Volume 2/ Issue 3/ August 2024

Research Article

Microorganisms Isolated from Blood Cultures of Intensive Care Patients and Follow-up of Antibiotic Susceptibilities in the Last Five Years

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Özmen, P., Akman, N., & Güler, İ. (2024). Microorganisms Isolated from Blood Cultures of Intensive Care Patients and Follow-up of Antibiotic Susceptibilities in the Last Five Years. *Cappadocia Health Science Journal*, 2(3), 317-328. DOI: https://doi.org/10.58241/ksbd.26

Submission Date/Gönderilme tarihi: 26.07.2024 Accepted Date/Kabul tarihi: 20.08.2024; Publication Date/Yayın tarihi: 28.08.2024

Microorganisms Isolated from Blood Cultures of Intensive Care Patients and Follow-up of Antibiotic Susceptibilities in the Last Five Years

Abstract

Objective: This study aimed to determine the antimicrobial resistance profiles of microorganisms isolated from blood cultures of patients hospitalized in intensive care units of a secondary-level state hospital.

Materials and Methods: Samples sent to the Microbiology Laboratory between 2018 and 2022 from patients receiving treatment in intensive care units of Nevşehir State Hospital were studied with conventional methods and automated system, and the results of the samples for which identification and antimicrobial susceptibility tests were performed were evaluated retrospectively.

Results: Gram-negative bacteria growth was detected in 54.5% of all samples, gram-positive bacteria growth was detected in 40.7%, and yeast growth was detected in 4.8%; Among gram-negative bacteria, *Acinetobacter baumanni* with a maximum of 28% (n = 47); *Enterococcus faecalis* was isolated as gram-positive bacteria with a maximum of 20.3% (n = 34). The rate of methicillin resistance in CNSs was found to be 92.8% (26/28), and in *Staphylococcus aureus*, it was 33% (2/6). Extended-spectrum beta-lactamase (ESBL) positivity was detected in 72% (13/18) and 80% (20/25) of *Escherichia coli* and *Klebsiella pneumonia* isolates, respectively. Carbapenem resistance was observed in all *A.baumanii* isolates (100%). The antibiotics *E. coli* and *K. pneumonia* were most sensitive to, and they were imipenem, meropenem (100%), and amikacin, respectively. The most sensitive antibiotics in all gram-positive isolates were linezolid and glycopeptides.

Conclusion: To guide empirical treatment, each center should examine its own blood culture results, question the antimicrobial resistance status, and make rational antibiotic selection, aiming to reduce mortality in cases of sepsis and bacteremia.

Key words: Blood culture, antibiotic resistance, bloodstream infections, intensive care unit

Yoğun Bakım Hastalarının Kan Kültürlerinden İzole Edilen Mikroorganizmalar ve Son Beş Yılda Antibiyotik Duyarlılıklarının Takibi

Öz

Amaç: Bu çalışmada, ikinci basamak bir devlet hastanesinin yoğun bakım ünitelerinde yatan hastaların kan kültürlerinden izole edilen mikroorganizmaların antimikrobiyal direnç profillerinin belirlenmesi amaçlandı.

Gereç ve Yöntem: Nevşehir Devlet Hastanesi yoğun bakım ünitelerinde tedavi gören hastalardan 2018-2022 yılları arasında Mikrobiyoloji Laboratuvarı'na gönderilen örnekler konvansiyonel yöntemlerle ve otomatize sistemle çalışılarak, identifikasyon ve antimikrobiyal duyarlılık testleri yapılan örneklerin sonuçları geriye dönük olarak değerlendirildi.

Bulgular: Tüm numunelerin %54,5'inde gram negatif bakteri üremesi, %40,7'sinde gram pozitif bakteri üremesi, %4,8'inde maya üremesi tespit edildi; Gram-negatif bakteriler arasında en fazla %28 (n=47) ile Acinetobacter baumanni; Enterococcus faecalis gram pozitif bakteri olarak maksimum %20,3 (n=34) oranında izole edildi. Metisilin direnci MSS'lerde %92,8 (26/28), Staphylococcus aureus'ta ise %33 (2/6) olarak belirlendi. Escherichia coli ve Klebsiella pneumonia izolatlarında sırasıyla %72 (13/18) ve %80 (20/25) oranında genişlemiş spektrumlu beta-laktamaz (ESBL) pozitifliği tespit edildi. A.baumanii izolatlarının tamamında (%100) karbapenem direnci gözlendi. E. coli ve K. pneumonia antibiyotiklerine en duyarlı olanlar sırasıyla imipenem, meropenem (%100) ve amikasindir. Tüm gram pozitif izolatlarda en duyarlı antibiyotikler linezolid ve glikopeptitlerdir.

