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Microbial Agents and Antimicrobial Resistance Patterns in Blood Cultures of Intensive Care Unit Patients: Pre- and Post-COVID-19 Pandemic Analysis

Yoğun Bakım Ünitesi Hastalarının Kan Kültürlerinde Mikrobiyal Etkenler ve Antimikrobiyal Direnç Paternleri: COVID-19 Pandemisi Öncesi ve Sonrası Analiz

© Berna Erdal¹, © Benu Baylan², © Hülya Duran³, © Nuri Kiraz⁴, © Yavuz Uyar⁴

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ABSTRACT

Objective: This study aimed to identify the microbial agents isolated from blood cultures of intensive care unit (ICU) patients and their antibiotic resistance rates before and after the Coronavirus Disease 2019 (COVID-19) pandemic.

Methods: Blood culture samples from general ICU-1 and ICU-2, collected between 2018-2022, were retrospectively analyzed.

Results: Of the samples analyzed, 44.4% showed positive culture growth, 46.1% showed no growth, and 9.5% were determined to be skin contaminants. In both ICUs, coagulase-negative staphylococci were the most frequently isolated microorganisms, followed by *Enterococcus* species. Methicillin resistance in *Staphylococcus aureus* significantly decreased in ICU-1 after the pandemic but increased significantly in ICU-2. Resistance rates to vancomycin and teicoplanin in *Enterococcus* species significantly increased during the pandemic in both ICUs. No colistin resistance was detected in *Escherichia coli*, but colistin resistance rates significantly increased in other Gram-negative isolates during the pandemic, except for *Pseudomonas aeruginosa* in ICU-1. After the pandemic, *Klebsiella pneumoniae* in ICU-1 and *Acinetobacter baumannii* in ICU-2 showed the highest colistin resistance rates.

Öz

Amaç: Bu çalışmada Koronavirüs Hastalığı 2019 (COVID-19) pandemisi öncesi ve sonrası yoğun bakım ünitesinde (YBÜ) yatan hastalara ait kan kültürlerinde üreyen etkenleri ve antibiyotik direnç oranlarını tespit etmeyi amaçladık.

Yöntemler: 2018-2022 tarihleri arasında genel (YBÜ-1) ve 2 (YBÜ-2)'de yatan hastalara ait kan kültür örnekleri retrospektif olarak değerlendirildi.

Bulgular: Kan kültürü örneklerinin %44,4'ünde üreme saptanırken %46,1'inde üreme olmadığı, %9,5'inin cilt flora bakterileriyle kontamine olduğu saptanmıştır. Her iki yoğun bakımda da en sık koagülaz negatif stafilokokların izole edildiği, bunu Enterokok türlerinin takip ettiği görülmüştür. Metisilin direnci *Staphylococcus aureus*'da genel YBÜ-1'de pandemi öncesine göre anlamlı şekilde azalırken genel YBÜ-2'de anlamlı şekilde artmıştır. *Enterococcus* spp. izolatlarında vankomisin ve teikoplanin direnç oranları her iki yoğun bakımda da COVID-19 pandemisiyle birlikte istatistiksel olarak anlamlı artış göstermiştir. *Escherichia coli* izolatlarında kolistin direnci saptanmamış, pandemiyle beraber kolistin direnç oranlarının genel YBÜ-1'den izole edilen *Pseudomonas aeruginosa* türleri hariç diğer Gram-negatif izolatlarda anlamlı oranda arttığı; pandemi sonrası genel YBÜ-1'den izole edilen *Klebsiella pneumoniae*, genel YBÜ-2'de ise *Acinetobacter baumannii* izolatlarının en yüksek kolistin direnç oranlarına sahip olduğu görülmüştür.

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Conclusion: This study revealed that, during the pandemic, there was a shift in the distribution of isolated pathogens, accompanied by increased resistance rates even to last-resort antibiotics such as vancomycin and colistin.

Keywords: Blood culture, COVID-19, pathogen microorganisms, antimicrobial resistance, pandemic, intensive care unit

Sonuç: Çalışmamızda pandemiyle birlikte kan kültüründe üreyen etkenlerin dağılımının değiştiği, direnç oranlarının ise vankomisin ve kolistin gibi son çare antibiyotiklerde bile arttığı saptanmıştır.

Anahtar Sözcükler: Kan kültürü, COVID-19, patojen mikroorganizmalar, antimikrobiyal direnç, pandemi, yoğun bakım ünitesi

INTRODUCTION

Bloodstream infections (BSIs) are among the most significant causes of morbidity and mortality worldwide. The primary diagnostic method, regarded as the gold standard, is blood culture testing, which is frequently conducted using automated blood culture systems. Blood culture allows for the identification of causative microorganisms and the determination of their antibiotic susceptibility patterns. This facilitates appropriate treatment for patients, thereby reducing morbidity and mortality rates (1-3).

Antibiotic resistance is a global public health problem worldwide. The widespread use of antibiotics is one of the most important reasons that triggers antibiotic resistance (4). Patients in intensive care units (ICUs) are particularly susceptible to resistant infections due to factors such as broad-spectrum antibiotic use, compromised immune systems, prolonged hospital stays, and invasive procedures. In particular, the Coronavirus Disease 2019 (COVID-19) pandemic has intensified the need for ICU care among COVID-19-positive patients and has led to an increase in broad-spectrum antibiotic use (5-7). While antibiotic resistance has risen over the years, the effect of the COVID-19 pandemic on this resistance has varied across different healthcare settings. Therefore, this study aimed to determine the pathogens that grew in the blood cultures of ICU patients over a four-year period, assess antibiotic resistance rates, and evaluate the effect of the COVID-19 pandemic on microbial resistance within our hospital.

MATERIALS AND METHODS

Study Design

This retrospective study involved the analysis of blood culture samples submitted to the microbiology laboratory from patients admitted to general ICU-1 and ICU-2 at Tekirdağ Namık Kemal University Hospital. The study period extended from March 11, 2018, to March 10, 2022. Our hospital is a tertiary care institution with a capacity of 430 beds (11 beds each for ICU-1 and ICU-2). It also provided uninterrupted care to all patients during the COVID-19 pandemic. ICU-1 was designated for intubated patients with confirmed COVID-19 infection [SARS-CoV-2 polymerase chain reaction (PCR)-positive], while ICU-2 catered to intubated patients with non-COVID-19 conditions (SARS-CoV-2 PCR-negative). Patients hospitalized in both ICU-1 and ICU-2, had similar clinical presentations except for their COVID-19 status (positive or negative). The study period was divided into two phases: the two years preceding the date when the first case was reported in Türkiye (March 11, 2018-March 10, 2020) and the two years following the pandemic onset (March 11, 2020-March 10, 2022).

Demographic data (gender and age) and clinical data (pathogen, antimicrobial susceptibility tests, inpatient service, etc.) were retrieved from the hospital information management system.

Ethics Committee approval Tekirdağ Namık Kemal University, Non-Interventional Clinical Research Ethics Committee, (decision number: 2023.133.06.19, date: 23.06.2023).

Microbiological Evaluation

For patients suspected of BSI, blood culture samples were collected in two sets, comprising a total of four bottles (two aerobic and two anaerobic bottles). These samples were monitored using the BD BACTEC automated blood culture system (Becton Dickinson, USA). Upon detecting a positive growth signal, the samples underwent Gram staining, and preliminary Gram results were promptly reported to the relevant clinical units. In our hospital, empirical treatment is initiated with the notification of blood culture gram-stain results; vancomycin is frequently preferred when Gram-positive bacteria (GPB) are seen, and carbapenems are frequently preferred when Gram-negative bacteria (GNB) are seen. Afterwards, de-escalation is performed according to the culture-antibiogram results of the microbiology laboratory.

Blood culture bottles with positive signals were inoculated onto blood agar (Bes-Lab, Türkiye), eosin methylene blue agar (Bes-Lab, Türkiye), and chocolate agar (Bes-Lab, Türkiye). All plates were incubated at 37 °C for 24-48 hours. Isolates were identified using conventional methods (colony morphology, gram staining, catalase, coagulase, and oxidase tests) and automated identification systems (VITEK®2 Compact, Biomerieux, France, and BD Phoenix System, Becton Dickinson, USA). The presence of coagulase-negative staphylococci (CoNS) in culture was evaluated based on guideline recommendations. If growth was observed in a single bottle, it was considered a potential skin flora contaminant, and species identification and methicillin resistance testing were performed, with results reported as contamination. If growth occurred in both bottles, species identification and antibiogram testing were conducted. When the same microorganism was isolated in both bottles, it was deemed the causative agent, whereas the isolation of different CoNS species was considered contamination. Mixed skin flora growth in culture was directly reported as contamination (8).

Antibiotic susceptibility tests were performed using manual Kirby-Bauer disc diffusion (Bioanalyse, Türkiye, and Oxoid, UK) and automated antibiogram systems (VITEK®2 Compact, Biomerux, France, and BD Phoenix System, Beckton Dickinson, USA) in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria (9):

- Methicillin resistance in staphylococcal isolates was determined using the disk diffusion method with cefoxitin disk (Oxoid, UK).
- Vancomycin and teicoplanin resistance detected in enterococcal isolates was confirmed using gradient tests (Bioanalyse, Türkiye).
- Carbapenem resistance in *Klebsiella pneumoniae* isolates was evaluated via the combined disc diffusion method (Bioanalyse, Türkiye).

- Colistin resistance was assessed using the broth microdilution method (Micronaut-S, Merlin, Germany).
- Antifungal susceptibility testing of yeast isolates was performed using the microdilution method (Mikronaut-AM, Bruker, Germany).

For patients with multiple samples, only the first isolate was included in the study. When two sets of blood cultures obtained simultaneously yielded the same pathogen, the isolates were counted as one. SARS-CoV-2 PCR testing was performed using the Bio Speedy SARS-CoV-2 RT-qPCR kit (Bioeksan, Türkiye).

Statistical Analysis

The data obtained from the study were entered into SPSS version 22.0 (SPSS Inc, Chicago, IL, USA) for statistical analyses. Categorical data were given as percentages. The chi-square test was used to compare independent groups with categorical variables. Cases where the p-value was below 0.05 were considered statistically significant.

RESULTS

Over the course of four years, 1,702 blood culture sets (3,942 bottles) were submitted from 728 patients. The demographic data indicated that 59.2% (n=431) of the patients were male and 40.8% (n=297) were female. The distribution by ICU was similar: ICU-1 had 59.4% male and 40.6% female patients, while ICU-2 had 59% male and 41% female patients. The mean patient age was 66.5±16.6 years (range: 17-100 years), with no significant differences in age or gender between the patients in ICU-1 (mean age: 67.5±16.3 years) and those in ICU-2 (mean age: 65.2±16.7 years) (p>0.05).

Before the pandemic, 198 patients were followed up in ICU-1, with 466 blood culture sets requested. During the pandemic, the number of patients in ICU-1 decreased to 191, while the number of sets increased to 524. In contrast, in ICU-2, the number of patients rose from 160 to 179, while the number of sets decreased from 385 to 327.

Of the samples analyzed, 44.4% showed positive culture growth, 46.1% showed no growth, and 9.5% were determined to be skin contaminants. After the COVID-19 pandemic, both ICUs showed decreases in culture positivity and contamination rates, with an increase in no-growth samples (before pandemic ICU-1; culture positive 48.4%, culture negative 41.8%, contamination 9.7%, ICU-2; culture positive 42.2%, culture negative 46.3%, contamination 11.5%. After pandemic ICU-1; culture positive 44.3%, culture negative 48.6%, contamination 7.1%, ICU-2; culture positive 41.9%, culture negative 47.6%, contamination 10.5%). However, these changes were not statistically significant (p>0.05). When blood culture contamination rates were evaluated separately over the years, contamination rates decreased in 2019 and 2020 in both units. However, these changes were not statistically significant (ICU-1: 2018-14.2%, 2019-6.8%, 2020-6.0%, 2021-9.2%, ICU-2: 2018-14.4%, 2019-9.2%, 2020-10.1%, 2021-11.6%) (p>0.05).

Among isolates deemed clinically significant and subjected to susceptibility testing, 55.7% were GPB, 38.1% were GNB, and 6.2% were yeast species (*Candida* spp.). Over four years, ICU-1 isolates consisted of 54.3% GPB, 38.7% GNB, and 7.0% yeast, while ICU-2

isolates comprised 57.7% GPB, 37.3% GNB, and 5.0% yeast. The comparison of the pre- and post-pandemic data revealed a decline in GNB isolation in both ICUs. While ICU-1 showed an increase in yeast isolation, ICU-2 showed an increase in GPB isolation. In both units, CoNS were the most frequently isolated pathogens, followed by *Enterococcus* spp. (*E. faecium*/*E. faecalis*). Among GNB, *Acinetobacter baumannii* was most commonly isolated in ICU-1, while *Pseudomonas aeruginosa* was predominantly observed in ICU-2 (Table 1).

The rate of methicillin-resistant *Staphylococcus aureus* (MRSA) was 43.8% in ICU-1 (pre-pandemic: 50.0%, post-pandemic: 33.3%) and 58.8% in ICU-2 (pre-pandemic: 33.3%, post-pandemic: 62.5%). The MRSA rate significantly decreased in ICU-1 after the pandemic (p=0.015) but significantly increased in ICU-2 (p≤0.001). The rate of methicillin resistance in CoNS was 77.9% in ICU-1 (pre-pandemic: 78.0%, post-pandemic: 77.6%) and 72.0% in ICU-2 (pre-pandemic: 72.6%, post-pandemic: 71.4%), with no significant changes (p>0.05). No resistance to vancomycin, teicoplanin, or linezolid was observed in either *S. aureus* or CoNS isolates (Table 2).

Among *Enterococcus* spp. isolates, vancomycin and teicoplanin resistance rates were 10.5% in ICU-1 and 9.5% in ICU-2. Resistance significantly increased in both units during the pandemic (p=0.038 for ICU-1, p=0.018 for ICU-2) (Table 2).

For *A. baumannii* isolates, resistance rates to all tested antibiotics except colistin decreased during the pandemic in both ICUs. In ICU-1, decreases in carbapenem and ciprofloxacin resistance were statistically significant (p=0.001 and p=0.002, respectively). In ICU-2, significant decreases were observed for ciprofloxacin and trimethoprim/sulfamethoxazole resistance (p=0.001 and p≤0.001, respectively). However, colistin resistance rates increased in both ICUs, revealing a statistically significant (p=0.050) (Table 3).

For *P. aeruginosa*, resistance to piperacillin/tazobactam (TZP), cephalosporins, and carbapenems increased in both ICUs during the pandemic, while amikacin resistance decreased. TZP and cephalosporin resistance significantly increased in both units, while meropenem resistance significantly increased only in ICU-1 (p<0.05). Colistin resistance decreased in ICU-1 but increased significantly in ICU-2 (p=0.013) (Table 3).

In ICU-1, the resistance of *K. pneumoniae* isolates to all tested antibiotics, including colistin, increased during the pandemic. This increase was statistically significant for all antibiotics except gentamicin (p<0.05). In ICU-2, resistance to cephalosporins and ciprofloxacin decreased, while resistance to TZP, carbapenems, gentamicin, amikacin, trimethoprim/sulfamethoxazole, and colistin increased significantly (p<0.05) (Table 4).

No colistin resistance was observed for *E. coli* in either ICU. However, resistance rates to all other antibiotics increased after the pandemic, except for gentamicin in ICU-2. Significant increases were observed for all antibiotics in ICU-1 except ertapenem, which approached the statistical significance level of 0.05. In ICU-2, significant increases were observed for ceftazidime, cefepime, and ciprofloxacin resistance (p<0.05) (Table 4).

Table 1. Distribution of microorganisms isolated from blood cultures (n/%)

Microorganisms	Before COVID-19						After COVID-19						Four-year period					
	2018			2019			2020			2021			TOTAL			ICU-1		
	ICU-1	ICU-2	n	ICU-1	ICU-2	n	ICU-1	ICU-2	n	ICU-1	ICU-2	n	ICU-1	ICU-2	n	ICU-1	ICU-2	Total
GPB																		
n			%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	%
S. aureus			6	5.1	3	2.8	8	5.2	6	5.9	8	5.5	6	5.4	1	1.0	2	3.3
CoNS			36	30.8	37	34.9	46	29.7	25	24.8	42	29.0	46	41.4	25	26.3	24	39.3
Enterococcus spp.			23	19.7	21	19.8	26	16.8	16	15.8	19	13.1	16	14.4	27	28.4	10	16.4
Other GPB			1	0.9	1	1.0	3	1.9	3	3.0	4	2.8	1	0.9	3	3.2	2	3.3
GNB																		
NFGN			10	8.5	8	7.5	6	3.8	6	5.9	23	15.9	11	9.9	12	12.6	5	8.2
P. aeruginosa			10	8.5	4	3.8	16	10.3	12	11.9	16	11.0	10	9.0	5	5.3	7	11.5
Other NFGN			3	2.7	2	1.9	14	9.1	10	9.9	2	1.4	2	1.8	3	3.2	-	-
K. pneumoniae			10	8.5	7	6.6	4	2.6	5	5.0	13	9.0	6	5.4	7	7.4	2	3.3
E. coli			10	8.5	7	6.6	12	7.7	9	8.9	3	2.1	4	3.6	2	2.1	3	4.9
Others			8	6.8	6	5.7	7	4.5	7	6.9	1	0.6	5	4.6	1	1.0	3	4.9
Candida spp.			-	-	10	9.4	13	8.4	2	2.0	14	9.6	4	3.6	9	9.5	3	4.9
Total			117	100	106	100	100	155	100	101	100	145	100	111	100	95	100	61

ICU: Intensive care unit, GPB: Gram-positive bacteria, CoNS: Coagulase-negative Staphylococci, Other GPB: Other Gram-positive bacteria, GNB: Gram-negative bacteria, NFGN: Non-fermentative Gram-negative, COVID-19: Coronavirus Disease 2019

Table 2. Antibiotic resistance rates of CoNS and *Enterococcus* spp. isolates before and after the pandemic (%)

Antibiotic	CoNS						<i>Enterococcus</i> spp.					
	Before COVID-19 (2018-2019)		After COVID-19 (2020-2021)		p-value		Before COVID-19 (2018-2019)		After COVID-19 (2020-2021)		p-value	
	ICU-1 (n=82)	ICU-2 n=62	ICU-1 n=67	ICU-2 n=70	ICU-1	ICU-2	ICU-1 n=49	ICU-2 n = 37	ICU-1 n = 46	ICU-2 (n=46)	ICU-1	ICU-2
MET	78.0	72.6	77.6	71.4	0.996	0.753	-	-	-	-	-	-
PEN	79.3	77.4	97.0	77.1	≤0.001	0.997	-	-	-	-	-	-
CIP	64.6	66.1	68.7	67.1	0.547	0.881	-	-	-	-	-	-
LEV	-	-	-	-	-	-	40.8	21.6	23.9	11.5	0.010	0.060
VAN	0.0	0.0	0.0	0.0	-	-	6.1	5.4	15.2	15.4	0.038	0.018
TEC	0.0	0.0	0.0	0.0	-	-	6.1	5.4	15.2	15.4	0.038	0.018
GEN	45.1	45.2	46.3	45.7	0.887	0.886	-	-	-	-	-	-
E	78.0	77.4	83.6	64.3	0.279	0.044	-	-	-	-	-	-
DA	54.9	54.8	65.7	55.7	0.112	0.887	-	-	-	-	-	-
TE	56.1	46.8	38.8	35.7	0.016	0.114	-	-	-	-	-	-
LIN	0.0	0.0	0.0	0.0	-	-	0.0	0.0	0.0	0.0	-	-

CoNS: Coagulase-negative *Staphylococci*, COVID-19: Coronavirus Disease 2019, ICU: Intensive care unit, MET: Methicillin, PEN: Penicillin, CIP: Ciprofloxacin, LEV: Levofloxacin, VAN: Vancomycin, TEC: Teicoplanin, GEN: Gentamicin, E: Erythromycin, DA: Dclindamycin, TE: Tetracycline, LIN: Linezolid

Table 3. Antibiotic resistance rates of *Acinetobacter baumannii* and *Pseudomonas aeruginosa* isolates before and after the pandemic (%)

Antibiotic	Antibiotic												
	<i>A. baumannii</i>						<i>P. aeruginosa</i>						
	Before COVID-19 (2018-2019)		After COVID-19 (2020-2021)		p-value		Before COVID-19 (2018-2019)		After COVID-19 (2020-2021)		p-value		
	ICU-1 (n=16)	ICU-2 (n=14)	ICU-1 (n=35)	ICU-2 (n=16)	ICU-1	ICU-2	ICU-1 (n=26)	ICU-2 (n=16)	ICU-1 (n=21)	ICU-2 (n=17)	ICU-1	ICU-2	
TZP	-	-	-	-	-	-	-	46.2	37.5	61.9	52.9	0.023	0.033
CAZ	-	-	-	-	-	-	-	34.6	31.3	61.9	58.8	≤0.001	≤0.001
FEP	-	-	-	-	-	-	-	34.6	31.3	57.1	52.9	0.002	0.002
IMP	100	92.9	88.6	87.5	0.001	0.228	46.2	18.8	57.1	29.4	0.120	0.071	
MER	100	92.9	88.6	87.5	0.001	0.228	38.5	18.8	57.1	23.5	0.011	0.389	
GEN	93.8	71.4	91.4	68.8	0.579	0.758	-	-	-	-	-	-	
AK	100	85.7	97.1	81.3	0.081	0.341	34.6	18.8	4.8	11.8	≤0.001	0.171	
CIP	100	92.9	91.4	75.0	0.002	0.001	53.8	31.3	42.9	41.2	0.120	0.141	
TMP-SXT	81.3	85.7	74.3	62.5	0.236	≤0.001	-	-	-	-	-	-	
COL	6.3	14.3	11.4	25.0	0.205	0.050	11.5	0.0	4.8	5.9	0.076	0.013	

ICU: Intensive care unit, COVID-19: Coronavirus Disease 2019, TZP: Piperacillin-tazobactam, CAZ: Ceftazidime, FEP: Cefepime, IMP: Imipenem, MER: Meropenem, GEN: Gentamicin, AK: Amikacin, CIP: Ciprofloxacin, TMP-SXT: Trimethoprim-sulfamethoxazole, COL: Colistin

Table 4. Antibiotic resistance rates of *Klebsiella pneumoniae* and *Escherichia coli* isolates before and after the pandemic (%)

Antibiotic	<i>K. pneumoniae</i>						<i>E. coli</i>					
	Before COVID-19 (2018-2019)		After COVID-19 (2020-2021)		p-value		Before COVID-19 (2018-2019)		After COVID-19 (2020-2021)		p-value	
	ICU-1 (n=14)	ICU-2 (n=12)	ICU-1 (n=20)	ICU-2 (n=8)	ICU-1	ICU-2	COVID-19	ICU-2 (n=16)	ICU-1 (n=5)	ICU-2 (n=7)	ICU-1	ICU-2
AMC	50.0	75.0	90.0	75.0	≤0.001	-	(2018-2019)	68.8	100	71.4	≤0.001	0.758
TZP	50.0	50.0	80.0	75.0	≤0.001	≤0.001	27.3	31.3	60.0	42.9	≤0.001	0.079
CRO	50.0	83.3	85.0	62.5	≤0.001	0.001	72.7	68.8	100	71.4	≤0.001	0.758
CAZ	42.9	83.3	80.0	75.0	≤0.001	0.165	68.2	75.0	100	85.7	≤0.001	0.050
FEP	42.9	66.7	70.0	50.0	≤0.001	0.015	63.6	50.0	80.0	71.4	0.012	0.002
ERT	28.6	33.3	50.0	75.0	0.002	≤0.001	27.3	25.0	40.0	28.6	0.051	0.524
IMP	28.6	25.0	45.0	62.5	0.019	≤0.001	18.2	18.8	40.0	28.6	0.001	0.098
MER	21.4	25.0	45.0	62.5	≤0.001	≤0.001	18.2	18.8	40.0	28.6	0.001	0.098
GEN	57.1	25.0	60.0	62.5	0.667	≤0.001	31.8	50.0	60.0	42.9	≤0.001	0.321
AK	7.1	16.7	55.0	50.0	≤0.001	≤0.001	-	-	-	-	-	-
CIP	50.0	66.7	85.0	62.5	≤0.001	0.553	54.5	37.5	80.0	57.1	≤0.001	0.007
TMP-SXT	28.6	58.3	60.0	87.5	≤0.001	≤0.001	50.0	68.8	100	71.4	≤0.001	0.758
COL	7.1	0.0	30.0	12.5	≤0.001	≤0.001	0.0	0.0	0.0	0.0	-	-

ICU: Intensive care unit, COVID-19: Coronavirus Disease 2019, AMC: Amoxicillin-clavulanate, TZP: Piperacillin-tazobactam, CRO: Ceftriaxone, CAZ: Ceftazidime, FEP: Cefepime, ERT: Ertapenem, IMP: Imipenem, MER: Meropenem, GEN: Gentamicin, AK: Amikacin, CIP: Ciprofloxacin, TMP-SXT: Trimethoprim-sulfamethoxazole, COL: Colistin

DISCUSSION

BSIs are a significant health concern for hospitalized patients. COVID-19 infections have necessitated the admission of patients to ICUs and have exposed them to numerous secondary infections, including BSIs. Blood culture holds a pivotal role in diagnosis, and the proper collection of samples is critically important for accuracy (10,11). In our study, while the number of patients monitored in ICU-1 slightly decreased during the pandemic, an increase in the number of requested blood culture sets was observed. In contrast, in ICU-2, where patients intubated for reasons other than COVID-19 were monitored, the patient count increased, but the number of sets decreased. This discrepancy can be attributed to the frequent presentation of fever in COVID-19 infections. When analyzing blood culture results, the rate of culture positivity decreased in both clinics during the pandemic, likely due to the increased number of blood culture sets requested.

In addition to proper sampling, adequate skin antisepsis and the prevention of contamination are crucial steps in diagnosis (12,13). Aygar et al. (10) evaluated blood culture contamination rates in ICU patients before and during the pandemic and found an increase in contamination rates. In the current study, contamination rates decreased in both ICUs during the pandemic compared to pre-pandemic levels. An annual analysis showed a reduction in contamination rates in ICU-1, in 2019 compared to 2018, reaching the lowest levels during 2020 (the first pandemic year), followed by an increase thereafter. During the COVID-19 pandemic, infection

control measures in our hospital were increased, and antisepsis rules were followed more strictly. This decrease in contamination rates may be related to the enhanced cleaning and antisepsis measures implemented in our hospital during the pandemic. However, since the detected contamination rate still exceeds the national target value of 3% (8), additional measures are deemed necessary in both clinics to further reduce these rates.

Studies report that the growth rate of GPB in blood culture samples ranges from 59.3% to 70.3%, GNB from 22.1% to 40.2%, and *Candida* species from 7.1% to 14.8%. The frequency of *Candida* isolation has been reported to increase during the pandemic (5-7,10). In our study, the distribution of microorganisms that grew in blood cultures was consistent with the literature. The isolation frequency of *Candida* species increased in ICU-1 but decreased in ICU-2 during the pandemic. Risk factors such as the use of broad-spectrum antimicrobial agents, prolonged ICU stays, and mechanical ventilation requirements in COVID-19 patients may have predisposed them to *Candida* infections.

At the species level, CoNS were the most frequently isolated pathogens, consistent with previous studies (5-7,14). *Enterococcus* spp. were also commonly isolated GPB (15). Among GNB, *Klebsiella* spp. and *Acinetobacter* spp. were frequently isolated, although their order of prevalence varies across studies (1,10). Arslan and Şahin (5) reported that *Acinetobacter* spp. were predominant among Gram-negative isolates before the pandemic, whereas *Klebsiella* spp. became more prominent during the pandemic. Aytaç et al. (7) demonstrated that while *Klebsiella* spp. were more frequently

identified before the pandemic, the prevalence of *Acinetobacter* spp. increased during the pandemic. In our study, CoNS and *Enterococcus* spp. were the most frequently isolated agents before and after the pandemic in both clinics. GNB were generally the third most frequently isolated agents, with *P. aeruginosa* being more common before the pandemic and *A. baumannii* increasing in prevalence after the pandemic. Rapid diagnosis of BSIs and initiation of appropriate empirical treatment are crucial for reducing mortality. Although the distribution of causative agents was similar in both ICUs, changes in isolation frequencies were observed during the pandemic. Therefore, regular analysis of the distribution of pathogens isolated from blood cultures in clinical settings is essential to guide empirical treatment strategies effectively. In addition, effective infection control measures should be taken to prevent the spread of infectious agents within the hospital and to prevent the transfer of pathogenic microorganisms between patients or clinics (16). Despite the stricter attention paid to isolation measures implemented in our hospital during the pandemic, the fact that the same physicians provided consultation services to patients in both ICUs may have contributed to the similar distribution of agents.

Methicillin resistance is a critical factor in the treatment of staphylococcal infections. Recent studies report methicillin resistance rates in staphylococcal species isolated from blood cultures ranging from 34.0% to 90.4% for CoNS and 28.2% to 61.5% for *S. aureus* (6,15,17). Our findings are consistent with these rates and similarly indicate higher methicillin resistance in CoNS compared to *S. aureus* (14). Methicillin resistance in CoNS remained consistent during the pandemic, while it decreased in *S. aureus* isolates from ICU-1 and increased in ICU-2, with the differences being statistically significant.

Vancomycin, teicoplanin, and linezolid are critical antibiotics for treating resistant GPB infections (18). In our study, all staphylococcal species isolated over the four-year period were sensitive to these agents. However, vancomycin resistance in *Enterococcus* species increased significantly from pre-pandemic levels of approximately 5-6% to 15% during the pandemic. According to the 2019 data from the Central Asian and Eastern European Surveillance on Antimicrobial Resistance (CAESAR) network, vancomycin resistance rates in *Enterococcus* species isolated from blood cultures were 1% in *E. faecalis* and 14% in *E. faecium* (19). In our study, the isolated *Enterococcus* species consisted of *E. faecium* and *E. faecalis*, with vancomycin resistance rates reported as aggregate data. The resistance rates we observed appear consistent with CAESAR data, considering that *E. faecium* isolates are more frequently implicated in hospitalized patients, particularly in ICUs (20). Furthermore, when clinicians suspect a BSI, they often initiate empirical antibiotic treatment, and frequently choose vancomycin to target GPB. Given the established link between antibiotic use and the development of resistance, the observed increase in resistance during the pandemic likely is attributed to the increased use of vancomycin.

Carbapenems are critical antimicrobials used in the empirical treatment of GNB-related BSIs in ICUs. Unfortunately, the emergence of carbapenem-resistant *Pseudomonas* and *Acinetobacter* species has become a significant public health issue globally (21). Bayraktar (20) reported meropenem resistance rates in ICU isolates collected between 2022 and 2023 as follows: 96.2% for *A. baumannii*, 45.5% for *K. pneumoniae*, 25.0% for *P. aeruginosa*, and 8.7% for *E. coli*.

Similarly, Albayrak et al. (22) observed imipenem and meropenem resistance in *A. baumannii* isolates from blood cultures at a rate of 95% in 2017, 81% in 2018, and 90% in 2019. Another study by Çınar (23) assessed febrile neutropenia episodes in patients with hematologic malignancies from 2019 to 2021, finding imipenem and meropenem resistance rates of 79.1% for *A. baumannii*, 48.1% for *K. pneumoniae*, 45.9% for *P. aeruginosa*, and 29.5% for *E. coli*. Arslan and Şahin (5) examined carbapenem resistance before and after the COVID-19 pandemic and reported increases across several species, including *Klebsiella* spp. (75% to 79.4%), *Acinetobacter* spp. (imipenem: 88.2% to 92.9%, meropenem: 88.2% to 85.7%), *Pseudomonas* spp. (0% to 60%), and *E. coli* (imipenem: 9.1% to 40%, meropenem: 27.3% to 53.3%).

In our study, *A. baumannii* showed the highest resistance to carbapenems. Resistance rates dropped from 100% and 92.9% before the pandemic to 88.6% and 87.5% after the pandemic in ICU-1 and ICU-2, respectively, and this reduction was statistically significant. For *P. aeruginosa*, imipenem resistance in ICU-1 increased from 46.2% to 57.1%, and meropenem resistance increased significantly from 38.5% to 57.1%. In ICU-2, although resistance rates were lower, a non-significant increase was observed. For *K. pneumoniae*, resistance rates increased significantly, from 21-29% before the pandemic to 45-50% after the pandemic in ICU-1 and from 25-34% to 63-75% in ICU-2. For *E. coli*, carbapenem resistance in ICU-1 increased significantly from a pre-pandemic range of 18-27% to 40% during the pandemic. In ICU-2, resistance rose from 19-25% to 29%, but this increase was not statistically significant. We attribute the observed rise in resistance to the increased use of carbapenems during the pandemic. This highlights the necessity of avoiding unnecessary and prolonged antibiotic use in hospitalized patients to mitigate the development of resistance.

The increasing prevalence of carbapenemase-producing GNB infections and the associated treatment challenges have brought colistin back into focus, despite its historical decline in use due to side effects. Although reserved as a last-line therapy, resistance to colistin is rising globally and in Türkiye. According to EUCAST recommendations, colistin susceptibility testing should be performed using the broth microdilution method for reliable results (24,25). Recent reports from centers in Türkiye using this method indicate colistin resistance rates of 16.7-41.7% for *K. pneumoniae*, 0-8.2% for *A. baumannii*, and 0-12.5% for *P. aeruginosa* (26-29). Süzük Yıldız et al. (30) conducted a study involving 28 hospitals from level-II statistical regions in Türkiye, reporting colistin resistance rates of 8.7% for *E. coli* and 28.4% for *K. pneumoniae* in 2019. Global studies have documented colistin resistance rates of 10.0-19.9% in *Enterobacteriales*, 2.5-4.0% in *A. baumannii*, and 1.0-5.0% in *P. aeruginosa* (31-35). In our study, colistin resistance was not detected in *E. coli* isolates, while rates for *K. pneumoniae* and *P. aeruginosa* were consistent with the literature. However, post-pandemic resistance rates for *A. baumannii* increased to 14.3% in ICU-1 and 25.0% in ICU-2. Resistance rates for colistin increased significantly with the pandemic in all isolates except for *P. aeruginosa* in ICU-1. The highest colistin resistance after the pandemic was observed in *K. pneumoniae* isolates from ICU-1 and *A. baumannii* isolates from ICU-2. These findings underscore the critical need to address colistin resistance in our hospital and suggest that resistance may become a severe issue if preventive measures are not implemented.

Furthermore, the pandemic has likely contributed to the increase in resistance rates, complicating the treatment of carbapenem-resistant GNB infections (24,25).

Study Limitations

The retrospective design of our study, the small number of microorganism species included, and the lack of access to clinical information about the patients are the limitations of the study.

CONCLUSION

In conclusion, BSIs are a significant cause of mortality among hospitalized patients, necessitating the rapid initiation of pathogen-specific empirical treatment. The most important reason for antibiotic resistance is the long-term use of antibiotics, which creates a vicious circle and makes treatment difficult. During the COVID-19 pandemic, the widespread use of broad-spectrum antibiotics and prolonged ICU stays affected blood culture and antibiogram results. In our study, pathogen distribution shifted during the pandemic, with resistance rates increasing even for last-resort antibiotics such as vancomycin and colistin. To reduce antibiotic resistance rates in our hospital, adherence to restricted antibiotic policies is essential. Additionally, enhancing infection control measures is critical to prevent the spread of resistant microorganisms.

Ethics

Ethics Committee Approval: Ethics Committee approval Tekirdağ Namık Kemal University, Non-Interventional Clinical Research Ethics Committee, (decision number: 2023.133.06.19, date: 23.06.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: B.E., H.D., Design: B.E., B.B., H.D., N.K., Y.U., Data Collection or Processing: B.E., B.B., Analysis or Interpretation: B.E., H.D., Literature Search: B.E., H.D., Writing: B.E., H.D., N.K., Y.U.

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Fear of COVID-19 During the Pandemic: Alcohol Craving Behavior and Compulsive Online Buying in Individuals with Potential Alcohol Use Disorder

Pandemi Döneminde COVID-19 Korkusu: Potansiyel Alkol Kullanım Bozukluğu Olan Bireylerde Alkol İsteği Davranışı ve Zorlayıcı Çevrim İçi Satın Alma

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ABSTRACT

Objective: This study aimed to examine the determinants of alcohol craving behavior and compulsive online shopping behavior among individuals with alcohol use disorder during the Coronavirus Disease 2019 (COVID-19) pandemic.

Methods: This cross-sectional and descriptive study collected data via an online survey created through Google Forms. Participants were invited through social media platforms. A total of 350 participants completed the survey; however, data from 22 participants were excluded due to missing critical variables, resulting in a final sample size of 328 participants. Data collection tools included the Sociodemographic Data Form, COVID-19 Phobia scale, Satisfaction with Life scale, Compulsive Online Shopping scale, CAGE test, and PACS.

Results: The findings revealed that psychosomatic symptoms of coronavirus phobia significantly predicted alcohol craving behavior. Additionally, compulsive online shopping behavior was significantly associated with the mood regulation sub-dimension. Women and younger individuals were found to be more prone to compulsive shopping behavior.

Conclusion: The study highlights the importance of supporting individuals with alcohol use disorder during the pandemic and improving their mood regulation strategies. Targeted interventions can help reduce maladaptive coping strategies. Further large-scale studies are needed to evaluate the long-term effects of the pandemic on addiction behaviors.

Keywords: COVID-19, alcohol craving, compulsive online shopping, mood regulation, pandemic

ÖZ

Amaç: Bu çalışma, Koronavirüs Hastalığı 2019 (COVID-19) pandemisi sırasında alkol kullanım bozukluğu olan bireylerde alkol aşırma davranışı ve zorlayıcı çevrim içi alışveriş davranışını etkileyen belirleyicileri incelemeyi amaçlamaktadır.

Yöntemler: Bu kesitsel ve tanımlayıcı çalışma, Google Formlar aracılığıyla oluşturulan çevrim içi bir anket kullanılarak yürütülmüştür. Katılımcılar sosyal medya platformları üzerinden davet edilmiştir. Toplam 350 katılımcı anketi tamamlamış ancak 22 katılımcının verileri kritik değişkenlerin eksikliği nedeniyle hariç tutulmuş ve böylece nihai örneklem büyüklüğü 328 olmuştur. Veri toplama araçları Sosyodemografik Veri Formu, COVID-19 Fobi Ölçeği, Yaşam Doyumu ölçeği, Zorlayıcı Çevrim İçi Alışveriş ölçeği, CAGE testi ve PACS'tır.

Bulgular: Bulgular, koronavirüs fobisinin psikosomatik semptomlarının alkol aşırma davranışını anlamlı şekilde yordadığını ortaya koymuştur. Ayrıca, zorlayıcı çevrim içi alışveriş davranışı, duygu düzenleme alt boyutu ile anlamlı olarak ilişkili bulunmuştur. Kadınlar ve genç bireylerin zorlayıcı alışveriş davranışına daha yatkın oldukları görülmüştür.

Sonuç: Çalışma, pandemi sırasında alkol kullanım bozukluğu olan bireylerin desteklenmesinin ve duygu düzenleme stratejilerinin geliştirilmesinin önemini vurgulamaktadır. Hedefe yönelik müdahaleler uyumsuz başa çıkma stratejilerinin azaltılmasına yardımcı olabilir. Pandeminin bağımlılık davranışları üzerindeki uzun vadeli etkilerini değerlendirmek için daha geniş ölçekli çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: COVID-19, alkol isteği, kompulsif çevrim içi alışveriş, duygu düzenleme, pandemi

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INTRODUCTION

In December 2019, the Coronavirus outbreak, which began in Wuhan, China, spread worldwide, causing feelings of danger and uncertainty across the globe, with no proven specific treatment available (1). While the virus has impacted societies broadly, behavioral changes associated with the pandemic have emerged, reshaping daily life (2).

Alcohol and other psychoactive substances are often used by individuals to cope with unpleasant emotions, stress, anxiety, and other psychological difficulties (3). In this context, the consumption of alcohol and other psychoactive substances has been proposed as a self-medication practice (4). According to the Global Status Report on Alcohol published by the World Health Organization, the prevalence of alcohol dependence among individuals over the age of 15 was reported as 2.6% in 2016. Data from the Institute for Health Metrics and Evaluation indicate that the rate of alcohol use disorder in Türkiye was reported as 0.78%. The Pan American Health Organization reported an increase in the consumption of informally produced alcohol, including homemade varieties, during the pandemic.

Various studies have reported an increase in the frequency of alcohol and substance use among individuals who develop psychological problems after disasters that affect society as a whole, such as pandemics. Conversely, individuals who increase their alcohol and substance use after such disasters are also more likely to develop psychological problems (5). When studies related to alcohol misuse during crisis periods are considered, concerns about increased alcohol consumption during the Coronavirus Disease 2019 (COVID-19) pandemic also arise (6). Additionally, quarantine and social isolation measures implemented as part of pandemic precautions are predicted to lead to changes in alcohol consumption (7). A study conducted by Nielsen Company (8) found a 240% increase in online alcohol sales. In another study (9), it was reported that during the coronavirus pandemic, some participants who had previously quit alcohol started drinking again, while some regular alcohol users increased their alcohol intake. Similarly, another study (10) showed that participants who consumed alcohol heavily before the pandemic, failed to develop effective coping strategies for stress, and had poor mental health, increased their alcohol consumption during the pandemic. During the Severe Acute Respiratory Syndrome (SARS) outbreak, a study (11) reported an increase in symptoms of alcohol dependence/misuse among healthcare workers exposed to the outbreak.

