HAMIDIYE MEDICAL JOURNAL
The Official Journal of University of Health Sciences Türkiye, Hamidiye Faculty of Medicine
E-ISSN: 2718-0956
September - 2025
Volume - 6
Issue - 3

ORIGINAL ARTICLES

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www.hamidiyemedj.com

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HAMIDIYE MEDICAL JOURNAL

2025
Volume 6
Issue 3

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Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Türkiye
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: September 2025 **E-ISSN:** 2718-0956
International periodical journal published three times in a year.

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HAMIDIYE MEDICAL JOURNAL

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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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HAMIDIYE
MEDICAL JOURNAL

2025
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Issue 3

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DOI: 10.4274/hamidiyemedj.galenos.2025.42713

Hamidiye Med J 2025;6(3):128-134

Evaluation of the Triglyceride-Glucose Index with Different Generations of Beta-Adrenergic Blockers

Farklı Nesil Beta-Adrenerjik Blokerlerde Trigliserit-Glukoz İndeksinin Değerlendirilmesi

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ABSTRACT

Background: Beta-blockers (β-blockers) work by blocking β-adrenergic receptors and differ in their metabolic effects and side effects. We aimed to compare the metabolic effects of different generations of β-blockers by evaluating the triglyceride-glucose (TyG) index in patients treated with this group of drugs.

Materials and Methods: Subjects using β-blockers were divided into three groups according to first-generation, second-generation, and third-generation β-blockers. The TyG index values of the subjects were calculated.

Results: There were no differences in age, sex, presence of hypertension, coronary artery disease, or use of medications among the three groups. Glucose, triglycerides, hemoglobin A1c and TyG index were significantly different between three groups of patients. A post-hoc analysis revealed group differences between the third-generation, second-generation, and first-generation, β-blockers. Patients taking third-generation β-blockers had the lowest TyG index and the lowest triglyceride and glucose levels. Univariable and multivariable linear regression analyses showed that age and the β-blocker group were independent predictors of TyG index values.

Conclusion: The use of third generation β-blockers was associated with better metabolic profiles.

Keywords: Triglyceride, glucose, β-blocker, metabolic profile

ÖZ

Amaç: Beta-blokerler (β-blokerler) β-adrenerjik reseptörleri bloke ederek çalışır ve kardiyovasküler hastalıklarda en sık kullanılan ilaçlar arasındadır. Metabolik etkileri ve yan etkileri bakımından farklılık gösterirler. Bu çalışmada amacımız β-blokerler ile tedavi edilen hastalarda trigliserid-glukoz indeksini (TyG) değerlendirerek farklı nesil β-blokerlerin metabolik etkilerini karşılaştırmayı amaçladık.

Gereç ve Yöntemler: β-bloker kullanan hastalar birinci, ikinci ve üçüncü nesil β-blokerlere göre üç gruba ayrıldı. Bu hastaların TyG indeks değerleri hesaplanarak karşılaştırıldı.

Bulgular: Üç grup arasında yaş, cinsiyet, hipertansiyon varlığı, koroner arter hastalığı veya ilaç kullanımı açısından fark yoktu. glukoz, trigliserit, hemoglobin A1c ve TyG indeksi üç hasta grubu arasında anlamlı derecede farklıydı. Post-hoc analiz, üçüncü nesil, ikinci nesil ve birinci nesil β-blokerler arasında grup farklılıkları olduğunu ortaya koydu. Üçüncü nesil β-bloker kullanan hastalar en düşük TyG indeksinin yanı sıra en düşük trigliserit ve glukoz seviyelerine sahipti. Tek değişkenli ve çok değişkenli doğrusal regresyon analizleri, yaşın ve β-bloker grubunun TyG indeks değerlerinin bağımsız belirleyicileri olduğunu gösterdi.

Sonuç: Üçüncü nesil β-blokerlerin kullanımı daha iyi metabolik profil ile ilişkilidir.

Anahtar Kelimeler: Trigliserid, glukoz, β-bloker, metabolik profil

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Received: 06.10.2024 **Accepted:** 15.07.2025 **Epub:** 02.09.2025 **Publication Date:** 30.09.2025

Cite this article as: Erciyes D, Yıldız C, Arpaç A, Turhan Çağlar AN. Evaluation of the triglyceride-glucose index with different generations of beta-adrenergic blockers. Hamidiye Med J. 2025;6(3):128-134

Introduction

Beta-blockers (β-blockers) exert their actions by blocking β-adrenergic receptors (1). However, they differed in terms of metabolic actions and side effects. Traditionally, β-blockers are divided into three groups with respect to their pharmacological features. First generation β-blockers non-selectively act on β-1 and β-2 receptors, whereas second generation β-blockers show greater affinity for β-1 receptors. More recently introduced third generation β-blockers differ by their cardioselective actions and have additional vasodilating properties by blocking alpha (α)-1 and activating β-3-adrenergic receptors (1). Various studies have investigated the metabolic adverse effects of these drugs. Metoprolol, atenolol, and propranolol, considered as conventional β-blockers, have negative effects on insulin sensitivity and glucose metabolism. They are found to be linked to heightened risk of new-onset diabetes mellitus (2). On the contrary, β-blockers with vasodilating actions have more favorable cardiometabolic effects (3,4).

Insulin resistance, reduced response to the circulating insulin, is closely associated with two common conditions, namely, metabolic syndrome and type 2 diabetes mellitus (5). Insulin, by affecting the insulin receptor tyrosine kinase, brings about a series of reactions in different cell types such as glucose uptake in skeletal muscle, inhibition of gluconeogenesis in liver, and suppression of lipolysis in adipocytes (6). Insulin resistance with resultant hypertriglyceridemia, low levels of high-density lipoprotein-cholesterol (HDL-C), high blood pressure level, proinflammatory status, and endothelial dysfunction make a large contribution to cardiovascular disease pathogenesis (7-11). Several methods have been used to diagnose insulin resistance with different sensitivities and complexities (12). The hyperinsulinemic-euglycemic glucose clamp is considered the best method (13) for the identification of insulin resistance, but it is expensive and requires expertise. The triglyceride-glucose (TyG) index is a novel biomarker that has been suggested to predict the insulin resistance status of the body in patients with or without diabetes (14,15). Clinical significance of this index has been shown in several diseases such as acute and chronic coronary syndromes, heart failure, cerebrovascular disease, and populations with high cardiovascular risk (16-20). The present study was aimed at measuring the metabolic effects of different generations of β-blockers by evaluating the TyG index in patients who were under treatment with this group of drugs.

Materials and Methods

We retrospectively screened the hospital files of the patients who applied to our cardiology clinic at a tertiary care hospital. We enrolled consecutive patients who met the inclusion criteria applied in our outpatient clinic from 1 June 2022 to 1 June 2023. Patients diagnosed with acute coronary syndrome, diabetes mellitus, thyroid diseases, hepatic or renal failure, malignancy, or inflammatory diseases were excluded from the study. Additionally, those using triglyceride-lowering drugs were not included. Patients' clinical characteristics, demographic features and biochemical variables were obtained from the hospital records. After the application of exclusion criteria 712 patients were enrolled in the study. Patients were using six different β-blockers, namely metoprolol, atenolol, carvedilol, propranolol, bisoprolol, and nebivolol. We divided the patients into three groups according to first, second, and third generations of β-blockers. These groups consisted of 162, 303 and 242 patients, respectively.

Since our study was retrospective, we used the patients' blood results from the hospital's electronic records. We collected information regarding their glucose, triglyceride, and HgbA1c levels. The multiplication of glucose and triglyceride values was divided by two. The natural logarithmic transformation of the obtained results gave the TyG index values.

No artificial intelligence assistance was used during the preparation of the manuscript. The Demiroğlu Bilim University Clinical Research Ethics Committee approved the study (approval number: 44140529, dated: 31.01.2023) and it was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

The normality of the data was analyzed using the Kolmogorov-Smirnov test. Data showing normal distribution are expressed as the mean and standard deviation; otherwise, they are expressed as the median and interquartile range. A one-way analysis of variance or a Kruskal-Wallis test was used to compare the three groups, depending on the distribution of the data. Post-hoc analysis between groups was performed using Bonferroni correction. Categorical variables were compared by using a chi-square test. To identify predictors of the TyG index, a univariate linear regression analysis was performed. Because the TyG index was multicollinear with triglyceride and glucose levels in the presence of diabetes mellitus, we did not use these variables in the linear regression analysis. Variables

with statistically significant results were then entered into a multivariable linear regression analysis. A p-value less than 0.05 was considered significant.

Results

Median age of the study population was 59.00 (55.00-62.00) years, 366 51.4% of them were male, 367 51.5% of them were hypertensive, 365 51.3% patients had coronary artery disease, 252 35.4% of them were taking angiotensin converting enzyme inhibitors (ACE-I), 111 15.6% of them were taking angiotensin receptor blockers (ARB), 339 47.6% of them were using calcium channel blockers (CCB), 94 13.2% of them were using thiazide type diuretics and 365 51.3% of them were using statins. Median fasting glucose and triglyceride levels of the study group were 97.00 (94.00-100.00) mg/dL and 131.00 (120.00-147.00) mg/dL, respectively. Median hemoglobin A1c (HbA1c) and TyG index values were 5.70 (5.60-5.90) and 8.73 (8.64-8.90), respectively. Average duration of β-blockers use was found to be 42.00 (24.00-53.00) months.

When comparing first, second, and third generation β-blockers, there were no differences in age, sex, presence of hypertension, coronary artery disease, or use of medications including ACE-I, ARB, CCB, thiazide-type diuretics, and statins. Glucose, triglyceride, HbA1c, and TyG index were significantly different between the three groups of patients. A post-hoc analysis revealed group differences between the third-generation, second-generation, and first-generation β-blockers. Patients taking third-generation β-blockers had the lowest TyG index, as well as the lowest triglyceride and glucose levels. Table 1 shows a comparison of the three groups' clinical and biochemical variables.

Univariable and multivariable linear regression analyses showed that age and the β-blocker group were independent predictors of TyG index values (Tables 2 and 3).

Table 1. Comparaison of three groups

	First generation group (n=162)	Second generation group (n=303)	Third generation group (n=242)	p-value	
Age (years)	59.00 (55.00-62.00)	59.00 (56.00-63.00)	58.00 (54.00-62.00)	0.083	
Gender (n,%)				0.162	
Female	84 (51.9)	154 (50.8)	108 (43.7)		(Group 3-2) p=0.097
Male	78 (48.1)	149 (49.2)	139 (56.3)		(Group 3-1) p=0.107
					(Group 2-1) p=0.833
Hypertension (n,%)	86 (53.1)	164 (54.1)	117 (47.4)	0.261	
					(Group 3-2) p=0.117
					(Group 3-1) p=0.258
					(Group 2-1) p=0.830
CAD (n,%)	79 (48.8)	150 (49.5)	136 (55.1)	0.332	
					(Group 3-2) p=0.195
					(Group 3-1) p=0.212
					(Group 2-1) p=0.879
ACE-I (n,%)	66(40.7)	102 (33.7)	84 (34)	0.269	
					(Group 3-2) p=0.932
					(Group 3-1) p=0.167
					(Group 2-1) p=0.130
ARB (n,%)	23 (14.2)	44 (14.5)	44 (17.8)	0.489	
					(Group 3-2) p=0.295
					(Group 3-1) p=0.334
					(Group 2-1) p=0.924
Ca-channel blockers (n,%)	68 (42)	149 (49.2)	122 (49.4)	0.263	
					(Group 3-2) p=0.959
					(Group 3-1) p=0.141

Table 1. Continued

	First generation group (n=162)	Second generation group (n=303)	Third generation group (n=242)	p-value	
					(Group 2-1) p=0.138
Thiazide diuretics (n,%)	18 (11.1)	39 (12.9)	37 (15)	0.515	
					(Group 3-2) p=0.476
					(Group 3-1) p=0.262
					(Group 2-1) p=0.581
Statin (n,%)	79 (48.8)	150 (49.5)	136 (55.1)	0.332	
					(Group 3-2) p=0.195
					(Group 3-1) p=0.212
					(Group 2-1) p=0.879
Glucose (mg/dL)	104.00 (95.00-109.00)	97.00 (93.00-99.75)	96.00 (93.00-98.00)	<0.001	
					(Group 3-2) p=0.002
					(Group 3-1) p<0.001
					(Group 2-1) p<0.001
Triglyceride (mg/dL)	136.12±17.19	133.94±17.00	127.81±11.43	<0.001	
					(Group 3-2) p<0.001
					(Group 3-1) p<0.001
					(Group 2-1) p<0.001
HbA1c	5.74±0.15	5.71±0.35	5.66±0.15	<0.001	
					(Group 3-2) p<0.001
					(Group 3-1) p<0.001
					(Group 2-1) p=0.001
TyG index	8.81±0.17	8.77±0.15	8.71±0.11	<0.001	
					(Group 3-2) p<0.001
					(Group 3-1) p<0.001
					(Group 2-1) p<0.001

ACE-I: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, CAD: Coronary artery disease, HbA1c: Hemoglobin A1c, TyG index: Triglyceride-glucose index

Table 2. Univariable linear regression analysis for TyG index

	β	p-value	95% CI
Age	0.190	<0.001	0.004-0.009
Beta-blocker group	-0.481	<0.001	-0.122--0.093
Gender	-0.042	0.269	-0.040-0.011
Hypertension	-0.030	0.427	-0.036-0.015

CI: Confidence interval, TyG index: Triglyceride-glucose index

Table 3. Multivariable linear regression analysis for TyG index

	β	p-value	95% CI
Age	0.146	<0.001	0.003-0.007
Beta-blocker group	-0.467	<0.001	-0.119--0.090

CI: Confidence interval, TyG index: Triglyceride-glucose index

Discussion

Our study showed that patients who were treated with the third generation of β-blockers had better metabolic profiles and lower values of the TyG index compared to patients who were treated with other types of β -blockers. Additionally, the use of third-generation β-blockers was an independent predictor of lower TyG values.

Both selective and non-selective β-blockers have been linked to the occurrence of insulin resistance and new-onset diabetes mellitus (21). Since this group of drugs is usually used in patients with high cardiovascular risk, their adverse effects have become important for clinicians. Over time, β-blockers with additional vasodilating and distinct metabolic activities have been developed, making them desirable in clinical practice.

Non-vasodilating β-blockers comprise first and second-generation β-blockers and their effects are mainly mediated through a decrease in cardiac output (22). They do not affect peripheral resistance, and administration of them is associated with unfavorable side effects. Several studies have been conducted in order to compare the metabolic side effects of different β-blockers. A post-hoc analysis of the Atherosclerosis Risk in Communities study has shown that patients who are treated with non-vasodilating β-blockers are at 28% higher risk of getting diabetes mellitus compared to patients who do not use them (21). Likewise, in the Losartan Intervention for Endpoint reduction study, the risk of diabetes mellitus development was 25% lower in patients who were treated with losartan in comparison to patients who were treated with atenolol (23). Carvedilol, a third generation β-blocker with non-selective β-adrenoceptor and α blocker activity, has been shown to improve insulin sensitivity and increase HDL-C levels (24). In a study in which carvedilol was compared with metoprolol, carvedilol has been associated with an increment of 8.5% in insulin sensitivity, where metoprolol decreased insulin sensitivity by up to 14% (24) In the GEMINI trial, carvedilol showed a more favorable metabolic effect in comparison to metoprolol. In that study, carvedilol decreased insulin resistance by 9.1%, whereas insulin resistance did not show any difference in patients treated with metoprolol (25). Nebivolol exerts its effects by blocking β-1 adrenergic receptors and increasing NO production, which might be the cause of more favorable metabolic effects of the drug (26). In comparison to nebivolol, metoprolol significantly reduced the insulin sensitivity index in patients with metabolic syndrome (27). In a study conducted by Poirier et al. (28), atenolol reduced insulin sensitivity by 20%, and insulin sensitivity was not preserved with atenolol.

The TyG index has been validated in numerous studies as a superior tool for the prediction and identification of insulin resistance compared to the homeostasis model assessment of insulin resistance model (29). Its utility for both prognosis and diagnosis has been demonstrated across multiple studies. Higher TyG index levels were associated with an increased risk of chronic kidney disease, type 2 diabetes mellitus, diabetic retinopathy, non-alcoholic fatty liver disease, dementia, and ischemic stroke (30). Zhang and Hou (31) examined NHANES data to investigate the relationship between the TyG index and heart failure. They discovered a significant J-shaped dose-response relationship between the TyG index and heart failure risk. In a study of the general population, Liu et al. (32) analyzed the dose-response relationship between the TyG index and cardiovascular disease and mortality, reporting that elevated TyG index levels were linked to a higher incidence of coronary artery disease and myocardial infarction. In the present study, we investigated the TyG index in patients who applied to our cardiology outpatient clinic. Our results showed that patients who were treated with the third generation of β-blockers had significantly lower levels of TyG index in comparison to patients who were treated with other types of β-blockers. In our study, third-generation β-blockers consisted of nebivolol and carvedilol. Comparison of these drugs showed that the TyG index was not different (p=0.352). Second-generation β-blockers consisted of atenolol, metoprolol, and bisoprolol. When these drugs were compared in a separate analysis, the analysis showed that there was a a difference between bisoprolol and atenolol groups. Patients using bisoprolol exhibit lowered TyG index values compared to patients who were using atenolol (8.81±0.18 vs. 8.72±0.12, demonstrating a statistically significant difference, p=0.004).

Study Limitations

Our sample size was small, and the study was conducted on a single-center population. We did not conduct long-term follow-ups of the patients, so we could not assess the prognostic value of the TyG index or whether its prognostic utility was superior to that of glucose and triglyceride values.

Conclusion

Use of third generation β-blockers was associated with better metabolic profile.

Ethics

Ethics Committee Approval: The Demiroğlu Bilim University Clinical Research Ethics Committee approved the study (approval number: 44140529, dated: 31.01.2023) and it was conducted in accordance with the Declaration of Helsinki.

Informed Consent: All patients gave informed consent before study participation.

Footnotes

Authorship Contributions

Concept: D.E., A.A., Design: D.E., F.N.T.Ç., Data Collection or Processing: D.E., C.Y., A.A., F.N.T.Ç., Analysis or Interpretation: D.E., C.Y., A.A., F.N.T.Ç., Literature Search: C.Y., Writing: D.E., C.Y.

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.2025.59244

Hamidiye Med J 2025;6(3):135-143

Is There Any Difference Between Pandemic and Pre-Pandemic Periods in Hemoptysis Management?

Hemoptizi Yönetiminde Pandemi ve Pandemi Öncesi Dönem Arasında Fark Var mıdır?

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ABSTRACT

Background: Since it can be a life-threatening condition, hemoptysis is one of the most important emergencies in pulmonology practice. We aimed to determine whether there was a difference in the frequency of hospitalizations due to hemoptysis, and in the etiology of hemoptysis, during the Coronavirus Disease 19 (COVID-19) pandemic period compared to the pre-pandemic period.

Materials and Methods: Retrospective, observational, cross-sectional. According to the date of hospitalization, the patients who were hospitalized during the pre-pandemic (March 11, 2019-March 10, 2020) and pandemic, (March 11, 2020-March 10, 2021) periods were evaluated for eligibility. The Z test was used to determine whether there was a difference between the pre-pandemic and pandemic groups in terms of the frequency of hospitalization due to hemoptysis. $p \leq 0.05$ was considered statistically significant.

Results: There was no significant difference between the groups according to age (p=0.20), gender (p=0.53), or median length of hospital stay (p=0.37). The hospitalization rate due to hemoptysis was 1.9% in the pre-pandemic group and 2.2% in the pandemic group (p=0.07). During the pandemic period, the decrease in the rate of hospitalization for all reasons was 30.0%, and the decrease in the rate of hospitalization for hemoptysis was 20.4% (p<0.0001). In terms of etiological causes, chronic obstructive pulmonary disease (p=0.029) and aspergilloma (p=0.017) were observed at significantly higher rates during the pre-pandemic period. COVID-19 was detected as the cause of hemoptysis in 21 (5.9%) cases.

Conclusion: There was no significant difference in the frequency of hospitalizations due to hemoptysis during the pandemic period. However the decrease in all hospitalizations; the decrease in hemoptysis-related hospitalizations was significantly lower. We consider that this may be due to the emergency nature of hemoptysis and the presence of patients with COVID-19 in the pandemic group. A similar proportion of etiological causes and idiopathic cases indicates that there was no difference in the approach to hemoptysis during the pandemic period.

Keywords: COVID-19, epidemiology, hemoptysis, hospitalization, mortality, pandemics

ÖZ

Amaç: Hayatı tehdit edici bir durum olabileceğinden hemoptizi, göğüs hastalıkları pratiğindeki en önemli acil durumlardan biridir. Çalışmamızda, pandemi öncesi dönemle karşılaştırarak, Koronavirüs Hastalığı 2019 (COVID-19) pandemi döneminde, hemoptizi nedeniyle hastaneye yatış sıklığında ve hemoptizi etyolojisinde farklılık olup olmadığını belirlemeyi amaçladık.

Gereç ve Yöntemler: Retrospektif, gözlemsel, kesitsel. Hastaneye yatış tarihine göre, pandemi öncesi (11 Mart 2019-10 Mart 2020) ve pandemi (11 Mart 2020-10 Mart 2021) dönemlerinde hastaneye yatırılan hastalar uygunluk açısından değerlendirildi. Hemoptizi nedeniyle hastaneye yatış sıklığı açısından pandemi öncesi ve pandemi grupları arasında fark olup olmadığını belirlemek için Z testi kullanıldı. $p \leq 0.05$ istatistiksel olarak anlamlı kabul edildi.

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Received: 17.02.2025 **Accepted:** 15.07.2025 **Epub:** 02.09.2025 **Publication Date:** 30.09.2025

Cite this article as: Hocaoğlu MA, Kavas M, Durmuş Koçak N. Is there any difference between pandemic and pre-pandemic periods in hemoptysis management? Hamidiye Med J. 2025;6(3):135-143

ÖZ

Bulgular: Gruplar arasında yaşa (p=0,20), cinsiyete (p=0,53) ve ortanca hastanede kalış süresine (p=0,37) göre anlamlı fark saptanmadı. Hemoptizi nedeniyle hastane yatış oranı pandemi öncesi grupta %1,9 iken pandemi grubunda %2,2 olarak bulundu (p=0,07). Pandemi döneminde tüm nedenlere bağlı hastane yatış oranındaki azalma %30,0 iken hemoptizi nedeniyle hastane yatış oranındaki azalma %20,4 (p<0,0001) idi. Etiyolojik nedenler açısından pandemi öncesi dönemde kronik obstrüktif akciğer hastalığı (p=0,029) ve aspergilloma (p=0,017) anlamlı olarak daha yüksek oranlarda gözlendi. Hemoptizi nedeni olarak 21 (%5,9) olguda COVID-19 saptandı.

Sonuç: Pandemi döneminde hemoptizi nedeniyle hastaneye yatış sıklığında anlamlı bir fark görülmemiştir. Ancak tüm hastaneye yatışlarda azalma olmasına rağmen hemoptizi ile ilişkili hastaneye yatışlarda azalma anlamlı olarak daha düşük olmuştur. Bunun hemoptizinin acil doğası ve pandemi grubunda COVID-19'lu hastaların bulunmasından kaynaklanabileceğini düşünmekteyiz. Ayrıca etiyolojik nedenlerin ve idiyopatik vakaların benzer oranda olması pandemi döneminde hemoptiziye yaklaşımda fark olmadığını göstermektedir.

Anahtar Kelimeler: COVID-19, epidemiyoloji, hemoptizi, hastaneye yatış, mortalite, pandemi

Introduction

Hemoptysis develops from hemorrhage originating from the pulmonary or bronchial vascular system and can clinically manifest as a mild form of streaking in the sputum or as a severe, life-threatening condition due to asphyxia. The etiology of hemoptysis includes many different conditions, such as inflammatory diseases [e.g., tuberculosis (TB)]; bronchial carcinomas and metastases; cardiovascular diseases (e.g., pulmonary embolism and mitral stenosis); and the use of anticoagulant and thrombolytic drugs (1). In Türkiye, TB, lung cancer, and bronchiectasis have been reported to be among the most common causes of hemoptysis (2).

Coronavirus Disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a member of the coronavirus family, and rapidly spread across the world from Wuhan, China. It was declared a pandemic by the World Health Organization on March 11, 2020 (3). SARS-CoV-2 causes the disease by entering cells containing high levels of angiotensin-converting enzyme-2 receptors, such as alveolar cells, myocytes, and vascular endothelial cells, and binding to these receptors (4). Although hemoptysis, is not a commonly observed symptom in the course of COVID-19 infection, there is evidence in the literature, particularly in case reports (5,6).

We planned this study based on our clinical observation of increased hospital presentations and hospitalizations due to hemoptysis during the pandemic period. Thus, we aimed to investigate whether there were differences in the frequency and etiology of hemoptysis among hospitalized patients during the pandemic period in comparison with thepre-pandemic period.

Materials and Methods

Study Design

Retrospective, observational, cross-sectional.

Patient Selection

All hospitalized patients during the pre-pandemic (March 11, 2019-March 10, 2020) and pandemic (March 11, 2020-March 10, 2021) periods were screened from the hospital's automation system, and those with the International Classification of Diseases (ICD) code of R04.2 (hemoptysis) were identified. The patients were divided into two groups according to their hospitalization date: the pre-pandemic group and the pandemic group.

The inclusion criteria were as follows:

1. Being aged 18 years or over;
2. Being hospitalized and treated due to hemoptysis;
3. Having the etiology of hemoptysis investigated through the examinations performed.

Pregnant women and outpatients were excluded from the study.

Independent Variables

Age, gender, laboratory parameters, length of hospital stay (LOHS, days), comorbidities, etiology of hemoptysis, and in-hospital mortality.

Endpoints

The primary endpoint was an increase in the frequency of hospitalization due to hemoptysis between the two periods. The secondary endpoint was whether there was a difference between the two periods regarding the etiology of hemoptysis.

