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Exploring the impact of comorbidities and drug resistance on mortality in ICU-acquired bloodstream infections

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Abstract

Hospital-acquired bloodstream infections (BSIs) seriously challenge critically ill patients. These infections in the ICU lead to significant morbidity, mortality, increased costs, and prolonged hospital stays. Therefore, the present study investigated this condition's prevalence and risk factors. This cross-sectional study was conducted on patients with neurological and nephrological issues admitted to general ICUs and trauma patients in two large hospitals in southeastern Iran. Bacteremia prevalence and mortality effects in ICU patients were analyzed from March 2020 to September 2022 during the COVID period. The results identified 127 patients with positive blood cultures, including 59 from the general ICU and 68 from the trauma ICU, yielding prevalences of 3.02% and 1.93%, respectively. The most common comorbidities included drug addiction (36.2%), chronic hypertension (35.4%), and type 2 diabetes (25.2%). *Klebsiella pneumoniae* was the most frequently isolated organism, followed by *Staphylococcus epidermidis, Staphylococcus aureus*, and *Acinetobacter*. The mortality rate was 93.2% in the general ICU and 60.3% in the trauma ICU. Risk factors associated with mortality included diabetes, hypertension, renal failure, drug addiction, a history of surgery in the last 30 days, ineffective experimental antibiotic treatment, and the administration of vasopressors. The prevalence of multiple drug resistance (MDR) was 33%, while Vancomycin-Resistant *Enterococcus* (VRE) was found in 9.4% of cases. These findings suggest that identifying and controlling risk factors associated with bacteremia in ICU patients is essential for reducing mortality.

Keywords Bacteremia, ICU-acquired bloodstream infection, Multiple drug resistance, Mortality

Introduction

Bacteremia, or ICU-acquired bloodstream infection (ICU-BSI), is a condition where bacteria invade the bloodstream following a bacterial infection (Culshaw et al. 2014). This infection can be classified as primary, originating in the blood, or secondary, spreading from another site such as the respiratory, digestive, or urinary tracts (Culshaw et al. 2014).

Despite advancements in antimicrobial drugs and medical science, the prevalence of resistant bacteria, particularly multi-drug-resistant Gram-negative bacteria, has increased among ICU patients (Vallés et al., 2008; Zilberberg and Shorr 2013). This trend makes bacteremia one of the leading causes of death and disability in affected patients (Bearman and Wenzel 2005).

Studies indicate that the incidence density of BSIs in ICUs has been reported to vary from 4.2 to 6.0 per 1,000 patient days (Erdem et al. 2009). It can be classified as a healthcare-associated BSI (HA-BSI) when the patient is

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admitted to the ICU or as an ICU-acquired BSI (which occurs 25–75% of the time). High-severity index risk factors for acquired infection include immunosuppression, liver disease, surgery, invasive devices, and catheters. Choosing the appropriate antibiotic treatment depends on various factors, including the suspected infection location, antibiotic resistance, multidrug-resistant (MDR) endemic pathogens, and the patient's history of antibiotic use (Timsit et al. 2020). Mortality rates for bacteremia range from 14% in community-acquired infections to up to 30% in cases with severe concomitant disease (Bartoletti et al. 2014; Islas-Muñoz et al. 2018). MDR bacteremia is associated with prolonged hospital stays, increased costs, and poor outcomes (Santoro et al. 2020), with mortality rates reaching 40–60% in cases of septic shock and multiple organ failure (Bassetti et al. 2016).

Identifying risk factors for bacteremia is crucial for prevention and effective treatment. Factors such as length of ICU stay, need for mechanical ventilation, suppressed immune system, Apache score, liver dysfunction, invasive procedures, and acquired injury play a significant role. Preventing sepsis is a priority of the World Health Organization, emphasizing the importance of understanding these risk factors and clinical symptoms (Prowle et al. 2011).