Compulsive buying is a type of behavioral addiction that has increased in prevalence over the last two decades (12). Studies indicate that behavioral addictions tend to rise during periods of crisis (9,13). Although there is no universally agreed-upon definition of compulsive buying, it is characterized by preoccupation with shopping, overspending beyond one's budget, and purchasing unnecessary items (14). In the literature, depression, anxiety, or feelings of dissatisfaction with oneself are reported as risk factors for this disorder (15). Additionally, health crises such as epidemics and pandemics can serve as significant triggers for compulsive buying. It has been suggested that compulsive buying might act as a maladaptive coping strategy during the COVID-19 pandemic (16). Due to shortened store hours and prolonged closures during the pandemic, consumers have experienced increased anxiety, leading

to heightened panic buying (17). E-commerce has surged during the pandemic, becoming a prominent component of economic activities (18,19). With the implementation of quarantine and social isolation measures during the pandemic, an increase in online shopping behavior has been observed (20,21).

Life satisfaction is defined as an individual's assessment of their quality of life based on their own criteria and is considered an essential component of well-being. High life satisfaction is positively associated with high self-esteem, strong social support, and better living conditions (22). In a multicenter study, an increase in distress, a decrease in social participation and individual well-being, and an overall decline in life satisfaction were reported during the coronavirus pandemic, similar to the SARS pandemic (23).

In this study, we aimed to identify the determinants affecting alcohol craving in individuals with alcohol use disorder during the COVID-19 pandemic. Additionally, the objective was to examine whether changes in purchasing behavior during the pandemic differ with respect to alcohol consumption.

Hypotheses

1. COVID-19 phobia significantly predicts alcohol craving behavior.
2. Compulsive online buying behavior is associated with mood regulation.
3. Compulsive buying behavior is more prevalent among women and younger individuals.

MATERIALS AND METHODS

This research is a cross-sectional descriptive study conducted between July and September 2020. The COVID-19 pandemic period, with lockdowns, quarantine measures, and restrictions on social life, posed significant challenges in reaching participants. In situations where accessing the target population is difficult, the snowball sampling method is known to be effective (24). Therefore, in this study, the purposive (non-probability) sampling method, specifically the snowball sampling technique, was employed. In studies utilizing non-probability sampling methods, the population is not clearly defined (25). Similarly, in our study, although the sample size was not precisely determined, the two primary groups in the sample consisted of healthcare workers from Gazi University, and their relatives.

The sample size for the study was calculated using the G*Power software package (26). A non-probability sampling method was employed, and the study was conducted with a cross-sectional and descriptive design. Individuals over the age of 18 without a diagnosis of psychotic disorders were included in the study. Using the snowball sampling method, it was planned to include 350 participants. To reach this sample size, an online survey link created via Google Forms was distributed to healthcare workers through social media. Additionally, healthcare workers who completed the survey were encouraged to share the research link with people in their networks.

After selecting the "I Agree" option on the electronic informed consent form, participants completed the survey. With approval obtained from the Gazi University Measurement and Evaluation Ethics Subcommittee, the survey link was shared between August 1, 2020, and October 1, 2020.

During this period, the survey was completed by 350 participants. Data from 22 participants were excluded from the study due to missing critical variables for the research. Finally, data from 328 participants were included in the analysis.

Scales

In the study, the sociodemographic information form, the Coronavirus-19 Phobia scale (C19P-S), the Satisfaction with Life scale (SWLS), the Compulsive Online Shopping scale (COSP), the CAGE Test, and the Penn Alcohol Craving scale (PACS) were used.

Sociodemographic Information Form

This form, created by the researchers, consists of 11 questions addressing age, gender, marital status, income level, work style, household size, psychiatric disorders, alcohol use, and online shopping behavior.

Coronavirus-19 Phobia Scale

Developed by Arpacı et al. (27), the C19P-S consists of 20 items designed to measure phobia related to the coronavirus. Participants rate each item on a 5-point Likert scale ranging from “Strongly Disagree (1)” to “Strongly Agree (5)” items 1, 5, 9, 13, 17, and 20 measure the

Psychological Sub-dimension

Items 2, 6, 10, 14, and 18 measure the somatic sub-dimension; items 3, 7, 11, 15, and 19 measure the social sub-dimension; items 4, 8, 12, and 16 measure the economic sub-dimension.

Satisfaction with Life Scale

Developed by Diener et al. (28), the SWLS consists of 5 items. The Turkish validity and reliability study was conducted by Dağlı and Baysal (29). The scale is based on a 5-point Likert scale, ranging from “Strongly Disagree” to “Strongly Agree”.

Compulsive Online Shopping Scale

Developed by Bozdağ and Alkar (29) as an adaptation of the Bergen Shopping Addiction scale for compulsive online shopping behavior. The scale consists of 28 items, rated on a 5-point Likert scale ranging from “Strongly Disagree” to “Strongly Agree”. It includes five dimensions: Problematic behavior, mood regulation, tolerance, preoccupation, and withdrawal.

CAGE Test

Developed by Ewing (30), the CAGE test is widely used for screening alcoholism. It consists of four yes/no questions, answered directly by the participant.

Penn Alcohol Craving Scale

Developed by Flannery et al. (31), the PACS is a 5-item self-report questionnaire designed to assess craving in individuals with alcohol use disorder. It evaluates the severity of alcohol craving over the previous week, including frequency, intensity, duration, resistance, and overall craving. Each item is scored on a scale ranging from 0 to 6. The Turkish validity and reliability study was conducted by Evren et al. (32).

Ethics Committee Approval

This study was reviewed by the Gazi University Measurement and Evaluation Ethics Subcommittee and received ethical approval (references number: 91610558-604.01.02, research code: 2020-324, date: 06.06.2020).

Statistical Analysis

The study data were analyzed using the SPSS 23.0 software package. Descriptive statistics were expressed using frequency, percentage, mean, and standard deviation. The chi-square test was used to compare categorical variables between groups, and Fisher’s exact test was applied when necessary. Since the skewness and kurtosis values of the numerical variables ranged between -1 and $+1$, it was assumed that the numerical data followed a normal distribution (33). Therefore, parametric tests were used in the analysis. Numerical variables between two groups were analyzed using the independent samples t-test. In the multiple linear regression analysis, the PACS total score was considered the dependent variable. The stepwise regression method was applied in this analysis. The model included age, gender, marital status, income level, education level, family type, SWLS, C19P-S sub-dimensions, and COSP sub-dimensions. For statistical analyses, a p-value <0.05 was considered significant.

RESULTS

The sociodemographic characteristics of the sample are shown in Table 1. The mean age of the participants was 32; 62.2% were female; 58.5% were university graduates; 69.8% were single; and 68% lived in a nuclear family structure. This educational profile does not align well with the general population. There was a significant difference between groups with low and high risk of alcohol use disorder in terms of marital status ($\chi^2=4.365$, $p=0.037$). However, the groups were similar in terms of age ($t=$, $p=$), gender ($\chi^2=3.480$, $p=0.062$), education level ($\chi^2=1.874$, $p=0.599$), income level ($\chi^2=3.889$, $p=0.421$), work system ($\chi^2=3.653$, $p=0.455$), and family structure ($\chi^2=1.228$, $p=0.268$). Among individuals with a high risk of alcohol dependence, 49.4% ($n=41$) reported having a psychiatric disorder, while this rate was 32.7% ($n=80$) in those with a low risk of alcohol dependence. When participants were asked about their frequency of online shopping, among those at low risk of alcohol dependence, 19.2% ($n=47$) reported shopping once a year, 49.8% ($n=122$) reported shopping once a month, 19.2% ($n=47$) reported shopping once a week, and 8.6% ($n=21$) reported shopping more than once a week. In individuals with a high risk of alcohol dependence, these rates were: 13.3% ($n=11$) reported shopping once a year, 43.4% ($n=36$) reported shopping once a month, 15.7% ($n=13$) reported shopping once a week, and 18.1% ($n=15$) reported shopping more than once a week. Participants who reported not engaging in online shopping made up 4.9% ($n=16$) of the sample. The groups showed a significant difference in terms of online shopping frequency ($\chi^2=12.445$, $p=0.014$).

The comparison of the applied scales based on alcohol dependence risk is shown in Table 2. Among individuals with a high risk of alcohol dependence, the psychosomatic ($p=0.010$) and economic ($p=0.036$) sub-dimension scores of the C19P-S were found to be significantly higher.

The evaluation of variables predicting alcohol craving in patients with a high risk of alcohol misuse using multiple linear regression analysis is shown in Table 3. To avoid issues with multicollinearity, the stepwise method was used in the multiple linear regression analysis. In the constructed model, age, gender, marital status, income level, education level, family type, SWLS, C19P-S sub-dimensions, and the sub-dimensions of the COSP were not significant predictors. The PACS was used as the dependent variable. The model was statistically significant and explained 11% of the variance ($F=10.959$, $p<0.001$). The only variable significantly associated with alcohol craving was the psychosomatic sub-dimension of the C19P-S scale ($\beta=3.310$, $p<0.001$).

DISCUSSION

There is widespread concern that the physical, social, and mental health of alcohol and substance users, as well as individuals with addiction, could be significantly affected by the COVID-19 pandemic. Harmful alcohol consumption leads to neuroadaptations that intensify alcohol craving during periods of stress (34). Therefore, social isolation, changes in employment status, or uncertainty about

the future can trigger increased alcohol consumption in individuals with alcohol use disorder (6).

In our study, as psychosomatic symptoms related to COVID-19 phobia increased, craving also increased in individuals at high risk of alcohol dependence. A bidirectional relationship can be discussed here. During alcohol withdrawal, physical complaints such as pain, tension, sleep problems, and palpitations may occur. Complaints related to alcohol withdrawal are among the internal triggers for alcohol consumption in individuals who are attempting to quit drinking (35). Indeed, an increase in craving has been reported among individuals with alcohol use disorder during the pandemic (36).

A three-path psychobiological model has been proposed for craving. One of the components of this model, relief drinking, refers to the consumption of alcohol to eliminate aversive psychological or physical conditions (37). It is well known that alcohol is used to alleviate physical complaints such as pain and tension (4,38). In one study, it was reported that pain intensity increased during quarantine compared to the pre-quarantine period in patients with

Table 1. Sociodemographic characteristics of the sample

Variable		Low risk of alcohol dependence (n=245)		High risk of alcohol dependence (n=83)		Total (n=328)	
		Mean	SD	Mean	SD	Mean	SD
Age		32.38	10.61	32.30	9.01		
		n	%	n	%	n	%
Gender	Female	160	65.3	44	53.0	204	62.2
	Male	85	34.7	39	47.0	124	37.8
Education level	Primary school	5	2.0	0	0.0	5	1.5
	High school	47	19.2	17	20.5	64	19.5
	University	142	58.0	50	60.2	192	58.5
	Postgraduate	51	20.8	16	19.3	67	20.4
Marital status	Single	163	66.5	66	79.5	229	69.8
	Married	82	33.5	17	20.5	99	30.2
Income level	0-2324	72	29.4	20	24.1	92	28.0
	2325-4000	51	20.8	25	30.1	76	23.2
	4001-6000	42	17.1	11	13.3	53	16.2
	6001-10000	45	18.4	17	20.5	62	18.9
	Above 10000	35	14.3	10	12.0	45	13.7
Family type	Nuclear family	162	66.1	61	73.5	223	68.0
	Extended family	83	33.9	22	26.5	105	32.0
Work system	Shift work	30	12.2	8	9.6	38	11.6
	Home office	64	26.1	26	31.3	90	27.4
	Unemployed during pandemic	24	9.8	13	15.7	37	11.3
	Not working before/after pandemic	74	30.2	21	25.3	95	29.0
	Same work pattern	53	21.6	15	18.1	68	20.7

Note: * $p<0.05$ indicates statistical significance.

SD: Standart deviation

Table 2. Comparison of applied scales based on alcohol dependence risk

Scales and subscales		Alcohol dependence low risk (n=245)	Alcohol dependence high risk (n=83)	Statistical analysis	
		Mean + SD	Mean + SD	t	p
C19P-S	Psychological	21.80±5.25	22.59±5.09	-1.180	0.239
	Psychosomatic	8.57±3.76	9.92±4.93	-2.597	0.010
	Social	14.20±4.43	14.65±4.64	-0.790	0.430
	Economic	8.53±2.93	9.34±3.33	-2.108	0.036
COSP	Problem	15.04±5.63	15.21±6.34	-0.238	0.812
	Preoccupation with thoughts	7.04±2.68	6.72±2.62	0.960	0.338
	Mood regulation	8.22±4.28	8.73±4.75	-0.919	0.359
	Withdrawal	9.06±2.32	9.08±2.57	-0.049	0.961
	Tolerance	9.02±4.32	9.21±4.72	-0.342	0.733
Satisfaction with life scale		13.86±4.77	13.34±5.05	0.832	0.406
CAGE test		0.33±0.47	2.77±0.78	-33.769	<0.001

*p<0.05 indicates statistical significance

C19P-S: COVID-19 Phobia scale, COSP: Compulsive Online Shopping scale, SD: Standard deviation

Table 3. Evaluation of variables predicting alcohol craving in patients with high risk of alcohol dependence using multiple linear regression analysis

	Unstandardized coefficients		Standardized coefficients	t	p-value	95.0% Confidence interval for B		CI
	B	Standard error	Beta (β)			Lower	Upper	
C19P-S psychosomatic	0.559	0.169	0.345	3.310	0.001	0.223	0.894	4.283

Model Fit: F=10.959, p<0.001, R²=0.11

*p < 0.05 indicates statistical significance

CI: Confidence interval, C19P-S: COVID-19 Phobia scale

chronic pain (39). In this case, the sensation of pain poses a risk for alcohol consumption. Additionally, alcohol can be used hypnotically in cases of insomnia (40). However, individuals with alcohol use disorder develop tolerance to the hypnotic effects of alcohol, leading to chronic insomnia. In one study (41), insomnia in individuals with alcohol use disorder was found to be associated with higher craving levels.

Craving is a strong predictor of relapse in individuals with alcohol use disorder (42). Moreover, craving is a significant phenomenon in the development of alcohol dependence in all individuals (43). Furthermore, alcohol craving increases during periods of stress even in individuals without alcohol use disorder (44). Therefore, during pandemic conditions, craving and subsequent alcohol dependence may emerge in individuals at high risk.

As shopping has increasingly shifted to online platforms globally, compulsive buying behavior has also found a new domain online. The internet offers a wide variety of shopping options, simultaneous access to multiple online stores, and instant gratification of emotional and identity-related expectations. Additionally, accessibility, anonymity, availability, and affordability-characteristics unique to the internet-have been associated with compulsive online shopping behavior (45).

A review of the literature shows that studies examining compulsive online shopping behavior during the pandemic are limited. In one study (20), an increase in impulsive online shopping behavior was reported during the pandemic. Compulsive buying is more commonly observed as a response to negative affect. Relief from negative emotions or experiencing euphoria is among the most common psychological outcomes of compulsive buying (46). Compulsive buying may also be associated with dysfunction in emotion regulation (12).

In our study, in line with the literature, a significant relationship was observed between COVID-19 phobia and the mood regulation sub-dimension of online shopping behavior. Young women are more prone to developing compulsive buying behavior (47). The higher prevalence of compulsive shopping among women has been linked to sociocultural factors, such as the perception of shopping as a recreational activity (48). In our study, it was also observed that women and young individuals engaged in more frequent online shopping to regulate their mood.

The findings of our study reveal that during the pandemic period, the emotional and physical symptoms of individuals with alcohol use disorder have led to increased alcohol craving. Similarly, compulsive buying behavior was observed as being used as an emotion regulation strategy.

Study Limitations

Despite the significant findings obtained from our study, there are some limitations. Conducting our study with a larger sample size could have enhanced the generalizability of the findings, providing stronger and more meaningful results. Furthermore, evaluating alcohol use disorder based on the CAGE scale cut-off score and using a non-probability sampling method (snowball sampling) are additional limitations of our study.

CONCLUSION

Our results indicate that fear of COVID-19 is associated with an increase in alcohol craving, online shopping for mood regulation, and preoccupation with online shopping activity. In individuals at high risk of alcohol dependence, increased fears and bodily sensations related to COVID-19 are associated with higher craving levels. Therefore, during the pandemic, alcohol craving may increase in individuals at high risk of alcohol dependence. Additionally, women, young individuals, and those in the high-income group engage in more frequent online shopping as a mood regulation strategy.

The COVID-19 pandemic has had a significant impact on alcohol craving and compulsive buying behavior. It is recommended that individuals with alcohol use disorder should receive support during the pandemic aimed at improving mood regulation skills and enhancing support mechanisms. Further research involving larger populations and encompassing other areas of addiction is needed to evaluate the broader impact of the pandemic on addiction-related behaviors.

Ethics

Ethics Committee Approval: This study was reviewed by the Gazi University Measurement and Evaluation Ethics Subcommittee and received ethical approval (references number: 91610558-604.01.02, research code: 2020-324, date: 06.06.2020).

Informed Consent: It was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.C., Concept: S.C., Design: S.C., Data Collection or Processing: S.C., Ç.H.Y., Analysis or Interpretation: S.C., Ç.H.Y., Literature Search: S.C., Ç.H.Y., Writing: S.C.

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

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Comprehensive Prediction of *FBN1* Targeting miRNAs: A Systems Biology Approach for Marfan Syndrome

FBN1 Hedefleyen miRNA'ların Kapsamlı Tahmini: Marfan Sendromu için Sistem Biyolojisi Yaklaşımı

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ABSTRACT

Objective: Marfan syndrome (MFS) is a genetic connective tissue disorder primarily caused by mutations in the *FBN1* gene. Emerging evidence highlights the regulatory role of microRNAs (miRNAs) in modulating gene expression in MFS, but a systematic investigation into miRNAs targeting *FBN1* is lacking. This study aimed to comprehensively identify miRNAs interacting with the *FBN1* transcript to reveal potential molecular regulators and therapeutic targets.

Methods: Human miRNA sequences were retrieved from miRBase (Release 22.1), and the canonical *FBN1* transcript (RefSeq: NM_000138.5) was used for target prediction. Computational interaction analysis was conducted using the psRNATarget server with stringent parameters to detect potential miRNA binding sites. Expression profiles and disease associations of the top candidate miRNAs were further investigated through database integration and literature review.

Results: Out of 2656 human mature miRNAs analyzed, 251 were predicted to bind *FBN1*, with the hsa-miR-181 family exhibiting the highest number of predicted interactions. Evidence from the literature highlighted dysregulation of hsa-miR-181 expression in MFS patients, suggesting a functional role in disease pathophysiology.

Conclusion: This study identifies key members of the hsa-miR-181 family as post-transcriptional regulators of *FBN1*, offering new insights into miRNA-driven mechanisms in MFS. These findings support the potential of RNA-based diagnostics and therapeutic strategies targeting miRNA-*FBN1* interactions.

Keywords: Marfan syndrome, *FBN1*, microRNAs, hsa-miR-181, bioinformatics, post-transcriptional regulation

Öz

Amaç: Marfan sendromu (MFS), genellikle *FBN1* genindeki mutasyonlardan kaynaklanan genetik bir bağ dokusu bozukluğudur. Son yıllarda, gen ekspresyonunu post-transkripsiyonel düzeyde düzenleyen mikroRNA'ların (miRNA'lar) bu hastalığındaki rolü ön plana çıkmaktadır. Bu çalışmanın amacı, *FBN1* transkriptini hedef alan miRNA'ları sistematik olarak tanımlamak ve potansiyel düzenleyici etkileşimleri ortaya çıkarmaktır.

Yöntemler: İnsan miRNA dizileri miRBase (Sürüm 22.1) veri tabanından alınmış ve *FBN1* geninin referans transkripti (RefSeq: NM_000138.5) Ulusal Biyoteknoloji Bilgi Merkezi üzerinden elde edilmiştir. psRNATarget sunucusu kullanılarak *FBN1* ile etkileşime giren miRNA'lar tahmin edilmiştir. En güçlü etkileşime sahip aday miRNA'ların ekspresyon düzeyleri ve hastalıklarla ilişkileri veri tabanları ve literatür taramaları ile değerlendirilmiştir.

Bulgular: Toplamda 2656 insan miRNA'sı analiz edilmiş ve bunlardan 251'inin *FBN1* transkripti ile potansiyel bağlanma bölgeleri olduğu öngörülmüştür. Özellikle hsa-miR-181 ailesi çok sayıda bağlanma bölgesiyle dikkat çekmiştir. Literatür bulguları, bu miRNA ailesinin MFS hastalarında aşağı düzenlendiğini göstermektedir.

Sonuç: Bu çalışma, hsa-miR-181 ailesinin *FBN1* üzerindeki düzenleyici etkisini ortaya koyarak MFS'ndeki potansiyel moleküler mekanizmalara ışık tutmaktadır. Elde edilen bulgular, RNA temelli tedavi yaklaşımları için yeni hedeflerin geliştirilmesinde kullanılabilir.

Anahtar Sözcükler: Marfan sendromu, *FBN1*, mikroRNA, hsa-miR-181, biyoinformatik, gen ekspresyon düzenlemesi

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INTRODUCTION

Marfan syndrome (MFS) is a systemic, autosomal dominant connective tissue disorder with manifestations affecting the skeletal system, eyes, cardiovascular system, and lungs. Clinical hallmarks include aortic aneurysm and dissection, ectopia lentis, scoliosis, and tall stature. The disorder arises primarily from mutations in the *FBN1* gene, which encodes *FBN1*, a structural glycoprotein essential for the formation of elastic fibers in connective tissue (1). Pathogenic variants in *FBN1* result in abnormal microfibril formation and dysregulated transforming growth factor-beta (TGF- β) signaling, contributing to tissue fragility and disease progression (2). In modern practice, healthcare providers use the revised Ghent criteria from 2010 to diagnose related conditions. When there is no positive family history, a diagnosis requires either (i) an aortic-root Z-score of 2 or higher in combination with ectopia lentis, or (ii) an aortic-root Z-score of 2 or higher along with a pathogenic variant in the *FBN1* gene. If a first-degree relative is affected, the criteria are less strict; a diagnosis can be made with either one major sign (such as aortic dilatation or ectopia lentis) or a total score of 7 or higher based on skeletal, craniofacial, and pulmonary features. These guidelines emphasize the importance of *FBN1* genetics while also taking measurable physical signs into account, highlighting the need to explore factors that regulate *FBN1* after it is transcribed (3).

While genetic testing can confirm the diagnosis of MFS, significant variability in phenotype even among individuals with the same *FBN1* mutation suggests the presence of additional regulatory factors (4). In recent years, microRNAs (miRNAs)-short, non-coding RNA molecules that regulate gene expression post-transcriptionally have emerged as key players in disease modulation (5). miRNAs influence diverse biological processes such as extracellular matrix remodeling, apoptosis, and inflammation-hallmarks of cardiovascular pathology in MFS (6,7). Despite advances in understanding *FBN1*-related pathology, systematic investigations into miRNA-mediated regulation of *FBN1* remain scarce (7,8). Previous studies have identified miRNA dysregulation in MFS patients, such as downregulation of hsa-miR-181 in serum samples (6) which may affect aortic wall integrity through modulation of smooth muscle cell behavior (9). Moreover, miRNAs like hsa-miR-143 and hsa-miR-145 have been implicated in the phenotypic plasticity of vascular cells (10), potentially contributing to the progression of aneurysms.

This study aimed to bridge this knowledge gap by applying a bioinformatics pipeline to systematically predict and prioritize miRNAs that target the *FBN1* transcript. By integrating interaction prediction, expression profiling, and disease association data, we highlight key miRNA regulators with potential therapeutic relevance in MFS.

MATERIALS AND METHODS

Figure 1 illustrates a schematic representation of the study workflow employed in this research.

Retrieval of miRNA and mRNA Sequences

Human mature miRNA sequences were downloaded from miRBase (Release 22.1), and the canonical transcript of the human *FBN1* gene (RefSeq: NM_000138.5) was retrieved from the National Center for Biotechnology Information database.

Prediction of miRNA-*FBN1* Interactions

Target prediction was conducted using the psRNATarget web server. The following parameters were used: Maximum expectation = 5.0; HSP length = 19; Seed region = nucleotides 2-13; Mismatches allowed = 2; Penalties: pairing between Guanine and Uracil = 0.5, mismatch = 1.0, opening gap = 2.0, extending gap = 0.5; Bulges in target allowed; Seed weight = 1.5.

Prioritization of Candidate miRNAs

Predicted miRNAs with high binding frequency and complementarity were further analyzed for their expression and disease associations using Human MicroRNA Disease Database (HMDD) v.4.0 v4.0 and literature search.

Statistical Analysis

Descriptive statistics summarized the binding distributions. All computational analysis was performed using R free and open-source software package (version 4.2.0).

RESULTS

Broad Prediction of miRNAs Targeting *FBN1*

Out of 2656 human mature miRNAs analyzed, 251 were predicted to have binding sites on the *FBN1* transcript. The number of binding sites per miRNA varied, with certain families showing enriched targeting.

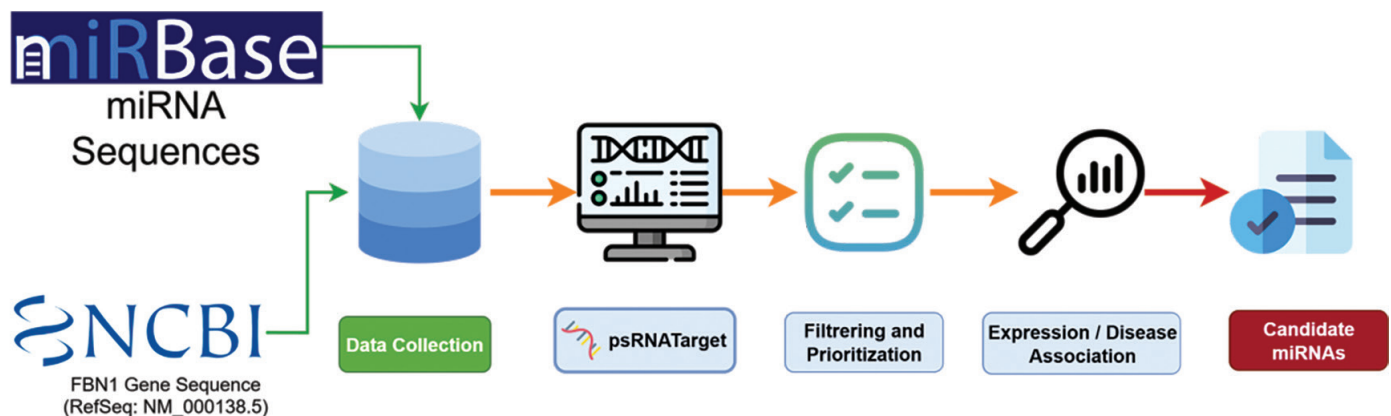


Figure 1. The schema of the study workflow.

NCBI: National Center for Biotechnology Information

The hsa-miR-181 family emerged as particularly prominent, with multiple members exhibiting 10 or more binding interactions with *FBN1* (Table 1 and Figure 2).

High-Confidence miRNA–mRNA Interactions

Table 1 summarizes representative alignments of hsa-miR-181d-5p, hsa-miR-181b-5p, and hsa-miR-181a-5p with distinct regions on the *FBN1* mRNA. These alignments were characterized by high complementarity in the seed regions and occurred in both coding and 3' untranslated regions of the transcript.

Expression Profiles and Disease Associations

Cross-referencing with HMDD v4.0 showed that the hsa-miR-181 family is associated with over 400 disease states, with cardiovascular and connective tissue conditions frequently appearing. Notably, hsa-miR-181d was found to be downregulated in MFS patient plasma samples (6), suggesting its potential involvement in disease modulation. This aligns with prior findings on miRNA dysregulation in aneurysmal diseases (7-9).

DISCUSSION

This study provides a systems-level exploration of miRNAs that may regulate *FBN1*, the primary gene mutated in MFS. Our analysis revealed that members of the hsa-miR-181 family exhibit extensive potential for *FBN1* regulation through multiple high-affinity binding sites, supported by experimental and computational data.

Previous investigations into MFS-related miRNAs have predominantly been candidate-driven, concentrating on select miRNAs or restricted expression panels analyzed in patient blood, or aneurysmal tissues. To date, no study has implemented a comprehensive whole-miRNome screening approach encompassing all 2,656 mature human miRNAs against the canonical *FBN1* transcript. Furthermore, there has been a lack of integration of binding-site density with cross-cohort expression data and disease association meta-analyses. Our methodology, therefore, offers the first systems-level mapping of potential miRNA regulators of *FBN1*, resulting in a prioritized catalogue that can inform targeted experimental validation and facilitate therapeutic development.

Functional Implications of miRNA-*FBN1* Regulation

Given the central role of *FBN1* in maintaining connective tissue elasticity, its post-transcriptional regulation by miRNAs may directly

influence phenotypic severity in MFS. The hsa-miR-181 family has been previously implicated in cardiovascular remodeling, vascular smooth muscle cell apoptosis, and extracellular matrix regulation-pathways relevant to MFS aortopathy (10-12).

Translational Relevance

The miR-181 family demonstrates promising translational potential in human cohorts, potentially offering additional clinical insights beyond conventional *FBN1* genotyping. In a two-stage blood profiling study involving patients with MFS (discovery cohort n=7, validation cohort n=26), Abu-Halima et al. (6) identified a down-regulation of miR-181d-5p, which exhibited an inverse correlation with aortic root Z-scores and left ventricular diameter. This study asserts that these miRNAs are minimally invasive biomarkers for assessing disease severity. Further supporting these findings, a recent serum analysis involving 388 patients with thoracic aortic aneurysm (TAA) established that levels of miR-181b-5p were independently correlated with TAA presence, achieving an area under the receiver operating characteristic curve of 0.82 for differentiating TAA from both coronary artery disease and healthy controls (13). The integration of these findings with established functional connections to extracellular matrix turnover and TGF- β signaling pathways suggests that circulating miR-181 levels could serve to inform: (i) baseline risk stratification, (ii) longitudinal monitoring of aortic dilation, and (iii) the selection of patients for potential miRNA-modulating therapies.

The study's findings support the feasibility of RNA-targeted therapeutics in MFS. Technologies such as antagomirs, miRNA mimics, and lipid nanoparticle-mediated delivery could be leveraged to normalize miRNA expression and rebalance *FBN1* levels. Personalized medicine approaches may incorporate miRNA expression profiling to predict disease progression or treatment response (12-17).

Study Limitation

Predictions were based on in silico data and required experimental validation through reporter assays or transcript knockdown models. To convert our ranked catalog into biologically credible candidates, future work should follow a staged validation roadmap. This process includes (i) molecular confirmation of the highest-affinity binding sites using dual-luciferase assays; (ii) mapping of endogenous

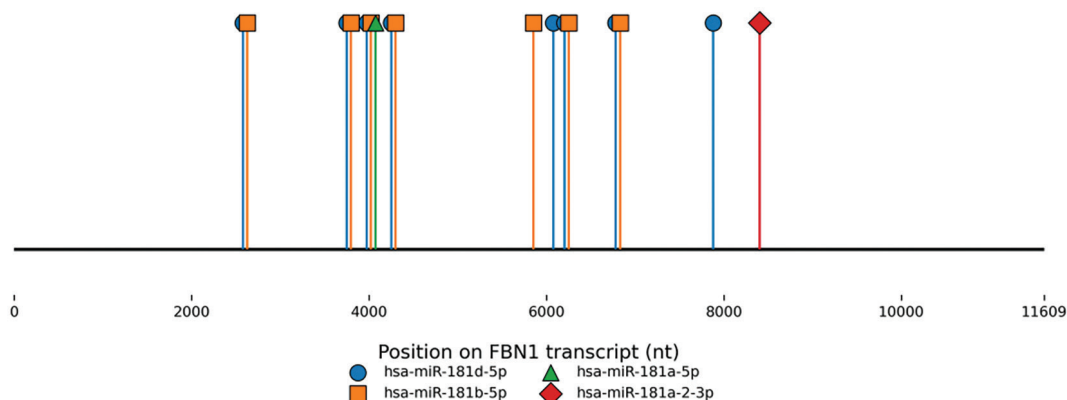


Figure 2. Lollipop plot of miR-181 binding sites on *FBN1*.

Table 1. Predicted binding sites of hsa-miR-181 family members on *FBN1* transcript

miRNA	Alignment
hsa-miR-181d-5p	miRNA 23 UGGGUGGCUGUUGUUACUUACAA 1 . . Target 3772 GUGUAUCGACAUCAUGAAUGUG 3794
hsa-miR-181d-5p	miRNA 23 UGGGUGGCUGUUGUUACUUACAA 1 . . Target 4021 AUGCACCGACAUCGAUGAGUGUG 4043
hsa-miR-181d-5p	miRNA 23 UGGGUGGCUGUUGUUACUUACAA 1 . Target 4273 CUGUACAGACAUCAUGAAUGUG 4295
hsa-miR-181d-5p	miRNA 23 UGGGUGGCUGUUGUUACUUACAA 1 . . . Target 7879 CUGCAUUGAUAAACAUGAAUGCA 7901
hsa-miR-181d-5p	miRNA 23 UGGGUGGCUGUUGUUACUUACAA 1 Target 2602 CUGCGUUGAUUUAAUGAAUGUG 2624
hsa-miR-181d-5p	miRNA 23 UGGGUGGCUGUUGUUACUUACAA 1 . . . Target 6079 CCUUUCUCACAACAUGACUGUA 6101
hsa-miR-181d-5p	miRNA 23 UGGGUGGCUGUUGUUACUUACAA 1 Target 6805 AUGUGUAGAUACUGAUGAAUGUU 6827
hsa-miR-181d-5p	miRNA 23 UGGGUGGCUGUUGUUACUUACAA 1 Target 6226 CUGUGUGGAUAUCAAUGAAUGUC 6248
hsa-miR-181b-5p	miRNA 23 UGGGUGGCUGUCGUUACUUACAA 1 . . Target 3772 GUGUAUCGACAUCAUGAAUGUG 3794
hsa-miR-181b-5p	miRNA 23 UGGGUGGCUGUCGUUACUUACAA 1 . . . Target 4021 AUGCACCGACAUCGAUGAGUGUG 4043
hsa-miR-181b-5p	miRNA 23 UGGGUGGCUGUCGUUACUUACAA 1 . Target 4273 CUGUACAGACAUCAUGAAUGUG 4295
hsa-miR-181b-5p	miRNA 23 UGGGUGGCUGUCGUUACUUACAA 1 Target 2602 CUGCGUUGAUUUAAUGAAUGUG 2624
hsa-miR-181b-5p	miRNA 23 UGGGUGGCUGUCGUUACUUACAA 1 . . . Target 5854 GUGCAAUGAUCGUAUGAAUGUC 5876
hsa-miR-181b-5p	miRNA 23 UGGGUGGCUGUCGUUACUUACAA 1 Target 6805 AUGUGUAGAUACUGAUGAAUGUU 6827
hsa-miR-181b-5p	miRNA 23 UGGGUGGCUGUCGUUACUUACAA 1 Target 6226 CUGUGUGGAUAUCAAUGAAUGUC 6248

Table 1. Continued

miRNA	Alignment
hsa-miR-181a-5p	miRNA 23 UGAGUGGCUGUCGCAACUUACAA 1 . Target 4021 AUGCACCGACAUCGAUGAGUGUG 4043
hsa-miR-181a-2-3p	miRNA 22 CCAUGUCAGUUGCCAGUCACCA 1 Target 8404 CCCAGAGCCACCUGUCAGUGGU 8425

Base pair interactions and alignment sites on the corresponding RNA sequences are shown in the alignment column. “|” indicates matches, “.” shows pairing between Guanine and Uracil

interactions through RT-qPCR or high-throughput sequencing following Argonaute immunoprecipitation; (iii) conducting perturbation studies, such as transient delivery of miR-181 mimics or inhibitors, or clustered regularly interspaced short palindromic repeats editing of seed sites, in vascular smooth muscle and fibroblast models; and (iv) investigating the clinical correlation of circulating miR-181 levels with aortic-root growth in longitudinal cohorts of MFS patients. Although these experimental steps extend beyond the scope of our current computational study, they are crucial next steps for transforming *in silico* predictions into mechanistically and clinically actionable insights.

CONCLUSION

This study offers a comprehensive computational analysis of miRNAs that potentially regulate *FBN1*, the principal gene implicated in MFS. By applying a stringent target prediction approach, we identified members of the hsa-miR-181 family as top candidate regulators with multiple high-confidence binding sites on the *FBN1* transcript. The literature supports the downregulation of these miRNAs in MFS patients, implicating them in the disease's molecular etiology.

These findings reinforce the concept that miRNA-based regulation may significantly influence connective tissue homeostasis and suggest that therapeutic modulation of miRNA expression could serve as a strategy to restore *FBN1* function. Furthermore, the study advocates for integrating miRNA profiling into personalized medicine frameworks, enabling tailored risk assessment and treatment planning in genetically complex disorders like MFS.

Future directions include experimental validation of predicted interactions using luciferase assays, as well as *in vivo* studies to assess the phenotypic consequences of miRNA modulation. These steps are critical to translating the current findings into clinical applications.

Ethics

Ethics Committee Approval: This study did not require ethical approval because it is entirely based on the analysis of publicly available datasets. No experiments involving humans, animals, or the use of personally identifiable information were performed.

Informed Consent: Not applicable, as no individual persons' data are included in this manuscript.

Footnotes

Authorship Contributions

Concept: M.E.O., Y.M.D., M.D.S.D., Design: M.D.S.D., Data Collection or Processing: M.E.O., Y.M.D., M.D.S.D., Analysis or Interpretation: M.E.O., Y.M.D., M.D.S.D., Literature Search: M.E.O., Y.M.D., M.D.S.D., Writing: M.E.O., Y.M.D., M.D.S.D.

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Comparative Evaluation of Large Language Models in Addressing Autism-Related Information Queries: Insights from ChatGPT, Gemini, and Copilot

Otizm ile ilişkili Soruları Yanıtlamada Büyük Dil Modellerinin Karşılaştırmalı Değerlendirilmesi: ChatGPT, Gemini ve Copilot'tan Elde Edilen Bulgular

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ABSTRACT

Objective: While large language models (LLMs) have been increasingly evaluated for medical inquiries, their responses to questions about autism spectrum disorder (ASD) remain underexplored. This study aims to evaluate and compare four publicly available LLMs—ChatGPT-3.5, ChatGPT-4.0, Google Gemini, and Microsoft Copilot—regarding autism-related queries.

Methods: Nineteen frequently asked autism-related questions categorized into symptoms, diagnosis, treatment, and general information. The responses from each LLM were evaluated by three child and adolescent psychiatrists using the patient education materials assessment tool and the Global Quality Score. Thematic analysis was conducted to identify key topics. A majority consensus approach determined the final ratings, and sentiment analysis was performed to assess emotional polarity and subjectivity.

Results: ChatGPT-4.0 demonstrated superior overall response quality compared to Microsoft Copilot and Google Gemini ($p=0.006$, $p=0.009$). While the overall understandability of responses was similar across all LLMs, ChatGPT-4.0 scored significantly higher than Microsoft Copilot on the content subscale ($p=0.026$), and Google Gemini outperformed ChatGPT-4.0 in word choice and style ($p=0.041$). Thematic analysis revealed that all chatbots emphasized early diagnosis and behavioral issues. Sentiment analysis indicated a high degree of objectivity across all models. Google Gemini displayed the highest polarity score (0.115),

ÖZ

Amaç: Büyük dil modellerinin (large language models, LLM'ler) tıbbi sorulara verdikleri yanıtlar gün geçtikçe daha fazla araştırılmaktadır; ancak, bu modellerin otizm spektrum bozukluğu (OSB) ile ilgili sorulara verdikleri yanıtlar literatürde yeterince incelenmemiştir. Bu çalışma, otizmle ilişkili sorulara verdikleri yanıtlar açısından dört genel erişime açık LLM'i — ChatGPT-3.5, ChatGPT-4.0, Google Gemini ve Microsoft Copilot — değerlendirmeyi ve karşılaştırmayı amaçlamaktadır.

Yöntemler: Otizmle ilişkili sık sorulan on dokuz soru; belirtiler, tanı, tedavi ve genel bilgi olmak üzere dört kategoriye ayrılmıştır. Her bir LLM'nin yanıtları, üç çocuk ve ergen psikiyatristi tarafından Hasta Eğitimi Materyalleri Değerlendirme Aracı ve Küresel Kalite Skoru kullanılarak değerlendirilmiştir. Tematik analiz ile temel konular belirlenmiş; çoğunluk görüşü yaklaşımıyla nihai puanlar oluşturulmuştur. Duygu analizi, yanıtların duygusal kutupluluğunu ve öznellik düzeyini incelemek amacıyla gerçekleştirilmiştir.