Statistical Analysis

Demographic data, laboratory parameters, comorbidities, LOHS, final diagnosis at discharge, and the presence of in-hospital mortality were compared between the pre-pandemic and pandemic groups. Demographic data were presented with descriptive statistics [number, percentage, mean and standard deviation, median, and interquartile range (IQR)]. The chi-square test was used to compare categorical variables between the groups, and parametric (Student's t-test) and non-parametric (Mann-Whitney U) tests were used to compare continuous variables, depending on the type of data distribution. The Z test was used to evaluate whether there was a proportional difference between the two groups in terms of hospitalization due to hemoptysis within the total hospitalizations. A p-value of ⩽0.05 was taken as the statistical significance level. Analyses were carried out using Statistical Package for the Social Sciences (SPSS) 17.5 software program (IBM® SPSS®, Chicago, IL, USA).

Ethics

Prior to the study, a scientific research application was made to the Republic of Turkey Ministry of Health, and approval was obtained. Ethical approval of the study protocol, which was prepared in accordance with the Declaration of Helsinki and Good Clinical Practices, was received from the University of Health Sciences Türkiye, Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital Ethics Committee (approval number: 116.2017.R-218, dated: 01.04.2021). Informed consent was not required since this was a retrospective study that used the hospital database system.

Results

A total of 516 patients hospitalized due to hemoptysis during the pre-pandemic period and 408 patients hospitalized due to hemoptysis during the pandemic period were evaluated for eligibility for participation in the study. After applying the exclusion criteria, 442 patients were included in the pre-pandemic group and 352 patients in the pandemic group (Figure 1). In the pre-pandemic group and pandemic group the ratio of male sex (69.5% vs. 71.6%, p=0.532) and the mean age (58.8±15.5 vs. 57.4±15.2 years, p=0.203) were not different. The median LOHS (IQR, 25-75) was 6.0 (4.0-9.0) days for the pre-pandemic group and 6.0 (4.0-8.0) days for the pandemic group (p=0.368).

Considering the patients in both groups (n=794), the most common comorbidities were hypertension (n=100, 12.6%), followed by chronic obstructive pulmonary disease (COPD) (n=89, 11.2%), coronary artery disease (CAD) (n=66, 8.3%), and diabetes mellitus (DM) (n=63, 7.9%). No significant difference was found between the two groups in terms of the frequency of comorbidities, except for CAD and

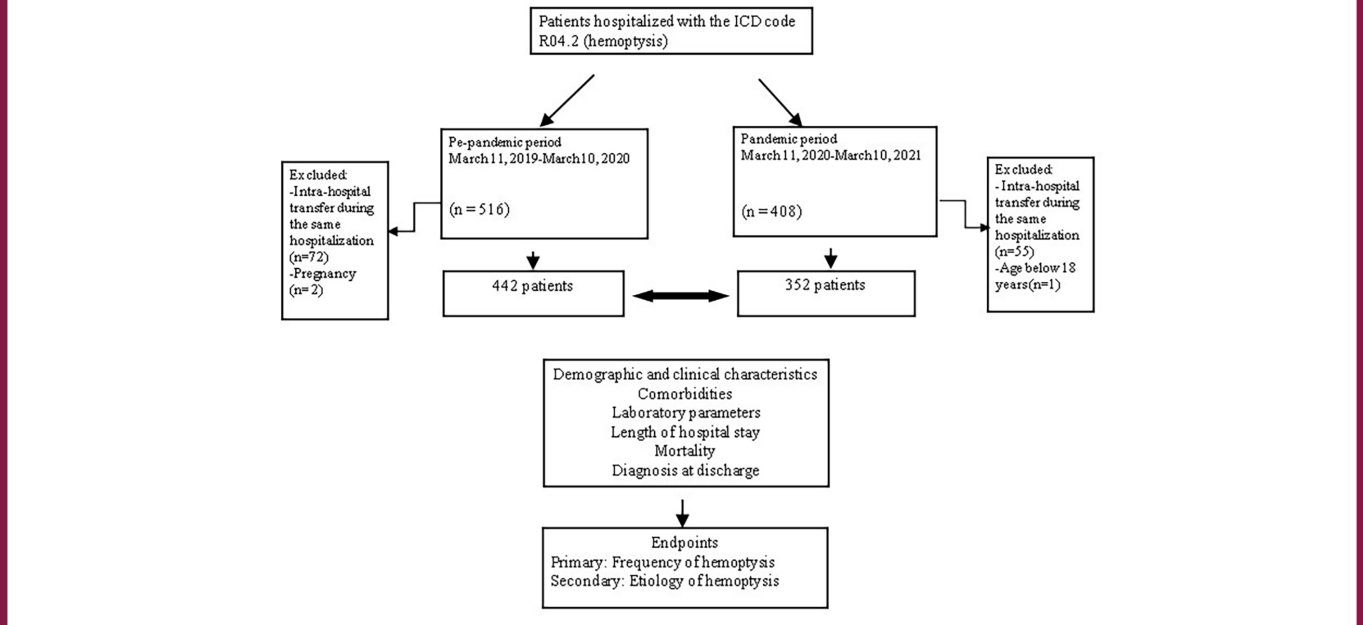

Figure 1. Study flow chart
ICD: International classification of iseases

hypertension, which were observed at significantly higher rates among the pre-pandemic group (10.1% vs. 5.9%, p=0.038, and 14.4% vs. 9.9%, p=0.053, respectively) (Table 1).

The comparison of the two groups according to laboratory parameters revealed a significantly lower C-reactive protein level in the pre-pandemic group (p=0.011) and a significantly lower serum troponin level in the pandemic group (p=0.020) (Table 2).

The examinations performed for the etiology of hemoptysis revealed that the most common diagnoses received by patients in the pre-pandemic group were lung cancer (n=96, 21.7%), lower respiratory tract infections (n=85, 19.2%), and bronchiectasis (n=77, 17.4%), while 11.1% of the cases were idiopathic (Figure 2A). Similarly, in the pandemic group, the most common etiological diagnoses were lung cancer (n=87, 24.7%), bronchiectasis (n=54, 15.3%), and lower respiratory tract infections (n=52, 14.8%), and the rate of idiopathic cases was 11.6% (Figure 2B). The comparison of the two groups according to the etiology of hemoptysis indicated significantly higher rates of COPD (9.3% vs. 5.1%, p=0.029) and aspergilloma (3.4% vs. 0.9%, p=0.017) in the pre-pandemic group. In the pandemic group, the cause of hemoptysis was COVID-19 in a total of 21 (5.9%) patients (Table 3).

In the pre-pandemic period, the total number of hospitalized patients was 23,301, of whom 442 (1.9%) were hospitalized due to hemoptysis. During the pandemic period, the total number of hospitalized patients was 16,321 with hemoptysis being the reason for hospitalization in 352 (2.2%) of these cases. When we applied the Z test to determine whether there was a difference between the two periods in terms of the frequency of hospitalization due to hemoptysis, we found no significant difference (p=0.071). However, despite the 30.0% decrease in total patient hospitalizations during the pandemic period, the decrease in hospitalizations due to hemoptysis was 20.4%, and there was a statistically significant difference between these two rates (p<0.0001).

In-hospital mortality was observed in eight of the 442 patients (1.8%) in the pre-pandemic group and eight of the 352 patients (2.3%) in the pandemic group (p=0.80).

Table 1. Distribution of demographic characteristics and comorbidities in the groups

Variables	Pre-pandemic (n=442)	Pandemic (n=352)	p-value
Sex, n (%) Male Female	 307 (69.5) 135 (30.5)	 252 (71.6) 100 (28.4)	 0.532
Age, mean (SD)	58.8 (15.5)	57.4 (15.2)	0.203
Comorbidities, n (%)			
Diabetes mellitus	41 (9.3)	22 (6.3)	0.146
Hypertension	65 (14.7)	35 (9.9)	**0.053**
Coronary artery disease	45 (10.1)	21 (5.9)	**0.038**
Atrial fibrillation	13 (2.9)	6 (1.7)	0.351
Heart failure	19 (4.3)	12 (3.4)	0.584
COPD	56 (12.6)	33 (9.4)	0.174
Asthma	17 (3.8)	15 (4.3)	0.856
Benign prostate hyperplasia	6 (1.4)	2 (0.6)	0.477
Hypothyroidism	2 (0.4)	3 (0.9)	0.660
Respiratory failure	32 (7.2)	25 (7.1)	1.000
GIS tumor	4 (0.9)	2 (0.6)	0.699
Breast cancer	1 (0.2)	3 (0.9)	0.327
Sepsis	8 (1.8)	1 (0.3)	0.086
Rheumatological disease	9 (2.0)	6 (1.7)	0.799
Reflux	8 (1.8)	5 (1.4)	0.783
Renal failure	8 (1.8)	4 (1.2)	0.564
Dementia	6 (1.4)	2 (0.6)	0.477

Pre-pandemic: March 11, 2019-March 10, 2020, Pandemic: March 11, 2020-March 10, 2021.
COPD: Chronic obstructive pulmonary disease, GIS: Gastrointestinal system, SD: Standard deviation

Table 4 presents the demographic, clinical, and radiological characteristics of the 21 (5.9%) cases diagnosed with COVID-19 in the pandemic group. In this sub-group of patients, 16 (76.2%) were male, the median age was 54.0 (44.5-69.0) years, and the median LOHS was 5.5 (2.0-8.5) days.

Discussion

In this study, in which we compared the frequency of hospitalizations due to hemoptysis and etiological factors during the pandemic period with the pre-pandemic period, we did not detect any significant difference between the two groups, which was the primary endpoint of the study. Although, the decrease in the rate of hospitalizations due to hemoptysis was less than the decrease in the rate of all hospitalizations during the pandemic period, the difference between these rates was found to be statistically significant. During the pandemic period, COVID-19 was identified as the etiological factor in a total of 21 (5.9%) patients.

It is evident that studies within the literature exhibit significant variations in both the causes and prevalence of hemoptysis across different countries. In large series, the mean age of patients varies between 40 and 70 years, and the male sex is significantly predominant (7-9). For example, in a study examining the five-year records of a national hospital in France, to which approximately 15,000 cases of hemoptysis are admitted every year, the mean age was reported to be 62 years, and the male/female ratio was found to be 2/1 (10). In the current study, the mean age of the patients in both groups was approximately 60 years, and approximately 70% of the cases were male. The pre-pandemic and pandemic groups did not significantly differ according to demographic characteristics. In a retrospective study conducted in Japan, and including 28,539 patients, the mean LOHS was found to be 19±43 days among

Table 2. Comparison of laboratory parameters between the groups

Parameter	Pre-pandemic (n=442)	Pandemic (n=352)	p-value
WBC count, median (IQR)	7.8 (6.4-9.8)	7.5 (6.1-9.6)	0.373
Lymphocyte count, mean ± SD	1690.0±0.7	1730.0±0.8	0.444
Hemoglobin, mean ± SD	12.0±2.0	12.0±2.1	0.861
Hematocrit, mean ± SD	36.8±6.4	36.9±6.1	0.924
Platelet, median (IQR)	260.0 (211.0-343.0)	253.0 (209.0-326.0)	0.150
Urea, median (IQR)	32.0 (26.0-42.0)	32.0 (24.0-41.0)	0.372
Creatinine, median (IQR)	0.8 (0.6-0.9)	0.7 (0.6-0.9)	0.104
Troponin, median (IQR)	5.7 (2.4-13.2)	3.7 (1.9-8.3)	**0.020**
Pro-BNP, median (IQR)	153.2 (54.7-676.7)	145.0 (53.1-419.0)	0.407
CRP, median (IQR)	11.2 (3.9-11.2)	16.4 (53.1-419.0)	**0.011**
D-dimer, median (IQR)	0.5 (0.3-1.2)	0.9 (0.3-0.8)	0.076
INR, median (IQR)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	0.057
Procalcitonin, median (IQR)	0.11 (0.05-0.12)	0.05 (0.04-0.13)	0.100

Pre-pandemic: March 11, 2019-March 10, 2020, Pandemic: March 11, 2020-March 10, 2021. BNP: B-type natriuretic peptide, CRP: C-reactive protein, INR: International normalized ratio, IQR: Interquartile range, SD: Standard deviation, WBC: White blood cell

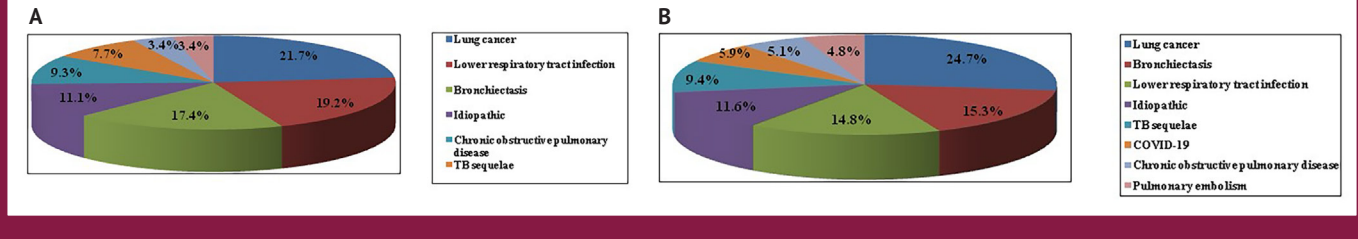

Figure 2. A) Distribution of the etiological causes of hemoptysis in the pre-pandemic group. B) Distribution of the etiological causes of hemoptysis in the pandemic group
COVID-19: Coronavirus Disease 19, TB: Tuberculosis

patients who were not given tranexamic acid and 15±17 days among those who were administered this agent (11). The LOHS may vary depending on the etiology and severity of hemoptysis and the medical or surgical methods applied. In another retrospective study, the mean LOHS in patients with moderate and severe hemoptysis was reported to be 8.6 days when bronchial artery embolization was not performed (12). Bronchial artery embolization was not performed in our center during both specified periods. Our patient population was heterogeneous in both groups, and the etiology of hemoptysis varied greatly. However, the median LOHS was calculated to be 6 days, with no significant difference between the groups.

Table 3. Group comparisons according to the etiology of hemoptysis

Etiological cause	Pre-pandemic (n=442) n (%)	Pandemic (n=352) n (%)	p-value
Lung cancer	96 (21.7)	87 (24.7)	0.310
Pulmonary embolism	15 (3.4)	17 (4.8)	0.364
COPD	41 (9.3)	18 (5.1)	**0.029**
Bronchiectasis	77 (17.4)	54 (15.3)	0.501
TB sequelae	34 (7.7)	33 (9.4)	0.441
Pulmonary TB	10 (2.3)	9 (2.6)	0.818
COVID-19	0 (0.0)	21 (5.9)	**0.000**
HF, heart valve disease	4 (0.9)	4 (1.1)	0.737
Anticoagulantdrug use, coagulation disorder	5 (1.1)	4 (1.1)	1.000
Aspergilloma	15 (3.4)	3 (0.9)	**0.017**
Idiopathic	49 (11.1)	41 (11.6)	0.822
Upper respiratory tract infection	6 (1.4)	2 (0.6)	0.477
Lower respiratory tract infection	85 (19.2)	52 (14.8)	0.109
Laryngeal cancer	0 (0.0)	2 (0.6)	0.195
Vascular pathology	1 (0.2)	2 (0.6)	0.587
Interstitial disease, sarcoidosis	5 (1.1)	2 (0.6)	0.477

Pre-pandemic: March 11, 2019-March 10, 2020; Pandemic: March 11, 2020-March 10, 2021.
COPD: Chronic obstructive pulmonary disease, COVID-19: Coronavirus Disease 19, HF: Heart failure, TB: Tuberculosis

Table 4. Demographic, clinical, and radiological characteristics of patients with Coronavirus Disease 19

Patient number	Age/sex	Radiological findings	Comorbidity	LOHS	Mortality
1	67/M	Sequelae changes, consolidation, and bilateral ground glass infiltration	Atrial fibrillation and lung cancer	3 days	Present
2	54/M	Bilateral patchy ground glass infiltration	COPD	14 days	Absent
3	45/M	Bilateral ground glass infiltration and unilateral consolidation	COPD	7 days	Absent
4	71/M	Bilateral bronchial wall thickening and unilateral tree-in-bud pattern	HF	13 days	Absent
5	44/F	Focal consolidation	Asthma	2 days	Absent
6	73/F	Bilateral band atelectasis	None	6 days	Absent
7	62/M	Focal infiltration	Lung cancer	11 days	Absent
8	71/M	Unilateral consolidation	None	10 days	Absent
9	45/M	Traction bronchiectasis and bilateral patchy ground glass infiltration	None	2 days	Absent
10	39/M	Unilateral consolidation	Hepatitis C	4 days	Absent
11	46/M	Unilateral consolidation with sequel findings	Reflux	5 days	Absent
12	56/M	Bilateral peripheral ground glass opacity	Emphysema	9 days	Absent

Table 4. Continued

Patient number	Age/sex	Radiological findings	Comorbidity	LOHS	Mortality
13	94/F	Bilateral bronchial wall thickening	CAD	8 days	Absent
14	49/M	Paraseptal emphysema, bilateral ground glass infiltration, and consolidation	None	4 days	Absent
15	65/F	Bilateral focal ground glass infiltration, tree-in-bud pattern, and consolidation	Lymphoma	6 days	Absent
16	82/M	Bilateral minimal fluid, emphysema, and ground glass infiltration	HF and COPD	6 days	Absent
17	37/M	Paraseptal emphysema and ground glass infiltration	None	7 days	Absent
18	29/M	Diffuse ground glass infiltration and bronchiectasis	None	1 days	Absent
19	31/F	No parenchymal lesions	None	2 days	Absent
20	63/M	Paraseptal emphysema and unilateral ground glass opacity	Hypertension	2 days	Absent
21	51/M	Diffuseground glass infiltration and mild bronchiectasis	None	7 days	Absent

CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, F: Female, HF: Heart failure, LOHS: Length of hospital stay, M: Male

The most common comorbidities in our patients were determined to be COPD, hypertension, CAD, and DM. Although this situation did not change, the rates of patients presenting to the hospital with the comorbidities of hypertension and CAD were significantly lower during the pandemic. It has been reported that non-COVID-19 hospital admissions have decreased since the onset of the pandemic. In the USA, this decrease has been determined to be approximately 40% for COPD and asthma (13). In our study, we found this to be valid for hypertension and CAD, which are chronic cardiac conditions. Hospitalization rates were similar for other comorbidities. However, in the evaluation of these findings, the few patients among our group with other comorbid conditions should be taken into consideration.

In terms of etiological factors, lung cancer was the most common cause of hemoptysis in both groups (pre-pandemic: 21.7%, pandemic: 24.7%). In previous studies conducted in Türkiye, lung cancer was reported as the most common cause, with a rate of approximately 28% (2-14). Underlying factors may vary across different regions and socio-economic levels around the world, and this variation is also associated with the severity of hemoptysis. It has been proven that lung cancer (30.3%) and bronchiectasis (27.9%) are the leading causes of moderate and severe hemoptysis in North America. (12) In developing countries where TB is endemic, TB has an important place in the etiology of hemoptysis (15-17). In a retrospective study conducted in Portugal with 237 patients, the most common causes of hemoptysis in adults were determined to be pulmonary TB, sequelae, and bronchiectasis. Active infections, such as pneumonia and tracheobronchitis, were held responsible for hemoptysis in 51 of the cases (18). Bronchiectasis, pneumonia, and malignancies are also prominent in other publications addressing the etiology of hemoptysis (19,20). Our comparison of the groups according to the underlying factors for hemoptysis revealed that the rates of hemorrhages due to COPD and aspergilloma were significantly higher during the pre-pandemic period. Pulmonary aspergilloma is a saprophytic infection that develops in cavitary lung diseases, especially in post-tuberculosis sequela lesions. It is an important and common risk factor, especially for the development of massive hemoptysis (21-23). We did not detect any difference between the two periods in terms of the frequency of active pulmonary TB. However, considering the chronic course of both COPD and aspergilloma, this proportional difference may have emerged due to changes in how patients presented during the pandemic. Interestingly, we found that the idiopathic cases were very similar, having a rate of approximately 11% for both periods. There are highly variable data in the literature concerning the frequency of idiopathic hemoptysis across different centers and countries. In Türkiye, two different centers reported this rate to be 7.7% and 21.8% (14-24). In a retrospective study conducted abroad with 772 patients, researchers observed that lung cancer developed in seven of 135 (19%) patients with unknown etiology during long-term follow-up, (mean: 6 years) (25). As is known, flexible and rigid bronchoscopy are important interventional methods in the diagnosis and management of patients presenting with hemoptysis. In our center, these procedures continued to be performed during the pandemic period, with the necessary precautions taken in clinical cases with indications such as hemoptysis. The

fact that the rate of idiopathic cases was similar before and during the pandemic period, and that our hospital's data was compatible with the general literature, suggests that there was no difference in the approach to patients with hemoptysis during this period.

Although the hospitalization rate due to hemoptysis was lower in the pre-pandemic group, no significant difference was detected between the two periods. However, while there was a 30.0% decrease in all hospitalizations during the pandemic period, this rate was 20.4% in hospitalizations due to hemoptysis. This difference was statistically significant. To the best of our knowledge, no comprehensive studies have investigated the frequency of hospital presentations or hospitalizations due to hemoptysis during the pandemic period. There may be two reasons why hospitalizations due to hemoptysis were less affected than all hospitalizations during the pandemic. First, there were 21 COVID-19 cases during the pandemic period, representing approximately 6% of all causes of hemoptysis, which may have had an impact on the result. Second, hemoptysis is one of the important chest disease emergencies. It is a symptom that cannot delay the patient's presentation to the hospital.

The evaluation of the demographic and clinical characteristics of the 21 cases diagnosed with COVID-19 as a cause of hemoptysis, in the pandemic group, showed that the median age and LOSH were slightly lower among these patients than in the overall pandemic group. Hemoptysis is a rare symptom in patients with COVID-19 and is occasionally reported in case reports. In a study conducted in China, hemoptysis was observed in 0.9% of 1,099 patients with COVID-19 (26). In a study examining the symptoms and findings of 1,487 outpatients with COVID-19 in France, hemoptysis was detected at a rate of 3% (27). Venous and arterial thrombotic complications, and extensive lung damage, which are likely to develop during the course of COVID-19, are considered to be predisposing factors for the development of hemoptysis. Cases of hemoptysis have been reported in the presence of pulmonary embolism (28). In a series from Türkiye describing three cases diagnosed with COVID-19 which had massive hemoptysis, radiological findings accompanying these cases were reported to include bronchiectasis, and ground glass opacities, suspicion of malignancy in one case (5). Atypical localized consolidation or ground glass infiltration, and multiple cavitary lesions have been observed in patients with hemoptysis as the presenting symptom (29,30). Pulmonary embolism was not detected in any of our cases; however, two patients had lung cancer. We consider that underlying bronchiectasis, malignancies, and sequelae are important for increased susceptibility to hemoptysis in the presence of a viral condition such as COVID-19 infection.

Study Limitations

The single-center nature of our study and the use of data obtained from a tertiary hospital may pose a limitation in terms of generalizing the results. Additionally, regarding the study design, it is possible that certain factors contributing to the development of hemoptysis were not adequately represented. Another limitation is related to the absence of long-term follow-up data, which is particularly necessary for COVID-19 cases hospitalized due to hemoptysis, especially in those with underlying conditions that constitute risk factors for hemoptysis. Since patient selection was made according to the ICD-10 (R04.2) diagnosis code, cases may be missed due to incorrect coding or incomplete documentation. This is considered another potential limitation. Nevertheless, there is no similar, comprehensive study in the literature investigating the frequency and etiology of hemoptysis during the pandemic period. We anticipate that our research will make a valuable contribution to the existing body of knowledge on hemoptysis, an important chest disease emergency.

Conclusion

We found no significant difference in the frequency of hospitalizations due to hemoptysis during the pandemic period compared to the pre-pandemic period. However, the decrease in the rate of hospitalizations due to hemoptysis was found to be less compared to the decrease in the number of all hospitalizations during the pandemic period. This may be due to the inclusion of COVID-19 in the etiology or the emergent nature of hemoptysis. The similarity of etiological causes between the pre-pandemic and pandemic periods, including idiopathic cases, indicates that there was no difference in the approach to hemoptysis during the pandemic period.

Ethics

Ethics Committee Approval: Ethical approval of the study protocol, which was prepared in accordance with the Declaration of Helsinki and Good Clinical Practices, was received from the University of Health Sciences Türkiye, Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital Ethics Committee (approval number: 116.2017.R-218, dated: 01.04.2021).

Informed Consent: Informed consent was not required since this was a retrospective study that used the hospital database system.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.A.H., M.K., N.D.K., Concept: M.A.H., N.D.K., Design: M.K., N.D.K., Data Collection or Processing: M.A.H., M.K., N.D.K., Analysis or Interpretation: M.K., N.D.K., Literature Search: M.A.H., M.K.,Writing: M.A.H., N.D.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.2025.71667

Hamidiye Med J 2025;6(3):144-146

Evaluating the Accuracy of AI-Generated Text Detection in Scientific Writing

Bilimsel Yazında YZ Tarafından Üretilen Metinlerin Tespitinde Doğruluğun Değerlendirilmesi

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ABSTRACT

Background: The rapid advancement of artificial intelligence (AI) tools, especially in natural language processing, is transforming scientific writing by improving efficiency, consistency and accessibility, especially for non-native English speakers and early-career researchers. This study aimed to evaluate the effectiveness of Compilatio, a widely used plagiarism detection software, in identifying AI-generated scientific content.

Materials and Methods: Four commonly used and freely available AI tools [ChatGPT, Gemini, Perplexity, and synthesis of topic outlines through retrieval and multi-perspective question asking (STORM)] were prompted to generate introductory texts on the burden of diabetes. Each output was copied into a Word document, uploaded and analyzed by Compilatio, which provided integrity score, similarity index, and likelihood of AI-generated content.

Results: Integrity scores varied substantially, ranging from 32% (STORM) to 100% (Gemini), while similarity indices remained consistently low (0-6%), indicating minimal direct text overlap with existing sources. The likelihood of AI authorship also varied, with STORM yielding the lowest detection rate (27%) while Gemini yielded the highest (100%).