The epidemiology and causes of bacteremia have changed in recent years due to various factors. Identifying the risk factors for bacteremia is crucial for prevention and effective treatment. This study investigated bacteremia's prevalence, risk factors, severity, and mortality in ICU patients. The findings would enhance our understanding of the epidemiology and susceptibility of common strains of this disease.

Materials and methods

This cross-sectional study was conducted at two large hospitals in Kerman province, southeast Iran, from 2020 March 21 to 2021 September 21, over 18 months. The Research Ethics Committee of Kerman University of Medical Sciences approved the protocol for this study with ID: IR.KMU.AH.REC.1401.280. One ICU admitted patients with neurological and nephrology problems, while the other ICU admitted trauma patients.

First, ICU patients eligible for positive blood culture tests were identified by electronic search in the microbiology laboratories of the two hospitals. Then, the patients were selected and examined according to the inclusion and exclusion criteria.

Inclusion criteria

The study included patients admitted to the ICU who had at least one positive blood culture test (regardless of the type of causative organism) 48 h after admission and exhibited symptoms of infection.

Exclusion criteria

Patients under 18 and those with positive blood culture results were excluded before ICU admission. If patients were admitted to the ICU multiple times during the study, they were re-enrolled only if there was a more than four-week interval. However, if the patient's blood cultures were positive again during the ICU stay, they would not be re-entered into the study.

Data collection

After identifying and selecting the patients, their demographic and clinical data were extracted from the patient files and recorded in prepared forms, ensuring full compliance with the principles of medical ethics. The data collected included age, gender, underlying diseases, history of abdominal or chest surgery in the last 30 days, use of antibiotics in the last 30 days, source of infection, organism causing the infection, length of ICU stay before positive blood culture, use of central venous catheter before positive blood culture, dialysis, use of artificial respiration devices before positive blood culture, use of complete intravenous nutrition, use of steroids before positive blood culture, antibiotics used to treat the infection, type of microbial Gram, antibiotic resistance pattern, experimental antibiotic treatment, and patient mortality.

Data analysis

The collected data were analyzed using SPSS-16 software. Descriptive statistics, including frequency, percentage, and mean ± standard deviation (SD), were used to summarize the data. The chi-square test was used to the relationship between mortality and MDR with qualitative variables. Additionally, logistic regression analysis was conducted to examine the effect of risk factors on resistant infections. A significance level of less than 0.05 was considered statistically significant.

Results

A total of 4,146 patients were admitted to the ICUs of the two hospitals, with 635 in the general ICU (neurology and nephrology) and 3,511 in the trauma ICU. Of these, 137 had positive blood cultures. However, 2 patients were excluded from the study due to a lack of clinical symptoms and a possible infection, while 8 patients were excluded due to the unavailability of their medical data, leading to a final sample of 127 patients (59 in the general ICU and 68 in the trauma ICU).

Among the 127 patients, 61.4% were male and 38.6% were females. The mean age of the patients was 57 ± 20 years (range 18–94 years), with the general ICU patients averaging 62.47 years and trauma ICU patients averaging 51.54 years. The average length of stay was 35.90 ± 32.16 days in the general ICU and 34.53 ± 40.50 days in the

trauma ICU. The most common comorbidities were drug addiction (36.2%), chronic hypertension (35.4%), and type 2 diabetes (25.2%). Most patients (20.5%) underwent neurosurgery and 15.7% underwent organ surgery.

In this study, the prevalence of bacteremia was 3.02%. Additionally, 59 patients with a prevalence of 9.29% were admitted to the general ICU, while 68 patients with a prevalence of 1.93% were admitted to the trauma ICU. The most common causes of bloodstream infections in these patients were *Klebsiella pneumoniae* (30.7%), *Staphylococcus epidermidis* (19.7%), *Staphylococcus aureus* (14.2%), and *Acinetobacter* (13.4%).

The antibiotics most commonly used to treat the patients' bloodstream infections were vancomycin (59.8%), meropenem (53.5%), levofloxacin (22.8%), and imipenem (16.5%). The most significant risk factors for bacteremia included a history of antibiotic use, mechanical ventilation (68.5%), and central venous access (64.4%).

