight routes and total passenger volume were significant risk factors in the spread of COVID-19 (30). Oztig and Askin (33), in their study involving 144 countries, found that countries with higher volumes of airline passenger traffic and more airports were associated with more COVID-19 cases. Due to the limitations mentioned in our study, we cannot provide a reliable explanation for the number of international passengers and the course of COVID-19 cases throughout the year (Figure 5).

In the COVID-19 data shared publicly by the Ministry of Health there are some differences in the definition and representation of patient and case (symptomatic-asymptomatic) categories in the daily coronavirus table over time (13,34). Unfortunately, since these differences do not provide an accurate representation during the process of the course and development of the total number of cases, examining changes in the numbers of international passengers and cases constitutes a limitation of the study. Also, seasonality analysis could not be performed due to data limitations.

Conclusion

This study demonstrated a substantial decrease in the number of international air passengers at Türkiye's airports during 2020, coinciding with the implementation of international travel restrictions and public health measures in response to the COVID-19 pandemic. While this decline was expected, the analysis identified that key turning points in passenger volumes were temporally aligned with major regulatory actions, such as flight suspensions and testing requirements. However, it remains unclear to what extent these measures directly contributed to controlling the spread of the virus, due to the lack of case-based epidemiological data.

These findings underscore the need for future studies that integrate transportation data with robust epidemiological indicators to better assess the effectiveness of airport-based public health interventions. In prolonged outbreaks, public health strategies in the aviation sector should be guided by multidimensional risk assessments that incorporate not only infection rates but also mobility trends, behavioral responses, and international policy shifts. Strengthening data systems and analytic capacity at PoE will be essential for evidence-informed decision-making in future public health emergencies.

Ethics

Ethics Committee Approval: The necessary approvals for conducting the research were obtained from the Non-Interventional Research Ethics Committee of Hamidiye University of Health Sciences (approval number: 2021/29, dated: 17/09/2021).

Informed Consent: Not required.

Footnotes

Authorship Contributions

Concept: G.B., Design: G.B., Data Collection or Processing: G.B., Z.T., Analysis or Interpretation: G.B., Z.T., Literature Search: Z.T., Writing: Z.T.

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

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

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ORIGINAL ARTICLE

DOI: 10.4274/hamidiyemedj.galenos.2025.49369

Hamidiye Med J 2025;6(2):102-109

Evaluation of the Reliability, Utility, and Quality of the Pneumatic Retinopexy Videos on YouTube: Cross Sectional Study

YouTube'da Yer Alan Pnömatik Retinopeksi Videolarının Güvenilirlik, Fayda ve Kalitesinin Değerlendirilmesi: Kesitsel Çalışma

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ABSTRACT

Background: This study aimed to assess the quality, reliability, and educational value of pneumatic retinopexy (PR) videos on YouTube.

Materials and Methods: This retrospective, cross-sectional analysis evaluated the first 250 YouTube videos identified using the keyword "Pneumatic Retinopexy". Data collected included the number of views, likes, dislikes, video duration, content type (surgical or non-surgical), purpose, and upload source. Sources were categorized as healthcare professionals or patients. Video quality and educational value were assessed using the modified DISCERN (mDISCERN), Health on the Net Foundation (HONcode), Journal of the American Medical Association (JAMA), and Global Quality (GQ) scoring systems.

Results: Of the 250 videos screened, 194 were included. Median scores were 2 (range: 0-5) for mDISCERN, 2 (range: 0-8) for HONcode, 1 (range: 0-4) for JAMA, and 3 (range: 1-5) for GQ. Healthcare professionals uploaded 83.5% (n=162) of videos, while patients uploaded 16.5% (n=32). Videos uploaded by healthcare professionals received significantly higher quality ratings ($p<0.001$). Surgical content videos were longer and demonstrated higher quality scores compared to non-surgical videos ($p<0.05$). Correlation analysis revealed that higher numbers of views, daily view rates, and comments were positively associated with increased like rates.

Conclusion: This study demonstrates that the most reliable and educationally valuable PR videos on YouTube are primarily uploaded by healthcare professionals. Enhancing the availability of high-quality PR content on YouTube may significantly improve educational outcomes for both patients and healthcare providers.

Keywords: Pneumatic retinopexy, DISCERN score, Global Quality score, JAMA score, HONcode score, YouTube

ÖZ

Amaç: Bu çalışmanın amacı, YouTube platformunda bulunan pnömotik retinopeksi (PR) ile ilgili videoların kalitesini, güvenilirliğini ve eğitsel değerini değerlendirmektir.

Gereç ve Yöntemler: Bu retrospektif, kesitsel çalışma kapsamında, YouTube'da "Pnömotik retinopeksi"" anahtar kelimesi ile belirlenen ilk 250 video incelendi. Videoların izlenme sayısı, beğeni ve beğenmeme sayıları, video süresi, içerik türü (cerrahi veya cerrahi olmayan), amaç ve yükleme kaynağı gibi veriler kaydedildi. Video kaynakları sağlık profesyonelleri ve hastalar olarak kategorize edildi. Video kalitesi ve eğitsel değer, modifiye DISCERN (mDISCERN), Health on the Net Foundation (HONcode), Journal of the American Medical Association (JAMA) ve Global Quality (GQ) skor sistemleri kullanılarak değerlendirildi.

Bulgular: İncelenen 250 videodan 194'ü çalışmaya dahil edildi. Videoların medyan puanları mDISCERN için 2 (aralık: 0-5), HONcode için 2 (aralık: 0-8), JAMA için 1 (aralık: 0-4) ve GQ için 3 (aralık: 1-5) olarak belirlendi. Videoların %83,5'i (n=162) sağlık profesyonelleri tarafından, %16,5'i (n=32) ise hastalar tarafından yüklenmişti. Sağlık profesyonelleri tarafından yüklenen videolar anlamlı derecede daha yüksek kalite skorları aldı ($p<0,001$). Cerrahi içerikli videolar, cerrahi olmayan videolara kıyasla daha uzun süreliydi ve daha yüksek kalite puanlarına sahipti ($p<0,05$). Korelasyon analizi, daha yüksek izlenme sayısı, günlük izlenme oranı ve yorum sayısının artan beğeni oranları ile pozitif ilişkilendirildiğini ortaya koydu.

Sonuç: Bu çalışma, YouTube platformunda bulunan PR videolarından en güvenilir ve eğitsel açıdan değerli olanların büyük çoğunlukla sağlık profesyonelleri tarafından yüklendiğini göstermektedir. YouTube'da yüksek kaliteli PR içeriğinin artırılması, hem hastalar hem de sağlık profesyonelleri için eğitim sonuçlarını önemli ölçüde iyileştirebilir.

Anahtar Kelimeler: Pnömatik retinopeksi, DISCERN skoru, Küresel Kalite skoru, JAMA skoru, HONcode skoru, YouTube

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Received: 01.11.2024 **Accepted:** 05.06.2025 **Publication Date:** 04.07.2025

Cite this article as: Ermiş S, Özal E, Karapapak M, Uran M, Özal SA. Evaluation of the reliability, utility, and quality of the pneumatic retinopexy videos on YouTube: cross sectional study. Hamidiye Med J. 2025;6(2):102-109

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Introduction

Rhegmatogenous retinal detachment (RRD) is the most common type of retinal detachment (RD) and can lead to significant visual sequelae. Among procedures used to treat RRD, pneumatic retinopexy (PR) is unique in that it can be performed in an office setting rather than an operating room (1).

There are several clear advantages of PR, including faster visual recovery, avoidance of systemic anesthesia, reduced risk of cataract formation, and lower procedural costs (1-4). However, PR may not be appropriate for eyes with certain high-risk conditions, such as aphakia, extensive lattice degeneration, or proliferative vitreoretinopathy. Clinical studies have demonstrated that PR achieves anatomical outcomes comparable to pars plana vitrectomy, and it may be preferable in specific patient groups due to its lower morbidity. Although randomized clinical trials and medium-sized observational studies support PR as an effective treatment, further large-scale studies are necessary to confirm these findings (2,5-9).

In recent years, the internet has become an important source of medical information, with patients frequently utilizing it as a resource for obtaining health-related knowledge. YouTube currently ranks as the second most visited website worldwide (10). Usage of this platform continues to grow significantly, with an average of two billion active users per month and over one million videos uploaded daily (11). Medical videos on YouTube are frequently viewed, and approximately 80% of users discuss the information they acquire from these videos with their physicians (12). Moreover, 75% of patients report that YouTube videos influence their treatment decisions, particularly for chronic medical conditions (13). Despite these advantages, there are certain problematic aspects associated with the use of YouTube for medical information, such as patient-uploaded content, opinions shared without sufficient knowledge or expertise, promotional materials, inadequate information on contraindications, and complications, and the absence of a regulated review process (14).

Although YouTube hosts a substantial amount of content offering information on various medical conditions and their treatment methods, no study has yet evaluated videos specifically related to PR. Therefore, the aim of this study is to assess the reliability, quality, effectiveness, and utility of YouTube videos pertaining to PR.

Materials and Methods

This retrospective, record-based, cross-sectional study was conducted by searching YouTube (www.youtube.com) on 15 September 2023, using the keyword "Pneumatic Retinopexy". To ensure search accuracy, no personal YouTube or Google accounts were used, and both Google and computer caches were cleared. A total of 250 videos were initially analyzed. However, only videos uploaded in English were included and videos were evaluated only once. All videos were independently reviewed by two ophthalmologists (S.E., M.U.), and any discrepancies were resolved by a third ophthalmologist (M.K.). Since the data were collected from publicly accessible videos and no patient-specific data were involved, ethical approval from the local research ethics committee and patient consent were not required.

The study evaluated the following parameters: the number of views, video duration (minutes), age of the video (time until 15 September 2023), number of likes and dislikes, number of comments, and daily views, video type (with or without subtitles), content type (surgical vs non-surgical), purpose (clinical knowledge, treatment procedure, and postoperative period), and source (patients, doctors, hospital institutions, or commercial health channels). The exclusion criteria are summarized in Figure 1.

The quality and educational value of the videos were assessed using the Health on the Net Foundation (HONcode), modified DISCERN (mDISCERN), Journal of the American Medical Association (JAMA), and Global Quality (GQ) scoring systems. The HONcode was developed to enhance transparency and the trustworthiness of health information dissemination. Websites adhering to HONcode principles have been demonstrated to provide high-quality health information to users (15,16). In this study, video quality was evaluated based on the eight original HONcode

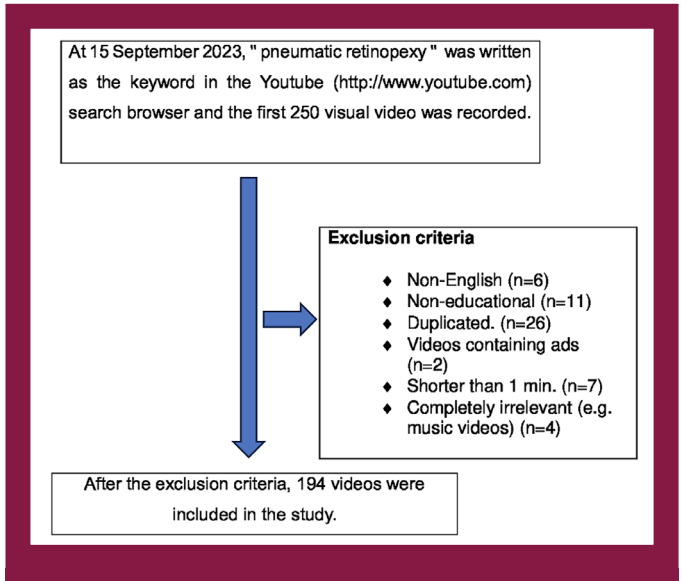


Figure 1. Exclusion criteria

principles, assigning each video a score of 1 for adherence and 0 for non-adherence, resulting in a total HONcode score. The JAMA scoring system was utilized to assess the reliability of video content (17). This widely used evaluation tool consists of four categories: authorship, attribution, disclosure, and currency, with each category scored as either 0 or 1, and a maximum score of 4 indicating the highest quality. The DISCERN instrument helps users evaluate the quality of written health information. In this study, video reliability and transparency were assessed using a modified five-point DISCERN scale (18), with scores ranging from 1 to 5 based on five criteria adapted from the original DISCERN questionnaire. Additionally, a GQ score was assigned to each video, rating overall quality on a five-point scale, with 1 representing poor quality and 5 representing excellent quality (Table 1) (19).