Conclusion: These findings highlight the distinct textual characteristics produced by different AI models and demonstrate the overall effectiveness of Compilatio in identifying AI-generated content from three out of four tools. However, the limited performance observed with STORM-generated text underscores the need for more sophisticated and adaptable detection systems to uphold academic integrity in the evolving landscape of AI-supported scientific writing.

Keywords: Artificial intelligence, scientific writing, ethics

ÖZ

Amaç: Yapay zeka (YZ) araçlarının, özellikle doğal dil işleme alanındaki hızlı gelişimi, bilimsel yazımı daha verimli, tutarlı ve erişilebilir hale getirerek özellikle ana dili İngilizce olmayanlar ve kariyerinin başındaki araştırmacılar için önemli değişiklikler yaratmaktadır. Bu çalışma, yaygın olarak kullanılan bir intihal tespit yazılımı olan Compilatio'nun YZ tarafından üretilen bilimsel içerikleri tespit etmedeki etkinliğini değerlendirmeyi amaçlamıştır.

Gereç ve Yöntemler: Dört yaygın ve ücretsiz YZ aracı [ChatGPT, Gemini, Perplexity, ve synthesis of topic outlines through retrieval and multi-perspective question asking (STORM)], diyabet yükü hakkında giriş metinleri üretmeleri için yönlendirilmiştir. Her bir çıktı bir Word belgesine kopyalanmış, Compilatio'ya yüklenmiş ve analiz edilmiştir. Yazılım; özgünlük puanı, benzerlik indeksi ve içeriğin YZ tarafından üretilmiş olma olasılığı gibi veriler sunmuştur.

Bulgular: Özgünlük puanları önemli ölçüde değişmiş, STORM için %32'den Gemini için %100'e kadar çıkmıştır. Buna karşılık, benzerlik indeksleri genellikle düşük kalmış (%0-6), yani mevcut kaynaklarla doğrudan metin örtüşmesinin çok az olduğunu göstermiştir. YZ ile yazılmış olma olasılığı da değişiklik göstermiş; STORM en düşük tespit oranını (%27), Gemini ise en yüksek tespiti (%100) sağlamıştır.

Sonuç: Bu bulgular, farklı YZ modelleri tarafından üretilen metinlerin belirgin dilsel özellikler taşıdığını ortaya koymakta ve Compilatio'nun dört araçtan üçüyle oluşturulan YZ içeriğini tespit etmede genel olarak etkili olduğunu göstermektedir. Ancak,

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Received: 16.06.2025 **Accepted:** 17.07.2025 **Epub:** 02.09.2025 **Publication Date:** 30.09.2025

Cite this article as: Lippi G, Mattiuzzi C, Evaluating the accuracy of AI-generated text detection in scientific writing. Hamidiye Med J. 2025;6(3):144-146

ÖZ

STORM tarafından üretilen metinlerde tespit performansının sınırlı olması, akademik dürüstlüğü korumak için daha gelişmiş ve uyarlanabilir tespit sistemlerine duyulan ihtiyacı vurgulamaktadır.

Anahtar Kelimeler: Yapay zeka, bilimsel yazım, etik

Introduction

The exponential rise of artificial intelligence (AI) tools in recent years, has not only contributed significantly to various aspects of daily life, but has also revolutionized scientific writing (1). These advancements, especially in natural language processing and machine learning, are transforming academic research and communication among non-native English speakers, as well as early-career scientists who are still in the process of developing their writing skills (1). The ability of AI tools to streamline tasks that traditionally need substantial time and effort, such as conducting literature reviews and improving the clarity and consistency of written scientific communication, has made them an invaluable resource (2).

Freely available tools like ChatGPT, Gemini, and Perplexity, along with specialized resources such as STORM (Synthesis of Topic Outlines through Retrieval and Multi-perspective Question Asking), are becoming very attractive for drafting, refining, and summarizing scientific content, especially the introduction of academic papers. In fact, this section of the article often requires clearly presenting the problem by summarizing previous evidence, and is hence well-suited to be generated with the support of AI (3). However, the increased adoption of AI in scientific writing also raises significant ethical concerns, such as questions about authorship integrity and balance between human creativity and machine support (4).

Some software programs have been developed to detect both plagiarism and AI-generated text in scientific papers. In this study, we evaluate the effectiveness of one of these tools in identifying AI-generated content.

Materials and Methods

Four widely used AI tools were employed, including three free online "generic" resources (ChatGPT 3.5, Gemini 2.5, and Perplexity 2.0) and STORM 1.1.0, a specialized AI-powered tool developed by Stanford University for creating comprehensive, Wikipedia-style articles. Each tool was prompted with the following generic request: "Please write an introduction about the epidemiology, clinical, social and economic burden of diabetes". The resulting outputs from each of the four AI tools were copied into separate Word documents, which were then sequentially uploaded to Compilatio (https://www.compilatio.net/it), a plagiarism detection software used by many academic institutions. This software provides an "integrity score" expressed as a percentage, along with three additional metrics: similarity index (the percentage of content matched from other sources), likelihood of AI-generated text (also expressed as percentage), and unrecognized language. The software analyzes documents by comparing the uploaded text with a vast array of online sources, academic papers, and databases, employing stylometric techniques such as vocabulary diversity, sentence structure, average sentence length, and word rarity to detect AI-generated content. The performance of the four distinct models for detecting plagiarism and AI-generated text was evaluated using a χ^2 test. Access to Compilatio is free and unlimited for members of Verona University. Ethical approval was not required due to the use of publicly available web resources.

Results

The results of our analysis are summarized in Table 1 and Figure 1. The word count of the AI-generated documents varied broadly, from 168 (Gemini) to 1604 (STORM). The integrity scores also varied significantly, from a minimum of 32% for STORM to a maximum of 100% for Gemini. The similarity index remained relatively low for all tools (ranging from 0% to 6%) while the percentage of likely AI-written text varied considerably, with STORM having a minimum of 27% and Gemini displaying a maximum of 100%. An area of overlap between AI-generated text and similar content was detected by Compilatio in the content generated by ChatGPT. The χ^2 test revealed a substantial difference in the performance of the four models to detect plagiarism and/or AI-generated text (χ^2=56.02; p<0.001), suggesting that their outputs differ substantially in these metrics.

Table 1. Efficacy of Compilatio, a plagiarism and AI-content detector, in identifying scientific content generated by four freely available AI tools

	Word count	Integrity score	Similarity	AI-written text
ChatGPT	266	79%	6%	79%
Perplexity	302	74%	0%	74%
Gemini	168	100%	0%	100%
STORM	1604	32%	5%	27%

AI: Artificial intelligence, STORM: Synthesis of topic outlines through retrieval and multi-perspective question asking

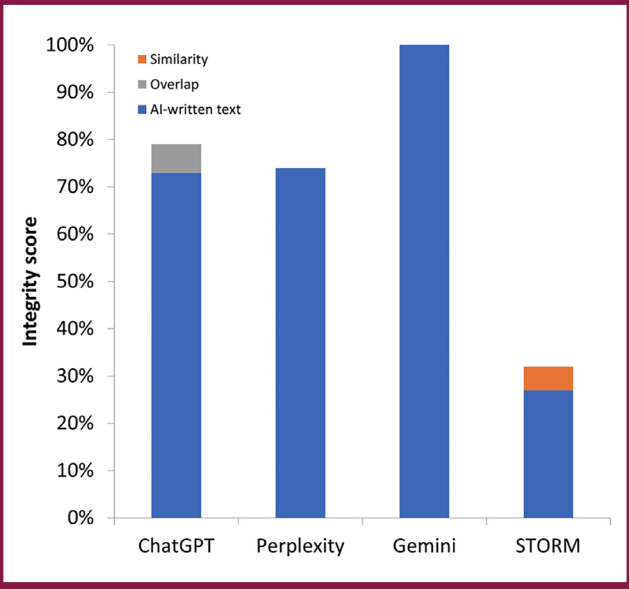

Figure 1. Analysis using plagiarism detection and text analysis software Compilatio of text generated by four AI models (ChatGPT, Perplexity, Gemini, and STORM) for similarity (percentage of content identified as matching previously published sources), AI-written text (percentage of content flagged as likely produced by an AI system) and overlap (percentage of text simultaneously flagged as both similar to existing content and AI-generated)
AI: Artificial intelligence, STORM: Synthesis of topic outlines through retrieval and multi-perspective question asking

Discussion

The results of this analysis reveal that AI-generated text seems to vary in terms of both quality and likelihood of being flagged as "AI-written" by Compilatio, one of the most commonly used plagiarism and AI-generated text detection software programs in Italian universities. Gemini generated content that was flagged with a 100% integrity score, and this is likely because of its succinct and broadly comprehensive output. STORM, which is specifically designed to generate in-depth and structured scientific content, yielded a substantially lower integrity score (32%) despite the considerably higher word count of the text produced. This difference can mostly be attributed to the nature of the web resources, as STORM provides more comprehensive content, likely accessing a larger number of sources and ideas, which may ultimately contribute to diluting or even masking its "AI fingerprints". The similarity index was found to be low across all tools, suggesting that the content generated by the four freely available AI resources used in this study may not have been directly copied and pasted from other existing sources indexed by Compilatio. However, the significant variation in the proportion of AI-written text highlights the different approaches that these tools use for generating content. ChatGPT and Perplexity produced text with high percentages of AI-written content (79% and 74%, respectively), suggesting that they may heavily rely on pre-trained models. Gemini, on the other hand, produced text that was entirely flagged as AI-written likely due to its minimalist and direct strategy. STORM, although producing less AI-sounding content, still had a modest portion (27%) that was identified as AI-generated.

Conclusion

This study highlights the increasing significance of tools designed to detect AI-generated text. The ability of Compilatio to identify AI-written content from the three "general" LMs demonstrates its real utility when unmodified text obtained from these three freely available web resources is used. Nonetheless, its performance was found to be considerably decreased when detecting text generated by STORM, suggesting that these resources still require further refinement when used for ensuring academic research integrity.

Ethics

Ethics Committee Approval: Ethical approval was not required due to the use of publicly available web resources.

Informed Consent: It is not necessarry.

Footnotes

Authorship Contributions

Concept: G.L., C.M., Analysis or Interpretation: G.L., C.M., Writing: G.L., C.M.

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.2025.95867

Hamidiye Med J 2025;6(3):147-161

Evaluation of Surgery Services in Terms of Health Management During the COVID-19 Pandemic

COVID-19 Pandemisinde Cerrahi Hizmetlerin Sağlık Yönetimi Açısından Değerlendirilmesi

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ABSTRACT

Background: The Coronavirus Disease 2019 (COVID-19) pandemic has negatively affected global health, social welfare, and the economy at a level unprecedented in modern history. study aimed to compare surgery services in a training and research hospital in İstanbul before and after COVID-19 and evaluate these services regarding health management.

Materials and Methods: This retrospective study encompassed all surgical procedures conducted in the hospital's operating room from 2019 to 2023. The data were analyzed using frequency, percentage and chi-square tests.

Results: The dataset encompasses 46,041 surgical procedures and 18 different disease groups. Major surgical procedures account for 66.8% of emergency surgeries and 84.2% of elective surgeries. 71.5% of the major surgeries, 88% of the moderate surgeries, and 83.4% of the minor surgeries are emergencies. Major surgical procedures are prevalent across all age demographics. 11,834 (25%) surgeries were performed in 2019, and 4,344 (9%) surgeries were performed in 2020. The pandemic significantly reduced emergency (n=3984, 11%) and elective (n=360, 3%) surgeries. There was a notable rise in the frequency of hospital visits after surgeries involving the circulatory system, ocular interventions, and operations in the middle ear as age progressed.

Conclusion: The pandemic period witnessed notable reductions in the volume of emergency, elective, major, medium, and minor surgical procedures. Surgeries experienced a decline across all disease categories, except for two: foreign body, implant, and graft surgeries, and incidents involving accidents, poisoning, contact with sharp objects, and weapons. Most surgeries can be classified as emergency procedures, with notable prevalence in cases involving the eye and middle ear, genitourinary system, skeletal structure, circulatory system, digestive tract, and respiratory ailments. Emergency, eye, and middle ear surgeries were more prevalent among individuals aged 60 and above, whereas elective surgeries were more frequently observed in the 19-30 age group. Most emergency and elective surgeries were major surgeries. The number of postoperative check-ups increased among the older age demographics.

Keywords: COVID-19, pandemic, surgery, health management

ÖZ

Amaç: Koronavirüs Hastalığı 2019 (COVID-19) salgını, küresel sağlık, sosyal refah ve ekonomiyi modern tarihte benzeri görülmemiş bir düzeyde olumsuz etkilemiştir. Çalışmanın amacı, İstanbul'daki bir eğitim ve araştırma hastanesinde COVID-19 öncesi ve sonrası dönemde sunulan cerrahi hizmetleri karşılaştırmak ve sağlık yönetimi açısından değerlendirmektir.

Gereç ve Yöntemler: Bu retrospektif çalışma, hastanenin ameliyathanesinde 2019'dan 2023 yılına kadar gerçekleştirilen tüm cerrahi prosedürleri kapsamaktadır. Veriler, frekans, yüzde ve ki-kare testleri kullanılarak analiz edilmiştir.

Bulgular: Veriler, 46.041 ameliyat ve 18 farklı hastalık grubundan oluşmaktadır. Acil ameliyatların %66,8'i, elektif ameliyatların ise %84,2'si büyük ameliyatlardır. Büyük ameliyatların %71,5'i, orta ameliyatların %88'i, küçük ameliyatların %83,4'ü acil ameliyatlardır. Her yaş grubunda büyük ameliyatların yoğunlukta olduğu görülmektedir. 2019 yılında 11.834 (%25); 2020 yılında ise 4344 (%9) ameliyatın yapıldığı görülmüştür. Bu durum hem acil (n=3984, %11) hem de elektif (n=360, %3) ameliyat rakamlarında ciddi

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Received: 21.03.2025 **Accepted:** 04.08.2025 **Epub:** 02.09.2025 **Publication Date:** 30.09.2025

Cite this article as: Ünkür P, Esen ES, Kantaş Yılmaz F, Esen MF. Evaluation of surgery services in terms of health management during the COVID-19 pandemic. Hamidiye Med J. 2025;6(3):147-161

öz

düşüşlerin yaşanmasına sebep olmuştur. Yaş ilerledikçe dolaşım sistemi ile göz ve orta kulak ameliyatları sonrası hastaneye gelme sıklıklarının arttığı görülmüştür.

Sonuç: Pandemi döneminde acil, elektif, büyük, orta ve küçük ameliyatların sayısında ciddi oranda düşüşler görülmüştür. İki hastalık grubu (yabancı cisim, implant ve greft operasyonları ile kazalar, zehirlenme, keskin cisimlerle-ateşli silahlarla temas) dışındaki tüm hastalık gruplarındaki ameliyat sayılarında düşüşler görülmüştür. Türlerine göre ameliyatların büyük çoğunluğunu acil ameliyatlar oluşturmakta olup, göz ve orta kulak, genitoüriner, iskelet, dolaşım, sindirim ve solunum sistemi hastalıkları ön plana çıkmaktadır. Altmış yaş ve üzeri bireylerde acil, göz ve orta kulak hastalıkları ameliyatlarının 19-30 yaş grubunda ise elektif ameliyatların yoğun olduğu görülmüştür. Acil ve elektif ameliyatların çoğunluğu büyük ameliyatlardır. İlerleyen yaş gruplarında ameliyat sonrası kontrole gelme sıklığının arttığı tespit edilmiştir.

Anahtar Kelimeler: COVID-19, pandemi, ameliyat, sağlık yönetimi

Introduction

Surgical care has been an important component of health care for centuries. As the prevalence of cancers, cardiovascular diseases and traumatic injuries continues to increase, the impact of surgical intervention on public health will continue to grow (1). Some European Union countries performed over four million cataract surgeries and one million cesarean sections (2). As the aged population expands, cardiovascular disorders have emerged as the predominant cause of morbidity and mortality among those over 75 years of age in recent years, illustrated by the percentage of cardiac surgeries (3,4). Advancements in health technology have led to a preference for novel uses, such as robotic surgery, over traditional open surgical methods (5). The Coronavirus Disease 2019 (COVID-19) pandemic has negatively affected global health, social welfare, and the economy, at a level unprecedented in modern history (6). It has also led to significant changes in healthcare services. The number of patients visiting emergency services has almost halved during COVID-19 (7). Besides its detrimental impact on public health, the virus has caused the disruption and cancellation of surgical operations. Moreover, patients have had challenges receiving surgical care, prompting the formulation of a plan specifically for post-pandemic (6,8). Hospitals were considered high-risk environments, with intensive care units and operating rooms identified as the most hazardous regions (9). In the pre-COVID-19 period (2019), elective surgeries were four times more frequent than emergency surgeries, but during the pandemic period, they decreased to twice (10). In the first two months of the pandemic, emergency general surgery applications dropped 37.1% and 43.7%, respectively. Acute appendicitis, cholecystitis, and intestinal obstruction were the most common surgical emergencies encountered during the pandemic (11). In Türkiye, the number of surgeries conducted in 2019 was over 5 million, but it declined to 3 million in 2020, subsequently rising in the ensuing years following the conclusion of the pandemic (12). The pandemic caused elective surgeries to be postponed, and healthcare personnel prioritized COVID-19 patients, leading to disruptions in the provision of other healthcare services (7,13). The pandemic's unprecedented challenges required a fundamental restructuring of global surgical care delivery. Health authorities, including the World Health Organization, Centers for Disease Control and Prevention, and European Centre for Disease Prevention and Control, along with surgical societies such as the American College of Surgeons, European Association for Endoscopic Surgery, and European Society of Coloproctology, promptly released evidence-based guidelines to reduce infection risks and conserve essential resources. The guidelines focused on several fundamental operational pillars:

Tiered Triage Systems: Elective surgeries were prioritized rigorously according to urgency and cancer risk, employing frameworks such as the Medically Necessary Time-Sensitive (MeNTS) scoring system. Surgeries were classified into tiers, including Emergency, Urgent, Semi-Urgent, and Postponable, and the classification was evaluated continuously based on the local COVID-19 burden and resource availability. This frequently resulted in considerable delays for non-urgent procedures such as bariatric and benign hernia surgeries (14).

Enhanced Preoperative Protocols: These protocols mandate universal Severe Acute Respiratory Syndrome Coronavirus 2 screening, typically conducted via reverse transcription – polymerase chain reaction, within 24-72 hours prior to surgery for all patients, including those who are asymptomatic. Preoperative isolation was recommended when feasible. Telemedicine was extensively utilized for preoperative evaluations and consent procedures to reduce hospital exposure (15).

Modifications in Operational Procedures within the Operating Room:

- Infection Control: Rigorous compliance with enhanced personal protective equipment (N95/FFP2 respirators, eye protection, gowns, gloves) is essential for all operating room personnel, particularly during aerosol-generating

procedures such as intubation or laparoscopy. Operating rooms for COVID-19 equipped with negative pressure ventilation were utilized where feasible.

• Personnel and Workflow: Team sizes were reduced, and staff movement between COVID-positive and non-COVID areas was limited. Operating times were optimized, and non-essential equipment was eliminated.

• Surgical Technique: Given the evolving evidence on viral aerosolization, recommendations frequently suggested reducing the use of energy devices (such as electrocautery and ultrasonic scalpels) during laparoscopy and implementing effective smoke evacuation systems (16).

Postoperative Care Adjustments: The procedures involved modifications to pathways aimed at expediting discharge when deemed safe, such as the implementation of enhanced recovery after surgery protocols (17). Dedicated surgical wards and intensive care units free from COVID-19 were established to safeguard non-infected surgical patients. Postoperative follow-up increasingly employs telehealth.

Ethical and Safety Frameworks: These frameworks underscore the importance of equitable resource allocation, transparent communication with patients regarding risks and delays, and the ethical duty to deliver surgical care when deferral may result in substantial harm, such as cancer progression or limb threat. The regulations were primarily motivated by patient safety and the protection of healthcare workers (18).

Surgeons' daily practices and training have been profound, enabling them to become a significant source of personnel in the fight against the virus (19). Restrictions on access to non-urgent care and elective surgeries have postponed bariatric and metabolic surgeries worldwide. Therefore, delaying surgery for patients experiencing a rapid progression of obesity and diabetes has increased the risks of morbidity and mortality (20).

The pandemic has created considerable challenges in managing healthcare services, necessitating that healthcare systems remain flexible and adaptable to these processes. Given that the pandemic yields critical insights for implementing measures against potential future pandemics, it is imperative to monitor this scenario concerning healthcare management. This study evaluates operating room practices during the pre- and post-COVID-19 periods. The study attempts to clarify the influence of the COVID-19 criterion on healthcare planning for the literature and policymakers and to provide resources.

Materials and Methods

Research Design

The retrospective research aimed to statistically evaluate the data obtained from patients who underwent surgery in a 654-bed general education and research hospital in İstanbul Türkiye between 01.01.2019 and 01.10.2023.

Population and Sample

The study universe consists of 46,041 surgeries and 18 different disease groups. All surgeries were analyzed without selecting a sample. The surgery classification was based on the medical standard of surgery; depending on their volume and complexity, surgeries may be minor, medium and major (complex). The disease definition of 46.041 surgeries was made using the International Classification of Diseases-10 (ICD-10) diagnostic codes. The current study included elective and emergency cases as a kind of surgery. Emergency cases occur unpredictably and require immediate attention on the same day. Elective cases may be scheduled for subsequent dates (21).

Ethical Approval

Institutional permission was obtained before the study was conducted, and ethics committee approval was obtained from the University of Health Sciences Türkiye, Hamidiye Scientific Research Ethics Committee (approval number: 1/34, dated: 25.01.2024).

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences 25.0 for Windows (SPSS Inc., Chicago, IL, USA). Multiple limitations require attention. This single-center study conducted at a tertiary hospital in İstanbul may not accurately represent patterns observed in community hospitals or rural settings, where resource constraints vary. Secondly, variations in diagnostic coding within electronic health records (EHRs), such as the misclassification of "urgent" versus "elective", may impact the accuracy of disease groupings, even with the standardized application of ICD-10. Third, we did not monitor long-term outcomes of delayed surgeries, such as cancer progression in deferred biopsies, which would elucidate the clinical implications of triage decisions. Fourth, confounding factors such as local COVID-19 surges, staff shortages, and patient avoidance behaviors were not quantified, although they likely impacted surgery volumes. Ultimately, our data do not evaluate the consistent application of priority frameworks across surgical specialties, which is a recognized challenge during crises. Data were expressed as frequencies and

percentages. The chi-square test was used to evaluate the frequency differences between disease groups. The significance level was accepted as $p<0.05$.

Results

Emergency and elective surgeries, as well as minor, medium, and major surgeries, have decreased during the pandemic (Table 1). The number of surgeries in 2020 decreased by 81% relative to 2019; albeit this reduction differs by disease group. The 34,950 emergency surgeries over a five-year span declined from 24.40% in 2019 to 11.40% in 2020, while 11,091 elective procedures fell from 29.81% to 3.25%. Similarly, there has been a reduction of 90% in the incidence of major procedures. All disease groups, exhibited a reduction in the number of procedures except for two categories: foreign body (implant and graft surgeries), and incidents involving accidents, poisoning, contact with sharp objects, and weapons (Table 1).

Most emergency surgeries involved eye and middle ear diseases (18.8%), genitourinary system diseases (18.2%), skeletal system diseases (10.6%), circulatory system diseases (9.3%), digestive system diseases (7.2%), and respiratory system diseases (5.7%) (Table 2).

Elective surgeries are performed for diseases (36.8%), digestive system diseases (8.9%), muscle-tendon injuries and fractures (8.7%), and skeletal system diseases (8.6%) (Table 2).

Between 2019 and 2023, 73.4% of all surgeries in the 0-18 age group were major, and 70.3% were urgent. These surgeries were mostly performed for respiratory system diseases (15.2%), digestive system diseases (11.7%), injuries due to contact with sharp objects (8.1%), congenital and chromosomal disorders (7.4%), skeletal system diseases (7.3%), muscle-tendon injuries and fractures (6.5%) (Table 3).

Eighty point eight percent of surgeries between the ages of 19 and 30 were major, and 51.4% were elective.