Sonuç: Ampirik tedaviyi yönlendirmek için her merkezin kendi kan kültürü sonuçlarını incelemesi, antimikrobiyal direnç durumunu sorgulaması ve sepsis ve bakteriyemi vakalarında mortaliteyi azaltmayı hedefleyerek akılcı antibiyotik seçimi yapması gerekmektedir.

Anahtar Kelimeler: Kan kültürü, antibiyotik direnci, kan dolaşımı enfeksiyonları, yoğun bakım ünitesi

INTRODUCTION

Bloodstream infections are one of the clinical conditions that are seen as a cause of serious morbidity and mortality in patients with signs of systemic infection and positive blood culture. 40% of sepsis and septic shock cases in the intensive care unit are community-acquired, and 20% are hospital-acquired. High mortality is observed in cases where correct antibiotic treatment is delayed and poorly managed (Timsit et al., 2020; Zahar et al.,2011). Despite low reproduction rates, blood culture is still the gold standard in identifying the causative agent of bloodstream infections.

Microorganisms that cause bacteremia are often gram-positive bacteria such as *Streptococcus pneumoniae, Staphylococcus aureus,* and *Enterococcus faecium*, and gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa.* In addition to these factors, it is also possible to detect coagulase-negative staphylococci (CoNS), viridans Streptococci, and normal flora enterococci in immunocompromised neutropenic individuals. Mycobacterium tuberculosis and atypical mycobacteria, non-fermentative gram-negative bacilli, and opportunistic fungi also cause bacteremia and fungemia (Taramasso et al., 2016).

Rapid and accurate identification of the causative agent is important in treating infections such as bacteremia, fungemia, infective endocarditis, catheter-related bloodstream infections, and osteomyelitis. This reduces the patient's length of stay and the risk of nosocomial infection.

This study aimed to determine the antimicrobial resistance profiles of microorganisms isolated from blood cultures of patients hospitalized in intensive care units of a secondary-level state hospital and to guide empirical treatment.

MATERIALS AND METHODS

The study is cross-sectional, and the hemoculture results of patients treated in Nevşehir State Hospital Intensive Care Units between January 1, 2018, and December 31, 2022, are evaluated retrospectively. Ethical approval for the study was received from Nevşehir Hacı Bektaş Veli University Non-invasive Clinical Research Publication Ethics Committee (Decision number: 2023/12, Date: 19.04.2023).

The samples sent to the Microbiology Laboratory on the specified dates were incubated in the Render BC64 (Render Biotech Co., China) automatic blood culture system, and the samples with positive signals were included in the study. The results of the samples performed for identification and antimicrobial susceptibility tests using conventional methods and the Vitek2 automated system (Biomerieux Inc., USA) were investigated retrospectively.The study included one of the same isolates grown in more than one blood culture from the same patient;

Corynebacterium spp., Propionibacterium species, and *coagulase-negative Staphylococci (CoNS)* grown in a single set, thought to belong to the skin flora, were accepted as contamination.

The double-disk synergy method evaluated the presence of extended-spectrum beta-lactamase (ESBL) in gram-negative bacteria. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint tables evaluated their antibiotic susceptibility. SPSS 22 program was used to analyze the data, and categorical variables were expressed as numbers and percentages.

RESULTS

Of the 1496 blood culture samples sent to the Microbiology Laboratory from the hospital's intensive care units, 167 (11.1%) gave a positive signal. Among the samples coming from general, coronary, and cardiovascular intensive care units, the most samples came from the general intensive care unit in all years. The year with the highest number of samples was 2021 (n = 508), and the year with the fewest was 2018 (n = 114). Table 1 shows the distribution of samples by year and intensive care services.