Statistical Analysis

In this study, continuous variables were expressed as mean ± standard deviation or median (minimum-maximum), while categorical variables were summarized using frequencies and percentages. The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Mann-Whitney U test was used for comparisons between two independent groups, whereas the Kruskal-Wallis H test was applied for comparisons involving three or more independent groups, depending on data distribution. Categorical variables were analyzed using Pearson's chi-square test, Fisher's exact chi-square test, or the Fisher-Freeman-Halton test, as appropriate. Relationships between variables were evaluated by Spearman correlation analysis. All statistical analyses were conducted using IBM SPSS Statistics (version 28). A confidence level of 95% was adopted, and p-values less than 0.05 were considered statistically significant.

Table 1. Assessment methods and scoring systems applied

A. Modified DISCERN (1 point for each yes, 0 points for each no)
Reliability of information
1. Are the aims clear and achieved? 2. Are reliable sources of information used (i.e., publication cited, speaker is board-certified ophthalmologist)? 3. Is the information presented balanced and unbiased? 4. Are additional sources of information listed for patient reference 5. Are areas of uncertainty mentioned?
B. HONcode score (1 point for each yes, 0 points for each no) number criteria
1. Any medical or health advice given in the video must come from a qualified health professional unless it is explicitly indicated that the information does not come from a qualified health source 2. The information provided in the videos must be designed to support the patient's self-management, but is not meant to replace a patient-physician relationship. 3. The information in the video respects and maintains the confidentiality of the individual patient featured 4. Each video references the source data of information presented or a specific HTML link 5. Each video containing claims on the benefits or performance of specific skills/behaviors, interventions, treatments, and products must be supported by evidence through references or HTML links 6. The video must provide the viewer with contact information or a website link to more information 7. Any individual or organization that contributes funds, services, or material, in the posted video must be clearly identified in the video or video description 8. If advertising provides funding for the video or the video's developers, it must be clearly stated. Included advertising must be clearly differentiable to the viewer: there should be a clear difference between the advertising material and the educational material in the video
C. JAMA Benchmark criteria (1 point for each yes, 0 points for each no)
1. Authorship: Authors and contributors, their affiliations, and relevant credentials should be provided 2. Attribution: References and sources for all content should be listed clearly, and all relevant copyright information should be noted 3. Disclosure: Website "ownership" should be prominently and fully disclosed, as should any sponsorship, advertising, underwriting, commercial funding arrangements or support, or potential conflicts of interest 4. Currency: Dates when content was posted and updated should be indicated
D. Global Quality Score
1. Poor quality, very unlikely to be of any use to patients 2. Poor quality but some information present, of very limited use to patients 3. Suboptimal flow, some information covered but important topics missing, somewhat useful to patients 4. Good quality and flow, most important topics covered, useful to patients 5. Excellent quality and flow, highly useful to patients
HONcode: Health on the Net Foundation, JAMA: Journal of the American Medical Association

Table 2. Descriptive statistics of Youtube videos

Variables		n=194
Duration (minutes)		9.4 (1.1-106.0)
Groups by mean duration	<5 minutes	52 (26.8)
	5-10 minutes	46 (23.7)
	>10 minutes	96 (49.5)
Likes		8 (0-2700)
Dislikes		0 (0-22)
Comments		0 (0-736)
Views		429 (0-322724)
View ratio (number of views per day)		0.8 (0-124.4)
Time since uploaded (days)		952 (5-5033)
Frequency of subtitle		34 (17.5)
Surgical content		154 (79.4)
Source uploader	Healthcare professionals	162 (83.5)
	Patients	32 (16.5)
mDISCERN score		2 (0-5)
HONcode total		2 (0-5)
JAMA score		1 (0-4)
GQ score		3 (0-5)

Categorical variables are presented as numbers and percentages (%), and continuous variables are presented as median (minimum-maximum) values
JAMA: Journal of the American Medical Association, mDISCERN: Modified DISCERN, GQ: Global Quality, HONcode: Health on the Net Foundation

Results

In this study, we identified a total of 250 YouTube videos meeting the specified inclusion criteria, of which 194 were included in the analysis. The median duration of these videos was 9.4 minutes, and 49.5% of them were longer than 10 minutes. Table 2 provides a descriptive summary of the characteristics of the 194 analyzed videos.

Table 3 compares video characteristics according to the detailed distribution of upload sources. Significant differences were observed between groups regarding the the number of comments, the video purpose, the surgical content, and all scoring metrics. Pairwise comparisons revealed statistically significant differences across all scoring metrics between videos uploaded by patients and those uploaded by physicians or hospital institutions.

Table 4 summarizes the comparative analysis of videos according to their content type. Notable differences were observed among groups regarding video length, number of comments, and all scoring parameters. Videos containing surgical content tended to have longer durations and demonstrated higher quality scores. Additionally, a positive and statistically significant correlation was identified between the number of likes and both the total number of views and the daily view ratio. Table 5 presents the correlation coefficients among all analyzed variables.

Discussion

The widespread use of YouTube, combined with the ease and free nature of video uploading, has made the platform a prominent resource for individuals seeking to share or access information. However, despite its potential benefits, YouTube can also facilitate the dissemination of inaccurate or potentially harmful information. For this reason, numerous studies in the field of ophthalmology have evaluated the reliability and quality of content available on YouTube (20-26). Kunze et al. (20) concluded that videos related to meniscus injuries were generally of poor quality and low reliability in their analysis of YouTube videos, using the keyword "Meniscus". In another study focusing on retinitis pigmentosa, only 31.5% of the videos were found to contain valuable and scientifically accurate information (22). Sahin et al. (23) similarly reported the presence of negative, contradictory, and misleading information in YouTube videos related to retinopathy of prematurity. As a consequence of such misinformation, some patients may refuse specific treatments, while others may have unrealistic expectations regarding treatment success rates.

Previous studies have employed various scoring systems to assess the accuracy and reliability of online videos. In our study, the median scores for mDISCERN, GQ score, JAMA, and HONcode were 2, 3, 1, and 2, respectively. Similar findings of low-quality scores have been reported in studies examining videos related to refractive and vitreoretinal surgeries, aligning closely with our results (27,28).

Our analysis revealed a significant discrepancy in the number of comments based on the source of the uploaded videos, with videos uploaded by patients receiving a higher number of responses (p=0.005). This may be attributed to viewers with similar medical conditions preferring to engage with and learn from the experiences of other patients, who typically communicate without complex medical terminology. Similar to our findings, previous research also indicates that videos uploaded by physicians, despite their higher reliability, tend to attract fewer views (29-31). The extensive scientific content, detailed explanations, and longer duration of physician-uploaded videos might contribute to their lower engagement rates, as indicated by fewer views and comments.

It has been established that videos uploaded by healthcare professionals are generally rated higher in terms of quality and reliability compared to those uploaded by patients. Additionally, patient-uploaded videos predominantly focus on postoperative experiences, whereas those uploaded

Table 3. Comparison of the data on videos on the upload source

Variables		Patients (n=32)	Ophthalmologist (n=122)	Private hospital advertisement (n=30)	Commercial health channel (n=10)	p-value
Duration (minutes)		9.2 (1.2-39.5)	10.4 (1.1-106)	14.1 (2.3-104.2)	4.3 (1.1-76.2)	0.291†
Groups by duration	<5 minutes	12 (37.5)	28 (23.0)	6 (20.0)	6 (60.0)	0.609††
	5-10 minutes	6 (18.8)	32 (26.2)	8 (26.7)	0 (0.0)	
	>10 minutes	14 (43.8)	62 (50.8)	16 (53.3)	4 (40.0)	
Likes		11 (0-926)	9 (0-2700)	4 (0-309)	7 (0-251)	0.922†
Dislikes		0 (0-6)	0 (0-22)	0 (0-12)	0 (0-0)	0.370†
Comments		1 (0-297)	0 (0-736)	0 (0-6)	0 (0-12)	**0.026**†,*
Time since upload date (days)		908 (281-4048)	1039 (5-5033)	692 (30-3348)	1131 (370-2133)	0.684†
Views		1145 (6-134142)	468 (0-322724)	329 (3-54573)	287 (67-16161)	0.880†
View ratio (number of views per day)		1.3 (0-120.4)	0.8 (0-124.4)	0.7 (0.1-29)	0.2 (0.1-43.7)	0.868†
Purpose	**Clinical information**	6 (18.8)	12 (9.8)	4 (13.3)	0 (0.0)	**<0.001**††,*
	Treatment	6 (18.8)	88 (72.1)	10 (33.3)	4 (40.0)	
	Clinical & treatment	4 (12.5)	16 (13.1)	14 (46.7)	4 (40.0)	
	Postoperative guidance	16 (50.0)	6 (4.9)	2 (6.7)	2 (20.0)	
mDISCERN score		1 (0-3)	3 (0-5)	2 (2-4)	1 (1-3)	**<0.001**†,*
HONcode total		1 (0-5)	2 (0-5)	3 (1-5)	2 (1-3)	**0.025**†,*
JAMA score		0.5 (0-1)	1 (0-4)	1 (1-2)	1 (0-2)	**<0.001**†,*
GQ score		3 (1-4)	4 (0-5)	3 (3-4)	2 (2-4)	**<0.001**†,*
Frequency of subtitle Positive	Negative	32 (100.0)	98 (80.3)	24 (80)	6 (60.0)	0.089††
	0 (0.0)	24 (19.7)	6 (20.0)	4 (40.0)		
Surgical content Positive	Negative	32 (100.0)	2 (1.6)	0 (0.0)	6 (60.0)	**<0.001**††,*
	0 (0.0)	120 (98.4)	30 (100.0)	4 (40.0)		

Categorical variables are presented as numbers and percentages (%), continuous variables are presented as median (minimum-maximum) values. †Kruskal-Wallis H test, ††Fisher-Freeman-Halton, *p<0.05
JAMA: Journal of the American Medical Association, mDISCERN: Modified DISCERN, GQ: Global Quality, HONcode: Health on the Net Foundation

Table 4. Comparison of videos surgical content and non-surgical content

Variables		Non-surgical content (n=40)	Surgical content (n=154)	p-value
Duration (minutes)		8.6 (1.1-39.5)	11.1 (1.1-106)	0.039*†
Groups by duration	<5 minutes	18 (45.0)	34 (22.1)	0.112††
	5-10 minutes	6 (15.0)	40 (26.0)	
	>10 minutes	16 (40.0)	80 (51.9)	
Likes		8 (0-926)	8 (0-2700)	0.508†
Dislikes		0 (0-6)	0 (0-22)	0.598†
Comments		0.5 (0-297)	0 (0-736)	0.008*†
Time since upload date (days)		908 (281-4048)	1020 (5-5033)	0.735†
Views		729 (6-134142)	429 (0-322724)	0.467†
View ratio (number of views per day)		0.6 (0-120.4)	0.7 (0-124.4)	0.662†
mDISCERN score		1 (0-3)	3 (0-5)	<0.001*
HONcode total		1 (0-5)	2 (0-5)	0.002*†
JAMA score		0 (0-1)	1 (0-4)	<0.001*†
GQ score		2.5 (1-4)	4 (0-5)	<0.001*†
Frequency of subtitle	Negative	36 (90.0)	124 (80.5)	0.263†††
	Positive	4 (10.0)	30 (19.5)	

Categorical variables are presented as numbers and percentages (%), continuous variables are presented as median (minimum-maximum) values. †Mann-Whitney U test, †† Fisher-Freeman-Halton, †††Fisher Exact test, *p<0.05
JAMA: Journal of th e American Medical Association, mDISCERN: Modified DISCERN, GQ: Global Quality, HONcode: Health on the Net Foundation