Table 1. Percentage distribution of surgery data according to variables by year

Variables	Categories	Year (%)					
		2019	2020	2021	2022	2023	Total number
Kind of surgery	Emergency	24.40	11.40	12.20	24.50	27.50	34950
	Elective	29.81	3.25	7.72	28.11	31.12	11091
Size of surgery	Major	30.33	2.22	3.02	22.57	41.85	32697
	Medium	34.56	4.23	9.13	24.65	27.43	9848
	Minor	26.74	8.32	11.53	24.49	28.92	3496
Disease group	Infectious diseases	24.30	10.05	12.15	27.34	26.17	428
	Neoplasms and immune system diseases	25.57	4.96	9.85	26.12	33.49	1654
	Endocrine and metabolic diseases	27.15	8.28	12.91	24.83	26.82	302
	Nervous system diseases	19.82	3.69	5.99	15.67	54.84	217
	Eye and middle ear diseases	24.40	8.49	7.96	28.13	31.02	6911
	Circulatory system diseases	24.28	2.65	3.44	30.31	39.32	3431
	Respiratory system diseases	19.83	3.53	7.57	33.69	35.38	2179
	Digestive system diseases	24.38	2.82	6.49	33.03	33.29	3515
	Skin diseases	29.99	2.97	6.56	24.44	36.04	1784
	Skeletal system diseases	26.55	4.94	7.90	24.48	36.13	4656
	Genitourinary system diseases	24.39	2.67	9.28	24.49	39.16	6884
	Gynecological-obstetric diseases	24.39	1.43	10.21	30.46	33.51	5026
	Congenital and chromosomal disorders	24.19	3.74	9.73	21.70	40.65	401
	Unclassified abnormal clinical and laboratory findings*	24.35	3.12	6.29	24.47	41.76	1700
	Muscle-tendon injuries and fractures	24.35	5.17	12.14	23.91	34.43	1606
	Foreign body, implant and graft operations	19.62	20.35	18.73	20.50	20.80	678
	Accidents, poisoning, contact with sharp objects-firearms	19.06	19.33	19.95	20.04	21.63	1128
	Examination, follow-up, observation**	27.22	2.63	15.02	24.48	30.64	3541

*Includes cases coded as R00-R99. These cases cover specific disease categories, a wide range of clinical signs, symptoms, and abnormal test results, and abnormal test results, and are also kept in the surgery database. **It is included as a category in the health information system because it is indexed in the surgery database

Table 2. Distribution of disease groups according to surgery types

Variable	Categories	Types of surgery					
		Emergency			Elective		
		n	Row, n%	Column, n%	n	Row, n%	Column, n%
Disease groups	Infectious diseases	359	83.9	1.0	69	16.1	0.6
	Neoplasms and immune system diseases	1572	95	4.5	82	5.0	0.7
	Endocrine and metabolic diseases	284	94	0.8	18	6.0	0.2
	Nervous system diseases	189	87.1	0.5	28	12.9	0.3
	Eye and middle ear diseases	6554	94.8	18.8	357	5.2	3.2
	Circulatory system diseases	3239	94.4	9.3	192	5.6	1.7
	Respiratory system diseases	1987	91.2	5.7	192	8.8	1.7
	Digestive system diseases	2526	71.9	7.2	989	28.1	8.9
	Skin diseases	1510	84.6	4.3	274	15.4	2.5
	Skeletal system diseases	3698	79.4	10.	958	20.6	8.6
	Genitourinary system diseases	6345	92.2	18.2	539	7.8	4.9
	Gynecological-obstetric diseases	940	18.7	2.7	4086	81.3	36.8
	Congenital and chromosomal disorders	352	87.8	1.0	49	12.2	0.4
	Unclassified abnormal clinical and laboratory findings*	1349	79.4	3.9	351	20.6	3.2
	Muscle-tendon injuries and fractures	646	40.2	1.8	960	59.8	8.7
	Foreign body, implant and graft operations	318	46.9	0.9	360	53.1	3.2
	Accidents, poisoning, contact with sharp objects-firearms	117	10.4	0.3	1011	89.6	9.1
	Examination, follow-up, observation**	2965	83.7	8.5	576	16.3	5.2

*Includes cases coded as R00-R99. These cases are also kept in the surgery database and cover specific disease categories, a wide range of clinical signs, symptoms and abnormal test results. **It is included as a category in the health information system because it is indexed in the surgery database

These surgeries were mainly for gynecological diseases (37.9%), the skeletal system (8.4%), the skin (8%), the respiratory system (7.3%), and the digestive system (6.3%) (Table 3).

Sixty-seven point eight percent of surgeries between the ages of 31 and 45 were major, and 73.7% were urgent. These surgeries were mainly performed on genitourinary system diseases (18.7%), gynecological diseases (15.9%), circulatory system diseases (12%), skeletal system diseases (10.2%), digestive system diseases (7.2%), and eye and middle ear diseases (5.4%) (Table 3).

Sixty-four point one percent of the surgeries between the ages of 46 and 59 were major, and 87.7% were urgent. These surgeries mainly involved the genitourinary system (22.5%), eye and middle ear (17.2%), skeletal system (12.2%), circulatory system (10%), and digestive system (8.6%) (Table 3).

Seventy-three point three percent of the surgeries performed on individuals over the age of 60 were major, and 89% were urgent. Surgeries were performed for eye and middle ear diseases (37.2%), genitourinary system diseases (14.4%), skeletal system diseases (10.3%), digestive system diseases (6.6%), neoplasms and immune system diseases (5.6%), and circulatory system diseases (4.8%) (Table 3).

Sixty-six point eight percent of emergency surgeries and 84.2% of elective surgeries are major. Seventy-one point five percent of major surgeries, 88% of moderate surgeries, and 83.4% of minor surgeries are urgent. Surgeries are generally included in the major surgery group. However, it was determined that foreign body, implant, and graft surgeries (49.3%) and circulatory system diseases (31.1%) constitute the majority of the minor surgery group (Table 4).

The frequency of individuals coming to the hospital after surgery increases in older age groups. The frequency of hospital visits increases with age, especially for individuals having minor surgeries, and diseases of the circulatory system, eye, and middle ear between the ages of 19 and 59 (Table 5).

The predominant types of gynecological procedures include spontaneous vertex deliveries (n=2754) and emergency and elective cesarean deliveries (n=766). In genitourinary system disorders, procedures for abnormal uterine and vaginal hemorrhage (n=1401) and irregular menstruation (n=1252) are primarily conducted. Chronic venous insufficiency (n=2528) is predominantly conducted in circulatory system diseases, with a significant majority in the 31-45 age. The predominant types of

Table 3. Distribution of surgeries by age groups, size, type and disease groups

Variables	Categories	Age groups															Total (%)
		0-18			19-30			31-45			46-59			60+			
		Count	Row	Column	Count	Row	Column	Count	Row	Column	Count	Row	Column	Count	Row	Column	
Size of surgery	Major	3205	9.8%	73.4%	6240	19.1%	80.8%	8602	26.3%	67.8%	6642	20.3%	64.1%	8008	24.5%	73.3%	32697 (100%)
	Medium	1105	11.2%	25.3%	926	9.4%	12.0%	2570	26.1%	20.3%	2850	29.0%	27.5%	2397	24.4%	22.0%	9848 (100%)
	Minor	58	1.7%	1.3%	556	15.9%	7.2%	1504	43.1%	11.9%	866	24.8%	8.4%	512	14.6%	4.7%	3496 (100%)
Kind of surgery	Emergency	3071	8.8%	70.3%	3750	10.7%	48.6%	9333	26.7%	73.7%	9078	26.0%	87.7%	9718	27.8%	89.0%	34950 (100%)
	Elective	1303	11.7%	29.7%	3966	35.8%	51.4%	3336	30.1%	26.3%	1281	11.5%	12.3%	1205	10.8%	11.0%	11091 (100%)
Disease group	Infectious diseases	24	5.6%	0.6%	86	20.1%	1.1%	144	33.5%	1.1%	89	20.8%	0.9%	85	19.9%	0.8%	428 (100%)
	Neoplasms-immune system diseases	32	1.9%	0.7%	110	6.7%	1.4%	433	26.1%	3.4%	474	28.7%	4.6%	605	36.7%	5.6%	1654 (100%)
	Endocrine and metabolic diseases	2	0.7%	0.0%	25	8.3%	0.3%	103	34.1%	0.8%	97	32.1%	0.9%	75	24.8%	0.7%	302 (100%)
	Nervous system diseases	11	5.1%	0.3%	13	6.0%	0.2%	39	18.0%	0.3%	86	39.6%	0.8%	68	31.3%	0.6%	217 (100%)
	Eye and middle ear diseases	109	1.6%	2.5%	278	4.0%	3.6%	684	9.9%	5.4%	1783	25.8%	17.2%	4057	58.7%	37.2%	6911 (100%)
	Circulatory system diseases	13	0.4%	0.3%	331	9.7%	4.3%	1526	44.5%	12.0%	1035	30.2%	10.0%	526	15.3%	4.8%	3431 (100%)
	Respiratory system diseases	664	30.5%	15.2%	562	25.8%	7.3%	480	22.0%	3.8%	251	11.5%	2.4%	222	10.2%	2.0%	2179 (100%)
	Digestive system diseases	509	14.5%	11.7%	488	13.9%	6.3%	908	25.8%	7.2%	894	25.4%	8.6%	716	20.4%	6.6%	3515 (100%)
	Skin diseases	281	15.8%	6.4%	615	34.5%	8.0%	435	24.4%	3.4%	253	14.2%	2.4%	200	11.2%	1.8%	1784 (100%)
	Skeletal system diseases	319	6.9%	7.3%	650	14.0%	8.4%	1297	27.9%	10.2%	1263	27.1%	12.2%	1127	24.2%	10.3%	4656 (100%)
	Genitourinary system diseases	256	3.7%	5.9%	357	5.2%	4.6%	2370	34.4%	18.7%	2327	33.8%	22.5%	1574	22.9%	14.4%	6884 (100%)
	Gynecological-obstetric diseases	65	1.3%	1.5%	2927	58.3%	37.9%	2011	40.0%	15.9%	23	0.4%	0.2%	0	0.0%	0.0%	5026 (100%)

Table 3. Continued

Variables	Categories	Age groups 0-18 Count	0-18 Row	0-18 Column	19-30 Count	19-30 Row	19-30 Column	31-45 Count	31-45 Row	31-45 Column	46-59 Count	46-59 Row	46-59 Column	60+ Count	60+ Row	60+ Column	Total (%)
Disease group	Congenital-chromosomal disorders	324	81.0%	7.4%	39	9.5%	0.5%	16	4.0%	0.1%	7	1.8%	0.1%	15	3.8%	0.1%	401 (100%)
	Unclassified abnormal clinical-laboratory findings*	87	5.1%	2.0%	212	12.5%	2.8%	479	28.2%	3.8%	472	27.8%	4.6%	450	26.4%	4.1%	1700 (100%)
	Muscle-tendon injuries and fractures	286	17.8%	6.5%	283	17.6%	3.7%	327	20.4%	2.6%	317	19.8%	3.1%	393	24.4%	3.6%	1606 (100%)
	Foreign body, implant-graft operations	216	32.1%	5.0%	117	17.2%	1.5%	183	27.0%	1.4%	110	16.2%	1.1%	52	7.4%	0.5%	678 (100%)
	Accidents, poisoning, contact with sharp objects-firearms	356	31.6%	8.1%	203	18.0%	2.6%	281	25.0%	2.2%	166	14.7%	1.6%	122	10.7%	1.1%	1128 (100%)
	Examination, follow-up, observation**	814	23.0%	18.6%	422	11.9%	5.4%	960	27.2%	7.6%	715	20.2%	6.9%	630	17.8%	5.8%	3541 (100%)

*Includes cases coded as R00-R99. These cases are also kept in the surgery database and cover specific disease categories, a wide range of clinical signs, symptoms and abnormal test results. **It is included as a category in the health information system because it is indexed in the surgery database

respiratory system diseases involve issues of the nose and nasal sinuses, with procedures for nasal septum deviation (n=408) and other conditions (n=467). In surgical procedures necessitated by accidents, poisoning, and injuries from sharp objects and weapons, those resulting from bites and stings of non-poisonous insects and arthropods (n=520) are particularly prominent, significantly impacting the 0-18 age demographic. Likewise, other surgical procedures conducted across the 0-18 age demographic include foreign body removal, implant placement, and graft surgery. Many individuals undergoing surgery for eye and middle ear problems are aged 60 and above. Diabetic retinopathy procedures (n=1418) and senile cataract surgeries (n=965) are the most prominent in this group (Table 6).

In procedures for the digestive system, a substantial difference was noticed in patients aged 19 to 59. A significant difference was observed in the 19-59 age group for surgeries performed due to venous insufficiency (chronic peripheral), varicocele, and hemorrhoids in circulatory system diseases; in contrast, surgeries performed for abnormal uterine and vaginal bleeding, a significant difference was observed between all age groups, except for the 0-18 age group, in surgeries performed for abnormal uterine and vaginal bleeding. There was a substantial difference in all procedures performed for gynecological illnesses in the 19 to 45 age group. In procedures performed for soft tissue and back pain in skeletal system illnesses, there was a substantial difference within the 19-59 age group. There was a substantial difference in neoplasms and immune system diseases between the 31-60 age group and those above, regarding benign lipomatous neoplasm, trunk skin and subcutaneous tissue neoplasms, benign skin neoplasm, and malignant bladder neoplasm. Eye and middle ear surgeries among individuals aged 31-60 differ significantly from those performed on older individuals. Respiratory system procedures between 18 and 31 years old (excluding nasal septum deviation) differ significantly. All genitourinary system illnesses (excluding benign prostatic hyperplasia) show a substantial variation in the 19- to 59-year-old age group (Table 6).

Table 4. Distribution of surgery sizes by surgery types and disease groups

Variables	Categories	Size of surgery								
		Major			Medium			Minor		
		Count (n)	Row %	Column %	Count (n)	Row %	Column %	Count (n)	Row %	Column %
Kind of surgery	Emergency	23363	66.8	71.5	8671	24.8	88.0	2916	8.3	83.4
	Elective	9334	84.2	28.5	1177	10.6	12.0	580	5.2	16.6
Disease group	Infectious diseases	373	87.1	1.1	54	12.6	0.5	1	0.2	0.0
	Neoplasms and immune system diseases	1564	94.6	4.8%	87	5.3	0.9	3	0.2	0.1
	Endocrine and metabolic diseases	267	88.4	0.8	24	7.9	0.2	11	3.6	0.3
	Nervous system diseases	205	94.5	0.6	7	3.2	0.1	5	2.3	0.1
	Eye and middle ear diseases	3904	56.5	11.9	1927	27.9	19.6	1080	15.6	30.9
	Circulatory system diseases	2018	58.8	6.2	324	9.4	3.3	1089	31.7	31.1
	Respiratory system diseases	1766	81.0	5.4	120	5.5	1.2	293	13.4	8.4
	Digestive system diseases	3298	93.8	10.1	215	6.1	2.2	2	0.1	0.1
	Skin diseases	698	39.1	2.1	1083	60.7	11.0	3	0.2	0.1
	Skeletal system diseases	4066	87.3	12.4	478	10.3	4.9	112	2.4	3.2
	Genitourinary system diseases	3412	49.6	10.4	3248	47.2	33.0	224	3.3	6.4
	Gynecological-obstetric diseases	4876	97.0	14.9	149	3.0	1.5	1	0.0	0.0
	Congenital and chromosomal disorders	372	92.8	1.1	29	7.2	0.3	0	0.0	0.0
	Unclassified abnormal clinical and laboratory findings*	1357	79.8	4.2	208	12.2	2.1	135	7.9	3.9
	Muscle-tendon injuries and fractures	1576	98.1	4.8	30	1.9	0.3	0	0.0	0.0
	Foreign body, implant and graft operations	329	48.5	1.0	15	2.2	0.2	334	49.3	9.6
	Accidents, poisoning, contact with sharp objects-firearms	973	86.3	3.0	133	11.8	1.4	22	2.0	0.6
	Examination, follow-up, observation**	1643	46.4	5.0	1717	48.5	17.4	181	5.1	5.2

*Includes cases coded as R00-R99. These cases are also kept in the surgery database and cover specific disease categories, a wide range of clinical signs, symptoms and abnormal test results. **It is included as a category in the health information system because it is indexed in the surgery database

Discussion

This study aimed to compare operating room services in a training and research hospital in İstanbul before and after COVID-19 and to evaluate them in terms of health management. The number of surgeries performed in 2020 varied by disease groups but decreased by 81% compared to 2019. Thirty-four thousand nine hundred fifty emergency surgeries performed in the five-year period decreased from 24.40% in 2019 to 11.40% in 2020, and 11,091 elective surgeries decreased from 29.81% to 3.25%. Similarly, the rate of major surgeries decreased by more than 90%.

In alignment with the study findings, İlhan et al. (10) examined the impact of the COVID-19 pandemic on emergency and elective surgeries, revealing a decline from 947 surgeries performed in 2019 to 165 in 2020, representing a reduction of approximately 90%. They also reported a decline in the elective surgery rate from 80% in 2019 to 34.5% in 2020 (10). Previous studies indicate that the pandemic adversely affected procedures (22,23). The effective management of patients requiring

Table 5. Distribution of postoperative hospital visit frequency by age groups

Variables	Categories	Age groups				
		0-18	19-30	31-45	46-59	60+
Size of surgery	Major	1	1	2	2	2
	Medium	1	2	1	2	4
	Minor	1	2	3	3	2
Kind of surgery	Emergency	1	2	2	2	2
	Elective	1	1	1	2	1
Disease group	Infectious diseases	1	1	2	2	1
	Circulatory system diseases	1	4	5	5	2
	Eye and middle ear diseases	1	1	2	3	3
	Nervous system diseases	2	2	1	1	1
	Examination, follow-up, observation**	1	2	2	3	2
	Neoplasms and immune system diseases	1	1	1	1	2
	Respiratory system diseases	1	1	1	1	2
	Endocrine and Metabolic diseases	2	1	1	1	1
	Skin diseases	1	1	1	1	1
	Skeletal system diseases	1	1	1	1	2
	Genitourinary system diseases	1	1	1	1	2
	Gynecological-obstetric diseases	1	1	1	2	.
	Congenital and chromosomal disorders	2	1	1	1	1
	Unclassified abnormal clinical and laboratory findings*	1	1	2	2	1
	Muscle-tendon injuries and fractures	1	2	1	1	1
	Foreign body, implant and graft operations	1	1	1	1	2
	Accidents, poisoning, contact with sharp objects-firearms	2	1	1	1	1
	Digestive system diseases	1	1	1	1	1

*Includes cases coded as R00-R99. These cases are also kept in the surgery database and cover specific disease categories, a wide range of clinical signs, symptoms and abnormal test results. **It is included as a category in the health information system because it is indexed in the surgery database

surgical intervention during the pandemic is crucial for preventing mortality from emergencies and for the ongoing, healthy treatment of cancer patients (24). During this period, surgeons experienced a reduction in elective surgical operations to mitigate virus transmission, while the postponement of these surgeries posed significant challenges (25). Due to the necessity of direct interaction between the patient and the surgeon in surgical diseases, remote healthcare services are deemed inadequate. Therefore, the surgical workforce faced greater challenges than internal medicine during the COVID-19 pandemic (26). Surgeons were instructed to make decisions regarding the prioritization and postponement of surgeries in relation to patient exposure to COVID-19 (27). Similarly, surgeries for patients infected with the virus were deferred, and it was deemed essential to perform surgeries with minimal medical staff in emergency situations (28). Consequently, a significant finding of the present research is that COVID-19 reduced the number of surgeries, which aligns with existing literature. Nonetheless, research indicates that the pandemic did not alter the incidence of certain cases, although the number of such cases studied is limited (29).

Emergency surgeries are categorized by kind as follows: eye and middle ear (18.8%), genitourinary system (18.2%), skeletal system (10.6%), circulatory system (9.3%), digestive system (7.2%), and respiratory system (5.7%). The predominant severe consequence in COVID-19 patients is acute hypoxemic respiratory failure or acute respiratory distress syndrome necessitating oxygen and ventilation interventions (30). Given that elective surgeries were predominantly suspended during the pandemic, and emergency procedures were conducted on patients diagnosed with or suspected of COVID-19 (30), it can be asserted that COVID-19-related complications (such as arrhythmias and acute cardiac damage) also influence the categories of surgeries performed.

Table 6. Frequency table for distribution of surgeries by age groups

Disease groups and types	Age groups, n (%)					n	Disease groups and types	Age groups, n (%)					n	Disease groups and types	Age groups, (%)					n
Circulatory system diseases	**0-18**	**19-30**	**31-45**	**46-59**	**60+**	**n**	**Digestive system diseases**	**0-18**	**19-30**	**31-45**	**46-59**	**60+**	**n**	**Neoplasms/ immune system diseases**	**0-18**	**19-30**	**31-45**	**46-59**	**60+**	**n**
Venous insufficiency	15_a	250_b	1695_c	522_d	46_e	2528	Unilateral/ unspecified inguinal hernia	114_a	47_a	209_b	239_b	140_a	749	Benign lipomatous neoplasm	12_a	31_a	229_b	137_c	52_a	461
Hemorrhoids	-	23_a	80_b	29_a	12_c	144	Gallbladder stones and diseases	6_a	74_b	303_c	230_c	88_b	701	Benign skin neoplasm	10_a	33_a	122_b	44_a	15_a	224
Atherosclerotic heart disease	-	15_a	12_a	55_b	36_b	118	Acute appendicitis	156_a	207_a	200_a	49_b	18_b	630	Malignant neoplasm of bladder	-	-	13_a	41_b	55_b	109
Occlusion/ astenosis of the carotid artery	-	-	7_a	17_a	76_b	100	Anal fissure & anal fistula	8_a	72_b	174_c	56_b	13_a	323	Benign neoplasm of bladder	-	-	12_a	34_b	59_b	105
Varicocele	13_a	30_b	33_b	9_a	7_a	92	Cholelithiasis	7_a	16_a	82_b	66_b	19_a	190	Uterine leiomyoma	-	6_a	62_b	18_a	6_a	92
Congenital and chromosomal disorders	**0-18**	**19-30**	**31-45**	**46-59**	**60+**	**n**	**Gynecological-obstetric diseases**	**0-18**	**19-30**	**31-45**	**46-59**	**60+**	**n**	**Unclassified abnormal clinical and laboratory findings***	**0-18**	**19-30**	**31-45**	**46-59**	**60+**	**n**
Cryptorchidism	110	-	3	-	-	113	Spontaneous vertex delivery	-	1867_a	887_b	-	-	2754	Abnormal cytological findings in specimens from female genital organs, unspecified	6_a	36_a	200_b	65_a	7_a	314
Hypospadias	97	-	-	-	-	97	Emergency cesarean section	-	617_a	544_a	15_b	-	1176	Abdominal pain	59_a	67_a	92_b	40_a	32_a	290
Talipes equinovarus	39	-	-	-	-	39	Elective cesarean section	-	303_a	463_b	-	-	766	Hematuria	6_a	5_a	49_b	84_b	72_b	216
Pektus excavatum	18	14	1	-	-	33	Abortion	-	54_a	37_a	-	-	91	Skin changes	7_a	20_a	83_b	33_a	15_a	158
Hypertrophic nails	1	9	3	3	2	18	Ectopic pregnancy	-	7_a	30_b	-	-	37	Urinary incontinence	8_a	5_a	55_b	52_b	16_a	136
Endocrine/ metabolic diseases	**0-18**	**19-30**	**31-45**	**46-59**	**60+**	**n**	**Skin diseases**	**0-18**	**19-30**	**31-45**	**46-59**	**60+**	**n**	**Muscle-tendon injuries/ fractures**	**0-18**	**19-30**	**31-45**	**46-59**	**60+**	**n**
Thyroid disorders	-	10_a	46_b	30_b	11_a	97	Nail disorders	152_a	246_a	167_a	45_b	36_b	646	Distal radius fracture	12_a	13_a	42_b	41_b	10_a	118

Table 6. Continued

Disease groups and types	Age groups, n (%)					n	Disease groups and types	Age groups, n (%)					n	Disease groups and types	Age groups, (%)					n
Vitamin D deficiency	-	-	19_a	6_b	8_b	35	Pilonidal cyst	101_a	285_b	123_a	13_c	10_c	532	Distal humerus fracture	91_a	6_b	8_b	6_b	6_b	117
Iodine deficiency-related multinodular goiter	-	8_a	17_b	5_a	5_a	35	Skin abscess, furuncle-carbuncle	-	34_a	64_b	32_a	13_c	143	Rotator cuff injury	6_a	7_a	23_a	56_b	16_a	108
Obesity	-	4	11	3	-	18	Epidermoid cyst	8_a	10_a	48_b	22_a	8_a	96	Femoral neck fracture	6_a	6_a	13_a	12_a	69_b	106
Obesity due to excess calorie intake	-	5	8	1	-	14	Dermatitis	7_a	8_a	22_b	25_b	12_a	74	Pertrochanteric fracture	-	-	7_a	6_a	74_b	87
Nervous system diseases	**0-18**	**19-30**	**31-45**	**46-59**	**60+**	**n**	**Skeletal system diseases**	**0-18**	**19-30**	**31-45**	**46-59**	**60+**	**n**	**Foreign body, implant and graft operations**	**0-18**	**19-30**	**31-45**	**46-59**	**60+**	**n**
Carpal tunnel syndrome	-	-	53_a	76_b	19_c	148	Soft tissue disorders	241_a	488_a	1189_b	598_a	313_a	2829	Ocular foreign body	11_a	85_b	186_c	51_b	8_a	341
Epilepsy	1	5	-	3	1	10	Low back pain	7_a	19_a	177_b	160_b	78_b	341	Internal orthopedic devices, implants, and grafts	54_a	8_b	18_b	5_b	19_b	104
Headache syndromes	-	2	2	5	-	9	Gonarthrosis	-	6_a	8_a	57_b	114_c	179	Nasal foreign body	80	-	-	1	-	81
Blepharospasm	-	-	1	3	-	4	Trigger finger	7_a	6_a	45_b	66_b	14_a	138	Ear foreign body	37_a	6_b	10_b	7_b	7_b	67
Hydrocephalus	3	-	-	1	-	4	Meniscal displacement	-	11_a	43_b	26_a	8_a	81	Oral foreign body	10	-	2	2	-	14
Eye and middle ear diseases	**0-18**	**19-30**	**31-45**	**46-59**	**60+**	**n**	**Genitourinary system diseases**	**0-18**	**19-30**	**31-45**	**46-59**	**60+**	**n**	**Accidents, poisoning, contact with sharp objects-firearms**	**0-18**	**19-30**	**31-45**	**46-59**	**60+**	**n**
Diabetic retinopathy	-	-	84_a	781_a	553_b	1418	Abnormal uterine and vaginal bleeding	-	36_a	946_b	349_c	70_a	1401	Bite and sting by non-venomous insects and arthropods	195_a	64_b	166_a	70_b	22_c	520
Senile cataract, other	-	6_a	28_a	283_b	647_c	965	Irregular menstruation	-	42_a	928_b	259_c	23_a	1252	Sharp object injury	33_a	36_a	59_b	21_a	6_c	155
Macular/ posterior pole degeneration	-	7_a	43_b	267_c	476_d	793	Acute vaginitis	-	49_a	436_b	149_c	32_a	666	Fall	30_a	19_a	21_a	18_a	24_a	112
Senile cataract	-	-	21_a	152_b	447_c	620	Benign prostatic hyperplasia	-	-	21_a	252_b	386_c	659	Collision with objects	21_a	13_a	21_a	13_a	11_a	79

Table 6. Continued

Disease groups and types	Age groups, n (%)					n	Disease groups and types	Age groups, n (%)					n	Disease groups and types	Age groups, (%)					n
Other disorders of the lacrimal gland	6_a	33_b	104_c	126_d	107_c	376	Ureteral stone	3_a	51_b	249_c	87_b	37_b	427	Gunshot wound	7_a	31_b	15_a	6_a	8_a	64
Respiratory system diseases	**0-18**	**19-30**	**31-45**	**46-59**	**60+**	**n**	**Infectious diseases**	**0-18**	**19-30**	**31-45**	**46-59**	**60+**	**n**	**Examination, follow-up, observation****	**0-18**	**19-30**	**31-45**	**46-59**	**60+**	**n**
Disorders of the nose/nasal sinuses	24_a	209_b	178_b	48_c	8_d	467	Viral warts	6_a	46_b	67_b	7_a	7_a	133	Postoperative recovery	87_a	121_a	218_b	154_b	127_a	707
Nasal septum deviation	-	191_a	175_b	42_c	-	408	Other infectious diseases	10_a	11_a	18_a	13_a	21_a	93	Gynecological examination	5_a	20_a	379_b	130_b	28_a	562
Adenoid hypertrophy	225_a	8_b	7_b	7_b	5_b	252	Salmonella infections	-	6_a	17_b	16_b	9_a	48	Routine & Religious circumcision	541_a	6_b	5_b	1_b	-	553
Tonsillar hypertrophy	235_a	6_b	7_b	-	-	248	Anogenital warts	-	8_a	22_b	7_a	-	37	Physical examination	47_a	46_a	198_b	121_b	72_a	484
Conchal hypertrophy	7_a	45_b	68_b	12_a	7_a	139	Other bacterial agents	3	2	5	1	3	14	Observation for suspected disease	14_a	34_a	60_b	22_a	33_a	163

The cells with an expected count of less than 5 or with zero counts are removed from the analysis. *Includes cases coded as R00-R99. These cases are also kept in the surgery database and cover specific disease categories, a wide range of clinical signs, symptoms and abnormal test results. **It is included as a category in the health information system because it is indexed in the surgery database

The decline in elective surgeries corresponds with the tiered prioritization frameworks established globally during the pandemic. International guidelines categorize surgical urgency into four levels: Emergency (requiring immediate intervention within hours to avert mortality), Urgent (time-sensitive procedures necessary within the days), Semi-urgent (procedures necessary within the 1-4 weeks), and Elective (deferrable for the ≥3 months without substantial harm) (31). This stratification facilitated organized resource distribution and reduced the risks associated with COVID-19 transmission. Our data indicate an 81% overall reduction, with elective surgeries decreasing to 3.25%, which reflects strict adherence to protocols that deferred Category 3-4 procedures (32,33). The prevalence of gynecological-obstetric surgeries, comprising 36.8% of elective procedures, highlights the prioritization of obstetric time-sensitivity and maternal-fetal health factors (34). The increased frequency of foreign body/implant surgeries may indicate their classification as Category 2 procedures, where delays pose a risk of infection or functional impairment (35). The necessity of these triage decisions may have worsened surgical backlogs for chronic conditions, highlighting a crucial aspect for future health system preparedness (36).