Table 1. Samples from intensive care units will be distributed by years and services

Service	2018	2019	2020	2021	2022
General Intensive Care	95 (83.3%)	176 (89,8%)	306 (84,2%)	411 (81%)	256 (81,2%)
Coronary Intensive Care	5 (4,3%)	1 (0,5%)	23 (6,3%)	59 (11,6%)	20 (6,3%)
Cvc Intensive Care	14 (12,2%)	19 (9,7%)	34 (9,3%)	38 (7,4%)	39 (12,4%)
Total N=1496	n=114	n=196	n=363	n=508	n=315

**CVC: Cardiovascular*

Gram-negative bacteria growth was detected in 54.5% of all samples, gram-positive bacteria growth was detected in 40.7%, and yeast growth was detected in 4.8%; Among gram-negative bacteria, *Acinetobacter baumanni* with a maximum of 28% (n = 47); *Enterococcus faecalis* was isolated as gram-positive bacteria, with a maximum of 20.3% (n = 34). Figure 1 shows the numerical distribution of isolated microorganisms by year.

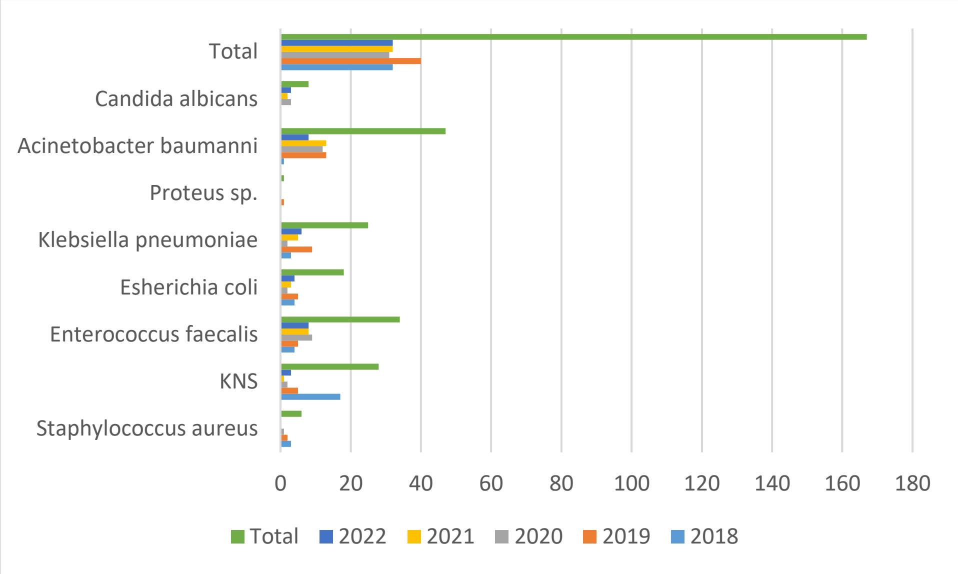

Figure 1. Microorganisms isolated by year

Extended-spectrum beta-lactamase (ESBL) positivity was detected in 72% (13/18) and 80% (20/25) of *Escherichia coli* and *Klebsiella pneumonia* isolates, respectively. Carbapenem resistance was observed in all *Acinetobacter baumanii* isolates (100%), and all isolates were sensitive to colistin. The antibiotics E. coli and K. pneumonia were most sensitive to were imipenem, meropenem (100%), and amikacin, respectively (Figure 2).

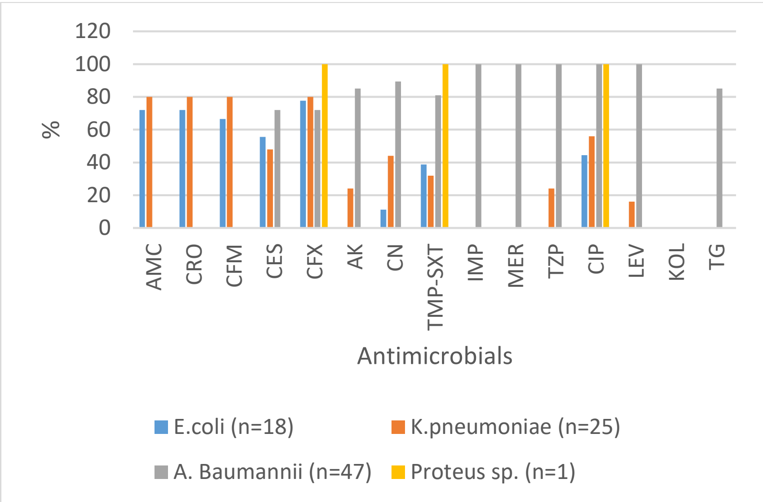

Figure 2. Antimicrobial resistance profiles in % of gram-negative bacteria

As the sensitivity of trimethoprim-sulfamethoxazole (SXT) and erythromycin in *S. aureus*, one of the gram-positive bacteria, was found to be 66%, the antibiotics to which all gram-positive isolates were most sensitive were determined to be linezolid and glycopeptide group antibiotics. While vancomycin and linezolid resistance was not observed in all Enterococ isolates, The methicillin resistance rate was found to be 92.8% (26/28) in CoNSs and 33% (2/6) in *Staphylococcus aureus* (Figure 3).

