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Nosocomial carbapenem-drug resistant *Acinetobacter baumannii*, related factors and clinical outcomes in Northeast Iran

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Abstract

Background and objectives Nosocomial infections, including drug-resistant *Acinetobacter baumannii* infections, continue to impact the health of hospitalized patients. This study sought to determine the prevalence of these infections and assess the associated risk factors and clinical outcomes in Gorgan, Iran.

Methods A retrospective cross-sectional study was conducted on 143 infected patients with *Acinetobacter baumannii* in two educational hospitals in Gorgan city, Iran between 2016 and 2018. Patient information including age, gender, reason and duration of hospitalization, background of diseases, type of sample culture, symptoms, laboratory findings, prescribed antibiotics, and antibiogram were collected and analyzed. The Logistic regression and survival statistical methods were used by software of SPSS 26.

Results A total of 37 patients (25.87%) died during hospitalization. The less than one year and 45–65 years age groups demonstrated more deaths (29.7%; p-value < 0.001). Being single (not being married) was found to be a risk factor in increasing the chance of death among patients (OR = 2.154, 95% CI: 1.02–4.53; $p = 0.048$). Hospitalization in intensive care units (ICUs) was a risk factor for the death of patients (OR = 4.655, 95% CI: 7.6–83.2). The resistance to carbapenems was reported to be an important risk factor for the death of patients.

Conclusions *Acinetobacter baumannii* infections, particularly those resistant to carbapenems, are a significant risk for patients in ICUs and can lead to higher mortality rates.

Keywords Nosocomial infections, Carbapenem resistance, Multidrug resistance, Survival, *Acinetobacter baumannii* infection

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Introduction

"Nosocomial infections" are still a major health issue, affecting the burden of diseases among hospitalized patients by increasing their morbidity and mortality rates [1]. The World Health Organization (WHO) indicates that the prevalence of nosocomial infections in developed and developing countries is equal to 5–10% and more than 25%, respectively [2]. The overall prevalence of nosocomial infections in Iranian hospitals is 6.4% [3]. The most common causes of nosocomial infections are *Escherichia coli* at the rate of 18.8%, followed by *Klebsiella* spp. at the rate of 18.44%, and *Acinetobacter baumannii* spp. at the rate of 14.72% [4, 5].

As one of the most important causative agents of nosocomial infections, *Acinetobacter baumannii* species are aerobic gram-negative bacteria with the ability to survive on both wet and dry surfaces, as well as being resistant to a variety of common disinfectants, letting them to survive in hospital environments [6]. Although there are more than 50 species in the diverse genus of *Acinetobacter baumannii*, the majority are non-pathogenic environmental organisms. The most common species causing infections are *Acinetobacter baumannii*, followed by *Acinetobacter calcoaceticus* and *Acinetobacter lwoffii* [7]. *Acinetobacter baumannii* has the worst outcome among all, which can survive on human skin or dry surfaces for weeks and is resistant to a variety of disinfectants, making it easy to distribute in a hospital setting [8]. It is one of the main causes of hospital-acquired pneumonia, especially ventilator-associated cases, and has been reported in various other infections, including skin and wound infections, bacteremia, urinary tract infection (UTI), secondary meningitis, and infective endocarditis [9, 10]. The outer membrane porins, phospholipases, proteases, lipopolysaccharides (LPS), capsular polysaccharides, protein secretion systems, and iron chelating systems are among the most crucial virulence factors of the bacteria [11]. Although the capsular polysaccharides are the main factors causing immune evasion, and LPS causes septic shock, the main driver of diverse clinical outcomes is antibiotic resistance [12].

The clinical importance of *Acinetobacter baumannii* is due (in part) to its capacity to develop resistance to many available antibiotics. Due to the prevalence of infections and outbreaks caused by multidrug-resistant (MDR) *Acintobacter*, few antibiotics could be effective [13]. Recent publications reported the resistance to broad-spectrum cephalosporins, beta-lactam antibiotics, aminoglycosides, and quinolones [14]. Since multidrug resistant *Acinetobacter baumannii* (MDR-AB) is rapidly becoming a global threat, as resistance to major classes of antibiotics and carbapenem-resistant isolates are increasing worldwide, the administration of effective initial therapy is essential to improve survival and reducing mortality [13].

