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Evaluation of Clinical Outcomes, Pathogens, and Antibiotic Resistance Rates in Bloodstream Infections Followed in the Intensive Care Unit

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Abstract

Aim: The aim of this study was to evaluate the distribution of pathogens, antibiotic resistance rates, and factors affecting mortality in patients with healthcare-associated bloodstream infections (BSIs) followed in a tertiary intensive care unit (ICU).

Study Design: This was a retrospective cohort study. Demographic data, comorbidities, 28-day mortality, identified pathogens, and susceptibility patterns related to BSIs were retrospectively collected from patient files and hospital records.

Results: A total 221 patients diagnosed with BSI were included in the study. Of these, 62.9% were male, and the median age was 70 years (interquartile range [IQR]: 59-76). The median ICU stay was 18 days (IQR: 8-29), and the median overall hospitalization was 25 days (IQR: 14-39). Gram-negative microorganisms were identified in 132 patients (59.7%), gram-positive in 74 (33.5%), and *Candida spp.* in 15 (6.8%). Among the gram-negative pathogens, *Acinetobacter spp.* [24/25 (96%)] and *Klebsiella spp.* [42/48 (87.5%)] exhibited the highest rates of carbapenem resistance. Vancomycin resistance was detected in two (4.8%) cases of *Enterococcus spp.* All-cause 28-day mortality was observed in 54 patients (24.4%). In multivariate regression analysis, only the presence of sepsis was found to be an independent predictor of mortality (odds ratio: 5.492, 95% confidence interval: 1.836-16.424, p=0.002).

Conclusions: In this study, gram-negative pathogens were the most frequently detected organisms in patients with healthcare-associated BSIs. Carbapenem resistance rates were high among gram-negative pathogens. The presence of sepsis was identified as an independent predictor of mortality in patients diagnosed with BSI.

Keywords: Bloodstream infectious; Critical care; Drug Resistance.

Introduction

Bloodstream infections (BSIs) are a significant cause of mortality and morbidity in intensive care units (ICUs).[1] In ICUs, BSIs substantially increase both the length of hospitalization and associated healthcare costs.[2, 3] The incidence of sepsis and septic shock in ICU-acquired BSIs can reach up to 40%.[2, 3] Patients in ICUs are often exposed to multiple invasive interventions that predispose them to bloodstream

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infections, including the use of central venous catheters, extracorporeal membrane oxygenation, and continuous renal replacement therapy.[1] Additionally, the high mortality rates associated with BSIs are largely attributable to the rising incidence of antimicrobial resistance in recent years. The microbiological profile of healthcare-associated BSIs varies globally. Gram-positive pathogens predominate in certain regions, such as the United States, whereas gram-negative microorganisms are more commonly isolated in Latin America, Asia, and Europe.[1] Understanding the epidemiology of the microorganisms responsible for infections in ICUs is crucial for the timely and appropriate diagnosis, antimicrobial therapy, and implementation of infection control measures. These actions may help reduce the spread of resistant pathogens and lower mortality and morbidity in patients.[4] This study aimed to evaluate the distribution of gram-positive and gram-negative pathogens, antibiotic resistance rates, mortality rates, and factors affecting mortality in patients with healthcare-associated BSIs in a tertiary ICU.

Materials and Methods

This retrospective cohort study was conducted in a tertiary care ICU between October 2021 and November 2022. Healthcare-associated BSI was defined as the growth of pathogenic microorganisms in blood cultures obtained under sterile conditions, accompanied by at least one clinical sign of BSI (hypotension, chills, or fever) occurring 48 hours after hospital and/or ICU admission.[5] Adult patients aged ≥18 years with clinical features of infection and positive monomicrobial blood cultures obtained 48 hours after hospital admission were included in the study. Patients with polymicrobial infections or positive blood cultures contaminated with skin flora were excluded. Ethics committee approval was obtained from the Health Sciences of University İzmir Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee on 07.12.2022 (Approval Number: 2022/68-77, Date: 07.12.2022). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data Collection and Analysis

Patient data, including age, gender, comorbidities, presence of sepsis, duration of hospitalization, 28-day mortality, and susceptibility patterns of BSI-causing pathogens, were retrospectively collected from patient files and hospital records. Sepsis and septic shock were defined according to the Sepsis-3 criteria.[6]

The primary endpoint was to determine the distribution of causative pathogens and local resistance rates in patients diagnosed with BSI. Secondary endpoints included 28-day mortality rates and factors influencing mortality.