Bulgular: ChatGPT-4.0, genel yanıt kalitesi açısından Microsoft Copilot ve Google Gemini'ye kıyasla üstün performans göstermiştir ($p=0.006$, $p=0.009$). Yanıtların genel anlaşılabilirliği tüm modeller arasında benzer bulunmakla birlikte, ChatGPT-4.0 içerik alt ölçeğinde Microsoft Copilot'tan anlamlı derecede yüksek puan almıştır ($p=0.026$). Buna karşılık, Google Gemini kelime seçimi ve üslup açısından ChatGPT-4.0'dan daha iyi performans göstermiştir ($p=0.041$). Tematik analiz büyük dil modellerinin erken tanı ve davranışsal sorunlara vurgu

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while subjectivity scores were moderately high across all chatbots, with ChatGPT-4.0 exhibiting the highest subjectivity score (0.452).

Conclusion: This study highlights the potential of LLMs, particularly ChatGPT-4.0, to deliver high-quality and easily understandable information regarding ASD. However, given the limitations of LLMs, including their susceptibility to biases and lack of real-world reasoning, further research is needed.

Keywords: Autism spectrum disorder, large language models, artificial intelligence, ChatGPT, Gemini, Copilot

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social communication and interaction and restrictive, repetitive patterns of behavior, activity or interests (1). Receiving the diagnosis of ASD can have negative effects on the entire family system, which includes the need for new skills in adjustment, coping, advocacy, and seeking services for the child (2).

After a diagnosis, parents may experience different stages of emotions, such as shock, fear, grief, and guilt (3). These emotional responses and complexities of the process highlight the considerable challenges faced by parents in caring for individuals with ASD.

Recent years have seen a marked rise in the prevalence of ASD. For example, between 2016 and 2020, prevalence rates rose from one in fifty-four children aged eight years to one in thirty-six (4). This growing prevalence has created a greater demand for mental health services. But there is an inadequate number of qualified mental health professionals and limited infrastructure, leaving families with relatively few available resources (5). As a result, many parents focus on finding solutions and seeking help for their children diagnosed with autism (6).

The process of looking for information on ASD and its management is often described as challenging by parents (7). Several studies suggest that when looking for information and support, parents first seek help from their own social networks (8). Nevertheless, despite these efforts, a variety of parents have noted stigma from their neighboring communities, or have even blamed themselves and other relatives for their child's behavior (9). Such social dynamics can weaken broader support networks and increase feelings of isolation (10,11). This dynamic also makes it even more difficult to access medical support for autism, and pushes caregivers toward alternative ways of gaining information.

The internet has increasingly become a vital resource for families seeking information about ASD and other neurodevelopmental conditions. This trend correlates with the rising prevalence of ASD and the increasing number of online platforms such as social media and online communities (2,12). Online information can be of variable reliability and accuracy, raising questions about the overall quality control of available resources (13). This has increased the need for several online platforms to share trustworthy and easily accessible information with parents (14).

In recent years, machine learning and artificial intelligence (AI) have been increasingly integrated into many aspects of daily life. This

yaptığını ortaya koymuştur. Duygu analizi sonuçları, tüm modellerde yüksek düzeyde nesnellik sergilendiğini göstermiştir. Google Gemini en yüksek kutupluluk skoruna (0,115) sahipken, öznellik puanları tüm modellerde orta-yüksek düzeyde bulunmuş, ChatGPT-4.0 en yüksek öznellik skorunu (0,452) göstermiştir.

Sonuç: Bu çalışma, özellikle ChatGPT-4.0'ın, OSB hakkında yüksek kaliteli ve kolay anlaşılabilir bilgiler sunma potansiyeline sahip olduğunu ortaya koymaktadır. Bununla birlikte, LLM'lerin önyargılara yatkın oluşu ve gerçek hayata uygun akıl yürütme eksikliği gibi sınırlılıkları göz önüne alındığında, bu alanda daha fazla araştırmaya ihtiyaç vardır.

Anahtar Sözcükler: Otizm spektrum bozukluğu, büyük dil modelleri, yapay zekâ, ChatGPT, Gemini, Copilot

integration has made significant progress in the healthcare sector, evidenced by the use of chatbots to facilitate easy access to medical information for individuals (15). Large language models (LLMs) have advanced significantly from conventional natural language processing (NLP) models, introducing innovative capabilities in healthcare services. One of the most popular examples of LLMs is ChatGPT. GPT has evolved considerably since it was introduced in 2018, with the latest model as of March 2023 being GPT4. In addition to ChatGPT, other AI-powered chatbots, such as Google Bard and Microsoft Copilot, are also integrated into several services (16).

LLMs have orders of magnitude more parameters than earlier models. Combined with self-supervised learning on vast datasets, this enables models to generate more human-like responses. These models have introduced innovative approaches to addressing medical inquiries, facilitating computer-aided diagnosis, recommending treatment, and providing health education (16-19). Moreover, they have the ability to inform patients about any health-related issues, answer inquiries relating to health maintenance and disease prevention, as well as provide insights into how social and environmental determinants affect an individual's own health (20,21).

A recent study found that almost 80% of participants (n=607) considered using ChatGPT for self-diagnosis (22). This implies that people turn to chatbots such as ChatGPT to learn more in the health domain, especially symptoms, diagnosis, and treatment. Given that many parents are often not well equipped with knowledge and experience in dealing with ASD, these chatbots serve as a useful and easily available source of information.

Unfortunately, the information obtained from these technologies is not perfect. LLMs have a diversity of major shortcomings, including biases in the training data, the ability to produce disinformation, and a lack of true reasoning capabilities (23,24). A recent study indicated that while ChatGPT demonstrated potential regarding accuracy, comprehensiveness, and speed in clinical psychiatry, it also revealed shortcomings in pharmaceutical information. The shortfall was attributed to ChatGPT's training being predominantly based on web-based information rather than textbooks in the field (25). Hence, it is vital to understand both the pros and cons of these technologies to ensure that they are used efficiently and reliably. For this reason, there is a need for academic research that evaluates the quality of the information provided by such technologies.

The use of LLMs in the healthcare emphasizes how important it is for these systems to respond in a language that is not just clear and understandable, but also non-stigmatizing, empathetic and human-

like the one used by health providers. Previous research examining chatbot responses to health-related questions has shown that they can exhibit empathy and provide accurate answers (26). However, other studies indicate that even LLMs with advanced NLP capabilities may not completely and accurately represent empathy (27,28).

In another study, Spallek et al. (24) examined the accessibility, impartiality, and potential presence of stigmatizing or incorrect language in the outputs of ChatGPT-4. The findings indicated that while the first outputs of ChatGPT-4 were commendable and potentially practical, they still exhibited certain accessibility issues, occasionally employed stigmatizing language, and lacked a diverse array of supportive evidence. These results point to the dangers of LLMs in language use. Accordingly, there is a risk of misguiding or stigmatizing individuals if the language is incorrect or insensitive. These risks are particularly exacerbated in the case of autism-related questions as language has a critical role in shaping attitudes and beliefs about autism (29). Recent studies by the autism research community emphasize the importance of language use in influencing public understanding of autism and related risks (30). Hence, the choice of terminology to characterize autism, particularly the language favored when discussing autistic persons, is crucial in shaping definitions, attitudes, and stigma (31). Consequently, a thorough qualitative assessment of the manner in which AI chatbots handle nuanced and sensitive language when formulating responses to questions about autism is essential for their effective use.

Over the past years, studies have been published on LLMs and their responses to common questions asked in a variety of medical disciplines including cirrhosis, dementia, migraines, uro-oncology, head and neck surgery and vision disorders (14,32-35). However, the exploration of LLM responses to caregivers' frequently asked questions about individuals with neurodevelopmental disorders is not well documented. In this area, McFayden et al. (36) conducted a study assessing the quality of responses given by ChatGPT-4, a widely used AI chatbot, to questions related to ASD. In general, the study showed that ChatGPT-4 was able to generate accurate, concise and easy-to-understand content. However, the study also highlighted areas for improvement, especially with respect to the actionability of the knowledge gained.

To interpret these findings accurately and generalize further, there is a need for research evaluating how well AI systems can answer autism-related frequently asked questions. Investigation of the effectiveness of other AI chatbots like Google's Gemini or Microsoft's Copilot in answering autism-related questions could also help bridge the gap in the literature.

In this study, we evaluate and compare four publicly available LLMs: OpenAI's ChatGPT-3.5 and GPT-4.0 models, Google's Gemini, and Microsoft's Copilot on frequently asked autism-related questions. We then rate each chatbot's responses on understandability and quality based on previously established standards. Furthermore, we conduct qualitative analyses to assess the thematic nature and emotional polarity of the responses generated by the chatbots. Results of these analyses would help understand potential advantages and disadvantages of using AI-powered tools to answer autism-related questions. The study is expected to pave the way for a more comprehensive understanding of how health communication shapes the role and impact of AI-powered chatbots.

MATERIALS AND METHODS

Procedure

The question database was created from informational materials published by organizations such as the American Academy of Child and Adolescent Psychiatry (AACAP), the International Association for Child and Adolescent Psychiatry and Allied Professions, and the European Society for Child and Adolescent Psychiatry. To ensure representation of public and patient concerns, frequently asked questions about ASD from Google Trends were also added to the database. Questions that were repetitive or did not contain medical information were excluded from the study. The questions were categorized into four topics: symptoms, diagnosis, treatment, and general information (Table 1). Grammar corrections were made to ensure clarity and readability. The 19 questions created were directed to ChatGPT-3.5, ChatGPT-4.0, Google Gemini, and Microsoft Copilot in English on April 2, 2024, World Autism Awareness Day. The responses were collected and analyzed using new accounts with no previous activity. If parents did not ask the same question twice, a response was requested for each question only once. Each response was independently rated by three child and adolescent psychiatrists with clinical experience in ASD using the Global Quality Score (GQS) and patient education material assessment tool (PEMAT). The medical accuracy of the responses was evaluated according to the AACAP guidelines. As there were no patients involved in the study, ethical approval was not required.

Measures

Global Quality Score

The GQS is a scale designed as an evaluation tool for online sources. The lowest score is 1 ("poor quality, poor flow of the site, most information missing, not at all useful for patients"), and the highest score is 5 ("excellent quality and excellent flow, very useful for patients"). Researchers use this scale to assess the flow, usability, and quality. A score of 4 or 5 is considered high quality, a score of 3 is considered moderate quality, and scores of 1 or 2 are considered low quality (29).

The Patient Education Materials Assessment Tool

The PEMAT was developed by Shoemaker et al. (37) in 2014 to evaluate the understandability and actionability of print and audiovisual patient education materials. PEMAT uses an inventory of both desirable and undesirable features of patient education materials to generate separate scores for comprehensibility and usability, ranging from 0 to 100. Each item on the scale is evaluated with a score of 0 (disagree) or 1 (agree), and some items have a third option, "no assessment", if applicable.

Table 1. Sample questions from each category

Topics	Sample questions
Symptoms	"What are some symptoms of autism that parents and caregivers can look for?"
Diagnosis	"How do health care providers diagnose autism?"
Treatment	"Are there treatments available for autism?"
General information	"How common is autism?"

PEMAT has two versions: PEMAT-P for print materials and PEMAT-A/V for audiovisual materials. In our study, PEMAT-P was used for evaluation. PEMAT-P includes 17 items for measuring understandability and 7 items for assessing actionability. Since the materials we evaluated and our study objectives do not focus on assessing any action, we planned to use only the 17 items related to understandability. The items in the scale are divided into six categories: content (e.g., “this material makes its purpose completely evident”), and word choice and style (e.g., “the material uses common, everyday language”), use of numbers (e.g., “numbers appearing in the material are clear and easy to understand”), organization (e.g., “the material presents information in a logical sequence”), layout and design (e.g., “the material uses visual cues to draw attention to key points”), and use of visual aids (e.g., “the material’s visual aids have clear titles or captions”). The validity and reliability of the Turkish version of the assessment tool were established by Paylan Akkoç and Orgun (38) in 2020.

Statistical Analysis

Statistical analyses were implemented using SPSS version 28. The sum of the scores from the three researchers represented the total scores for each question. The mean total scores of the questions in general and each categorized topic were compared between the four Chatbots. The continuous variables were analyzed using one-way ANOVA. Post-hoc comparisons were conducted using the Bonferroni-corrected t-tests. The findings of the variables were expressed as mean and standard deviation. Statistical significance was considered $p < 0.05$.

RESULTS

Without categorizing by topic, there was a significant difference in word count between Gemini (197.47) and ChatGPT-3.5 (290.26) ($p=0.009$), as well as between Gemini (197.47) and ChatGPT-4 (306.74), ($p=0.001$) (Figure 1). Although no significant differences were found between the groups in terms of overall PEMAT understandability percentages, significant differences emerged when evaluating PEMAT subscale scores (Table 2). Specifically, content scores differed significantly between Microsoft Copilot (4.58) and ChatGPT-4 (5.68) ($p=0.026$.) Likewise, word choice and style scores showed a significant difference between Gemini (8.00) and ChatGPT-4 (6.21) ($p=0.041$). No significant differences were observed between the groups in the remaining PEMAT subscales. GQS differed significantly between Microsoft Copilot (9.11) and ChatGPT-4 (12.16) ($p=0.006$), as well as between Gemini (9.26) and ChatGPT-4 (12.16) ($p=0.009$), (Figure 2).

For the general information category, the only noteworthy difference observed was in word choice and style scores, with Gemini (9) outperforming ChatGPT-4 (6) ($p=0.20$). In the diagnosis category, GQS differed significantly between Microsoft Copilot (6.40) and ChatGPT-3.5 (11.20), ($p=0.009$), as well as between Microsoft Copilot (6.40) and ChatGPT-4 (12.80), ($p<0.001$).

There were no differences in the category of symptoms or treatment questions.

The analysis of the responses from chatbots (ChatGPT-3.5, ChatGPT-4.0, Google Gemini, and Microsoft Copilot) regarding common autism-related question themes is visualized in Figure 3. This stacked bar chart illustrates the contribution of each AI chatbot to the various identified themes, based on the frequency of relevant

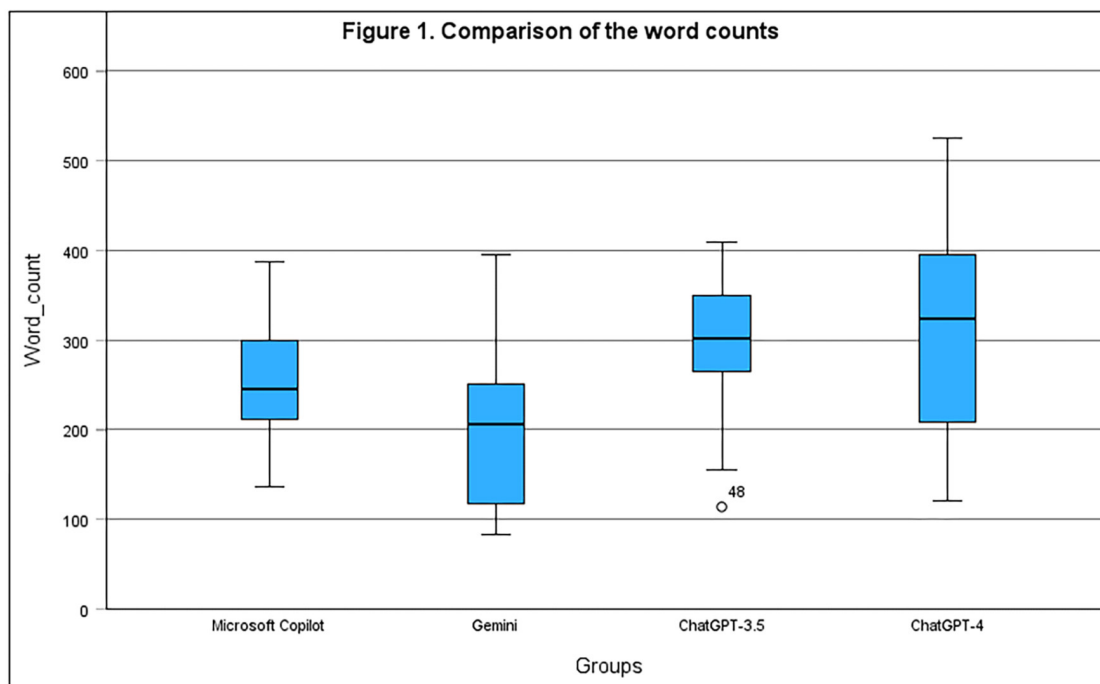


Figure 1. Comparison of word counts of answers to questions about ASD between chatbots.

ASD: Autism spectrum disorder

keywords. Each bar represents a theme, with different colors indicating the contributions from each chatbot. The total frequency of each theme is also labeled on the right of the bars.

Frequency distribution of content generated by four AI chatbots (GPT-3, GPT-4, Gemini, and Co-Pilot) across eight autism-related themes: early diagnosis, social challenges, communication difficulties, behavioral issues, intervention strategies, parental support, educational support, and therapeutic approaches. Values represent the number of chatbot responses assigned to each theme.

Table 3 below summarizes the themes identified from the responses to common autism-related questions. Each theme is associated with specific keywords, and the table indicates how frequently these keywords appear in the responses of each chatbot.

The sentiment analysis was conducted on the responses to common autism-related questions from ChatGPT-3.5, ChatGPT-4.0, Google

Gemini, and Microsoft Copilot. The analysis aimed to determine the overall emotional tone of the responses by calculating average polarity (indicating positive or negative sentiment), and subjectivity (indicating the degree of personal opinion). Polarity scores range from -1 to 1, where -1 indicates a very negative sentiment, 0 indicates a neutral sentiment, and 1 indicates a very positive sentiment. The average polarity scores for all participants are slightly positive, indicating that the responses generally convey a positive sentiment towards the topics discussed. Subjectivity scores range from 0 to 1, where 0 indicates a fact-based response and 1 indicates a highly subjective or opinion-based response. The average subjectivity scores are moderately high, suggesting that the responses contain a mix of objective information and personal opinions or interpretations.

Table 2. Comparison of mean scores of PEMAT across groups using one-way ANOVA

Mean (SD)	Microsoft Copilot	Gemini	ChatGPT-3.5	ChatGPT-4	F	p-value	η_p^2
Understandability percentage	79.53 (10.46)	82.16 (9.50)	77.84 (9.30)	75.79 (9.72)	1.45	0.235	0.06
Content	4.58 (1.78)	5.21 (1.18)	5.53 (0.91)	5.68 (0.48)	3.25	0.026*	0.12
Word choice and style	6.63 (2.03)	8.00 (1.67)	6.58 (1.58)	6.21 (2.68)	2.83	0.044*	0.11
Use of numbers	4.42 (1.54)	4.26 (1.52)	3.63 (1.26)	4.26 (1.52)	1.09	0.361	0.04
Organization	8.74 (1.94)	7.89 (2.64)	7.95 (1.39)	7.68 (1.80)	1.02	0.390	0.04
Layout and design	2.84 (0.69)	2.53 (1.12)	2.21 (1.36)	2.05 (1.43)	1.65	0.185	0.06

*Post-hoc comparisons were conducted using the Bonferroni-corrected post-hoc t-tests. All error bars represent s.e.m. Significant results are bolded ($p < 0.05$). PEMAT: Patient education material assessment tool, SD: Standard deviation

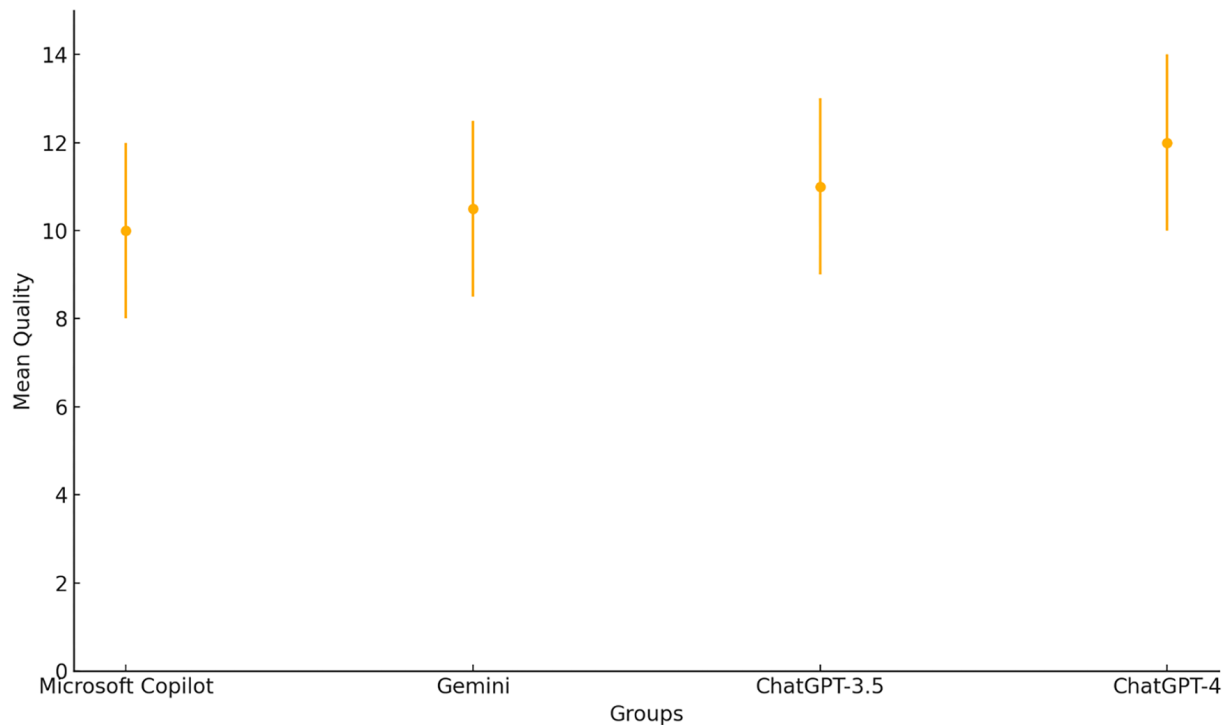


Figure 2. Comparison of Quality Scores of answers to questions about ASD between chatbots. Error bars represent 95% confidence intervals.

ASD: Autism spectrum disorder

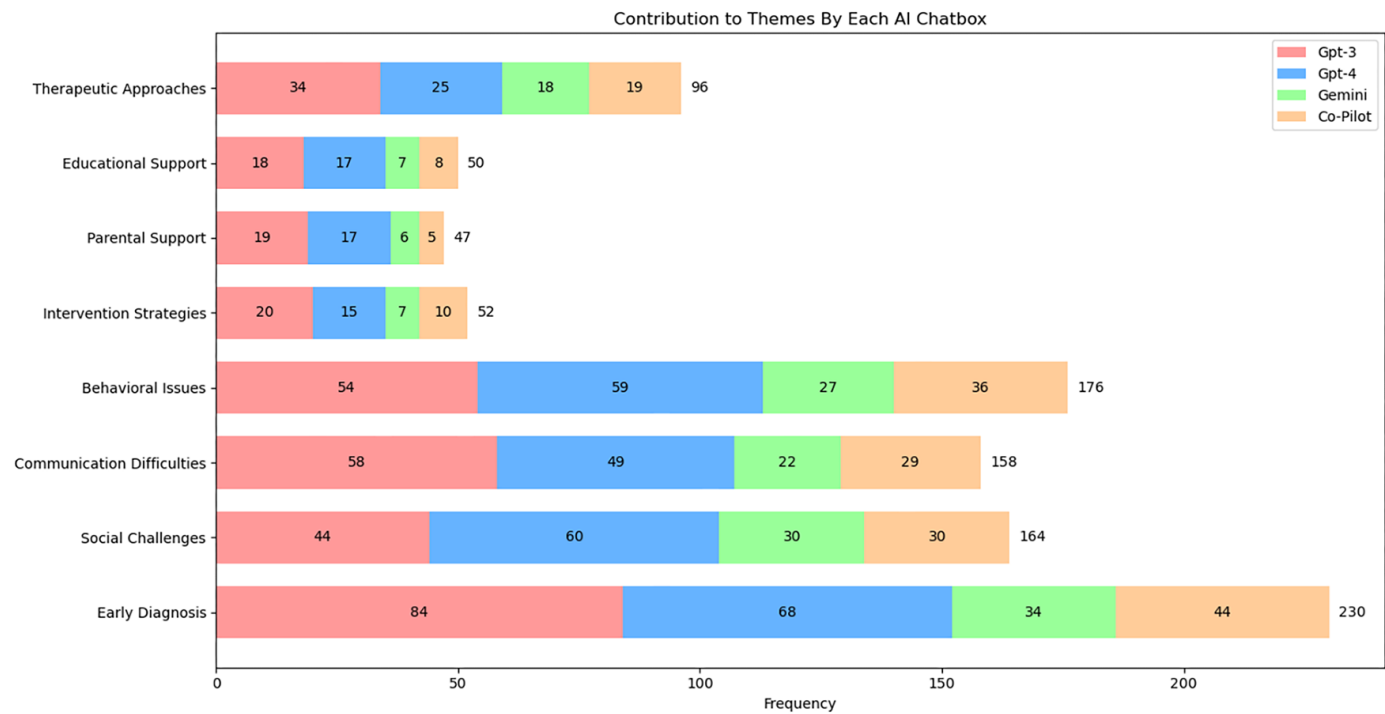


Figure 3. Themes and contribution to themes by each AI chatbot.
AI: Artificial intelligence

Table 3. Theme analysis by chatbots

Theme	Keywords	Frequency	ChatGPT-3	ChatGPT-4	Gemini	Copilot
Early diagnosis	Early, diagnose	230	84	68	34	44
Social challenges	Social	164	44	60	30	30
Communication difficulties	Communication	158	58	49	22	29
Behavioral issues	Behavior	176	54	59	27	36
Intervention strategies	Intervention, therapy	61	20	15	7	10
Parental support	Parent	47	19	17	6	5
Educational support	School, education	50	18	17	7	8
Therapeutic approaches	Therapy	96	34	25	18	19

Table 4. Polarity analysis of chatbots

AI chatbot	Polarity	Subjectivity
ChatGPT-3.5	0.092	0.442
ChatGPT-4.0	0.088	0.452
Gemini	0.115	0.436
Microsoft Copilot	0.088	0.446

AI: Artificial intelligence

DISCUSSION

This study analyzed the responses of several prominent chatbots, including ChatGPT-3.5, ChatGPT-4.0, Microsoft Copilot, and Google Gemini, to the most frequently asked questions regarding ASD. While the overall understandability scores, evaluated using the PEMAT tool, were comparable among chatbots, notable disparities were observed in the subscales of content, word choice, and style. While ChatGPT achieved a significantly higher score than Microsoft Copilot in the content subscale, Gemini also outperformed ChatGPT in word choice and style. ChatGPT had much better overall quality ratings compared to Microsoft Copilot and Gemini. Moreover, a thematic analysis of the AI-driven chatbot's written responses revealed that issues associated with "early diagnosis" were the most frequently emphasized. Sentiment analysis of responses from various chatbots consistently revealed a high degree of objectivity, with minimal polarity of emotions and a consistent neutral stance. The findings underscore the potential of AI systems to provide understandable and high-quality information, particularly regarding ASD, for individuals seeking such information. Nevertheless, this potential is not without its constraints. To the best of our knowledge, this study is the first to evaluate the responses generated by widely used chatbots to frequently asked questions about autism using both quantitative and qualitative methods. Furthermore, the data for this study was collected on world autism awareness day aims to raise awareness about autism from a different perspective.

In our study, the understandability scores assessed through 17 items on the PEMAT revealed that all chat bots demonstrated similar scores, generally producing comprehensible responses. These results are consistent with the study by McFayden et al. (36) on the responses of ChatGPT-4.0 to autism inquiries, which found similar understandability. Notwithstanding similar levels of understandability, ChatGPT-4.0 outperformed Microsoft Copilot in terms of the content subscale, while Google Gemini achieved higher scores than ChatGPT-4.0 in terms of word choice and style, subscale. This indicates that although overall understandability is similar, there are notable differences in the depth of content and linguistic precision each platform offers. Thus, our study, by evaluating not only ChatGPT but also other commonly used LLMs, enables a more comprehensive understanding of the relative strengths and weaknesses of these models in the dissemination of ASD-related health information. This study adds to the growing body of evidence indicating that in poorly resourced settings, AI-driven tools could have potential application for public health education, especially in scenarios where access to professional healthcare is compromised.

Among the evaluated AI-driven chatbots, ChatGPT-4.0 consistently stood out by providing responses to common ASD-related questions, and achieved the highest average overall quality score, with statistically significant differences compared to Microsoft Copilot and Google Gemini. These findings align with previous studies, which also emphasized GPT-4.0's superiority in radiological decision-making and its responses to myopia-related queries (34,39). Other studies have further highlighted GPT-4.0's reliability and depth in addressing complex medical conditions, supporting the potential of this technology in disseminating medical information (40).

The current variability in performance within LLMs, such as ChatGPT-4, Google Gemini, and Microsoft Copilot, is primarily due to

architectural differences and the datasets these models have been exposed to. A few other reasons contribute to better performance in ChatGPT-4, especially in giving high-quality and more detailed responses regarding ASD. The difference between GPT-4 and the older versions, such as GPT-3.5, is that it has many more parameters and makes use of much more advanced transformer architectures (41). This means it will be able to learn even more complicated patterns in language and then reproduce them, thus giving more subtle and contextually appropriate answers, especially in medical contexts. Apart from that, GPT-4 has undergone extensive fine-tuning, especially by Reinforcement Learning from Human Feedback, which enhances its potential for responses in line with human-like values of empathy; fine-tuning is useful, especially in sensitive topics such as autism, where it is imperative to consider tone and factual accuracy. Other models such as Google Gemini and Microsoft Copilot, however, though very powerful with respect to general tasks, have not been as thoroughly fine-tuned in domain-specific contexts like healthcare. While Google Gemini does a good job in terms of choosing words and style, its interest seems more in linguistic refinement than the actual content accuracy observed with GPT-4 (42). Domain-specific knowledge integration likely varied during training. Microsoft's Copilot is also not well-suited for medical guidance, for which it is not optimized; it is more biased toward tasks and code-driven applications. These architectural differences affect information quality, especially in specialized domains like ASD. Similar significant values associated with these findings indicate that domain-specific training and fine-tuning of LLMs for practical applications is mandatory, especially in healthcare, where accuracy, empathy, and contextual relevance of responses remain critical (41).

Considering the rising incidence of ASD worldwide (4), the gross inadequacy of mental health professionals, especially in low- and middle-income countries (5), as well as ongoing stigma against neurodevelopmental disorders like ASD (9,11,43), our results indicate that AI-chatbots could be pivotal in addressing these needs. Specifically, ChatGPT-4.0's ability to provide detailed and comprehensible information can be highly beneficial in closing the knowledge gap for families and healthcare providers, especially in regions with limited access to mental health services. However, it is important to note from our findings, that ChatGPT-3.5 also demonstrated comparable performance to ChatGPT-4.0 in responding to common ASD-related questions. For lower-middle-income countries, where access to more advanced models like ChatGPT-4.0 could be heavily restricted by monetary barriers, ChatGPT-3.5 might even be considered a relatively cheap alternative. This provides a reminder to evaluate both the cost and performance factors when considering AI-driven technologies to achieve healthcare access parity across socioeconomic contexts. Future studies should investigate the adaptation of these tools in clinical practice, within regions where health care access is challenging, and understanding outcomes on a real-world basis, including patient-reported benefits, while also exploring increasing information dissemination.

In the results by category, both ChatGPT-3.5 and ChatGPT-4.0 had statistically higher overall quality scores for the "diagnosis" compared to those of other chatbots. This finding is particularly important because families often seek information at critical moments when their child has either been diagnosed with ASD or when they suspect ASD (44). In these circumstances, access to reliable and accurate

diagnostic information is essential. Early diagnosis significantly minimizes the delay in intervention, thereby enhancing the long-term developmental outcomes for children with ASD (45). Thus, inaccurate data and ambiguity in sources can lead to considerable delays in the diagnostic process (46). In the context of ASD where early diagnosis and intervention are key to better outcomes, having accurate and understandable information widely available is incredibly important. As a consequence, if patients or caregivers utilize poorly structured or deceptive advice based on information retrieved from AI-driven chatbots or other online sources, patients and caregivers may be left confused, which might impede them from reaching crucial medical consultation. This highlights the need for AI systems not only to provide accurate, but also understandable medical content that directs users to proper clinical care. Thus, it is advisable that chatbots maintain updates of their diagnostic data and use technologies that provide readability to this available information so that they provide accurate information and make their users interact accordingly. Future research should explore how these AI-powered tools can be optimized to provide more specific and context-based information for both families and professionals.

A thematic analysis of the responses generated by AI-powered chatbots identified “early diagnosis” as the most frequently emphasized keyword, underscoring the critical importance of early intervention in ASD. The existing literature extensively documents that early diagnosis, by enabling timely and effective interventions, can significantly improve developmental outcomes (47). As such, it has become a fundamental theme for families seeking information regarding ASD (44). The prominence given to early diagnosis by ChatGPT-3.5 and ChatGPT-4.0, compared with other chatbots, reflects a notable strength of these models. It is recommended that other chatbots, particularly Microsoft Copilot and Google Gemini, prioritize integrating early diagnosis into their content to enhance the effectiveness of public health messaging.

In addition to early diagnosis, other key themes identified included social challenges and communication difficulties. ChatGPT-4.0 placed greater emphasis on social challenges, whereas ChatGPT-3.5 had a greater focus on communication difficulties, reflecting the necessity of targeted interventions in these core areas of ASD. These findings suggest that AI-powered chatbots not only provide general information but can also be optimized to offer more specific and contextual guidance regarding the distinct challenges faced by individuals with ASD and their families.

Behavioral issues also emerged as a critical theme, highlighted by the contributions of both ChatGPT-4.0 and ChatGPT-3.5. This emphasizes the importance of behavioral interventions in the effective management of behaviors associated with autism. The ability of these chatbots to recognize the variability in ASD symptoms is particularly significant, aligning with the current clinical understanding that no two individuals with autism present identical behavioral profiles (48). This recognition underscores the necessity for personalized therapeutic approaches in the diagnosis and treatment of individuals with ASD.

Furthermore, intervention strategies and therapeutic approaches were identified as salient themes, with ChatGPT-3.5 demonstrating superior performance in discussions of various therapeutic interventions. The emphasis on therapeutic approaches is

particularly relevant, as individualized therapies—whether applied behavior analysis, medication, cognitive therapy, or sensory-based—are crucial for addressing the specific needs of individuals with ASD (49,50). Parental and educational support, extensively recognized in the literature as essential components in the effective management of autism, further enhances the value of the information generated by these chatbots.

Sentiment analysis indicated that nearly all chatbots employed a neutral, objective emotional tone when their polarity and subjectivity were measured. The results are both predictable and acceptable, given that the study evaluated chatbot responses related to health conditions. This serves as a crucial reminder to provide health education based on objective and factual information, particularly in discussions regarding clinical conditions such as ASD (51). This resource will assist families navigating the complex and emotionally burdening process of ASD by providing accurate and impartial information to empower them. The relatively high subjectivity scores may stem from the nature of LLMs’ training data, which largely consists of human-authored, interpretive texts rather than strict clinical guidelines. Additionally, the responses of the models are not presented in a formal academic format but instead adopt an explanatory style for general audiences, which inherently incorporates more interpretive language.

There are several limitations that should be considered when interpreting the findings of our study. First, LLMs are dynamic systems that continually update their data and adjust their responses based on user interactions. As a result, the responses analyzed in our study may differ from those generated before or after when the questions were asked. This makes it harder to maintain chatbots’ output consistently over time, especially when additional information is included in their databases. Future work can study what impact these updates have on the quality and accuracy of answers, especially for urgent health-related questions. Second, we attempted to capture a broad sample by aggregating questions across platforms, but the questions included may not cover all possible concerns that families have in practice. The same applies in the scenario of ASD, which is also context-specific because there may be different concerns depending on individual cases and family dynamics. Investigators should aim to enhance the generalizability of their data by including additional sources of feedback, such as caregivers, as well as clinicians, in future studies. Lastly, yet the questions were posed in English, therefore making it difficult to generalize our findings to non-English-speaking populations. The language in which a chatbot response is formulated can have a major impact on its clarity, and the effectiveness of these mechanisms requires further research depending on the cultural and linguistic contexts. This is particularly relevant in areas with poor health services and the promotion of information on healthcare, which could be a key role for chatbots. This limitation must be mitigated to understand the potential generalizability of LLMs as global health information aids.

In conclusion, our study presented an evaluation of responses to frequently asked questions about ASD using four of the most used AI-powered chatbots. The responses were rated similarly on overall understandability across all chatbots but varied on two sub-dimensions: content and word choice. When assessed in terms

of overall response quality, ChatGPT-4.0 demonstrated superior performance compared to Microsoft Copilot and Google Gemini. As AI increasingly influences the dissemination of health content, it becomes essential that the information provided by these platforms is both accurate and precise. For effective delivery of health tools to the public, it is essential that chatbots offer real-time, scientifically grounded health information. The next step involves evaluating the enduring efficacy of AI-driven chatbots and investigating whether modifications in machine learning models result in enhanced information quality. It is necessary to evaluate the usability of these tools across various languages and cultures. This is essential for understanding the potential impact of AI on global health challenges and for addressing inequities in access to health information.

Ethics

Ethics Committee Approval: Since our study was not a study involving humans and animals, ethics committee approval was not required.

Informed Consent: Patient consent was not required.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.D., C.D.H., Concept: D.B., A.Ö., Design: D.B., A.Ö., Data Collection or Processing: G.D., M.S., C.D.H., Analysis or Interpretation: M.S., D.B., A.Ö., Literature Search: G.D., C.D.H., Writing: G.D., C.D.H.

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Relationship Between Idiopathic Granulomatous Mastitis and ABO Blood Groups

İdiyopatik Granülomatöz Mastitis ve ABO Kan Grupları Arasındaki İlişki

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ABSTRACT

Objective: This study aimed to evaluate whether the A, B and O blood groups (ABO) subgroup distribution of patients with idiopathic granulomatous mastitis (IGM) is different or not differs from that of the general population.

Methods: The patients with IGM who were followed up in the breast unit and applied for routine control between July 2021 and October 2021 were included in the study.

Results: During this period, 101 IGM patients were enrolled. The patients' age ranged between 21 and 61 years (median, 33 years). The most common ABO blood subgroup in both the patient and control groups was Group A (48.5% and 44.7%, respectively). Between the groups, the difference in ABO subgroups was not statistically significant ($p=0.122$). Eight patients had erythema nodosum. In 75% of patients with erythema nodosum, the most common ABO subgroup was Group A. Eight patients developed relapses. The ABO subgroup was A in five of the patients who had a relapse. However, the comparison of ABO subgroups according to both erythema nodosum and relapse status could not be performed because there were few such cases, and the data did not satisfy the necessary assumptions for the chi-square test.

Conclusion: In our study, the ABO blood group distributions in both patient and control groups were similar, and our data did not support a relationship between IGM and ABO blood groups.

Keywords: Idiopathic granulomatous mastitis, ABO subgroups, etiology

Öz

Amaç: Bu çalışmada, idiyopatik granülomatöz mastit (İGM) hastalarının A, B ve O kan grupları (ABO) kan alt grup dağılımının genel popülasyondan farklı olup olmadığının değerlendirilmesi amaçlanmıştır.

Yöntemler: Temmuz 2021-Ekim 2021 tarihleri arasında meme ünitesinde takip edilen ve rutin kontrollere başvuran İGM hastaları çalışmaya dahil edildi.

Bulgular: Bu dönemde 101 İGM hastası çalışmaya dahil edildi. Hastaların yaşları 21 ile 61 arasında değişiyordu (ortanca, 33 yıl). Hem hasta hem de kontrol grubunda en sık görülen ABO kan alt grubu Grup A idi (sırasıyla %48,5 ve %44,7). Gruplar arasında, ABO alt grupları arasındaki fark istatistiksel olarak anlamlı değildi ($p=0,122$). Sekiz hastada eritema nodozum vardı. Eritema nodozumlu hastaların %75'inde en sık görülen ABO alt grubu Grup A idi. Sekiz hastada nöks gelişti. Nüks gelişen beş hastanın ABO alt grubu A idi. Ancak, hem eritema nodozum hem de nöks durumuna göre ABO alt gruplarının karşılaştırılması, bu tür vakaların az olması ve verilerin ki-kare testi için gerekli varsayımları karşılamaması nedeniyle yapılamadı.

Sonuç: Çalışmamızda, hem hasta hem de kontrol gruplarında ABO kan grubu dağılımları benzerdi ve verilerimiz IGM ile ABO kan grupları arasında bir ilişki olduğunu desteklemedi.