Antibiotic resistance poses a significant risk worldwide, in terms of mortality and economic burden [15]. However, the developing countries due to the widespread misuse of antibiotics, use of inhumane antibiotics, low quality of drugs, insufficient supervision and factors related to individual and national poverty (low standard of health care, malnutrition, chronic and frequent infections), and lack of access to more effective but more expensive drugs, are more affected [16]. Access to up-to-date epidemiological information on antimicrobial resistance in commonly encountered bacterial pathogens and its association with clinical symptoms and patient outcomes is not only crucial for determining treatment strategies but also for developing effective antimicrobial programs in hospitals [17]. Accordingly, this study aimed to determine the percentage of patients with drug-resistant *Acinetobacter baumannii* infection and evaluate the risk factors and clinical outcomes of these infections in patients admitted to hospitals in Gorgan city, Iran in 2016–2018.

Materials and methods

The information of all patients with positive culture of *Acinetobacter baumannii* (143 samples), who were hospitalized in different departments of Sayyad Shirazi or 5 Azar educational hospitals in Gorgan city between 2016 and 2018, were included in this retrospective cross-sectional study. The incompleteness of patients' information in the medical record was considered as an exclusion criteria for the study.

According to the instructions available in the hospital laboratory, the samples were cultured using BACTEC bottles and/or conventional bacterial agar media, which included Chocolate agar, MacConkey agar, and Trypticase Soy Agar with glycerol. The bottles were analyzed using a BACTEC 9240 system (Becton Dickinson Microbiology Systems, Franklin Lakes, NJ, USA). If necessary, subcultures were performed on the same Chocolate agar plates. The initial incubation period was three days at 37 °C. Potential *Acinetobacter baumannii* isolates were identified using standard biochemical tests, including oxidase, catalase, OF, TSI, motility, Simon Citrate, MR, VP, carbohydrate fermentation tests, or by utilizing API-20NE System kits (BioMérieux, France) [18].

Antibiotic susceptibility testing was conducted using the disk diffusion method and E-test (AB Biodisk, Sweden) following the guidelines of the Clinical and Laboratory Standards Institute (CLSI). For carbapenem susceptibility of the isolates, the minimal inhibitory concentration (MIC) breakpoints recommended by CLSI were utilized with E-tests. Carbapenem resistance was defined as an MIC of ≥8 μg/mL for imipenem or

meropenem antibiotics [19]. Drug-Resistant *Acinetobacter baumannii* was defined defined as the isolate resistant to at least three classes of antimicrobial agents, all penicillins and cephalosporins (including inhibitor combinations), fluroquinolones, and aminoglycosides.

After obtaining the necessary legal and ethical permits, the patient's information including age, gender, reason and duration of hospitalization, background of diseases that the patient was involved with during hospitalization or was initially diagnosed at the hospital (such as liver, kidney, heart, lung, digestive, endocrine, neoplasms, immunodeficiency, and diabetes), the type of sample culture sent to the hospital during hospitalization (urine, blood, sputum, pleural fluid, pus, CSF, intra-abdominal fluid, feces, or others), patient's symptoms (fever, weakness and fatigue, decreased level of consciousness, headache, dyspnea, chest pain, abdominal pain, nausea, vomiting, urinary symptoms, symptoms of upper respiratory infection, etc.), and laboratory findings were extracted and recorded.

Moreover, the type of prescribed antibiotics and the antibiogram were also recorded.

All necessary information was derived based on the ethical considerations of Golestan University of Medical Sciences) (GoUMS), the study design was approved by the committee of ethics at GoUMS (IR.GOUMS.REC.1399.144), and the patients' information remained confidential. The data was analyzed in two categories of descriptive and analytical sections, using SPSS v.26.0. Using the frequency, percentage, minimum and maximum, average and standard deviation indicators. The assumptions were then assessed using chi-square, logistic regression, and survival statistical methods. The *p*-values lower than 0.05 were considered to be statistically significant.