Most elective surgeries were performed in the 19-30 age group (35.8%), primarily due to gynecological diseases (36.8%). The incidence of cesarean deliveries is rising globally and within Türkiye. When cesarean delivery is conducted based on medical need, it significantly decreases perinatal mortality and morbidity; nevertheless, when performed electively, it may result in adverse outcomes for maternal and child health, akin to other surgical procedures (37,38). The study's findings indicate that while the incidence of spontaneous vertex births is elevated, elective and emergency cesarean births occur at comparable rates.

Many emergency procedures are conducted on patients aged 60 and over, accounting for 27.8%. The aging process alters the body's structure and functioning across various dimensions. Therefore, this circumstance requires that surgical interventions on older patients be conducted with increased caution and precision (39). Aging-related physiological changes elevate the incidence of chronic diseases, as well as mortality and morbidity rates among older adults (40). The use of health services by older people is rising due to the prevalence of chronic diseases (41). Therefore, chronic disease management is a pivotal concern that necessitates emphasis on the effective and efficient delivery of health services. The research demonstrated that the incidence of hospital visits after surgery for circulatory system ailments increased with

age. This condition can be linked to the rising prevalence of chronic diseases correlated with age.

Recent literature emphasizes the necessity of guaranteeing the reliability and authenticity of medical databases in hospitals through the implementation of standardized procedures. The accuracy of EHRs is essential for clinical decision-making, healthcare operations, and research. Nonetheless, errors frequently emerge from erroneous data entry, absence of standardization, irregular updates, and similar factors. Recent studies support the implementation of standardized data entry protocols, including the utilization of consistent coding systems like Systematized Nomenclature of Medicine – Clinical Terms and ICD-10, to reduce heterogeneity in clinical documentation (42). Furthermore, routine audits and error-checking systems, including automated data validation procedures, are essential for preserving data integrity. Hospitals must develop staff training programs to ensure healthcare personnel are proficient in these requirements and the proper utilization of EHRs (43). By formalizing these standardized procedures, hospitals can reduce the risks of errors that jeopardize data integrity and patient safety.

Regarding the validity of health data, the literature recommends integrating real-time monitoring systems that can flag inconsistencies and alert clinicians to potential data inaccuracies (44). This could involve using artificial intelligence-driven tools to identify incorrect or missing information patterns, enabling timely corrections. Another recommendation is to use interoperable data exchange systems, allowing for the seamless sharing of patient data across different healthcare institutions, which can reduce redundancy and enhance data accuracy (45). These interoperable systems, combined with regular quality checks and continuous improvement processes, ensure that data remains current, relevant, and valid. Hospitals can enhance the trustworthiness and utility of their medical databases through such structured and regularized procedures, thus improving patient outcomes and supporting data-driven healthcare advancements.

Conclusion

The COVID-19 pandemic has resulted in alterations to nearly all medical procedures, particularly surgical treatments. This study analyzed 46,041 procedures conducted from January 1, 2019, to October 1, 2023, at a prominent teaching and research hospital in İstanbul province, assessing data from 18 distinct illness groups based on numerous variables.

Substantial reductions were noted during the pandemic in emergency, elective, major, medium, and minor surgical procedures. All illness groups exhibited a reduction in the number of procedures, except for two categories: foreign body, implant, and graft surgeries, as well as accidents, poisoning, and contact with sharp objects and weapons. The majority of surgeries are classified as emergency procedures, including conditions of the eye, middle ear, genitourinary system, skeletal system, circulatory system, digestive system, and respiratory system. Emergency surgeries for eye and middle ear diseases were predominantly conducted on those aged 60 and above, while elective procedures were primarily carried out on those aged 19 to 30. Most emergency and elective procedures are classified as major surgeries. The incidence of surgical follow-up visits escalates with older age demographics.

Critical care requirements for COVID-19 patients significantly diminished surgical resources, resulting in a 90% reduction in capacity for major surgeries and redirecting emergency attention towards time-sensitive conditions, such as ocular and genitourinary emergencies in the elderly. Moreover, the fear of nosocomial infection led to a decrease in hospital presentations, especially for "semi-urgent" conditions such as chronic venous insufficiency, thereby worsening age-related disparities in post-operative follow-up.

The COVID-19 pandemic revealed significant weaknesses in surgical systems, including insufficient contingency planning for aging populations, as indicated by disproportionate emergency surges among individuals aged 60 and older. The contrast between sustained obstetric volumes and the collapse of elective procedures highlighted the inflexible triage protocols for time-sensitive non-emergent care. Furthermore, unaddressed backlog risks were exemplified by delays in chronic disease management. The identified gaps require a fundamental restructuring of surgical practices to enhance resilience against pandemics. This can be achieved through the establishment of institutionalized tiered prioritization frameworks, such as MeNTS, which dynamically balance resource limitations with procedural urgency; the development of age-optimized pathways that include dedicated operating room slots and rapid discharge protocols for vulnerable elderly patients; and the implementation of real-time backlog surveillance systems aimed at high-risk deferred cases, including circulatory disorders and cancer diagnostics, to mitigate complications. Incorporating these strategies into surgical disaster planning is crucial for ensuring the continuity of essential care during future crises.

During the pandemic, isolation measures were essential for delivering a comprehensive and well-equipped health service. Planning the operating room process requires the implementation of infection control measures. Preparing crisis plans for potential outbreaks in hospital medical

processes is essential, as is developing specific emergency plans for surgical and operating room procedures, which are specialized units. Effective human resource planning necessitates the organization of the surgical team and the ongoing training of assistants and nurses. The management of patients diagnosed with COVID-19 prior to, during, and following the surgical procedures requires thorough examination. The surgical team must focus on patient management during both the preoperative and postoperative phases. Health managers should prioritize and plan for both emergency and elective surgeries, oversee the management of materials and devices, optimize time management, implement infection control measures, and maintain effective communication and high staff motivation within operating room processes during the pandemic.

Ethics

Ethics Committee Approval: Institutional permission was obtained before the study was conducted, and ethics committee approval was obtained from the University of Health Sciences Türkiye, Hamidiye Scientific Research Ethics Committee (approval number: 1/34, dated: 25.01.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: P.Ü., E.S.E., F.K.Y., M.F.E., Design: P.Ü., E.S.E., F.K.Y., M.F.E., Data Collection or Processing: E.S.E., M.F.E., Analysis or Interpretation: E.S.E., F.K.Y., M.F.E., Literature Search: P.Ü., E.S.E., F.K.Y., M.F.E., Writing:P.Ü., E.S.E., F.K.Y., M.F.E.

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.2025.98698

Hamidiye Med J 2025;6(3):162-170

Possible Functional Impact of *ESR1* and *GREB1* Variants in Endometriosis: an *in silico* Approach

Endometrioziste *ESR1* ve *GREB1* Varyantlarının Olası Fonksiyonel Etkisi: *in silico* Yaklaşım

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ABSTRACT

Background: Endometriosis is a chronic, estrogen-dependent inflammatory disorder that affects a significant proportion of women of reproductive age. Although the pathophysiology of the disease remains incompletely understood, genetic and hormonal factors are believed to play key roles. Two genes of particular interest in this context are *Estrogen Receptor 1 (ESR1)* and *Growth Regulation by Estrogen in Breast Cancer 1 (GREB1)*, both of which are integral to estrogen signaling and cell proliferation. This study aimed to investigate the potential contribution of missense *Single Nucleotide Polymorphisms (SNPs)* in the *ESR1* and *GREB1* genes to the pathogenesis of endometriosis using an *in silico* approach.

Materials and Methods: Publicly available data from National Center for Biotechnology Information and SNP database were used to identify missense variants in *ESR1* and *GREB1*. The functional impact of each variant was predicted using six bioinformatics tools: Sorting Intolerant From Tolerant, Polymorphism Phenotyping v2, Protein Variation Effect Analyzer, SNPs and Gene Ontology, Protein Analysis Through Evolutionary Relationships, and PredictSNP. Protein-protein interaction networks were constructed via the Search Tool for the Retrieval of Interacting Genes/Proteins and Gene Multiple Association Network Integration Algorithm platforms, and disease and pathway associations were analyzed using the Kyoto Encyclopedia of Genes and Genomes and DISEASES databases.

Results: *ESR1* was found to be a central node in estrogen signaling, with strong predicted interactions with *GREB1* and other hormone-regulated genes. Several SNPs in both genes were consistently classified as deleterious across all predictive tools. Disease enrichment analysis further linked these genes to endometriosis, as well as to other estrogen-responsive conditions such as breast and ovarian cancers.

Conclusion: This study identifies potentially high-risk *ESR1* and *GREB1* variants and highlights their involvement in key estrogen-regulated pathways. These findings support the role of genetic variation in the molecular pathogenesis of endometriosis and lay the groundwork for future experimental validation.

Keywords: *GREB1*, *ESR1*, *in silico*, endometriosis, immunoinformatics

ÖZ

Amaç: Endometriozis, üreme çağındaki kadınların önemli bir kısmını etkileyen, kronik ve östrojene bağımlı enflamatuvar bir hastalıktır. Hastalığın patofizyolojisi tam olarak aydınlatılamamış olmakla birlikte, genetik ve hormonal faktörlerin önemli rol oynadığı düşünülmektedir. Bu bağlamda özellikle dikkat çeken iki gen, östrojen sinyal iletimi ve hücre proliferasyonu açısından kritik olan *Östrojen Reseptörü 1 (ESR1)* ve *Meme Kanserinde Östrojenle Düzenlenen Büyüme Geni 1*'dir *(GREB1)*. Bu çalışma, *in silico* bir yaklaşımla *ESR1* ve *GREB1* genlerindeki anlamsal (missense) *Tek Nükleotid Polimorfizmlerinin (SNP'ler)* endometriozis patogenezine olası katkısını araştırmayı amaçlamıştır.

Gereç ve Yöntemler: *ESR1* ve *GREB1* genlerindeki anlamsal varyantları belirlemek için Ulusal Biyoteknoloji Bilgi Merkezi ve Tek Nükleotid Polimorfizmi Veri Tabanı gibi halka açık veri tabanları kullanılmıştır. Her bir varyantın fonksiyonel etkisi; Tolere Edilemeyen Değişiklikleri Ayırma Aracı, Polimorfizm Fenotipleme Aracı, Versiyon 2, Protein Varyasyonu Etki Analizörü, SNPs ve Gen Ontolojisi Aracı, Evrimsel İlişkiler Üzerinden Protein Analizi ve PredictSNP olmak üzere altı farklı biyoinformatik aracıyla tahmin edilmiştir. Protein-

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Received: 19.04.2025 **Accepted:** 06.08.2025 **Epub:** 02.09.2025 **Publication Date:** 30.09.2025

Cite this article as: Özbey G, Kırkık D. Possible functional impact of *ESR1* and *GREB1* variants in endometriosis: an *in silico* approach. Hamidiye Med J. 2025;6(3):162-170.

ÖZ

protein etkileşim ağları etkileşimli gen/proteinleri bulma aracı ve gen çoklu ilişki ağlarını entegre etme algoritması platformları aracılığıyla oluşturulmuş, hastalık ve yolak ilişkileri Kyoto genler ve genomlar ansiklopedisi ve DISEASES veri tabanı kullanılarak analiz edilmiştir.

Bulgular: *ESR1*'nin, östrojen sinyal yolaklarında merkezi bir düğüm olduğu ve *GREB1* ile diğer hormonla düzenlenen genlerle güçlü etkileşimler gösterdiği tespit edilmiştir. Her iki gendeki bazı SNP'ler, tüm tahmin araçlarında tutarlı şekilde zararlı olarak sınıflandırılmıştır. Hastalık zenginleştirme analizleri, bu genleri endometriozis ile birlikte meme ve over kanseri gibi diğer östrojen duyarlı hastalıklarla da ilişkilendirmiştir.

Sonuç: Bu çalışma, *ESR1* ve *GREB1* genlerindeki potansiyel yüksek riskli varyantları ortaya koymuş ve bu genlerin östrojenle düzenlenen temel yolaklardaki rolüne dikkat çekmiştir. Bulgular, genetik varyasyonların endometriozisin moleküler patogenezindeki rolünü desteklemekte ve ileri deneysel doğrulama çalışmaları için bir temel oluşturmaktadır.

Anahtar Kelimeler: *GREB1*, *ESR1*, *in silico*, endometriozis, immünoinformatik

Introduction

Endometriosis is a chronic, estrogen-dependent inflammatory disorder characterized by the presence of functional endometrial tissue outside the uterine cavity. Although the ectopic endometrial lesions are most frequently located within the pelvic region, affecting structures such as the ovaries, pouch of Douglas, sacrouterine ligaments, pelvic peritoneum, rectovaginal septum, and cervix, there are documented cases of extra-pelvic involvement. Rarely, a comma is included endometriotic foci have been identified in organs including the lungs, pleura, diaphragm, intestines, gallbladder, kidneys, ureters, umbilicus, skin, central nervous system, and extremities (1,2).

The prevalence of endometriosis among women of reproductive age ranges from 3% to 37%, and despite its high frequency and significant impact on quality of life and fertility, the pathogenesis of the disease remains incompletely understood (3). One of the major contributing factors to this knowledge gap is the complex nature of its genetic background. Current evidence suggests a polygenic and multifactorial inheritance pattern, wherein disease development results from a combination of genetic predisposition and environmental influences (4).

Identifying specific genetic contributors is complicated by several factors. The necessity for invasive procedures, such as laparoscopy or laparotomy, for definitive diagnosis limits early detection and may result in underdiagnosis (5). Furthermore, endometriosis is now considered a heterogeneous condition encompassing multiple subtypes such as superficial peritoneal lesions, ovarian endometriomas, and deeply infiltrating endometriosis, each with potentially distinct genetic and molecular characteristics. Environmental exposures, particularly to endocrine-disrupting chemicals like dioxins, may further influence disease development and expression (6,7).

In this study, the investigation of genes such as *Estrogen Receptor 1 (ESR1)* and *Growth Regulation by Estrogen in Breast Cancer 1 (GREB1)* has gained attention due to their pivotal roles in estrogen signaling, cell proliferation, and endometrial receptivity, all of which are relevant in the etiology and progression of endometriosis (7-11). This study aims to explore the potential contribution of missense *Single Nucleotide Polymorphisms (SNPs)* in the *ESR1* and *GREB1* genes to the pathogenesis of endometriosis using a comprehensive *in silico* bioinformatics approach. By evaluating the functional impact of these genetic variants, mapping protein-protein interactions (PPIs), and analyzing disease-associated pathways, we seek to identify high-risk mutations and elucidate possible molecular mechanisms through which these genes may influence the development and progression of endometriosis.

Materials and Methods

Retrieval of Protein Sequences and Missense Variants for *ESR1* and *GREB1* Genes

Publicly available data from the National Center for Biotechnology Information (NCBI) and the NCBI Single Nucleotide Polymorphism database were used to investigate the *ESR1* and *GREB1* genes associated with endometriosis. Protein sequences and known SNPs for both genes were retrieved and analyzed. The focus was on missense mutations, as these variants result in amino acid changes that may alter the protein's structure and impair its normal biological function. Such changes can affect processes like hormone binding or gene regulation, which are critical in the pathogenesis of endometriosis. Bioinformatics tools were then applied to evaluate the potential effects of these mutations on protein function (12,13).

Interaction Analysis of *GREB1* and *ESR1*

To explore the functional and physical interactions involving the *GREB1* and *ESR1* genes, the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database

(version 11.5) was employed using a medium confidence interaction score threshold (≥0.4). This platform was used to build a comprehensive PPI network and to predict associations based on known and predicted interactions. In parallel, the Gene Multiple Association Network Integration Algorithm (GeneMANIA) tool (version 3.5.2) was used to further investigate gene-gene relationships and to identify additional genes functionally linked to *GREB1* and *ESR1*. This analysis included co-expression, shared pathways, co-localization, and physical interaction data. The results obtained from GeneMANIA were cross-referenced with the STRING analysis to confirm the consistency and biological relevance of the predicted interactions. All computational analyses were conducted between February 2 and 8, 2025, ensuring up-to-date and reliable data integration (14,15).

Identifying the Most Deleterious SNPs

To assess the potential functional consequences of non-synonymous SNPs identified in the *ESR1* and *GREB1* genes, six independent *in silico* prediction tools were employed: Sorting Intolerant From Tolerant (SIFT) (https://sift.jcvi.org), Protein ANalysis THrough Evolutionary Relationships (PANTHER) (https://www.pantherdb.org/tools), Polymorphism Phenotyping v2 (PolyPhen-2) (https://genetics.bwh.harvard.edu/pph2/), SNPs&Gene Ontology (GO) (https://snps.biofold.org/snps-and-go/), Protein Variation Effect Analyzer (PROVEAN) (https://provean.jcvi.org), and PredictSNP (https://loschmidt.chemi.muni.cz/predictsnp). These tools were used to evaluate the likelihood of deleterious effects caused by each amino acid substitution. Variants that were consistently classified as damaging by all six tools were considered to be high-risk mutations with strong potential to impair protein function. Each tool applies a different algorithm to determine the pathogenicity of SNPs. SIFT utilizes sequence homology to determine whether an amino acid change is tolerated, flagging substitutions with a probability score below 0.05 as deleterious. PANTHER evaluates evolutionary conservation and functional domains to estimate the effect of substitutions. PolyPhen-2 predicts the potential structural and functional consequences of amino acid changes based on multiple sequence alignments and protein structure features. SNPs&GO integrates gene ontology data with machine learning (support vector machine-based) models to associate mutations with disease. PROVEAN applies a sequence-based approach to assess whether amino acid substitutions are functionally disruptive, using a cut-off score of -2.5 to classify variants. Lastly, PredictSNP combines predictions from several algorithms (including SIFT, PolyPhen-2, Multivariate Analysis of Protein Polymorphism, Screening for Non-Acceptable Polymorphisms, and Predictor of Human Deleterious-SNP) to generate a consensus assessment of each SNP's deleterious potential.

Pathway and Disease Association Analysis of *GREB1* and *ESR1*

Pathway and disease analyses for the *GREB1* and *ESR1* genes were performed using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database to explore their roles in essential molecular pathways, particularly those associated with hormone signaling and estrogen-responsive mechanisms relevant to endometriosis. Access to the KEGG pathway data was facilitated through the KEGG application programming interface, allowing systematic mapping of gene functions in biological processes such as estrogen signaling, cell proliferation, and transcriptional regulation.

To complement these findings, disease associations were extracted from the DISEASES database (JensenLab, 2024 version), which provided insight into the clinical relevance of *GREB1* and *ESR1* in endometriosis and other hormone-related disorders. Additionally, the STRING database was used to construct PPI networks, further validating the involvement of these genes in interconnected regulatory systems. This integrated bioinformatics approach revealed key functional pathways and disease links associated with *GREB1* and *ESR1* (16-18).

Statistical Analysis

All bioinformatics and *in silico* statistical analyses were conducted using integrated online platforms and computational tools. Functional predictions of missense variants were obtained from SIFT, PolyPhen-2, PROVEAN, PANTHER, SNPs&GO, and PredictSNP web servers. Protein-protein interaction networks were analyzed via STRING (version 11.5; European Molecular Biology Laboratory, Heidelberg, Germany) and GeneMANIA (version 3.5.2; University of Toronto, Toronto, Canada). Pathway and disease enrichment analyses were performed using the KEGG database (KEGG, Kyoto University, Kyoto, Japan) and DISEASES database (JensenLab, Copenhagen, Denmark). All analyses were performed between February 2 and February 10, 2025, and descriptive statistics were automatically calculated by the respective bioinformatics servers.

Results

Identifying the Most Deleterious SNPs

Although this study primarily focused on missense variants, all listed *GREB1* SNPs are intronic and were included due to their potential regulatory relevance as supported by prior literature. These variants were therefore excluded from functional prediction analyses.

The initial step of our analysis involved the identification and curation of SNPs within the *GREB1* and *ESR1* genes, both of which are implicated in estrogen signaling and have been associated with hormone-dependent conditions including endometriosis. Table 1 presents the complete list of selected variants, annotated with reference SNP cluster IDs, allelic composition, ancestral alleles, Human Genome Variation Society nomenclature-compliant transcript-based nomenclature, chromosomal positions, and minor allele frequencies (MAFs). Importantly, all variants listed under *ESR1* are exonic and classified as missense mutations, thus, eligible for functional prediction analysis *via in silico* tools such as SIFT, PolyPhen-2, and PROVEAN. In contrast, all *GREB1* variants in our dataset are located in intronic regions, rendering them non-coding and thereby outside the scope of classical missense-based prediction algorithms. Nevertheless, these *GREB1* variants were retained due to their high population frequency and potential regulatory roles, as suggested by previous genome-wide association and transcriptomic studies linking *GREB1* expression to estrogen-mediated proliferation in endometrial tissues.

Among the *ESR1* variants, rs753014570 (c.728G > A) and rs779180038 (c.727C > T) occur in close proximity within the coding sequence, possibly affecting the same functional domain, and may act in tandem as a multi-nucleotide polymorphism in certain haplotypes. Variant rs773500294 also appears as a duplicated entry in public databases, with different reported alternative alleles (C > A and C > G), which requires cautious interpretation due to possible annotation inconsistencies. The low MAFs (<0.01) of several *ESR1* variants suggest they may represent rare, potentially pathogenic alterations with relevance to disease susceptibility. These prioritized SNPs served as the foundation for downstream analyses, including PPI mapping and disease association profiling.

Interaction Analysis of *GREB1* and *ESR1*

PPI analysis revealed that *ESR1* occupies a central position within the interaction network, engaging in numerous functional associations with other proteins relevant to estrogen signaling and transcriptional regulation. Notably, *GREB1* and its paralog *GREB1L* demonstrated strong connectivity with *ESR1*, supporting their known roles as estrogen-responsive genes. The presence of thick interaction lines indicates high-confidence associations, suggesting a direct regulatory relationship. Similarly, a prominent interaction was observed between *ESR1* and progesterone receptor (PGR), highlighting the interplay between estrogen and progesterone pathways in hormone-regulated tissues (Figure 1).

The corresponding interaction network is presented in Figure 1. In the GeneMANIA-derived visualization, different edge colors represent distinct types of functional associations: pink lines indicate co-expression, blue lines denote physical interactions, green lines correspond to co-localization, and orange lines reflect predicted interactions. These integrated networks provide evidence for the functional linkage between *ESR1* and *GREB1*, particularly within estrogen-responsive signaling pathways.