Microbiological Evaluation

Blood cultures were obtained under sterile precautions from patients suspected of having healthcare-associated BSIs. Samples were analyzed using a liquid automated blood culture system (*BacT Alert, bioMérieux, Marcy l'Etoile, France*). Gram staining and inoculation onto eosin methylene blue (EMB), chocolate, and 5% sheep blood agar were performed from bottles flagged as positive. Bacterial identification at the species level was carried out using both conventional methods and automated systems. Drug susceptibility testing was performed according to the recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Resistance to at least one antimicrobial agent in three or more antimicrobial classes was defined as multidrug-resistant (MDR). Resistance to all but one or two antimicrobial classes was defined as extensively drug-resistant (XDR), and resistance to all antimicrobial agents was defined as pan drug-resistant (PDR).[7]

Statistical Analysis

Continuous variables were presented as median and interquartile range (IQR) due to non-normal distribution. Categorical variables were presented as n (%). Patients with gram-positive and gram-negative bacteria isolated from blood cultures were compared; this analysis excluded 15 patients with *Candida albicans* and non-*albicans Candida species* isolated from their blood cultures. Additionally, factors associated with 28-day mortality were analyzed by comparing patients who survived with those who did not. The Mann-Whitney U test was used for continuous variables, and the Chi-square test was used for categorical variables. A multivariate analysis was conducted to identify independent risk factors associated with mortality. Variables included in the multivariate logistic regression model (age, gender, body mass index, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, gram-negative bacteremia, need for invasive mechanical ventilation, and sepsis) were selected based on a combination of statistical significance in the univariate analysis ($p<0.20$) and clinical relevance established in the literature and clinical practice. This approach ensured that the model accounted for both statistically associated factors and those known to be important predictors of outcomes in critically ill patients.

A p-value <0.05 was considered statistically significant. Data were analyzed using SPSS version 26.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY).

Results

Demographic and Clinical Characteristics

During the study period, a total of 261 patients were suspected of having BSI, and blood cultures were obtained. Of these, 25 patients were excluded due to the growth of polymicrobial pathogens, and 15 were excluded due to contamination with microorganisms considered part of the skin flora. The study ultimately included 221 patients diagnosed with healthcare-associated monomicrobial BSI. Of the included patients, 62.9% were male, and the median age was 70 years (IQR: 59-76). The most common comorbidities were chronic obstructive pulmonary disease (COPD, 34.4%), diabetes mellitus (DM, 24.9%), and solid tumors (21.7%). The median ICU stay was 18 days (IQR: 8-29), and the median total hospitalization was 25 days (IQR: 14-39). All-cause 28-day mortality occurred in 54 patients (24.4%). Demographic characteristics and comorbidities of patients with gram-positive and gram-negative BSIs are shown in Table 1. Alzheimer's