Table 1 Changes in clinical indicators of patients

Clinical indicator	Mean (Standard deviation)			*p*-value
	At the beginning of hospitalization	During hospitalization	At the time of discharge	
Systolic blood pressure	122.05 (22.93)	118.47 (16.41)	114.59 (14.17)	0.013
Diastolic blood pressure	76.40 (14.62)	73.93 (10.68)	71.39 (10.89)	0.079
Breathing rate	19.41 (4.63)	20.77 (16.56)	20.40 (16.65)	0.148
Pulse rate	91.75 (17.37)	88.24 (13.45)	85.58 (13.40)	**0.0001**
Body temperature	37.61 (0.84)	37.36 (0.53)	37.13 (0.39)	**0.0001**
Level of consciousness (GCS)	14.44 (1.46)	14.98 (0.19)	15 (0.0)	0.366

P.value less than 0.05 is statistically significant

Results

Among all 143 infected patients, 74 (51.7%) were male and the mean age of the patients was 47.77 ± 24.81 years. The majority of patients were hospitalized in the ICU, while the minorities were not receiving intensive cares. Most of the patients were suffering from sepsis (27.65%), respiratory diseases (22.15%) and burns (16.05%). The type of disease leading to hospitalization was different in men and women ($p=0.037$). Regarding the origin of *Acinetobacter baumannii* infection, the highest frequency was related to the infections acquired during hospitalization with the number of 113 patients. A total of 104 patients had at least one underlying disease. The most observed clinical symptoms included weakness and fatigue in 58, fever in 42, and symptoms of upper respiratory infection in 40 patients.

Regarding the obtained clinical samples for bacterial culture, blood samples had the highest frequency, followed by wound samples, samples from airways, tissue fluids and urine samples. Among 116 *Acinetobacter baumannii* isolates that had complete data regarding the antibiotic resistance, the frequency of multidrug-resistant isolates was 69. According to the results of antibiogram and carbapenem resistance diagnostic tests, among 70 isolates with complete information, 33 isolates were resistant to carbapenems. None of the demographic and clinical characteristics of the patients were significantly different between the two groups of antibiotic-resistant *Acinetobacter baumannii* isolates, and also the sensitive or resistant groups to carbapenems. We also evaluated the frequency of prescribed antibiotics before and after the antibiogram test. It was shown that the prescription was changed, while meropenem prescription increased from 40 to 53%, and Ceftriaxone showed a decrease in consumption from 45 to 21% (Table 1).

As shown in Table 2, the outcome of the disease had a significant difference based on the age group, while the majority of the deceased cases were observed in the age group of less than one year (10 out of 11). The outcome of the disease was significantly different based on the marital status ($p<0.001$), while being married was a protective factor against the death of patients (OR = 0.573; 95% CI: 0.41–0.81), and being single was considered a risk factor for the death of the patients (OR = 3.402, 95% CI: 1.96–5.89). By excluding the infants who died under the age of one year, being single remained as a risk factor for the death of patients (OR = 2.154, 95% CI: 1.02–4.53; $p=0.048$). The outcome of the patients was different based on the hospitalization department ($p<0.001$), while 70.3% of the deceased patients were

Table 2 Frequency of death outcome based on demographic and hospitalization characteristics

