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RESEARCH ARTICLE

PREDICTORS OF MORTALITY IN GRAM-NEGATIVE BLOODSTREAM INFECTIONS

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ABSTRACT

Purpose: Bloodstream infection (BSI) is the most common healthcare-associated infection in intensive care units (ICUs) and is associated with high mortality rates. In this study, we aimed to evaluate the etiological pathogens and susceptibility distribution and factors affecting mortality in patients followed up in the ICU with the diagnosis of healthcare-associated gram-negative BSI.
Material and Methods: This study was designed as a retrospective cohort study. Patients diagnosed with healthcare-associated BSI during ICU follow-up were included in the study. Patients demographic data, source of BSI, causative microorganisms and their antimicrobial susceptibility and mortality (any cause) rates were collected retrospectively from patient files and patient information sheets. Patients were divided into survival and non- survival groups according to the prognosis and differences in clinical data between the two groups were compared.
Results: The study included 162 patients with gram-negative BSI, of whom 85 (52.5%) died during their ICU stay. The three most common pathogens detected in patients were; *Klebsiella pneumoniae* [60/162(37%)], *Acinetobacter baumannii* [32/162(19.75%)] and *Stenotrophomonas maltophilia* [25/162(15.43%)]. The highest carbapenem resistance rates belonged to *A. baumannii* and *K. pneumoniae* with 93.75% and 81.66%, respectively. Multivariate logistic regression analysis identified, patients requiring invasive mechanical ventilation (IMV) had over three times the odds of death (OR: 3.10, 95% CI: 1.23–7.80, P = 0.016). Septic shock was associated with a nearly threefold increased risk of mortality (OR: 2.78, 95% CI: 1.29–6.00, P = 0.009), and continuous renal replacement therapy also significantly increased mortality risk (OR: 2.52, 95% CI: 1.11–5.71, P = 0.026).
Conclusion: IMV, septic shock, and the need for CRRT during ICU follow-up are risk factors for mortality in gram-negative BSI patients followed in the ICU. Among the etiologic pathogens, the highest resistance rates were found in *A. baumannii* and *K. pneumoniae,* respectively.

Keywords: Bloodstream infectious, intensive care unit, mortality, risk factors

INTRODUCTION

Bloodstream infection (BSI) is the most common healthcare-associated infection in intensive care units (ICUs) and is associated with high mortality rates (1,2). BSIs due to gram-negative pathogens have been observed with increasing frequency over the years (3). The management of gram-negative BSIs presents numerous challenges. Of particular concern is the rapid emergence and spread of carbapenem resistance in isolates, as these bacteria are frequently resistant to many other classes of antibiotics (4). This results in a high rate of clinically inappropriate initial treatment and/or the use of less effective drugs. The increasing carbapenem resistance rates in gram-

negative bacteria is a serious public health problem of global concern. According to the World Health Organization (WHO) 'Antimicrobial resistance surveillance in Europe 2023' report, the carbapenem resistance rate for *Acinetobacter spp.* in Turkey was reported as 91.5% in 2017 and 93.3% in 2021; the carbapenem resistance rate for *Klebsiella spp*. was reported as 32.5% in 2017 and 49.1% in 2021 (5). Knowledge of local epidemiology is useful for determining etiological distributions of antibiotic resistance, factors associated with mortality, guiding infection control, antimicrobial stewardship policies and informing clinicians about the best treatment approach (4). In this study, we aimed to evaluate the etiological pathogens and susceptibility distribution and factors affecting mortality in patients followed up in the ICU with a diagnosis of healthcare-associated gram-negative BSI.

MATERIALS AND METHODS

Study population

This study was designed as a retrospective cohort study. Ethics committee approval was obtained from Non-Pharmaceutical Clinical Research Ethics Committee of Izmir Health Sciences University, Dr.Suat Seren Chest Diseases and Surgery Training and Research Hospital (Date: 04/12/2024, Decision No: 2024/16-10). Patients aged ≥18 years with positive blood cultures for gram-negative pathogens between January 2022 and June 2024 were included in the study. Healthcare-associated BSI was defined as a positive blood culture obtained from a peripheral vein or central catheter at least 48 hours after hospitalization. Clinical signs of bacteremia were considered as the presence of at least one of hypotension, fever or chills. Only the first episode of patients who had more than one BSI during ICU follow-up was included in the study. Patients demographic data, source of BSI, causative microorganisms and their antimicrobial susceptibility, choice of empirical antibiotic therapy, details of any surgery within the previous month, and mortality (any cause) rates were collected retrospectively from patient files and patient information sheets. Patients were divided into survival and non- survival groups according to the prognosis and differences in clinical data between the two groups were compared.