Table 1. Demographic and clinical characteristics of patients

	All Patients (n=221)	Gram-Negative (n=132)	Gram-Positive (n=74)	p
Age, median (IQR), years	70 (59-76)	70 (58-77)	71 (61-76)	0.573
Gender, male, n (%)	139 (62.9)	87 (65.9)	40 (54.1)	0.093
BMI, median (IQR), kg/m^2	24.5 (22.2-27.8)	24. 7 (22.5-27.7)	24.5 (22.5-29.4)	0.701
Comorbidities, n (%)				
DM	55 (24.9)	37 (28.0)	16 (21.6)	0.298
COPD	76 (34.4)	46 (34.8)	26 (35.1)	0.967
CAD	10 (4.5)	9 (6.8)	1 (1.4)	0.081
CHF	33 (14.9)	20 (15.2)	12 (16.2)	0.825
Solid tumor	48 (21.7)	29 (22.0)	14 (18.9)	0.587
Hematologic malignancy	8 (3.6)	4 (3.0)	3 (4.1)	0.448
Alzheimer's disease	9 (4.1)	2 (1.5)	7 (9.5)	**0.007**
CVD	7 (3.2)	4 (3.0)	2 (2.7)	0.899
Connective tissue diseases	5 (2.3)	3 (2.3)	1 (1.4)	0.641
APACHE II score, median (IQR)	21 (15-26)	20 (13-25)	22 (17-27.7)	0.630
Infection site, n (%)				
CLA-BSI	164 (74.2)	103 (78.0)	51 (68.9)	0.174
Pneumonia	5 (2.3)	4 (3.0)	1 (1.4)	
Unknown source	52 (23.5)	25 (18.9)	22 (29.7)	
Sepsis, n (%)	24 (10.9)	10 (7.6)	14 (18.9)	**0.015**
NIV, n (%)	10 (4.5)	5 (3.8)	4 (5.4)	0.594
IMV, n (%)	171 (77.4)	107 (81.1)	52 (70.3)	0.077
Central venous catheter, n (%)	164 (74.2)	103 (78.0)	51 (68.9)	0.367
Tracheostomy, n (%)	11 (5.0)	9 (6.8)	1 (1.4)	0.080
COVID-19, n (%)	116 (52.5)	77 (58.3)	34 (45.9)	0.087
Immunosuppressive treatment, n (%)	24 (10.9)	8 (6.1)	12 (16.2)	0.250
ICU stay before bacteremia, median (IQR), days	11 (4-20)	13 (5-22)	5 (3-16)	**0.002**
LOS in ICU, median (IQR), days	18 (8-29)	20 (10-33)	15 (8-24)	**0.014**
LOS of hospital stay, median (IQR), days	25 (14-39)	25 (14-39)	22 (13-36)	0.893
28-day mortality, n (%)	54 (24.4)	30 (22.7)	21 (28.4)	0.535

APACHE II: Acute Physiology and Chronic Health Evaluation II; BMI: Body Mass Index; CAD: Coronary Artery Disease; CHF: Congestive Heart Failure; CLA-BSI: Central Line-Associated Bloodstream Infection; COPD: Chronic Obstructive Pulmonary Disease; COVID-19: Coronavirus Disease 2019; CVD: Cerebrovascular Disease; DM: Diabetes Mellitus; ICU: Intensive Care Unit; IMV: Invasive Mechanical Ventilation; IQR: Interquartile Range; LOS: Length of Stay.

disease was more common among patients with gram-negative BSI (9.5% vs. 1.5%, p=0.007). ICU length of stay was shorter in patients with gram-positive BSI compared to those with gram-negative BSI (median 15 vs. 20 days, p=0.014).

Among the healthcare-associated BSIs, 164 (74.2%) were central catheter-related, five (2.3%) were secondary to pneumonia, and the primary source was unknown in 52 cases (23.5%). Regarding empirical treatment, the most commonly used antibiotics were carbapenems [106/221 (48.9%)], followed by cephalosporins [54/221 (24.4%)], quinolones [44/221 (19.9%)], piperacillin-tazobactam [38/221 (17.2%)], and vancomycin [13/221 (5.9%)]. Empirical antifungal treatment was administered to 6.8% of the patients.

Pathogens and Antimicrobial Susceptibility Patterns

Among the 221 patients diagnosed with healthcare-associated BSI, gram-negative microorganisms were identified in 132 (59.7%), gram-positive microorganisms in 74 (33.5%), and *Candida spp.* in 15 (6.8%) patients. The most frequently detected gram-negative pathogens were *Klebsiella pneumoniae* [48 (21.7%)], *Acinetobacter baumannii* [25 (11.3%)], and *Stenotrophomonas maltophilia* [20 (9%)]. Among gram-positive pathogens, *Enterococcus spp.* [41 (18.5%)] and coagulase-negative staphylococci (CNS) [28 (12.6%)] were most common. Fungal pathogens were isolated in 6.8% of cases, with non-*albicans Candida* species (4.1%) being more common than *Candida albicans* (2.7%).