The primary sources of bloodstream infections were central venous catheters (39.4%) and lower airways (14.2%), with 24.4% of cases having unknown sources of infection.

Comparison of mortality and MDR in terms of sex and clinical data of patients

The mortality rate was significantly higher in the patients with diabetes mellitus ($P=0.001$), chronic hypertension ($P=0.031$), renal failure ($P=0.006$), drug addiction ($P=0.025$) and taking vasopressors ($P=0.001$), and history of surgery ($P=0.009$) compared to the patients who did not have these diseases. Furthermore, the mortality rate was higher in patients who received ineffective experimental treatment than in those who did not receive it ($P=0.001$). However, the patients who had organ surgery had a lower mortality rate ($P=0.004$; Table 1).

The percentage of MDR pathogens in patients who did not have ineffective experimental treatment was significantly higher than the patients who had ineffective experimental treatment ($P=0.001$), but there was no statistically significant relationship between the percentage of drug resistance and other clinical characteristics of patients (Table 1).

The frequency of outcomes in the patients

An analysis of the frequency of outcomes revealed that 33% (42 cases) of the patients had resistant Gram-negative bacteremia, while 9% had resistant Gram-positive bacteremia. The total mortality rate was 76%. Additionally, the mortality rates in the general ICU and trauma ICU were 93% and 60%, respectively. Re-infections occurred in 9 cases, accounting for 7% (Fig. 1).

The relationship of age and length of stay with mortality and MDR

The data showed a statistically significant relationship between age and death, with the mortality rate being higher in older patients ($P<0.001$). However, there was no significant association between the length of ICU ($P=0.101$) and hospital stay with death ($P=0.094$). MDR had no significant relationship with age ($P=0.938$) and the length of stay in ICU ($P=0.485$) and hospital ($P=0.615$; Table 2).

Comparison of the frequency of infection sources in terms of mortality and MDR

There was no statistically significant relationship between the frequency of infection sources and MDR ($P=0.239$). Only one patient had CSF (0.8%) and Permicat infections (0.8%). However, there was a statistically significant relationship between the frequency of infection sources and mortality ($P=0.042$). All patients with Shaldon (100.0%), CSF (100.0%), and urine infections (100.0%) died (Fig. 2).

The risk factors associated with Gram-positive resistant bloodstream infection

The analysis of patients with Gram-positive infections showed a significant association between the resistance of Gram-positive bacterial infections and a history of receiving antibiotics ($P=0.014$), as well as the presence of a central venous catheter for more than 48 h ($P=0.049$; Table 3).

The relationship between the recurrence or re-infection with the risk factors

An analysis of the relationship between recurrence or re-infection and risk factors showed a significant association with renal failure ($P=0.018$), a history of receiving antibiotics ($P=0.009$), and a history of ICU stay for more than 72 h ($P<0.0001$; Table 4).

Discussion

The present study examined 127 patients admitted to the ICUs of two hospitals with at least one positive blood culture test. The key findings included:

1. *Risk Factors and Mortality*: The risk factors, including diabetes, hypertension, renal failure, drug addiction, a history of surgery in the last 30 days, ineffective experimental antibiotic treatment, and receiving vasopressors, had a statistically significant relationship with patient mortality.
2. *Mortality Rates*: The mortality rate in the general ICU was 93.2% with a prevalence of 9.29%, while the mortality rate in the trauma ICU was 60.3% with a prevalence of 1.93%. The prevalence of MDR was 33%, and VRE was 9%.

