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The Risk Factors for Carbapenem-Resistant *Klebsiella pneumoniae* and Carbapenem-Resistant *Escherichia coli* Infections in a Tertiary Care Hospital

Üçüncü Basamak Bir Hastanede Karbapenem Dirençli *Klebsiella pneumoniae* ve Karbapenem Dirençli *Escherichia coli* İnfeksiyonları için Risk Faktörleri

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ABSTRACT

Introduction: *Identifying risk factors associated with carbapenem-resistant Enterobacteriaceae infections is crucial for developing effective infection control strategies. However, previous studies have reported inconsistent and sometimes conflicting results, making it challenging to establish a clear and practical approach. This study aimed to evaluate the risk factors for infections caused by carbapenem-resistant Klebsiella pneumoniae and carbapenem-resistant Escherichia coli.*

Materials and Methods: *A total of 164 patients with infections caused by carbapenem-resistant K. pneumoniae or carbapenem-resistant E. coli were retrospectively analyzed. The control group consisted of 220 patients hospitalized during the same period in whom no carbapenem-resistant Enterobacteriaceae were detected.*

Results: *Multivariate analysis in patients with carbapenem-resistant K. pneumoniae infections identified intensive care unit (ICU) admission, prolonged ICU stay, higher Acute Physiology Assessment and Chronic Health Evaluation II scores, prior carbapenem use, and the presence of a central venous catheter as independent risk factors for infection. Among patients with carbapenem-resistant E. coli infections, prolonged ICU stay and a history of abdominal surgery were found to be significantly associated with infection in the multivariate analysis.*

Conclusion: *Given that infections caused by carbapenem-resistant Enterobacteriaceae are associated with increased morbidity and mortality, identifying modifiable risk factors and implementing targeted infection control measures are essential. These risk factors may vary across patient populations and should be addressed accordingly.*

Key Words: *Carbapenem; Klebsiella pneumonia, Esherichia coli; resistance*

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ÖZ

Giriş: *Karbapenem dirençli Enterobacteriaceae infeksiyonları ile ilişkili risk faktörlerinin belirlenmesi, infeksiyon kontrol stratejilerinin geliştirilmesi açısından büyük önem taşımaktadır. Ancak bu alanda yapılan önceki çalışmaların tutarsız ve zaman zaman birbiriyle çelişen sonuçlar bildirmesi, kesin ve uygulanabilir bir yaklaşım geliştirilmesini güçleştirmektedir. Bu çalışma, karbapenem dirençli Klebsiella pneumoniae ve karbapenem dirençli Escherichia coli'nin neden olduğu infeksiyonlara ilişkin risk faktörlerini değerlendirmeyi amaçlamaktadır.*

Materyal ve Metod: *Karbapenem dirençli K. pneumoniae ve karbapenem dirençli E. coli kaynaklı infeksiyonu bulunan toplam 164 hasta retrospektif olarak incelendi. Kontrol grubu olarak aynı dönemde hastanede yatışı olan ancak karbapenem dirençli Enterobacteriaceae üremesi saptanmayan 220 hasta alındı.*

Bulgular: *Karbapenem dirençli K. pneumoniae infeksiyonu gelişen hastalarda yürütülen çok değişkenli analiz sonucunda, yoğun bakım ünitesi (YBÜ)'ne yatış, YBÜ'de uzun süreli kalış, yüksek acute physiologic assessment and chronic health evaluation II skoru, karbapenem kullanımı ve santral venöz kateter varlığı infeksiyon gelişimi için bağımsız risk faktörleri olarak belirlendi. Karbapenem dirençli E. coli infeksiyonu olan hastalarda ise uzamış YBÜ yatışı ve abdominal cerrahi öyküsü infeksiyon gelişimi ile anlamlı şekilde ilişkili bulundu.*

Sonuç: *Karbapenem dirençli Enterobacteriaceae infeksiyonları artmış morbidite ve mortalite ile ilişkili olduğundan, hasta gruplarına göre farklılık gösterebilen değiştirilebilir risk faktörlerinin belirlenmesi ve buna yönelik etkili infeksiyon kontrol önlemlerinin uygulanması büyük önem taşımaktadır.*