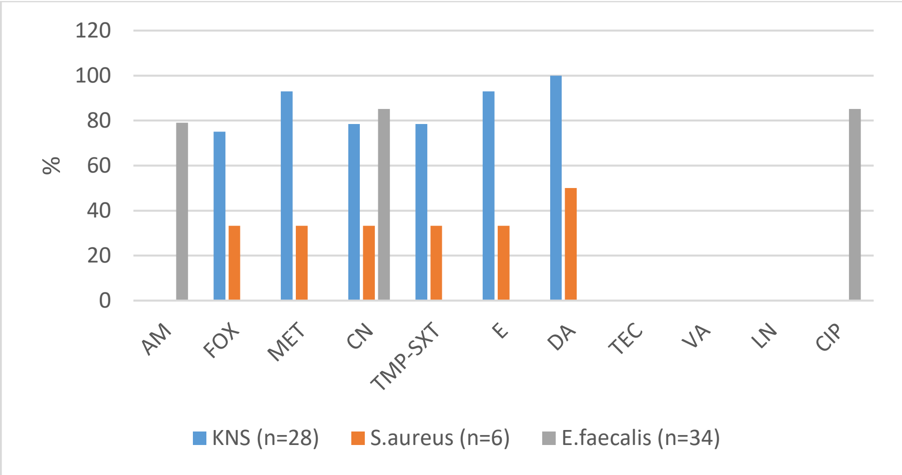

Figure 3. Antimicrobial resistance profiles in % of gram-positive bacteria

While methicillin-resistant CNS was most frequently observed in 2018 at 15% (17/114), the only year MRSA was monitored was 2018 at 1.8% (2/114). The year ESBL positivity was most frequently detected was 2019 for both *E.coli* and K. *pneumoniae*, and the rates were 2% (4/196) and 4.6% (9/196), respectively. *Carbapenem-resistant Acinetobacter baumanii* (CRAB) isolates were most frequently seen in 2019 (6.6%) and 2021 (2.5%). While the highest number of resistant isolates in all samples was from 2018, with 22% (25/114), the lowest resistance rate was detected in 2021, with 3.5% (18/508). Table 2 shows the distribution of resistant microorganisms by year.

Table 2. Percentage and frequency distributions of resistant isolates by years

Resistant Microorganisms	**2018** **n=114**	**2019** **n=196**	**2020** **n=363**	**2021** **n=508**	**2022** **n=315**
MRCoNS	17 (15%)	5 (2.5%)	2 (0.55%)	0	2 (3.19%)
MRSA	2(1,8%)	0	0	0	0
ESBL (+) E. coli	3 (2.6%)	4 (2%)	1 (0.27%)	2 (0.4%)	3 (0.95%)
ESBL (+) K. pneumoniae	2 (1.8%)	9 (4.6%)	2 (0.55%)	3 (0.6%)	4 (1.26%)
CRAB	1 (0.87%)	13 (6.6%)	12 (3.3%)	13 (2.5%)	8 (2.5%)

Total	25 (22%)	31 (15.8%)	17(4.7%)	18 (3.54%)	17 (5.3%)

Abbreviations : MRCoNS: Methisilin Resistant Coagulase Negative Staphylococcus, MRSA: Methicillin Resistant Staphylococcus aureus, ESBL: Extended Spectrum beta-lactamase, CRAB: Carbapenem-Resistant Acinetobacter baumanii

DISCUSSION

Factors such as invasive interventions applied to intensive care unit patients, broad-spectrum antibiotics, and long-term hospitalization increase the risk of developing bloodstream infections (Kern & Rieg, 2020). Bloodstream infection agents are of hospital and community origin; hospital-acquired pathogens and their mortality-related characteristics show very different epidemiology from community-acquired infections regarding species, portals of entry, antimicrobial resistance pattern, and appropriateness of empirical antimicrobial therapy.