Microbiological data-Blood Culture

The blood culture bottle, which was appropriately taken and delivered to the laboratory, was loaded into the liquid automated blood culture (*BacT Alert, bioMérieux, Marcy l'Etoile, France*) device. When a positive growth signal was obtained, the blood culture bottle was removed from the device and gram staining was performed for microscopic examination, and at the same time, each bottle was passaged into 5% sheep blood, chocolate, and eosin methylene blue (EMB) agar and incubated at 37°C for 18-24 hours. Pure colonies were selected from the growth detected plates and bacterial identification at species level was performed using both classical traditional methods and automated systems (*Phoenix, Becton Dickinson Instrument Systems, Sparks, MD, USA*), and drug susceptibility tests were performed according to the recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Statistical Analysis

The normality of the data was assessed using the Kolmogrov-Smirnov test. Continuous variables were presented as medians and interquartile ranges (IQR) and compared between survivors and non-survivors using the Mann-Whitney U test due to non-normal distributions. Categorical variables were presented as frequencies and percentages, and group comparisons were performed using the chi-square test or Fisher's exact test as appropriate.

Multivariate logistic regression analysis was conducted to identify independent factors associated with mortality. Variables with a *P* value of less than 0.2 in univariate analyses were included in the multivariate model, along with clinically significant variables regardless of their univariate significance. Results were reported as odds ratios (OR) with 95% confidence intervals (CI).

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL, USA), version 26. A P value of <0.05 was considered statistically significant.

RESULTS

The study included 162 patients with BSI, of whom 85 (52.5%) died during their ICU stay. The median age of all patients was 68 years (IQR: 56–75), with non-survivors being significantly older than survivors (71 vs. 64 years, $P = 0.028$). The majority of patients were male (63.6%), though gender distribution was not statistically different between groups ($P = 0.051$). Body mass index was comparable between groups (median: 24.5 kg/m², $P = 0.948$). Common

Table 1. Demographic and clinical characteristics of patients

	All Patients (n=162)	Survivors (n=77)	Non-survivors (n=85)	P value
Age, median (IQR), years	68.0 (56.0 – 75.0)	64 (53 – 71)	71 (58 – 79)	**0.028**
Gender, male, n (%)	103 (63.6)	43 (55.8)	60 (70.6)	0.051
Body mass index, median (IQR), kg/m^2	24.5 (22.2 – 27.7)	24.2 (22.2 – 27.8)	24.5 (22.3 – 27.7)	0.948
Comorbidities, n (%)				
Diabetes mellitus	44 (27.3)	25 (32.5)	19 (22.4)	0.148
COPD	56 (34.6)	31 (40.3)	25 (29.4)	0.147
Congestive heart failure	22 (13.6)	9 (11.7)	13 (15.3)	0.503
Coronary artery disease	9 (5.6)	3 (3.9)	6 (7.1)	0.380
End-stage kidney disease	11 (6.8)	4 (5.2)	7 (8.2)	0.442
Solid organ tumors	35 (21.6)	14 (18.2)	21 (24.7)	0.314
Hematologic malignancies	4 (2.5)	1 (1.3)	3 (3.5)	0.265
Cerebrovascular diseases	6 (3.7)	2 (2.6)	4 (4.7)	0.478
Respiratory support, n (%)				
NIMV	7 (4.3)	1 (1.3)	6 (7.1)	0.072
IMV	124 (76.5)	49 (63.6)	75 (88.2)	**<0.001**
Source of bacteremia, n (%)				
CLA-BSI	121 (74.4)	61 (79.2)	60 (70.6)	N/A
Pneumonia	5 (2.1)	1 (1.3)	4 (4.7)	
Unknown	36 (22.2)	16 (20.8)	20 (23.5)	
Antimicrobial treatment, n (%)				
Carbapenems	79 (48.8)	34 (44.2)	45 (52.9)	N/A
Cephalosporins	35 (21.6)	20 (26.0)	15 (17.6)	
Quinolones	34 (21.0)	15 (19.5)	19 (22.4)	
Piperacillin+Tazobactam	30 (18.5)	14 (18.2)	16 (18.8)	
Vancomycin	11 (6.8)	3 (3.9)	8 (9.4)	
Antifungals	11 (6.8)	8 (10.4)	3 (3.5)	
Sepsis and Septic Shock, n (%)	58 (35.8)	19 (24.7)	39 (45.9)	**0.005**
Continue renal replacement therapy, n (%)	50 (30.9)	16 (20.8)	34 (40.0)	**0.008**
ECMO, n (%)	8 (4.9)	4 (5.2)	4 (4.7)	0.886