Characteristics		Outcome (N: 143) Number (%)		Test result and significance
		Live (106)	Death (37)	
Gender	Male	55 (51.9)	19 (51.4)	0.955
	Female	51 (48.1)	18 (48.6)	
Marital status	Single	16 (15.1)	19 (51.4)	*p*-value = 0.0001 OR = 5.938 (95%CI: 2.13–57.69)
	Married	90 (84.9)	18 (48.6)	
Underlying disease	Yes	24 (22.6)	15 (40.5)	*p*-value = 0.035 OR = 2.330 (95%CI: 1.5-50.18)
	No	82 (77.4)	22 (59.5)	
Hospitalization ward	ICU	16 (15.1)	26 (70.3)	*p*-value = 0.0001 OR = 0.075 (95%CI: 0.03–0.18)
	Non-ICU	90 (84.9)	11 (29.7)	
Age group (Years)	< 1	1 (0.9)	11 (29.7)	*p*-value = 0.0001
	1–25	8 (7.5)	5 (13.5)	
	26–45	30 (28.3)	5 (13.5)	
	46–65	37 (34.9)	11 (29.7)	
	> 65	30 (28.3)	5 (13.5)	
Type of disease	Burn	11 (91.7)	1 (8.3)	*p*-value = 0.503
	Sepsis	37 (94.9)	2 (5.1)	
	Infectious brain disease	0 (0)	6 (100)	
	Cancer	0 (0)	12 (100)	
	Respiratory disease	3 (9.4)	29 (90.6)	
	Kidney disease	0 (0)	14 (100)	
	Wound infection	5 (83.3)	1 (16.7)	
	Diabetes	7 (100)	0 (0)	
Origin *Acinetobacter baumannii*	Community	29 (27.4)	1 (2.7)	*p*-value = 0.152
	Hospital	77 (72.6)	36 (97.3)	
Duration of hospitalization	≤ 5 days	52 (96.3)	2 (3.7)	*p*-value = 0.149
	6–10 days	26 (86.7)	4 (13.3)	
	11–20 days	26 (100)	0	
	> 20 days	14 (93.3)	1 (6.7)	

hospitalized in intensive care units, and it was considered as a risk factor for the death of patients (OR = 4.655, 95% CI: 7.6–83.2).

As report in Table 3, the risk ratio for community-acquired *Acinetobacter baumannii* was 0.099 (95% CI: 0.01–0.7), which indicated the protective role of community-acquired infections for the death of patients, and the risk ratio for hospital-acquired *Acinetobacter baumannii* was 1.339 (95% CI: 1.18–1.52), which indicated their role as possible risk factors. The death/survival risk ratio for patients resistant to carbapenems was 3.358 (95% CI: 1.01–10.28), which delineated that the patients infected with carbapenem-resistant *Acinetobacter baumannii* may possess a 3.358 times higher possibility of not surviving. The 28-days survival rate was significantly different based on the age groups ($p = 0.004$), and hospitalization wards ($p < 0.001$). Moreover, the survival rate of patients hospitalized in intensive care units was almost 9 days less than other units (15.39 days versus 24.29 days).

Table 3 Frequency of death outcome based on *Acinetobacter baumannii* origin, drug resistance, and Carbapenem resistance

Characteristics		Outcome (N: 143) Number (%)		Test result and significance
		Live (106)	Death (37)	
Acinetobacter baumannii origin (N: 143)	Hospital	77 (72.6)	36 (97.3)	*p*-value = 0.002 OR[a] = 0.074 (95%CI: 0.01–0.56)
	Community	29 (27.4)	1 (2.7)	
Drug-Resistant *Acinetobacter baumannii* (N: 116)	Resistant	50 (55.6)	19 (73.1)	*p*-value = 0.109
	Sensitive	40 (44.4)	7 (26.9)	
Carbapenem resistance (N: 66)	Resistant	20 (39.2)	13 (68.4)	*p*-value = 0.029 OR = 3.358 (95%CI: 1.01–10.28)
	Sensitive	31 (60.8)	6 (31.6)	

a = Risk ratio for death to survival

Table 4 Short-term survival rate of 28 days based on demographic and clinical characteristics