Table 5. Data on correlations between various aspects of the videos

		Duration (minutes)	Likes	Dislikes	Comments	Time since upload date (days)	Total views	View ratio (number of views per day)	HONcode total	JAMA score	mDISCERN score
Likes	r	-0.163	-								
	p	0.110	-								
Dislikes	r	-0.004	0.222	-							
	p	0.968	**0.029***	-							
Comments	r	-0.126	0.517	0.128	-						
	p	0.220	**<0.001***	0.210	-						
Time since upload date (days)	r	-0.129	0.305	-0.019	0.162	-					
	p	0.207	**0.002***	0.851	0.114	-					
Views	r	-0.204	0.889	0.151	0.476	0.497	-				
	p	**0.045***	**<0.001***	0.139	**<0.001***	<0.001*	-				
View ratio (number of views per day)	r	-0.202	0.882	0.178	0.455	0.165	0.901	-			
	p	**0.047***	**<0.001***	0.080	**<0.001***	0.106	**<0.001***	-			
HONcode total	r	0.196	0.082	0.050	0.010	0.129	0.122	0.080	-		
	p	0.054	0.422	0.626	0.926	0.210	0.235	0.434	-		
JAMA score	r	0.312	-0.006	-0.032	-0.220	0.037	0.014	0.003	0.735	-	
	p	**0.002***	0.954	0.754	**0.030***	0.720	0.895	0.976	**<0.001***	-	
mDISCERN score	r	0.416	-0.040	-0.012	-0.224	0.052	-0.033	-0.060	0.682	0.798	-
	p	**<0.001***	0.701	0.906	**0.027***	0.611	0.747	0.559	**<0.001***	**<0.001***	-
GQ score	r	0.341	0.067	0.017	-0.129	0.118	0.085	0.048	0.736	0.821	0.845
	p	**<0.001***	0.513	0.867	0.208	0.249	0.406	0.642	**<0.001***	**<0.001***	**<0.001***

*p<0.05. r: Spearman's rho correlation coefficient, JAMA: Journal of the American Medical Association, mDISCERN: Modified DISCERN, GQ: Global Quality, HONcode: Health on the Net Foundation

by physicians and other healthcare providers typically emphasize the treatment process itself. This difference may stem from the fact that patients commonly share videos to explain their motivations for undergoing surgery and offer recommendations for postoperative head positioning, while healthcare professionals' videos regarding PR typically adopt a more scientific approach, covering topics such as etiology, surgical techniques, treatment options, potential complications, and prognosis.

In our study, we identified a significant correlation between video length and both JAMA and GQ scores, which aligns with previous findings reported in the literature (32,33). Specifically, longer videos typically offered more comprehensive explanations regarding surgical techniques, clinical information, postoperative care, and potential complications, suggesting they might possess greater educational value.

The daily view count is widely considered a critical indicator for evaluating a video's relevance to current topics. Nevertheless, it has been proposed that integrating daily views with likes, dislikes, and comments may provide a more comprehensive and objective assessment (34). Our findings revealed a positive correlation between the daily view count and the total number of likes, dislikes, and comments, thus supporting this integrated assessment approach.

Study Limitations

This study has certain limitations that must be acknowledged. Firstly, the videos were evaluated at a single point in time. Given the dynamic nature of YouTube content, videos and the information they contain may evolve, potentially yielding different outcomes if assessed at a later date. Secondly, our analysis exclusively included English-language videos, which may limit the generalizability of

our results. However, English remains the predominant language used on the internet.

Conclusion

In conclusion, this study is the first in the literature to evaluate the quality, utility, and reliability of YouTube videos concerning PR. Our findings indicate that videos labeled "Pneumatic Retinopexy" on YouTube generally demonstrate low content quality and reliability. To enhance the reliability and educational value of these videos as sources of information, it is essential that all relevant procedural details be accurately presented by qualified healthcare professionals.

Ethics

Ethics Committee Approval: Since the data were collected from publicly accessible videos, ethical approval from the local research ethics committee was not required.

Informed Consent: Patient consent was not required as no patient-specific information was included.

Footnotes

Authorship Contributions

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

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

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

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ORIGINAL ARTICLE

DOI: 10.4274/hamidiyemedj.galenos.2025.18853

Hamidiye Med J 2025;6(2):110-118

Investigation of Virulence Factors by Phenotypic and Genotypic Methods and Evaluation of Their Relationship with Antibiotic Resistance in *Klebsiella pneumoniae* Strains Isolated from Clinical Specimens

Klinik Örneklerden İzole Edilen *Klebsiella pneumoniae* Suşlarında Virülans Faktörlerinin Fenotipik ve Genotipik Yöntemlerle Araştırılması ve Antibiyotik Direnci ile İlişkilerinin İncelenmesi

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ABSTRACT

Background: Infections caused by *Klebsiella pneumoniae (K. pneumoniae)*, have become a challenging health issue, especially with the emergence of extensively drug-resistant (XDR) strains. The widespread use of antibiotics to treat infections caused by *K. pneumoniae* has led to the development and spread of resistance to these drugs. This study aims to identify the virulence factors of *K. pneumoniae* isolates obtained from clinical specimens using phenotypic and genotypic methods and to examine their relationship with antimicrobial resistance.

Materials and Methods: A total of 100 *K. pneumoniae* isolates were included in the study, and their identification and antimicrobial susceptibility tests were performed using the VITEK-2 automated system. The production of capsule and alpha-hemolysin, biofilm formation ability, and hypermucoviscosity phenotype were examined by phenotypic methods; the presence of adhesin (*ycfM, mrkD, kpn*), invasin (*traT*), siderophore (*entB*, *iutA, fyuA, iroN*), and toxin (*hlyA*) genes were investigated using genotypic methods.

Results: The production of alpha-hemolysin and the hypermucoviscosity phenotype were only detected in eight strains (8%). Among the adhesin genes, *ycfM* was positive in 99%, *mrkD* in 97%, and *kpn* in 46% of the isolates; among the invasin genes, *traT* was positive in 2%; among the siderophore genes, *entB* was positive in 96%, *iutA* in 79%, *fyuA* in 71%, and *iroN* in 3%; and among the toxin genes, *hlyA* was positive in 2% of the isolates.

Conclusion: In evaluating the virulence factors of the isolates categorized as XDR, multidrug-resistant (MDR), and susceptible based on antibiotic susceptibility results, it was found that the aerobactin siderophore receptor gene *iutA* was significantly more prevalent in the XDR and MDR groups, that the two isolates with the *traT* virulence gene were in the MDR group, and that the *kpn* and *iroN* genes were more frequently observed in isolates from the MDR and susceptible groups, suggesting a possible negative correlation with antibiotic resistance.

Keywords: *Klebsiella pneumoniae*, antibiotic resistance, virulence factors

ÖZ

Amaç: Enterobactericeae ailesinin en önemli fırsatçı patojenlerinden biri olan *Klebsiella pneumoniae (K. pneumoniae)*'nın neden olduğu enfeksiyonlar, özellikle çok ilaca dirençli (ÇİD) suşların ortaya çıkmasıyla birlikte tedavi edilmesi güç bir sağlık sorunu haline gelmiştir. *K. pneumoniae*'nın neden olduğu enfeksiyonları tedavi etmek için antibiyotiklerin yaygın olarak kullanılmaya başlanması, bu ilaçlara karşı direncin ortaya çıkmasına ve yayılmasına sebep olmuştur. Bu çalışmada, klinik örneklerden izole edilen *K. pneumoniae*

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Received: 15.08.2024 **Accepted:** 12.06.2025 **Publication Date:** 04.07.2025

Cite this article as: Serbest İ, Baylan O, Karakuş M, Boz E, Bürkük N. Investigation of virulence factors by phenotypic and genotypic methods and evaluation of their relationship with antibiotic resistance in Klebsiella pneumoniae strains isolated from clinical specimens. Hamidiye Med J. 2025;6(2):110-118

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ÖZ

izolatlarının virülans faktörlerinin fenotipik ve genotipik yöntemlerle belirlenmesi ve antimikrobiyal ilaçlara karşı direnç durumuyla ilişkisinin incelenmesi hedeflenmiştir.

Gereç ve Yöntemler: Çalışmaya 100 *K. pneumoniae* izolatı dahil edilmiş, izolatların tanımlama ve antimikrobiyal duyarlılık testleri VITEK-2 otomatize sistemi ile yapılmıştır. Kapsül ve alfa hemolizin üretimi, biyofilm oluşturma yeteneği ve hipermukoviskozite fenotipi özelliği fenotipik yöntemlerle incelenmiştir.

Bulgular: Yüz izolat, yaygın ilaca dirençli (YİD), ÇİD ve duyarlı olmak üzere üç grupta incelenmiştir. Tüm izolatlarımızda kapsüle sahip olduğu ve biyofilm oluşturduğu bulunmuştur. Alfa hemolizin üretimi ve hipermukoviskozite fenotipi özelliği ise yalnızca sekiz suşta (%8) tespit edilmiştir. Adezin genlerinden *ycfM* %99, *mrkD* %97 ve *kpn* %46; invazin genlerinden *traT* %2; siderofor genlerinden *entB* %96, *iutA* %79, *fyuA* %71, *iroN* %3 ve toksin genlerinden *hlyA* ise %2 oranında pozitif bulunmuştur.

Sonuç: Çalışmamızda antibiyotik duyarlılık sonuçlarına göre YİD, ÇİD ve duyarlı olmak üzere üç gruba ayrılan izolatların virülans faktörleri açısından değerlendirilmesinde; aerobaktin siderofor reseptör geni *iutA*'nın YİD ve ÇİD grupta anlamlı derecede fazla bulunduğu, *traT* virülans genine sahip iki izolatın da ÇİD grupta yer aldığı, *kpn* ve *iroN* geninin ÇİD ve duyarlı grupta bulunan izolatlarda daha fazla görüldüğü, bu nedenle antibiyotik direnci ile arasında negatif bir kolerasyon olabileceği sonucuna varılmıştır.

Anahtar Kelimeler: *Klebsiella pneumoniae*, antibiyotik direnci, virulans faktörleri

Introduction

Klebsiella pneumoniae (K. pneumoniae) is a significant opportunistic pathogen, particularly causing various infections in immunocompromised patients, often associated with risk factors such as urinary catheterization, mechanical ventilation, surgical procedures, and prolonged stays in intensive care units (ICUs) (1). It is commonly linked to urinary tract infections (UTIs), pneumonia, sepsis, and wound infections (2). Hospital isolates of *K. pneumoniae* frequently exhibit multidrug-resistant (MDR) phenotypes due to the presence of extended-spectrum beta-lactamases (ESBLs) or carbapenemases, complicating the selection of appropriate antibiotics for treatment (3). The bacterium's ability to reproduce rapidly enhances its ability to develop mutations, which in turn increases its ability to develop antibiotic resistance. In addition to its high prevalence, *K. pneumoniae* is a significant factor in the spread of antibiotic resistance. Clinical isolates of *K. pneumoniae* often display MDR phenotypes due to the presence of ESBLs or carbapenemases, making it challenging to choose appropriate antibiotics for treatment (4). MDR strains of *K. pneumoniae* are frequently isolated as causative agents of hospital infections.

In recent years, strains of *K. pneumoniae* with MDR have posed serious problems in many countries, including Türkiye, and virulence factors significantly contribute to the infections caused by the bacteria (5). Virulence is defined as the ability of a microorganism to infect the host and cause disease. Virulence factors are molecules which assist the bacterium in colonizing the host. These factors can be secretory, membrane-associated, or cytosolic by nature. Cytosolic factors facilitate the bacterium's rapid, adaptive, metabolic, physiological, and morphological changes. Membrane-associated virulence factors aid the bacterium in adhering to and evading host cells. The secretory virulence factors possessed by the bacterium are crucial components that help it evade the host's innate and adaptive immune responses. In extracellular pathogens, secretory virulence factors act synergistically to kill host cells (6). The differences in the clinical features of *K. pneumoniae* infections are associated with the characteristics and number of virulence factors expressed (7). Although *K. pneumoniae* is considered one of the most important Gram-negative opportunistic pathogens, the mechanisms by which this bacterium causes different diseases remain unclear, and many studies have limitations because of the limited number of investigated virulence factors (8). The pathogenicity of *K. pneumoniae* is associated with the expression of various virulence factors, including capsular polysaccharide, lipopolysaccharide, iron acquisition systems (siderophores), adhesins, hypermucoviscosity, and outer membrane lipoprotein (6).