Anahtar Kelimeler: *Karbapenem; Klebsiella pneumonia; Esherichia coli; Direnç*

INTRODUCTION

Carbapenem-resistant Enterobacteriaceae (CRE) have been classified as an urgent health threat by the World Health Organization (WHO)[1]. Infections caused by these resistant bacteria are associated with worse clinical outcomes, prolonged hospital stays, and increased costs compared to their susceptible counterparts[1,2]. In Türkiye, CRE infections were reported as sporadic hospital outbreaks until 2013 but became endemic after 2014–2015[3]. According to the 2022 reports of the WHO, carbapenem resistance was detected in 48.2% of *Klebsiella pneumoniae* and 3.7% of *Escherichia coli* isolates in Türkiye[4]. In addition, the 2021 report by the National Healthcare-Associated Infections Surveillance Network data revealed that *K. pneumoniae* exhibited meropenem resistance rates ranging from 42.1% to 75.7%, and imipenem resistance rates between 39.6% and 70.2%, depending on the infection site[5]. In the same report, *E. coli* exhibited meropenem resistance rates ranging from 2.2% to 22.6% and imipenem resistance rates ranging from 2.7% to 17.6%[5]. Considering that these infections increase morbidity and mortality, variable risk factors should be identified and control measures should be implemented. The objective of this study was to investigate the risk factors in patients with infections caused by carbapenem-resistant *K. pneumoniae* (CRKP) and carbapenem-resistant *E. coli* (CREC) in a tertiary care hospital.

MATERIALS and METHODS

This retrospective cross-sectional study was conducted at Süleyman Demirel University Faculty of Medicine, Research and Application Hospital, a 600-bed facility with six intensive care units (ICUs) and 94 intensive care beds.

Study Period and Study Population

A total of 164 patients diagnosed with CRE-associated infections at Süleyman Demirel University Faculty of Medicine, Research and Application Hospital between January 2020 and June 2022 were designated as the case group. Concurrently, 220 hospitalized patients without CRE growth were included as the control group. Patients with CRE infections were classified and analyzed into two subgroups: CRKP and CREC. Exclusion criteria included CRE colonization, lack of evidence for healthcare-associated infection, infections caused by strains other than *K. pneumoniae* or *E. coli*, outpatient admission, age under 18 years, and hospitalization duration of less than 48 hours. The study was conducted after obtaining ethical approval (Decision No: 137, dated April 27, 2022) from the Ethics Committee of Süleyman Demirel University Research and Application Hospital.

Patient-Related Risk Factors

Possible patient-related risk factors evaluated were age, sex, admission diagnosis, the unit where the patient was followed [intensive care unit

(ICU) or ward], comorbidities, Acute Physiology Assessment and Chronic Health Evaluation (APACHE)-II score, and Charlson Comorbidity Index (CCI). As measures of disease severity, the APACHE-II score and CCI at ICU admission were used for patients monitored in the ICU, whereas the CCI at hospital admission was used for patients followed in the ward. Recorded comorbidities included diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD), asthma, chronic obstructive pulmonary disease (COPD), chronic renal failure (CRF), need for hemodialysis, heart failure (HF), cirrhosis, malignancy, neutropenia, obesity, immunosuppression, transplantation, and cerebrovascular event (CVE).

Healthcare-Associated Risk Factors

Recorded healthcare-associated risk factors included duration of hospital stay, duration of ICU stay, history of hospitalization within the previous three months, hemodialysis, presence of a central venous catheter (CVC), mechanical ventilation (MV), tracheostomy, abdominal surgery and other surgical procedures, detection of multidrug-resistant (MDR) microorganisms prior to carbapenem-resistant Enterobacteriaceae (CRE) infection, and detection of vancomycin-resistant *Enterococcus* spp. (VRE) colonization.

Antibiotic Use

Information on antibiotic use within the previous three months was recorded. If antibiotics had been used, the specific antibiotic(s) administered were documented. Identification and antibiotic susceptibility testing of isolated microorganisms were performed using the BD Phoenix 100 automated system (Becton-Dickinson, USA). Antibiotic susceptibility test results were interpreted according to zone diameter breakpoints and MIC values published in the EUCAST 2022 guidelines[6]. The broth microdilution method was used to assess colistin susceptibility.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences 25.0 software. For categorical variables, frequencies and percentages were reported. For continuous variables, mean ± SD (standard deviation) was used, and median (min–max) values were provided for skewed distributions. The Chi-square test was used to analyze categorical variables. For continuous variables, Student's t-test was applied, and the Mann-Whitney U test was used for variables with non-normal distributions. Variables found to be significant in univariate analysis were included in a logistic regression model. The Backward likelihood ratio (LR) method was used for the analysis. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated, and $p< 0.05$ was considered statistically significant.