Among gram-negative pathogens, *A. baumannii* [24/25 (96%)] and *K. pneumoniae* [42/48 (87.5%)] showed the highest rates of carbapenem resistance. These were followed by *Enterobacter spp.* (33.3%) and *Pseudomonas aeruginosa* (30%). In *K. pneumoniae*, 77% (37/48) of isolates were XDR, and 10.4% (5/48) were PDR. Among *A. baumannii* isolates, 96% (24/25) were classified as PDR. Vancomycin resistance was observed in 2 out of 41 (4.8%) *Enterococcus spp.* isolates. All *Enterococcus spp.* were susceptible to linezolid (100%). Among *S. aureus* isolates, the rate of methicillin-resistant *S. aureus* (MRSA) was 1 out of 5 (20%). All *S. aureus* isolates were susceptible to both vancomycin and linezolid (100%). Detected pathogens and their antimicrobial resistance rates are shown in Table 2.

Table 2. Isolated pathogens and antibiotic susceptibilities

	Total Patients (n=221)
Gram-Negative Bacteria, n (%)	132 (59.7)
Klebsiella pneumoniae	48 (21.7)
Carbapenem-resistant	42 (87.5)
XDR	37 (77)
PDR	5 (10.4)
Acinetobacter baumannii	25 (11.3)
Carbapenem-resistant	24 (96)
XDR	0
PDR	24 (96)
Escherichia coli	12 (5.4)
Carbapenem-resistant	0
XDR	0
PDR	0
Pseudomonas aeruginosa	10 (4.5)
Carbapenem-resistant	3 (33.3)
XDR	0
PDR	0
Other Gram-Negative Bacteria	6 (4.5)
Enterobacter spp.	3 (1.3)
Proteus spp.	2 (0.9)
Serratia spp.	1 (0.45)
Carbapenem-resistant	1 (16.6)
XDR	1 (16.6)
PDR	0
Stenotrophomonas maltophilia	20 (9.0)
Burkholderia cepacia	11 (4.97)
Gram-Positive Bacteria, n (%)	74 (33.5)
Enterococcus spp.	41 (18.5)
VRE	2 (4.8)
Staphylococcus aureus	5 (2.2)
MRSA	1 (20)
Coagulase-Negative Staphylococcus	28 (12.6)
MRCNS	10 (35)
Fungal Pathogens, n (%)	15 (6.8)
Candida spp.	6 (2.7)
Non-albicans Candida spp.	9 (4.1)

MRCNS: Methicillin-Resistant Coagulase-Negative Staphylococcus; MRSA: Methicillin-Resistant Staphylococcus aureus; XDR: Extensively Drug-Resistant; PDR: Pan Drug-Resistant; VRE: Vancomycin-Resistant Enterococcus.

Factors Associated with Mortality

Fifty-four (24.4%) of the 221 patients died within 28 days of BSI onset. Non-survivors had significantly higher APACHE II scores (median 25 vs. 20, p=0.047). The development of sepsis was significantly more common in non-survivors (29.6% vs. 4.8%, p<0.001). Central

Table 3. Factors associated with mortality

	Survivors (n=167)	Non-Survivors (n=54)	p
Age, median (IQR), years	70 (58-75)	71 (63-79)	0.851
Gender, male, n (%)	104 (62.3)	35 (64.8)	0.737
BMI, median (IQR), kg/m^2	24.5 (22.2-27.8)	24.4 (22.0-27.7)	0.876
COVID-19, n (%)	93 (55.7)	23 (42.6)	0.094
Gram-negative bacteremia, n (%)	102 (61.1)	30 (55.6)	0.367
Gram-positive bacteremia, n (%)	53 (31.7)	21 (38.9)	
Comorbidities, n (%)			
DM	43 (25.9)	12 (22.2)	0.587
COPD	61 (36.5)	15 (27.8)	0.239
CHF	24 (14.5)	9 (17.0)	0.655
ESKD	14 (8.4)	5 (9.3)	0.851
Solid tumor	32 (19.3)	16 (29.6)	0.110
Sepsis, n (%)	8 (4.8)	16 (29.6)	**<0.001**
IMV, n (%)	126 (75.4)	45 (83.3)	0.229
Central venous catheter, n (%)	130 (77.8)	34 (63.0)	**0.030**
APACHE II score, median (IQR)	20 (14-25)	25 (16-29)	**0.047**