The primary virulence factors involved in the pathogenicity of *K. pneumoniae* include capsule formation, biofilm formation, alpha-hemolysin production, hypermucoviscosity, fimbriae, siderophores, and toxins (9). *K. pneumoniae* possesses several virulence genes encoding factors such as *mrkD*, *kpn*, *ycfM* (adhesins), *traT* (invasin), *entB* (enterobactin siderophore), *iutA* (aerobactin siderophore), *fyuA* (yersiniabactin siderophore), *iroN* (catechols receptor), and *hlyA* (toxin) (5). These virulence factors enable the bacterium to survive under adverse conditions and manage the pathogenesis of infection through critical mechanisms such as biofilm formation, capsule formation, adhesin, and invasion capabilities, siderophores, and toxin production (10). Although there have been some studies focused solely on the virulence factors of *K. pneumoniae*, there are a limited number of studies examining the relationship between

virulence factors in extensively or MDR strains and those in susceptible strains (8).

The aim of this study was to determine the presence of capsules, biofilm formation ability, hypermucoviscosity, and alpha-hemolysin production in *K. pneumoniae* strains isolated from clinical specimens using phenotypic methods, to investigate the presence of adhesin, invasion, siderophore, and toxin genes using genotypic methods, and to evaluate the potential virulence factors together with their relationship to antimicrobial resistance.

Material and Methods

This study was conducted with the approval of the University of Health Sciences Türkiye, Hamidiye Scientific Research Ethics Committee Presidency (approval number: 35/13, dated: 19.11.2021). Following ethical approvals, informed consent was obtained from participants included in this study. Our study included 100 *K. pneumoniae* isolates which were obtained as causative pathogens from various clinical specimens submitted by inpatients to the Medical Microbiology Laboratory of the University of Health Sciences Türkiye, Sultan 2. Abdülhamid Han Training and Research Hospital between January 2021 and December 2021. In cases where *K. pneumoniae* strains were isolated from different clinical specimens of the same patient, only the strain isolated from the first clinical specimen was included in the study. The isolates were stored in stock medium at -80 °C until the study was conducted. The bacterial identification and determination of antibiotic susceptibility were performed using the automated VITEK-2 system (bioMérieux, France). Colistin susceptibility was determined using the broth microdilution method according to the recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST). The antibiotic susceptibilities of the isolates were evaluated according to EUCAST criteria (11). The presence of a capsule in *K. pneumoniae* isolates was investigated using the India ink staining method. For this method, the isolates were first sub-cultured onto 5% sheep blood agar medium and incubated at 37 °C for 24 hours. The following day, a loopful of fresh colonies from this medium was mixed with a drop of India ink on a slide. The mixture was spread as a thin smear using another slide and left to dry at room temperature. After drying, the slides were stained with crystal violet for one minute; then they were washed and left to dry again at room temperature. The presence of a capsule was investigated under a microscope using a 100x objective with immersion oil. At the end of the method, the bacteria appeared purple, the background black, and the capsule around the bacteria was seen as a white halo.

Investigation of Biofilm Formation Ability

The biofilm formation capacity of *K. pneumoniae* isolates was investigated using the microplate method. For this process, the isolates were subcultured daily for three days in sterile glass tubes containing Luria-Bertani (LB) medium (Thermo Scientific, USA). After the third day, the bacterial density in each glass tube was adjusted to 0.56-0.64 using a McFarland densitometer. Two hundred microliters of the adjusted culture samples were transferred into a 96-well microplate. Two wells containing only LB medium were used as controls. The microplate was incubated at room temperature for 24 hours. After incubation, 25 µL of crystal violet stain was added to each well. The microplate was shaken in an HTX Multi-Mode Microplate Reader (Synergy, Germany) for one minute and then left at room temperature for 15 minutes. Subsequently, the medium and dye in the wells were carefully discarded into a disinfectant-containing container by inverting the microplate. The microplate was then thoroughly washed three times with phosphate-buffered saline, and 200 µL of 96% ethanol was distributed into each well. The microplate was then placed back into device for measurement, with the device set to a wavelength of 590 nm. The absorbance values of the wells containing bacteria had their absorbance value subtracted. Based on the new value obtained, the isolates were classified as high-level biofilm producers [optical density (OD >0.500)], moderate-level biofilm producers (OD between 0.100 and 0.500), and weak-level biofilm producers (OD <0.100).

Investigation of Hypermucoviscosity Presence

To detect the presence of hypermucoviscosity, *K. pneumoniae* isolates were inoculated onto brain heart infusion agar (Merck, Germany) plates using the dilution streaking method and incubated at 37 °C for 24 hours. Afterward, a standard disposable loop was touched to the colonies on the medium and slowly lifted. If the bacterial structure extended upward by more than 5 mm, hypermucoviscosity was considered positive.

Investigation of Alpha-Hemolysin Production

To investigate alpha-hemolysin production, *K. pneumoniae* isolates were inoculated onto 5% sheep blood agar medium and incubated at 37 °C for 18-24 hours. At the end of the incubation period, if a greenish zone formed around the bacterial colonies due to incomplete lysis of erythrocytes, the isolate was considered positive for alpha-hemolysin.

Investigation of Virulence Genes by Polymerase Chain Reaction (PCR)

DNA extraction from *K. pneumoniae* isolates was performed using the boiling method. The presence of virulence genes was investigated using the PCR method. The virulence genes included *ycfM* (outer membrane lipoprotein), *mrkD* (type 3 adhesin), *kpn* (*FimH*-like adhesin), *traT* (outer membrane lipoprotein associated with serum resistance), *entB* (enterobactin biosynthesis), *iutA* (aerobactin receptor), *iroN* (salmochelin catecholate siderophore receptor), *fyuA* (yersiniabactin receptor), and *hlyA* (hemolysin A) (Table 1). The following markers were used as reported in previous articles (12-14).

The PCR reaction mixture was prepared in PCR tubes with a total volume of 25 µL. Amplification of the gene regions encoding virulence factors was performed under reaction conditions suitable for the primers, utilizing a T100 Thermal Cycler (Bio-Rad, USA). The amplified PCR products were visualized using gel electrophoresis. The agarose gel was prepared with 1X TAE buffer at a 2% agar concentration, and the samples were run at 110V for 1 hour. The amplification products were visualized using the GBox Chemi XX6 (Syngene, UK) gel imaging system, and the images were analyzed using the GeneSys software.

Statistical Analysis

Statistical analysis was performed using the SPSS software. The chi-square test was used to determine the statistical relationship between categorical data (phenotypic tests, virulence genes, and antibiotic susceptibility profiles) and a p-value of <0.05 was considered statistically significant.

Results

Distribution of Clinical Samples

Of the studied samples, tracheal aspirate fluid was the sample from which *K. pneumoniae* was most frequently isolated, accounting for 50% (n=50) of all samples. at 50% (n=50). This was followed by blood at 16% (n=16), urine at 11% (n=11), wound swabs at 9% (n=9), sputum at 8% (n=8), bronchoalveolar lavage fluid at 4% (n=4), and catheter tip samples at 2% (n=2). Of these clinical samples, 70% were collected from patients in ICUs, while 30% were from patients in clinical wards.

Antibiotic Susceptibility of *K. pneumoniae* Isolates

The antibiotic susceptibilities of the 100 *K. pneumoniae* isolates included in the study were determined using the VITEK-2 (bioMérieux, France) automated system. Colistin susceptibility was assessed by the broth microdilution method, and the susceptibility results were evaluated according to EUCAST criteria. Based on these results, the isolates were categorized into three distinct groups.

Group 1: consisted of 67 extensively drug-resistant (XDR) isolates that were susceptible to two or fewer antibiotic classes. Group 2: Comprising 17 MDR isolates that were resistant to three or more antibiotic classes. Group 3: Included 16 isolates that were resistant to fewer than three antibiotic classes.

Antibiotic Resistance Profiles

Group 1 (XDR): The isolates in the XDR group showed 100% resistance to amikacin, gentamicin, amoxicillin/clavulanic acid, ertapenem, meropenem, piperacillin/tazobactam, cefepime, cefoxitin, ceftazidime, ceftriaxone, ciprofloxacin, and trimethoprim/sulfamethoxazole. They exhibited 70% resistance to colistin.

Group 2 (MDR): The isolates in the MDR group were 100% susceptible to colistin. The susceptibility to other antibiotics was as follows: 88% to amikacin, 82% to ertapenem and meropenem, 65% to cefoxitin, 59% to gentamicin, 35% to piperacillin/tazobactam, 24% to cefepime, 18% to amoxicillin/clavulanic acid and trimethoprim/sulfamethoxazole, and 6% to ceftazidime, ceftriaxone, and ciprofloxacin.

Group 3 (Susceptible): The isolates in group 3 were 100% susceptible to amikacin, gentamicin, ertapenem, meropenem, colistin, and ciprofloxacin. The susceptibility rates were 94% to cefoxitin, 87% to piperacillin/tazobactam and cefepime, 81% to ceftazidime, ceftriaxone, and trimethoprim/sulfamethoxazole, and 75% to amoxicillin/clavulanic acid (Table 2).

Microscopic Analysis of Capsule Presence and Biofilm Formation in *K. pneumoniae* Isolates

Using the Chinese ink staining technique, all 100 *K. pneumoniae* isolates examined under a microscope displayed the presence of capsules. Since capsules were observed in all isolates, no statistically significant difference was found among the groups (p>0.05).

All isolates in our study were observed to possess biofilm-forming ability. The number of isolates forming strong biofilms was 37, forming moderate biofilms was 42, forming weak biofilms was 21. The distribution of strong biofilm formers was as follows: 32 (47.8%) in the XDR group, 3 (17.7%) in the MDR group, and 2 (12.5%) in Group 3. Moderate biofilm formers numbered 24 (35.8%) in the XDR group, 5 (29.4%) in the MDR group, and 13 (81.3%) in Group 3. Weak biofilm formers included 11 (16.4%) in the XDR group, 9 (52.9%) in the MDR group, and 1 (6.2%) in Group 3. Statistical evaluation revealed a significant difference in biofilm formation among the groups (p<0.05).

Table 1. List of primers used in this study

Primer	Nucleotide sequence (5'-3')	TA (°C)	Amplicon size (bp)	Reference
ycfM-F	ATCAGCAGTCGGGTCAGC	55	160	8
ycfM-R	CTTCTCCAGCATTCAGCG			
mrkD-F	CCACCAACTATTCCCTCGAA	52	240	12
mrkD-R	ATGGAACCCACATCGACATT			
kpn-F	GTATGACTCGGGGAAGATTA	55	626	8
kpn-R	CAGAAGCAGCCACCACACG			
traT-F	GGTGTGGTGCGATGAGCACAG	63	290	13
traT-R	CACGGTTCAGCCATCCCTGAG			
entB-F	ATTTCCTCAACTTCTGGGGC	57	371	8
entB-R	AGCATCGGTGGCGGTGGTCA			
iutA-F	GGCTGGACATCATGGGAACTGG	63	300	13
iutA-R	CGTCGGGAACGGGTAGAATCG			
iroN-F	AAGTCAAAGCAGGGGTTGCCCG	63	665	13
iroN-R	GACGCCGACATTAAGACGCAG			
fyuA-F	GCGACGGGAAGCGATGATTTA	56	547	14
fyuA-R	TAAATGCCAGGTCAGGTCACT			
hlyA-F	AACAAGGATAAGCACTGTTCTGGCT	63	1177	13
hlyA-R	ACCATATAAGCGGTCATTCCCGTCA			