Disease association analysis performed using the

Table 1. Summary of selected SNPs in *ESR1* and *GREB1* genes, including their HGVS nomenclature, genomic location, ancestral and alternative alleles, and MAF. All *GREB1* variants listed are intronic and not eligible for functional prediction via missense-specific tools

Source	rs ID	Allele	Ancestral	HGVS name	Location	MAF
GREB1	rs13394619	A/G	A	ENST00000234142.9: c.1160-1365G > A	Chromosome 2:11587381	0.50
	rs11674184	A/T	T	ENST00000234142.9: c.901+577T > A	Chromosome 2:11581409	0.37
	rs12470971	A/G	G	ENST00000234142.9: c.902-46G > A	Chromosome 2:11585115	0.50
	rs11686574	C/G	C	ENST00000381483.6: c.-159+1064C > G	Chromosome 2:11543881	0.47
	rs6740248	C/G	C	ENST00000234142.9: c.454+110C > G	Chromosome 2:11566766	0.22
	rs2930961	C/T	T	ENST00000336148.10: c.305-20263A > G	Chromosome 8:94431578	0.40
	rs1250248	A/G	G	ENST00000323926.10: c.1394-127T > C	Chromosome 2:215422370	0.22
ESR1	rs139960913	C/T	C	ENST00000206249.8: c.16C > T	Chromosome 6:151807928	0.01
	rs746521050	G/A	G	ENST00000206249.8: c.269G > A	Chromosome 6:151808181	<0.01
	rs773500294	C/A	C	ENST00000206249.8: c.296C > A	Chromosome 6:151808208	<0.01
	rs149308960	**G/A/C/T**	**G**	**ENST00000206249.8: c.478G > T**	**Chromosome 6:151842622**	**0.01**
	rs779180038	**C/T**	**C**	**ENST00000206249.8: c.727C > T**	**Chromosome 6:151880738**	**<0.01**
	rs753014570	**G/A**	**G**	**ENST00000206249.8: c.728G > A**	**Chromosome 6:151880739**	**<0.01**

ESR1: Estrogen Receptor 1, GREB1: Growth Regulation by Estrogen in Breast Cancer 1 Like, HGVS: Human Genome Variation Society, MAF: Minor allele frequencies, rs ID: Reference SNP identification number, SNP: Single Nucleotide Polymorphism

DISEASES database (JensenLab) revealed that both *ESR1* and *GREB1* are strongly linked to a variety of hormone-dependent and estrogen-responsive conditions. *ESR1* showed high-confidence associations with several diseases, most notably breast cancer (Z: 9.0), carcinoma (Z: 7.4), endometriosis (Z: 7.1), and ovarian cancer (Z: 6.6). These associations reflect *ESR1*'s pivotal role in estrogen signaling, transcriptional regulation, and reproductive tissue homeostasis.

Similarly, *GREB1*—a gene regulated by *ESR1* and known to mediate estrogen-stimulated cell proliferation—also demonstrated associations with estrogen-sensitive pathologies. The strongest connections were observed with breast cancer (Z: 5.3), endometriosis (Z: 4.7), amelogenesis imperfecta type 1G (Z: 4.6); and various gynecologic malignancies such as uterine cancer, ovarian cancer, and uterine fibroids (Figures 2 and 3).

Collectively, these findings reinforce the functional interplay between *ESR1* and *GREB1* in estrogen-regulated pathways and highlight their shared involvement in the pathogenesis of endometriosis and other hormone-related disorders.

Figure 4 shows the representation of the estrogen signaling pathway based on the KEGG pathway map. The pathway includes both membrane-initiated and nuclear-initiated steroid signaling mechanisms. *ESR1* acts as a central transcription factor activated by estrogen, leading to downstream signaling events including activation of MAPK/ERK and PI3K/AKT pathways. *GREB1*, indicated as a target gene, is transcriptionally regulated by *ESR1* upon estrogen binding, suggesting its role as a downstream effector in estrogen-dependent biological processes such as cell proliferation, differentiation, and survival.

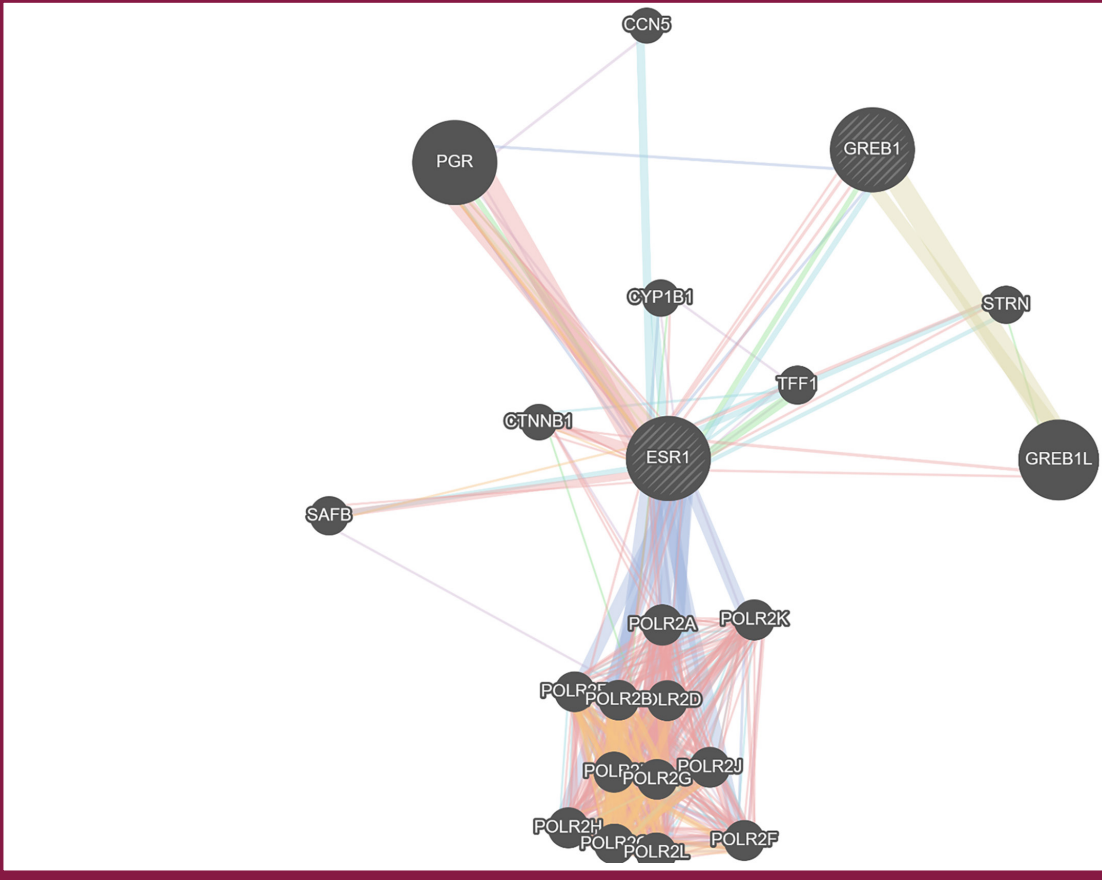

Figure 1. The PPI analysis was conducted using the STRING database (v11.5) and further supported by GeneMANIA (v3.5.2)
CYP19A1: Cytochrome P450 Family 19 Subfamily A Member 1, ESR1: Estrogen Receptor 1, GeneMANIA: Gene Multiple Association Network Integration, GREB1: Growth Regulation by Estrogen in Breast Cancer 1, GREB1L: Growth Regulation by Estrogen in Breast Cancer 1 Like, NCOA1: Nuclear Receptor Coactivator 1, PGR: Progesterone receptor, POLR2A: RNA Polymerase II Subunit A, PPI: Protein-protein interaction, SPDEF: SAM Pointed Domain Containing ETS Transcription Factor, STC2: Stanniocalcin 2 STRING: Search Tool for the Retrieval of Interacting Genes/Proteins, TFF1: Trefoil Factor 1

Discussion

In this study, a comprehensive *in silico* analysis was performed to investigate the potential contribution of missense SNPs in the *ESR1* and *GREB1* genes to the pathogenesis of endometriosis. These genes were selected due to their critical roles in estrogen signaling, cell proliferation, and reproductive tissue regulation, all of which are highly relevant to the etiology of endometriosis (7-11). By integrating data from multiple bioinformatics platforms—including SNP prediction tools, PPI networks, and disease association databases—we sought to identify high-risk variants that may influence disease susceptibility and progression.

Our PPI analysis revealed that *ESR1* serves as a central hub within the estrogen signaling network, demonstrating strong associations with *GREB1* and other key genes such as PGR, CYP1B1, and CTNNB1 (14,15). These interactions support previous findings that *ESR1* and *GREB1* are not only co-expressed but also functionally interlinked in hormone-responsive pathways (8,10,11).

Further connections between *ESR1* and components of the RNA polymerase II complex (including POLR2A, POLR2F, POLR2J, among others) emphasize its role in the transcriptional activation of downstream target genes. Additionally, interactions with genes such as CYP1B1, TFF1, CTNNB1, and SAFB reflect *ESR1*'s broad involvement in cellular processes including hormone metabolism, cell

Name	Z-score	Confidence
Breast cancer	9.0	★★★★☆
Amelogenesis imperfecta type 1G	8.1	★★★★☆
Carcinoma	7.4	★★★★☆
Ductal carcinoma in situ	7.2	★★★★☆
Endometriosis	7.1	★★★★☆
Osteoporosis	6.9	★★★★☆
Prostate cancer	6.7	★★★★☆
Ovarian cancer	6.6	★★★★☆
Lung cancer	6.5	★★★★☆
Colorectal cancer	6.4	★★★★☆

Figure 2. Disease association of *ESR1* based on text mining analysis from the DISEASES database
ESR1: Estrogen Receptor 1

Name	Z-score	Confidence
Breast cancer	5.3	★★★☆☆
Endometriosis	4.7	★★★☆☆
Amelogenesis imperfecta type 1G	4.6	★★★☆☆
Uterine cancer	4.0	★★☆☆☆
Uterine fibroid	3.9	★★☆☆☆
Ovarian cancer	3.8	★★☆☆☆
Carcinoma	3.8	★★☆☆☆
Ovarian sex-cord stromal tumor	3.7	★★☆☆☆
Prostate cancer	3.7	★★☆☆☆
Adenosarcoma	3.6	★★☆☆☆

Figure 3. Disease association of *GREB1* based on DISEASES database text mining
GREB1: Growth Regulation by Estrogen in Breast Cancer 1 Like

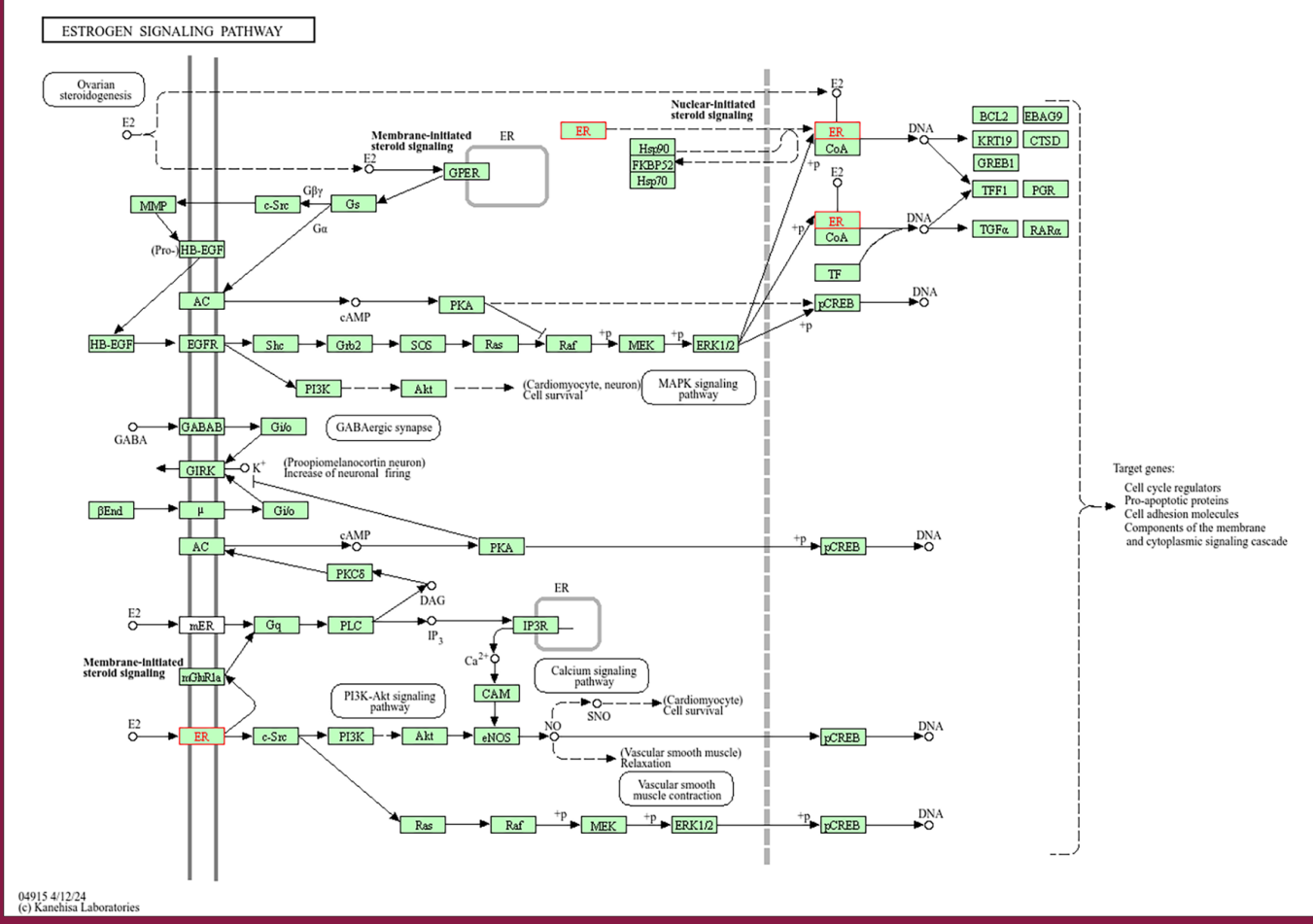

Figure 4. Estrogen signaling pathway showing ESR1 activation and downstream regulation of GREB1 (adapted from KEGG)
ESR1: Estrogen Receptor 1, GREB1L: Growth Regulation by Estrogen in Breast Cancer 1 Like, KEGG: Kyoto Encyclopedia of Genes and Genomes

proliferation, and chromatin remodeling (14,16). In addition to the molecular pathway relevance of these genes, the clinical significance of the identified variants was also examined. To further contextualize the relevance of the identified SNPs, we explored existing literature and variant databases to determine whether these polymorphisms have previously been associated with endometriosis or other estrogen-dependent conditions. While none of the *ESR1* or *GREB1* variants listed in Table 1 has been directly linked to endometriosis in large genome-wide association studies, some—such as *ESR1* rs753014570 (c.728G > A)—have been implicated in hormone-responsive cancers including breast and ovarian cancer, where dysregulated estrogen signaling is a common pathological feature (19,20). This overlap is noteworthy, given the shared molecular mechanisms between these diseases and endometriosis, including estrogen-driven proliferation, progesterone resistance, and inflammatory microenvironment remodeling. Additionally, the low-frequency variants identified in *ESR1* (e.g., rs779180038, rs746521050) may represent rare, potentially functional mutations that could alter receptor conformation, DNA binding affinity, or cofactor recruitment, ultimately influencing downstream gene transcription. Although the *GREB1* variants identified in this study are intronic and have not been directly associated with endometriosis, prior evidence suggests that regulatory SNPs in intronic regions can affect gene expression via splicing efficiency, enhancer disruption, or transcription factor binding site modulation (21,22). Therefore, these variants may contribute to altered *GREB1* expression levels in estrogen-responsive tissues. Future experimental validation and population-based association studies are required to assess the biological significance of these candidate variants in endometriosis pathogenesis (23,24). The functional link between *ESR1* and

GREB1, in particular, underscores a shared role in estrogen-mediated gene expression, suggesting that genetic variants affecting these proteins may contribute to the molecular pathology of endometriosis (10,11). The rationale for selecting *ESR1* and *GREB1* in this study stems from their well-established roles in estrogen signaling, which is central to the pathogenesis of endometriosis (25,26). *ESR1* encodes Estrogen Receptor α (ERα), a nuclear hormone receptor that regulates the transcription of estrogen-responsive genes upon ligand binding (27,28). *GREB1* is one such early response gene directly upregulated by *ESR1* via estrogen-bound ERα complexes (29). Multiple studies have demonstrated that *GREB1* expression is tightly correlated with estrogen stimulation in hormone-responsive tissues including the endometrium and that it functions as a key mediator of estrogen-driven cellular proliferation and differentiation (30-32). Specifically, chromatin immunoprecipitation assays have shown that ERα binds to enhancer regions within the *GREB1* gene locus, activating its transcription (33). This regulatory axis is critical in endometrial biology, as dysregulation of estrogen signaling is known to promote the ectopic growth and invasiveness characteristic of endometriotic lesions. Therefore, the functional interplay between *ESR1* and *GREB1* reflects a direct transcriptional hierarchy, wherein polymorphisms in either gene may disrupt normal hormonal responses, leading to altered gene expression patterns that favor the development or persistence of endometriosis (8-34,35).

Several missense mutations in both *ESR1* and *GREB1* were identified, some of which were predicted to be deleterious across multiple algorithms. Variants such as rs779180038 and rs753014570, although classified as multi-nucleotide variants with ambiguous impact, highlight the complexity of interpreting *in silico* predictions and the necessity for future experimental validation. These findings suggest that specific SNPs may alter protein structure or function, potentially disrupting ER activity or its downstream gene targets (12-13).

Pathway and disease enrichment analyses supported these observations, linking *ESR1* and *GREB1* not only to endometriosis but also to other estrogen-dependent conditions such as breast cancer, ovarian cancer, and uterine fibroids (16,17). These overlapping associations underline the shared molecular mechanisms underlying these diseases and reinforce the importance of studying *ESR1* and *GREB1* in a broader hormonal context (7-9).

Collectively, our results emphasize the value of integrated bioinformatics approaches in identifying candidate variants for further investigation. While *in silico* predictions provide important insights, they should be followed by functional assays and population-based studies to validate the clinical relevance of the identified mutations. Understanding how these genes and their variants contribute to estrogen signaling and endometrial pathophysiology may ultimately aid in the development of more personalized diagnostic and therapeutic strategies for endometriosis.

Conclusion

Although *silico*-based approaches cannot fully replace experimental validation, they serve as valuable tools for prioritizing candidate variants for further functional and clinical research. The integration of these results with future laboratory and population-level studies may enhance our understanding of endometriosis and facilitate the development of targeted diagnostic and therapeutic strategies.

Ethics

Ethics Committee Approval: Since this study was entirely based on publicly available bioinformatics databases and performed using *in silico* analyses, no ethical approval was required.

Informed Consent: As no human participants or patient data were involved in this *in silico* study, informed consent was not applicable.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.Ö., D.K., Concept: G.Ö., D.K., Design: G.Ö., D.K., Data Collection or Processing: G.Ö., D.K., Analysis or Interpretation: G.Ö., Literature Search: G.Ö., D.K., Writing: G.Ö., D.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.2025.73745

Hamidiye Med J 2025;6(3):171-177

Understanding Prostate Cancer Risk Using Statistical and Machine Learning Approaches: A Comparative Methodological Analysis

İstatistiksel ve Makine Öğrenmesi Yaklaşımlarını Kullanarak Prostat Kanseri Riskini Anlamak: Karşılaştırmalı Metodolojik Analiz

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ABSTRACT

Background: Prostate cancer is one of the most common and lethal malignancies among men worldwide, making accurate risk prediction tools essential for early diagnosis and personalized care. This study aimed to compare the predictive ability of traditional binary logistic regression with machine learning (ML) algorithms, including support vector machines (SVM), K-nearest neighbors (KNN), chi-squared automatic interaction detection (CHAID), and C5.0, in identifying key risk factors and classifying prostate cancer status.

Materials and Methods: The study included 501 male participants (248 diagnosed cases and 253 controls) who completed a structured 20-item questionnaire covering demographic, clinical, and lifestyle characteristics.

Results: Age, smoking status, and family history of cancer consistently emerged as significant predictors across models. Additional indicators included blood in semen or urine, frequency of urination, and daily activity level. Logistic regression achieved the highest accuracy (92.2%), followed by CHAID (91.36%), SVM (89.92%), KNN (88.48%), and C5.0 (88%).

Conclusion: Logistic regression provided the best accuracy and interpretability for structured clinical data, while ML models offered complementary insights by identifying complex, nonlinear associations.

Keywords: Prostate cancer, risk prediction, logistic regression, machine learning, classification algorithms

ÖZ

Amaç: Prostat kanseri, erkekler arasında en yaygın ve ölümcül malignitelerden biridir. Erken tanı ve kişiselleştirilmiş bakım için doğru risk tahmin araçlarının geliştirilmesi büyük önem taşır. Bu çalışmada, prostat kanseri risk faktörlerini belirleme ve hastalık durumunu sınıflandırmada ikili lojistik regresyon ile makine öğrenimi (ML) algoritmalarının (SVM, KNN, CHAID ve C5.0) öngörü performansları karşılaştırılmıştır.

Gereç ve Yöntemler: Çalışmaya, demografik, klinik ve yaşam tarzı özelliklerini içeren 20 soruluk yapılandırılmış anketi dolduran 501 erkek (248 hasta ve 253 kontrol) dahil edilmiştir.

Bulgular: Yaş, sigara kullanımı ve ailede kanser öyküsü tüm modellerde anlamlı öngörücüler olarak bulunmuştur. Ek olarak semen veya idrarda kan, idrara çıkma sıklığı ve günlük aktivite düzeyi de belirleyici olmuştur. Lojistik regresyon %92,2 doğrulukla en yüksek performansı göstermiştir. CHAID %91,36, SVM %89,92, KNN %88,48 ve C5.0 %88 doğruluk oranına ulaşmıştır.

Sonuç: Lojistik regresyon yapılandırılmış klinik verilerde en yüksek doğruluk ve yorumlanabilirliği sağlarken, ML algoritmaları karmaşık ve doğrusal olmayan ilişkileri ortaya çıkararak tamamlayıcı katkılar sunmuştur.

Anahtar Kelimeler: Prostat kanseri, risk tahmini, lojistik regresyon, makine öğrenmesi, sınıflandırma algoritmaları

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Received: 29.04.2025 **Accepted:** 06.08.2025 **Epub:** 02.09.2025 **Publication Date:** 30.09.2025

Cite this article as: Aktaş S, Kirişçi M, Akçay M, Çiçek M. Understanding prostate cancer risk using statistical and machine learning approaches: a comparative methodological analysis. Hamidiye Med J. 2025;6(3):171-177

Introduction

Regression models are fundamental statistical tools used to examine the relationships between dependent and independent variables. These models require different assumptions depending on the structure of the data and the characteristics of the variables. In this context, logistic regression (LR) is a widely used, powerful, and flexible method for analyzing binary outcome variables (1,2).

One of the main advantages of LR is that it is not strictly bound by classical parametric assumptions such as normal distribution, linear relationships, or homogeneity of variances (2,3). This makes it highly reliable in fields such as clinical research, where complex data structures are common (4). Moreover, LR allows for the simultaneous evaluation of multiple independent variables and enables statistical testing of their individual and combined effects on the dependent variable (5).

In recent years, the increasing computational power and accessibility of large datasets have brought machine learning (ML) techniques to the forefront as alternatives to traditional statistical methods. First introduced in the 1950s, ML encompasses mathematical models that enable computers to learn from data and make predictions (6). Today, ML algorithms are widely used across various disciplines, including finance, engineering, and healthcare, due to their high accuracy, flexibility, and modeling capacity (7,8).

ML is generally categorized into supervised, unsupervised, and semi-supervised learning approaches (6,9). Supervised learning is applied when the outcome variable in the dataset is known and includes methods such as support vector machines (SVM), decision trees, and classification algorithms. Unsupervised learning aims to uncover hidden patterns or groupings in the data without any labeled outcome variable. Semi-supervised learning, on the other hand, is a hybrid model that utilizes both labeled and unlabeled data (10).

Today, the increasing volume and complexity of clinical data-especially in multifactorial diseases such as cancer-have created a need for more effective tools for risk prediction. Accordingly, ML algorithms have become valuable tools in healthcare for early diagnosis, treatment planning, and personalized medicine.

Prostate cancer is the second most common malignancy among men worldwide and ranks second in cancer-related mortality (11). Similar epidemiological trends have been observed in Türkiye. This highlights the critical public health importance of early detection and accurate identification of risk factors.

This study aims to comparatively evaluate the performance of binary LR and various ML algorithms, including SVM, K-nearest neighbors (KNN), chi-squared automatic interaction detection (CHAID), and C5.0, in identifying risk factors for prostate cancer and predicting disease status. By combining traditional statistical methods with modern ML approaches, this study reflects an integrated modeling strategy that can contribute to the development of effective clinical decision support systems.

This article is derived from the doctoral dissertation titled "a study on determining prostate cancer risk factors with LR analysis and ML algorithms", completed at İstanbul University-Cerrahpaşa, Institute of Health Sciences.

Materials and Methods

This study utilized a cross-sectional design involving 501 male participants: 248 diagnosed with prostate cancer and 253 without prostate cancer. Participants were recruited from the Urology Outpatient Clinic of Göztepe Training and Research Hospital in İstanbul between April 2021 and September 2021. Data were collected face-to-face using a structured questionnaire, and informed consent was obtained from all participants through a signed consent form prior to participation.

The questionnaire was developed based on a review of current clinical guidelines and epidemiological literature on prostate cancer risk. It consisted of 20 items grouped into three domains: (i) sociodemographic characteristics (e.g., age, education level, marital status), (ii) clinical and urological symptoms (e.g., urinary frequency, hematuria, erectile dysfunction), and (iii) lifestyle-related and behavioral factors (e.g., smoking status, physical activity level, alcohol use, dietary fat intake). The questionnaire was reviewed by two urologists and a biostatistician for content relevance and clinical appropriateness before implementation.

Sample size determination was based on the rule of having at least ten cases per independent variable for LR analysis (1,12). After excluding incomplete or inconsistent data, the final sample comprised 501 individuals. Ethics approval was obtained from the University of Health Sciences Türkiye, Hamidiye Scientific Research Ethics Committee (approval number: 21/125, dated: 19.03.2021).

Statistical Analysis

All analyses were conducted using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA) and its Modeler module. Descriptive statistics were calculated for all variables. Categorical variables were summarized using frequencies and percentages, while continuous variables were presented as means and standard deviations.