Characteristics		Estimated median survival (days)	Standard Error	95% CI	*p*-value
Overall survival		**20.19**	**1.05**	**18.12–22.25**	
Gender	Male	20.25	1.50	17.29–23.16	*P* = 0.708 $X^2 = 0.140$
	Female	20.13	1.52	17.14–23.11	
Marital status	Single	18.18	1.82	14.61–21.75	*P* = 0.267 $X^2 = 1.234$
	Married	21.21	1.38	18.51–23.92	
Underlying disease	Yes	20.33	1.86	17.75–22.90	*P* = 0.579 $X^2 = 0.308$
	No	19.85	1.31	16.21–23.49	
Hospitalization ward	ICU	15.39	1.59	12.63–18.49	*P* = 0.0001 $X^2 = 19.281$
	Non-ICU	24.29	1.27	21.80-26.77	
Age group (Years)	< 1	12.25	2.95	6.47–18.03	*P* = 0.004 $X^2 = 15.557$
	1–25	19.32	2.69	14.05–24.58	
	26–45	24.57	1.70	21.24–27.91	
	46–65	19.37	2.30	14.86–23.87	
	> 65	21.41	2.26	16.97–25.84	

As demonstrate in Table 4, the overall estimated median short-term survival was 20.19 days and the age group of 26 to 45 years had the longest estimated median

Table 5 The 28-days survival rates of patients based on the characteristics of *Acinetobacter baumannii* infection, including the origin of *Acinetobacter baumannii*, multidrug resistance to antibiotics, and resistance to carbapenems

Characteristics		Estimated median survival (days)	Standard Error	95% CI	*p*-value
Acinetobacter baumannii origin (N: 143)	Hospital	20.05	1.08	17.93–22.16	$P=0.544$
	Community	7.67	0.32	7.03–8.30	$X^2=0.369$
Multidrug resistance (N: 116)	Resistant	19.26	1.53	16.26–22.26	$P=0.240$
	Sensitive	22.86	1.92	19.10-26.62	$X^2=1.382$
Carbapenem resistance (N: 66)	Resistant	12.07	1.61	8.90-15.23	$P=0.0001$
	Sensitive	23.43	1.69	20.13–26.76	$X^2=13.969$

survival (24.57 days). As shown in Table 5, although the survival rate of patients with community-acquired *Acinetobacter baumannii* infection was 13 days lower than the hospital-acquired infections, this difference was not statistically significant due to the low frequency of deaths in the community-acquired group ($p=0.544$). Resistance to carbapenems led to a significant decrease in the survival of patients with *Acinetobacter baumannii* infection (12.07 days for Carbapenem-resistant patients versus 23.43 days survival for Carbapenem-sensitive patients, $p<0.001$) as shown in Fig. 1.

Discussion

The results of the study on *Acinetobacter baumannii* bacteremia highlight several important findings that have implications for patient care and infection control measures in healthcare settings. The high frequency of infections acquired during hospitalization underscores the need for robust infection control measures to prevent hospital-acquired infections [20]. This includes strict adherence to hand hygiene protocols, proper disinfection of medical equipment and surfaces, and effective isolation of infected patients to prevent the spread of *Acinetobacter baumannii* [21]. The demographic and clinical characteristics of the patients, such as age, marital status, and hospitalization department, were found to significantly impact patient outcomes. The higher mortality rate among infants less than one year old is concerning and suggests the need for special attention and tailored interventions for this vulnerable population. Additionally, the finding that being unmarried was a risk factor for