TA: Annealing temperature

Table 2. Resistance status of isolates to tested antibiotics

Antibiotics	XDR group		MDR group		Susceptible group		All isolates	
	Susceptible	Resistant	Susceptible	Resistant	Susceptible	Resistant	Susceptible	Resistant
Amikacin	0 (0%)	67 (100%)	15 (88%)	2 (12%)	16 (100%)	0 (0%)	31 (31%)	69 (69%)
Gentamicin	0 (0%)	67 (100%)	10 (59%)	7 (41%)	16 (100%)	0 (0%)	26 (26%)	74 (74%)
Amoxicillin/Clavulanic acid	0 (0%)	67 (100%)	3 (18%)	14 (82%)	12 (75%)	4 (25%)	15 (15%)	85 (85%)
Ertapenem	0 (0%)	67 (100%)	14 (82%)	3 (18%)	16 (100%)	0 (0%)	30 (30%)	70 (70%)
Meropenem	0 (0%)	67 (100%)	14 (82%)	3 (18%)	16 (100%)	0 (0%)	30 (30%)	70 (70%)
Piperacillin/Tazobactam	0 (0%)	67 (100%)	6 (35%)	11 (65%)	14 (87%)	2 (13%)	20 (20%)	80 (80%)
Colistin	20 (30%)	47 (70%)	17 (100%)	0 (0%)	16 (100%)	0 (0%)	53 (53%)	47 (47%)
Cefepime	0 (0%)	67 (100%)	4 (24%)	13 (76%)	14 (87%)	2 (13%)	18 (18%)	82 (82%)
Cefoxitin	0 (0%)	67 (100%)	11 (65%)	6 (35%)	15 (94%)	1 (6%)	26 (26%)	74 (74%)
Ceftazidime	0 (0%)	67 (100%)	1 (6%)	16 (94%)	13 (81%)	3 (19%)	14 (14%)	86 (86%)
Ceftriaxone	0 (0%)	67 (100%)	1 (6%)	16 (94%)	13 (81%)	3 (19%)	14 (14%)	86 (86%)
Ciprofloxacin	0 (0%)	67 (100%)	1 (6%)	16 (94%)	16 (100%)	0 (0%)	17 (17%)	83 (83%)
Trimethoprim/Sulfamethoxazole	0 (0%)	67 (100%)	3 (18%)	14 (82%)	13 (81%)	3 (19%)	16 (16%)	84 (84%)

XDR: Extensively drug-resistant, MDR: Multidrug-resistant

For the detection of hypermucoviscosity, 100 *K. pneumoniae* isolates were cultured on Brain Heart Infusion agar,with eight isolates (8%) showing the hypermucoviscosity phenotype. The remaining 92 isolates (92%) were negative for hypermucoviscosity. Statistical analysis showed no significant difference in hypermucoviscosity presence among the groups (p>0.05).

When testing for alpha-hemolysis on 5% sheep blood agar, alpha-hemolysin production was observed in eight isolates (8%). Statistical analysis did not reveal a significant difference in alpha-hemolysis among the groups (p>0.05).

The presence of the *ycfM* gene was investigated using PCR. This virulence gene was found in 99 out of 100 isolates, with only one isolate not exhibiting this gene. *ycfM* was the most frequently detected virulence gene in our study. Statistical analysis did not reveal a significant difference in the presence of the *ycfM* gene among the groups (p>0.05). The presence of the *mrkD* gene was detected in 97 out of 100 *K. pneumoniae* isolates, (97%), making it the second most frequent virulence gene in our study. Statistical analysis showed no significant difference in the presence of the *mrkD* gene among the groups (p>0.05). The *kpn* gene was detected in 46 out of 100 *K. pneumoniae* isolates (46%). This virulence gene was more prevalent in isolates from Group 1 and 2. Statistical analysis revealed a significant difference in the presence of the *kpn* gene among the groups (p<0.05). The *traT* gene was detected in only two out of 100 *K. pneumoniae* isolates (2%), both of which were in the MDR group. Statistical analysis indicated a significant difference in the presence of the *traT* gene among the groups (p<0.05). The *entB* gene was found in 96 out of 100 *K. pneumoniae* isolates. No significant difference was detected in the presence of the *entB* gene among the groups (p>0.05). The *iutA* gene was positive in 79 out of 100 *K. pneumoniae* isolates (79%). This virulence gene was predominantly found in the XDR and MDR groups, with statistical analysis revealing a significant difference among the groups (p<0.05). The *fyuA* gene was detected in 71 out of 100 *K. pneumoniae* isolates (71%). Statistical analysis did not reveal a significant difference in the presence of the *fyuA* gene among the groups (p>0.05). The *iroN* gene was found in three out of 100 *K. pneumoniae* isolates (3%). Of these, two were in group 2 and one in Group 3. Statistical analysis indicated a significant difference in the presence of the *iroN* gene among the groups (p<0.05).

The presence of the *hlyA* gene was observed in only two out of 100 *K. pneumoniae* isolates (2%). Statistical analysis did not show a significant difference in the presence of the *hlyA* gene among the groups (p>0.05). The amplicon sizes for the investigated virulence genes were as follows: *ycfM* (160 bp), *traT* (290 bp), *mrkD* (240 bp), *kpn* (626 bp), *entB* (371 bp), *iutA* (300 bp), *fyuA* (547 bp), *iroN* (665 bp), and *hlyA* (1177 bp) (Table 3).

Table 3. Genotypic and phenotypic resistance status of the tested isolates

	Phenotypic methods				Hypermucoviscosity	Alpha Hemolysis	Genotypic resistance markers										
	Capsul	Biofilm					Adhesin			Invasin	Siderophore					Toxin	
		Strong	Medium	Weak			*ycfM*	*mrkD*	*kpn*	*traT*	*iutA*	*entB*	*fyuA*	*iroN*		*hlyA*	
XDR group (n=67,%67)	67 (100%)	32 (47.8%)	24 (35.8%)	11 (16.4%)	6 (8.9%)	7 (10.4%)	66 (98%)	65 (97%)	22 (33%)	0 (0%)	62 (92%)	63 (94%)	46 (69%)	0 (0%)		1 (1.4%)	
MDR group (n=17,%17)	17 (100%)	3 (%17.7%)	5 (29.4%)	9 (52.9%)	0 (0%)	0 (0%)	17 (100%)	16 (94%)	12 (70%)	2 (11.8%)	12 (70%)	17 (100%)	13 (76%)	2 (12%)		0 (0%)	
Susceptible grup (n=16,%16)	16 (100%)	2 (125%)	13 (81.3%)	1 (6.2%)	2 (12.5%)	1 (6.2%)	16 (100%)	16 (100%)	12 (75%)	0 (0%)	5 (31%)	16 (100%)	12 (75%)	1 (6%)		1 (6%)	
Total		37 (37%)	42 (42%)	21 (21%)	8 (8%)	8 (8%)	99 (99%)	97 (98%)	46 (46%)	2 (2%)	79 (79%)	96 (96%)	71 (71%)	3 (3%)		2 (2%)	
p	p>0.05	**p<0.05**			p>0.05	p>0.05	p>0.05	p>0.05	**p<0.05**	**p<0.05**	**p<0.05**	p>0.05	p>0.05	**p<0.05**		p>0.05	

XDR: Extensively drug-resistant, MDR: Multidrug-resistant

Discussion

The widespread use of antibiotics for treating infections caused by *K. pneumoniae* has led to the emergence and spread of resistance to these drugs (15). According to data from a 2019 surveillance study by the European Centre for Disease Prevention and Control, approximately 40% of *K. pneumoniae* isolates in Europe exhibit resistance to at least one class of antibiotics used in treatments, including fluoroquinolones, third-generation cephalosporins, aminoglycosides, and carbapenems (16). Identifying the virulence factors that play a crucial role in the pathogenesis of *K. pneumoniae* is essential for addressing this resistance issue and developing alternative treatment strategies. In our study aimed at contributing to anti-virulence therapeutic strategies, we investigated various virulence factors in *K. pneumoniae* isolates categorized into three groups based on antibiotic susceptibility. The presence of factors such as capsule formation, biofilm production, hypermucoviscosity phenotype, and alpha-hemolysin production was examined using phenotypic methods, while the presence of adhesin, invasion, siderophore, and toxin genes was assessed using genotypic methods. The relationship between these virulence factors and antibiotic resistance was analyzed.

One of the most important factors in the pathogenesis of *K. pneumoniae* is its capsule. In this study, capsule presence was examined using the Chinese ink staining method, and all isolates were found to produce capsules. Kuş et al. (5) investigated capsule presence in 53 *K. pneumoniae* isolates using the Chinese ink staining technique in Konya in 2015, detecting capsule formation in all isolates. Although the capsule is considered a significant virulence factor, no association was found among the groups, and there was no statistically significant difference ($p>0.05$).

For bacteria to colonize and cause disease, they must first adhere to the host cells. Bacteria use surface extensions such as pili, fimbriae, and flagella to adhere to surfaces (17). Clinical *K. pneumoniae* strains have two types of fimbrial adhesins: type 1 and type 3 fimbriae (18). The type 1 fimbrial adhesin encoded by the *FimH* virulence gene plays a significant role in UTIs caused by these strains, while the type 3 fimbrial adhesin encoded by the *mrkD* virulence gene promotes biofilm development (19). El Fertas-Aissani et al. (8) reported positivity rates of 96.3% for *mrkD*, 96.3% for *ycfM*, and 63% for *kpn* genes in their study with 54 *K. pneumoniae* isolates. In our study, the *mrkD* gene was found positive in 97% of *K. pneumoniae* isolates. The other adhesin genes, *ycfM* and *kpn*, were positive in 99% and 46% of isolates, respectively. Statistical analysis revealed no significant difference among the three groups for the *mrkD* and *ycfM* genes ($p>0.05$); however, a significant difference was found for the *kpn* gene. The positivity rates for the *kpn* gene were 70% in the Group 2, 75% in the Group 3, and 33% in Group 1. These results suggest a potential negative correlation of antibiotic resistance with the presence of the *kpn* gene. Further studies are needed to support this hypothesis. The *traT* gene was detected in only 2% of the 100 isolates in our study. Both isolates with the *traT* invasion gene were in Group 2. Statistical analysis detected a significant difference among the groups ($p<0.05$), but more isolates are needed for clearer results.

Bacteria have developed siderophores, which are iron acquisition tools, to compete with the host. *K. pneumoniae* expresses four types of siderophores: enterobactin, yersiniabactin, salmochelin, and aerobactin (20,21). The *iutA* gene was found in 79% of our isolates. Candan and Aksöz (1) reported a 26% positivity rate for the *iutA* gene. Statistical analysis showed a significant difference among the groups ($p<0.05$). The *iutA* gene was detected in 96% of isolates in Group 3 and 70% in Group 2, suggesting a positive correlation between antibiotic resistance and the *iutA* gene. The *entB* gene was detected in 96% of the isolates, and the *fyuA* gene was found in 71%. Eghbalpoor et al. (22) reported 100% positivity for the *entB* gene in their study in Iran. No significant differences were observed between the groups for *entB* and *fyuA* genes ($p>0.05$). The *iroN* gene was detected in 3% of isolates. Two positive isolates were in Group 2, and one was in Group 3. Statistical analysis revealed a significant difference among the groups ($p<0.05$), suggesting a possible negative correlation between *IroN* and antibiotic resistance. However, the low number of positive isolates should be considered when interpreting these results. Further research on salmochelin siderophore genes is needed. In studies examining the correlation between virulence factors and antibiotic resistance, Eghbalpoor et al. (22) reported that the *traT* and *fyuA* genes correlated with antibiotic resistance. In our study, we observed a correlation between the presence of *kpn, traT, iutA,* and *iroN* virulence genes and antibiotic resistance.

Hemolysins are toxins that make certain nutrients, such as iron ions in hemoglobin, available and also form pores (23). In our study, alpha-hemolysin production was examined both phenotypically and genotypically. Alpha-hemolysin formation was observed in 8% of the 100 *K. pneumoniae* isolates on 5% sheep blood agar. The *hlyA* gene was detected in only 2% of isolates. Among these, one isolate exhibited alpha-hemolysis, while the other did not. Statistical analysis found no significant differences among the groups for alpha-hemolysis and the *hlyA* gene ($p>0.05$). Pereira and Vanetti (24) did not detect alpha-hemolysin production in any of the 21 *K. pneumoniae* isolates studied in Brazil in 2015.

The hypermucoviscosity phenotype has long been associated with invasive infections in healthy individuals caused by *K. pneumoniae*. In our study, 8% of the 100 *K. pneumoniae* isolates exhibited the hypermucoviscosity phenotype. When evaluating the relationship between this virulence factor and antibiotic resistance, it was observed that six of the eight hypermucoviscous isolates were in Group 1, while two were in Group 3. No statistically significant difference was found among the groups for the hypermucoviscosity phenotype ($p>0.05$), indicating that more isolates should be included for further evaluation.