RESULTS

Between January 2020 and June 2022, 424 patients with CRE growth were monitored in the wards and intensive care units of Süleyman Demirel University Faculty of Medicine, Research and Application Hospital. Of these patients, 62 were excluded from the study for being outpatients, 70 due to colonization, 72 because of incomplete data, 46 owing to insufficient evidence of healthcare-associated infection, and 10 due to infections caused by microorganisms other than *E. coli* or *Klebsiella* spp. A total of 164 cases, 129 of whom were diagnosed with CRKP infection and 35 of whom were diagnosed with CREC infection, were included in the study. The control group included 220 patients who met the criteria specified in the Materials and Methods section. Patients diagnosed with hospital-acquired CRKP and CREC infections were evaluated as two separate case groups.

Among patients with CRKP infections, 34 (26%) were diagnosed with bloodstream infections (29 of which were catheter-related), 33 (25.6%) with catheter-associated urinary tract infections, 32 (24.8%) with ventilator-associated pneumonia, 14 (11%) with surgical site infections, 12 (9%) with community-acquired pneumonia, two (1.5%) with soft tissue infections, and two (1.5%) with intra-abdominal infections. In the group with CREC infections, the distribution of infection types was as follows: 12 (34.3%) catheter-associated urinary tract infections, 10 (28.6%) community-acquired pneumonia, four (11.4%) surgical site infections, three (8.6%) intra-abdominal infections, three (8.6%) bloodstream infections (one of which was catheter-related), and three (8.6%) ventilator-associated pneumonia.

Table 1. Demographic characteristics of the cases with carbapenem-resistant *K. pneumonia* and carbapenem-resistant *E. coli* infections

Demographic characteristics	CRKP (n= 129) %	p	CREC (n= 35) %	p	Control (n= 220) %
Age (mean ± SD)	65.2 ± 16.6	0.079	65.9 ± 15.2	0.575	68.1 ± 43.3
Sex		0.480		0.203	
Female	41.1		48.6		37.3
Male	58.9		51.4		62.7
Diagnosis at admission		0.023		0,009	
Neurological diseases	21.7		11.4		15.9
Pulmonary diseases	10.9		0.0		16.4
Metabolic and internal diseases	18.6		11.4		12.7
Infection	6.2		8.6		10.0
Trauma-surgical emergency	16.3		2.9		9.5
Elective surgery	15.5		37.1		20.5
COVID-19	7.8		20.0		4.5
Hematologic diseases	0.8		0.0		3.2
Cardiovascular diseases	2.3		8.6		7.3
Location		0.034		0.309	
ICU	58.1		37.1		46.4
Ward	41.9		62.9		53.6

ICU: Intensive care unit.

The demographic characteristics of the cases with CRKP and CREC infections and the control group, as well as their distribution according to the clinical departments where they were followed, are presented in Table 1. In univariate analysis, follow-up in the ICU was found to be significantly more frequent in the group diagnosed with CRKP infection compared to the control group (p= 0.034). There were no statistically significant differences in demographic characteristics or admission diagnoses between the case and the control groups.

According to the results of the univariate analysis, the variables investigated as potential risk factors for CRKP and CREC infections are presented in Table 2.

Table 2. Potential risk factors for carbapenem-resistant *K. pneumoniae* and carbapenem-resistant *E. coli* infections

	CRKP (n= 129) %	p	CREC (n= 35) %	p	Control (n= 220) %
Diabetes mellitus	36.4	0.215	31.4	0.864	30
Hypertension	37.2	0.942	45.7	0.314	36.8
COPD	7.0	0.178	0	0.031	11.4
Asthma	7.0	0.116	11.4	1.000	12.3
Coronary artery disease	20.9	0.845	37.1	0.078	21.8
Chronic renal failure	21.7	0.007	8.6	0.732	10.5
Heart failure	9.3	0.189	11.4	0.797	14.1
Cirrhosis	2.3	0.363	2.9	0.359	0.9
Malignancy	29.5	0.251	31.4	0.643	35.5
Neutropenia	1.7	0.854	2.9	1.000	3.6