In our study, the growth rate indicating bacteremia in hemoculture samples sent from intensive care services over five years was 11%. In a similar retrospective study by Yılmaz et al. (2013), this rate was found to be 14%, and in Taşçı et al.'s (2016) study, it was found to be 22%. The most important reason for this difference in rates can be shown as the outbreak of the COVID-19 pandemic at the time our study was conducted and the predominance of viral pneumonia and related complications in most of the patients treated in intensive care units.

Gram-negative bacteria are the leading cause of sepsis and other bloodstream infections in intensive care units, and they cause more mortality than gram-positive bacteria due to the continuous development of antimicrobial resistance mechanisms (Livermore, 2012). In this study, gram-negative bacteria showed dominant growth at a rate of 54.5%, which is consistent with the general literature.

Extended-spectrum beta-lactamase positivity (ESBL), which is commonly observed in Escherichia coli and Klebsiella pneumonia, members of the Enterobacteriaceae family, was found to be 72% and 80%, respectively, in the study. While these rates can frequently be seen in hospital-acquired infections, in the mid-2000s, they can also be seen in community-acquired infections (Doi et al., 2013). In their study investigating the antimicrobial resistance of agents in bloodstream infections, Amanati et al. found the rates of ESBL-producing E.coli and K. pneumoniae isolates to be 66.7% and 60.7%. They evaluated it as an important factor that increases mortality, especially in neutropenia groups treated in the intensive care unit (Amanati et al. , 2021).

Hospital-acquired bloodstream infections contribute significantly to mortality. For this reason, the carbapenem and glycopeptide combination, the most common empirical antibiotic regimen preferred by clinicians, cannot prevent hospital-acquired infections due to resistant bacteria and cannot meet the appropriate antimicrobial treatment criteria (Mun et al, 2022).

Our study observed carbapenem resistance in all Acinetobacter baumanii strains, commonly isolated in hospital-acquired transmission, especially in intensive care units. It has been shown in the study of Lee et al. (2022) that carbapenem-resistant A. baumanii (CRAB) bacteremias cause rapid mortality in intensive care patients, with a period as short as three to five days, and a long hospital stay, mixed bacteremia and male mortality. Gender has been stated as a risk factor.

The majority of cases with early mortality are infected with hospital-acquired strains. The fact that the CRAB rate in our study was 100% necessitates the management of rational empirical treatment options in patients with the mentioned risk factors. Colistin sensitivity was found to be 100% in the same isolates, indicating that a colistin-resistant CRAB strain has yet to be observed in the hospital flora and that retrospective analyses are a validation study in creating empirical options.

Of course, rapidly developing resistance mechanisms present increasingly difficult scenarios for intensive care units to treat multidrug-resistant Acinetobacter baumanii isolates. In an in vitro study conducted for this purpose, the in vitro synergistic and bactericidal activity of different antimicrobial combinations (with or without colistin) against CRAB strains was examined, and it was shown that they were effective on isolated strains of patients with CRAB infection whose clinical data were presented (Oliva et al, 2019). These results indicate that the combination of colistin + vancomycin or colistin + rifampin is effective against CRAB and may be a valid therapeutic option for serious infections caused by multidrug-resistant A. baumanni.

The study determined that the most dominant species in the distribution of Gram-positive bacteria growing in the positive signal-received bottles was *Enterococcus faecalis*, followed by *CoNS* and *Staphylococcus aureus*. It is known that vancomycin-resistant Enterococces and methicillin-resistant Staphylococcus are serious causes of mortality in intensive care units and carbapenem-resistant non-fermenters (Mac et al., 2019).