APACHE II: Acute Physiology and Chronic Health Evaluation II; BMI: Body Mass Index; CHF: Congestive Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; COVID-19: Coronavirus Disease 2019; DM: Diabetes Mellitus; ESKD: End-Stage Kidney Disease; ICU: Intensive Care Unit; IMV: Invasive Mechanical Ventilation; IQR: Interquartile Range.

venous catheter use was less frequent in non-survivors compared to survivors (63.0% vs. 77.8%, p=0.030). Factors associated with mortality are presented in Table 3. In the multivariate logistic regression analysis, the presence of sepsis was identified as the only independent predictor of ICU mortality (odds ratio [OR]: 5.492, 95% confidence interval [CI]: 1.836-16.424, p=0.002) (Table 4).

Table 4. Multivariate logistic regression analysis for intensive care unit (ICU) mortality

	OR (95% CI)	p
Age	1.006 (0.979-1.034)	0.668
Gender (male)	0.636 (0.264-1.534)	0.314
BMI	0.974 (0.907-1.046)	0.470
Gram-negative bacteremia	0.559 (0.239-1.307)	0.180
IMV	1.253 (0.472-3.323)	0.651
Sepsis	**5.492 (1.836-16.424)**	**0.002**
APACHE II Score	1.027 (0.978-1.078)	0.282

APACHE II: Acute Physiology and Chronic Health Evaluation II; BMI: Body Mass Index; CI: Confidence Interval; IMV: Invasive Mechanical Ventilation; OR: Odds Ratio.

Discussion

In this study, we analyzed the causative microorganisms and resistance profiles of healthcare-associated BSIs in a tertiary hospital ICU. The 28-day mortality rate was 24.4%. BSIs caused by gram-negative pathogens were the most common. The most frequently detected pathogens were *K. pneumoniae*, *Enterococcus spp.*, and A. baumannii, respectively. The highest rates of carbapenem resistance among gram-negative pathogens were observed in *A. baumannii* and *K. pneumoniae*, with resistance rates of 96% and 87.5%, respectively. In the comparison between non-survivors and survivors, sepsis and higher APACHE II scores were more common in the non-survivors group. In multivariate logistic regression analysis, sepsis was identified as the only independent predictor of ICU mortality.

In our study, the most common BSIs were caused by gram-negative pathogens (59.7%). In a retrospective observational study that evaluated 150,948 ICU patients diagnosed with BSI between 2009 and 2015, the most frequently detected pathogens were *S. aureus*, *S. pneumoniae*, and *E. coli*.[8] In a prospective observational cohort study conducted in Spain between 2016 and 2017, *E. coli*, *S. au-*

reus, and *Klebsiella spp.* were the most commonly isolated pathogens.[9] Similarly, in a prospective international cohort study involving 2,600 patients diagnosed with healthcare-associated BSI between 2019 and 2021, *Klebsiella spp.*, *Enterococcus spp.*, and *S. aureus* were reported as the most frequent pathogens.[10] In light of these data, it can be concluded that while gram-positive pathogens have declined in prevalence among healthcare-associated BSI cases over the years, gram-negative pathogens have become increasingly dominant. Studies from India and other parts of Asia have also reported gram-negative organisms as the most common pathogens in BSIs.[11,12] Similar to our study, Liao et al.[12] found that *K. pneumoniae* was the most common microorganism associated with nosocomial BSIs, whereas in the study conducted by Mathur et al.,[13] *Acinetobacter spp.* was reported as the predominant microorganism in nosocomial BSIs. In a recent prospective observational study conducted in Türkiye, 67.1% of 599 isolated pathogens were gram-negative, 21.5% were gram-positive, and 11.2% were fungal.[14]