APACHE, Acute Physiology and Chronic Health Evaluation; CLA-BSI, Central Line Associated Bloodstream Infection; COPD, Chronic Obstructive Pulmonary Disease; COVID-19, Coronavirus Disease-19; ECMO, Extracorporeal Membrane Oxygenation; IMV, Invasive Mechanical Ventilation; IQR, Interquartile Range; NIMV, Non-Invasive Mechanical Ventilation

comorbidities included chronic obstructive pulmonary disease (34.6%), diabetes mellitus (27.3%), and solid organ tumors (21.6%), with no significant differences between survivors and non-survivors. Key demographic and clinical characteristics of patients were summarized in Table 1.

The three most common pathogens detected in patients followed up with a diagnosis of gram-negative BSI in the ICU were; *Klebsiella pneumoniae* [60/162(37%)], *Acinetobacter baumannii* [32/162(19.75%)] and *Stenotrophomonas maltophilia* [25/162(15.43%)], respectively. The highest resistance rate was detected in *A. baumannii*. Carbapenem, fluoroquinolone, and third-generation cephalosporin resistance was 93.75% in *A. baumannii*. The second highest carbapenem resistance was detected in *K. pneumoniae* with a rate of 81.66%. In *K. Pneumoniae*, quinolone and third-generation cephalosporin resistance (91.66%) and gentamicin resistance (53.33%) were detected. Resistance rates were lower in *Escherichia coli* and *Pseudomonas aeruginosa*. All detected pathogens and resistance rates are shown in Table 2.

The primary source of bacteremia was central line-associated bloodstream infections (74.4%), followed by pneumonia (2.1%). In 22.2% of cases, the source was unidentified. The most frequently used empirical antimicrobials were carbapenems (48.8%), cephalosporins (21.6%), and quinolones (21.0%). Other empirical treatments initiated for the patients are shown in Table 1. Invasive mechanical ventilation (IMV) was more prevalent among non-survivors (88.2% vs. 63.6%, $P < 0.001$). Septic shock occurred in 35.8% of patients and was significantly more common in non-survivors (45.9% vs. 24.7%, $P = 0.005$). Non-survivors were also more likely to require

Table 2. Pathogens and resistance rates

Pathogens	AMP resistance n (%)	GN resistance n (%)	MEM resistance n (%)	CIP resistance n (%)	TZP resistance n (%)	CRO resistance n (%)	CAZ resistance n (%)
Klebsiella spp. (n=60)	35 (58,33)	32 (53,33)	49 (81,66)	55 (91,66)	55 (91,66)	55 (91,66)	53 (88,33)
Escherichia coli (n=14)	0	3 (21,42)	0	10 (71,4)	7 (50)	9 (64,28)	9 (64,28)
Proteus Mirabilis (n=2)	0	1 (50)	0	1 (50)	0	1 (50)	0
Serratia (n=1)	0	0	0	0	0	0	0
Acinetobacter baumannii (n=32)	30 (93,75)	-	30 (93,75)	30 (93,75)	30 (93,75)	-	30 (93,75)
Pseudomonas aeruginosa (n=15)	1 (6,6)	1 (6,6)	4 (26,66)	4 (26,66)	5 (30)	5 (30)	5 (30)
Enterobacter cloacae (n=3)	1 (33,33)	1 (33,33)	1 (33,33)	1 (33,33)	1 (33,33)	1 (33,33)	1 (33,33)
Stenotrophomonas maltophilia (n=25)*	-	-	-	-	-	-	-
Burkholderia Cepacia (n=10)	0	0	0	0	0	0	0

*AMP: Ampicillin, GN: Gentamicin, MEM: Meropenem, CIP: Ciprofloxacin, TZP: Piperacillin tazobactam, CRO: ceftriaxone, CAZ: Ceftazidime. *All agents of Stenotrophomonas maltophilia were sensitive to trimethoprim and sulfamethoxazole.*

continuous renal replacement therapy (CRRT) (40.0% vs. 20.8%, *P* = 0.008). Multivariate logistic regression identified several factors independently associated with mortality. Patients requiring IMV had over three times the odds of death (OR: 3.10, 95% CI: 1.23–7.80, *P* = 0.016). Septic shock was associated with a nearly threefold increased risk of mortality (OR: 2.78, 95% CI: 1.29–6.00, *P* = 0.009), and CRRT also significantly increased mortality risk (OR: 2.52, 95% CI: 1.11–5.71, *P* = 0.026) (Table-3).