Table 2. Potential risk factors for carbapenem-resistant *K. pneumoniae* and carbapenem-resistant *E. coli* infections (continue)

	CRKP (n= 129) %	p	CREC (n= 35) %	p	Control (n= 220) %
Obesity	2.6	0.059	2.9	1.000	2.7
Immunosuppression	29.5	0.058	37.1	0.787	39.1
Transplantation	2.3	0.750	5.7	0.357	3.2
Cerebrovascular event	24	0.190	5.7	0.065	18.2
APACHE-II score (mean ± SD)	17.2 ± 10	0.01	14.1 ± 8.0	0.733	14.1 ± 8.0
CCI (mean ± SD)	4.6 ± 2.76	0.187	4.3 ± 2.4	0.258	4.3 ± 2.4
Healthcare-associated factors					
Length of hospitalization (median. min-max)	39 (2-428)	<0.001	32 (3-232)	<0.001	12 (3-120)
Length of ICU stay [median (min-max)]	16 (0-390)	<0.001	9 (0-220)	<0.001	3 (0-76)
Hospitalization within the previous three months	44.2	0.006	42.9	0.115	29.5
Hemodialysis	15.5	0.015	2.9	0.705	6.8
Central venous catheter	65.9	<0.001	37.1	0.208	26.8
Urinary catheter	83.7	0.024	85.7	0.112	73.2
Mechanical ventilation	55	<0.001	28.6	0.398	35.9
Tracheostomy	16.3	0.022	8.6	0.863	7.7
Infection with an MDR microorganism	52.7	<0.001	40	0.005	17.7
VRE colonization	8.5	0.087	5.7	0.529	3.5
Immunosuppressive treatment	19.4	0.902	28.6	0.342	21.4
Abdominal surgery	18.6	0.078	37.1	0.002	10.5
Other surgical interventions	51.9	0.691	62.9	0.150	49.6
Antibiotic use					
Antibiotic use within the previous three months	98.5	0.005	100	0.052	90.0
Quinolone	37.2	0.348	34.3	0.813	32.3
Third generation cephalosporin	31	0.613	34.3	0.940	33.6
Aminoglycoside	4.7	0.371	0	1.000	2.7
Carbapenem	58.1	<0.001	51.4	0.001	22.3
Ertapenem	13.2	0.073	11.4	0.308	6.8
Meropenem	50.4	<0.001	37.1	0.067	21.4
Imipenem	2.3	0.079	2.9	0.592	2.3
Glycopeptide	54.3	<0.001	37.1	0.116	24.5
Vancomycin	19.4	0.001	5.7	1.000	6.8
Teicoplanin	40.3	<0.001	34.3	0.083	19.6
Piperacillin-tazobactam	27.1	<0.001	17.1	0.115	20
Ampicillin-sulbactam	31	0.007	11.4	0.765	10
Linezolid	17.8	0.018	5.7	0.748	8.7
Antifungal agents	24.8	<0.001	14.3	0.372	9.5
Colistin	17.1	0.001	8.6	0.441	5.5
TMP-SMX	8.5	0.052	5.7	0.632	3.6
Daptomycin	7.8	0.093	5.7	0.632	3.6
Metronidazole	18.6	0.911	31.4	0.077	19.1

COPD: Chronic obstructive pulmonary disease, APACHE: Acute Physiology and Chronic Health Evaluation, CCI: Charlson Comorbidity Index, ICU: Intensive care unit, MDR: Multidrug-resistant, VRE: Vancomycin-resistant Enterococcus.

Table 3. Carbapenem-resistant *K. pneumoniae* risk factors (multivariate analysis)

	Multivariate analysis	
Variable	**p**	**OR (95% CI)**
ICU admission	0.017	2.972 (1.215 – 7.270)
Length of ICU stay	<0.001	1.049 (1.027 – 1.072)
APACHE-II score	0.001	1.068 (1.025 – 1.112)
Carbapenem use	0.004	2.856 (1.398 – 5.836)
Central venous catheter	<0.001	4.160 (1.997 – 8.665)

ICU: Intensive care unit, OR: Odds ratio, CI: Confidence interval, APACHE: Acute Physiology and Chronic Health Evaluation.