Anahtar Sözcükler: İdiyopatik granülomatöz mastit, ABO alt grupları, etiyoloji

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INTRODUCTION

Idiopathic granulomatous mastitis (IGM) still has mysterious aspects since its first description in 1972 by Kessler and Wolloch (1). These mysterious issues are ethnicity, etiopathogenesis that cannot be exactly explained, and the fact that an appropriate treatment approach has not yet been fully established (2-4). Why is IGM more common in some countries, such as Türkiye, China, and Iran, although ethnicity is a significant factor? There is limited information on this subject. The possible relationship between human leukocyte antigens (HLA) classes I and II, and IGM was revealed in a study conducted in Türkiye (5). We believe that the distribution of HLA antigens is associated with IGM and should be investigated in other countries where IGM is common. Another important subject is the etiopathogenesis of IGM. Although some issues about autoimmunity and dysregulation in the immune system have been emphasized recently in IGM, the etiopathogenesis has not been exactly explained until now. Recent studies on the coincidence of extramammary manifestations, like erythema nodosum and arthritis with rheumatological diseases, such as Sjögren's syndrome, support the role of autoimmunity and immune dysregulation in the etiopathogenesis of IGM (2-4, 6-15).

The relationship between blood group antigens and certain diseases has been an interesting topic of research for more than a century. The associations between blood group antigen profiles and hematologic, cognitive, infectious, malignant, and metabolic diseases are known (16,17). A, B and O blood groups (ABO) antigens are found as membrane antigens on the erythrocytes' surfaces, platelets, vascular epithelial cells, intestinal, cervical, and mammary gland epithelial cells, as well as in plasma, milk, urine, and feces (16,17). The possible association of ABO blood groups with the etiopathogenesis of IGM may be of interest since ABO antigens are also found on mammary gland epithelial cells.

In this study, our aim was to evaluate whether the ABO subgroup distribution of patients with IGM was different from the general population without IGM.

MATERIALS AND METHODS

Patients

The newly diagnosed IGM patients and the patients histopathologically diagnosed with IGM, were treated and under follow-up between July 2021 and October 2021, were included in this cross-sectional study. Another inclusion criterion was that the patients gave consent to participate in the study. In addition to routine microscopic examination with hematoxylin and eosin stain, the Ehrlich-Ziehl-Neelsen stain was used to exclude tuberculosis in IGM patients. Refusal to participate in the study was the only exclusion criterion. The patients' age, parity status, history of breastfeeding, smoking, use of oral contraceptive pills, period since their last delivery, diagnosed chronic diseases, and medications were recorded. Furthermore, the patients' complaints at the time of diagnosis, the duration of complaints, physical examination findings, treatment approaches, and outcomes of treatment were noted.

The IGM patients were classified as patterns A (mass without inflammation), B (mass with inflammation), C (abscess-like), or

D (mass with ulcer, sinus, or fistula), clinically according to the classification by Yaghan et al. (18).

During this period, blood groups determined at the Selçuk University Medical Faculty Hospital Blood Bank were taken as the control group. These blood groups belonged to patients, excluding IGM, donors, or people who wanted to know their blood group.

Assessment of ABO/Rh Blood Groups

The blood samples were taken from newly diagnosed IGM patients at the time of diagnosis, and from patients who were either in remission or still under treatment at the control visit. The DG Gel ABO/Rh card (Diagnostic Grifols®, Barcelona, Spain) was used for the determination of. The test was conducted according to catalogue information and the manufacturer's recommendations.

This study was approved by Selçuk University Local Ethical Committee (approval number: 2021/345, date: 23.06.2021). The principles outlined in the Declaration of Helsinki were followed. Written consent was obtained from all participants.

Statistical Analysis

The GraphPad Prism 9 Software (La Jolla, CA, USA) was used for the statistical analysis in this study. The frequency and percentage values were used for the categorical data. There was no numerical data other than age. The minimum and maximum ages were reported alongside the median age. The chi-square test and Fisher's exact test were used for the comparison of categorical data, depending on whether they met the necessary assumptions. The p-value <0.05 was considered statistically significant.

RESULTS

A total of 101 of the 185 IGM patients followed up in the Breast Unit between July 2021 and October 2021 were included in the study. The patients' age ranged between 21 and 61 years (median, 33 years). Most of the patients were premenopausal (n=96, 95%).

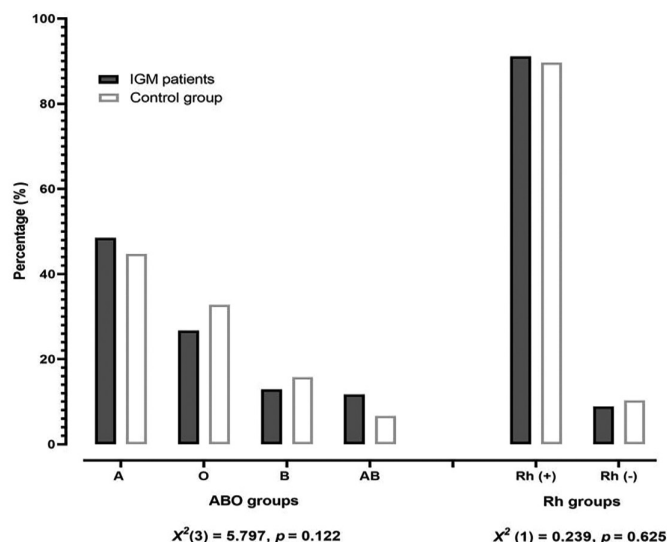


Figure 1. The blood subgroups of patients with idiopathic granulomatous mastitis and control groups.

IGM: Idiopathic granulomatous mastitis, ABO: A, B and O blood groups

There were 97 parous (96%) and 4 nulliparous (4%) patients. Ninety-seven of the patients had a history of breastfeeding. Twenty-five patients (24.8%) were using oral contraceptive pills. Furthermore, seven patients (6.9%) had a history of smoking.

The most common ABO blood subgroup both in the patient and control groups was Group A (48.5% and 44.7%, respectively). The chi-square test showed no statistically significant difference between the patient and control groups from the point of ABO subgroups [χ^2 (3)=5.797, $p=0.122$] (Figure 1; Table 1). Thus, the null hypothesis was accepted. Eight patients had erythema nodosum (8%). The distribution of ABO blood subgroups in patients without erythema nodosum is given in Table 2.

In 75% of patients with erythema nodosum, the most common ABO subgroup was A, while the most common ABO subgroup in patients without erythema nodosum was also A (46.2%). However, the ABO subgroup comparison of patients with and without erythema nodosum could not be performed statistically, since the necessary assumptions for the chi-square test were not met.

Eight patients developed relapse. The ABO subgroup distribution of these patients is in Table 2. The ABO subgroup was A in five of the patients who had a relapse. Similarly, the ABO subgroup comparison of patients with and without relapse could not be calculated because the necessary assumptions for the chi-square test were not met.

DISCUSSION

IGM has remained a mystery since it was first described. The etiology of IGM has not been exactly explained, and no ideal treatment approach has been established. However, studies about the role of the immune system in etiology have been increasing in recent years (2-4,6-8,10,11). Another important point is ethnicity. Why is IGM more common in some countries like Türkiye, China, Iran, South America, and so forth? However, the importance of immune dysregulation and autoimmunity remains a mystery.

ABO antigens are found on the surface of many cells in the human body, such as erythrocytes, platelets, vascular epithelial cells, and intestinal, cervical, and mammary cells. These antigens are also found in plasma, milk, urine, and feces (16,17). Blood group antigens have been used to predict the inheritance of diseases that are coded by genes closely located to the blood group genes on the same chromosome. Also, the discussions on the relationships of blood group antigens and antibodies with some diseases are ongoing. Given all this information, our study aimed to evaluate whether ABO subgroup distribution of patients with IGM is different from the general population.

Almost all of the studies showing the relationship between breast diseases and the ABO subgroup associate these diseases with breast

Table 1. The comparisons of the blood subgroups of patients with idiopathic granulomatous mastitis and control groups

	Patient Group		Control Groups		Statistics		
	n	%	n	%	χ^2	df	p-value
ABO subgroups					5.797	3	0.122
A	49	48.5	1119	44.7			
O	27	26.7	821	32.8			
B	13	12.9	397	15.9			
AB	12	11.9	167	6.7			
Rh subgroups					0.239	1	0.625
Positive	92	91.1	2243	89.6			
Negative	9	8.9	261	10.4			

ABO: A, B and O blood groups, df: Degrees of freedom

Table 2. ABO and Rh subgroups according to pattern, erythema nodosum and relapse status

	ABO subgroups				p-value	Rh groups		p-value
	A n, (%)	O n, (%)	B n, (%)	AB n, (%)		Positive	Negative	
Pattern					0.860			0.476
Non-complicated A + B, (n=39)	18, (46.2)	10, (25.6)	5, (12.8)	6, (15.4)		37, (94.9)	2, (5.1)	
Complicated C + D, (n=62)	31, (50)	17, (27.4)	8, (12.9)	6, (9.7)		55, (88.7)	7, (11.3)	
Erythema nodosum					*			<0.9999
Positive, (n=8)	6, (75)	1, (12.5)	0, (0)	1, (12.5)		8, (8.7)	0, (0)	
Negative, (n=93)	43, (46.2)	26, (28)	13, (14)	12, (11.8)		84, (91.3)	9, (100)	
Relapse					*			0.149
Developed, (n=93)	5, (62.5)	3, (37.5)	0 (0)	0, (0)		86, (93.5)	7, (7.5)	
Undeveloped, (n=8)	44, (47.3)	24, (37.5)	13, (100)	12, (100)		6, (6.5)	2, (22.2)	

*Statistical analysis could not be performed because the necessary assumptions for chi-square tests could not be satisfied

cancer (19-22). In their prospective cohort study, Gates et al. (19) investigated whether there were any relationships between the ABO subgroups and the known risk factors of breast cancer and survival. The authors found no association between the ABO subgroups and risk factors for breast cancer nor between the ABO subgroups and survival. Another study on this subject was a case-control study of Flavarjani et al. (20). The authors investigated the relationship between the ABO subgroups and breast cancer. The distribution of blood groups of both breast cancer patients and the control group was similar. Likewise, they found no difference between different breast cancer types, including invasive ductal carcinoma, medullary carcinoma, invasive lobular carcinoma, and Paget's disease. In their case-control study, Bothou et al. (21) found a relationship between breast cancer and blood group A, marking it as the first study in the literature to demonstrate this relationship. The most important limitation of this study, as emphasized by the authors, was the low number of both patients and subjects in the control groups. In another case-control study by Bezek et al. (22), the ABO subgroups of breast cancer patients and the control group were compared both genotypically and phenotypically. The authors found no difference. Similarly, no relationship could be demonstrated between tumor grade and tumor receptor status and the ABO subgroups.

In our study, we aimed to investigate whether there is a relationship between IGM and ABO subgroups in the context of the presence of ABO antigens in mammary epithelial cells. The most common ABO subgroup in the patients and the controls was subgroup A. There was no statistical difference between the distribution of ABO blood groups the patient group and the control group in our study.

Study Limitations

The most important limitation of our study is the small number of IGM patients with erythema nodosum or relapses, which limits the ability to perform precise statistical analysis.

CONCLUSION

A biochemical understanding of blood subgroups has enabled us to comment on their associations with some diseases. To shed light on the underlying responsible mechanisms, a large series of patients is needed to clarify the possible relationships between certain blood subgroup antigens and diseases thought to be associated.

Ethics

Ethics Committee Approval: This study was approved by Selçuk University Local Ethical Committee (approval number: 2021/345, date: 23.06.2021). The principles outlined in the Declaration of Helsinki were followed.

Informed Consent: Written consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.T., H.K., E.B., K.G., M.Ç., Concept: F.T., U.A., K.G., Design: H.K., U.A., E.B., Data Collection or Processing: F.T., U.A., K.G., M.Ç., Analysis or Interpretation: H.K., E.B., Literature Search: H.K., K.G., M.Ç., Writing: F.T., U.A., E.B., M.Ç.

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

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PATHOS Score as a Predictor of In-Hospital Mortality in Patients with Acute Cardiogenic Pulmonary Edema Presenting to the Emergency Department

Acil Servise Başvuran Akut Kardiyojenik Pulmoner Ödem Hastalarında Hastane İçi Mortaliteyi Öngörmede PATHOS Skoru

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ABSTRACT

Objective: The platelets, age, troponin, heart rate, oxygenation, and systolic blood pressure (PATHOS) score, was assessed in this study for its ability to predict in-hospital mortality in patients with acute cardiogenic pulmonary edema (ACPE), who were admitted to the emergency department (ED).

Methods: Between March 1, 2023, and 2025, the study was carried out retrospectively in the ED of a tertiary university hospital. Adult patients with an ACPE diagnosis who were at least 18 years old were enrolled. Admission data were used to calculate PATHOS scores and analyze outcomes between survivors and non-survivors.

Results: A total of 622 patients satisfied the inclusion requirements for this investigation. Of these, 531 patients (85.4%) survived hospitalization, while 91 (14.6%) died. In multivariate logistic regression analysis, the PATHOS score emerged as an independent predictor of in-hospital mortality, with an odds ratio of 2.27 [95% confidence interval (CI): 1.47-3.52; p<0.001]. Receiver operating characteristic analysis revealed an area under the curve of 0.814 (95% CI: 0.781-0.844), indicating strong discriminative performance. A threshold value greater than 3 for the PATHOS score yielded a sensitivity of 79.1%, specificity of 74.2%, and a negative predictive value of 95.4% for predicting in-hospital mortality.

Conclusion: The PATHOS score stands out as an effective tool for predicting in-hospital mortality risk among patients presenting to the ED with ACPE. As it can be easily calculated via routine admission data, this score may be utilized for early risk stratification in clinical practice.

Keywords: Emergency service, hospital, hospital mortality, prognosis, pulmonary edema, risk assessment

ÖZ

Amaç: Bu çalışmada, acil servise (AS) başvuran akut kardiyojenik pulmoner ödem (AKPÖ) hastalarında hastane içi mortaliteyi öngörme yeteneği açısından platelet, yaş, troponin, kalp hızı, oksijenasyon ve sistolik kan basıncı (PATHOS) skoru değerlendirildi.

Yöntemler: Çalışma, 1 Mart 2023-2025 tarihleri arasında üçüncü basamak bir üniversite hastanesinin AS'inde retrospektif olarak gerçekleştirildi. Çalışmaya en az 18 yaşında olan AKPÖ tanısı almış yetişkin hastalar dahil edildi. Başvuru verileri kullanılarak PATHOS skorları hesaplandı ve hayatta kalanlar ile kaybedilenler arasındaki sonuçlar analiz edildi.

Bulgular: Toplam 622 hasta çalışmaya dahil edilme kriterlerini karşıladı. Bunlardan 531 hasta (%85,4) taburcu olurken, 91 hasta (%14,6) öldü. Çok değişkenli lojistik regresyon analizinde PATHOS skoru, 2,27'lik bir olasılık oranıyla [%95 güven aralığı (GA): 1,47-3,52; p<0,001] hastane içi mortalitenin bağımsız bir öngörücüsü olarak saptandı. Alıcı işlem eğrisi analizinde eğri altında kalan alan 0,814 (%95 GA: 0,781-0,844) bulundu ve güçlü ayırt edici performans gösterdi. PATHOS skoru için 3'ten büyük bir eşik değeri, hastane içi mortaliteyi tahmin etmek için %79,1'lik bir duyarlılık, %74,2'lik bir özgüllük ve %95,4'lük bir negatif öngörü değeri sağladı.

Sonuç: PATHOS skoru, AKPÖ ile AS'e başvuran hastalarda hastane içi mortalite riskini tahmin etmede etkili bir araç olarak öne çıkmaktadır. Rutin başvuru verileri ile kolayca hesaplanabildiği için, bu skor klinik uygulamada erken risk sınıflandırması için kullanılabilir.

Anahtar Sözcükler: Acil servis, hastane, hastane mortalitesi, prognoz, pulmoner ödem, risk değerlendirmesi

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INTRODUCTION

Acute cardiogenic pulmonary edema (ACPE) is a severe cardiovascular emergency characterized by a sudden appearance of pulmonary fluid accumulation, usually due to increased left-sided intracardiac pressures stemming from compromised left ventricular function. It presents abruptly and requires urgent intervention (1,2). This condition, which typically presents with marked hypoxemia and acute respiratory distress, is commonly encountered in emergency departments (EDs) and is considered high-risk owing to its potential for rapid clinical deterioration. Prompt identification of the condition and initiation of appropriate therapy, at an early stage, are crucial to prevent adverse outcomes, minimize the need for escalation to critical care, and ensure a shorter duration of inpatient treatment (3).

The fact that the current reported mortality rates in patients hospitalized with ACPE exceed 10% further underscores the need for early and effective risk stratification, particularly for those patients who are at risk of rapid clinical deterioration (4-6). The time constraints and high degree of clinical heterogeneity inherent in ED settings make the reliable prediction of short-term prognosis a fundamental requirement for treatment success (7). Within this context, clinical scoring systems developed for such settings provide an objective foundation for clinical decision-making and contribute to the standardization of patient care (8). However, since the majority of existing systems are designed for broad patient populations, they may not adequately capture the unique characteristics of syndromes such as ACPE, which exhibit a distinctive clinical course and rapid progression (9).

The platelets, age, troponin, heart rate, oxygenation, and systolic blood pressure (PATHOS) score was initially introduced as a prognostic tool for estimating the likelihood of in-hospital death among individuals diagnosed with pulmonary embolism (PE), and it gained attention due to its clinical utility and ease of use. This model, based on six fundamental parameters provides an objective and rapid tool for risk assessment (10). Initially validated in patients diagnosed with PE, the PATHOS score has subsequently been tested in various patient populations and has demonstrated strong predictive performance for mortality (11).

Given the lack of rapid and reliable prognostic models specifically tailored for ACPE, there is a growing need for simple, objective tools that can be applied upon ED presentation to aid in early risk assessment (12). The PATHOS score encompasses several variables, including hypoxia, hypotension, and myocardial injury markers, which are highly relevant to the pathophysiological features of ACPE, thereby supporting its potential applicability in this setting. Therefore, the objective of this study was to evaluate the relationship between the PATHOS score and 30-day in-hospital mortality in patients presenting to the ED with ACPE.

MATERIALS AND METHODS

Study Setting, Population, and Ethical Considerations

This retrospective observational study was conducted between March 1, 2023, and March 1, 2025, and included patients who presented to a tertiary-level ED, with approximately one million annual visits. The study was approved by the Local Ethics Committee

of University of Health Sciences Türkiye, Ankara Etlik City Hospital (approval number: AEŞH-BADEK-2025-0247, date: 12.03.2025). Owing to the retrospective nature of the study, informed consent was not required from the participants. All procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The data obtained within the scope of the study were stored in encrypted electronic systems accessible only to the research team, and patient identifiers were anonymized in compliance with confidentiality principles prior to analysis.

This retrospective study was conducted on patients aged ≥ 18 years who presented to the ED of Ankara Etlik City Hospital and were diagnosed with ACPE. Eligible patients were identified retrospectively through a review of cardiology, intensive care, and pulmonology consultation records initiated by ED physicians for cases of acute dyspnea. Patients were included if they met the diagnostic criteria for ACPE based on clinical presentation, radiological findings, and specialist consultation notes. Patients were excluded if they received palliative care for advanced malignancy, exhibited signs of active infection or sepsis, had a history of trauma, were pregnant, were referred from another healthcare facility, stayed in the hospital for less than 24 hours, or had missing medical records. In cases with more than one hospital admission, only the initial presentation was considered for analysis, while all subsequent visits were excluded.

Definition of Acute Cardiogenic Pulmonary Edema

In this study, ACPE was defined based on the most recent guidelines of the European Society of Cardiology for acute heart failure, incorporating clinical findings, oxygen levels, and radiological assessments (13). By finding interstitial or alveolar infiltrates consistent with edema on chest radiography or computed tomography, the diagnosis was confirmed in patients presenting with a sudden onset of dyspnea, orthopnea, tachypnea, bilateral crackles on auscultation, and oxygen saturation below 90% on room air.

Data Collection and Variables

The data analyzed in this study were retrospectively obtained from the hospital's digital health records system. For each patient, demographic information such as age and sex; vital parameters at presentation [systolic and diastolic blood pressure, oxygen saturation, heart rate, Glasgow Coma Scale (GCS)], and comorbid conditions (e.g., hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, congestive heart failure, and dyslipidemia) were recorded.

Laboratory evaluations included complete blood count, arterial blood gas analysis, serum electrolyte levels, high-sensitivity troponin T, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and renal function tests. To assess the clinical course, additional parameters such as the use of non-invasive mechanical ventilation (NIMV) in the ED, the need for intubation, the length of hospital stay, and early in-hospital mortality within the first 30 days were also analyzed. Patients with missing or inconsistent clinical or laboratory records were excluded from the study.

Venous blood gas analyses were performed using the Siemens RapidLab 1265 (Germany), and complete blood counts were conducted using the Siemens XN-1000 (Germany). The biochemical

parameters were analyzed via a Cabos 8001 instrument (China). The positivity threshold was set at 14 ng/L for hs-Troponin T and 624 ng/L for NT-proBNP.

PATHOS Score Calculation

The PATHOS score is a system developed to provide rapid and effective risk stratification in clinical practice, based on six simple parameters. The score includes the following criteria: platelet count <100 or >400, $10^3/\mu\text{L}$, age >80 years, troponin level above the laboratory upper reference limit, heart rate >100 beats per minute, peripheral oxygen saturation <90%, and systolic blood pressure <100 mmHg. Each positive finding is assigned 1 point, and the total score ranges from 0 to 6 (10).

Outcome Measures

The primary outcome of this study was 30-day in-hospital mortality among patients presenting to the ED with ACPE. Secondary outcomes included the need for intubation in the ED, the requirement for NIMV, and the duration of hospital stay.

Statistical Analysis

IBM SPSS Statistics software (version 26.0; IBM Corp., Armonk, NY, USA) was used to conduct statistical analyses. The Kolmogorov-Smirnov test was applied to assess the distribution of continuous parameters. Data with normal distribution were presented as means $\pm$ standard deviations, while the rest of the variables were summarized as medians with interquartile ranges. Frequencies and percentages were used to represent categorical data. For group comparisons, normally distributed data were analyzed using the independent samples t-test, while non-parametric variables were analyzed using the Mann-Whitney U test. Associations between categorical variables were assessed using the Pearson's chi-square test or Fisher's exact test where appropriate. Univariate and multivariate logistic regression models identified predictors of in-hospital mortality. To identify independent predictors of mortality, variables were initially examined using univariate logistic regression analysis. Variables with p-value <0.05 in univariate analysis were analyzed with multivariate logistic regression. Prior to establishing the final model, a multicollinearity analysis was conducted. If two or more of the factors retained in the multivariate analysis were highly correlated, then only one factor was selected for further modeling to avoid collinearity. The PATHOS score's discriminative ability was assessed using receiver operating characteristic (ROC) curve analysis. The Youden index was used to identify the optimal threshold after computing sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the area under the curve (AUC). Statistical significance was defined as a p-value <0.05.

RESULTS

A total of 622 patients were included in the final analysis. The process summarizing the inclusion and exclusion criteria for patient selection is presented as a flow diagram in Figure 1. Among them, 91 individuals (14.6%) died during hospitalization, while 531 patients (85.4%) survived. The average age in the mortality group was 79.4 ± 10.6 years, which was significantly higher than that in the survivor group (74.2 ± 11.9 years; $p < 0.001$). Systolic and diastolic blood pressure readings were both significantly reduced in patients

who died (130.5 ± 45.0 mmHg and 73.7 ± 23.9 mmHg respectively) compared to those who survived ($p = 0.005$ and $p = 0.017$) (Table 1). Arterial blood gas analysis showed a lower mean pH value of 7.34 (0.15) in the mortality group ($p < 0.001$). Additionally, the median serum lactate concentration was elevated among deceased patients, 2.9 (2.1) mmol/L, relative to survivors 2.6 (1.3) mmol/L ($p = 0.022$). Similarly, median serum creatinine was higher in the mortality group 1.57 (0.99) mg/dL than in the survivor group 1.21 (0.70) mg/dL ($p < 0.001$). Regarding prognostic scoring, the mean PATHOS score was significantly elevated in patients who died (4.09 ± 0.90) compared to those who survived (2.76 ± 1.11 ; $p < 0.001$). Overall, statistically significant differences were identified between the two groups in terms of age, systolic and diastolic blood pressure, heart rate, oxygen saturation, GCS, arterial pH, lactate and creatinine concentrations, PATHOS score, and the requirement for endotracheal intubation at ED presentation.

The prognostic performance of the PATHOS score in estimating in-hospital mortality was examined through ROC analysis. The AUC was found to be 0.814 [95% confidence interval (CI): 0.781-0.844], demonstrating strong discriminatory ability. When a threshold value of three or more was applied, the sensitivity reached 79.1% (95% CI: 69.3-86.9), while the specificity was 74.2% (95% CI: 70.3-77.9). The corresponding PPV was 34.4% (95% CI: 28.0-41.3), and the NPV was 95.4% (95% CI: 92.9-97.2) (Figure 2 and Table 2).

In the multivariate logistic regression analysis, endotracheal intubation in the ED, [odds ratio (OR) = 1.32; 95% CI: 1.18-3.85; $p < 0.001$], and PATHOS score components were identified as independent risk factors for in-hospital mortality (Table 3).

DISCUSSION

In the ED setting, rapid identification of critically ill patients and timely escalation to the appropriate level of care are crucial for preventing delays in management and improving patient outcomes (14). ACPE, which is associated with a high risk of early mortality and has an abrupt onset, is one of the most prominent examples of high-risk clinical conditions requiring prompt intervention (15). In this study, the performance of the PATHOS score in predicting in-hospital mortality among patients with ACPE who presented to the ED was evaluated. The findings revealed that the PATHOS score was significantly greater in non-survivors than in survivors and that a cut-off value greater than 3 was identified as an independent prognostic factor associated with an approximately 2.3-fold increased risk of in-hospital mortality. Furthermore, ROC curve analysis demonstrated an AUC of 0.814, indicating strong discriminative ability. This prognostic strength suggests that the PATHOS score may serve as a practical and effective decision-support tool, particularly in situations where rapid clinical deterioration is likely to occur.

The PATHOS score was initially developed by Spampinato et al. (10) in a multicenter study to predict short-term mortality risk in patients diagnosed with PE, and it demonstrated statistically robust prognostic performance. In that study, the AUC values for the derivation and validation cohorts were reported as 0.827 and 0.74, respectively. The PATHOS score has demonstrated promising discriminative ability in previous studies, and its prognostic accuracy has been favorably compared with traditional tools, such as the Shock index, Simplified Pulmonary Embolism Severity

Index and Pulmonary Embolism Severity Index (10). Similarly, in a validation study by Alışkan and Kılıç (11) in patients with PE, the PATHOS score, which uses a cut-off value of greater than 2, showed

significant prognostic accuracy, with a sensitivity of 70.8% and a specificity of 71.3%. Additionally, a recent retrospective analysis by Sert and Kokulu (16), focusing on the geriatric population, reported

Table 1. Comparison of clinical, laboratory, and prognostic parameters between survivors and non-survivors in patients with acute cardiogenic pulmonary edema

Variable	Survivors (n=531)	Non-survivors (n=91)	p-value
Age, years	74.2±11.9	79.4±10.6	<0.001
Sex, male	292 (55.0%)	53 (58.2%)	0.564
Vital signs			
SBP (mmHg)	143.6±41.0	130.5±45.0	0.005
DBP (mmHg)	79.8±22.8	73.7±23.9	0.017
HR (beats/min)	101±24	116±24	<0.001
Oxygen saturation (%)	76±11	73±11	0.003
GCS	15.0 (1.0)	15.0 (2.0)	0.001
Cardiovascular co-morbidities			
Hypertension	331 (62.3%)	63 (69.2%)	0.207
Diabetes mellitus	353 (66.5%)	62 (68.1%)	0.757
Atrial fibrillation	208 (39.2%)	38 (41.8%)	0.641
Coronary artery disease	327 (61.6%)	60 (65.9%)	0.429
Congestive heart failure	306 (57.6%)	52 (57.1%)	0.931
Dyslipidaemia	72 (13.6%)	9 (9.9%)	0.337
Previous acute pulmonary edema	312 (58.8%)	51 (56.0%)	0.628
Acute myocardial infarction	77 (14.5%)	15 (16.5%)	0.623
Ejection fraction	40.0±10.8	39.9±9.6	0.617
Arterial blood pH	7.38 (0.11)	7.34 (0.15)	<0.001
Partial arterial CO ₂ pressure	41.5 (13.5)	42.9 (23.1)	0.291
Arterial blood lactate (mmol/L)	2.6 (1.3)	2.9 (2.1)	0.022
White blood cells count (×10 ⁹ /L)	9.65 (5.07)	10.42 (6.02)	0.076
Hemoglobine (g/dL)	11.4 (3.5)	11.4 (3.1)	0.554
Creatinine (mg/dL)	1.21 (0.70)	1.57 (0.99)	<0.001
Sodium (mmol/L)	138 (5)	137 (8)	0.055
Potassium (mmol/L)	4.64 (0.88)	4.81 (1.28)	0.072
NT-proBNP (pg/mL)	7190 (11913)	9895 (12450)	0.092
PATHOS score	2.76±1.11	4.09±0.90	<0.001
P: Platelet count <100 or >400×10 ³ /μL	59 (11.1%)	19 (20.9%)	0.009
A: Age >80 years	200 (37.7%)	57 (62.6%)	<0.001
T: Troponin level > cut-off	318 (59.9%)	84 (92.3%)	<0.001
H: Heart rate >100 bpm	292 (55.0%)	81 (89.0%)	<0.001
O: Oxygenation (SpO ₂ <90%)	486 (91.5%)	89 (97.8%)	0.036
S: Systolic blood pressure <100 mmHg	114 (21.5%)	45 (49.5%)	<0.001
Non-invasive MV at ED	393 (74.0%)	70 (76.9%)	0.556
Endotracheal intubation at ED	29 (5.5%)	84 (92.3%)	<0.001
Days of hospitalization	5.0 (5.0)	4.0 (6.0)	0.176

Data are presented as mean ± standard deviation, median (interquartile range), or number (percentage), as appropriate

DBP: Diastolic blood pressure, ED: Emergency department, GCS: Glasgow Coma Scale, HR: Heart rate, MV: Mechanical ventilation, NT-proBNP: N-Terminus pro-B-type natriuretic peptide, SBP: Systolic blood pressure

that the PATHOS score independently predicts in-hospital mortality in intensive care patients aged 65 years and older (OR: 3.80, 95% CI: 3.07-4.70), with an AUC value of 0.827. Our results align closely with the existing literature. In the clinical context of ACPE, which is characterized by a high potential for sudden deterioration, a PATHOS score exceeding three was found to be associated with an approximately 2.3-fold increased likelihood of in-hospital death. This rate is similar to data reported for patients with PE, and geriatric intensive care patients, suggesting the PATHOS score's validity extends beyond thromboembolic conditions to various clinical scenarios. Therefore, our study makes a novel contribution to the literature regarding the use of the PATHOS score in ACPE, suggesting that this scoring system may serve as a practical and reliable tool for risk prediction in patients with ACPE. Notably, each component of the PATHOS score showed an independent association with in-hospital mortality in our patient population. This observation not only underscores the clinical importance of these individual parameters but also confirms the internal

coherence and reliability of the scoring model. Furthermore, the congruence between their predictive roles and the established pathophysiological mechanisms in ACPE lends strong support to their inclusion within the score.

ACPE, which is associated with a high risk of short-term mortality, clearly highlights the need for rapid and effective risk stratification in EDs. Various scoring systems have been developed to address this clinical need, each based on distinct sets of parameters. For example, the 3CPO score, as described by Gray et al. (17), was designed to predict short-term prognosis in patients with ACPE complicated by acidosis. However, the model's reliance solely on fundamental clinical indicators, while excluding laboratory data, has limited its predictive power and confined its applicability to a specific patient subgroup, thereby restricting its use in general clinical practice. In contrast, the PATHOS score used in this study integrates both vital signs and fundamental laboratory parameters comprehensively, making it a practical risk assessment tool, particularly in patients with ACPE. The Emergency Heart Failure Mortality Risk Grade score,

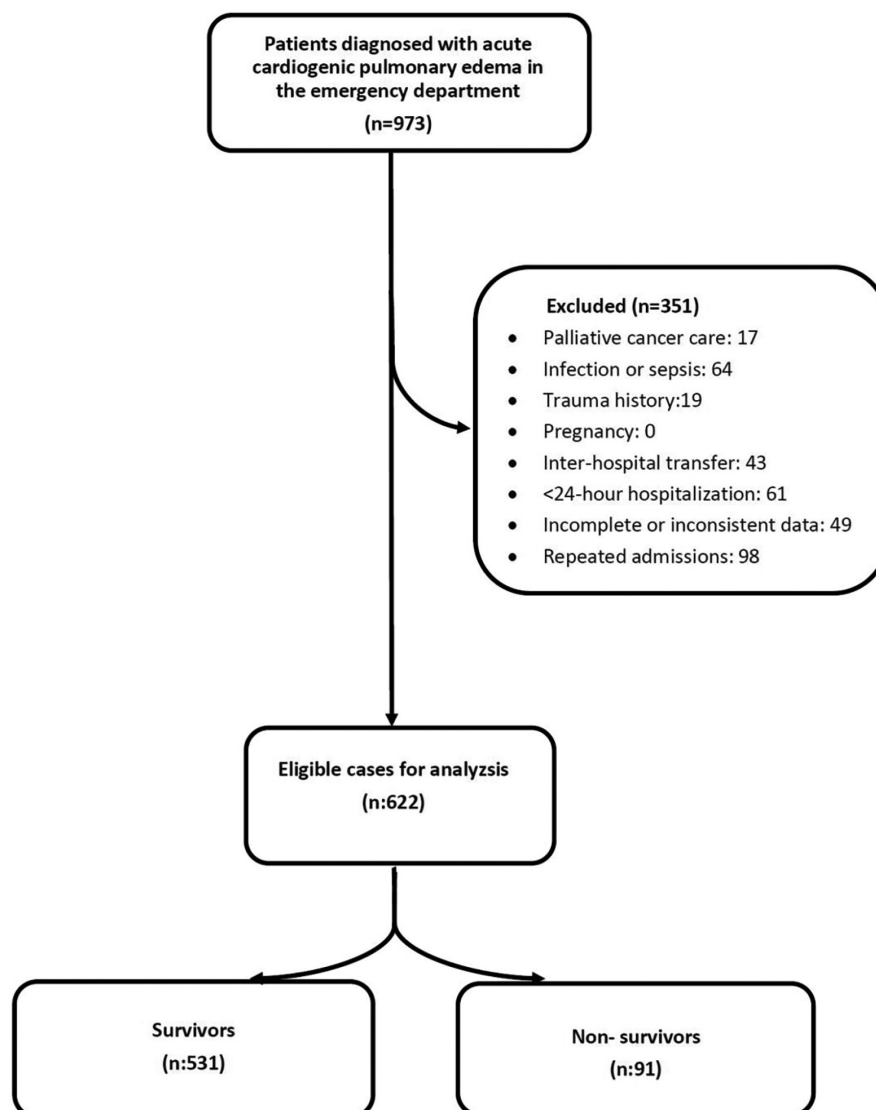


Figure 1. Flowchart of patient selection based on predefined inclusion and exclusion criteria

developed by Lee et al. (18), is a comprehensive system aimed at predicting 7-day mortality in patients presenting to the ED with heart failure. It incorporates numerous parameters, including age, vital signs, troponin, creatinine, and potassium levels, as well as a history of active malignancy. However, this model may lack sufficient specificity and sensitivity in certain clinical scenarios, such as ACPE. In contrast, the PATHOS score has been tested exclusively in a patient group with ACPE, and individuals with a history of malignancy were excluded from the study, allowing for a more targeted and streamlined assessment.

Another model proposed by Zhao et al. (19) demonstrated high accuracy in predicting short-term mortality by incorporating biomarkers such as NT-proBNP and creatinine. However, the applicability of this score may be limited in some EDs due to the need for advanced laboratory tests. In contrast, the PATHOS score, which includes commonly used biomarkers such as troponin, relies primarily on basic clinical and laboratory parameters, offering a straightforward structure that is easily applicable across different healthcare settings. This characteristic provides a functional advantage in facilitating rapid decision-making during emergencies.

Table 2. Prognostic performance of PATHOS score in predicting in-hospital mortality at different cut-off levels

Cut-off values for PATHOS score	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
≥0	100 (96-100)	0 (0-1)	-	-	-
>0	100 (96-100)	2 (1-3)	15 (12-18)	100 (66-100)	-
>1	99 (94-100)	14 (11-17)	16 (13-20)	99 (93-100)	0.52 (0.33-0.70)
>2	97 (91-99)	39 (35-43)	21 (18-26)	99 (96-100)	0.73 (0.66-0.92)
>3*	79 (69-86)	74 (70-78)	34 (28-41)	95 (93-97)	0.81 (0.78-0.84)
>4	29 (20-39)	95 (93-97)	50 (36-64)	88 (85-91)	0.65 (0.52-0.69)
>5	5 (2-12)	99 (98-100)	71 (29-96)	86 (83-87)	0.46 (0.28-0.75)

*Cut-off level was calculated using Youden's index

AUC: Area under curve, CI: Confidence interval, NPV: Negative predictive value, PPV: Positive predictive value, PATHOS: Platelets, age, troponin, heart rate, oxygenation, and systolic blood pressure

Table 3. Univariate and multivariate logistic regression analyses of risk factors associated with in-hospital mortality in patients with acute cardiogenic pulmonary edema

Risk factor	Univariate logistic regression			Multivariate logistic regression		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.04	1.02-1.67	<0.001	-		
Gender, male	0.87	0.55-1.37	0.564	-		
SBP	0.68	0.40-0.88	0.008	-		
DBP	0.81	0.34-0.95	0.024	-		
HR	2.29	1.44-3.18	<0.001	-		
Oxygen saturation	0.57	0.28-0.94	0.005	-		
GCS	0.79	0.67-0.92	0.003	1.05	0.65-1.32	0.384
Arterial blood pH	0.41	0.15-0.78	<0.001	0.50	0.012-2.66	0.229
Arterial blood lactate	1.30	1.14-1.49	0.022	-		
Creatinine	1.20	1.02-1.41	<0.001	1.44	0.68-1.96	0.393
Endotracheal intubation at ED	1.54	1.37-4.63	<0.001	1.32	1.18-3.85	<0.001
PATHOS score						
P: Platelet count <100 or >400×10 ³ /μL	1.56	1.21-2.98	0.011	1.44	1.17-2.36	<0.001
A: Age >80 years	1.74	1.34-3.65	<0.001	1.16	1.05-3.81	0.03
T: Troponin level > cut-off	2.68	1.85-4.40	<0.001	1.32	1.11-4.58	<0.001
H: Heart rate >100 bpm	3.15	1.64-5.57	<0.001	2.33	1.46-6.18	<0.001
O: Oxygenation (SpO ₂ <90%)	1.52	1.09-2.02	0.039	1.29	1.11-3.04	0.05
S: Systolic blood pressure <100 mmHg	2.18	1.58-2.67	<0.001	1.96	1.37-3.16	<0.001

CI: Confidence interval, DBP: Diastolic blood pressure, ED: Emergency department, GCS: Glasgow Coma Scale, OR: Odds ratio, PATHOS: Platelets, age, troponin, heart rate, oxygenation, and systolic blood pressure, SBP: Systolic blood pressure, HR: Heart rate

On the other hand, the model developed by Leela-Amornsri et al. (20) was specifically designed to predict extubation success in patients receiving non-invasive positive pressure ventilation (NIPPV). This model is based on six key clinical indicators: age, systolic blood pressure, heart rate, level of consciousness, urine output, and the presence of pneumonia. Although this approach is beneficial for anticipating the success of ventilation, its applicability is limited compared to the PATHOS score, as it is limited to patients undergoing NIPPV and does not provide an overall mortality prediction for broader clinical conditions such as ACPE. Additionally, our study revealed a significant difference in endotracheal intubation rates between survivors and non-survivors, with intubation performed considerably more frequently among patients who did not survive. This finding suggests that elevated PATHOS scores may reflect not only the risk of mortality but also the need for advanced airway management and intensive care support. From this perspective, the PATHOS score may serve not only as a prognostic tool but also as a valuable guide in planning critical care interventions.

The recently proposed SABIHA score has enriched the literature by targeting the identification of patients with ACPE who are at elevated risk of short-term mortality. This model is based on six key parameters-systolic blood pressure <110 mmHg, age ≥ 75 years, blood urea nitrogen ≥ 33 mg/dL, need for intubation, heart rate ≥ 110 bpm, and presence of anemia-and was developed using a large, multicenter patient cohort. It showed strong prognostic performance across both the model development and external validation stages, achieving AUC scores of 0.879 and 0.840, respectively, which reflect high discriminatory capability (9). In

particular, the SABIHA score has drawn attention as an effective tool for early mortality risk stratification. However, the need for clinical intervention data (e.g., intubation) makes its calculation relatively complex in ED settings, where rapid decision-making is critical. At this point, the PATHOS score stands out as an effective alternative in busy clinical environments such as EDs since it can be calculated using only basic vital signs and routine biochemical parameters available at admission. In this context, our study expands the scope of the literature by demonstrating the prognostic value of the PATHOS score in a clinical scenario characterized by high mortality and an urgent need for interventions, such as ACPE. Owing to its simple structure, rapid applicability, and strong discriminatory performance, the PATHOS score is thought to have significant potential as a decision-support tool for time-sensitive patient management in EDs.