In this study, antimicrobial resistance rates were generally high, with carbapenem resistance particularly frequent among gram-negative bacteria. The increasing antimicrobial resistance in gram-negative pathogens represents a serious global public health threat.[15,16] In our cohort, carbapenem resistance was especially prevalent in *K. pneumoniae* and *A. baumannii*, with resistance rates of 87.5% and 96%, respectively. In a prospective multinational observational cohort study, carbapenem resistance rates for *A. baumannii* and *K. pneumoniae* were reported as 84.6% and 37.8%, respectively.[10]. The World Health Organization (WHO) European Antimicrobial Resistance Surveillance 2023 data reported the carbapenem resistance rate in Türkiye for 2021 as 93.3% in *Acinetobacter spp.* and 49.1% in *Klebsiella spp.*[17] In a retrospective study including 414 BSI cases, the carbapenem resistance rate in *Acinetobacter spp.*, similar to our findings, was reported as 77.8%.[18] Consistent with the literature, the gram-negative microorganism with the highest carbapenem resistance in our study was *A. baumannii*. In contrast to these findings, a retrospective cohort study involving 155 patients reported an *A. baumannii* resistance rate of 1.94%.[19] The carbapenem resistance rate for *K. pneumoniae* in the same study was 80%.[19] In our study, the MRSA rate was 20%. According to the WHO European Antimicrobial Resistance Surveillance 2023 report, the MRSA rate in Türkiye for 2021 was 30%.[17] In the study by Aslan et al.,[14] the MRSA rate was reported as 42.9%.

In our study, 74.2% of BSIs were associated with central venous catheters. Of the 164 catheter-related infections, 101 (61.5%) involved central venous catheters placed in the femoral vein, 50 (30.4%) in the subclavian vein, and 13 (7.9%) in the jugular vein. The compliance rate with hand hygiene protocols before and after catheterization was high. A survey study on the prevention and control of central line-associated BSIs, covering 201 ICUs, reported that the subclavian vein was the most frequently used site for catheterization in 65% of ICUs.[20] It was also reported that 81% and 77% of ICUs had standardized hand hygiene protocols before and after catheterization, respectively.[20] The risk of infection can be minimized through catheter bundle practices, which include selecting the jugular or subclavian vein for catheterization, applying skin antisepsis beforehand, and adhering to hand hygiene protocols.

In our study, when factors associated with 28-day mortality were analyzed, sepsis emerged as the only independent predictor of mortality. This finding is consistent with previous studies, in which the presence of sepsis and septic shock has been associated with increased mortality.[19-21] Sepsis has been reported as a predictor of mortality in patients diagnosed with BSI.[22] In a multicenter prospective observational study conducted in Türkiye, high Sequential Organ Failure Assessment (SOFA) scores in monomicrobial gram-negative BSIs were associated with increased mortality in patients with healthcare-associated BSI.[14] Similarly, in a retrospective study including 179 patients diagnosed with BSI, sepsis and septic shock at the onset of infection were identified as independent predictors of mortality, aligning with our findings.[11]

Limitations

The most significant limitation of this study is that it was conducted in a single center. Other limitations include its retrospective design, the lack of analysis of carbapenemase types in carbapenem-resistant pathogens, and the inability to assess antifungal resistance.

Conclusion

In this study, gram-negative pathogens were the most frequently detected pathogens in patients with healthcare-associated BSI. Carbapenem resistance rates were high among gram-negative isolates. The presence of sepsis was identified as an independent predictor of mortality in patients diagnosed with BSI.

Ethics Committee Approval: Ethics committee approval was obtained from Health Sciences of University İzmir Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee on 07.12.2022 (Approval Number: 2022/68-77, Date: 07.12.2022).

Informed Consent: Informed consent could not be obtained due to the retrospective nature of the study.

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