Table 4. Carbapenem-resistant *E. coli* risk factors (multivariate analysis)

	Multivariate analysis	
Variable	**p**	**OR (95% CI)**
Length of ICU stay	0.001	1.065 (1.026 – 1.106)
Abdominal surgery	<0.001	11.709 (3.207 – 42.752)

ICU: Intensive care unit.

The demographic data and the variables identified as significant risk factors in the univariate analysis were further evaluated by logistic regression analysis. The results revealed that ICU admission, length of ICU stay, APACHE-II score, carbapenem use within the previous three months, and central venous catheter use were statistically significant independent risk factors for CRKP infection (Table 3). Length of ICU stay and abdominal surgery were identified as independent risk factors for CREC infection (Table 4).

DISCUSSION

In this study, we examined risk factors by classifying the CRE group into two subgroups, CRKP and CREC. Effective prevention of CRE infections is essential, but previous studies have yielded conflicting results, particularly regarding potentially variable risk factors. Therefore, it is difficult to establish conclusive evidence[7-11]. Understanding these risk factors is a prerequisite for developing effective prevention strategies and has important implications for screening and resource allocation[12].

The selection of an appropriate control group is methodologically critical in studies investigating risk factors for CRKP infection, as it directly impacts the validity of findings. While some studies have utilized carbapenem-susceptible *K. pneumoniae* (CSKP) isolates as controls, this approach introduces statistical selection bias[13-20]. Carbapenem-susceptible *K. pneumoniae* strains account for a limited proportion of hospital-acquired infections and may not be representative. Furthermore, differential antibiotic effects, whereby certain agents selectively inhibit CSKP but not CRKP, artificially reduce observed antibiotic exposure frequencies in CSKP cohorts, potentially inflating perceived risk factors for CRKP[21]. In our study, patients without CRKP infection were included in the control group. The patients in the control group were those monitored in the same ward during the same period, and cases with CSKP infection were also included in this group.

Although some comorbid conditions increase the risk of infection, univariate analysis revealed a significant increase in the risk of CRKP only in patients with chronic renal failure (Table 2). In the literature, two studies have reported that chronic renal failure as a risk factor for CRKP infection in univariate analysis; however, similar to our study, it was not found to be significant in multivariate analysis[16,22]. According to the results of the Risk factors for infections caused by carbapenem-resistant Enterobacterales: an international matched case-control-control study (EURECA), chronic renal failure was significantly more common in the CRE group than in the CSE and non-infected groups in univariate analysis. Based on logistic regression analysis, it was reported as an independent variable that increased the risk of CRE infection by 2.81-fold[23]. In our study, the loss of significance in multivariate analysis may be attributed to the inclusion of all patients without infection in the control group, as well as those with infections caused by pathogens other than CRKP.

Published studies have reported that ICU admission is associated with a 2.48 to 6.85-fold higher odds ratio for developing CRKP infections compared with non-ICU settings[11,24,25]. Consistent with these findings, the results of our study demonstrated that ICU admission independently elevates the risk of CRKP infection

by nearly threefold. Prolonged hospitalization not only leads to the use of more invasive procedures and treatments but also increases the risk of cross-contamination and colonization. A retrospective observational study from Türkiye, which included 78 patients, identified previous healthcare-associated infection as an independent risk factor for CRKP. Conversely, in our study, although MDR was found to be a significant risk factor in univariate analysis, it did not reach statistical significance in the multivariate model[26].

Several studies have found no statistically significant difference in APACHE-II scores between CRKP-infected patients and controls[17,27]. Two studies reported statistically significant differences in univariate analyses, but these associations were not retained in multivariate models[22,28]. In our cohort, the mean APACHE-II score was significantly higher in CRKP-infected patients (17.2 ± 1.0) compared to controls (14.1 ± 8.0). Higher APACHE-II scores were independently associated with CRKP infection in both univariate and multivariate analyses (p= 0.001; adjusted OR: 1.068, 95% CI: 1.025–1.112). Critically ill patients are at greater risk for infections with resistant strains, likely due to more frequent invasive interventions and extended ICU admissions[29]. CVC use is among the invasive procedures that can increase the risk of healthcare-associated infections. In our study, the use of CVC, identified as another independent variable, was found to increase the risk of CRKP infection by 4.1 times. Central venous catheterization was identified as an independent variable by logistic regression analysis in the study by Zheng et al. and has also been reported as a risk factor in two meta-analyses[11,27,30]. In EURECA study conducted by Perez-Galera and colleagues, which included 235 CRE patients, urinary catheter use was reported to be 1.78 times more frequent than in the CSE group and 3.68 times more frequent than in the non-infected group[23]. In our study, only hospitalized patients were included, and the rate of urinary catheter use was high even in the control group. Therefore, although urinary catheter use was more common in the CRKP-infected group, it was not statistically significant due to the high rate in controls.