The earlier the sensitivity-resistance relationship of these resistant bacteria with antimicrobials, identified with rapid automated systems, is determined, the hospital stay can be reduced by starting empirical treatment, and the risk of nosocomial infection can be minimized (Forrest et al., 2008). Vancomycin and linezolid resistance was not found in the *Enterococcus faecalis* strains isolated as the causative agent in this study. In a similar study conducted in our country, antibiotic resistance was investigated in all enterococci isolated from blood cultures; Vancomycin and linezolid resistance was not observed in *E. faecalis* isolates, but vancomycin resistance was found in 24% of *E. faecium* isolates (Berktaş et al., 2013). In a nationwide surveillance study conducted by Wisplinghoff et al. (2004) in the United States, vancomycin resistance was 2% in *E. faecealis* and 60% in *E. faecium*. The fact that Enterococci have intrinsic resistance against beta-lactams, aminoglycosides, trimethoprim-sulfamethoxazole, and lincosamides has made glycopeptide group antibiotics an important option. Although the resistance rates we have obtained show that resistant strains are not currently encountered in patients with bacteremia in the intensive care unit, the rapid increase in antibiotic resistance may reverse this situation. According to limited antibiogram reports, this situation can be prevented by the rational use of antibiotics and the regulation of prescriptions.

One of the common infections in patients receiving treatment in intensive care units is catheter-related bloodstream infections. These infections constitute a serious and increasing problem among healthcare-associated infections. Chief among them is intravascular catheter (central venous catheter) infections, which cause serious mortality and morbidity that increase the duration and cost of hospitalization (Böll et al., 2021). Especially intensive care patients with underlying chronic diseases, bone marrow transplant patients, neutropenic and malnutrition patients, total parenteral fed, elderly patients, and burn patients with compromised skin integrity are in the risk group for catheter-related bloodstream infections (Kalın & Türkoğlu, 2018).

The most common factors in catheter-related bloodstream infections are coagulase-negative Staphylococcus (CoNS), Staphylococcus epidermidis, S. aureus, Enterococcus species, and Candida genus fungi (Phan et al., 2020). In our study, although the distribution of CoNSs varied by year, it was detected as 1.9% (28/1496) in all samples, and the methicillin resistance rate in these isolates was 92.8% (26/28).

Many CoNS infections are associated with foreign objects (e.g. catheters) that facilitate biofilm formation, contributing to the pathogenicity of CoNS. When investigating the disease-causing potential of *Staphyloccocus aureus* and CoNS, while countless literature can be accessed for S. aureus, the same is not true for CoNS. The reason why CoNS-related infections are often overlooked may be because they are common commensal members of the skin microbiota. The distinction between infection and contamination in CoNS is not always clear, and attempts to find one or more definitive markers have mostly been unsuccessful (Michels et al., 2021). Factor identification procedures generally applied to blood culture evaluations were also applied in this study; Bacteria of the Corynebacterium genus, which are considered members of the skin flora, and isolates grown in a single set from CoNSs (even if grown in both bottles) were not included in the study. Since the samples that were not included and considered contaminants were not stated numerically, the contaminant/agent growth rate could not be determined. For this reason, although the CoNS reproduction rate is observed to be low, it is obvious that methicillin resistance is common as a resistance profile.

The study shows that resistant bacterial agents were commonly observed to be high in the pre-pandemic period, and the number of isolated pathogenic bacteria decreased inversely proportional to the increase in the number of patients between 2020-2022. COVID-19 outbreaks negatively affect hospital infection rates and create infection clusters in hospitals, which leads to COVID-19 outbreaks. It emphasizes balancing health-related demands with routine hospital infection prevention measures (Baker et al, 2022). This explains the lack of high growth in cultures taken for possible infection prevention measures, especially in patients with viral pneumonia treated in the intensive care unit.

CONCLUSION

Empirical treatment is an inevitable method in intensive care infections. Since delayed treatments increase mortality, broad-spectrum antibiotics may be recommended in initial treatments. However, unnecessary long-term administration of broad-spectrum antibiotics should be avoided. For this reason, local microbiological data from regional retrospective studies and determining the resistance patterns of potentially causative bacteria are important in managing sepsis and bacteremia cases, especially in intensive care units, to guide empirical treatment.

Acknowledgement: We would like to thank Nevşehir Provincial Health Directorate for supporting us in providing and classifying the data.

Funding: The study is a retrospective study and no financial support was used.

Conflict of interest: The authors declare no conflict of interest.

Ethical Considerations: Ethical approval for the study was received from Nevşehir Hacı Bektaş Veli University Non-invasive Clinical Research Publication Ethics Committee (Decision number: 2023/12, Date: 19.04.2023).

Author Contributions: Conception and design: PÖ, NA; Data curation, Writing- Original draft preparation; PÖ, NA, İG, Visualization, Investigation; PÖ, NA, Writing- Reviewing, Supervision and Editing; PÖ.

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