In this context, transparent reporting of cut-off selection is essential for enhancing the reproducibility and comparability of prognostic scoring systems across diverse clinical settings (21). Beyond its prognostic utility, a high PATHOS score at admission may assist emergency physicians in making informed triage decisions by identifying patients who would benefit from closer observation, expedited intensive care unit consultation, or more intensive monitoring. Moreover, its reliance on readily available parameters at the time of initial evaluation allows for seamless integration into existing emergency care protocols without impeding urgent treatment decisions. In resource-limited or high-volume settings, such integration may help standardize care and enhance early recognition of clinical deterioration.

Study Limitations

This study has certain methodological constraints that must be acknowledged when evaluating the results. Primarily, its retrospective and single-center nature may restrict the extent to which these findings can be extrapolated to broader clinical settings and diverse patient groups. Additionally, since the data were retrospectively obtained from hospital information management systems, some clinical and laboratory variables may have been incompletely, non-standard, or heterogeneously recorded. Only routinely assessed parameters were included in the study, and advanced biomarkers such as NT-proBNP were excluded. Furthermore, the analysis was limited to mortality occurring during hospitalization; outcomes such as long-term survival after discharge, readmission, or the development of complications were not evaluated. The lack of systematic examination of treatment protocols and interventional differences among patients could be confounding factors affecting short-term outcomes. The study also did not include timing variables, such as the interval between symptom onset and presentation. Additionally, the exclusion of patients with a hospital stay of less than 24 hours may have limited the ability to assess the specificity of the PATHOS score. Some of these patients may have been clinically stable and discharged early, and their exclusion could have led to an underestimation of the score's false-positive rate. Finally, no subgroup analysis was performed according to different etiological subtypes of ACPE (e.g., ischemic, hypertensive, or valvular causes). For these reasons, multicenter, prospective, and interventional studies are needed to validate our findings and extend their applicability to broader clinical settings.

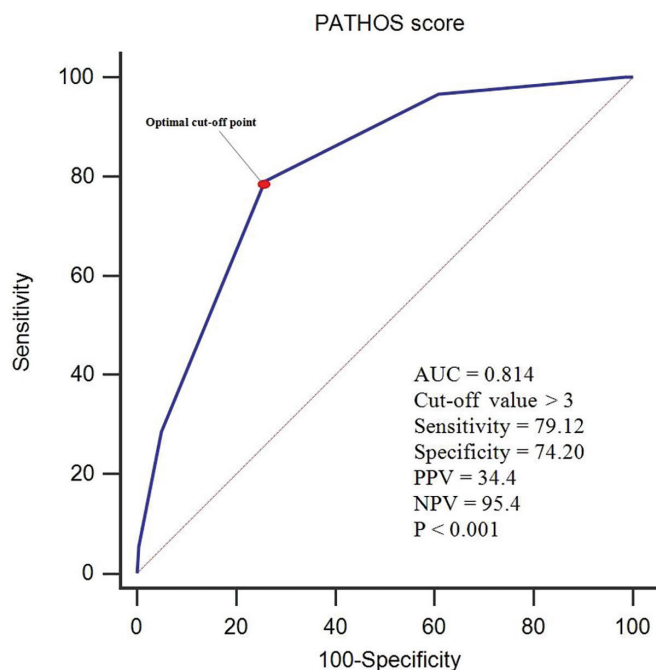


Figure 2. Receiver operating characteristic curve illustrating the prognostic performance of the PATHOS score in predicting in-hospital mortality

AUC: Area under curve, NPV: Negative predictive value, PPV: Positive predictive value, PATHOS: Platelets, age, troponin, heart rate, oxygenation, and systolic blood pressure

CONCLUSION

ACPE is an emergency condition characterized by sudden-onset respiratory failure and hemodynamic instability; it poses a significant threat to patient survival. This study evaluated the performance of the PATHOS score, based on readily available basic clinical and laboratory findings at admission, in predicting short-term in-hospital mortality. These findings indicate that the PATHOS score may offer a practical approach to early risk stratification in patients with ACPE. Its simple structure and rapid calculation suggest that the score has the potential to contribute to clinical decision support, particularly in the timesensitive environment of the ED.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of University of Health Sciences Türkiye, Ankara Etlik City Hospital (approval number: AEŞH-BADEK-2025-0247, date: 12.03.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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

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Prognostic Value of Serum Lactate Dehydrogenase (LDH) Levels in Small Cell Lung Cancer Patients Receiving Thoracic Radiotherapy and Prophylactic Cranial Irradiation

Toraks Radyoterapisi ve Profilaktik Kraniyal Işınlama Alan Küçük Hücreli Akciğer Kanseri Hastalarında Serum Laktat Dehidrogenaz (LDH) Düzeylerinin Prognostik Değeri

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ABSTRACT

Objective: Small cell lung cancer (SCLC) accounts for 15% of all lung cancers and is more aggressive than other types of lung cancer. In these cases, the most important prognostic factor is the presence of brain metastases. According to the National Comprehensive Cancer Network Guidelines, prophylactic cranial irradiation (PCI) is a treatment option to prevent brain metastasis. However, brain metastases develop within four years in 45% of patients despite PCI. Therefore, it is important to identify predictive factors for brain metastases. Serum lactate dehydrogenase (LDH) levels have long been recognized as a prognostic factor in many cancer contexts. In this study, we aim to evaluate the relationship between serum LDH levels and intracranial progression-free survival (ICPFS) as well as overall survival (OS) in SCLC patients receiving PCI and thoracic radiotherapy (TRT).

Methods: This study evaluated 50 patients who underwent PCI and TRT for SCLC between July 2012 and April 2024. Pre-treatment serum LDH levels and maximum serum LDH (mLDH) levels were recorded during the study. An increased serum LDH level was defined as a value exceeding 346 IU/mL. The relationship between serum LDH levels, OS, and ICPFS was evaluated using Kaplan-Meier analysis.

Results: The median mLDH level was determined to be 346 IU/L. Of the total number of patients (n=50), 25 exhibited elevated mLDH levels. No differences were observed between patients with normal and elevated mLDH levels regarding their characteristics. The median ICPFS for the elevated and normal mLDH groups was 15 and 29 months, respectively (p=0.01). The median OS was 25 months in

Öz

Amaç: Küçük hücreli akciğer kanseri (KHAK) tüm akciğer kanserlerinin %15'ini oluşturur ve diğer akciğer kanseri türlerine göre daha agresiftir. Bu vakalarda en önemli prognostik faktör beyin metastazlarının varlığıdır. Bu nedenle profilaktik kraniyal ışınlama (PKI) KHAK için standart tedavidir. Ancak, PKI'ya rağmen hastaların %45'inde dört yıl içinde beyin metastazı gelişmektedir. Bu sebeple beyin metastazları için öngörücü faktörlerin belirlenmesi önemlidir. Serum laktat dehidrogenaz (LDH) düzeyleri uzun zamandır birçok kanserde prognostik bir faktör olarak kabul edilmektedir. Bu çalışmada, PKI ve torasik radyoterapi (TRT) uygulanan KHAK hastalarında serum LDH düzeyleri ile intrakraniyal progresyonsuz sağkalım (IKPFS) ve genel sağkalım (GS) arasındaki ilişkiyi değerlendirmek amaçlandı.

Yöntemler: Bu çalışmada, Temmuz 2012 ile Nisan 2024 tarihleri arasında KHAK nedeniyle PKI ve TRT uygulanan 50 hasta retrospektif olarak taranmıştır. Tedavi öncesi serum LDH düzeyleri ve çalışma sırasındaki maksimum serum LDH (mLDH) düzeyleri kaydedilmiştir. Artmış serum LDH düzeyi 346 IU/mL'yi aşan bir değer olarak tanımlanmıştır. Serum LDH düzeyleri ile GS ve IKPFS arasındaki ilişki Kaplan-Meier analizi kullanılarak değerlendirilmiştir.

Bulgular: Ortanca mLDH düzeyi 346 IU/L olarak belirlenmiştir. Toplam hasta sayısının (n=50) 25'inde mLDH düzeyi yüksekti. Normal ve yüksek mLDH düzeylerine sahip hastalar arasında özellikleri açısından herhangi bir fark gözlenmemiştir. Yüksek ve normal mLDH grupları için medyan IKPFS sırasıyla 15 ay ve 29 aydı (p=0,01). Ortanca GS, yüksek ve normal mLDH grupları için sırasıyla 25 ay ve ulaşılmadı (p=0,034).

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ABSTRACT

the elevated mLDH group and was not reached in the normal mLDH group ($p=0.034$). In the multivariate analysis, only mLDH levels were independently associated with OS (hazard ratio: 3.92; 95% confidence interval: 1.15-13.3; $p=0.02$).

Conclusion: Serum mLDH levels during TRT and PCI predict intracranial progression and survival in SCLC patients, helping identify at-risk patients who may benefit from aggressive treatment.

Keywords: Small cell lung cancer, lactate dehydrogenase, prophylactic cranial irradiation

ÖZ

Çok değişkenli analizde, yalnızca mLDH düzeylerinin bağımsız olarak GS ile ilişkili olduğu bulunmuştur (tehlike oranı: 3,92; %95 güven aralığı: 1,15-13,3; $p=0,02$).

Sonuç: KHAK'lı hastalarda TRT ve PKI esnasında ölçülen mLDH düzeyleri intrakraniyal progresyon ve sağkalımı predikte eder.

Anahtar Sözcükler: Küçük hücreli akciğer kanseri, laktat dehidrogenaz, profilaktik kraniyal ışınlama

INTRODUCTION

Small cell lung cancer (SCLC) represents approximately 15% of all lung cancer cases (1). SCLC is a highly aggressive tumor type with a proclivity for metastasis (2). The two-year overall survival (OS) rate for limited-stage SCLC is 40%, while it is less than 10% for extensive-stage SCLC (3,4).

In SCLC, the most important prognostic factor is the presence of brain metastasis. At the time of diagnosis, 10% of SCLC patients present with brain metastasis (5), and approximately 50% of patients develop brain metastasis as the disease progresses. In cases of brain metastasis, the median OS is six months (6). In light of these considerations, prophylactic cranial irradiation (PCI) has emerged as a significant intervention strategy. A meta-analysis revealed that PCI provided a 5.4% improvement in three-year OS for SCLC patients (7). However, even with the administration of PCI, the likelihood of developing brain metastasis remains at 15% after three years and 45% after four years (8,9). Therefore, it is crucial to identify new factors that can aid in predicting the development of brain metastasis.

Lactate dehydrogenase (LDH) regulates the conversion of glucose to lactic acid, and its elevated levels have been identified as an adverse prognostic factor in lung cancer cases (10). A subsequent study has shown that high levels of LDH are linked to decreased OS in lung cancer patients receiving whole brain radiotherapy (WBRT) (11).

In conclusion, it is hypothesised that maximum serum LDH (mLDH) levels during the study may help predict new brain metastases and survival in SCLC patients undergoing thoracic radiotherapy (TRT) and PCI.

MATERIALS AND METHODS

We identified a total of 50 patients with SCLC who underwent TRT and PCI in our department between July 2012 and April 2024. We recorded the stage at diagnosis, the systemic therapies administered, the characteristics of radiotherapy, pre-treatment LDH levels, and mLDH levels. It is recommended that patients receive brain magnetic resonance imaging (MRI) and thoracoabdominal computed tomography scans every three months during the first two years and then every six months thereafter. The intracranial progression-free survival (ICPFS) is defined as the interval between the pathological diagnosis and the onset of brain metastasis MRI. This study was approved by the Ethics Committee of University of Health Sciences Türkiye, Gülhane

Training and Research Hospital (approval number: 2025/128, date: 12.06.2025). Informed consent form was not obtained since it was a retrospective study.

Statistical Analysis

The statistical analysis was conducted using IBM SPSS version 25 software. The patients' characteristics were subjected to descriptive statistical analysis. The LDH level cut-off was determined according to a median value of 346 IU/L. A chi-squared test and a t-test were used to evaluate the differences in clinical characteristics between the normal and elevated mLDH groups. A Kaplan-Meier analysis determined any differences in OS and ICPFS based on mLDH values. Ultimately, the Cox proportional hazards model was utilized to identify the most significant prognostic factors.

RESULTS

Patients Characteristics

The patients' characteristics are summarized in Table 1. The majority of patients were male. The median age of the patients was 59 years (range 46-75). Eighty percent of patients were classified as Eastern Cooperative Oncology Group (ECOG) score 1. All patients underwent thoracic chemoradiotherapy and subsequently received PCI. The TRT dose was 45-60 Gray (Gy) in 25-30 fractions, and the PCI dose was 25 Gy in 10 fractions. Concurrent chemoradiotherapy was administered to 41 patients (82%), while 9 patients (18%) underwent sequential treatment. Fifty-two percent of patients completed six cycles of chemotherapy, with the majority receiving the cisplatin-etoposide regimen. No significant differences were observed between patients with mLDH levels of ≤ 346 IU/L and those with levels greater than 346 IU/L.

Patient Outcomes

The median follow-up period was 21.5 months (range 6 to 122 months). After treatment with TRT and chemotherapy, 34 patients (64%) exhibited a partial response, while 16 patients (36%) demonstrated a complete response. After TRT and PCI, 10 patients (20%) experienced intracranial failure. The median time to failure was 15 months (range 9-35 months). Of the 10 patients, eight were in the high mLDH group. The median ICPFS was significantly lower in the high mLDH group compared to the low mLDH group (15 months vs. 29 months, $p=0.01$). The relationship between mLDH levels and ICPFS is illustrated in Figure 1.

In the univariate analysis for ICPFS, only mLDH was identified as a significant factor. However, the multivariate analysis did not identify any significant factors. The results of the multivariate analysis for ICPFS are presented in Figure 2.

The median survival time was 39 months in the general population. Patients with high mLDH levels exhibited inferior OS compared to those with low mLDH levels (25 months vs. not reached, respectively, $p=0.034$). The relationship between mLDH levels and OS is illustrated in Figure 3.

In both univariate and multivariate analyses, only mLDH levels were identified as an associated factor with OS (hazard ratio: 3.92; 95% confidence interval, 1.15-13.3, $p=0.02$). No association was found between OS and sex, age, ECOG, smoking status, or chemotherapy regimen/cycles (Figure 4).

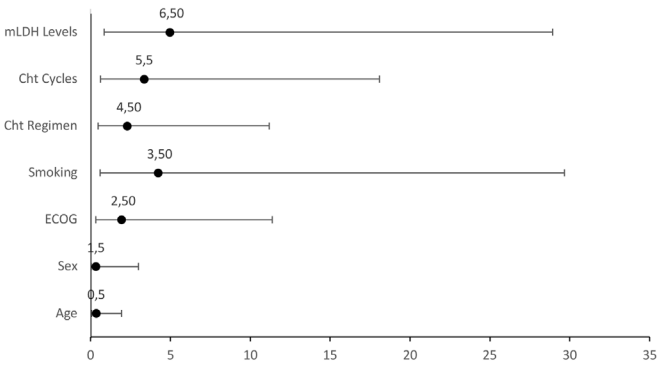


Figure 2. Multivariate analysis for ICPFS.
mLDH: Maximum serum lactate dehydrogenase, Cht: Chemotherapy, ECOG: Eastern Cooperative Oncology Group, ICPFS: Intracranial progression-free survival

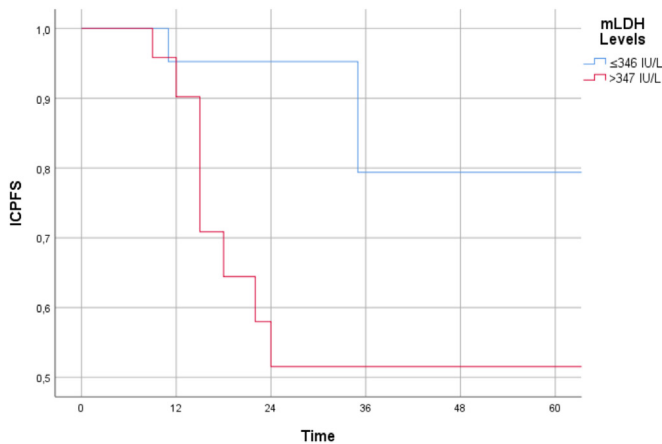


Figure 1. Kaplan-Meier curve of mLDH groups for ICPFS.
mLDH: Maximum serum lactate dehydrogenase, ICPFS: Intracranial progression-free survival

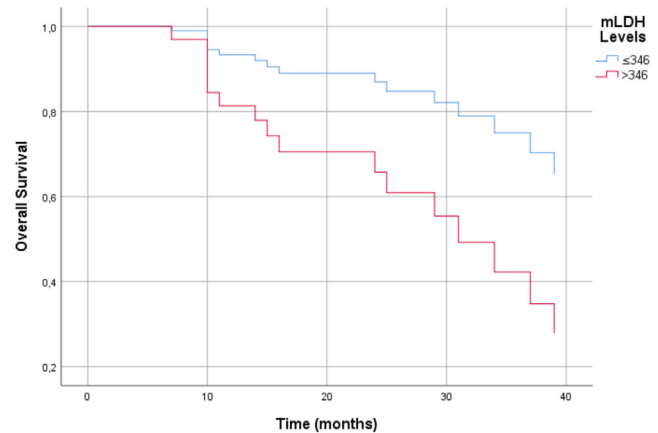


Figure 3. Kaplan-Meier curve of mLDH groups for OS.
mLDH: Maximum serum lactate dehydrogenase, OS: Overall survival

Table 1. Patients characteristics

Characteristic		Whole cohort	mLDH ≤346	mLDH >346	p-value
Age, years	≤59	26 (52%)	12 (48%)	14 (56%)	0.77
	>59	24 (48%)	13 (52%)	11 (44%)	
Sex	Male	39 (78%)	19 (76%)	20 (80%)	1
	Female	11 (22%)	6 (24%)	5 (20%)	
ECOG	0	8 (16%)	3 (12%)	5 (20%)	0.74
	1	40 (80%)	21 (84%)	19 (76%)	
	2	2 (4%)	1 (4%)	1 (4%)	
Smoking	Yes	33 (66%)	13 (52%)	20 (80%)	0.07
	No	17 (34%)	12 (48%)	5 (20%)	
Chemotherapy regimen	Cis-ETO	37 (74%)	17 (68%)	20 (80%)	0.51
	Carbo-ETO	13 (26%)	8 (32%)	5 (20%)	
Number of chemotherapy cycles	≤5	24 (48%)	15 (60%)	9 (36%)	0.67
	6	26 (52%)	10 (40%)	16 (64%)	

mLDH: Maximum serum lactate dehydrogenase, ECOG: Eastern Cooperative Oncology Group, Cis: Cisplatin, ETO: Etoposide, Carbo: Carboplatine

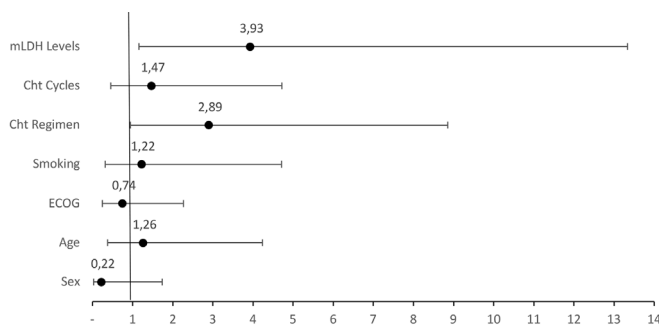


Figure 4. Multivariate analysis for OS.

mLDH: Maximum serum lactate dehydrogenase, Cht: Chemotherapy, ECOG: Eastern Cooperative Oncology Group, OS: Overall survival

DISCUSSION

SCLC is an aggressive cancer that has a strong tendency for brain metastasis (12,13). Therefore, the potential benefits of PCI have been discussed. In a meta-analysis published in 1999, Auperin et al. (7) found that PCI was associated with improved disease-free survival, OS, and a reduction in brain metastases. Subsequently, several studies corroborated these findings, establishing PCI as a standard of care for limited-stage SCLC (7,14-16). In extensive-stage SCLC, two pivotal studies have indicated that PCI may reduce the incidence of brain metastases. In the EORTC trial, a total of 286 patients with extensive stage SCLC were included. The incidence of symptomatic brain metastasis was significantly higher in the group that did not receive PCI (41.3% vs 16.8%, respectively). Patients in the PCI group exhibited significantly longer OS than those in the control group (6.7 months vs 5.4 months, $p=0.003$) (17). However, it should be noted that brain MRI is not mandatory for inclusion in the trial. As such, patients with brain metastases may be included, which could lead to a non-significant difference in OS. Subsequently, Takahashi et al. (18) conducted a trial in which brain MRI before randomization was mandatory. No significant difference in survival was observed between the PCI and control groups (11.6 months vs. 13.7 months, respectively; $p=0.094$). In conclusion, in limited-stage SCLC, PCI reduces the incidence of brain metastasis and improves OS. However, PCI reduces the incidence of brain metastasis in extensive-stage SCLC, it doesn't improve OS.

The benefit of PCI in patients with extensive stage and very early stage (stage 1) disease remains unclear, and there is ongoing debate regarding the appropriate candidates for this procedure. Therefore, it is crucial to ascertain the risk of recurrence following PCI. LDH is a key enzyme in glycolysis. Since tumor cells primarily derive their energy through glycolysis, LDH plays a significant role in tumor growth, invasion, and metastasis (19,20). Research has shown that serum LDH serves as a predictor for various types of cancer, such as prostate, gynecological, gastrointestinal, and thoracic cancers (21-23). Furthermore, numerous studies have investigated lung cancer, especially SCLC. A meta-analysis of fourteen studies involving 4,084 patients indicated that elevated pre-treatment LDH levels were significantly associated with decreased OS in lung cancer patients (10). In a study of patients with brain metastatic lung cancer who

were treated with WBRT, pre-treatment LDH levels were associated with poor survival outcomes (11). Suzuki et al. (24) showed that high pre-treatment LDH levels were linked to a greater risk of brain metastasis. A study was subsequently conducted on patients with SCLC who had undergone TRT and PCI. This study identified the pre-treatment LDH levels and the mLDH levels during treatment as predictors of OS and ICPFS following TRT and PCI. The two-year OS and ICPFS rates were: 51.1% and 73.8% in the high mLDH group, and 74.2% and 91.7% in the low mLDH group, respectively ($p<0.01$ in both cases) (25).

The results of our research, indicate that elevated mLDH levels predict ICPFS and OS in patients undergoing treatment with TRT and PCI. Patients with elevated mLDH levels showed poorer OS and ICPFS outcomes compared to those with low mLDH levels (median OS: 25 months vs not reached months, respectively, $p=0.034$; median ICPFS: 15 months vs 29 months, $p=0.01$). These findings support previous research and confirm the link between LDH and prognosis. Given these findings, serum LDH levels can be used to predict the occurrence of brain metastasis and OS following PCI. This method allows for a more precise identification of patients who are likely to benefit from PCI.

Study Limitations

Our study has some limitations. Firstly, it is retrospective in design. Secondly, the sample size is small and the study is based on data from a single centre. Despite these limitations, it has demonstrated the prognostic value of LDH.

CONCLUSION

In conclusion, our findings indicate that the peak LDH levels during the treatment of patients with SCLC predict both intracranial failure and survival. The most significant limitation of this study is the relatively small sample size. Consequently, further research is needed to substantiate these findings.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences Türkiye, Gülhane Training and Research Hospital (approval number: 2025/128, date: 12.06.2025).

Informed Consent: Informed consent form was not obtained since it was a retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.N.Ü., H.H., H.B., Concept: A.N.Ü., H.B., Design: A.N.Ü., H.B., Data Collection or Processing: A.N.Ü., H.H., Analysis or Interpretation: A.N.Ü., Literature Search: A.N.Ü., Writing: A.N.Ü.

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

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The 3-dimensional Ovarian Volume Assessment to Evaluate Whether Menopausal Related Symptoms and Hormone Levels Correlate with the Ovarian Volume

Menopozla ilişkili Semptomlar ve Hormon Düzeylerinin Over (Yumurtalık) Hacmi ile ilişkili Olup Olmadığını Değerlendirmek için 3-boyutlu Over Hacmi Değerlendirmesi

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ABSTRACT

Objective: To evaluate whether ovarian volume is correlated with hormonal status and frequent symptoms in menopausal period.

Methods: Sixty-two postmenopausal women who applied for routine yearly gynecological control included. After measurement of ovarian volumes by using Virtual Organ Computer-aided Analysis volume analysis, hormonal levels, and evaluation of symptoms with standardized menopause-specific quality of life questionnaire, comparisons and correlation analysis were performed.

Results: When the time of menopausal period increases the ovarian volume decreased ($p=0.026$), and earlier menopause age correlated with lower ovarian volume ($p=0.014$). Although the results did not reach statistically significance, a negative correlation between ovarian volumes and follicle stimulating hormone levels and a positive correlation between ovarian volumes and Estradiol levels were found ($p=0.46$, $p=0.26$). There was no correlation between ovarian volume analyses with hormonal status and menopausal symptoms.

Conclusion: Both the severity and type of menopausal symptoms and hormonal status do not relate with ovarian volume after the menopause. This finding may be useful to decide to perform oophorectomy or not at the time of hysterectomy in menopausal ages.

Keywords: 3D ovarian volume, menopausal symptoms, three-dimensional ultrasonography, menopause

Öz

Amaç: Menopoz döneminde over hacminin hormonal durum ve sık görülen semptomlarla ilişkili olup olmadığını değerlendirmek.

Yöntemler: Rutin yıllık jinekolojik kontrol için başvuran 62 postmenopozal kadın çalışmaya dahil edildi. Sanal organ bilgisayar destekli analiz (Virtual Organ Computer-aided Analysis yöntemi) hacim analizi kullanılarak over hacimleri ölçüldükten sonra, hormonal düzeyler belirlendi ve semptomlar standartlaştırılmış menopoz-spesifik yaşam kalitesi anketi ile değerlendirildi. Daha sonra karşılaştırmalar ve korelasyon analizleri yapıldı.

Bulgular: Menopoz süresi arttıkça over hacminin azaldığı görüldü ($p=0,026$) ve daha erken menopoz yaşı, daha düşük over hacmi ile ilişkili bulundu ($p=0,014$). İstatistiksel anlamlılığa ulaşmamış olsa da, over hacimleri ile folikül uyarıcı hormon düzeyleri arasında negatif korelasyon ve over hacimleri ile Estradiol düzeyleri arasında pozitif korelasyon saptandı ($p=0,46$, $p=0,26$). Over hacmi analizleri ile hormonal durum ve menopoz semptomları arasında herhangi bir ilişki bulunmadı.

Sonuç: Menopoz sonrası dönemde, menopoz semptomlarının şiddeti ve tipi ile hormonal durumun over hacmi ile ilişkisi yoktur. Bu bulgu, menopoz yaşlarındaki histerektomi sırasında ooferektomi yapıp yapılmayacağına karar vermede yararlı olabilir.

Anahtar Sözcükler: 3B over hacmi, menopoz semptomları, üç boyutlu ultrasonografi, menopoz

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INTRODUCTION

Menopause, the complete cessation of menstrual periods, related with many symptoms that reduce quality of life (QOL) of postmenopausal women. The World Health Organization defines QOL "as an individual's perception of their position in life in the context of culture and values system in which they live, in reference to their goals, standards, and concerns in life" (1). The range and severity of menopausal symptoms vary widely due to lifestyle, cultural and genetical (2).

The most menopausal symptoms consist not only about female genital tracts but also vasomotor, physical, somatic, cardiovascular and skeletal symptoms. (2) Eighty-five percent of postmenopausal women have experienced menopause-related symptoms in terms of the vasomotor symptoms, arthralgia, headache, rapid weight gain, fatigue, sexual dysfunction and urinary incontinence (3). These symptoms decrease QOL during post-menopausal period.

As it is known ovarian volume increases as from the pubertal beginning. During the premenopausal period the volume gradually decreases. In postmenopausal time atrophy is seen in ovaries but personal variations can be monitored (4). There are many studies in the literature that compared the ovarian volume with specifically fertility potentials, body mass index (BMI), hormonal status and bone mineral density (BMD) (5,6).

To our knowledge although there are a number of studies on ovarian volume measurements in different periods of life, there is not any data about the relevance of ovarian volume and postmenopausal symptoms occurrence and severity. The purpose of our study was to evaluate the relationship between three- dimensional (3D) volume analyze and menopause-specific QOL (MSQOL) questionnaire and hormonal levels (7).

MATERIALS AND METHODS

After the approval of Ankara Numune Training and Research Hospital Ethics Committee of clinical trials (decision number E-15-517, date: 24.06.2015) was obtained, transvaginal 3D ultrasonography substructure support was provided by Gazi University local Projects of Scientific Investigation Committee. A power analysis was conducted to determine the required sample size, which was calculated to be 60 patients. This prospective study included 62 postmenopausal women that applied for annual routine gynecological controls to Gazi University Hospital outpatient clinics between November 2016 and November 2017. Written informed consent was obtained from all 62 women who participated in the study. Inclusion criteria were confirmed menopausal status and absence of previous hysterectomy, ovarian surgery, hormonal use currently or during the past 6 months and a personal history of gynecological malignancy. Given the broad age distribution of the patients, menopausal status was assessed based on the clinical criterion of amenorrhea lasting at least one year. If the patients that had ovarian and/or tubal masses during pelvic examination and chronic pelvic pain were excluded from the study.

Demographical characteristics of patients such as age, BMI, gravida, age of menopause and time that the patients spend in menopause were recorded. During routine pelvic examination, 3D ultrasonographic images were applied for ovarian volume analysis.

With 3D transvaginal ultrasonography probe, bilateral ovarian images were taken, and volume of ovaries were calculated by using Virtual Organ Computer-aided Analysis (VOCAL) volume analysis (GE Voluson E6 Ultrasound Systems). In order to enhance measurement reliability, all assessments were conducted by same physician. The VOCAL technique, a semi-automated 3D ultrasound method that enables accurate and reproducible volume measurements of irregularly shaped structures. Patients were questioned regarding the presence of stress urinary incontinence symptoms, and during the physical examination, the presence of incontinence was assessed by increasing intra-abdominal pressure and recorded accordingly. The blood serum levels of follicle stimulating hormone (FSH), estradiol (E2), free and total testosterone, dehydroepiandrosterone, androstenedione levels were assessed. In addition, mammography results and BMD measurements with dual-energy X-ray absorptiometry (DEXA) were also recorded.

In addition to these investigations, the postmenopausal symptoms that affect psychosocial, physical, and sexual functions of women were estimated upon to the serum hormone values and ovarian volumes. These estimations were done by using standard MSQOL questionnaire that was prepared by Sunnybrook Health Science Center (7).

Patients answered 29 different questions about vasomotor, physical, and sexual symptoms and were asked for grading their complaints with numbers 0 to 6.

Statistical Analysis

IBM Statistical package for the social sciences , version 22.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Mean levels of all patient's demographic data, 3D vocal volume analysis, serum hormone levels, MSQOL scoring results were calculated. The mean value differences between the groups with and without symptoms were tested using the Student's test or Mann Whitney U test whether the distribution of the data was normal or not, respectively. The correlation analysis was done with Pearson correlation (2-tailed) test. Differences were accepted as significant if the p values were less than 0.05.

RESULTS

Total number of 62 postmenopausal patients were included to the study. The demographic data of patients, serum levels of hormones, DEXA results and calculations of ovarian volume by 3D vaginal ultrasound were given in Table 1. The mean ovarian volume was calculated as 1.91 cm³. A negative correlation was found in the decrease of ovarian volume and the increase of menopausal period (p=0.026). In addition, a significantly positive correlation was seen between menopausal age and ovarian volume. The earlier menopause age significantly correlated with lower ovarian volume (p=0.014).

There was a non-significant negative correlation between FSH levels and positive correlation between E2 levels and ovarian volume were found (p=0.46 and p=0.26, respectively)

Patients' with and without postmenopausal symptoms were compared regarding ovarian volumes. No statistical difference was found between symptoms and 3D ovarian volume measurements (Table 2).

Table 1. The demographic data, DEXA values, hormone levels, mammography results and 3D ovarian volume calculations of patients

Variables	Mean Values $\pm$ SD
Age	55.51 $\pm$ 5.05
Menopause age	48.82 $\pm$ 4.23
Menopausal period	6.30 $\pm$ 5.38
Gravida	3.25 $\pm$ 2.28
BMI	29.66 $\pm$ 5.05
BMD T score (L1-4)	0.41 $\pm$ 1.57
BMD T score (Femur)	-0.86 $\pm$ 1.10
FSH (mIU/mL)	73 $\pm$ 24
E2 (pg/mL)	21.4 $\pm$ 11.2
T. test (ng/dL)	0.27 $\pm$ 0.21
DHEA (ng/mL)	109.7 $\pm$ 54.70
F. test (pg/mL)	1.51 $\pm$ 0.64
Androstenedion (ng/mL)	0.78 $\pm$ 0.36
TSH (mIU/mL)	2.40 $\pm$ 3.30
Mammography (BIRADS)	1.87 $\pm$ 0.74
OV (cm ³)	1.9 $\pm$ 1.3
ROV (cm ³)	1.99 $\pm$ 1.59
LOV (cm ³)	1.7 $\pm$ 1.4

SD: Standard deviation, BMI: Body mass index, BMD: Bone mineral density, FSH: Follicle stimulating hormone, E2: Estradiol, T. test: Total testosterone, DHEA: Dehydroepiandrosterone, F. test: Free testosterone, TSH: Thyroid stimulating hormone, OV: Total ovarian volumes, ROV: Right ovarian volumes, LOV: Left ovarian volumes, DEXA: Dual-energy X-ray absorptiometry

Table 3 shows the data of grading of vasomotor, psychosocial, physical and sexual symptoms according to MSQOL questionnaire in detail. Ovarian volume calculation was not significantly correlated with each of these symptoms and rating of the answers of the MSQOL questions.

DISCUSSION

This study evaluated the ovarian volume after the menopause with demographic, anthropometric and hormonal parameters and also menopausal symptoms and QOL of patients. According to our results, ovarian volume changes the hormonal values. However menopausal symptoms seem much more multifactorial; these symptoms were not associated with ovarian volume.

There is an ongoing debate on the impact of ovarian function on common menopausal symptoms after the menopause. This discrepancy may also lead to another uncertainty for the decision of prophylactic oophorectomy at the time of hysterectomy regarding to cause any iatrogenic benefit or harm to our patients.

During menopausal symptoms ovarian androgen secretion gradually decreases and postmenopausal ovaries maintain to be an important resource for androgens (8). In our study we aimed to analyze the correlation between the ovarian stromal volume and androgen values and also menopausal symptoms. There was no statistically meaningful correlation between the androgen levels and ovarian stromal volume decrease. This result can be interpreted in two different point. The ovaries are not an important resource for androgens during menopause or the ovarian androgen synthesis during menopause is minimal or negligible.

Previous studies evaluated 3D and 2D ultrasonographic ovarian volumes in women who were in reproductive ages. Nardo et al. (13) reported 3D ovarian stromal volume did not correlate with

Table 2. Comparison of 3D ovarian volume between presence and absence of menopausal symptoms

Vasomotor symptoms, (n)	Ovarian volume (cm ³)	p-value
Exist (22)	1.89 $\pm$ 0.95	0.713
Not exist (40)	2.03 $\pm$ 1.75	
Stress incontinence	Ovarian volume (cm ³)	p-value
Exist (5)	3.05 $\pm$ 3.73	0.512
Not exist (57)	1.85 $\pm$ 0.95	
Urge incontinence	Ovarian volume (cm ³)	p-value
Exist (8)	1.72 $\pm$ 0.58	0.356
Not exist (54)	2.01 $\pm$ 1.55	
Dyspareunia	Ovarian volume (cm ³)	p-value
Exist (8)	2.18 $\pm$ 1.09	0.579
Not exist (54)	1.92 $\pm$ 1.5	
Loss of libido	Ovarian volume (cm ³)	p-value
Exist (21)	1.72 $\pm$ 1.03	0.579
Not exist (41)	2.14 $\pm$ 1.67	

Data were given as mean $\pm$ standard deviation
3D: Three-dimensional

Table 3. MSQOL questionnaire results

Symptoms	Data
Vasomotor symptoms	8.69±6.25
Hot flushes/flushes	3.61±2.49
Night sweats	2.46±2.34
Sweating	2.63±2.2
Psychosocial symptoms	18.8±11.2
Being dissatisfied with my personal life	2.37±2
Feeling anxious or nervous	2.95±2.1
Experiencing poor memory	3.27±2.26
Accomplishing less than I used to	2.78±2.21
Feeling depressed/down/blue	2.69±1.98
Being impatient with other people	2.39±2.12
Feelings of wanting to be alone	2.39±1.94
Physical Symptoms	51.68±23.62
Flatulence(wind) or gas pains	2.8±2.37
Aching in muscles and joints	4.39±2.53
Feeling tired or worn out	3.75±2.28
Difficulty sleeping	3.24±2.79
Aches in back of neck or head	3.47±2.56
Decrease in physical strength	3.71±2.28
Decrease in stamina	2.93±2.24
Feeling a lack of energy	3.19±1.91
Drying skin	3.61±2.6
Weight gain	3.54±2.45
Increased facial hair	2.29±2.2
Changes in appearance, texture or tone of your skin	2.17±2
Feeling bloated	3.02±2.3
Low backache	3.78±2.75
Frequent urination	2.78±2.17
Involuntary urination when laughing or coughing	3.02±2.2
Sexual Symptoms	11.88±7.8
Change in your sexual desire	3.68±2.7
Vaginal dryness during intercourse	3.97±2.7
Avoiding intimacy	4.24±2.96

Data was given as mean ± standard deviation
MSQOL: Menopause-specific quality of life

biochemical indices of PCOS. Flaws et al. (14) found that hormone replacement therapy using did not change ovarian volume. However, till the negative correlation of FSH levels and positive correlation of E2 levels make think that menopausal period is also dynamic period of life.

Although many factors have impact on bone mineral density (BMD), in a study a positive correlation between ovarian volume and BMD at the femoral neck both in T scores and Z scores was reported (5).

Our results contrast with Armeni et al.'s (5) findings as there was not a significant difference in BMD T score of both femoral neck and lumbar spine according to ovarian volume values.

It is already come to be known that the prevalence of menopausal symptoms are related with many different factors like lifestyle, education of women, socioeconomic statute (15). There are different questionnaires that can evaluate the menopausal symptoms and QOL during this period. MSQOL is the most popular questionnaire for QOL evaluation during menopause period. As we already mentioned that menopausal symptoms are multifactorial and are affected by lifestyles; Korean and Chinese studies assessed the applicancy of this questionnaire in their countries. They found this questionnaire as a valid and reliable scale for assessment of menopausal symptoms and QOL (16,17). In our country, the studies that evaluated menopausal symptoms also used MENQOL questionnaire. According to the results of these studies this questionnaire seems as a valid assessment for our population (18,19). In our study the questionnaire results were compared with ovarian volume, a clear correlation cannot be found. The symptoms did not increase when the volume decreased.

Study Limitations

The main limitation of our study is the variability in patients' age ranges and duration of menopause. If the study is repeated with a larger sample size, patients can be stratified according to menopausal duration and age, allowing for group-based comparisons of symptoms and ovarian volumes. Such comparisons may enable a more objective and accurate evaluation of the relationship between ovarian volume, hormonal status, and clinical symptoms.

CONCLUSION

In our study, there was a correlation between hormone levels and ovarian volume; but this change did not reflect to symptoms. These results remarked that menopausal symptoms are multifactorial and affected by many other factors than hormonal status.

In conclusion ovarian volume was not correlated with menopausal symptoms and serum hormonal levels. This finding may be important and kept in mind for the decision of prophylactic oophorectomy at the time of hysterectomy after the menopause.

Ethics

Ethics Committee Approval: The approval is obtained Ankara Numune Training and Research Hospital Ethics Committee of clinical trials (decision number E-15-517, date: 24.06.2015).

Informed Consent: Written informed consent was obtained from all 62 women who participated in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.I.S., İ.G., E.İ.B., S.C.İ., N.B., M.A.O., Concept: İ.G., N.B., M.A.O., Design: İ.G., N.B., M.A.O., Data Collection or Processing: İ.G., E.İ.B., Analysis or Interpretation: G.I.S., İ.G., E.İ.B., S.C.İ., Literature Search: G.I.S., Writing: G.I.S., E.İ.B.

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

Financial Disclosure: Gazi University local project of scientific Investigation Committee.