Table 1 Comparison of mortality and MDR in terms of sex and clinical data of patients

Variable	Categories	Frequency (%)	MDR (%)	*P*-value	Mortality (%)	*P*-value
Gender	Male	78 (61.4)	43.6	0.758	78.2	0.758
	Female	49 (38.6)	40.8		71.4	
Comorbidities	Type 2 diabetes					
	Yes	32 (25.2)	46.9	0.564	96.9	0.001
	No	95 (74.8)	41.1		68.4	
	Chronic hypertension					
	Yes	45 (35.4)	40.0	0.67	86.7	0.031
	No	82 (64.6)	43.9		69.5	
	Renal failure					
	Yes	26 (20.5)	38.5	0.639	96.2	0.006
	No	101 (79.5)	43.6		70.3	
	Heart disease					
	Yes	27 (21.3)	44.4	0.82	88.9	0.07
	No	100 (78.7)	42.0		72.0	
	Chronic lung disease					
	Yes	15 (11.8)	46.7	0.729	93.3	0.088
	No	112 (88.2)	42.0		73.2	
	Drug addiction					
	Yes	46 (36.2)	52.2	0.097	87.0	0.025
	No	81 (63.8)	37.0		69.1	
History of surgery	History of surgery					
	Yes	67 (52.8)	50.0	0.593	40.6	0.009
	No	69 (47.2)	50.0		59.4	
	Abdominal surgery					
	Yes	17 (13.4)	52.9	0.35	70.6	0.606
	No	110 (86.6)	40.9		76.4	
	Chest surgery					
	Yes	7 (5.5)	42.9	0.985	100.0	0.122
	No	120 (94.5)	42.5		74.2	
	Organ surgery					
	Yes	20 (15.7)	40.0	0.804	50.0	0.004
	No	107 (84.3)	43.0		80.4	
	Neurosurgery					
	Yes	26 (20.5)	46.2	0.674	61.5	0.061
	No	101 (79.5)	41.6		79.2	
Drug therapy	History of taking antibiotics					
	Yes	115 (90.6)	42.6	0.950	76.5	0.449
	No	12 (9.4)	41.7		66.7	
	History of taking corticosteroids					
	Yes	65 (51.2)	35.4	0.096	81.5	0.110
	No	62 (48.8)	50.0		69.4	

Table 1 (continued)

Variable	Categories	Frequency (%)	MDR (%)	*P*-value	Mortality (%)	*P*-value
Risk factors in ICU	Mechanical ventilation					
	Yes	87 (68.5)	46.0	0.245	72.4	0.219
	No	40 (31.5)	35.0		82.5	
	Receiving a vasopressor					
	Yes	52 (40.9)	46.2	0.49	94.2	0.001
	No	75 (59.1)	40.0		62.7	
	CV line					
	Yes	84 (64.6)	46.3	0.240	70.7	0.085
	No	45 (35.4)	35.6		84.4	
	Shaldon					
	Yes	29 (22.8)	41.4	0.888	82.8	0.306
	No	98 (77.2)	42.9		73.5	
	Permicat					
	Yes	1 (0.8)	0.0	0.388	100.0	0.568
	No	126 (99.2)	42.9		75.4	
	TPN					
	Yes	12 (9.4)	50.0	0.582	66.7	0.449
	No	115 (90.6)	41.7		76.5	
	Ineffective experimental treatment					
	Yes	81 (63.8)	32.1	0.001	61.7	0.001
	No	40 (31.5)	62.5		100.0	

3. *Correlation with Antibiotic Resistance*: An analysis of the risk factors showed a significant relationship between ineffective experimental antibiotic treatment and multi-drug antibiotic resistance. Furthermore, an analysis of patients with Gram-positive infections revealed a significant relationship between resistance to Gram-positive bacterial infections (VRE) and a history of receiving antibiotics, as well as the presence of a central venous catheter for more than 48 h.
4. *Infection Relapse and Risk Factors*: The data on the relationship between the rate of infection relapse or re-infection and the risk factors revealed a significant association with renal failure, a history of receiving antibiotics, and a hospital stay of more than 72 h.

Bloodstream infection (BSI) is a common clinical scenario in the ICU. In cases of septic shock, immunodeficiency, and treatment delays, even with the control of the source of infection and appropriate antibiotic treatment, outcomes may be unfavorable (Bassetti et al. 2016).