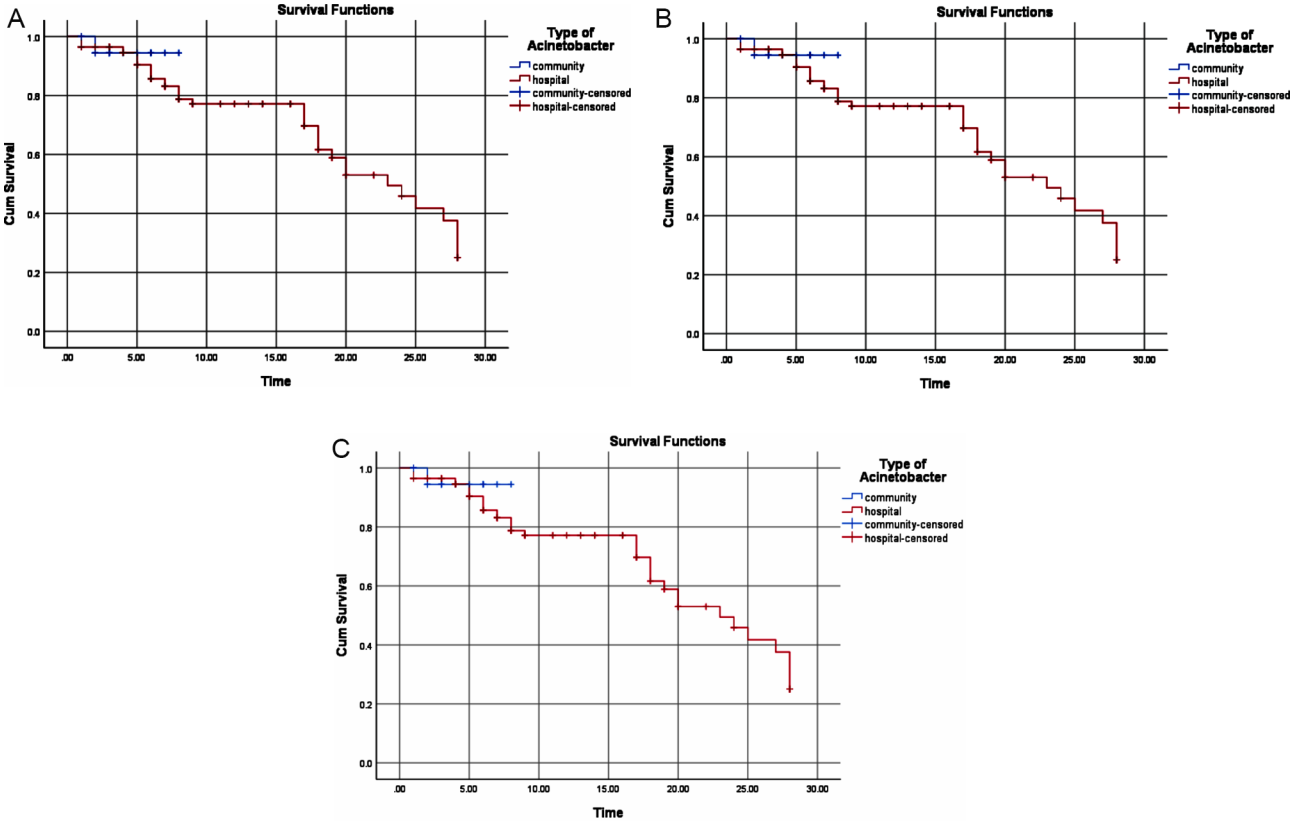

Fig. 1 The short-term survival graphs related to the origin of *Acinetobacter baumannii* (**A**), multidrug resistance (**B**) and resistance to carbapenems (**C**)

mortality highlights the importance of social support in patient outcomes. Healthcare providers should consider addressing the psychosocial needs of unmarried patients to improve their overall well-being and potentially reduce the risk of mortality [22].

The significant difference in patient outcomes based on hospitalization department, particularly the increased risk of mortality in intensive care units, emphasizes the need for close monitoring and prompt management of *Acinetobacter baumannii* infections in critically ill patients. This may include early detection of clinical symptoms and timely initiation of appropriate antibiotic therapy based on susceptibility testing [23]. The study also revealed the high frequency of multidrug-resistant isolates, indicating the urgent need for effective infection control measures and antimicrobial stewardship programs in healthcare settings. The implementation of targeted antibiotic therapy based on susceptibility testing, as evidenced by the increase in Meropenem prescription and decrease in Ceftriaxone consumption, can lead to more appropriate and effective treatment, ultimately improving patient outcomes and reducing the spread of antibiotic resistance [24].

Yang et al. [25] showed that 21.5% of patients who died had resistance to carbapenem and the patients with carbapenem-resistant *Acinetobacter baumannii* bacteremia had a 2.72 times higher risk for 30-day hospitalization and hospital mortality than those with carbapenem-sensitive *Acinetobacter baumannii*. Moreover, resistance to carbapenems was significantly associated with reduced survival in the short-term follow-up of 28 days, by increasing 3.358 times the probability of death to survival ratio, in line with the findings of Yang et al. found no significant relationship between carbapenem resistance and increased risk of in-hospital mortality, while carbapenem resistance increased the risk of admission to the intensive care unit and death in our study, which could be due to the differences in the type of infections of the patients in two different studies as well as the geographical differences, and differences in antibiotic resistance in different regions.