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A Case of Asymptomatic Bilateral Large Pulmonary Embolism Masquerading as ST Elevation Myocardial Infarction

Belirti Vermeyen İki Taraflı Büyük Pulmoner Emboli Olgusu: ST Elevasyonlu Miyokard İnfarktüsü Taklidi

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ABSTRACT

Pulmonary embolism (PE) is a common and life-threatening medical emergency, but it is still often misdiagnosed due to its wide variety of clinical manifestations. We report a case of a 78-year-old man who presented with urinary retention without any classical symptoms, and was found to have bilateral large PE as confirmed by computed tomography pulmonary angiogram. Initial electrocardiogram (ECG) showed ST segment elevation and T-wave inversion in anteroseptal and inferior leads, with reciprocal changes in lateral leads. Clinicians need to be aware that a diagnostic dilemma between PE and acute coronary syndrome is not uncommon, as both conditions can present with "ischemic-looking" ECG and elevated troponin levels. To our knowledge, this is the first case of an atypical, incidental finding of PE in a patient who presented with urinary retention reported in the literature. Careful analysis and interpretation of ECG are necessary to improve patient evaluation and support clinical decision-making in order to provide the best possible care.

Keywords: Pulmonary embolism, STEMI, urinary retention, prostate malignancy

Öz

Pulmoner emboli (PE), yaygın ve yaşamı tehdit eden bir acil durum olmasına rağmen, klinik belirtilerinin çeşitliliği nedeniyle sıklıkla yanlış tanı almaktadır. Biz, klasik semptomları olmayan ve üriner retansiyon ile başvuran 78 yaşında bir erkek olguyu sunuyoruz; yapılan bilgisayarlı tomografi pulmoner anjiyografi ile bilateral büyük PE saptanmıştır. İlk elektrokardiyogramda (EKG), anteroseptal ve inferior derivasyonlarda ST segment elevasyonu ve T dalga inversiyonu, lateral derivasyonlarda ise karşıt değişiklikler gözlenmiştir. Kliniklerin, PE ile akut koroner sendrom arasında tanısal ikilemlerin nadir olmadığını ve her iki durumun da "iskemiye benzer" EKG değişiklikleri ve artmış troponin seviyeleri ile kendini gösterebileceğini bilmesi önemlidir. Bildiğimiz kadarıyla, üriner retansiyon ile başvuran bir hastada PE'nin bu şekilde atipik ve tesadüfi olarak saptandığı ilk olgudur. Hastaların değerlendirilmesinde ve en iyi bakımın sağlanmasında EKG'nin dikkatli analizi ve yorumlanması, klinik karar verme sürecini desteklemek açısından gereklidir.

Anahtar Sözcükler: Pulmoner emboli, STEMI, üriner retansiyon, prostat malignitesi

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INTRODUCTION

Pulmonary embolism (PE) is a common cardiovascular emergency that is notoriously difficult to diagnose due to a wide spectrum of clinical manifestations. Classic presentations of PE include sudden-onset pleuritic chest pain associated with breathlessness. However, it can also manifest as silent PE, deep vein thrombosis, postural dizziness, or syncope, hemoptysis, sudden cardiac arrest, acute respiratory distress syndrome, arrhythmia, acute heart failure, abdominal pain, delirium, hypoxia, and shock. In some cases, there may be a less obvious connection to paradoxical embolism, such as myocardial infarction, stroke, or lower limb embolism (1). Electrocardiogram (ECG) changes in PE can be inconsistent and non-specific, with common findings including sinus tachycardia, a normal ECG, McGinn-White Sign (S1Q3T3 pattern), rightward axis shift, P pulmonale, complete or incomplete right bundle branch block (RsR' pattern in right precordial lead), atrial dysrhythmia, atrioventricular block, low voltage complexes, and T-wave inversion in the right precordial leads, as well as the less common ST segment elevation (2-6) and ventricular tachycardia (6). Some case reports propose that elevated troponin and ST segment elevation in PE may be due to two possible mechanisms: 1) right ventricular dilatation and failure resulting from increased right heart pressure and afterload due to outflow obstruction, leading to right ventricular ischemia; and 2) paradoxical coronary artery thromboembolism via intra-atrial communication (7). Here, we present a case of an elderly man with atypical presentation who was diagnosed with bilateral PE that mimicked ST-elevation myocardial infarction (STEMI) on the ECG.

CASE REPORT

A 78-year-old gentleman presented with a 20-hour history of urinary retention, abdominal distension for a week, and bilateral leg swelling for a month. Upon arrival at the emergency department, a urinary catheter was immediately inserted, as a bladder scan showed over 1000 mL of urinary retention, with over 2 litres of clear urine being drained. The patient denied experiencing any other symptoms such as breathlessness, chest pain, or urinary symptoms. His medical history included hypothyroidism, hypertension, mild aortic stenosis

(AS), and prostate cancer. He was on regular medication, including Levothyroxine 125 mcg, Tamsulosin 400 mcg modified release, and Verapamil 240 mg slow release for essential hypertension. Additionally, he received Leuprolerin injections every 3 months for prostate cancer. The patient is an ex-smoker and lives independently with his wife. Vital signs were relatively stable, with a temperature of 36 °C, blood pressure of 120/78 mmHg, pulse rate of 88 beats per minute, respiratory rate of 17 per minute, and oxygen saturation of 93% under room air. He was fully conscious and well oriented to time, place, and person. On cardiovascular examination, normal heart sounds were noted, along with an ejection systolic murmur. Reduced air entry was observed on the left side of the chest. The abdomen was slightly distended without shifting dullness, and bilateral pitting pedal edema was present.

The chest X-ray revealed a left-sided pleural effusion with consolidation underneath. Routine blood tests showed a slightly elevated white cell count of $12.9 \times 10^9/L$ (normal range: $4-11 \times 10^9/L$), neutrophil count of $9.6 \times 10^9/L$ (normal range: $2.0-7.5 \times 10^9/L$), a raised platelet count of $473 \times 10^9/L$ (normal range: $150-400 \times 10^9/L$), and normal electrolyte levels with creatinine of $10^9 \mu\text{mol/L}$ (normal range: $60-110 \mu\text{mol/L}$) and eGFR of $56 \text{ mL/min/1.73 m}^2$ (normal range: $>60 \text{ mL/min/1.73 m}^2$). The total protein level was 65 g/L (normal range: $60-80 \text{ g/L}$), albumin was 28 g/L (normal range: $35-50 \text{ g/L}$), CRP was 50 mg/L (normal range $<1 \text{ mg/L}$), and troponin was modestly raised at 89.1 ng/L (normal range $<14 \text{ ng/L}$). The Prostate-specific antigen level was 40 ng/mL (normal range: $<4 \text{ ng/mL}$), and D-dimer was 7754 ng/mL (normal range: $<500 \text{ ng/mL}$). International normalized ratio was 1.5 (normal range: 0.9-1.2); and prothrombin time and APTT were normal. A resting 12-leads ECG showed sinus rhythm, normal axis, and the S1Q3T3 pattern (presence of Q wave and T-wave inversion in Lead III, prominent S wave in Lead I). It also showed ST-segment elevation and T-wave inversion in Leads V1-4, Lead III, and aVF, along with reciprocal ST depression in Lead I and aVL (Figures 1, 2). These ECG findings led to a differential diagnosis of PE versus acute coronary syndrome (ACS). His echocardiogram showed normal biventricular size and wall thickness, normal systolic function with an estimated EF of ~60-65% (normal range: 55-70%), moderate AS, and 4 cm of left pleural effusion.

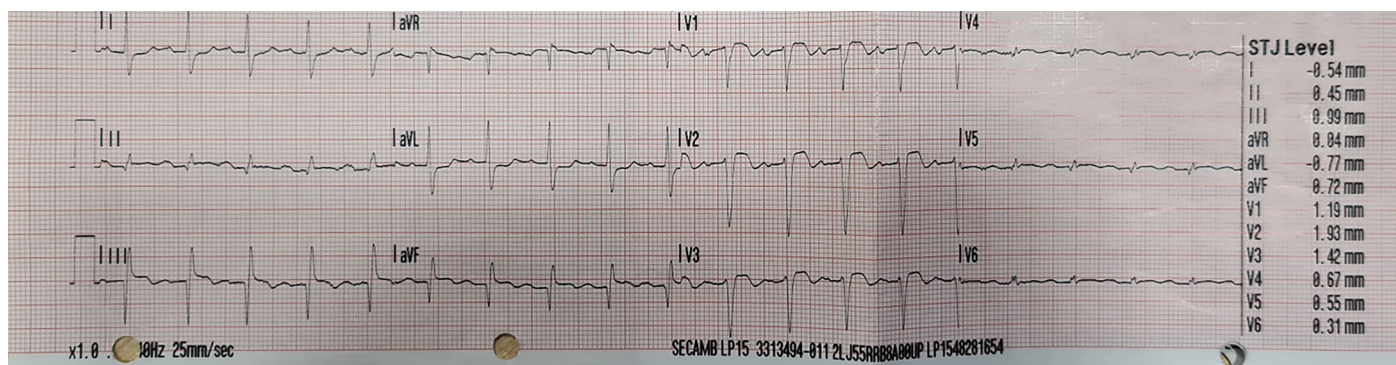


Figure 1. Electrocardiogram showed ST elevation in lead III, aVF, V1-4, along with reciprocal subtle ST depression in lead I, aVL, and an S1Q3T3 pattern.

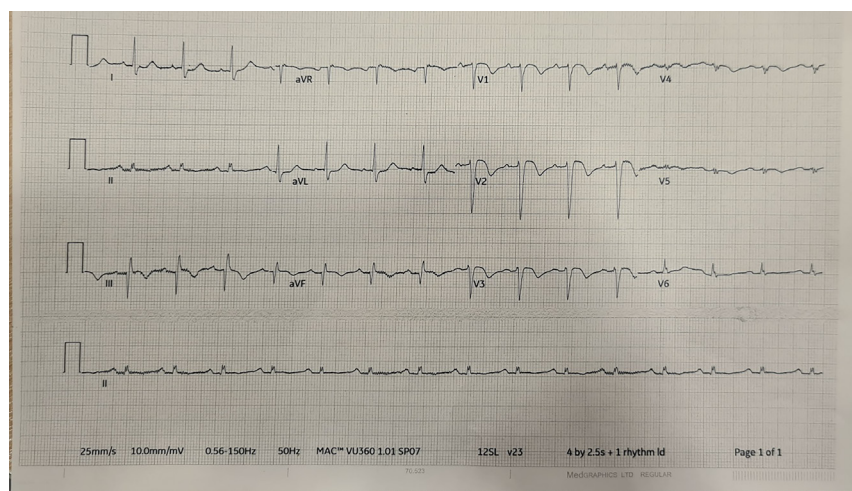


Figure 2. Electrocardiogram showed ST elevation in lead III, aVF, V1-4 along with subtle ST depression in lead I, aVL and S1Q3T3 pattern.

Nasal prong oxygen support of 2 liters was given, and Aspirin 300 mg was initially administered, considering the possibility of myocardial ischemia. Subsequent blood tests on serial troponin levels and an urgent computed tomography pulmonary angiogram (CTPA) were requested. As per trust protocol, Antibiotics were also provided to cover chest infection. The second troponin was measured at 187. CTPA revealed large volume central filling defects involving the left main pulmonary artery, extending just across the main bifurcation, and bilateral upper lobe and lower lobe pulmonary arteries, with an enlarged pulmonary artery measuring 32 mm and evidence of right heart strain (Figure 3). In the context of a hemodynamically stable condition, he was treated low molecular weight heparin (Dalteparin SC injection 15,000 units once daily) for bilateral PE. After treatment, normalized troponin levels and resolved ECG changes were reassuring to exclude an acute coronary event. Coronary angiogram was therefore not pursued (Figure 4). The case was discussed with the urology team and in. The bone scan revealed widespread osseous metastases within the spinal column, pelvic bones, ribs, scapulae and the proximal right femur (Figure 5). Bicalutamide 50 mg, for maximum androgen blockade treatment, was commenced, and then the patient was discharged home with oral anticoagulant (Apixaban 5mg twice daily), long-term catheter, and a follow-up plan with the urology team.

DISCUSSION

PE is a prevalent and potentially life-threatening cardiovascular condition with multiple diagnostic challenges. To our knowledge, this case represents a silent presentation of PE, mimicking STEMI, which is unique in the literature. It is also noteworthy that, despite having a large bilateral PE with right heart strain, the patient exhibited no chest pain, dyspnea, hypotension, or tachycardia, unlike other cases reported in the literature (4,5,8). Moreover, despite showing mildly low oxygen saturation, which is a common feature of massive or submassive PE, a relatively low suspicion of PE

was due to the presence of pleural effusion and consolidation on the chest radiograph.

Secondly, in our case, the patient's history and presentation did not suggest silent PE, which could have led to miss ECG examination due to the lack of indication and absence of classical cardiovascular or pulmonary symptoms. The literature on classical features of reciprocal ischemic ECG changes and modestly raised troponin levels with an upward trend, favors the alternative diagnosis of ACS rather than PE, which prompted ACS treatment initially. According to the literature, reciprocal ECG changes are specific for coronary ischemic disease with a high predictive value (9). However, it is worth noting



Figure 3. Computed tomography pulmonary angiogram showed bilateral pulmonary emboli.

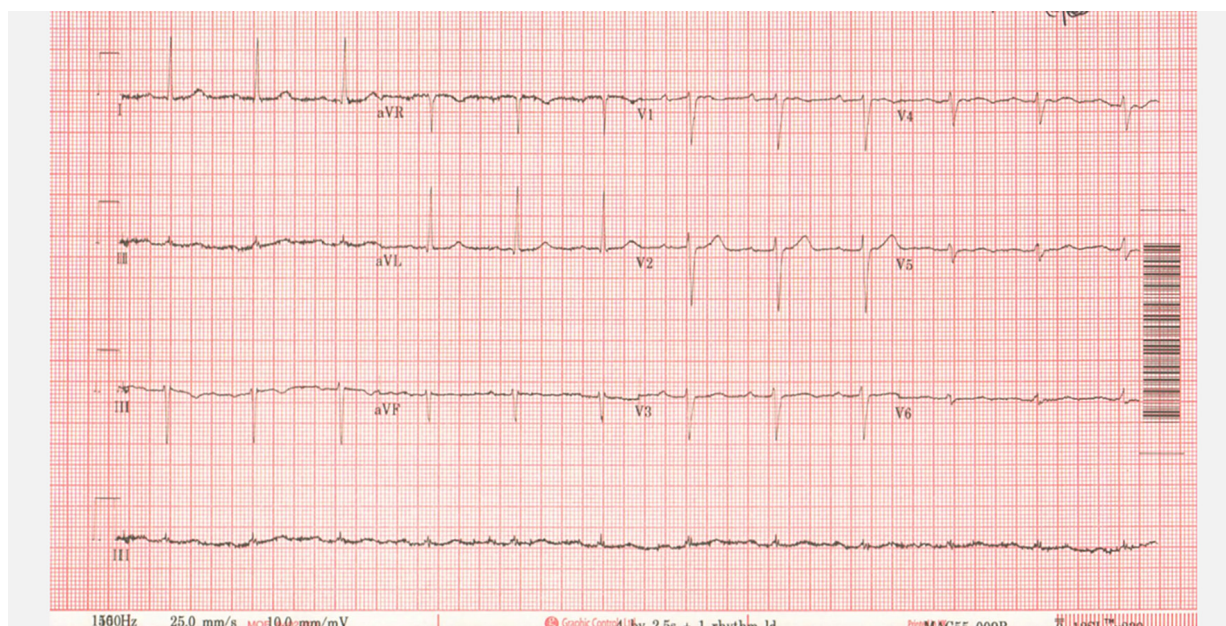


Figure 4. The electrocardiogram showed resolved changes of ischemia.

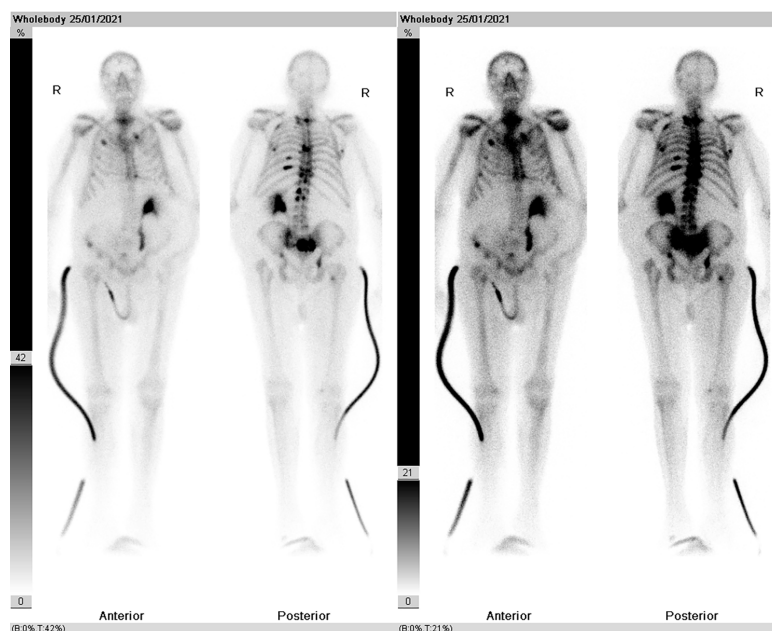


Figure 5. Bone scan showed extensive bone metastases.

that Ladage et al. (8) recently reported a non-coronary artery occlusion case with anterior STEMI and reciprocal ST changes in inferior leads, but without evidence of right heart strain in a patient with PE. Additionally, T-waves inversion in precordial or inferior leads, could indicate right heart strain in massive PE (4), but these findings can also be found in ACS.

In this case, the presence of active malignancy as a significant risk factor for PE, in the context of abnormal ECG findings, including right heart strain pattern, prompted investigation with CTPA, confirming bilateral large PE. Many cases of PE with ST elevation V1-V3/V4 have been described in the literature (3,4,8,9). If ST elevation is present

in PE, the likelihood of RV strain (100%), RV dysfunction (100%), and bilateral PE (75%) is high. Therefore, clinicians should be vigilant in carefully examining the ECG, even in elderly patients who do not complain of chest pain or dyspnea. Elevated troponin levels due to right ventricular ischemia and failure are associated with increased morbidity and mortality in patients with PE (10-13).

Timely diagnosis of acute PE is critical to prevent hemodynamic decompensation and potential complications, including cardiac arrest. Differentiating between acute and chronic PE in asymptomatic patients remains challenging (14). Certain features, such as ECG reversibility with anticoagulation, an enlarged pulmonary artery

diameter, and the difficulty in distinguishing acute from chronic PE in asymptomatic patients, suggest an acute PE diagnosis. Promptly distinguishing between PE and ACS is essential for appropriate management and to prevent mortality. Clinicians should be aware that bilateral PE can manifest atypically in elderly patients, resembling ST elevation myocardial infarction, due to right ventricular strain and ischemia.

CONCLUSION

Our case presents a unique and atypical presentation of bilateral large PE in an elderly patient without cognitive impairment. The absence of classical symptoms like chest pain or dyspnea posed diagnostic challenges, and the initial ECG findings mimicking ACS prompted timely treatment for ACS. However, thorough ECG analysis and subsequent investigations confirmed the diagnosis of PE. This case underscores the need for careful evaluation and a high index of suspicion to differentiate between PE and ACS promptly. It also highlights the importance of considering atypical presentations in elderly patients. Overall, our report adds clinical significance to the existing literature on PE and emphasizes the need for timely and accurate management decisions to prevent adverse outcomes and improve patient care.

Ethics

Informed Consent: The patient has provided informed consent for the publication of this case and has signed the consent form.

Footnotes

Authorship Contributions

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

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Waldenström Macroglobulinemia Mimicking A Primary Lung Carcinoma

Primer Akciğer Karsinomunu Taklit Eden Waldenström Makroglobulinemisi

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ABSTRACT

Waldenström macroglobulinemia (WM) is a rare hematological disease that accounts for 1-2% of non-Hodgkin lymphomas. WM is a variant of lymphoplasmacytic lymphoma and is characterized by bone marrow involvement as well as immunoglobulin M monoclonal gammopathy. It occurs as 3 to 4 cases per million each year. Extramedullary involvement of this entity is rare, and lung involvement may present radiologically as a mass, nodular lesion, diffuse infiltration, or pleural effusion. The diagnosis can be made by performing a biopsy of the pulmonary parenchyma, bronchoalveolar lavage, or cytological examination of pleural fluid. Here, we aimed to present a case of WM mimicking primary lung carcinoma radiologically.

Keywords: Waldenström macroglobulinemia, lung cancer, VATS, PET-CT

Öz

Waldenström makroglobulinemisi (WM), Hodgkin dışı lenfomaların %1-2'sini oluşturan nadir bir hematolojik hastalıktır. WM, lenfoplazmositik lenfomanın bir varyantıdır ve kemik iliği tutulumu ve immünoglobulin M monoklonal gammopati ile karakterizedir. Yılda milyonda 3-4 vakada görülür. Bu antitenin ektramedüller tutulumu nadirdir ve akciğer tutulumu radyolojik olarak kitle, nodüler lezyon, yaygın infiltrasyon veya plevral efüzyon olarak ortaya çıkabilmektedir. Tanı, pulmoner parankim biyopsisi, bronkoalveolar lavaj veya plevral sıvının sitolojik incelemesi ile konulabilmektedir. Burada, radyolojik olarak primer akciğer karsinomunu taklit eden bir WM olgusunu sunmayı amaçladık.

Anahtar Sözcükler: Waldenström makroglobulinemisi, pulmoner karsinom, VATS, PET-CT

INTRODUCTION

Waldenström macroglobulinemia (WM) is a rare hematological disease that accounts for 1-2% of non-Hodgkin lymphomas (NHL) (1). It is characterized by B lymphocytes, lymphoplasmacytoid cells, and plasma cell infiltration in the bone marrow, as well as serum immunoglobulin M (IgM) monoclonal gammopathy (2). It occurs as 3-4 cases per million each year. Extramedullary involvement is rarely seen in patients with WM and is usually seen found in the lungs, soft tissue, central nervous system, kidneys, and bone (3). Lung involvement of WM is rare and may present as a mass, nodular

lesion, diffuse infiltration, or pleural effusion (2). When a lung lesion is detected in patients with WM, extramedullary involvement of WM, pneumonia, primary, and metastatic lung carcinoma should be considered in the differential diagnosis (4). Here, we aimed to present a case of lung involvement of WM mimicking primary lung cancer.

CASE REPORT

A 58-year-old male patient, an active smoker, was admitted with left hip pain, and a mass lesion was detected in the left iliac wing. A

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biopsy was taken from the bone, and histopathological examination revealed that bone material contained B-cell lymphoid neoplasia with prominent plasmacytic differentiation. In further examinations, the bone marrow was observed to be normocellular. In laboratory findings, serum protein electrophoresis showed: beta globulin-9.73%; gamma globulin-44.28%; and an M-spike was observed. The final diagnosis was WM, and the patient received 2 cycles of rituximab and bendamustine. In the interim evaluation, a suspicious lesion was observed in the patient's chest X-ray. Thorax computed tomography (CT) was performed, and a nodular lesion with a 2 cm diameter was detected in the upper lobe of the right lung (Figure 1A). Positron emission tomography-CT showed pathologically increased uptake maximum standardized uptake (SUV_{max} : 5.9) of ^{18}F - fluorodeoxiglukoz on the pulmonary nodule, and there was neither mediastinal lymph node involvement nor extrapulmonary uptake (Figure 1B). Videothoroscopic wedge resection/frozen section procedure was planned because transthoracic fine needle aspiration biopsy was not diagnostic. Frozen section examination was reported to be a haematological malignancy. The postoperative period of the patient was uneventful, and he was discharged on the 4th day of the operation. Histopathological examination revealed low-grade B-cell lymphoma, with marked plasmacytic differentiation. Tumor consisted of lymphoid cells with small hyperchromatic nuclei, indistinct nucleoli, and layers of plasma cells containing prominent Russell bodies. The immunohistochemical study showed that lymphoid infiltration was stained with CD20, while plasma cell sheets were positive with CD138, MUM-1, and VS38C. Although plasma cells were Kappa negative, they were monotypic with lambda (Figures 2, 3). The third cycle of the rituximab and bendamustine protocol was administered to the patient, and the follow-up of the

patient continued uneventfully. The informed consent form was obtained from the patient for publication.

DISCUSSION

Here we present a case of pulmonary WM mimicking primary lung malignancy. It has been emphasized in the literature that the incidence of WM is higher at age 70 and in males (2). Although our case was male he was younger than those in the literature. Most of the WM patients with lung involvement are asymptomatic at the time of diagnosis, some may present with cough, shortness of breath and chest pain (5). Also, our case was asymptomatic in agreement with the literature. In radiological imaging, lung lesions can be observed as a mass, nodular lesion, diffuse infiltration, or pleural effusion (2). In our case, the lesion presented as a solitary pulmonary nodule, and it was not possible to rule out primary lung malignancies with radiological imaging alone. There are cases of coexistence of NHL with non-small cell carcinoma in the literature (6). Banwait et al. (2) reported the rate of extramedullary involvement of WM was 4.3% in a large series. Lung involvements occurred as mass, nodules, or pleural effusion. Patients with IgM monoclonal gammopathy of uncertain significance (MGUS) have an increased risk of developing WM. Therefore, IgM MGUS is thought to be the precursor of WM, and myeloid differentiation primary response 88 (MYD88) mutations in most cases of WM indicate the potential role of this mutation in pathogenesis. The definitive diagnosis of pulmonary WM is made by histopathological examination and immunohistochemical study. B cell markers; immunoglobulin light chain and Ig-M positivity; cyclin D1, CD5, and CD10 negativity were observed in immunohistochemical studies (3). Histopathological examination and immunohistochemical studies of our case were consistent with the literature. However, no

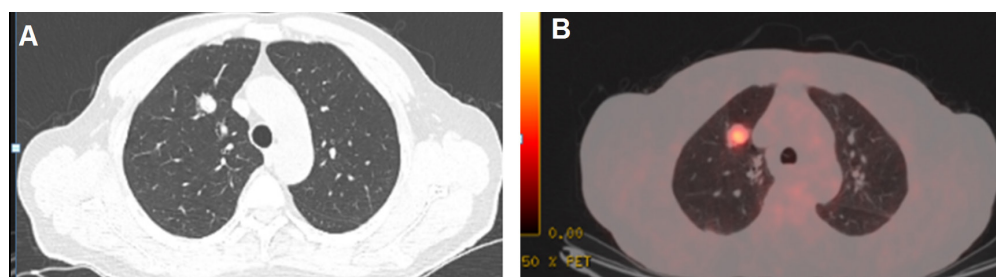


Figure 1. (A) Thorax computed tomography shows a solitary pulmonary nodule with a diameter of 2 cm in the right upper lobe. B) Pathologic increased uptake of ^{18}F -FDG on positron emission tomography/ computed tomography is seen (SUV_{max} : 5.9).

FDG: Florodeksiglukoz, Max: Maximum

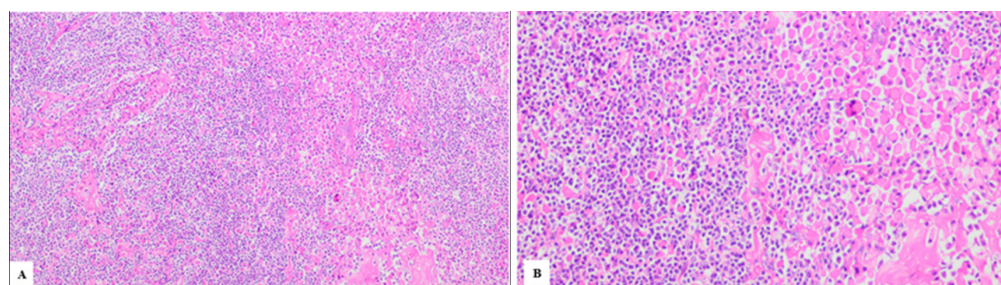


Figure 2. Hematoxylin and Eosin stain shows, low-grade B-cell lymphoma with marked plasmacytic differentiation and tumor cells consist of lymphoid cells with small hyperchromatic nuclei, indistinct nucleoli and layers of plasma cells containing prominent Russel bodies (A: 100 magnification, B: 200 magnification).

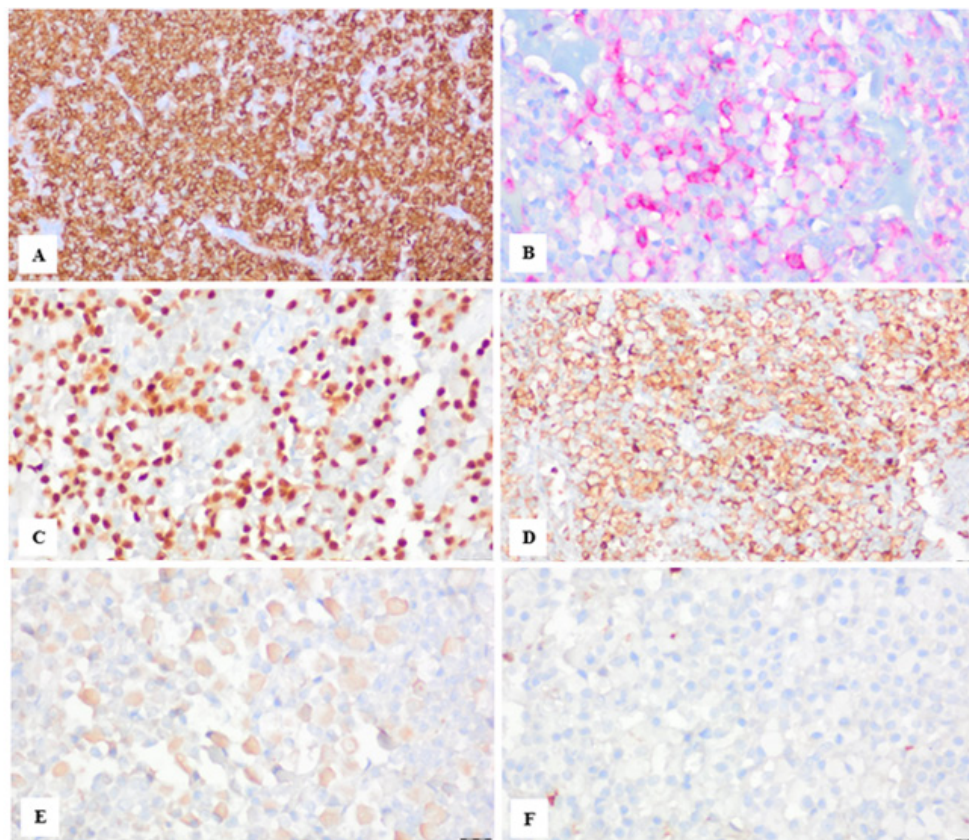


Figure 3. Immunohistochemical study of lesion; (A) lymphoid infiltration shows CD20 positivity, (B) plasma cell sheets are positive with CD138, (C) plasma cell sheets are positive with MUM-1, (D) plasma cell sheets are positive with VS38C, (E) plasma cells are monotypic with lambda, (F) kappa is negative.

MYD88 mutation was observed. WM is usually a slow-progressing disease, and the median survival is relatively good. Advanced age, peripheral blood cytopenia, high beta-2 microglobulin levels, and high serum IgM (>7 g/dL) levels were reported as poor prognostic factors (3). None of the poor prognostic factors was present in our case, and his follow-up continues uneventfully.

CONCLUSION

Although the association of NHL and pulmonary malignancies is rarely reported, pulmonary malignancies should be kept in mind in the differential diagnosis and histopathological confirmation should be performed. Informed consent form was obtained from the patient for publication

Ethics

Informed Consent: Informed consent form was obtained from the patient for publication.

Footnotes

Authorship Contributions

Surgical and Medical Practices: I.A., E.V., M.T., M.S., A.C., T.K., N.A., Concept: I.A., N.A., M.S., A.C., Design: I.A., N.A., M.S., A.C., Data Collection or Processing: I.A., E.V., M.T., M.S., T.K., N.A., Analysis or Interpretation: I.A., N.A., M.S., A.C., Literature Search: I.A., E.V., M.T., N.A., M.S., A.C., Writing: I.A., T.K., N.A., M.S., A.C.

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The Facial Emphysema After Bichat Fat Pad Closure of the Oroantral Communication: Case Report

Oroantral İletişimin Bichat Yağ Yastığı ile Kapatılmasından Sonra Gelişen Yüz Amfizemi: Olgu Sunumu

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ABSTRACT

Oroantral communication (OAC) is a common complication in oral and maxillofacial surgery and usually occurs after tooth extraction. The buccal fat pad (BFP) procedure is a relatively safe approach for closing an OAC. However, this procedure can lead to complications such as swelling, hematoma, infection, and subcutaneous facial emphysema (SFE). SFE is a swelling that increases by the invasion and spreading of air into the deep tissue and cervicofacial planes, causing dissection of the skin. The diagnosis of SFE is usually made by observing swelling, and the finding of crepitus through palpation. SFE is usually a self-limiting complication and managed by careful postoperative follow-up; however, in some cases, it may require antibiotic prophylaxis and surgical decompression. In this case report, a rare case of SFE, which was developed following treatment of OAC by using BFP, is described.

Keywords: Oroantral communication, buccal fat pad, emphysema

ÖZ

Oroantral açıklık (OAA), ağız, diş ve çene cerrahisinde sık görülen bir komplikasyondur ve genellikle diş çekimi sonrası ortaya çıkar. Bukkal yağ dokusunu (BYD) kullanarak OAA'nın kapatılması nispeten güvenli bir yaklaşımdır. Ancak bu prosedür; şişlik, hematoma, enfeksiyon ve subkutanöz fasiyal amfizem (SFA) gibi komplikasyonlara yol açabilir. SFA, havanın derin doku ve servikofasiyal planlara invazyonu ve yayılımı ile ortaya çıkan, derinin diseksiyonuna neden olan bir şişliktir. SFA'nın tanısı genellikle şişlik gözlemlenmesi ve palpasyonla krepitasyon bulgusunun saptanması ile konulur. SFA genellikle kendi kendini sınırlayan bir komplikasyondur ve dikkatli postoperatif takip ile yönetilir; ancak bazı vakalarda antibiyotik profilaksisi ve cerrahi dekompresyon gerekebilir. Bu olgu sunumunda, OAA'nın BYD kullanılarak tedavisini takiben gelişen nadir bir SFA vakası tanımlanmaktadır.

Anahtar Sözcükler: Oroantral açıklık, bukkal yağ yastığı, amfizem

INTRODUCTION

Oroantral communication (OAC) and development of an oroantral fistula (OAF) are common complications of tooth extraction (1). Various surgical methods have been described for the closure of the OAF/OAC, including buccal or palatal flaps and their modifications (2). The choice of the technique depends on the surgeon's decision.

In 1977, Egyedi described the application of the buccal fat pad (BFP) for the palatal defect. Since then, BFP has been used for

severe surgeries, including bone defects after tumor excision, the treatment of OAC/OAF, osteonecrosis of the jaws, and cleft repair and lift repair. Recently, the use of BFP for the reconstruction of OAC/OAA has become quite common (3).

BFP is a relatively safe surgical procedure; however, it may be associated with complications such as partial or complete loss of the flap, limited mouth opening, swelling, hematoma, and/or infection. This procedure may cause complications such as swelling, hematoma, infection, and subcutaneous facial emphysema (SFE) (1).

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The diagnosis of SFE is usually made by swelling and the finding of crepitus by palpation. SFE is usually a self-limiting complication and managed by careful postoperative follow-up; however, in some cases, it may require antibiotic prophylaxis and surgical decompression.

In the present case, a rare complication of SFE was described, which occurred following closure of OAC by means of BFP.

CASE REPORT

A 27-year-old male patient was referred to the oral and maxillofacial surgery department for the extraction of the left first molar. The medical history was unremarkable. Extraoral examination was within normal limits. On intraoral examination, an unrecoverable depth of caries was detected in tooth 26, and extraction was planned. A panoramic radiography examination showed the close relationship between posterior maxillary tooth roots and the maxillary sinus (Figure 1). Informed consent was obtained from the patient, and the extraction was performed without using high-speed air turbine drills. Following the extraction of the tooth, an OAC was observed. The defect was approximately 5 to 10 mm.

The treatment plan included double-layered closure of the OAC with BFP and oral mucosa. A trapezoidal mucoperiosteal flap was created by means of a sulcular incision along the alveolar ridge. Bichat adipose tissue was used to close the entire defect resulting from the OAC. Considering the anatomical position of the papilla parotidea, a 1 cm vertical incision was made posterior to the zygomatic buttress. Buccal extension of Bichat's fat pad was explored by blunt dissection through the buccinator muscle (4,5). The necessary amount of Bichat's fat pad was mobilized with light pressure to cover the OAF entirely. The full-thickness flap was sutured with resorbable suture without tension. Metronidazole 500 mg (Sanofi, İstanbul, Türkiye) and amoxicillin + clavulanic acid 1 g (GlaxoSmithKline, İstanbul, Türkiye) were prescribed twice daily for 14 days.

About 1 hour after the operation, the patient returned to the oral and maxillofacial surgery department with the complaint of facial swelling within a few seconds (Figure 2). The patient reported that he had a sudden swelling, which occurred immediately after running up the stairs. The swelling and crepitus were noted on palpation. On intraoral examination, the surgical area was intact, and no signs of bleeding were observed. In the postoperative follow-up period, the swelling decreased slightly after 12 hours (Figure 3), and minimal

bleeding and pain were observed. The subcutaneous emphysema was completely resolved in 10 days (Figure 4, 5).

DISCUSSION

OAC is a pathological pathway between the maxillary sinus and the oral cavity, and epithelization occurs over time. This process leads to the formation of OAF (6). The most frequent precipitating factor is the extraction of posterior maxillary molars. Dental implant surgery, excision of pathologic lesions, maxillary osteotomies, facial trauma and maxillary osteomyelitis are among the other conditions that may cause OAC (6).



Figure 2. Photographs taken 1 hours postoperatively showing SFE.
SFE: Subcutaneous facial emphysema



Figure 1. Orthopantomography showed the relationship between posterior maxillary tooth roots and the maxillary sinus.

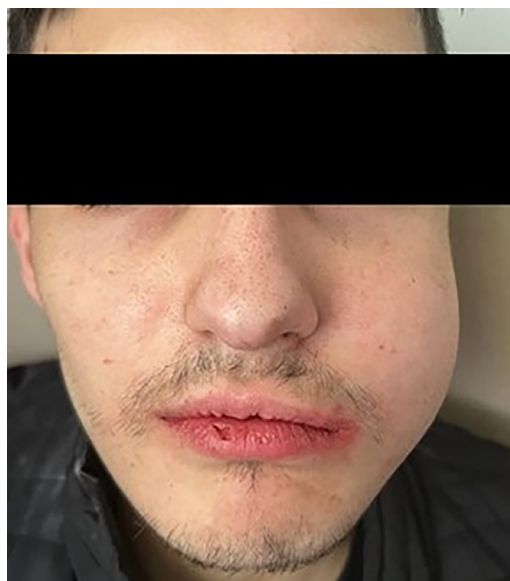


Figure 3. In the postoperative follow-up period, the swelling began to resolve slightly after 12 hours.



Figure 4. In the photograph taken after 24 hours, it is seen that SE decreases and is self-limiting.

SE: Swelling and erythema

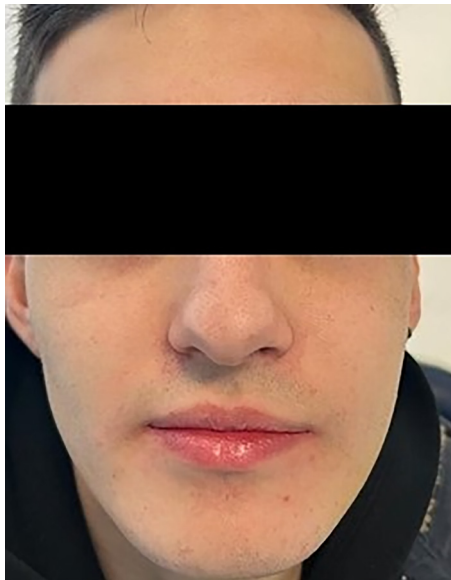


Figure 5. Photographs showing reswelling at 10 days postoperatively.

The surgical management of OAC depends on the location, quantity, and quality of tissue at the defect site, the dimension of OAC, vestibular depth, and the clinical experience of the surgeon (5). Treatment options are primary closure with local and distant sliding tissue flaps, autogenous bone grafts, allogeneous materials, xenografts, and synthetic metals (2).

BFP has been frequently used in oral and maxillofacial surgery, including the reconstruction of OAC (7). The effortless mobilization, rich blood supply, and minimal donor site morbidity make this method preferable to surgeons (8). Dolanmaz et al. (9) reported outcomes of their case series of 75 OAC patients. In this study, the

authors observed a favorable recovery period in all the patients, and the surgical areas were completely epithelialized in 3 to 4 weeks following surgery.

BFP is a well-established and relatively reliable procedure; however, this procedure may cause complications such as swelling, hematoma, and infection (6). Additionally, SFE has been described in the literature as a rare complication following OAC closure with BFP. There are a few reports regarding the cause and clinical course of SFE (1,6,10). Differential diagnosis of SFE should be made among conditions such as hematoma, allergic reactions, or angioedema that may cause an increase in facial volume (11).