The relationship between biofilm formation and antibiotic resistance has not yet been fully elucidated (25). Some studies have reported a positive correlation between biofilm formation and antibiotic resistance, while others have indicated a negative correlation (26,27). Our results showed that strong biofilm formation was observed in 47.8% of isolates in Group 1, compared to 17.7% and 12.5% in Group 2 and 3, respectively. A significant difference was found between strong and medium/weak biofilm formation in Group 1 ($p<0.05$). In Group 2, 52.9% of isolates formed weak biofilms, and in Group 3, medium-level biofilm formation was high (81.3%), with significant differences detected ($p<0.05$). Given the conflicting results, attributing antibiotic resistance solely to biofilm formation would be a bold claim.

Study Limitations

This study has several limitations that should be acknowledged. First, it was conducted in a single center, which may limit the generalizability of the findings to broader populations or different geographic regions. Second, although only the initial isolate from each patient was included to avoid duplication, genotypic analysis of these isolates could not be performed. The absence of molecular characterization restricts deeper insights into the genetic diversity and potential transmission dynamics of the isolates.

Conclusion

Our study on the virulence factors of *K. pneumoniae* revealed potential associations between antibiotic resistance and the presence of the *kpn* gene, *traT* gene, *iutA* gene, and *iroN* gene. Comparison of our data with other studies suggests that the high antimicrobial resistance potential of *K. pneumoniae* is not solely related to virulence factors but involves more complex mechanisms. Research into anti-virulence therapeutics underscores the importance of understanding bacterial pathogens and their interactions with host-environment factors. If virulence can be controlled, it is believed that the host immune system can overcome any non-therapeutic infection. In the absence of such control, anti-virulence therapies could be used synergistically with traditional antimicrobials to reduce antibiotic consumption.

Ethics

Ethics Committee Approval: University of Health Sciences Türkiye, Hamidiye Scientific Research Ethics Committee Presidency (approval number: 35/13, dated: 19.11.2021).

Informed Consent: Following ethical approvals, informed consent was obtained from participants included in this study.

Footnotes

Authorship Contributions

Concept: İ.S., O.B., M.K., E.S.B., Design: İ.S., O.B., Data Collection or Processing: İ.S., N.B., Analysis or Interpretation: İ.S., M.K., E.S.B., N.B., Literature Search: İ.S., O.B., M.K., N.B., Writing: İ.S., M.K.

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

Financial Disclosure: This study is supported by the Scientific Research Project Fund of the University of Health Sciences under project number 2022/042.

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ORIGINAL ARTICLE

DOI: 10.4274/hamidiyemedj.galenos.2025.06978

Hamidiye Med J 2025;6(2):119-123

Systemic Effects of Hip Fractures and Surgical Treatment

Kalça Kırıkları ve Cerrahi Tedavilerinin Sistemik Etkileri

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ABSTRACT

Background: Hip fractures are one of the common types of fractures observed in the elderly population, and various implants can be successfully used in their treatment. The aim of this study is to determine whether there is a significant difference in surgical stress and potential complications between osteosynthesis techniques and arthroplasty.

Materials and Methods: Seventy-nine patients who underwent surgery for hip fracture were included in the study. Age, gender, type of fracture, and the surgical procedure applied were recorded. The effects of hip fracture and the surgical method on the general systemic inflammation, muscle damage, the cardiovascular system, the kidney, and the liver were examined.

Results: Of the 79 patients included in our study, 28 (35%) were male, and 51 (65%) were female. Among these patients, 44 (56%) were treated with osteosynthesis, and 35 (44%) underwent hemiarthroplasty. When comparing the groups based on haemoglobin changes, it was not statistically significant (p=0.601), although there was a greater decrease in hemoglobin levels at the 6th postoperative hour in the hemiarthroplasty group. When patients were evaluated based on C-reactive protein values, the increase from preoperative levels in the hemiarthroplasty group was higher than that in the osteosynthesis group, but it was not statistically significant (p=0.816). Moreover, there was no significant difference between the two groups regarding creatine kinase, creatine kinase-MB isoenzyme, cardiac Troponin, aspartate aminotransferase, alanine aminotransferase, serum creatinine, and D-dimer values.

Conclusion: In the treatment of hip fractures, no significant difference was observed between hemiarthroplasty and osteosynthesis in terms of acute systemic effects.

Keywords: Intertrochanteric fractures, femoral neck fractures, hip replacement arthroplasty, osteosynthesis

ÖZ

Amaç: İleri yaştaki toplumda kalça kırıkları sık görülen kırık türlerinden biridir ve tedavisinde çeşitli implantlar başarı ile kullanılabilmektedir. Bu çalışmanın amacı; osteosentez teknikleri ve artroplasti arasında cerrahi stres ve olası komplikasyonlar açısından anlamlı bir farklılık olup olmadığının tespit edilmesidir.

Gereç ve Yöntemler: Kalça kırığı tanısı ile opere edilen 79 hasta çalışmaya dahil edildi. Kalça kırığının ve uygulunan cerrahi yöntemin; genel sistemik enflamasyon ve kas yıkımı, kardiyovasküler sistem, böbrek ve karaciğer üzerine etkileri incelendi. Bu amaçla ameliyat öncesi, ameliyat sonrası 6., 24. ve 72. saat hemogram, C-reaktif protein (CRP), kreatin kinaz, CK-MB, Troponin, aspartat aminotransferaz (AST), alanin aminotransferaz (ALT), kreatinin, D-dimer değerleri kontrol edildi.

Bulgular: Çalışmamıza dahil edilen 79 hastanın, 28'i (%35) erkek, 51'i (%65) kadındı. Bu hastalardan 44'üne (%56) tedavide osteosentez, 35'ine (%44) hemiartroplasti uygulanmıştı. Hemoglobin değişimine göre hasta grupları incelendiğinde; post operatif 6. saatteki hemoglobin düşüşü hemiartroplasti uygulanan grupta daha fazla olsa da istatiksel olarak anlamlı değildi (p=0,601). Hastalar CRP değerlerine göre değerlendirildiğinde hemiartroplasti grubunda pre-operatif değerlerle kıyaslandığında, CRP değerlerindeki artış osteosentez grubundan daha fazla olsa da istatiksel olarak anlamsız bulundu (p=0,816). Benzer şekilde CK, CK-MB, Troponin, AST, ALT, kreatinin ve D-dimer değerleri açısından incelendiğinde de hemiartroplasti grubu ile osteosentez grubu arasında anlamlı fark saptanmadı.

Sonuç: Kalça kırıklarının tedavisinde tercih edilebilecek yöntemlerden hemiartroplasti ve osteosentez arasında akut dönemde sistemik etkiler açısından anlamlı fark saptanmamıştır.

Anahtar Kelimeler: İntertrokanterik kırıklar, femur boynu kırıkları, kalça replasman artroplasti, osteosentez

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Received: 12.05.2025 **Accepted:** 30.06.2025 **Publication Date:** 04.07.2025

Cite this article as: Gök M, Sıvacıoğlu S, Çetin O. Systemic effects of hip fractures and surgical treatment. Hamidiye Med J. 2025;6(2):119-123

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Introduction

Hip fractures are one of the most common types of fractures in the elderly population, and various implants can be used successfully in their treatment. These include Dynamic Hip Screw (DHS), Cannulated screws, plate-screw fixation, Proximal Femur Nail (PFN), hemiarthroplasty, and total arthroplasty. Studies and discussions about which treatment to choose for hip fractures are still ongoing. One of the factors affecting the choice is the surgical stress on the patient, including soft tissue damage during surgery, blood loss, and duration of surgery. Treatment can be divided into osteosynthesis and arthroplasty. In general, osteosynthesis techniques are less invasive than arthroplasty techniques, which are thought to cause less surgical stress on the patient (1). The hypothesis of this study is that there will be less surgical stress in hip fractures treated with osteosynthesis compared to hemiarthroplasty. Our aim in this study was to determine whether there is a significant difference between osteosynthesis techniques and arthroplasty regarding surgical stress and possible complications.

Materials and Methods

In this study, we retrospectively evaluated patients aged 65 years and older who were admitted to a tertiary care hospital with a hip fracture between 2018 and 2019. All patients underwent surgical treatment, had low-energy trauma (simple fall from the same level) as the fracture etiology and underwent surgery within the first 48 hours after the fracture. Patients under 65 years of age with subtrochanteric fractures with additional concomitant injuries with irregular follow-up with conservative follow-up who underwent revision surgery who died in the period who could not be operated on within the first 48 hours were excluded from the study.

The operations were performed by the same surgical team. A proximal femur nail was applied after closed reduction using a traction table for osteosynthesis. In the arthroplasty group, all patients underwent hemiarthroplasty using the Lateral Hardinge approach. Age, gender, fracture type, American Society Anesthesiologists (ASA) score, body mass index (BMI), and type of surgery performed were recorded. The effects of hip fracture and surgical method on general systemic inflammation, muscle destruction, the cardiovascular system, the kidney, and the liver were analysed. For this purpose, haemogram, C-reactive protein (CRP), creatine kinase (CK), creatine kinase-MB isoenzyme (CK-MB), cardiac Troponin (Troponin), aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine (Creatinine), and D-dimer values were checked preoperatively, 6, 24, and 72 hours, postoperatively. Approval was received from the Ethics Committee of University of Health Sciences Türkiye, İzmir Bozyaka Training and Research Hospital, Clinical Research Ethics Committee (approval number: 2023/88, dated: 21.06.2023). Informed consent was obtained from the patients or their relatives.

Statistical Analysis

Statistical analyses were performed using IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA). Mean, standard deviation, and median values were used for descriptive analyses. Chi-square, t-test, and non-parametric tests were used to analyse numerical data. The normal distribution was evaluated using the Kolmogorov-Smirnov.

Results

Of the 79 patients included in our study, 28 (35%) were male and 51 (65%) were female. The mean age was 76.63±10.17 (65-93) years. Osteosynthesis and hemiarthroplasty were performed in 44 (56%) and 35 (44%) of these patients. Twenty-nine patients (37%) had AO A2 type fractures (Table 1). When analyzed according to fracture type progression from A1 to B2, more patients underwent hemiarthroplasty, and the difference in surgical method according to fracture type was significant (p=0.001). The mean age of the patients who underwent osteosynthesis was 73.32±12.0, while the mean age of those who underwent hemiarthroplasty was 80.77±7.3. A significant difference was found between the two groups in terms of age (p=0.001). When the decrease in hemoglobin (Hb) was analyzed based on fracture types, it was found that Hb decrease was significantly higher in patients with type B fractures than in patients with type A fractures (p=0.001). The mean ASA score was 2.61±0.72 in the osteosynthesis group and 2.63±0.54 in the hemiarthroplasty group (p=0.920). The mean BMI was 27.65±3.14 in the osteosynthesis group and 26.61±3.79 in the hemiarthroplasty group (p=0.736).

In all patients, the mean preoperative Hb was 11.7±0.1, the mean postoperative Hb at the 6th hour was 10.17±1.49, the mean Hb at the 24th hour was 9.6±0.12, and the mean Hb at the 72nd hour was 9.16±1.35. The postoperative Hb decrease was found to be significant regardless of the

Table 1: Distribution according to fracture type

Fracture type	Number (n)	Percentage (%)
A1	17	21.5
A2	29	36.7
A3	6	7.6
B1	7	8.9
B2	20	25.5
Total	79	100

surgical method (p=0.001) (Table 2). When the patient groups were analysed according to haemoglobin change, the mean post-operative Hb decrease at the sixth hour was 1.77±1.54 in the hemiarthroplasty group and 1.46±1.15 in the osteosynthesis group. Although the Hb decrease at the 6th post-operative hour was higher in the hemiarthroplasty group, it was not statistically significant (p=0.601). When the two groups were analysed according to the Hb decrease at the 24th post-operative hour the haemoglobin decrease in the hemiarthroplasty group (2.30±2.12) was higher than in the osteosynthesis group (2.08±1.48), but it was not statistically significant (p=0.787). The decrease in Hb at 72 hours postoperatively was 2.61±1.53 in the hemiarthroplasty group and 2.44±1.21 in the osteosynthesis group, with no statistically significant difference (p=0.836) (Table 3).