Qiao et al. [26] showed that the independent risk factors that increased the risk of death in patients with *Acinetobacter baumannii* bacteremia were mechanical ventilation, previous suppression of the immune system, and the use of carbapenem before isolating the patients, while the multidrug resistance of the strains was not reported as a risk factor. In our study, 25.87% of patients died during hospitalization, and the risk factors related to the death of the patients included being single, not having an underlying disease, hospitalization in the intensive care units, hospital-acquired infection, and resistance to carbapenems.

Xiao et al. [27] showed that 21.6% of hospitalized patients with *Acinetobacter baumannii* infection died in ICU. However, drug resistance was significantly higher in surviving patients than in deceased patients. The findings of the present study showed that 70.3% of hospitalized patients in intensive care units had died, and hospitalization in intensive care units was a risk factor for death for patients with *Acinetobacter baumannii* bacteremia, which was inconsistent with the findings of Xiao et al. Moreover, we reported no significant difference in multidrug resistance between survived and deceased patients. Choe et al. [28] demonstrated that among 74 cases of *Acinetobacter baumannii* bacteremia, 35.1% were resistant to carbapenem. The mortality rate in 30 days of hospitalization was 35.1%. They showed that carbapenem resistance, neutropenia, and prolonged ICU stay were independent risk factors for *Acinetobacter baumannii* -related mortality in children, which were consistent with the findings of the current study. We also determined that by correctly prescribing the drug and paying attention to the responses of the antibiograms at the time of prescription, with the correct selection of the antibiotics, a more favorable outcome could be observed.

One of the limitations of this study is the small sample size and reducing the statistical power of the analyses, which suggests that future studies should be conducted with a larger number of samples from different populations. Additionally, the retrospective design of the study posed limitations on the analysis of community samples. This study aimed to explore the differences between ICU and non- ICU wards. Future research could assess variations in drug resistance across different hospital wards. Given the cross-sectional nature of the study, the observed statistically significant relationships do not necessarily imply a causal association.

Conclusion

In conclusion, our findings provide valuable insights into the risk factors and clinical characteristics associated with *Acinetobacter baumannii* bacteremia, highlighting the need for a multifaceted approach to improve patient outcomes. This includes implementing infection control measures, optimizing antibiotic therapy based on susceptibility testing, addressing social and health-related vulnerabilities, and promoting preventive strategies to reduce hospital-acquired infections. Further research is warranted to explore additional factors influencing patient mortality and to develop targeted interventions for individuals at higher risk.

Abbreviations

WHO	World Health Organization
UTI	Urinary tract infection
LPS	Lipopolysaccharides
MDR-AB	Multidrug Resistant *Acinetobacter baumannii*

MDR	Multidrug-resistant
GOUMS	Golestan University of Medical Sciences
ICU	Intensive Care Unit
OR	Odds Ratio

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Author contributions
R.G conceived of the presented idea. Y.A and H. SA collection data management. R.G and H.SA and F.M designed the study and critically revising analysis and manuscript. F.M analysed the data, the computational framework, read and approved the final manuscript. R.G and Y.A and F.M and H. SA drafted the manuscript, contributed to the conception, and performed the analytic calculations and interpretation of data.

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Data availability
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Declarations

Ethics approval and consent to participate
Ethical approval for this study was obtained from the Ethics and Research Committee of Golestan University of Medical Sciences (IR.GOUMS.REC.1399.144). The guidelines on research involving the use of human subjects (beneficence, non-maleficence, veracity, confidentiality, and voluntarism) were strictly adhered to according to the Helsinki Declaration. Participants did not incur any cost by participating in this study and there was no financial inducement. The informed consent to participate was not obtained from all of the participants in the study. The informed consent of the patients was waived by an Institutional Review Board in ethics committee of the Golestan University of Medical Sciences.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

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