SFE is the result of the spread of air along the facial and deep tissue planes. It is characterized by swelling and crepitus on palpation (6). The presence of crepitus on auscultation is the specific pathognomonic sign of SFE on examination with a stethoscope (12). The presence of SFE can also be confirmed radiologically by the appearance of radiolucency in the facial spaces (13). The occurrence of SFE may be explained by 2 mechanisms, including the use of compressed air procedures (high-speed dental handpiece, air-water syringe) and the initiation of communication between the oral cavity and the deeper facial planes and subcutaneous space (14). In dentistry, the most common cause of SFE is the use of an air turbine handpiece during surgical the extraction of a mandibular third molar. Other conditions that do not develop due to dental treatments include traumatic intubation, mechanical ventilation, facial trauma, vomiting causing esophageal rupture, asthma exacerbation with alveolar rupture, intense Valsalva maneuver, and general anesthesia (15). Rocchia et al. (16) showed that air can diffuse to the surrounding tissues from the defects in the paranasal sinuses with the increase in pressure in the upper respiratory tract. The authors also explained that the air follows the path of least resistance while spreading to the connective tissues.

SFE is a self-limiting complication, and usually conservative (antibiotic and observation,) management is required. However, an extensive SFE may need multiple stab incisions to allow air pressure to escape and decompress (17). The extensive SFE could also be fatal as the emphysema may spread to the lateral pharyngeal space and reach the mediastinum by dissecting the visceral space and causing pneumomediastinum (17,18). Fink and Doyle. (19) described the development of emphysema following local anesthesia and optic neuropathy in which air bubbles form in the canalis opticus due to the pressure of SFE on the orbital tissues.

Occasionally, subcutaneous emphysema may cause cellulitis or necrotizing fasciitis (20). The rationale for antibiotic prescription is that air introduced subcutaneously could be nonsterile (6). Furthermore, some authors have applied corticosteroids to reduce edema in the treatment of SFE, but their benefit has not been proven. The management with %100 oxygen is useful for the replacement of the gas in facial planes (11). In the present case, antibiotic treatment was started, and the patient was followed up carefully. The crepitant pain and tenderness were observed, and periorbital ecchymoses were noted on the postoperative second day. No abscess formation was noted postoperatively.

In the oral and maxillofacial region, SFE is mostly encountered with air-turbine handpieces, surgical treatment, head and neck trauma, or infection. Shudo reported that the Valsalva maneuver may be a

causative factor of SFE after closure with BFP. Metin and Tatli. (1) observed SFE after the patient sneezed, and air pressure might have entered the facial planes in the maxillary sinus. Nizar and Nabil. (6) reported that after surgery, patients cleaning their throats with closed mouths may cause increased pressure in the paranasal sinuses. In the present case, SFE was observed after the patient tried to climb the stairs out of. The air pressure in the maxillary sinus probably increased when the patient breathed rapidly. Therefore, air might have entered the subcutaneous tissues.

The patient's cooperation with the postoperative instructions on sinus precautions is critical to inhibit SFE formation. SFE may be induced by the patient sneezing, coughing, avoiding gaping, blowing forcefully, and vomiting. Pipette use and smoking are also not allowed. Besides these precautions, medications such as antihistamines and nasal decongestants, which can reduce the patient's risk of sneezing, may be prescribed (6). Strenuous physical activity, which will increase intrasinusoidal pressure, should also be avoided (6).

CONCLUSION

BFP is frequently preferred to close the large OCA. An oral and maxillofacial surgeon should know the anatomy of the Bichat fat pad tissue very well, and should have a good grasp of the nature of complications. One of the rare complications of BFP is SFE. SFE is mostly benign and self-limiting, although in some cases it may be life-threatening. Conservative treatment with close follow-up is usually sufficient for the management of SFE.

Ethics

Informed Consent: Informed consent was obtained from the patient and the extraction was performed without using high-speed air turbine drills.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.B.Y., T.K., Concept: Y.K., Design: E.B.Y., T.K., Data Collection or Processing: E.B.Y., Y.K., Literature Search: T.K., Writing: T.K.

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

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Struma Ovarii: A Case Series and Literature Review of Current Management

Struma Ovarii: Güncel Yönetim Stratejilerine İlişkin Olgu Serisi ve Literatür İncelemesi

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ABSTRACT

Struma ovarii (SO), also known as ovarian goiter, is a rare monodermal teratoma. About 5-20% of mature teratomas contain thyroid tissue elements, but of these, only 2% are diagnosed as SO. We highlight three cases of large SO with varying clinical presentations and disease progressions. The first case involved a postpartum woman who presented with a ruptured ovarian tumour, while the second case involved a woman who presented with acute urinary retention due to compression by the ovarian mass. The diagnoses of malignant SO were based on histopathological studies in both cases. The third case is a lady with known follicular thyroid carcinoma, who came back with a metastatic left iliac fossa mass and underwent a trial of chemotherapy. As of now, no definite treatment guidelines have been established. A multidisciplinary team approach is needed to manage this rare entity.

Keywords: Struma ovarii, teratoma, thyroid cancer

Öz

Struma ovarii (SO), over guatrı olarak da bilinen, nadir görülen monodermal bir teratomdur. Olgun teratomların yaklaşık %5-20'sinde tiroid dokusu bulunmasına rağmen, yalnızca %2'si SO olarak tanı almaktadır. Bu çalışmada, farklı klinik prezentasyonlar ve hastalık seyirleri gösteren üç büyük SO olgusunun sunulması amaçlanmıştır. Birinci olgu, postpartum dönemde rüptüre over tümörü ile başvuran bir kadındır. İkinci olgu, over kitlesinin basısına bağlı akut üriner retansiyon ile başvuran bir kadını kapsamaktadır. Her iki olguda da malign SO tanısı histopatolojik incelemeler ile doğrulanmıştır. Üçüncü olgu ise, bilinen folliküler tiroid karsinomu öyküsü olan ve metastatik sol iliak fossa kitlesi ile başvurarak kemoterapi tedavisi denemesi yapılan bir hastadır. SO, nadir görülen ve değişken klinik bulgularla prezente olabilen bir tümördür. Günümüzde bu antitenin yönetimi için kesinleşmiş tedavi kılavuzları bulunmamaktadır. Optimal yaklaşım için multidisipliner bir ekip çalışması gerekmektedir.

Anahtar Sözcükler: Yumurtalık struma, teratom, tiroid kanseri

INTRODUCTION

Struma ovarii (SO) is a rare monodermal teratoma that comprises either entirely or more than 50% of thyroid tissue. It is also defined as any mature teratoma with less than 50% of thyroid tissue, which contains thyroid-associated malignancy or causes hyperthyroidism (1). It is the most common type of monodermal teratoma, 1%

of ovarian tumors. Ludwig Pick suggested that SO represents a teratoma in which thyroid tissue has overgrown the other elements (1). Approximately 5-20% of mature teratomas contain thyroid tissue elements, but of these, only 2% are diagnosed as SO. The age of onset varies widely, occurring mostly in women of fertile age, with a peak incidence in the fifth decade. Most cases occur unilaterally, usually affecting the left ovary and about 6% of cases occur bilaterally (2).

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We highlight three cases of large SO with varying presentations and disease progression.

CASE REPORT

Case 1

A 38-year-old woman presented with a right pelvic mass during her third pregnancy. Her abdominal ultrasound revealed a 13x8 cm right adnexal mass. She presented again at one month postpartum with abdominal pain. Exploratory laparotomy with right salpingo-oophorectomy, appendectomy, and washout was done. Intraop found a ruptured large right ovarian dermoid cyst with generalised peritoneal pus collections and dense adhesions between the cyst wall and greater momentum, ascending colon, transverse mesocolon, and anterior abdominal wall. This was complicated with a burst abdomen, which required a second laparotomy for adhesiolysis and washout. Histopathological analysis of the specimen revealed a uniloculated cyst measuring 12.5x11x6 cm. Microscopically, the teratoma consisted of all three germ cell layers: endoderm (skin appendages and hair follicles), mesoderm (fat, nerves, and blood vessels), and ectoderm (thyroid follicular cells, cuboidal and respiratory epithelium); contained papillary thyroid carcinoma arising from the mature cystic teratoma. Biological results showed an increased CA-125 level at 353 U/mL (35 U/mL). Her thyroid function test and neck sonography were normal. Total thyroidectomy followed by radio-ablation iodine (RAI) was offered to her, but she refused it.

Case 2

A 68-year-old woman with a history of hypertension presented with acute urinary retention symptoms. Clinical examination showed a palpable abdominal mass about 20-weeks in size. Computed tomography (CT) scan revealed a pelvic mass measuring 10.9x9.6x13.4 cm, which was thought to arise from the posterior wall of the uterus and a separate complex right ovarian cyst of 2.7x5.8 cm (Figure 1). The mass compressed both ureters, causing mild

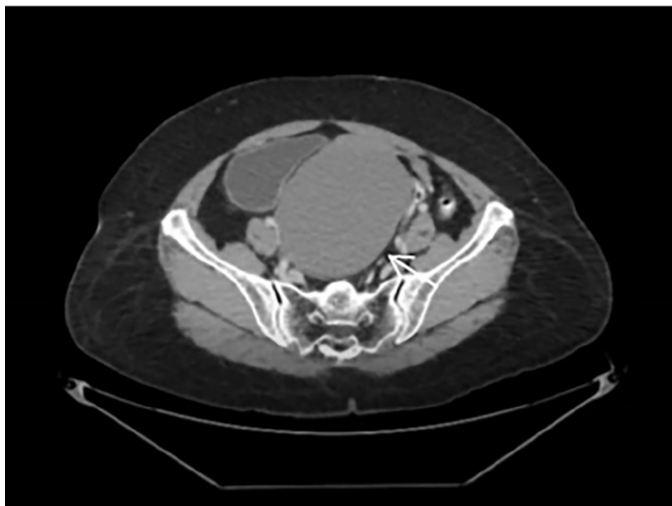


Figure 1. CT scan showing a large pelvic mass which was initially thought to arise from the posterior wall of the uterus causing local mass effect (white arrow).

CT: Computed tomography

hydroureteronephrosis. A laparotomy, total abdominal hysterectomy and bilateral salpingo-oophorectomy were done revealing a huge right ovarian cyst with an atrophic uterus. Histopathological analysis of the specimen showed a greyish multiloculated cyst weighing 620 grams, measuring 15.9x 11.9x8.9 cm. It had a dominant cystic space containing yellowish-tan jelly-like material. In focal areas of the cyst wall, there is ectopic thyroid tissue with variably sized thyroid follicles containing colloid. Focal malignant transformation was noted by neoplastic follicular cells growing in papillae, exhibiting enlarged, overlapping, optically clear nuclei with nuclear grooving and occasional pseudonuclear inclusions. Thyroid function tests, cancer antigen (CA)-125 levels, and neck sonography were unremarkable.

Case 3

A 54 years old lady with underlying asthma presented in 2004 with an ovarian tumor with raised CA-125. She underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy in the same year. Histopathology showed a left SO containing solid areas of lobules of thyroid follicles. The momentum showed spreading over thyroid cells. Subsequently, she defaulted on the follow-up for nine years. She came back in 2019 complaining of a left iliac fossa mass. CT scan showed a suspected appendicular mass with multifocal lung, liver metastasis, and extensive mediastinal lymphadenopathy. No focal thyroid lesion. Upper and lower endoscopy was normal.

An ultrasound-guided trucut biopsy of the left iliac mass showed metastatic follicular thyroid carcinoma. Immunohistochemistry staining was positive for pancytokeratin, TTF-1, thyroglobulin, and negative for synaptophysin and chromogranin, which excluded struma carcinoid. A repeat CT scan shows disease progression and demonstrates multiple solid cystic pelvic masses with calcification (Figure 2). The multidisciplinary meeting concluded that the patient has extensive metastatic disease and may not be able to shrink the tumor solely with RAI therapy and thyroidectomy. Hence, she was offered extensive surgery, which included thyroidectomy, debulking of pelvic, gastric, and mediastinal mass followed by radioactive iodine ablation. However, the patient refused both the operation and positron emission tomography scan to assess the extent of disease.

She remained asymptomatic from her SO. CT scan showed an enlarging mass with solid cystic component in the pelvic region, with central necrosis largest at the left iliac fossa, measuring 8x9.3x9.3 cm with multiple enlarged intra-abdominal and mediastinal nodes.

She underwent a trial of four cycles of palliative chemotherapy in which the tumour responded poorly. She could not proceed with the fifth cycle due to thrombocytopenia. The patient was subsequently tested positive for coronavirus disease-2019 infection.

DISCUSSION

SO has no specific clinical manifestation. They are often an incidental finding. If symptomatic, they may present with a palpable pelvic mass, abdominal or back pain, with vaginal bleeding, or frequent urination. Acute severe abdominal pain would suggest tumor rupture. In 5% of cases, there is hyperthyroidism. SO should therefore be considered in women with persistent hyperthyroidism



Figure 2. CT showing a lobulated heterogenous enhancing masses with solid cystic component at the pelvic region with central necrosis, largest at the left iliac fossa (white arrow).

CT: Computed tomography

and has absent goiter and radioactive iodine uptake in the neck with detectable serum thyroglobulin. Screening for pelvic ectopic thyroid tissue with iodine isotope imaging is recommended in such cases. Pseudo-Meigs' syndrome occurs in 17% of cases, and raised CA-125 levels occur in 30%, although CA-125 is non-specific (3).

The common thyroid-associated malignancies in SO are papillary and follicular thyroid carcinoma, and struma carcinoid (2). The presence of BRAF mutation in papillary thyroid cancers shows worse prognostic features including invasive growth, lymph node metastasis, and worse clinical outcomes than those which are negative for these mutations (4). The *BRAF* mutation suggests a common pathogenesis for papillary thyroid carcinoma in the thyroid gland and SO. In follicular thyroid carcinoma, mutations in the *RAS* gene predict poor prognosis, as the mutation rate of the *KRAS* gene is about 9% (2).

In our case series, there were no primary thyroid gland lesions. However, synchronous thyroid cancers can have an incidence of up to 9.1% as reported in one study.

Malignant SO (MSO) comprises 5-10% of all cases (2). This diagnosis is based on histology and the criteria for malignancy in SO are the same as those of a thyroid gland proper carcinoma (6). Prognosis of MSO is overall good with survival rates of 92–96.7% at 5 years, 85–94.3% at 10 years, 84.9% at 20 years and 79% at 25 years being reported (5). Ascites and/or pleural effusion, if present, usually

disappear after surgery. Histological malignancy in SO, however, does not necessarily indicate a biological malignancy, as histological malignancy was ineffective in predicting the subsequent clinical course (6).

Metastatic MSO confers a less favorable prognosis. The most common histologic subtype is follicular carcinoma. One explanation for implantation of metastatic foci is the rupture of the capsule of the SO. Another cause may be the spread of highly differentiated follicular carcinoma. The novel entity of highly differentiated follicular carcinoma of ovarian origin was described by Roth and Karseladze (7), who characterized the extraovarian dissemination of thyroid elements, which histologically resembles normal thyroid tissue.

Many treatments are recommended; however, due to the rarity of SO, no definite guidelines have been established. Surgical considerations include preservation of fertility and beta-blockade in hyperthyroidism. In early stages of MSO, unilateral laparoscopic salpingo-oophorectomy may be offered alone to reduce postoperative adhesions. In advanced disease, a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and lymph node sampling or debulking surgery can be undertaken (8). This is usually followed by adjuvant thyroid suppression therapy. A popular approach is early thyroidectomy and RAI as it is believed to reduce recurrence risk. Some authors suggest that such measures are only advised in metastatic disease or in cases where risk of recurrence has been identified. These risk factors include measurable disease of >10 mm, close surgical margins, aggressive histopathological features such as and/or BRAF mutations (8). As in thyroid cancers, thyroglobulin is used as a biochemical marker to detect recurrence, where an iodine isotope scan is warranted.

CONCLUSION

SO is a rare ovarian goiter with diverse manifestations. Although specific treatment guidelines for MSO are yet to be determined due to its rarity, a multidisciplinary team approach involving surgeons, nuclear medicine, and gynecology teams is needed to ensure the best treatment to the patient. In early stages of MSO, unilateral laparoscopic salpingo-oophorectomy alone may be offered; meanwhile, in advanced disease, a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and lymph node sampling or debulking surgery can be undertaken. This is usually followed by adjuvant thyroid suppression therapy and radio-iodine ablation therapy.

Ethics

Informed Consent: Informed consent has been obtained from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.Z.S., N.A.S.N.L., Concept: N.A.S.N.L., Design: C.L.P.S., Data Collection or Processing: C.L.P.S., Analysis or Interpretation: C.L.P.S., Literature Search: C.L.P.S., Writing: C.L.P.S.

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Hemoperitoneum is A Rare Clinical Manifestation of Crimean-Congo Hemorrhagic Fever in Children

Hemoperitoneum, Çocuklarda Kırım-Kongo Kanamalı Ateşinin Nadir Görülen Bir Klinik Belirtisidir

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ABSTRACT

Hemoperitoneum is a manifestation of abdominal bleeding of non-traumatic origin, leading to the outpouring of free blood into the abdominal cavity or retroperitoneal space. This condition is defined as a rare complication occurring in children with Crimean-Congo hemorrhagic fever (CCHF). To highlight the hemoperitoneum in children with CCHF and raise awareness of a rare complication among clinicians. A retrospective analysis was conducted on detected cases of CCHF in children, focusing especially on the features of the pre-hemorrhagic and hemorrhagic periods of the disease. Clinical cases with rare symptoms in children, such as hemoperitoneum, are described. The clinical picture of CCHF in children may manifest as a rare complication such as hemoperitoneum. The outcome of the disease depends on the severity of the hemorrhagic syndrome, the timeliness of etiologic and hemostatic therapy, and treatment and prevention of possible complications.

Keywords: Crimean-Congo hemorrhagic fever, hemoperitoneum, children, hemorrhagic syndrome

ÖZ

Hemoperitoneum, travmatik olmayan kökenli abdominal kanamanın bir belirtisidir ve karın boşluğuna veya retroperitoneal boşluğa serbest kan dökülmesine yol açar. Kırım-Kongo kanamalı ateşi (KKKA) olan çocuklarda görülen nadir bir komplikasyon olarak tanımlanmaktadır. KKKA olan çocuklarda hemoperitonu vurgulamak ve klinisyenler arasında nadir görülen bir komplikasyon hakkında farkındalık yaratmak. Çocuklarda tespit edilen KKKA vakalarının, özellikle hastalığın hemorajik öncesi ve hemorajik dönemlerinin özelliklerinin, çocuklarda hemoperiton gibi nadir semptomları olan klinik vakaların retrospektif bir analizi tanımlanmıştır. Çocuklarda KKKA klinik tablosu hemoperiton gibi nadir görülen bir komplikasyon olarak kendini gösterebilir. Hastalığın sonucu hemorajik sendromun ciddiyetine, etiyotropik ve hemostatik tedavinin zamanlamasına, olası komplikasyonların tedavisine ve önlenmesine bağlıdır.

Anahtar Sözcükler: Kırım-Kongo kanamalı ateşi, hemoperiton, çocuk, hemorajik sendrom

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INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne infection that is caused by the CCHFV virus from the Bunyaviridae family (1). CCHF is an endemic disease in some countries, and is one of the diseases prioritized for their pandemic potential (2-4). Possible ways of transmitting the virus to humans are through the bite of infected ticks or direct contact with infected blood or other body fluids (5). Currently, it is known that with CCHF there is a high mortality rate, which varies according to various data from 20 to 30% in hospitalized patients (6). However, according to various authors, despite the high mortality from CCHF, children still carry the disease in a milder form than adults (2,6). In addition, during the COVID-19 pandemic, many researchers found an increase in the number of cases of CCHF in children who manifested a more severe disease course and were mistakenly diagnosed as manifestations of coronavirus infection (2). In this study, we describe clinical cases of CCHF in children with a clinical manifestation of hemoperitoneum.

CASE REPORT

Case 1

An 11-year-old female child was admitted to the Hospital of Infectious diseases on 13.05.2019. Upon admission, she complained of an increase in body temperature to 38.1°C, runny nose, weakness, and headache. When collecting anamnesis, it was established. On 10.05.19, the girl was bitten by a tick in the yard of her house. Her parents went to the hospital, where medical workers successfully removed the tick. On 13.05.19, the child had fever up to 39.5°C, headache, runny nose, weakness, and the parents returned to the infectious hospital, where a general blood test was taken and showed that platelets were within the normal range $-272 \times 10^9/L$. The girl was hospitalized with a diagnosis of acute respiratory viral infection (ARVI) in severe form. The patient had a tick bite. Treatment of ARVI was started. At the beginning of the disease, febrile manifestations, manifestations of intoxication syndrome, and catarrhal symptoms characteristic of viral respiratory infection were noted; the normal number of platelets remained in blood tests. The dynamics of the girl's condition worsened on the 4th day: there was poor health; abdominal pain; vomiting once; leg aches; facial hyperemia; pronounced scleritis; conjunctivitis; 1-2 elements of petechial rashes on the abdomen; and hematomas at injection sites. Anemia, thrombocytopenia, up to $96 \times 10^9/L$, increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase were noted in blood tests. Signs of hypocoagulation were indicated by the coagulogram. The doctors diagnosed CCHF with moderate severity as a probable case. Etiotropic therapy with ribavirin was prescribed according to the scheme (initially 30 mg/kg, then 15 mg/kg every 6 hours for 4 days). On the 5th day, despite the treatment, hemorrhagic rashes appeared on the skin in the area of the knee joints, the upper half of the chest, and hemorrhages in the injection sites, pronounced abdominal pain, and joint pain. There has been excessive bleeding from the genital tract, unrelated to the menstrual cycle. Until now, the girl had no manifestations of regular menstruation. The "coffee grounds" type of discharge was noted from the nasogastric probe. In the analysis of feces for latent blood, a strongly positive result was obtained. As can be seen, the patient developed a severe hemorrhagic syndrome:

pallor of the skin and mucous membranes, "cold sweat", dizziness, weakness, darkening of the eyes, tachycardia, arterial hypotension, a hemorrhagic rash, uterine and gastrointestinal bleeding, and the clinical picture includes symptoms of hemoperitoneum, such as: abdominal pain; bluntness in sloping places; auscultation reveals muffling of intestinal noises. On the 6th day of the disease, against the background of continuing bleeding, the child had complaints of severe headaches, loss of consciousness, symptoms of coma, and acute cerebral circulation disorders of hemorrhagic type: difficulty swallowing; speech; weakness of the limbs with left-sided hemitype; impaired coordination. Anemia, leukopenia, thrombocytopenia with counts up to $40 \times 10^9/L$, and an increase in Erythrocyte sedimentation rate levels were observed in blood tests. On the 7th day, an ultrasound examination of the abdominal cavity revealed reactive cholecystitis, pericholecystitis, splenomegaly, free fluid in the pelvis in an amount of 72 cm³, and in the abdominal cavity in an amount of 30 cm³. Conducting the tests yielded positive results: the virus RNA was detected by polymerase chain reaction (PCR), and immunoglobulin M (IgM) antibodies were detected by ELISA. During ongoing treatment, positive changes were observed in blood tests as an increase in the number of platelets to $133 \times 10^9/L$, hemoglobin to 74 g/L, and erythrocytes to 2.9×10^{12} . On the 10th day of the illness, a positive ELISA test result for the CCHF virus was received again. The final clinical diagnosis was established for the child of CCHF, confirmed case, severe form with abdominal bleeding (gastric, intestinal, uterine). Complications: Hemoperitoneum. An acute disturbance of cerebral circulation due to hemorrhagic type occurs. The treatment included ribavirin with etiotropic purpose, freshly frozen plasma, immunized plasma with antibodies to the CCHF virus, hemostatic therapy, replacement therapy with blood components, and symptomatic therapy. Against the background of therapy, the general condition stabilized; the child came out of a coma and began to react to external stimuli; hemorrhagic and intoxication syndromes were stopped; sleep and appetite were restored. On the 22nd day of the illness, the child was discharged home with a significant improvement in condition under the supervision of a district doctor.

Case 2

A 12-year-old male child from a village arrived at the district residence in the Turkestan region on 9th July 2022, with complaints of fever up to 38-39°C, weakness, muscle pain, and headache. From the anamnesis on 7th January 2022: the boy independently removed the attached tick from the surface of the left thigh, while he himself crushed it and threw it away, but did not tell the matter about what had happened. On 7th April 2022 his body temperature rose to 38°C. The boy's mother gave antipyretics on her own, soldered fluids, the condition with a "cold disease". There was no improvement chills, weakness, muscle pain, headache joined the child's dynamics on 7th September 2022. The child's mother was infected on the same day. The boy was hospitalized in the infectious diseases department with a diagnosis of CCHF, a probable case. On subjective examination, the condition was regarded as severe due to intoxication syndrome, preserved consciousness, meningeal, and unwanted neurological symptoms. Hyperemia of the throat was noted; tonsils were loose, somewhat edematous, without plaque; the tongue was wet and covered with a white coating. The skin is clean, dry, warm to the touch, somewhat hyperemic, slightly puffy, the sclera is injected,

petechiae, ecchymosis, hemorrhages at the injection site without manifestations. Symptoms of «burning» were negative. The oxygenate saturation is 95%. Heart sounds are muffled, quickened. Pulse 96 in 1 min., arterial pressure 112/73 mmHg. The abdomen is soft accessible on palpation, somewhat sensitive in the epigastric region the symptoms of “acute abdomen” are negative. The liver was enlarged, and palpable below the edge of the costal arch by 1.5 cm the edge was light, b painless. Diuresis has been saved. Fecal occult blood test positive result. The institution conducted a laboratory blood test upon detection of severe thrombocytopenia $46 \times 10^9/L$, anemia Hb -85 g/L, leukopenia $L - 3.39 \times 10^9/L$, hypoproteinemia of total protein - 7.8 g/L, increase in ALT enzymes - 296.3 IU/L, AST - 51.1 IU/L. In the coagulogram manifestations of hypocoagulation: a decrease in the prothrombin index 59.3% increase in international normalized ratio 1.68 of prothrombin time - 21.9 seconds prolongation of blood clotting time beginning 07:25 minute/second - 08:50 minute/second. With the condition of the child, stable nutrition was maintained, weakness, lethargy, drowsiness persisted, hemorrhagic syndrome on the skin and mucous membranes manifested itself, there were no violations, weak sensitivity to palpation of the abdomen, repeated examination of the children's surgical syndrome of the acute state of “acute abdomen”. At the height of the disease, blood tests revealed a violation of hemostasis, a sharp increase in the enzymes ALT: 234.2 IU/L and AST: 697.1 IU/L, and a moderate increase in bilirubin up to $37 \mu\text{mol/L}$. Tests for markers of viral hepatitis are negative. The child was also examined by a hematologist and diagnosed with CCHF, a probable case. Syndrome of intravascular coagulation. Secondary thrombocytopenia. Ultrasound of the gastrointestinal tract detected the presence of free fluid in the abdominal cavity and a significant amount in the small pelvis. The patient has been diagnosed with ascites, hepatomegaly, diffuse changes in the liver parenchyma. When conducting a specific examination of CCHF, the analyses gave positive results: the PCR method revealed the RNA of the CCHF virus and ELISA detected IgM antibodies. The child was diagnosed with Crimean-Congo hemorrhagic fever, a confirmed case, a severe form characterized by abdominal bleeding (gastric, intestinal). Complication: hemoperitoneum. The child received CCHF therapy in accordance with the medical protocol for the diagnosis and treatment: with the delivery of receipts of ribavirin with an etiotropic purpose (initially 30 mg/kg, then 15 mg/kg for about 6 hours for 4 days), fresh frozen plasma, immunized plasma with antibodies to the CCHF virus, hemostatic therapy, replacement therapy with blood components, symptomatic therapy. On the background of treatment, blood tests returned to normal: total protein - 65 g/L, ALT - 7.5 IU/L, AST - 6 IU/L, total bilirubin - $8.4 \mu\text{mol/L}$, restoration of coagulogram parameters. On the 16th day of hospitalization, the child was discharged with improvement under the supervision of a local doctor, with recommendations for recovery.

DISCUSSION

The results of clinical manifestations are manifested by rare manifestations of CCHF in children in the form of hemoperitoneum and hemorrhagic stroke. Clinical presentation of hemorrhagic syndrome CCHF in areas experiencing leakage, with noted individual deviations. If in the first case we have an extended and vivid picture in a girl: hemorrhagic rashes on the skin, hemorrhages at injection sites, gastrointestinal and uterine hemorrhages, severe abdominal

pain, symptoms of hemoperitoneum, further development of coma against the background of acute cerebrovascular accident due to hemorrhagic pressure, then in the second patient, the clinic of hemorrhagic syndrome was without signs of hemorrhage on the skin and mucous membranes, in the presence of confirmed hemoperitoneum, more restrained abdominal symptoms. Epidemiological anamnesis was decisive in the diagnosis of the disease; the identification of initial foci in the blood test showing a sharp decrease in the level of platelets; a positive fecal occult blood test; PCR; and ELISA-confirmation of a specific examination for CCHF.

At the moment, there are several studies focused on CCHF in children, but they do not describe rare cases of hemoperitoneum. In one study conducted by scientists from Türkiye, a rare complication of CCHF was found as hemophagocytic lymphohistiocytosis with an unusually severe course (2). In another study, rare ocular symptoms were evaluated in children diagnosed with CCHF, and an increased tortuosity of retinal vessels was revealed (7). There is also a report of a rare case of myocarditis in a child with CCHF, which completely regressed after the convalescent period of the disease (8). In the modern literature, there is evidence of a rare complication in the form of reversible bradycardia occurring during the clinical course in children with CCHF (9,10).

Due to the scarce data available in the literature on the CCHF in children, it is noteworthy that, in most cases, the course of the disease in pediatric patients is much easier than in adults (11). At the same time, the disease is most often observed in older male children, and the main factor in the onset of the disease is direct contact with livestock (5). However, clinicians need to be wary of children with CCHF on the rare severe complications.

CONCLUSION

The probability of the disease of children with children increases during the active season of ticks, which are carriers of infection, if they have lived in natural focal areas, been bitten by a tick, or had contact with a confirmed case. The clinical picture of CCHF in children may have similarities with the manifestations of this infection in adults. Among the rare symptoms, hemoperitoneum is possible. The outcome of the disease depends on the severity of the hemorrhagic syndrome, the timeliness of etiotropic and hemostatic therapy, treatment and prevention of possible complications. In severe cases, timely initiation of etiotropic and hemostatic therapy gives a chance for a successful outcome.

Ethics

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.F.A., A.G.N., P.T.V., A.D.S., U.G.A., B.Y.B., Concept: B.F.A., A.G.N., Design: B.F.A., A.G.N., Data Collection or Processing: B.F.A., A.G.N., Analysis or Interpretation: B.F.A., A.G.N., U.G.A., Literature Search: P.T.V., Writing B.F.A., A.G.N., P.T.V., U.G.A., B.Y.B.

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A Case of Adjuvant Brigatinib in a Patient with ALK-rearranged R0 Resected Oligometastatic Lung Cancer

ALK-Rearranjmanı Olan Oligometastatik Akciğer Kanseri Tanılı R0 Rezekte Edilmiş Hastada Adjuvan Brigatinib Tedavisi

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ABSTRACT

Anaplastic lymphoma kinase (ALK) rearrangement is detected at a low rate in non-small cell lung cancer (NSCLC). Patients with ALK rearrangements have poor responses to conventional cytotoxic chemotherapy. Brigatinib is one of the ALK-tyrosine kinase inhibitors recommended for first-line treatment in metastatic NSCLC. Local ablative therapies are applied in the treatment of oligometastatic disease in NSCLC. In this case, a patient with lung adenocarcinoma with ALK-rearranged isolated adrenal metastasis was treated with adjuvant brigatinib after sequential surgery. A 23-month disease-free survival was obtained. The case reported here represents the use of adjuvant therapy with ALK inhibitors in ALK-positive oligometastatic NSCLC in eligible patients.

Keywords: ALK rearrangement, brigatinib, lung cancer, oligometastasis, targeted therapy

Öz

Anaplastik lenfoma kinaz (ALK) rearranmanı, küçük hücreli dışı akciğer kanserinde (KHDak) düşük oranda tespit edilir. ALK rearranmanı olan hastalar konvansiyonel sitotoksik kemoterapiye zayıf yanıt verir. Brigatinib, metastatik KHDak'de birinci basamak tedavi için önerilen ALK-tirozin kinaz inhibitörlerinden (ALK-TKI'ler) biridir. KHDak'de oligometastatik hastalığın tedavisinde lokal ablatif tedaviler uygulanır. Bu olgu, ALK-rearranmanı olan izole adrenal metastazlı akciğer adenokarsinomlu bir hastadır, ardışık cerrahi sonrası adjuvan brigatinib ile tedavi edilmiştir. Yirmi üç aylık hastalıksız sağkalım elde edilmiştir. Burada bildirilen vaka, ALK pozitif oligometastatik KHDak'li uygun hastalarda ALK inhibitörlerinin adjuvan tedavisinin kullanımını temsil etmektedir.

Anahtar Sözcükler: ALK rearranmanı, brigatinib, akciğer kanseri, oligometastaz, hedefli tedavi

INTRODUCTION

Non-small cell lung cancer (NSCLC), which accounts for most lung cancer cases, is the main cause of cancer-related mortality (1). Although there are many developments in immunotherapy and chemotherapy, the prognosis of patients with advanced disease is still poor. The advent of anaplastic lymphoma kinase-tyrosine

kinase inhibitors recommended (ALK-TKI) has completely altered the management strategy and prognosis of patients with advanced NSCLC with ALK fusion.

ALK gene rearrangements encode driver fusion oncoproteins and account for approximately 5% of NSCLC cases (2). After crizotinib, multiple second-generation (e.g., ceritinib, brigatinib, alectinib) and

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third-generation (e.g., lorlatinib) ALK-TKIs have been developed for patients with ALK-positive NSCLC, all with higher potency and greater central nervous system penetration than crizotinib (3).

Adjuvant-targeted therapy suggests a viable management option, and patients can also improve survival outcomes (4-6). However, no randomized controlled trials have been reported for patients with ALK-positive locally advanced NSCLC. Here, we present a patient with lung adenocarcinoma with isolated adrenal metastasis at the time of diagnosis, who underwent sequential surgery followed by brigatinib therapy.

CASE REPORT

A 56-year-old, never-smoker male patient applied to the Medical Oncology Clinic in February 2021 with complaints of cough and dyspnea, for a month. Computed tomography (CT) revealed a 29 mm mass in the upper lobe of the left lung (Figure 1a). A transthoracic biopsy was performed on the patient. The pathology result was reported as lung adenocarcinoma. Systemic positron emission tomography (PET)/CT imaging revealed a 26x24 mm mass, regional lymph node metastasis at the ipsilateral hilar and ipsilateral mediastinum lymph nodes, and isolated right adrenal (110x80x50 mm) (Figure 1b) metastasis (cT1cN2M1b, stage IVA, 8th AJCC). Molecular tests have been sent. There was no metastasis on cranial imaging. Gemcitabine (1000 mg/m², day 1 and day 8) plus cisplatin (75 mg/m², day 1) chemotherapy was started in the patient whose laboratory values were normal, and ECOG performance score was 1. It was reported from the pathology department that molecular tests could not be performed due to insufficient material. After four cycles of chemotherapy, partial response according to RECIST 1.1 criteria was obtained in control imaging (cT1bN1M1) (Figures 2a and 2b). At this stage, as a result of multidisciplinary discussion, sequential surgery was planned for the patient with lung cancer with isolated adrenal metastasis. The preoperative endocrinological evaluation was performed. First, right adrenalectomy surgery was performed. Afterwards, left upper lobectomy and mediastinal lymph node dissection were performed with video-assisted thoracic surgery.

Molecular tests were planned again from the lung surgical material. No pathology was detected in postoperative cranial magnetic resonance imaging, thoracic, and abdominal CT. The pathological tumor size was 0.4 cm, and one metastasis was detected in lymph node number 10 (pT1aN1M1). ALK expression was detected using immunohistochemistry (ALK D5F3, Ventana) and fluorescence *in situ* hybridization. An additional two cycles of platinum-based chemotherapy was planned for the patient. However, brigatinib 180 mg/day was started because ALK was positive. The patient's disease-free survival (DFS) with brigatinib was 23 months at the last follow-up. No grade 3/4 adverse events or disease progression occurred at the last follow-up in November 2023. The patient's treatment with brigatinib 180 mg/day and close follow-up continues.

DISCUSSION

Here, we present a 56-year-old male patient with lung adenocarcinoma with isolated adrenal metastasis at the time of diagnosis, who was treated with sequential surgery and adjuvant brigatinib after chemotherapy. Chemotherapy was started, and partial response was obtained in the patient who had isolated adrenal metastasis at the time of diagnosis and whose biopsy material was insufficient for molecular tests. We planned sequential surgery for our patient, who was evaluated as multidisciplinary. The postoperative treatment plan was changed after ALK rearrangement was detected in the surgical material.

Although the frequency of ALK rearrangements is very low, it is clinically important. The advent of oncogenic driver mutations, such as ALK mutations, means that a subset of patients have opportunities for targeted therapy. The clinical application of ALK-TKIs is primarily dependent on the positivity of the *ALK* gene, independent of the molecular characteristics of the fusion partner. Patients with ALK rearrangements have poor responses to conventional cytotoxic chemotherapy, but ALK inhibitors such as ceritinib, crizotinib, and alectinib may affect treatment efficacy and improve outcomes in these patients. On the other hand, it is important to note that tumor biopsy specimens taken from patients with advanced

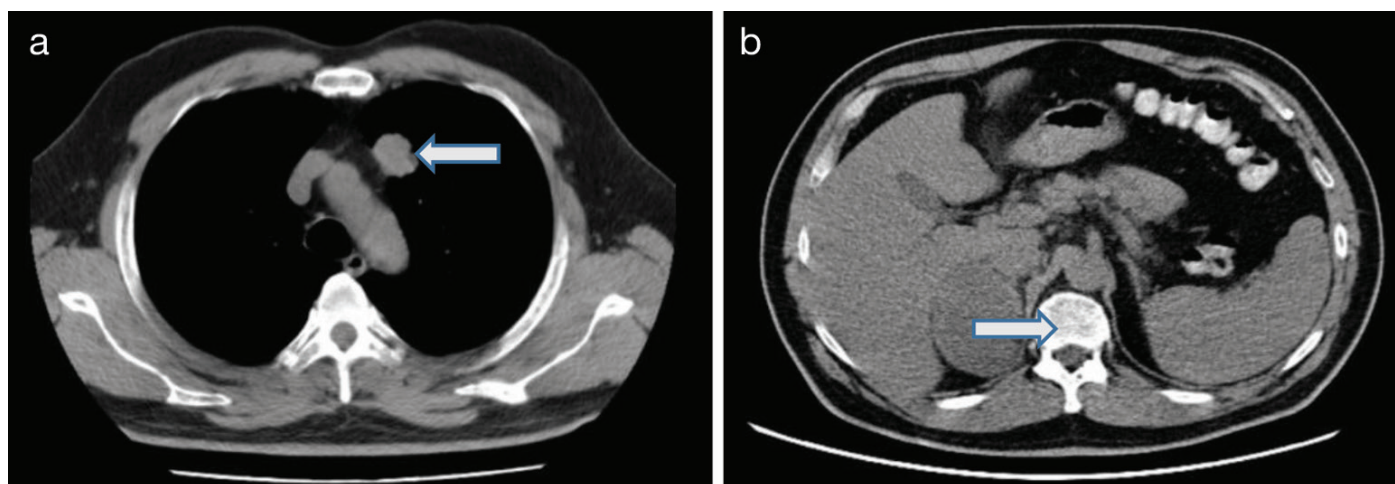


Figure 1. (a) Baseline radiological evaluation of the primary tumor. Computed tomography (CT) revealed a 2.9x2.2 cm mass in the left upper lung. (b) Baseline radiological evaluation of right isolated adrenal metastasis (11x8x5 cm) (PET/CT).

PET: Positron emission tomography.