When the postoperative CRP changes were analysed according to the preoperative CRP values of the patients, the preoperative CRP mean was 57.75±42.34 in the general patient group; it was 94.60±58.0 at the 6th postoperative hour, 146.51±50.88 at the 24th postoperative hour, and 201.24±71.60 at the 72nd postoperative hour. When the preoperative CRP mean was compared with the 6th hour (p=0.001), 24th hour (p=0.001), and 72nd hour (p=0.001), CRP means, a significant difference was found in all three groups. The mean CRP increased significantly as the postoperative period progressed (p=0.001). In all three evaluations, while the increase in CRP values was higher in the hemiarthroplasty group compared to the preoperative values than in the osteosynthesis group, it was not statistically significant.

In the general patient group, the mean pre-operative CK levels were 144.63±174.27, 450.25±448.72 at 6 hours post-operative, 610.87±177.02, at 24 hours post-operative, and 230.78±210.95 at 72 hours post-operative. Regardless of the surgical method, preoperative CK values and CK

Table 2. Preoperative and postoperative mean laboratory values and statistical analysis of preoperative and postoperative values in general patient population

	Pre-operative	Post-operative 6th hour		Post-operative 24th hour		Post-operative 72nd hour	
	Mean	Mean	p-value	Mean	p-value	Mean	p-value
Hemoglobin	11.76	10.17	0.001	9.61	0.001	9.16	0.001
Creatinine	1.13	1.17	0.506	1.14	0.887	1.26	0.404
CRP	57.76	96.75	0.001	143.22	0.001	196.38	0.001
CK	165.73	452.41	0.002	606.93	0.046	231.38	0.105
D-dimer	2242.09	4276.12	0.004	1489.23	0.205	1327.31	0.080
AST	27.46	38.70	0.004	46.55	0.017	32.47	0.218
ALT	17.82	26.16	0.004	25.22	0.028	21.76	0.199
Troponin I	0.02	0.03	0.338	0.08	0.098	0.04	0.001
CK-MB	2.38	5.97	0.001	6.89	0.028	3.14	0.401
Fibrinogen	478.75	497.25	0.403	516.60	0.011	714.51	0.001

CRP: C-reactive protein, CK: Creatine kinase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CK-MB: Creatine kinase myocardial band

Table 3: Preoperative and postoperative 6th, 24th and 72nd hour laboratory value averages and statistical comparison of osteosynthesis and hemiarthroplasty groups

	Post-operative 6th hour			Post-operative 24th hour			Post-operative 72nd hour		
	Osteosynthesis	Arthroplasty	p-value	Osteosynthesis	Arthroplasty	p-value	Osteosynthesis	Arthroplasty	p-value
Hemoglobin	9.97	10.13	0.601	9.47	9.59	0.787	9.07	9.28	0.836
Creatinine	1.15	1.19	0.113	1.11	1.17	0.173	1.23	29.53	0.443
CRP	85.76	110.95	0.816	130.56	163.78	0.461	178.88	217.04	0.080
CK	388.92	543.84	0.059	718.86	500.09	0.637	199.14	269.00	0.064
D-dimer	3887.33	4837.70	0.724	1504.81	1469.28	0.764	1591.06	986.62	0.705
AST	38.87	38.48	0.686	52.00	39.53	0.353	32.81	32.10	0.623
ALT	27.74	24.06	0.265	29.28	20.00	0.095	25.71	17.39	0.067
Troponin I	0.01	0.05	0.141	0.02	0.16	0.102	0.03	0.06	0.073
CK-MB	5.12	7.35	0.954	6.90	6.87	0.579	2.11	4.28	0.093
Fibrinogen	510.92	476.73	0.377	510.06	524.96	0.107	721.97	704.87	0.615

CRP: C-reactive protein, CK: Creatine kinase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CK-MB: Creatine kinase myocardial band)

increases at 6 hours postoperative (p=0.002) and 24 hours postoperative (p=0.046) were found to be significant, but CK values decreased at 72 hours postoperative to approach preoperative values (p=0.105). Although the CK increase in the first 6 hours was higher in the hemiarthroplasty group, it was not statistically significant (p=0.059) when a comparison was made in terms of CK levels.

When the D-dimer values of the patients were analysed, it was found that the preoperative mean D-dimer level was 2267.50±500.30, while the postoperative mean D-dimer level was 4983.25±726.04 at the 6th postoperative hour. D-dimer levels increased significantly at the 6th postoperative hour, when compared with the preoperative mean (p=0.004). However, it was found that the mean D-dimer level decreased at the 24th hour postoperatively compared to the 6th hour, and this decrease continued at the 72nd hour compared to the 24th hour. There was no statistically significant difference between postoperative 24-hour and 72-hour. D-dimer values compared to pre-operative levels (p=0.205 and p=0.08, respectively). When the patient groups were analysed in terms of surgical techniques, no significant difference was found between the two groups regarding the increase in D-dimer levels compared to preoperative values (p=0.724).

According to the creatinine values obtained at the 6th and 24th postoperative hours, no significant difference was found between the two groups in terms of creatinine increase (p=0.113, p=0.173). When AST values at postoperative 6th and 24th hours were analysed, no significant difference was found between the two groups (p=0.693 and p=0.353).

When CK-MB values were controlled, a significant difference was found between the preoperative mean and the mean values at the 6th and 24th hours postoperatively (p=0.001). There was no significant difference between surgical techniques in CK-MB values.

When analysis was conducted according to Troponin values, no significant difference was found between preoperative and postoperative 6 and 24 h Troponin values in the general patient group (p=0.338; p=0.098, respectively), whereas the increase in Troponin value at 72 h was significant (p=0.001).

Discussion

Wu et al. (2) reported that 190 of 213 patients (89%) operated for hip fracture had post-operative anaemia. In our study, a significant decrease in haemoglobin postoperatively was observed in patients operated on for hip fracture, independent of the surgical method, when compared with the preoperative values.

In a meta-analysis by Bhandari et al. (3), it was found that patients who underwent arthroplasty for hip fracture had more blood loss than patients who underwent internal fixation. In our study, although blood loss was numerically higher in the hemiarthroplasty group, the difference was not statistically significant between the two groups.

Neumaier et al. (1) studied 580 patients with proximal femur fracture and investigated the effect of osteosynthesis and arthroplasty on CRP levels in the treatment of hip fracture. It was found that CRP increase was higher in the arthroplasty group than in the osteosynthesis group. In this study, although there was no statistical difference between the two groups, CRP increased more in the hemiarthroplasty group. The highest CRP values were found at 72 hours.

Alagöz et al. (4) investigated the relationship between hip fracture and renal function and found that 47 of 238 patients had postoperative deterioration in renal function. Our patients were evaluated in terms of renal function using preoperative and postoperative creatinine values. No significant change was found in these values. Similarly, no difference was found between the surgical methods in terms of creatinine values.

Although AST and ALT are clinically used in the diagnosis and follow-up of liver diseases, both enzymes are also present in striated muscle tissue, with AST being more abundant, and both enzymes are increased in muscle damage or muscle tissue diseases (5,6). It is known that AST increases more than ALT in muscle tissue-related increases (7). In our study, for this purpose, AST and ALT values were monitored before and after surgery, and a significant increase was found in both values after surgery. No significant difference was found according to the surgical method.

CK is found in muscle tissue and is used in clinical practice as an indicator of muscle destruction and muscle ischaemia (8). Although there is no study in the literature comparing hemiarthroplasty and osteosynthesis in terms of CK values in patients with hip fracture, Wagman et al. included 359 patients who underwent surgery for intertrochanteric fracture and underwent proximal femoral nail or dynamic hip screw and investigated soft tissue damage according to the type of surgery. It was reported that CK value increased more in patients who underwent DHS compared to patients who underwent PFN (9). Similarly, Hong et al. (10) reported that there was no difference in CK values and soft tissue damage between the two groups in their study, in which they compared patients who underwent PFN and DHS for intertrochanteric fracture. In our study, no significant difference was found between hemiarthroplasty and osteosynthesis groups in terms of postoperative CK increase.

Since D-dimer is an indicator of endogenous fibrinolysis, it is used as a screening test for deep vein thrombosis and pulmonary thromboembolism. It is also a positive acute phase reactant and increases in conditions such as inflammation, infection and trauma (11,12). In a study conducted by Chen et al. (13) with 32 patients with hip

fracture, it was reported that there was a significant increase in postoperative D-dimer values and it returned to normal values within 1 week. In our study, D-dimer values increased significantly at the 6th postoperative hour and started to decrease at the 24th postoperative hour regardless of the surgical method. When surgical methods were compared, no significant difference was found between hemiarthroplasty and osteosynthesis groups in terms of D-dimer increase.

Troponin and CK-MB are biomarkers used as indicators of cardiac injury. CK-MB is also increased in skeletal muscle damage, and Troponin-I is a more specific indicator of cardiac damage. In our study, both CK-MB and Troponin-I values were monitored to determine the effect of hip fractures on the cardiac system. In the postoperative period, the mean CK-MB values were significantly higher than in the preoperative period, whereas no significant change was found in Troponin-I values. This suggests that the increase in CK-MB values may be due to muscle damage. When both values were compared according to surgical methods, no significant difference was found.

This study provides information on hip fractures, surgical treatments, and their systemic effects. The study's limitations include being a single-centre study, the failure to ensure homogeneity of fracture subtypes, the limited number of patients, and the lack of sufficient numbers of each fracture subtype.

Conclusion

In conclusion, hip fractures in the elderly population should be considered not only, as a pathology affecting the bone but also as a major health problem with systemic effects. There was no significant difference between hemiarthroplasty and osteosynthesis in terms of systemic effects in the acute period.

Ethics

Ethics Committee Approval: Approval was received from the Ethics Committee of University of Health Sciences Türkiye, İzmir Bozyaka Training and Research Hospital, Clinical Research Ethics Committee (approval number: 2023/88, dated: 21.06.2023).

Informed Consent: Informed consent was obtained from the patients or their relatives.

Footnotes

Authorship Contributions

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

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

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

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CASE REPORT

DOI: 10.4274/hamidiyemedj.galenos.2025.09226

Hamidiye Med J 2025;6(2):124-127

Delayed Diagnosis of Anti-GABA-B Antibody Paraneoplastic Limbic Encephalitis Characterized by Persecutory Delusions: A Case Report

Persekütif Sanrılarla Karakterize Anti-GABA-B Antikoru Paraneoplastik Limbik Ensefalitin Gecikmiş Tanısı: Bir Olgu Sunumu

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ABSTRACT

Limbic encephalitis (LE) is a rare clinical syndrome characterized by subacute limbic dysfunction, including seizures, memory impairment, and behavioral changes, often linked to autoimmune or paraneoplastic causes. Anti-gamma aminobutyric acid-B (anti-GABA-B) receptor-associated LE, frequently related to small cell lung cancer (SCLC), typically presents with neurological symptoms such as seizures and cognitive decline. However, prominent psychiatric symptoms, including psychosis, are rarely reported, posing diagnostic challenges. We report a 56-year-old woman presenting with acute disorganized behavior, paranoid delusions, and cognitive impairment, accompanied by status epilepticus. Initial investigations, including magnetic resonance imaging and cerebrospinal fluid (CSF) analysis, were inconclusive. While levetiracetam-induced psychosis and Hashimoto encephalitis were considered, her persistent symptoms prompted further evaluation. Thoracic imaging detected a lung mass confirmed as SCLC by biopsy; CSF analysis identified positive anti-GABA-B receptor antibodies. This confirmed a diagnosis of paraneoplastic LE. Treatment included pulse steroids, antipsychotics, and chemotherapy, leading to significant symptom improvement. This case emphasizes the importance of considering paraneoplastic autoimmune encephalitis in patients with prominent psychiatric symptoms and seizures. The identification of a lung mass during psychiatric evaluation was pivotal in diagnosing anti-GABA-B receptor LE. Early recognition and multidisciplinary management are essential to improve outcomes in such complex presentations.

Keywords: Limbic encephalitis, anti-GABA-B receptor, paraneoplastic syndrome, psychosis, stereotypic movements.