The higher mortality rate in the general ICU may be attributed to the greater mean age of patients compared to those in the trauma ICU, as well as a higher rate of comorbidities. Furthermore, 52% of the patients in this study had septic shock. The authors reviewed infection control methods, experimental antibiotic prescriptions, and hospital infection control protocols. Prowle et al. suggested that BSI causes a threefold increase in the risk of death among ICU patients and is associated with a mortality rate of 40–60% (Prowle et al. 2011). The prevalence of MDR was 33%, and VRE was 9.4% among the patients in the present study.

Patolia et al. (2018) examined 177 patients with bacteremia due to Gram-negative infections and reported that 26% of these cases were resistant Gram-negative bacteremia, with a 34% mortality rate (Patolia et al. 2018). Blot et al. (2002) studied 328 patients admitted to ICUs over nine years and reported that 36% of the patients were infected with multidrug-resistant bacteria, resulting in a mortality rate of 45% (Blot et al. 2002). Gudiol et al. (2013) examined 372 patients and reported that 13.7% of Gram-negative organisms were responsible for infections in multidrug-resistant neutropenic patients, with a mortality rate of 41%, compared to a 21% mortality rate caused by non-resistant bacteria (Gudiol et al. 2013).

This study used cross-sectional data from inpatients in two hospitals (general ICU and trauma ICU) with at least one positive blood culture test, regardless of the deterioration of the patient's condition. The high mortality rate observed in patients in this study, compared to the rates reported in other studies, may be attributed to numerous existing risk factors and resistant bacteria that potentially did not receive suitable antibiotics. It was impossible to check the minimum inhibitory concentration level of antibiotics in the centers and monitor their levels carefully. Conversely, a limitation of this study was our inability to document the severity of the disease, such as the Apache score and the Sofa score, which may have influenced the final analysis since a high Apache score