Variables with a p-value less than 0.05 in univariate analysis were entered into the multivariate logistic

regression model using the enter method. All statistical tests were two-sided, and p-values less than 0.05 were considered statistically significant.

Binary Logistic Regression: Binary logistic regression analysis was conducted to identify significant predictors of prostate cancer. Variables with a p-value less than 0.05 in univariate analysis were entered into the multivariate model using the enter method. Odds ratios (ORs), 95% confidence intervals (CIs), and p-values were reported.

SVM: The SVM model used a radial basis function kernel. Hyperparameters were optimized using a grid search approach combined with 10-fold cross-validation. Performance was assessed based on accuracy, sensitivity, specificity, and area under the curve (AUC) values.

KNN: The KNN model was implemented with k values ranging from 3 to 15. The optimal value of k was determined through cross-validation. The Euclidean distance metric was used for classification.

CHAID Decision Tree: The CHAID algorithm was used to construct a decision tree. Splits were based on chi-square tests with Bonferroni-adjusted significance levels. The model provided interpretable decision rules for classification.

C5.0 Decision Tree: The C5.0 model employed boosting and pruning to improve performance. This algorithm generated a set of classification rules and a decision tree to predict prostate cancer status. Model accuracy and AUC values were used for evaluation.

Model Evaluation: The dataset was randomly split into training (70%) and testing (30%) subsets. The performance of each model was evaluated on the test set using classification accuracy, sensitivity, specificity, and receiver operating characteristic (ROC) curves. AUC values were computed to assess discriminative power. Statistical significance was evaluated at a 95% confidence level.

Results

The demographic characteristics and clinical features of the participants are summarized in Table 1. Patients with prostate cancer had a significantly higher mean age (72±8.74 years) compared to healthy individuals (46±9.92 years). A significantly higher proportion of prostate cancer patients reported smoking, a family history of cancer, and urinary symptoms compared to the control group, as shown in Table 1.

Binary logistic regression identified several statistically significant risk factors: age (OR =1.103, p<0.001), smoking (OR =5.624, p<0.001), family history of cancer (OR =2.517, p=0.016), urinary frequency (OR =2.484 to 3.763, p<0.05), sedentary lifestyle (OR =2.672, p=0.004), and presence of blood in semen (OR =11.432, p<0.001). Binary logistic regression analysis revealed several statistically significant predictors of prostate cancer. Age was positively associated with cancer risk; each additional year of age increased the odds of prostate cancer by 10.3% (OR =1.103; 95% CI: 1.078-1.128; p=0.001). Smoking was one of the strongest predictors, increasing the risk more than fivefold (OR =5.624; 95% CI: 2.752-11.494; p=0.001). A positive family history of cancer doubled the likelihood of diagnosis (OR =2.517; 95% CI: 1.189-5.329; p=0.016).

Urinary frequency was another significant predictor. Compared to individuals who urinated five or fewer times per day, those who urinated 5-10 times had 2.48 times higher odds (OR =2.484; 95% CI: 1.095-5.637; p=0.029), and those who urinated more than 10 times had 3.76 times higher odds (OR =3.763; 95% CI: 1.491-9.496; p=0.005).

Sedentary behavior significantly increased the risk; individuals with sedentary behavior had 2.67 times higher odds compared to those who regularly exercised (OR =2.672; 95% CI: 1.638-14.487; p=0.004).

Notably, the presence of blood in semen was associated with an elevenfold increase in prostate cancer risk (OR =11.432; 95% CI: 2.763-47.289; p=0.001). The regression coefficients and full model statistics are presented in Table 2. Model fit was acceptable according to the Hosmer-Lemeshow test (χ^2 =12.112; p=0.146), and model performance metrics are shown in Figures 1 and 2.

The detailed regression coefficients and ORs are provided in Table 2. Each model identified overlapping but distinct sets of predictive variables. While age, smoking, and family history of cancer were common variables across models, SVM also included variables like fat consumption and chronic disease status, CHAID considered erectile dysfunction, and C5.0 emphasized urinary frequency and daily lifestyle. The variables identified by each model are summarized in Table 3.

The classification results for each algorithm are presented in Table 4. Additionally, confusion matrix-based classification metrics, such as sensitivity, specificity, accuracy, and approximate AUC values, are shown in Table 5.

Figure 1 shows the ROC curves for each classification model. logistic regression achieved the highest AUC value (0.922), indicating superior discriminative performance in distinguishing patients with and without prostate cancer. The CHAID model followed with an AUC of 0.914, while SVM and KNN showed comparable performance with AUCs of 0.897 and 0.884, respectively. The C5.0 model yielded the lowest AUC (0.885), which is still considered to have acceptable predictive power.

Figure 2 presents the cumulative gain chart for the classification models. Logistic regression demonstrated the steepest cumulative gain curve, indicating the most effective identification of true positive cases within a

Table 1. Demographic information of the participants

		Group n (%)	
		Patient	Healthy
Marital status	Single	50 (20%)	148 (59%)
	Married	176 (71%)	79 (31%)
	Other	22 (9%)	26 (10%)
Smoking	No	32 (12.9%)	189 (74.7%)
	Yes	216 (87.1%)	64 (25.3%)
Your level of education	Literate	13 (5.24%)	5 (1.97%)
	Primary school	78 (31.4%)	29 (11.4%)
	Middle school	51 (20.5%)	47 (18.5%)
	High school	81 (32.6%)	80 (31.6%)
	University	25 (10.0%)	92 (36.3%)
Alcohol use	Yes	86 (34.7%)	67 (26.5%)
	No	162 (65.3%)	186 (73.5%)
Profession	Labourer	23 (9.27%)	16 (6.32%)
	Self-employment	53 (21.3%)	42 (16.6%)
	Student	0 (0%)	37 (14.6%)
	Academic staff	14 (5.64%)	6 (2.37%)
	Civil servant	37 (14.9%)	45 (17.7%)
	Not working	18 (7.25%)	7 (2.76%)
	Pensioner	50 (20.1%)	36 (14.2%)
	Health personnel	30 (12.0%)	28 (11.0%)
	Teacher	23 (9.27%)	36 (14.2%)
Family history of cancer	No	135 (54.4%)	208 (82.2%)
	Yes	113 (45.6%)	45 (17.8%)

Patient: Individuals diagnosed with prostate cancer. Healthy: Individuals who have not been diagnosed with prostate cancer

Table 2. Binary logistic regression analysis results

	β	S.E.	Wald	p-value	OR (95% CI)
Your age	0.098	0.012	70.142	0.001	1.103 (1.078-1.128)
Cigarette (yes)	1.727	0.365	22.425	0.001	5.624 (2.752-11.494)
Presence of cancer in the family (yes)			5.824	0.016	2.517 (1.189-5.329)
How often do you urinate	0.923	0.383	8.898	0.012	
How often do you urinate (1)			4.741	0.029	2.484 (1.095-5.637)
How often do you urinate (2)	0.91	0.418	7.876	0.005	3.763 (1.491-9.496)
Lifestyle during the day	1.325	0.472	12.841	0.002	
Lifestyle during the day (1)			8.111	0.004	2.672 (1.638-14.487)
Lifestyle during the day (2)	0.983	0.556	0.973	0.324	0.683 (0.320-1.457)
Blood in semen	-0.381	0.387	11.31	0.001	11.432 (2.763-47.289)
Constant	2.436	0.724	29.771	0.001	

Hosmer-Lemeshow test (x^2=12,112; df=8; p=0.146); Omnibus test (x^2 =35,62; df=8; p=<0.001); -2log likehoold= 228,115; Cox-Snell R^2= 0.706; Nagelkerke R^2= 0.808; How often do you urinate= 5 and below How often do you urinate (1)= 5-10; How often do you urinate (2)= 10 or more; Lifestyle during the day= I do sports; Lifestyle during the day (1)= I am sedentary; Lifestyle during the day (2)= I do not do sports but I am active during the day. β: Beta, S.E.: Standard error, OR: Odds ratio, CI: Confidence interval

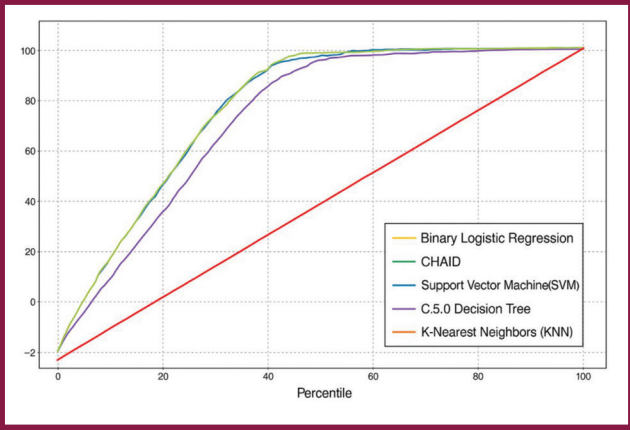

Figure 1. ROC curve of classification algorithms
ROC: Receiver operating characteristic, CHAID: Chi-squared automatic interaction detector

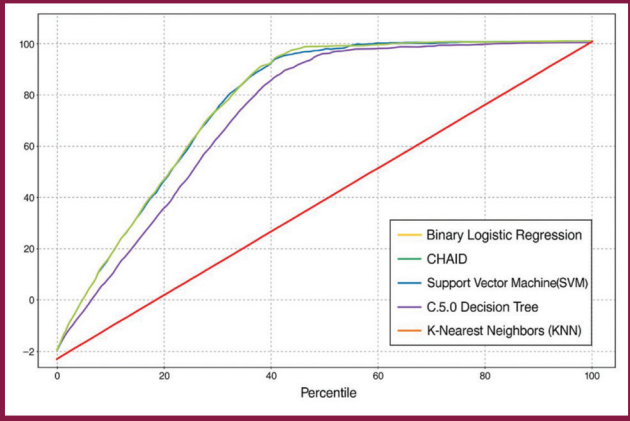

Figure 2. Cumulative gain chart comparing the classification performance of logistic regression, and algorithms
CHAID: Chi-squared automatic interaction detector

smaller portion of the population. This further supports the model's robustness in clinical screening contexts. SVM and CHAID also showed strong performance, while C5.0 and KNN were relatively less efficient in early-stage detection based on gain curve profiles.

Discussion

This study compared the predictive capabilities and risk factor identification accuracy of logistic regression analysis and several ML algorithms in the context of prostate cancer. Logistic regression emerged as the most effective method based on classification accuracy, which can be attributed to the linear nature of relationships in the dataset. These findings align with existing literature emphasizing the strength of logistic regression in clinical applications where model interpretability and probabilistic outcomes are essential (13). This is in line with findings from Morote et al. (14), who highlighted logistic regression's interpretability and robustness when applied to structured clinical datasets.

Nevertheless, ML methods provided additional insights by capturing non-linear interactions and incorporating a broader range of features. For instance, the SVM model identified variables such as dietary fat consumption and chronic illnesses, which were not prominent in the logistic regression model. This suggests that ML models may offer advantages in uncovering hidden patterns that are not easily detected by traditional statistical approaches (9). Similar results were reported by Chen et al. (15), who found that SVM and other ML models could identify non-linear relationships and less obvious predictors in prostate cancer datasets.

The CHAID and C5.0 decision tree algorithms also performed well, with CHAID achieving over 91% accuracy. These algorithms provide intuitive, rule-based outputs that can be useful in clinical settings, especially for decision support tools. KNN, while simpler, still demonstrated solid performance, though it may be less scalable with larger datasets or higher dimensionality (16).

Our findings are consistent with previous studies that support the integration of ML in medical diagnostics. Our identification of age, smoking, and family history as significant predictors aligns with well-established risk factors reported in epidemiological studies (17). However, one must consider the complexity and interpretability of ML models when applying them in clinical practice. Logistic regression retains value due to its transparency and ease of implementation, particularly when working with structured and relatively low-dimensional datasets (3).

A limitation of this study includes the sample size, which may affect the generalizability of the results. Additionally, imbalanced age distributions between patient and control groups may have influenced model performance. It is acknowledged that the observed age disparity between groups is inherent to the epidemiology of prostate cancer, as the disease predominantly affects older males (4). However, the strong predictive power of age might have overshadowed other relevant variables in both logistic regression and ML models. Future studies might benefit from age-stratified analyses to assess the isolated contribution of additional predictors.

Table 3. Risk factors of the models obtained from the analyses

Models	Risk factors
LR	Age, smoking, presence of cancer in the family, frequency of urination, lifestyle during the day and blood in semen and urine
SVM	Age, frequency of urination, smoking, family history of cancer, lifestyle during the day, fat used in food, presence of chronic diseases, blood in semen or urine, daily water consumption and discomfort in the groin area
KNN	Age, smoking, presence of cancer in the family
CHAID	Age, smoking, frequency of urination, erectile dysfunction and presence of cancer in the family
C5.0	Age, smoking, urinary frequency, daily lifestyle and family history of cancer

CHAID: Chi-squared automatic interaction detection, KNN: K-nearest neighbors, LR: Logistic regression, SVM: Support vector machine

Table 4. Classification rates of the analyses

Model	Classification	Education data	Trial data
	Number of independent variables	10	10
	Those with prostate cancer	97.1	94.4
SVM	Those without prostate cancer	98.92	85
	Percentage classification of correct	98	**89.92**
	Number of independent variables	3	3
	Those with prostate cancer	90.9	88.8
KNN	Those without prostate cancer	97.84	88
	Percentage classification of correct	94.47	**88.48**
	Number of independent variables	5	5
	Those with prostate cancer	93.18	90.54
CHAID	Those without prostate cancer	91.93	92.3
	Percentage classification of correct	92.54	**91.36**
	Number of independent variables	5	5
	Those with prostate cancer	90.34	87.5
C5.0	Those without prostate cancer	96.77	89.5
	Percentage classification of correct	93.64	**88.48**
	Number of independent variables	6	6
Binary logistic regression	Those with prostate cancer	94.2	92.1
	Those without prostate cancer	95.1	92.3
	Percentage classification of correct	94.6	**92.2**

CHAID: Chi-squared automatic interaction detection, KNN: K-nearest neighbors, SVM: Support vector machine

Table 5. Classification performance of models based on test data

Model	TP	FN	TN	FP	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC
SVM	68	4	57	10	94.4	85.0	89.92	89.76
KNN	64	8	59	8	88.8	88.0	88.48	88.47
CHAID	67	7	60	5	90.54	92.3	91.36	91.42
C5.0	63	9	60	7	87.5	89.5	88.48	88.53
Logistic reg.	70	6	60	5	92.1	92.3	92.2	92.21

AUC: Area under the curve, CHAID: Chi-squared automatic interaction detection, FN: False negative, FP: False positive, KNN: K-nearest neighbors, reg.: Regression, SVM: Support vector machine, TN: True negative, TP: True positive

Conclusion

This study demonstrated that both logistic regression and ML algorithms are effective in identifying significant risk factors and predicting prostate cancer. Logistic regression showed the highest overall classification accuracy and remains a robust choice for structured clinical data.

Key risk factors identified across models included age, smoking, family history of cancer, urinary frequency, and blood in semen. These findings highlight the importance of early detection and suggest that integrating both statistical and ML methods could enhance decision-making in prostate cancer screening and diagnosis.

Future studies should focus on expanding data diversity, improving model interpretability, and integrating additional clinical and genetic variables to support more personalized healthcare strategies. In light of these findings, the integration of hybrid analytical frameworks that combine traditional statistical models with ML algorithms should be encouraged in clinical settings. Such a blended approach can facilitate earlier risk stratification, support personalized decision-making, and contribute to the development of more effective prostate cancer screening protocols. Future research may also explore the implementation of these models into real-world clinical decision support systems to assess their practical utility and scalability.

Ultimately, blending statistical rigor with the predictive depth of ML may help transform prostate cancer screening from a reactive to a more proactive approach.

Ethics

Ethics Committee Approval: Ethics approval was obtained from the University of Health Sciences Türkiye, Hamidiye Scientific Research Ethics Committee (approval number: 21/125, dated: 19.03.2021).

Informed Consent: Data were collected face-to-face using a structured questionnaire, and informed consent was obtained from all participants through a signed consent form prior to participation.

Footnotes

Authorship Contributions

Concept: S.A., M.K., Design: S.A., M.K., Data Collection or Processing: S.A., M.A., M.Ç., Analysis or Interpretation: S.A., Literature Search: S.A., Writing: S.A.

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.2025.03521

Hamidiye Med J 2025;6(3):178-182

Evaluation of Health Board Documents Referred to the Tertiary Hospital for Objection and Referral in Terms of Ophthalmology

İtiraz ve Sevk Nedeni ile Üçüncü Basamak Hastaneye Yönlendirilen Sağlık Kurulu Evraklarının Göz Hastalıkları Açısından Değerlendirilmesi

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ABSTRACT

Background: Medical board examinations and scoring form a substantial part of the workload for specialized physicians in Türkiye. This study evaluates these tasks from the perspective of ophthalmology specialists and compares the ophthalmologic examination findings and disability scores recorded at our hospital with those from external centers in cases referred for objection or referral.

Materials and Methods: A retrospective review was conducted on patient files from our health board between December 2022 and January 2025. Patients were classified into an objection group (those contesting evaluations) and a referral group (those referred due to device limitations or other reasons). Ophthalmologic examination findings and disability scores from both our hospital and external centers were recorded. The proportions of patients receiving disability scores, their diagnoses, and the reasons for objection and referral were analyzed and compared.

Results: A total of 70 patients were included: 58 in the objection group and 12 in the referral group. In the objection group, 58.6% were male with a mean age of 58.3±17.6 years; in the referral group, gender distribution was equal and the mean age was 51.4±9.1 years. Within the objection group, 15.5% had higher external disability scores, 20.6% had lower scores, and 63.9% had matching scores, compared to our hospital's evaluations. The mean disability scores were 18.7±12.3 at our hospital versus 17.9±14.6 at external centers (p=0.641).

Conclusion: In patients referred due to objection, external and hospital ophthalmologic evaluations were largely consistent, with discrepancies mainly in visual acuity and scoring due to differing regulatory interpretations. Device shortages in secondary centers lead to variability in referrals, warranting economic and functionality analyses to improve device procurement and reduce referral-related costs.

Keywords: Health board, objection, optical coherence tomography, referral, tertiary hospital

ÖZ

Amaç: Türkiye'de, uzman hekimlerin iş yükünün önemli bir bölümünü sağlık kurulu muayeneleri oluşturmaktadır. Bu çalışmanın amacı, günlük pratikte sıkça gerçekleştirilen bu muayeneyi göz hastalıkları uzmanlarının bakış açısından detaylı olarak değerlendirmek ve eksiklikleri ile farklılıkları analiz etmektir. Ayrıca, itiraz ve sevk nedenleriyle üçüncü basamak hastaneye yönlendirilen sağlık kurulu belgelerindeki dış merkezlerde kaydedilen oftalmolojik muayene bulguları ve engellilik puanlarını, kendi hastanemizde kaydedilen verilerle karşılaştırmaktır.

Gereç ve Yöntemler: Aralık 2022-Ocak 2025 yılları arasında sağlık kurulumuza başvuran hastaların dosyaları geriye dönük olarak taranarak engellilik oranı için başvuranların dosyaları incelendi. İtiraz nedenli başvurular itiraz grubuna, sevk nedenli başvurular sevk grubuna eklendi. Tüm hastaların hastanemizde yapılan göz muayene bulguları ile dış merkez göz muayene bulguları kaydedildi. Engel puanı verilenlerin oranları, tanıları, itiraz ve sevk gerekçeleri değerlendirilerek karşılaştırıldı.

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Received: 25.02.2025 **Accepted:** 21.08.2025 **Epub:** 08.09.2025 **Publication Date:** 30.09.2025

Cite this article as: Karataş ME, Karataş G. Evaluation of health board documents referred to the tertiary hospital for objection and referral in terms of ophthalmology. Hamidiye Med J. 2025;6(3):178-182

ÖZ

Bulgular: Hastanemiz sağlık kuruluna, göz muayenesi gerekli olarak yapılan itiraz ve sevk nedenli başvurular belirlendi ve çalışmaya alındı. İtiraz grubundaki 58 hastanın 34'ü (%58,6) erkek, 24'ü (%41,4) kadındı, ortalama yaş 58,3±17,6 yıl idi. Sevk grubunda 12 hastanın 6'sı (%50) erkek, 6'sı (%50) kadındı, ortalama yaş 51,4±9,1 yıl idi. İtiraz grubunda dış merkez göz hastalıkları engellilik puanı hastanemizden yüksek olanlar 9 (%15,5) hasta, engel puanı hastanemizden düşük olanlar 12 (%20,6) hasta, 37 (%63,9) hastanın ise engel puanı aynıydı. İtiraz grubunun hastanemiz göz hastalıklarından aldıkları engellilik puan ortalaması 18,7±12,3 iken, dış merkezde 17,9±14,6 idi her iki grup arasında istatistiksel anlamlılık saptanmadı (p=0.641).

Sonuç: Üçüncü basamak hastanelere itiraz ile yönlendirilen hastaların dış merkez göz muayene bulguları ile hastanemiz sağlık kurulunda değerlendirilen hastaların göz muayene bulgularının çoğu benzer saptanmıştır. Saptanan en sık farklılık görme keskinliklerinde ve yönetmeliğin farklı yorumlanmasına bağlı olarak puan değerlendirilmesinde olmuştur. İkinci basamak sağlık kuruluşlarında mevcut olmayan cihazlar nedeni ile hastaların üst merkezlere sevki gerekmektedir, bu hastaneler arası çeşitlilik göstermektedir. Bu konuda ekonomi-işlevsellik çalışmaları yapılarak cihaz tedariği ile sevk maliyetinin önüne geçilmeye çalışılmalıdır.

Anahtar Kelimeler: Üçüncü basamak hastane, itiraz, optik kohorens tomografi, sağlık kurulu, sevk

Introduction

In our country, disability evaluations and ratings by the health board are conducted according to two regulations issued by the Ministry of Family and Social Services: the "Regulation on Disability Assessment for Adults" and the "Regulation on Special Needs Assessment for Children" (1). These regulations implement a standardized system for determining the overall degree of disability based on the disability percentages specified by relevant specialties.

While the 2002 "Türkiye Disability Survey" broadly defined visual impairment, more recent data; the Turkish Statistical Institute reports that, between 2019 and 2022, approximately 1.4 percent of the population in Türkiye, which corresponds to around 1,039,000 individuals, live with some degree of visual impairment (2,3). As ophthalmologists, it is our responsibility to define and evaluate the degree of visual impairment in patients in accordance with the existing regulations and guidelines.

In health board services, patients have the right to object to decisions. If patients believe the decisions are inappropriate, they can exercise this right and are referred to another hospital. Evaluations at arbitration hospitals are conducted by repeating examinations by health board physicians and reassessing the scores conducted by the health board physicians. This situation leads to a loss of time and labor due to the repetition of all healthcare service steps, resulting in a significant financial burden for patients, their relatives, and healthcare institutions. Consistency between the initial institution providing the service and the data from the arbitration hospital enhances the reliability of disability percentages determined by the health board and prevents unnecessary objections by patients and relatives. In this study, we aimed to evaluate the consistency of objection applications in ophthalmology, by comparing data from our hospital and external centers. Consequently, reducing unnecessary or unfounded objection applications would contribute to delivering higher-quality healthcare services.

In our country, many secondary hospitals provide health board services. In most cases, these services determine the patients' disability statuses, within those institutions. However, in some cases, patients are referred to tertiary hospitals (upper-level centers) for further tests or subspecialty consultations. One of the major challenges in healthcare accessibility is the burden of referrals, with health board referrals being a significant component of this issue. In this study, identifying the reasons for referral requirements in ophthalmology is aimed at helping address these deficiencies in the long-term. Consequently, this would ensure optimal cost-effectiveness for both patients and their relatives (e.g., travel costs, loss of workforce), and reduce the burden on patients and the workload on tertiary hospitals.

Materials and Methods

This retrospective cross-sectional study, conducted with patients who applied to the Health Board of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital between December 2022 and January 2025, was carried out in accordance with the Declaration of Helsinki and approved by the Ethics Committee of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital (approval number: 4734, dated: 11.02.2025).

The medical records of patients aged 18-92 years who applied to our Health Board of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital between December 2022 and January 2025 were retrospectively reviewed. Files of those who applied for an objection regarding their ophthalmological disability scores, and those referred from other centers were examined.

Patients who applied for an objection were included in the "objection group," while those referred were included in the "referral group". All patients who visited our hospital underwent comprehensive ophthalmological examinations, and their diagnoses, disability percentages according to the regulations, and examination findings were recorded. The ophthalmological examination findings conducted in our hospital, were compared with those from external centers by evaluating the disability scores assigned, diagnoses, and the reasons for objections and referrals.

Statistical Analysis

The data obtained from the study were analyzed using the SPSS 27.0 statistical software package (IBM Corp., Armonk, N.Y., USA). Descriptive statistical evaluations were conducted to assess the categorization and relationships of variables. The distribution of variables was evaluated with the Shapiro-Wilk test. In the objection group, the difference in mean disability scores between our hospital and external centers was analyzed using the Wilcoxon signed-rank test. A p-value of less than 0.05 ($p<0.05$) was considered statistically significant.

Results

A total of 312 patient files were reviewed in the objection group, of which 58 cases involved objections regarding ophthalmological disability scores. Among these, 34 patients (58.6%) were male, and 24 (41.4%) were female, with a mean age of 58.3±17.6 years. In the referral group, 12 patients were evaluated, with 6 (50%) male and 6 (50%) female patients, and a mean age of 51.4±9.1 years.

In the objection group, 9 patients (15.5%) had a higher disability score than assigned by external centers compared to our hospital, 12 patients (20.6%) had a lower score than assigned by external centers compared to our hospital, and 37 patients (63.9%) had identical scores. It was observed that all patients who received a higher disability percentage from external centers had a lower best-corrected visual acuity (BCVA) compared to evaluations at our hospital. Patients who were assigned a lower disability score by external centers most commonly had diagnoses of cataracts, glaucoma, hereditary retinal diseases, and optic nerve disorders. In the objection group, 21 patients (36.2%) demonstrated differences in BCVA between the external center and our hospital, while 4 patients (6.8%) showed differences in biomicroscopic findings. For 2 patients (3.4%), BCVA could not be evaluated in either centers.