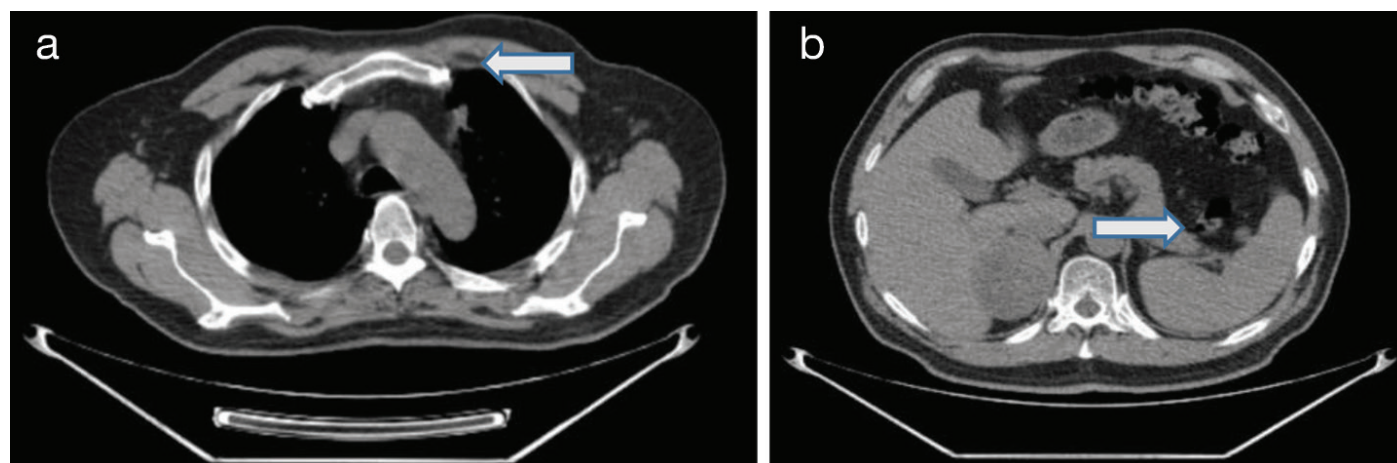


Figure 2. (a) Radiological evaluation of primary tumor after 4 cycles of chemotherapy (1.6x1.1 cm) (PET/CT). b) Radiological evaluation of isolated adrenal metastasis after 4 cycles of chemotherapy (10x7.5x5.5 cm) (PET/CT).

PET: Positron emission tomography, CT: Computed tomography.

NSCLC generally tend to be small, and it is unclear whether these specimens accurately represent tumor histology. Therefore, it is not possible to exclude the possibility that certain cells with ALK rearrangements are present in tumors. In such a situation, patients will lose the opportunity to receive appropriate treatment unless tests for ALK rearrangement are performed. In our case, the biopsy was insufficient for molecular tests at the time of diagnosis.

Local ablative therapies, surgery, or stereotactic radiotherapy (SABR) are now known to be an integral component in the treatment of oligometastatic disease in NSCLC (7,8). The NCCN guidelines suggest that local therapy (RT, SABR, or surgery) for primary and oligometastatic lesions should be used for the management of patients without progression on systemic chemotherapy.

Regarding adjuvant targeted therapy, previous trials (5,6) have explored the administration of oral TKIs for epidermal growth factor receptor-positive NSCLC patients and the results were encouraging. However, no randomized controlled trials have been reported for patients with ALK-positive locally advanced NSCLC. Our patient was oligometastatic and suitable for surgery. He then received adjuvant brigatinib therapy. Results supporting adjuvant therapy were obtained in patients with ALK rearrangement.

In summary, a patient with lung adenocarcinoma with ALK-rearranged isolated adrenal metastasis was treated with adjuvant brigatinib after sequential surgery, and 23 months of DFS was achieved. Our case is the first case in which brigatinib was used after metastasectomy and primary tumor surgery. The case reported here represents the use of adjuvant therapy of ALK inhibitors in ALK-positive oligometastatic NSCLC in eligible patients.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.Y., A.İ.T., Concept: O.Ü., A.Ö., Design: O.Ü., A.Ö., Data Collection or Processing: O.Ü., N.A., Analysis or Interpretation: O.Ü., N.A., A.Ö., Literature Search: O.Ü., Writing: O.Ü.

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Using Positron Emission Tomography/Computed Tomography to Diagnose Atypically Located Extranodal Natural Killer/T-Cell Lymphoma, Nasal Type, Mimicking Necrotising Soft Tissue Infection

Pozitron Emisyon Tomografi/Bilgisayarlı Tomografi Kullanılarak Tanı Konulan, Nekrotizan Yumuşak Doku Enfeksiyonunu Taklid Eden Atipik Yerleşimli Nazal Tip, Ekstranodal NK/T Hücreli Lenfoma

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ABSTRACT

Extranodal natural killer/T-cell lymphoma (ENKTL) is an Epstein-Barr virus-associated, rapidly spreading lymphoproliferative disorder with a poor prognosis. Although it usually manifests with nasal involvement, different clinical and histopathological features can be detected. In nasal form, it may be confused with mucormycosis. Identifying the appropriate biopsy site is crucial for an accurate ENKTL-nasal type diagnosis, and positron emission tomography/computed tomography (PET/CT) can facilitate this. In this paper, we share the case of a 73-year-old male who presented with nasal and skin involvement, and was diagnosed with an unfavourable prognosis using PET/CT-guided biopsy. Unfortunately, the initial biopsies were inconclusive and led to an unnecessary antimicrobial treatment. Combining fluorodeoxyglucose PET/CT images allowed us to pinpoint the biopsy location and assess the depth of tissue infiltration, resulting in a successful biopsy even in this rare case.

Keywords: Extranodal NK/T-cell lymphoma, positron emission tomography/computed tomography, skin

Öz

Ekstranodal nodal doğal öldürücü/T hücreli lenfoma (ENKTL) Epstein-Barr virüs ile ilişkili, hızla yayılan, kötü prognozlu lenfoproliferatif bir hastalıktır. Genellikle nazal bölgeyi etkilemekle birlikte farklı klinik ve histopatolojik özellikler de gösterebilmektedir. Nazal formu mukormikozis ile karışabilir. ENKTL kesin tanısı için doğru bölgeden biyopsi yapılması önemlidir, pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT) bu işlemi kolaylaştırabilir. Burada 73 yaşında, nazal ve deri tutulumu olan, PET/BT rehberliğinde biyopsi ile tanı konulan, kötü prognozla seyreden bir erkek hasta paylaşılmıştır. İlk biyopsi ile tanı konulamamış ve bu durum gereksiz antimikrobiyal tedavilere yol açmıştır. Florodeoksiglukoz PET/BT görüntüleri, biyopsi yerini tam olarak belirlememize ve doku infiltrasyonunun derinliğini değerlendirmemize ve bu nadir olguda başarılı bir biyopsiye imkan tanımıştır.

Anahtar Sözcükler: Ekstranodal NK/T hücreli lenfoma, pozitron emisyon tomografisi/ bilgisayarlı tomografi, deri

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INTRODUCTION

Extranodal natural killer/T-cell lymphoma, nasal type (ENKTL-NT), is a rare lymphoproliferative disorder associated with Epstein-Barr virus infection. It typically occurs in the nasal cavity but can affect other areas as well. Necrosis is common (1). The 5-year survival rate is 41% for the NT, but 22% for other sites. It is more common among Asians, Mexicans, and South Americans of Native American descent (2).

ENKTL-NT diagnosis involves histopathological findings, immunohistochemistry, flow cytometry, and T-cell receptor (TCR) rearrangement studies (3). Although biopsy improves diagnostic accuracy, selecting the most appropriate site for biopsy is challenging. Positron emission tomography/computed tomography (PET/CT) could be helpful in diagnosis and staging, and could guide biopsy (4,5). Fluorodeoxyglucose (FDG) PET/CT plays a crucial role in the primary staging, treatment response, and follow-up of lymphomas (5,6).

This article aims to share the experience of a patient with ENKTL-NT who had an atypical clinical course, a poor prognosis, and experienced a prolonged diagnostic process. Furthermore, it highlights the important role of PET/CT in diagnosis and biopsy guidance.

CASE REPORT

A 73-year-old male patient presented with persistent necrotising soft tissue infection on his right hand, forearm, and left under-eye (Figures 1 and 2). The patient had been presenting with lesions over the past 2-3 weeks, even after receiving empirical antibiotic treatment. The patient had no known chronic disease. The patient had experienced a wrist drop approximately 5-6 months ago; the cause could not be determined. He had been experiencing nasal congestion for a while. The patient was admitted to the department of infectious diseases and clinical microbiology; laboratory tests yielded the following results: haemoglobin: 11.1 g/dL, total leukocyte count: 4400/mm³, platelets: 114000/mm³, C-reactive protein: 5 mg/dL, erythrocyte sedimentation rate: 21 mm/h, and procalcitonin: 0.1 ng/mL. The results of the remaining biochemical and urinary tests demonstrated values within the reference range. Through the use of culture and serology, a number of infectious diseases-



Figure 1. Necrotic skin lesions appear on the left under-eye area, characterized by edema, erythema, and crusting.

specifically nocardiosis, cutaneous leishmaniasis, tuberculosis, and anthrax-were successfully eliminated. Paranasal CT showed opacity in the left maxillary sinus and nasal cavity. The lesion below the eye exhibited progression over the following days, and a white lesion emerged on the hard palate (Figure 3). Considering mucormycosis, liposomal amphotericin B was added to the treatment. A biopsy was taken from the patient's palate and under the eye. The biopsy results were negative for malignancy and microorganisms. However, after 40 days of hospitalisation, a decline in the patient's general condition was observed. An FDG PET/CT scan was conducted after 40 days to determine the potential presence of malignancy.

The PET/CT exam found thickening in the left maxillary region, diffuse hypermetabolic submucosal infiltration on the soft hemi-palate and parapharynx, obstructive maxillary sinusitis, and diffuse swelling on the unilateral orbital floor [maximum standard uptake value (SUV_{max}): 35.4]. Similar involvement with hypermetabolic subdermal infiltration was seen in the right forearm and hand (SUV_{max}: 15.6). A few bilateral cervical lymph nodes (SUV_{max}: 6.5) were noted, as well as an axillary and a left hilar lymph node (SUV_{max}: 4.2) were noted. In addition, the spleen was enlarged, and the liver/spleen metabolic ratio was increased (Figure 4).



Figure 2. The patient's right hand and forearm exhibit edematous, erythematous, and crusty necrotic skin lesions.

No concerning surface lymph nodes were found; therefore, a PET/CT-guided biopsy was conducted. The biopsy depth was determined by analysing forearm photos, emission images, and CT sections. The extensor sites of the hand and wrist were chosen for dermal and subdermal sampling.

Lymphoid cell infiltration with angiodestruction was detected in the adipose tissue of the hand and wrist. Immunostaining showed that the neoplastic cells were positive for CD3, CD5, CD7, CD56, T-cell intracellular antigen 1, granzyme B, and Epstein-Barr encoding region

(EBER). However, they were negative for CD20, CD4, CD8, CD30, PD-1, TCR beta, and TCR gamma/delta, indicating the presence of ENKTL (Figures 5 and 6).

The patient was referred to the haematology clinic for chemotherapy, but unfortunately, he passed away due to cardiac arrest.

DISCUSSION

Patients diagnosed with ENKTL-NT typically exhibit a low incidence of skin lesions occurring beyond the facial region. Skin lesions, whether singular or multiple, can often be mistaken for infections such as cellulitis, abscesses, and infective panniculitis. The histopathological patterns of cutaneous involvement in ENKTL-NT share similarities with other lymphoma variants, dermatitis, and infectious processes. Notably, angiocentricity, angioinvasion, and epidermotropism are common histopathological findings (7). Accurate diagnosis is often challenging due to extensive angioinvasion and necrosis, requiring multiple biopsies (4). In our case, skin lesions provided misleading clinical information, and the initial biopsy samples were non-diagnostic.

ENKTL-NT is characterised by bloody rhinorrhoea and nasal obstruction, as well as systemic symptoms such as prolonged fever and weight loss (4). Although the patient in our case presented with nasal obstruction, B symptoms were absent, except during the last period. The literature suggests that having two or more extranodal sites and being over 60 years old are factors that can lower overall survival rates (2). Unfortunately, in our case, the patient was diagnosed with ENKTL-NT at an advanced age, and multiple involvements in the skin, soft tissue, spleen, and liver indicated a poor prognosis. EBER positivity is also an important diagnostic indicator (4). In our case, the patient exhibited EBER positivity accompanying tissue lesions on pathological examination.



Figure 3. An observation has been made of a white lesion located on the hard palate.

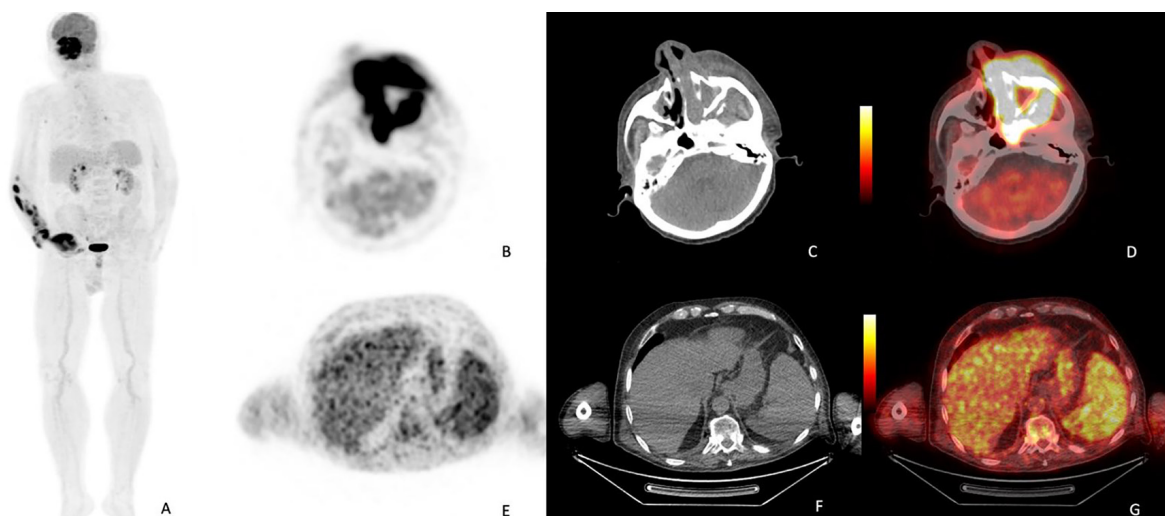


Figure 4. The whole body PET scan of the patient: maximum intensity projection image (MIP) increased metabolic activity in the face, the right forearm and hand (A). The first line; transaxial section of the face showing involvement around maxillary sinus and face skin, B) (emission), C) (computerized tomography), D) (PET/CT fusion) images, the second line: Transaxial section of liver and enlarged spleen. Splenic metabolic activity is increased compared to the liver. E) (emission), F) (computerized tomography), G) (PET/CT fusion) images.

PET: Positron emission tomography, CT: Computed tomography

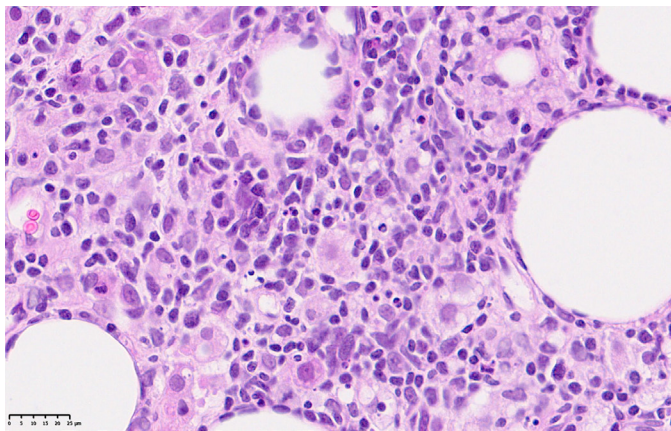


Figure 5. Dense deep infiltrate of the dermis with small, medium- sized and some large pleomorphic lymphocytes. Numerous mitosis are also seen (H&E, x600).

H&E: Hematoxylin and eosin

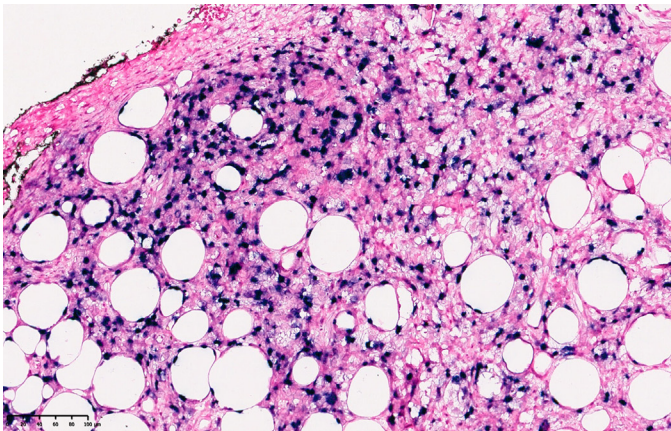


Figure 6. *In situ* hybridization for the Epstein-Barr encoding region (x400).

Several prognostic models have been studied for ENKTL-NT. PET/CT parameters are used in one of these models (8). Li et al. (6) reported that the patients in the high SUV_{max} group had significantly inferior progression-free survival and overall survival rates when the optimal SUV_{max} cut-off value was determined to be 9.5. SUV_{max} levels were very high in our patient, especially in the face and arm involvement. Moreover, PET/CT scans can play a significant role in guiding biopsies. We used PET/CT to determine the optimal site for biopsy in our patient.

In conclusion, ENKTL-NT remains a concerning lymphoma in terms of the diagnosis, follow-up, and treatment of patients. It is important to distinguish ENKTL-NT from other medical conditions such as necrotising soft tissue infections, mucormycosis, and dermatitis. In ENKTL-NT patients, unnecessary diagnostic and treatment

procedures lead to delays. PET/CT may help guide invasive procedures accurately and prevent unnecessary biopsies, resulting in patients being evaluated less invasively and more effectively.

Ethics

Informed Consent: The written informed consent form was obtained.

Authorship Contributions

Surgical and Medical Practices: Z.K., M.B., A.A., M.K., N.A., Ş.A.B., G.Y.T., C.B. Concept: Z.K., M.B., A.A., M.K., N.A., Ş.A.B., G.Y.T., C.B., Design: Z.K., M.B., A.A., M.K., N.A., Ş.A.B., G.Y.T., C.B., Data Collection or Processing: Z.K., M.B., A.A., M.K., N.A., Ş.A.B., G.Y.T., C.B., Analysis or Interpretation: Z.K., M.B., A.A., M.K., N.A., Ş.A.B., G.Y.T., C.B., Literature Search: Z.K., A.A., M.K. Writing: T Z.K., M.B., A.A., M.K., N.A., Ş.A.B., G.Y.T., C.B.

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An Unusual Case of Renal Angiomyolipoma Hemorrhage: Renal Angiomyolipoma Endowed with a Vascular Supply That Defied Tradition, Originating Directly from The Abdominal Aorta

Olağandışı Bir Renal Anjiyomiyolipom Kanaması Vakası: Geleneklere Aykırı Damarsal Kaynağa Sahip Olan, Doğrudan Abdominal Aorttan Kaynak Alan Renal Anjiyomiyolipom

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ABSTRACT

Renal angiomyolipomas typically receive their blood supply from the renal arteries. However we present a rare case of spontaneous renal angiomyolipoma hemorrhage, where the angiomyolipoma's arterial supply originated directly from the abdominal aorta rather than the renal artery. This case report outlines the clinical presentation, diagnosis, and successful management of this unique anomaly through coil embolization. To the best of our knowledge, this is the first reported case in the literature of a renal angiomyolipoma with abdominal aortic blood supply stabilized using coil embolization.

Keywords: Renal angiomyolipoma, hemorrhage, coil embolization, aorta

Öz

Renal anjiyomiyolipomlar genellikle kanlanmalarını renal arterlerden alırlar. Ancak burada anjiyomiyolipomun arteriyel kanlanmasının renal arter yerine doğrudan abdominal aorttan kaynaklandığı nadir bir spontan renal anjiyomiyolipom kanaması olgusunu sunuyoruz. Bu olgu sunumu, bu benzersiz anomalinin klinik tablosunu, tanısını ve coil embolizasyonu ile başarılı tedavisini özetlemektedir. Bildiğimiz kadarıyla, direkt abdominal aorttan kanlanmaya sahip renal anjiyomiyolipomun coil embolizasyonu ile stabilize edildiği literatürde bildirilen ilk olgudur.

Anahtar Sözcükler: Renal anjiyomiyolipom, hemoraji, coil embolizasyonu, aort

INTRODUCTION

Renal angiomyolipomas are rare benign tumors consisting of three components: smooth muscle, vascular structures, and fatty components (1). They are most commonly diagnosed. However, they may be associated with tuberous sclerosis complex and sporadic lymphangioleiomyomatosis (2). These benign tumors often present no cause for concern. However, although they are often asymptomatic and detected incidentally, they can cause gross hematuria, flank pain, palpable tender mass, and retroperitoneal hemorrhage (3). Renal angiomyolipomas are the most common

cause of retroperitoneal bleeding of non-traumatic renal origin (1). Various methods such as active surveillance, ablation, selective arterial embolization, and open or laparoscopic surgery are used in the treatment of renal angiomyolipomas, depending on their pathological and clinical features (4). The prevalence of sporadic renal angiomyolipomas in the general population was found to be 0.44% in a study of 61,400 patients, and increases with females (5). The diagnosis of renal angiomyolipomas is made more easily using ultrasonography, computed tomography (CT), magnetic resonance imaging, and biopsy (2).

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They are conventionally acknowledged as receiving their vascular nourishment from the intricate network of branches originating from the renal artery. In this exceptional instance, we chronicle the extraordinary revelation of a renal angiomyolipoma that defied convention by deriving its blood supply not from the renal arterial tributaries but directly from the abdominal aorta. This unprecedented vascular anomaly precipitated a cascade of events, culminating in a spontaneous and potentially life-threatening angiomyolipoma hemorrhage. That set the stage for an intricate clinical conundrum. As we delve into this remarkable case, it becomes evident that this phenomenon represents a medical enigma of the highest rarity, with no precedent or documentation in the annals of medical literature to illuminate the path we were about to traverse.

CASE REPORT

A 45-year-old female patient presented to the emergency department with complaints of weakness, right-sided abdominal pain three days, and hematuria occurring three days prior. The patient was free of comorbidities, had no substantial medical history, and had never had surgery. On physical examination, the patient had right costovertebral angle tenderness and no fever. Other system examinations were normal. Laboratory tests revealed a progressive drop in hemoglobin levels from 11.4 g/dL to 9.4 g/dL, to 7.2 g/dL, within one to two days. A dynamic renal ultrasonography confirmed the presence of an angiomyolipoma and a retroperitoneal hematoma. Abdominal CT scan, revealed a 132x92 mm cyst with thickened walls and partial contrast enhancement in the lower pole of the right kidney, suspected to be an angiomyolipoma. Additionally, a hematoma was observed within and around the angiomyolipoma, extending into the retroperitoneal space (Figure 1). The patient was hospitalized, stabilized with six units of erythrocyte suspension, and subsequently evaluated by interventional radiology.

Treatment and Management

Coil embolization was chosen as the treatment modality after evaluation. The aberrant vessel was responsible for the angiomyolipoma's hemorrhage. It was found to originate from the abdominal aorta and was successfully embolized using coils (Figure 2). Subsequent monitoring revealed the cessation of bleeding into the angiomyolipoma, and the patient remained stable (Figure 3). She was discharged in a stable condition. Follow-up exams at 1 and 3 months after discharge showed no sign of a recurrence of the angiomyolipoma hemorrhage, which was also supported by laboratory testing and CT scans.

DISCUSSION

Although renal angiomyolipomas are usually diagnosed incidentally, in some cases they may present with hemorrhage (6). Renal angiomyolipomas have long been associated with a consistent vascular supply, predominantly arising from branches stemming from the renal artery. However, our presented case challenges the very essence of this conventional understanding by unveiling a remarkable and exceedingly rare anomaly: a renal angiomyolipoma endowed with a vascular supply that defied tradition, originating directly from the abdominal aorta. This aberration, while perplexing, is not without precedent in the broader realm of vascular anomalies; nevertheless, its occurrence within the context of a renal angiomyolipoma, coupled with the consequential life-threatening spontaneous hemorrhage, elevates it to unparalleled uniqueness. Spontaneous retroperitoneal hemorrhage originating from the kidney was first described by Bonnet in 1700, and this rarely observed form of hemorrhage was given its name by Wunderlich in 1856 (7).

The case presented here highlights the intricate nature of renal vascular anatomy. While the majority of renal angiomyolipomas indeed derive their blood supply from the renal artery, aberrant

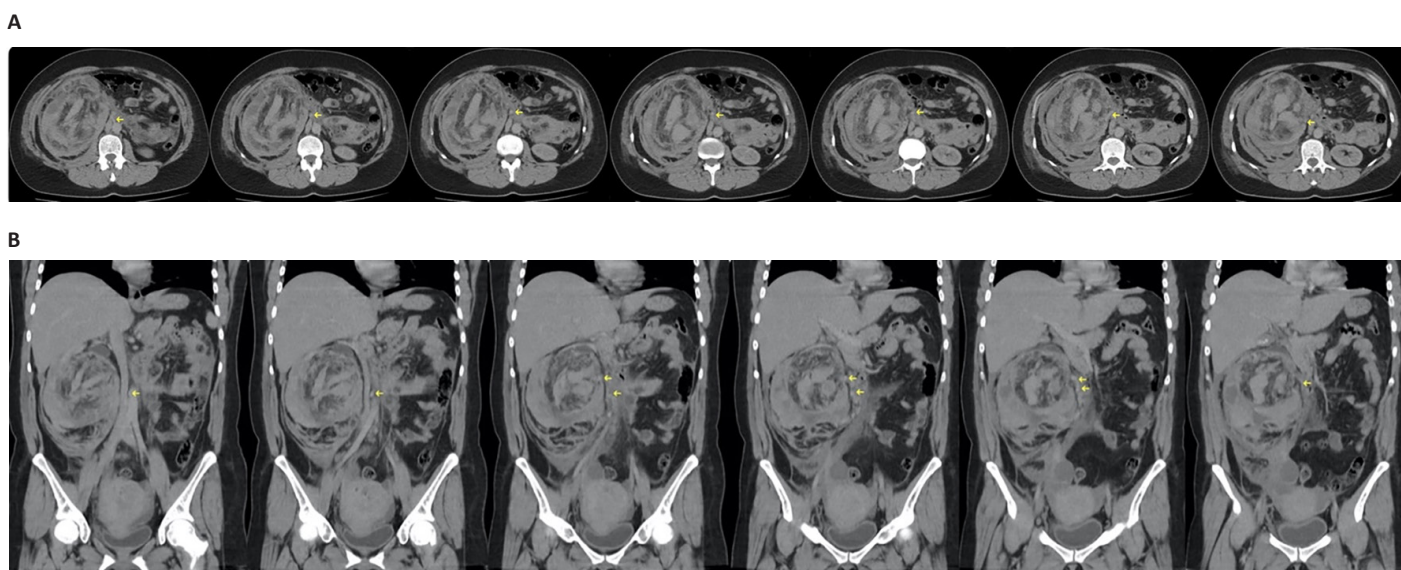


Figure 1. (A) Hemorrhagic renal angiomyolipoma and artery from the aorta on CECT image (Axial). B) Hemorrhagic renal angiomyolipoma and artery from the aorta on CECT image (Coronal).

CECT: Contrast-enhanced computed tomography



Figure 2. Coil embolization image of a renal angiomyolipoma artery originating from the abdominal aorta.

vascular patterns are not unheard of in the vascular landscape. Anomalous arterial origins have been previously documented in various anatomical contexts, such as renal vascular anomalies and abdominal aortic variants. However, the emergence of such an aberrant vascular supply in the context of a renal angiomyolipoma is an exceedingly rare occurrence. Its presentation as spontaneous hemorrhage is a clinical conundrum that demands meticulous exploration.

The precise craftsmanship of coil embolization is a hallmark of a well-known procedure in the field of interventional radiology. Also, it is crucial for non-invasive interventions, such as in this unusual instance. It has been shown by Kothary et al. (8) and Blakeley and Thiagalingham (9) that selective arterial embolization is an effective method for controlling hemorrhage resulting from benign renal lesions. As in our case, Wang et al. (10) successfully applied arterial embolization as a non-surgical treatment method to stop hemorrhage in the presence of spontaneous retroperitoneal hemorrhage caused by renal angiomyolipomas. We were able to occlude this aberrant vessel rooted from the abdominal aorta. Then, we effectively halted hemorrhage within the angiomyolipoma, and then we prevented the further bleeding. This intervention not only proved instrumental in stabilizing the patient but also paved the way for her complete recovery.

The successful outcome of this case serves as a testament to the crucial role of interventional radiology in managing intricate vascular anomalies. Coil embolization, with its precision and efficacy, stands as a valuable tool in the armamentarium of clinicians faced with such challenging scenarios. Our experience adds to the growing body of evidence supporting the utility of this intervention in managing not only renal angiomyolipoma hemorrhage but also other vascular anomalies with aberrant origins.



Figure 3. CECT image after coil embolization.

CECT: Contrast-enhanced computed tomography

While aberrant vascular supply to renal angiomyolipomas is a rarity, it is not entirely unprecedented in the broader context of vascular anomalies. Previous reports have highlighted variations in renal vascular anatomy, such as accessory renal arteries and cases where renal angiomyolipomas received their blood supply from unusual sources like the inferior mesenteric artery. However, the specific scenario of a renal angiomyolipoma directly supplied by the abdominal aorta is rarely sparse in the literature.

Our case report contributes to the existing knowledge base by showcasing the successful application of coil embolization in managing this exceptional anomaly. To the best of our knowledge, this is the first documented case where a renal angiomyolipoma with an abdominal aortic blood supply was stabilized and hemorrhage controlled using this method. The absence of precedent highlights the rarity of such cases and underscores the importance of sharing our experience.

CONCLUSION

This case highlights the importance of considering aberrant vascular anatomy when managing renal angiomyolipoma hemorrhage. While renal artery supply is the norm, anomalous cases such as this one should be kept in mind. Coil embolization emerged as an effective intervention in this instance, preventing recurrent hemorrhage and ensuring the patient's stability. Further research and reporting of similar cases are necessary to broaden our understanding of such rare anomalies.

Ethics

Informed Consent: Patient consent it was obtained.

Footnotes

Authorship Contributions

Concept: C.Y., A.Y., Design: C.Y., A.Y., Data Collection or Processing: C.Y., A.Y., Analysis or Interpretation: C.Y., A.Y., Literature Search: C.Y., A.Y., Writing: C.Y., A.Y., Critical Review: C.Y., A.Y.

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

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Mystery Behind Hidden Long Standing Perianal Fistula-mucinous Adenocarcinoma

Uzun Süreli Gizli Perianal Fistül-Musinöz Adenokarsinomun Arkasındaki Gizem

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ABSTRACT

Mucinous adenocarcinomas (MA) of the perianal region is a rare entity and have an uncertain etiopathogenesis. They are mostly contributed by, or MA arising from chronic perianal fistula (PF) has an indolent growth with locoregional spread, and increased rate of disease recurrence. Here, we report a rare case of a 58-year-old male presenting with MA of a left perianal exophytic growth for 20 years and hidden PF tract. Though abdomino-perineal resection remains mainstay of treatment, we were able to achieve effective response by doing wide local excision of malignant lesion with fistulous tract and primary reconstruction of the defect by V-Y flap and adjuvant chemotherapy.

Keywords: Perianal fistula, mucinous adenocarcinoma, V-Y flap

Öz

Perianal bölgenin müsinöz adenokarsinomları (MA) nadir görülen bir durumdur ve etiopatogenezi belirsizdir. Çoğunlukla kronik perianal fistülden (PF) kaynaklanan MA, yavaş büyüyen, bölgesel yayılım gösteren ve hastalık tekrarlama oranının yüksek olduğu bir hastalıktır. Burada, 20 yıldır sol perianal ekzofitik büyüme ve gizli PF traktına sahip MA ile başvuran 58 yaşında nadir bir erkek olguyu bildiriyoruz. Abdomino-perineal rezeksiyon tedavinin temelini oluşturmaya devam etse de, malign lezyonun fistül traktıyla birlikte geniş lokal eksizyonu ve defektin V-Y flap ve adjuvan kemoterapi ile primer rekonstrüksiyonu ile etkili yanıt elde edebildik.

Anahtar Sözcükler: Perianal fistül, musinöz adenokarsinom, V-Y flap

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INTRODUCTION

Perianal fistula (PF) is a common disease in proctological diseases. However, rare cases have reported the development of a mucinous adenocarcinoma (MA) from chronic anal fistula. Rosser et al. (1) in 1934 reported seven cases of fistula that had undergone malignant transformation. The pathogenesis of this malignancy remains a mystery. It exhibits slow growth, and although inguinal lymph nodal involvement is seen observed in advanced stages, distant metastases are uncommon (2-4). The aim of this study is to share our experience on diagnostic and therapeutic challenges, as there is a lack of data and uncertainty of disease presentation.

CASE REPORT

A 58-year-old male presented to the surgical out patient department with complaints of a mass over the left perianal region for 20 years, which has increased in size past over the 6 months (Figure 1). He did not reveal any history of pain, mucoid discharge, difficulty in passing stools, rectal bleeding, or weight loss. Inspection of the perianal region revealed a single ulcer proliferative lesion measuring 10x8 cm with no fixity to the underlying structure. The lesion did not bleed on touch, and no discharge was noted. Per rectal examination, there was no induration or fistulous opening noted. No inguinal lymphadenopathy. The patient underwent a colonoscopy, which had normal findings, and the histopathological report of the incisional biopsy suggested dysplastic glands in granulation tissue. A contrast-enhanced computed tomography of the Abdomen and Pelvis was done and reports are suggestive of a well-defined, heterogeneously enhancing exophytic lobulated lesion measuring 6.7x9.9x8.8 cm (Anterior-posterior x Transverse x Craniocaudal) with few internal calcific foci and hypodense areas noted. This lesion arises from the surface of the left gluteal region, with associated minimal skin thickening, obliterating the gluteal cleft, and extending to the anal verge and anorectal junction along the left lateral wall, with suspicious involvement of the anal canal and anorectal junction. The lesion is seen extending along the left ischioanal fossa measuring



Figure 1. Clinical picture.

6.2x2.2 cm, suspicious of malignancy; hence, the patient underwent wide local excision of the swelling, and a fistula tract was noted (site was marked) which was ligated (Figures 2, 3). Histopathological examination was suggestive of Mucin secretory adenocarcinoma in a fistulous tract; all margins were uninvolved (Figures 4, 5). The patient was scheduled for abdomino-perineal resection (APR). However, the patient was not willing to undergo the same procedure, and hence was planned for closure of the defect by V-Y flap (Figure 6, 7) with adjuvant chemotherapy (capecitabine and oxaliplatin). The post-operative period was uneventful. The follow-up was done for one year and was uneventful. Advised follow-up magnetic resonance imaging (MRI) of the abdomen and pelvis, but the patient refused due to financial constraints.

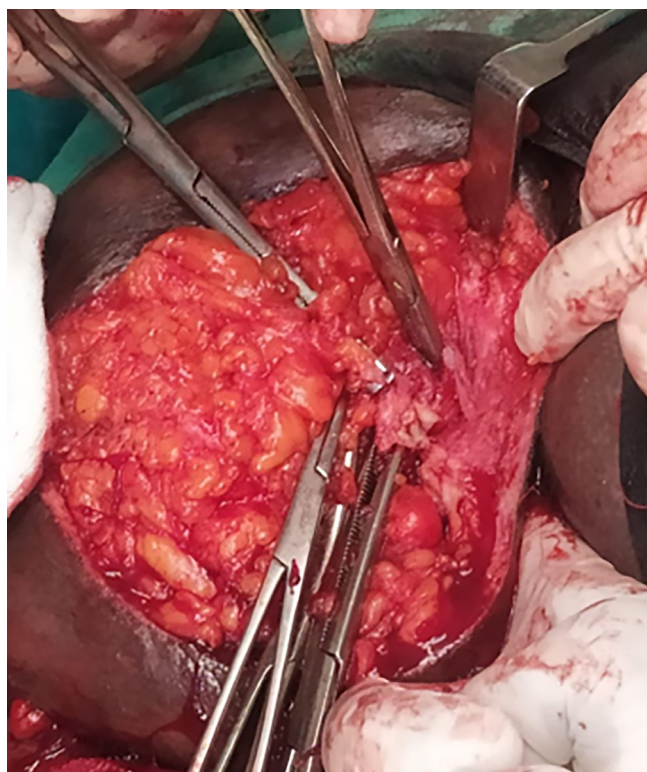


Figure 2. Intra operative fistulous tract picture.



Figure 3. Specimen picture.

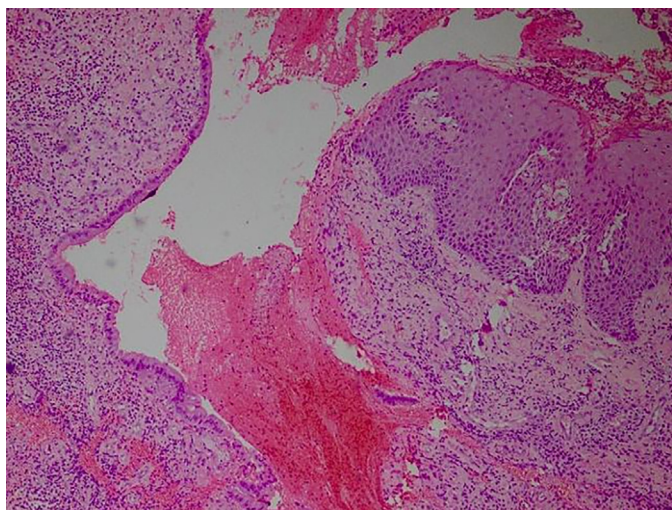


Figure 4. Histopathological picture.

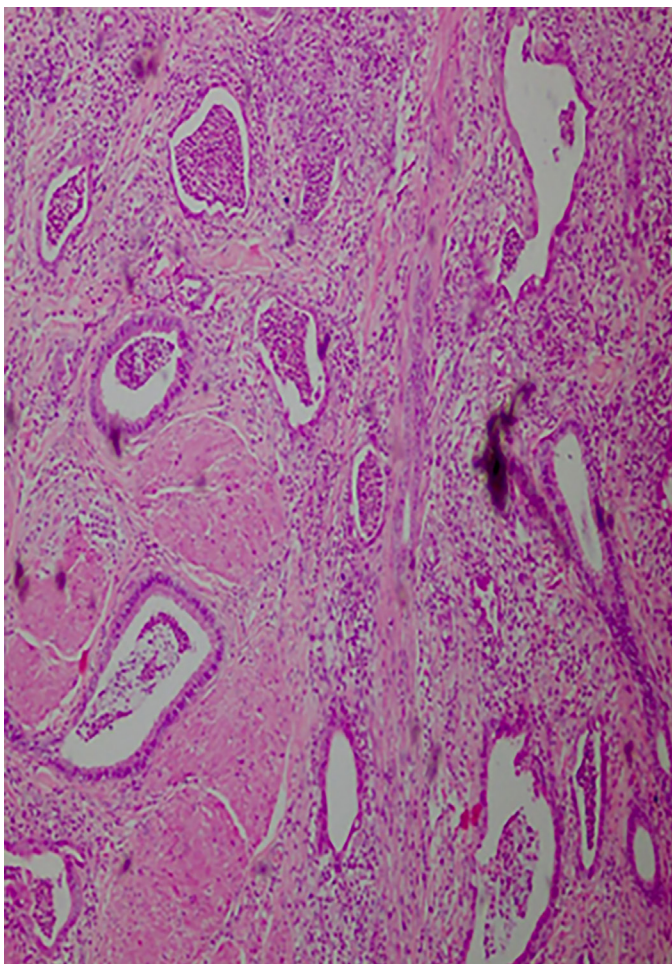


Figure 5. Histopathological picture.

DISCUSSION

It is been reported in the World Health Organization, MA is an invasive adenocarcinoma consisting of malignant glandular cells which contain intracytoplasmic mucin and the infiltrating glandular



Figure 6. Post operative picture.



Figure 7. Post operative picture.

structures are associated with mucoid stromal formation (5). Though few articles state that malignant transformation of a long-standing PF is attributed to mucosal regeneration, but few set of authors think that malignant cells settle in the fistulous granulation tissue arising from proximal gastrointestinal malignancy (6). Associated symptoms are pain in the perianal region, itching, mucinous discharge or pus discharge, and perianal ulcero-proliferative growth. However, rare involvement of the rectal mucosa, intestinal obstruction, or rectal bleeding are uncommon symptoms (7-9). While biopsy is remains the initial essential investigation for diagnosis, endoscopic ultrasound, colonoscopy, computed tomography, and MRI help in diagnosing perianal MA (PMA), with MRI being the most sensitive in demonstrating the mucinous structures (10). Many studies on PMA

indicate that the treatment of choice is radical surgical excision, with APR.

The role of neoadjuvant/adjuvant chemoradiotherapy in PMA is still controversial as it lacks proven data. However, The Journal of Surgical Oncology has provided data suggesting that neoadjuvant chemoradiotherapy can be a part of the treatment of PMA in order to reduce local recurrence and improve survival rate (11).

CONCLUSION

In this case report, we would like to highlight our patient did not present with typical symptoms and signs of malignancy which could have delayed the diagnosis and treatment, but with prompt investigation it is possible to come to the diagnosis at the earliest. Though APR is the definitive treatment for PMA, we were able to get good result with wide local excision and V-Y flap.

Ethics

Informed Consent: Informed consent it was obtained.

Footnotes

Authorship Contributions

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

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

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