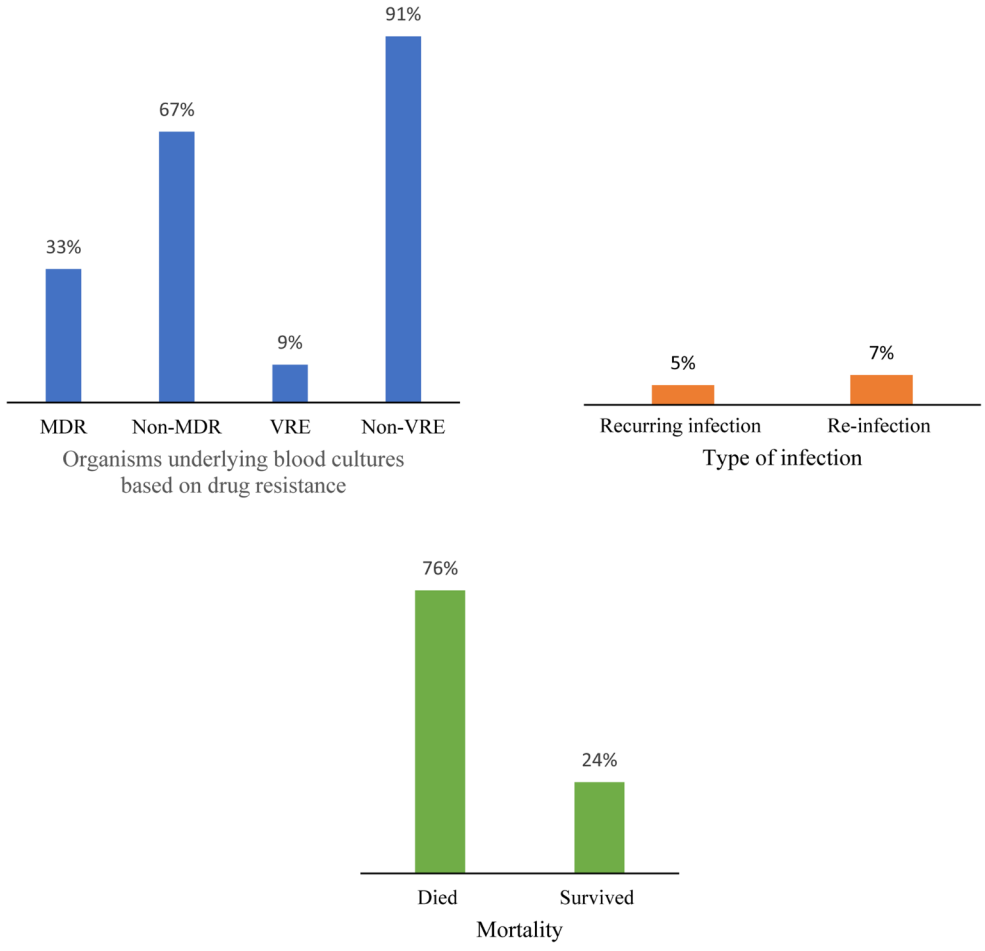


Fig. 1 The percentage of outcomes in the patients

Table 2 The relationship of age and length of stay with mortality and MDR

Variable	Outcome	Morality				MDR			
		N	Mean	Std. deviation	*P*-value	N	Mean	Std. deviation	*P*-value
Length of stay at the hospital	No	31	47.65	40.672	0.094	73	35.33	33.595	0.615
	Yes	96	32.10	28.116		54	36.67	30.427	
Length of stay in ICU	No	31	44.45	41.817	0.101	73	35.10	46.427	0.485
	Yes	96	31.32	39.759		54	33.76	31.149	
Age	No	31	42.97	20.752	0.001	73	57.22	20.502	0.938
	Yes	96	61.81	17.890		54	57.20	20.085	

upon ICU admission, independent of other factors, elevates the mortality risk. On the other hand, the mortality rate of trauma patients was lower than in general (93 versus 60%), primarily due to the younger average age of this group, which often correlates with better health and resilience. In the secondary study, the reason for the higher mortality rate of 90% in general ICU was inadequate nursing care in terms of infection control principles, lack of daily visits by an infectious disease specialist, and the absence of an ICU specialist, which was raised and is under revision and revision.

In the present study, the risk factors related to mortality included diabetes, hypertension, renal failure, drug addiction, a history of surgery in the last 30 days, ineffective experimental antibiotic treatment, and the administration of vasopressors. In a study by Ballouz, the risk factors associated with mortality identified through multivariate analysis were high corticosteroid doses and septic shock. The results indicated that prolonged ICU stays, along with increased antibiotic and corticosteroid use, affect the mortality of patients with bacteremia (Gudiol et al. 2013; Ballouz et al. 2017).