ÖZ

Limbik ensefalit (LE), nöbetler, hafıza bozukluğu ve davranış değişiklikleri gibi subakut limbik disfonksiyonla karakterize, nadir görülen bir klinik sendromdur ve genellikle otoimmün veya paraneoplastik nedenlerle ilişkilidir. Küçük hücreli akciğer kanseri (KHAK) ile sıkça ilişkili olan anti-gamma aminobutirik asit-B (anti-GABA-B) reseptörle ilişkili LE, genellikle nöbetler ve bilişsel gerileme gibi nörolojik semptomlarla ortaya çıkar. Ancak psikoz gibi belirgin psikiyatrik semptomlar nadiren bildirilmiş olup tanı zorluklarına yol açmaktadır. Bu makalede, akut dezorganize davranış, paranoid hezeyanlar ve bilişsel bozukluk ile birlikte status epileptikus tablosu sergileyen 56 yaşında bir kadın hasta sunulmaktadır. İlk tetkikler, dahil olmak üzere manyetik rezonans görüntüleme ve beyin omurilik sıvısı (BOS) analizi sonuçsuz kalmıştır. Levetirasetam kaynaklı psikoz ve Hashimoto ensefaliti düşünülmüşse de, kalıcı semptomlar ileri değerlendirmeyi gerekli kılmıştır. Torasik görüntüleme bir akciğer kitlesi ortaya koymuş ve biyopsi ile KHAK olarak doğrulanmıştır. BOS analizi ise pozitif anti-GABA-B reseptör antikorları tespit etmiş ve bu durum paraneoplastik LE tanısını doğrulamıştır. Tedavi; yüksek doz steroidler, antipsikotikler ve kemoterapiyi içermiş ve belirgin semptom iyileşmesi sağlanmıştır. Bu olgu, belirgin psikiyatrik semptomlar ve nöbetler sergileyen hastalarda paraneoplastik otoimmün ensefalitin dikkate alınmasının önemini vurgulamaktadır. Psikiyatrik değerlendirme sırasında bir akciğer kitlesinin tespiti, anti-GABA-B reseptör LE tanısında kilit rol oynamıştır. Erken tanı ve multidisipliner yaklaşım, bu tür karmaşık klinik tabloların sonuçlarını iyileştirmek için esastır.

Anahtar Kelimeler: Limbik ensefalit, anti-GABA-B reseptör, paraneoplastik sendrom, psikoz, stereotipik hareketler

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Received: 16.01.2025 **Accepted:** 22.06.2025 **Publication Date:** 04.07.2025

Cite this article as: Erarslan N, Pirdoğan Aydın E, Cerrahoğlu Şirin T, Akil Özer Ö. Delayed diagnosis of anti-GABA-B antibody paraneoplastic limbic encephalitis characterized by persecutory delusions: a case report. Hamidiye Med J. 2025;6(2):124-127

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Introduction

In recent years, the growing recognition and awareness of limbic encephalitis (LE) have underscored its importance as a critical diagnosis in the context of neuropsychiatric symptoms. This increased awareness can profoundly influence both the course of the disease and the treatment strategies. LE is a clinical syndrome characterized by a subacute onset of limbic symptoms, with structural and functional evidence of mesiotemporal damage in the absence of a more plausible explanation than an autoimmune or paraneoplastic cause (1,2). The paraneoplastic form of LE is associated with tumors such as small cell lung cancer (SCLC), germ-cell testicular tumors, breast cancer, Hodgkin's lymphoma, immature teratoma, and thymoma. Among these, SCLC is the most commonly linked with antibodies such as anti-Hu, anti-Ma2, anti-NMDAR, anti-AMPA, and anti-gamma aminobutyric acid-B (anti-GABA-B) often targeting the limbic system. Patients may present with mood and sleep disturbances, seizures, hallucinations, and short-term memory loss, which may progress to dementia (3).

The discovery of newly identified antibodies related to LE has expanded our understanding of the condition's clinical spectrum. Lancaster and colleagues were the first to describe a case series of fifteen patients with LE associated with GABA-B receptor antibodies (4). LE linked to anti-GABA-B antibodies is predominantly characterized by neurological symptoms, including epileptic seizures, status epilepticus, and rapid cognitive decline. However, psychiatric symptoms may include personality changes such as loss of interest, irritability, emotional instability, and increased aggression (e.g., verbal or physical outbursts). Affective symptoms like sadness are relatively common, while psychotic features such as hallucinations and paranoid thoughts are rare but have been documented in the literature (5,6).

Here, we report the case of a 56-year-old woman who presented with persecutory delusions, disorganized behavior, rapidly progressive cognitive impairment, and seizures. She was diagnosed with LE associated with anti-GABA-B receptor antibodies, confirmed by a biopsy revealing SCLC. The patient and her son were informed about the study, and written informed consent was obtained.

Case Report

A 56-year-old housewife living with her two sons was admitted to our psychiatric clinic with acute disorganized behavior, speech disturbances, and paranoid delusions. At admission, she displayed stereotypic hand movements, disorientation to time and place, and disorganized speech.

Her medical history included hypothyroidism, treated tuberculosis, and chronic obstructive pulmonary disease. Five years earlier, she had been treated with fluoxetine for two years for a non-psychotic major depressive episode.

Three months prior to admission, she experienced her first generalized tonic-clonic seizure and visited the emergency department. Brain magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analyses showed no abnormalities. Scalp interictal electroencephalogram revealed continuous 5-6 Hz theta waves. She was discharged on levetiracetam 1000 mg/day. However, she experienced three additional seizures over the following three months, the last of which evolved into status epilepticus, requiring a 28-day stay in the intensive care unit (ICU). Upon ICU discharge, her levetiracetam dose was increased to 3000 mg/day, and she remained seizure-free for the following month.

Approximately one month after ICU discharge, she began to display increasing behavioral disturbances, including disorganized behavior, speech disturbances, and paranoid delusions. These symptoms progressively worsened and led to her psychiatric admission two months later.

At psychiatric evaluation, she appeared older than her stated age and wore oversized clothing. Her son reported mild weight loss and a decline in personal hygiene. She showed limited cooperation, increased psychomotor activity, and perseverative, disorganized, and incoherent speech. Her thought processes were tangential, with impaired goal-directedness and paranoid ideation, but no hallucinations were noted. Her appetite was decreased, and her sleep was also decreased. She smoked 1.5 packs of cigarettes daily and reported no alcohol or substance use.

Premorbidly, her son described her as anxious and introverted, with normal developmental milestones and motor skills. Family history was notable for epilepsy in all three of her sons: one with absence seizures, and two with generalized tonic-clonic seizures that resolved in adulthood.

Neurological examination revealed impaired orientation to time and place but no cranial nerve, cerebellar, or pyramidal signs. Mental status examination confirmed confusion, disorientation, impaired concentration, and poor cooperation. According to her son, her baseline intellectual functioning had been normal.

During hospitalization, psychosis due to an underlying medical condition was considered the preliminary diagnosis. Differential diagnoses included levetiracetam-induced psychotic disorder, postictal psychosis, Hashimoto's encephalopathy, autoimmune LE, and catatonia. Her vital signs were within normal limits. Neuroimaging and laboratory investigations, including thoracic radiography, thoracoabdominal computed tomography (CT), and lumbar puncture, were performed. Except for thyroid function

tests, hematological and biochemical parameters were within the normal range. Thyroid tests showed TSH: 55.90, Anti-TPO: >600, and free T4: 6.32. Despite these findings, Hashimoto's encephalopathy was ruled out by endocrinology consultation.

Levetiracetam-induced psychosis was also considered, and her medication was gradually replaced with carbamazepine. However, no improvement in psychiatric symptoms was observed. Repeat brain MRI revealed increased FLAIR signal intensity in the right medial temporal lobe. Thoracic CT revealed a 35 mm mass in the lower lobe of the left lung, obstructing the bronchus. Bronchoscopy and biopsy confirmed stage IV SCLC, which strongly supported the diagnosis of paraneoplastic LE. A subsequent lumbar puncture revealed anti-GABA-B receptor antibody positivity, confirming the diagnosis.

Treatment and Outcome

Initial treatment consisted of carbamazepine, haloperidol, and biperiden, which was later revised to risperidone and quetiapine. Due to persistent psychiatric symptoms and the confirmed diagnosis of LE, the patient received 1 g/day intravenous methylprednisolone for five consecutive days. This resulted in substantial symptom reduction and marked cognitive improvement. Her psychiatric medications were then adjusted to olanzapine 10 mg and quetiapine 100 mg.

She has been followed up for eight months by psychiatry, neurology, and oncology services. During this time, she completed eight cycles of chemotherapy and initiated radiation therapy. In the post-steroid and chemotherapy period, the patient remained seizure-free and showed sustained cognitive improvement. Positron emission tomography imaging revealed regression of SCLC; oncological treatment was completed. However, three months after completing chemotherapy, seizures recurred. Follow-up brain MRI showed increased FLAIR hyperintensity in the right temporal lobe.

Discussion

This case highlights the unique clinical features of GABA-B receptor-associated LE, in which the diagnosis was complicated by the initial neurological presentation, prominent psychiatric symptoms, and rapidly progressive cognitive decline. A key factor was the delayed recognition of encephalitis, despite the occurrence of status epilepticus during the patient's ICU stay. Autoimmune LE often presents with a combination of psychiatric and neurological symptoms, which can obscure the underlying neurological etiology and contribute to diagnostic delays (2).

The patient's prominent psychiatric symptoms including disorganized behavior, paranoid delusions, and stereotypical gestures were particularly noteworthy. Although such motor behaviors are less frequently reported, they have been described in autoimmune encephalitis cases, where stereotyped movements and disorganized thought processes can mimic primary psychiatric disorders (4,6). This underscores the importance of considering autoimmune encephalitis in patients who present primarily with psychiatric manifestations.

The incidental discovery of a lung mass during the psychiatric evaluation was pivotal in narrowing the diagnosis to paraneoplastic GABA-B receptor encephalitis, which is strongly associated with SCLC (7). This link between GABA-B receptor LE and paraneoplastic syndromes is well-established in the literature (2).

GABA-B receptor LE typically presents with seizures, status epilepticus, and rapidly progressing cognitive deterioration. Psychiatric symptoms such as anxiety, mood disturbances, and confusion may accompany these neurological signs but are generally considered secondary to seizure activity (8). The early occurrence of status epilepticus is a hallmark feature of GABA-B receptor LE and can lead to a swift progression of cognitive and behavioral disturbances, including memory impairment and thought disorganization (5).

In the present case, the patient initially experienced generalized tonic-clonic seizures that culminated in status epilepticus, consistent with the classic presentation of GABA-B receptor LE. However, the subsequent emergence of prominent psychiatric symptoms such as disorganized behavior, paranoid ideation, and stereotypic hand movements added diagnostic complexity. Unlike the typical course, in which psychiatric manifestations follow neurological symptoms, this patient's psychiatric features became central to her clinical presentation.

Autoimmune LE was considered the leading diagnosis based on the coexistence of seizures, cognitive decline, and psychiatric symptoms. Levetiracetam-induced psychosis was deemed unlikely due to the persistence of symptoms despite drug discontinuation. Postictal psychosis was ruled out due to the prolonged and progressive nature of the symptoms. Although hypothyroidism was present, it was not considered the primary etiology after the identification of anti-GABA-B antibodies and a confirmed paraneoplastic syndrome. Catatonia, suggested by the presence of disorganized behavior and stereotypies, was also considered as part of the broader autoimmune encephalitis spectrum.

A thorough diagnostic approach is essential in patients presenting with unexplained psychiatric and neurological symptoms, as an underlying malignancy may be a critical clue in identifying paraneoplastic autoimmune conditions (3).

Conclusion

In conclusion, we present a compelling case of GABA-B receptor LE characterized by psychosis, stereotyped movements, and cognitive impairment, with a history of status epilepticus; underscoring the diagnostic challenges posed by overlapping psychiatric and neurological features.

Ethics

Informed Consent: The patient and her son were informed about the study, and written informed consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practies: N.E., E.P.A., T.C.Ş., Ö.A.Ö., Concept: N.E., E.P.A., Design: N.E., E.P.A., T.C.Ş., Data Collection of Processing: N.E., E.P.A., Literature Search: N.E., E.P.A., Writing: N.E., E.P.A., T.C.Ş.

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

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

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