DISCUSSION

Evaluation of in-hospital mortality risk factors in gram-negative BSIs, which carry a high risk of morbidity and mortality due to increasing resistance rates, is important to improve outcomes of BSIs. The most important finding in this study was that IMV, presence of septic shock, and the need for CRRT during ICU follow-up increased mortality in gram-negative BSIs. In addition, when the distribution of pathogens was analyzed, the most common pathogens following *K. pneumonia*, *A. baumannii* and *S. maltophilia.*

Table 3. Multivariate logistic regression analysis for mortality in patients with bacteremia

	OR	95%, CI	P Value
Age	1.02	0.99 – 1.05	0.125
Gender, male	1.30	0.61 – 2.79	0.501
Invasive mechanical ventilation	3.10	1.23 – 7.80	0.016
Sepsis and Septic Shock	2.78	1.29 – 6.00	0.009
Continue renal replacement therapy	2.52	1.11 – 5.71	0.026

CI, Confidence Interval; OR, Odd Ratio

In our study, the fatality rate of gram-negative BSI was reported as 52.5%. In the study conducted by Ergönül et al., the fatality rate in healthcare-associated BSIs was reported as 44%, and in the study conducted by Kaye et al., it was reported as 49% (6,7). In our study, the number of patients over 65 years of age was statistically significantly higher in the non-survival group than in the survival group (*P* = 0.028). In many studies, mortality in BSIs has been found to be significantly higher in patients over 65 years of age compared to the younger population (6,8). In one study, it was suggested that septic shock, respiratory failure, and multiorgan failure were more common in the elderly population and therefore mortality was higher (8). In our study, although the frequency of advanced age was higher in the mortality group, consistent with the literature, it was found that it did not predict mortality in the multivariate regression analysis. It was thought that this situation may be due to the limited number of patients included in the study.

In our study, similar to the literature, no difference was found in mortality rates in gram-negative BSIs according to gender (9).

In this study, the three most common pathogens were *K. pneumoniae, A. baumannii,* and *S. Maltophilia*, respectively. It was especially striking that *S. Maltophilia* was one of the three most common pathogens. The highest carbapenem resistance rates belonged to *A. baumannii* and *K. pneumoniae* with 93.75% and 81.66%, respectively. In a prospective observational multicontinental cohort study, carbapenem resistance was reported as 90.4% in *Acinetobacter spp*., 53.1% in *Klebsiella spp.* and 48.8% in *Pseudomonas spp.* (10).

In this study, IMV was significantly more frequent in the non-surviving patient group and increased the risk of death threefold. In a retrospective cohort study, similar to our study, mechanical ventilation was significantly associated with death and poor outcome in patients with gram negative BSI (11). Another retrospective cohort study reported that mortality in BSIs was associated with age (P = .034), ICU hospitalization (P = .04), and invasive procedures (P < .001) (12). In a retrospective cohort study including 433 patients, mechanical ventilation was similarly reported as a risk factor for mortality in BSI patients (13).

Sepsis and septic shock are independent risk factors for mortality in the ICU (14). Although the incidence of gram-positive bacteria in the etiology of sepsis has shown an increasing trend over the last decade, gram-negative bacteria remain the predominant pathogen and have a higher ICU mortality rate in sepsis patients compared to gram-positive bacterial infection (15,16). In a retrospective cross-sectional analysis, a significantly higher SOFA score was reported in patients with gram-negative BSI in the mortality patient group than in the survival group (p<0.0001) (17). In a meta-analysis, septic shock, need for mechanical ventilation, indwelling central venous catheter, neutropenia, concomitant hematological malignancies, chronic kidney disease, inappropriate antimicrobial therapy, and previous antibiotic use were reported as risk factors for mortality (18).

CONCLUSION

IMV, septic shock, and the need for CRRT during ICU follow-up are risk factors for mortality in gram-negative BSI patients followed in the ICU. Among the etiologic pathogens, the highest resistance rates were found in *A. baumannii* and *K. pneumoniae,* respectively.

Limitations

The most important limitation of the study is the relatively small number of patients participating in the study and the fact that it was conducted in a single center. Other limitations were the retrospective design of the study and the fact that carbapenemase genes could not be analyzed for carbapenem-resistant strains.

Author contribution: Study design: TTK Data collection:TTK. Data analysis: SY Study supervision: SY Manuscript writing: TTK, SY Critical revisions for important intellectual content: TTK, SY.
Conflict of interests: The authors declare no competing interests.
Ethical approval: Ethics committee approval was obtained from Non-Pharmaceutical Clinical Research Ethics Committee of Izmir Health Sciences University, Dr.Suat Seren Chest Diseases and Surgery Training and Research Hospital (Date: 04/12/2024, Decision No: 2024/16-10).
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