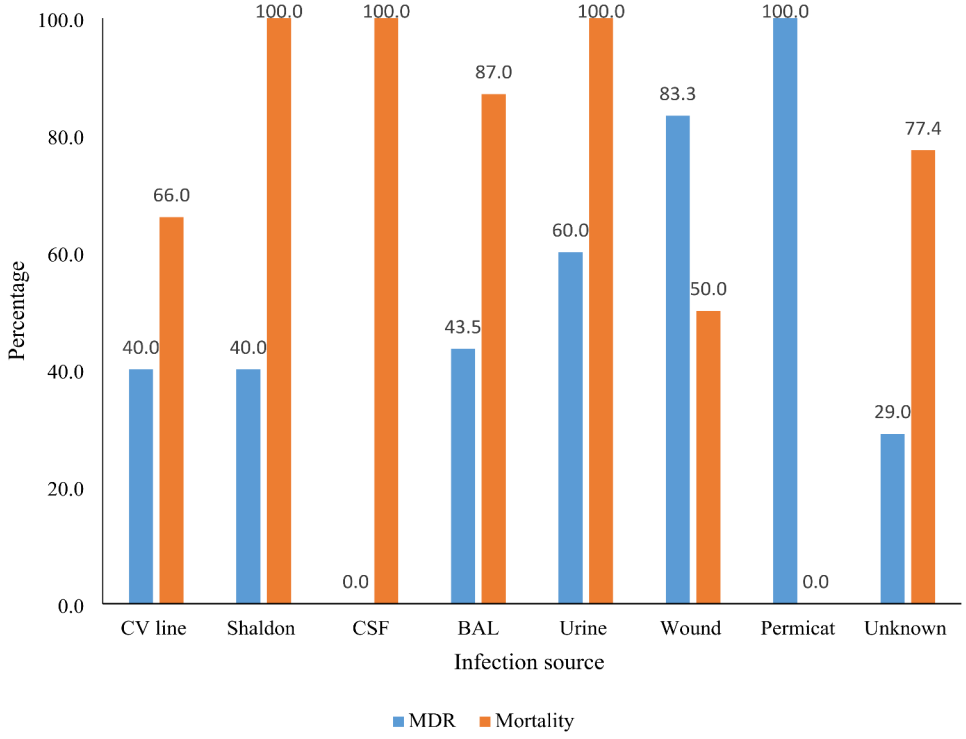


Fig. 2 The percentage of infection sources in terms of Mortality and MDR

Table 3 The risk factors associated with Gram-positive resistant bloodstream infection

Risk factors	VRE	Non-VRE	*P*-value
Mechanical ventilation (> 48 h)	7 (58.3%)	80 (69.6%)	0.938
History of receiving antibiotics (before positive blood culture)	9 (75%)	106 (92.2%)	0.014
Type 2 diabetes	1 (8.3%)	31 (27%)	0.061
Renal failure	2 (16.7%)	24 (20.9%)	0.729
CV Line (> 48 h before positive blood culture)	8 (66.7%)	99 (86.1%)	0.049
Length of ICU stay (> 72 h)	9 (75%)	98 (85.2%)	0.887
Infection sources			
BAL	3 (25%)	0.079	1.000
Urine	0 (0%)	1.000	1.000
CSF	0 (0%)	1.000	1.000
Wound	0 (0%)	1.000	1.000
Multiple sources	1 (8.3%)	1.000	1.000
Unknown	2 (16.7%)	1.000	1.000

Table 4 Multivariate analysis of risk factors for recurrence of bloodstream infection or re-infection

Risk factors	Risk ratio (CI = 95%)	*P*-value
Renal failure	8.83 (1.45–53.57)	0.018
Mechanical ventilation (> 48 h)	1.07 (0.13–8.67)	0.945
Ineffective experimental antibiotic treatment	0.45 (0.08–2.32)	0.343
Receiving vasopressors (after positive blood culture)	0.98 (0.96–1.00)	0.122
History of receiving antibiotics (before positive blood culture)	0.04 (0.01–0.44)	0.009
Length of hospital stay (> 72 h)	1.05 (1.02–1.08)	0.0001
Length of ICU stay	1.00 (0.96–1.04)	0.791
Gram-negative multidrug-resistant infection	0.71 (0.17–2.98)	0.642
Gram-positive multidrug-resistant infection	0.13 (0.00–6.74)	0.319
Infection sources		
CV line	1.09 (0.18–6.43)	0.921
BAL	4.81 (0.71–32.36)	0.106
Urine	93.47 (1.53–577.519)	0.031

Swati Patolia's study identified malignant liver failure, intra-abdominal infection, urinary tract infection, and ineffective experimental antibiotic treatment as risk factors associated with mortality in Gram-negative bacteremia (Patolia et al. 2018). Additionally, high age, high Apache score, ICU stay duration, and concurrent pneumonia were introduced (Lye et al. 2012).

The most common bacterium found in this study was *Klebsiella*, with a prevalence of 33% of MDR. Furthermore, ineffective experimental antibiotic treatment was linked to an increased mortality rate. Similarly, Kohler found that ineffective experimental antibiotic treatment significantly reduced mortality among carbapenem-resistant and carbapenem-sensitive patients (Kohler et al. 2017).