Evaluation of antibiotic use revealed that antibiotic therapy including carbapenems, glycopeptides, ampicillin-sulbactam, linezolid, antifungal agents, and colistin within the previous three months was identified as a significant risk factor in univariate analysis; however, only carbapenem use was identified as an independent risk factor. In two studies conducted on the same subject in our country, carbapenem use was reported as an independent risk factor for CRKP infection[26,31]. Previous antibiotic use has also been identified as a significant risk factor in other studies[11,25,30-33]. A study by Del-Mar et al. indicated a strong link between carbapenem use and the development of carbapenemase-producing *K. pneumoniae* strains[34]. Intense exposure to a particular class of antibiotics increases selection pressure and creates a favorable environment for microorganisms to develop resistance mechanisms[35]. In a meta-analysis conducted by Zu and colleagues, the use of carbapenems and aminoglycosides was identified as a risk factor for CRKP infection[36]. In our study population, aminoglycoside use within the previous three months was low overall, but it was higher in the CRKP group than in the control group; however, the difference was not statistically significant. In Türkiye, carbapenems and glycopeptide antibiotics may be used only with the approval from an infectious diseases specialist, in accordance with a regulation issued by the Ministry of Health. However, certain β-lactam/β-lactamase inhibitor combinations and fluoroquinolones can be used without such approval. Continuous education is crucial for reducing antibiotic exposure, which is one of the modifiable risk factors, and plays a critical role in preventing the emergence and spread of resistance.

The number of studies examining the risk factors for CREC infection is limited. In these studies, patient-related and healthcare-related independent variables such as urinary tract disease, chronic liver disease, history of hospitalization, hemodialysis, presence of a CVC, tracheostomy, and presence of biliary drainage have been reported[357-39]. In studies investigating previous antibiotic use, logistic regression analysis results have identified the use of quinolones, carbapenems, glycopeptides, and

metronidazole as independent risk factors[37-40]. In our study, prolonged ICU stay and abdominal surgery were identified as risk factors in the multivariate analysis. *E. coli* is among the primary pathogens causing intra-abdominal infections[41]. Abdominal surgery and the resulting disruption of barrier integrity may have contributed to an increased risk of infection. However, in two studies examining surgical procedures, including abdominal surgery as a potential risk factor, no significant difference was found between the case and control groups[37,38]. Prospective studies involving a larger number of cases would be beneficial for elucidating the issue.

Our study has several limitations, including its retrospective design, single-center setting, relatively small sample size, and the absence of an analysis of antibiotic exposure duration.

CONCLUSION

In our study, antibiotic use, particularly carbapenem use, was identified as the most important modifiable risk factor for CRKP infection. In the fight against antimicrobial resistance, hospitals should routinely monitor local antimicrobial susceptibility profiles, identify risk factors, implement targeted infection control measures, and improve stewardship efforts to ensure the rational use of antibiotics. Since CVC use was identified as a significant risk factor for CRKP infections, a re-evaluation of infection control practices regarding both insertion and maintenance procedures is planned. Regarding CREC infections, the observation and auditing of abdominal surgical practices in terms of infection control measures have been placed on the agenda.

ETHICS COMMITTEE APPROVAL

This study was approved by the Süleyman Demirel University Faculty of Medicine Clinical Researchs Ethics Committee (Decision no: 10/137, Date: 27.04.2022).

CONFLICT of INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: GRY

Analysis/Interpretation: MY, GRY

Data Collection or Processing: MY, GRY, OÜ, ENT

Writing: MY, GRY, OÜ, OK, FZA

Review and Correction: GRY, OK, ENT, FZA

Final Approval: All authors

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