The mean ophthalmological disability score assigned by our hospital in the objection group was 18.7±12.3, compared to 17.9±14.6 in external centers, with no statistically significant difference between the two groups (p=0.641). The most frequent diagnoses in the observation group were diabetic retinopathy (DR), cataracts, amblyopia, glaucoma, corneal diseases (e.g., corneal opacities and keratoconus), optic nerve diseases, age-related macular degeneration, hereditary retinal diseases, and diplopia-ptosis. The distribution of patient numbers by diagnosis in the observation group is presented in Table 1.

The BCVA of all patients in the referral group was assessable at both centers. The mean ophthalmological disability score assigned by our hospital for the referral group was 15.8±11.7. The most frequent diagnoses in the referral group were DR, amblyopia, optic nerve disorders, and keratoconus.

When the referral group was evaluated based on their diagnoses, it was determined that patients with DR were referred because the absence of an optical coherence tomography (OCT) device prevented the objective documentation diabetic macular edema and/or ongoing intravitreal injection treatments. Patients diagnosed with amblyopia and optic nerve disorders were referred when their examination findings and BCVA were inconsistent due to the lack of a Visual Evoked Potential test. Additionally, patients with suspected keratoconus were referred for a definitive diagnosis owing to the unavailability of a corneal topography device.

Discussion

The completion of examinations in relevant departments, proper documentation, and the security of medical records for patients applying to the health board are of utmost importance. Despite the standardization of disability rates through relevant regulations and calculated scores in accordance with these regulations, discrepancies are observed in the final assessments. This study aims to

Table 1. Distribution of patients according to the diagnosis of the objection group

Diseases	Number of people and rate
Diabetic retinopathy	18 (31%)
Cataract	11 (18.9%)
Amblyopia	9 (15.5%)
Glaucoma	5 (8.6%)
Corneal diseases	5 (8.6%)
Optic nerve diseases	4 (6.8%)
Age-related macular degeneration	3 (5.4%)
Hereditary retinal diseases	2 (3.4%)
Diplopia-pitosis	1 (1.8%)

identify inter-institutional and inter-physician differences by examining objections and to highlight potential and remediable deficiencies in our healthcare system by determining the frequency and reasons for referrals.

In our country, there are two separate scoring systems for disability and incapacity assessments based on health board applications. In the field of ophthalmology, total vision loss, visual acuity scoring, and diagnoses/symptoms such as nystagmus, diplopia, ptosis, and photophobia are evaluated and scored differently (4). In the context of Health Board disability evaluations, the assessment of ophthalmic impairments extends beyond mere measurements of visual acuity. Comprehensive evaluation encompasses visual field abnormalities and various structural and functional deficits affecting the visual system. Notably, binocular visual field losses-such as homonymous hemianopia, quadrantanopia, or central/paracentral scotomas-are recognized as significantly impairing an individual's environmental awareness and ability to perform daily activities. These conditions are therefore quantified through a standardized scoring system outlined in the Visual Field Assessment Table included in the guideline (5).

In addition, various ocular conditions categorized under "Other Structural and Functional Deficits" are also taken into consideration, even in the absence of marked visual acuity or field loss (5). These include functional disorders such as lagophthalmos, which carries a risk of corneal exposure; diplopia, which disrupts binocular fusion; severe ptosis, especially when the visual axis is obscured; and lacrimal system obstructions that result in recurrent infections or functional limitation (5). Each of these conditions may independently contribute to the overall disability rating based on the degree of visual function compromise they produce.

This integrative approach, which takes into account both anatomical damage and functional capacity, facilitates a more accurate, fair, and clinically meaningful representation of the individual's visual disability, aligning medical assessment with real-world functional impact. The examination process should begin with verifying the patient's identity information, taking the application request into consideration. These controls are crucial to prevent errors arising from such differences.

A previous thesis study found that the most common reason for cases being referred to the General Assembly of the Forensic Medicine Institute, for incapacity determination or objection, was inconsistencies between reports, particularly the confusion between disability and incapacity ratings (6). Conversely, it is possible that applications for disability assessment may mistakenly be evaluated under the incapacity regulation. In our study, we consider this to be one of the possible reasons for discrepancies in scoring and assessment.

In the objection group, the most significant difference in scores, because cataract diagnoses at external centers were not assigned any points or percentages, between our hospital and external centers was that the scoring could change with surgical intervention. However, according to the "Regulation on Disability Assessment for Adults", even if patients refuse treatment, conditions such as diplopia, persistent epiphora, functionally impairing eyelid disorders, and vision-threatening ocular diseases that are surgically treatable are to be addressed through "time-limited reports valid for two years" (5). At our hospital, we follow this regulation and assign scores for cataract patients for varying durations up to 2 years, ensuring that the patient does not lose out on his or her score during the time period recommended by the physician. Once the duration expires, and if the treatment is not completed, the score will be removed, preventing any loss for the insurance system and closing the door to potential abuse. Another difference is seen in diseases such as glaucoma, optic nerve disorders, and hereditary retinal diseases (especially retinitis pigmentosa), where central vision is initially preserved but peripheral vision loss occurs. The failure to assess the visual field, or the lack of a visual field test in the hospital, has resulted in lower scores at external centers compared to our hospital. This discrepancy leads to objections, which in turn increase the workload at other healthcare institutions. We believe that special meetings and training to establish a consensus on medical board examinations and scoring could prevent such issues. However, overall, there was no statistically significant difference in the disability scoring for eye diseases between our hospital and external centers, demonstrating consistency among institutions and physicians.

In ophthalmology specialty training, there is no mandatory education process related to medical board evaluations (7). This results in the lack of use of the "Regulation on Disability Assessment for Adults" during residency, causing a lack of knowledge regarding the examination process, scoring, and decision-making system in medical board evaluations. As a result, we believe that the regulation is not sufficiently understood by specialist physicians, and this leads to differences in the interpretation of examination findings and scoring. To address this gap, the inclusion should be in the planning of specialty training or professional associations, with mandatory rotations and focused training on these topics. This approach would prevent discrepancies in interpretation between institutions and physicians.

DR, a common and specific microvascular complication of diabetes mellitus, is one of the leading causes of vision loss worldwide (8). In our study, DR was the most frequent diagnosis in the objection group. Given the high prevalence of DR in our population, it is inevitable that vision impairment caused by DR is one of the most common reasons for medical board referrals. In modern ophthalmology, certain devices have become indispensable for diagnosis and treatment. OCT for DR monitoring and corneal topography for keratoconus diagnosis are prime examples of this (9,10). In our study, the most common reason for referral was the absence of an OCT device at the external centers to objectively and quantitatively detect macular edema due to DR. By ensuring that necessary devices are provided to relevant institutions in a cost-effective manner, unnecessary referrals and the associated costs in terms of time, labor, and transportation can be minimized. These referrals result in losses of time and labor for both patients and healthcare providers, as well as repeat tests due to quality inadequacies, leading to financial losses for the insurance system. With proper planning, cost-effective device procurement for relevant centers can address all these issues.

Study Limitations

The limitations of our study include its retrospective nature and the small number of patient files evaluated. However, given the generally low number of disability objections and referral requests for eye diseases, we believe this sample size is sufficient for this study. Conducting this study in a tertiary care hospital enabled access to a relatively large patient population within this field.

As ophthalmologists actively involved in medical board services at secondary and tertiary care hospitals, we find that a significant portion of our workload consists of medical board examinations. These examinations require a thorough understanding and application of the relevant regulations. Standardization of this healthcare service is crucial, not only for us as physicians but also for our patients. This study highlights both the scope of eye diseases causing permanent disability (resulting in disability scores) in our society and the consistency of evaluations by institutions, physicians providing these services. We believe that future studies involving larger patient populations will increase awareness of preventable sequelae and help in improving public health.

Conclusion

In this study, we analyzed patients who required additional evaluations resulting from objections and referrals in the context of medical boards. It was determined that the disability rates for eye diseases assessed in a tertiary care hospital were comparable to those reported by external centers. This result, reflects the consistency of medical board services among hospitals. However, there were individual variations in the outcomes, and we believe that the interpretation of these results, along with our suggestions for improvements, will help enhance the quality of healthcare services and provide guidance for future research.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital (approval number: 4734, dated: 11.02.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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

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

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ORIGINAL ARTICLE

DOI: 10.4274/hamidiyemedj.galenos.2025.28278

Hamidiye Med J 2025;6(3):183-187

Impact of Single-Level Transforaminal Lumbar Interbody Fusion on Spinopelvic Parameters and Functional Status in Lumbar Degenerative Disease

Lomber Dejeneratif Hastalıkta Tek Seviyeli Transforaminal Lomber İnterbody Füzyonun Spinopelvik Parametreler ve Fonksiyonel Durum Üzerindeki Etkisi

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ABSTRACT

Background: The present retrospective cohort study aimed to evaluate the functional and radiological outcomes of single-level transforaminal lumbar interbody fusion (TLIF) in patients suffering from degenerative lumbar spine conditions.

Materials and Methods: The present study comprised 48 patients (29 women and 19 men, with a mean age of 54.9±14.2 years) who underwent single-level TLIF between January 2017 and January 2022. Spinopelvic parameters, encompassing pelvic incidence, pelvic tilt, sacral slope, and lumbar lordosis (LL), were meticulously measured preoperatively and postoperatively. The assessment of pain and disability was conducted using the visual analog scale (VAS) and the Oswestry disability index (ODI).

Results: The mean follow-up duration was 5.6±1.4 years. Despite the lack of statistical significance in the observed changes to spinopelvic parameters, a subtle tendency towards enhanced LL and improved pelvic alignment was identified post-operatively. The mean preoperative VAS score demonstrated a statistically significant decrease from 8.7±2.1 to 2.0±2.6 postoperatively ($p<0.001$), and the ODI score exhibited an improvement from 40.6±9.8 to 7.1±10.8 ($p<0.001$).

Conclusion: The findings of this study indicate that single-level TLIF can yield clinically significant benefits in terms of pain relief and functional capacity, even in the absence of substantial radiological correction. Further research with larger patient populations is necessary to comprehensively elucidate the relationship between sagittal realignment and long-term clinical outcomes.

Keywords: Transforaminal lumbar interbody fusion, degenerative lumbar spine, spinopelvic parameters, lumbar lordosis

ÖZ

Amaç: Mevcut retrospektif kohort çalışmasının amacı, dejeneratif lomber omurga rahatsızlıkları olan hastalarda tek seviyeli transforaminal lomber interbody füzyonun (TLIF) fonksiyonel ve radyolojik sonuçlarını değerlendirmektir.

Gereç ve Yöntemler: Bu çalışma, Ocak 2017 ile Ocak 2022 arasında tek seviyeli TLIF uygulanan 48 hastayı (29 kadın ve 19 erkek, ortalama yaşları 54,9±14,2 yıl) içermektedir. Pelvik insidans, pelvik eğim, sakral eğim ve lomber lordozu (LL) kapsayan spinopelvik parametreler, ameliyat öncesi ve sonrası ölçüldü. Ağrı ve hastalık seviyesi değerlendirmesi görsel analog skala (VAS) ve Oswestry sakatlık indeksi (ODI) kullanılarak yapıldı.

Bulgular: Ortalama takip süresi 5,6±1,4 yıl idi. Spinopelvik parametrelerde gözlenen değişikliklerde istatistiksel olarak anlamlı bir fark olmamasına rağmen, ameliyat sonrası LL'de artış ve pelvik hizalanmada iyileşme yönünde hafif bir eğilim tespit edildi. Ameliyat öncesi ortalama VAS skoru, ameliyat sonrası 8,7±2,1'den 2,0±2,6'ya istatistiksel olarak anlamlı bir düşüş gösterdi ($p<0,001$) ve ODI skoru 40,6±9,8'den 7,1±10,8'e gelişme gösterdi ($p<0,001$).

Sonuç: Bu çalışmanın bulguları, tek seviyeli TLIF'nin, önemli bir radyolojik düzeltme olmasa bile, ağrı kesici ve fonksiyonel kapasite açısından klinik olarak anlamlı faydalar sağlayabileceğini göstermektedir. Sagital yeniden hizalama ile uzun vadeli klinik sonuçlar arasındaki ilişkiyi kapsamlı bir şekilde açıklamak için daha geniş hasta popülasyonlarıyla daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: Transforaminal lomber interbody füzyon, dejeneratif lomber omurga, spinopelvik parametreler, lomber lordoz

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Received: 27.08.2025 **Accepted:** 29.09.2025 **Publication Date:** 30.09.2025

Cite this article as: Sıvacıoğlu S. Impact of single-level transforaminal lumbar interbody fusion impact on spinopelvic parameters and functional status in lumbar degenerative disease. Hamidiye Med J. 2025;6(3):183-187

Introduction

Chronic lumbar pain is a prevalent condition in clinical practice and is acknowledged as a significant contributor to global functional impairment. It can arise from various etiologies, including disc herniation, scoliosis, facet joint arthrosis and, most commonly, disc degeneration (1,2). These conditions are collectively categorized as degenerative spinal diseases, with treatment modalities ranging from conservative management to surgical intervention (3). Surgical approaches for disc degeneration typically involve excision of the pathological disc and application of an interbody cage to facilitate osteosynthesis between adjacent vertebral bodies (4). One such surgical technique is transforaminal lumbar interbody fusion (TLIF), which is extensively performed to restore spinal stability in patients with single-level degenerative disc disease, spondylolisthesis, or spinal stenosis (5). TLIF offers several advantages, including a unilateral surgical approach, preservation of posterior elements, and restoration of disc height and sagittal alignment (6). Given that sagittal imbalance can negatively impact surgical outcomes, the restoration or maintenance of spinopelvic alignment, including parameters such as pelvic incidence (PI), pelvic tilt (PT), sacral slope (SS), and lumbar lordosis (LL), is essential for preventing adjacent segment pathology and ensuring favorable clinical results (7). Analyzing the changes in these parameters before and after TLIF provides valuable insights into the procedure's biomechanical efficacy and its influence on global spinal alignment. Despite extensive research on the radiological outcomes of TLIF, few studies have assessed the relationship between spinopelvic alignment and clinical improvement, particularly in patients undergoing single-level TLIF. This study aimed to examine the functional and radiological outcomes of patients who underwent single-level TLIF.

Materials and Methods

This retrospective cohort study was conducted at a single center, focusing on patients who underwent single-level TLIF surgery between January 2017 and January 2022. Approval from the International Review Board was obtained from the İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (approval number: 10840098-202.3.02, dated: 30.08.2025). Informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki. Of the 59 patients initially reviewed, 11 were excluded because of incomplete preoperative records, resulting in a final cohort of 48 patients. Complete radiographic datasets were available for both preoperative and postoperative assessments for all included patients. The inclusion criteria were as follows: age ⩾18 years, diagnosis of degenerative lumbar disc disease or low-grade spondylolisthesis, single-level TLIF surgery, and availability of complete preoperative and postoperative radiological and clinical data. The exclusion criteria included multilevel fusion, revision surgery, history of spinal trauma, tumors or infection, and insufficient clinical or radiological documentation (Table 1).

All surgical interventions were performed by a single spine surgeon at the same academic institution, utilizing a conventional posterior approach with patients positioned prone under general anesthesia. At the specified spinal level, an interbody cage filled with either an autologous bone graft or a suitable bone substitute was inserted. Posterior stabilization was achieved by applying pedicle screw instrumentation. Radiographic evaluation entailed the analysis of key spinopelvic alignment parameters, including PI, PT, SS, and LL, which were measured by a senior orthopedic specialist blinded to patient outcomes. All angles were measured in degrees, according to the Cobb technique. Pain and disability were assessed using validated outcome measures, specifically the visual analog scale (VAS) and Oswestry disability index (ODI). These assessments were conducted either in person or via telephone interviews, with a mean follow-up duration of 5.6±1.4 years post-surgery.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics (version 22.0; IBM Corp., Armonk NY, USA). The distribution characteristics of the variables were evaluated using the Shapiro-Wilk test to assess normality. Depending on whether the variables met the assumptions of normality, either the Paired samples t-test or Wilcoxon signed-rank test was employed for pre- and postoperative comparisons. A $p<0.05$ was considered statistically significant. Table 2 provides an overview of the demographic and surgical distributions of the patient cohort.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age ⩾18 years	Multilevel fusion surgery
Diagnosis of degenerative lumbar disc disease or low-grade spondylolisthesis	History of revision surgery
Underwent single-level transforaminal lumbar interbody fusion	History of spinal trauma, tumor, or infection
Availability of complete preoperative and postoperative radiographic data	Incomplete clinical or radiological data
Availability of clinical follow-up data	–

Most procedures were performed at the L4-5 segment (n=26), with fewer cases involving the L5-S1 (n=13), L3-4 (n=8), and L2-3 (n=1) levels. Throughout the perioperative period, encompassing both the intraoperative and early postoperative phases, no complications were observed in the patients included in this study.

Results

The mean age was 54.9±14.2 years, and the cohort comprised 29 women (60%) and 19 men (40%). This retrospective cohort study aimed to evaluate the functional and radiological outcomes of single-level TLIF in patients with degenerative lumbar spine conditions. The study included 48 patients (29 women, 19 men; mean age 54.9±14.2 years) who underwent single-level TLIF between January 2017 and January 2022. Spinopelvic parameters, including PI, PT, SS, and LL, were measured preoperatively and postoperatively. Pain and disability were assessed using the VAS and ODI. The mean follow-up duration was 5.6±1.4 years. Although changes in spinopelvic parameters did not reach statistical significance, a subtle tendency toward improved LL and pelvic alignment was observed postoperatively. The mean preoperative VAS score significantly decreased from 8.7±2.1 to 2.0±2.6 postoperatively ($p<0.001$), and the ODI score improved from 40.6±9.8 to 7.1±10.8 ($p<0.001$). These findings suggest that single-level TLIF can provide clinically relevant benefits in pain relief and functional capacity, even in the absence of significant radiological correction. Further research with larger patient populations is necessary to comprehensively elucidate the relationship between sagittal realignment and long-term clinical outcomes. The mean preoperative PI was 47.0±8.5°, whereas the postoperative PI was 46.8±11.3°, indicating a minimal change in this parameter ($p=0.786$).

Similarly, PT increased slightly from 18.3°±8.0° preoperatively to 19.6°±6.0° postoperatively ($p=0.106$). The SS was recorded as 28.5±8.9° before surgery and 27.2±6.7° after surgery ($p=0.112$). LL showed a negligible change from 45.2°±13.5° preoperatively to 45.9°±8.6° postoperatively ($p=0.551$) (Table 3).

Minor variations were detected across all measured spinopelvic parameters; however, these changes were not statistically significant. Nonetheless, imaging findings revealed a subtle inclination toward postoperative

Table 2. Demographic characteristics of the study group

Surgical level	Number of patients (n=48)
L4-5	26
L5-S1	13
L3-4	8
L2-3	1

Figure 1. Measurement of preoperative sagittal parameters

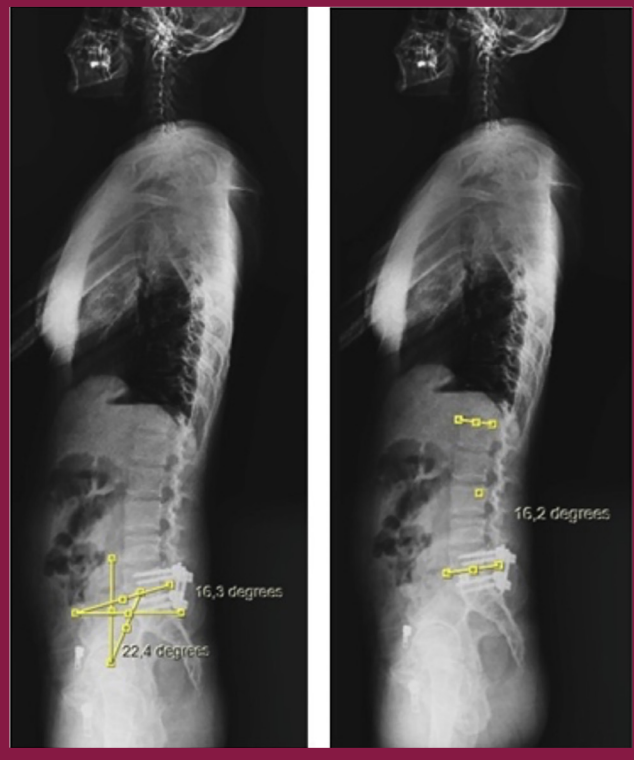

Figure 2. Measurement of postoperative sagittal parameters

improvement in the LL and pelvic alignment. Regarding functional outcomes, the mean preoperative VAS score was 8.7±2.1, which significantly decreased to 2.0±2.6 postoperatively (p<0.001). Similarly, the ODI, which assesses the degree of functional limitation, improved markedly from 40.6±9.8 preoperatively to 7.1±10.8 postoperatively (p<0.001) (Table 4).

Discussion

TLIF is widely adopted in the surgical management of degenerative lumbar spine conditions, largely because of its ability to achieve three-column stabilization, restore intervertebral disc height, and improve sagittal alignment (4,5).

This study examined the influence of single-level TLIF on sagittal spinal alignment. Although alterations in spinopelvic orientation metrics, specifically PI, PT, SS, and LL, did not reach statistical significance, radiographic data suggested a postoperative tendency toward improved alignment, particularly in lumbar curvature.

Sagittal alignment, particularly the restoration of LL, plays a crucial role in achieving favorable clinical outcomes following lumbar fusion surgery and in reducing the risk of adjacent segment disease (7,8). In our study group, the mean LL increased from 45.2° to 46.5°, which is consistent with previous studies reporting modest but clinically relevant improvements in lordotic angles after TLIF (9). The relatively small change in lordosis may be attributed to the use of standard cages, lack of aggressive corrective maneuvers, and inclusion of only single-level fusions.

Previous studies have suggested that TLIF may help preserve or slightly improve spinopelvic alignment in appropriately selected patients. For instance, single-level TLIF resulted in significant improvement in LL in patients with low preoperative lordosis. However, some studies have emphasized that single-level procedures may be insufficient to achieve adequate correction in cases with more pronounced sagittal imbalance (10).

In our study, the pelvic parameters, such as PI, PT, and SS, remained relatively stable. This finding is consistent with the notion that PI is a fixed morphological parameter, whereas PT and SS generally show compensatory changes only in more severe cases of imbalance (11). The slight increase in postoperative PT may reflect a subtle compensatory mechanism aimed at maintaining sagittal balance.

Although the radiological improvements observed in this study did not reach statistical significance, their clinical relevance cannot be overlooked. Even minor improvements in sagittal alignment have been shown to contribute to pain control, enhance the quality of life, and reduce mechanical stress on adjacent segments (12,13).

Similarly, a study conducted by Ünsal et al. (14) reported that radiographic changes in spinopelvic parameters after single-level TLIF were not statistically significant. However, despite these limited angular corrections, significant improvements were observed in clinical parameters, such as pain and function. This supports the idea that TLIF may provide meaningful clinical benefits, even in the absence of marked radiographic changes, when applied to appropriately selected patients.

In our cohort, the mean preoperative VAS score significantly decreased from 8.7±2.1 to 2.0±2.6 postoperatively (p<0.001). Similarly, the ODI score improved from 40.6±9.8 to 7.1±10.8 (p<0.001). The results presented in this study are in agreement with those reported in previous studies. Notably, Foley et al. (15) reported that the ODI decreased from approximately 37.5±15.5 preoperatively to 13.5±12.5 postoperatively, and the VAS score for low back pain improved from 43.5±30.4 to 17.9±22.6 (p<0.001).

In our study, even more pronounced improvements in pain and disability were observed. The preoperative VAS score, categorized as "very severe," improved to the "mild" level postoperatively. Likewise, the ODI score, initially indicating "severe disability," improved to the level of "minimal disability."

The limited number of cases may have compromised the statistical strength of the study, thereby reducing the likelihood of identifying subtle, but clinically meaningful, differences. To better understand the association between radiological changes and clinical outcomes after single-level TLIF, future research should focus on larger cohorts with extended follow-up durations.

Table 3. Comparison of preoperative and postoperative spinopelvic parameters

Parameter	Preoperative (°)	Postoperative (°)	p-value (<0.05)
Pelvic incidence	47.0±8.5	46.8±11.3	0.786
Pelvic tilt	18.3±8.0	19.7±6.0	0.106
Sacral slope	28.5±8.9	27.2±6.7	0.112
Lumbar lordosis	45.2±13.5	45.9±8.6	0.551

Values expressed as mean ± standard deviation

Table 4. Comparison of preoperative and postoperative functional parameters

Parameter	Preoperative	Postoperative	p-value (<0.05)
VAS	8.7±2.1	2.0±2.6	$<0.01\times10^{-11}$
ODI	40.6±9.8	7.1±10.8	$<0.008\times10^{-13}$

Values expressed as mean ± standard deviation. VAS: Visual analog scale, ODI: Oswestry disability index

Conclusion

Based on the findings of this study, single-level TLIF may be a valuable surgical intervention for enhancing clinical outcomes in patients with degenerative lumbar spinal conditions. Although the observed changes in spinopelvic parameters, including PI, PT, SS, and LL, did not reach statistical significance, subtle improvements were radiographically evident, particularly in LL and pelvic alignment.

Notably, patients exhibited meaningful postoperative gains in pain relief and functional capacity, as reflected by substantial reductions in the VAS and ODI scores. These results indicate that even in the absence of major radiological correction, TLIF can yield clinically relevant benefits when applied to appropriately selected patients. Further longitudinal research involving larger patient populations is necessary to comprehensively elucidate the connection between sagittal realignment and long-term clinical outcomes.

Ethics

Ethics Committee Approval: Approval from the International Review Board was obtained from the İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (approval number: 10840098-202.3.02, dated: 30.08.2025).

Informed Consent: Informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki.

Footnotes

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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