The present study also showed that central venous catheters (39.4%) and lower airways (14.2%) were the most common sources of infection, while 24.4% of cases had unknown origins. Likewise, Kurt reported that central venous catheters (42.5%) and lower airways (38.9%) were the most common sources of infection in COVID-19 patients (Kurt et al. 2022). The Eurobact study revealed that 24% of BSI in ICUs occurred due to abdominal infections, 21% from catheters, and 21% due to pneumonia, with 24% of cases having unknown origins (Tabah et al. 2012). Thus, controlling infections caused by central catheters and nosocomial pneumonia is essential. Additionally, managing abdominal infections in ICU surgeries is crucial for the prevention and control of sepsis.

In the present study, the prevalence of VRE was 9.4%, and a significant relationship was found between VRE, a history of receiving antibiotics, and the presence of a central venous catheter for more than 48 h. Therefore, it is vital to adhere to prevention measures and control the colonization of infections through handwashing, gloving, and isolating patients.

However, Young-Bem examined 446 patients in a non-surgical ICU, reporting an incidence of VRE at 6.1%. Moreover, a Glasgow Coma Scale (GCS) score of less than 8, a Foley tube duration of more than two weeks, an ICU stay of more than two weeks, and proximity to a positive patient were identified as unrelated risk factors (Se et al. 2009).

Johnstone examined bone marrow transplant patients, finding that organ transplants in the ICU were risk factors for developing VRE bacteremia, with a reported mortality rate of 40% within 30 days (Johnstone et al. 2018). Jung studied 210 patients with VRE bacteremia in the ICU and showed that higher disease severity and ineffective treatment were associated with 28-day mortality (Ye et al. 2018).

In the present study, the recurrence of bloodstream infections had a significant relationship with renal failure, a history of hospital stays exceeding 72 h, and a history of antibiotic use, confirming the impact of these important risk factors in causing bacteremia. However, further research should examine recurrence rates with a larger sample size. Until culture results are available, combined antibiotic treatment appears effective in improving survival in the ICU (Di Franco et al. 2021). Nevertheless, infection control policies and appropriate antibiotic use remain essential.

The strength of the present study was the comprehensive examination of risk factors in two hospitals with different patients, and its weakness was its small sample size compared to other studies. Besides, given the retrospective nature of the study, it was not possible to conduct a more comprehensive examination of other complications during the ICU stay that could affect mortality. Thus, comprehensive studies need to explore the risk factors for bacteremia and sepsis with a larger sample size and examine the effect of the infection sources and their control methods to reduce the incidence of sepsis and mortality. Furthermore, the patients who experience recurrence of infection should be examined separately.

Our results showed a significant relationship was found between ineffective experimental antibiotic treatment and multi-drug antibiotic resistance. Accordingly, selecting an effective antibiotic regime based on the identified risk factors and the types of common pathogens in each ICU can improve the survival of sepsis patients. Furthermore, developing new methods to determine microbial burden more rapidly in all countries is vital. Therefore, the importance of regular visits to an infectious disease specialist and the presence of an ICU specialist for careful and daily monitoring of patients is emphasized.

Author contributions

Mahdieh Sharifzadeh Kermani: Supervision, Resources, Project administration, Conceptualization. Writing—review and editing. Shiva Pouradeli: Formal analysis, Writing—review and editing. Reihaneh Sadeghian: Witing, Writing—review and editing. Zahra Momen Abadi: Data collection performed. All authors read and approved the final manuscript.

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Availability of data and materials

Data is available for researchers.

Declarations

Ethical approval

This research was MD thesis which approved by the ethics committee of Kerman University of Medical Sciences (Grant number: No. 401000765; IR.KMU.AH.REC.1401.280) and conducted in compliance with the principles of the Declaration of Helsinki.

Competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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