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Risk Factors and Treatment Determinants of Mortality in Carbapenem-Resistant Gram-Negative Bloodstream Infections in the Intensive Care Unit

Yoğun Bakım Ünitesinde Karbapeneme Dirençli Gram-Negatif Bakteriyemilerde Mortaliteyi Etkileyen Risk Faktörleri ve Tedavinin Değerlendirilmesi

Altıntaş Öner et al. Risk Factors for Mortality Caused by Carbapenem-Resistant Gram-Negative Bacteria

Betül Altıntaş Öner[1]*, Nurettin Erben[2], Elif Doyuk Kartal[3], Saygın Nayman Alpat[4], Hasip Kahraman[5], Birgül Yelken[6]

[1]Eskişehir Osmangazi University Faculty of Medicine Hospital, Department of xxx, Eskişehir, Türkiye
[2]Eskişehir Osmangazi University Faculty of Medicine Hospital, Department of xxx, Eskişehir, Türkiye
[3]Eskişehir Osmangazi University Faculty of Medicine Hospital, Department of xxx, Eskişehir, Türkiye
[4]Eskişehir Osmangazi University Faculty of Medicine Hospital, Department of xxx, Eskişehir, Türkiye
[5]Eskişehir Osmangazi University Faculty of Medicine Hospital, Department of xxx, Eskişehir, Türkiye
[6]Eskişehir Osmangazi University Faculty of Medicine Hospital, Department of xxx, Eskişehir, Türkiye

Betül Altıntaş Öner, MD. Eskişehir Osmangazi University Faculty of Medicine Hospital, Department of xxx, Eskişehir, Türkiye
betulaltintas4390@gmail.com
0000-0003-0955-3923

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Abstract
Introduction:
Carbapenem-resistant Gram-negative bacteria (CR-GNB) represent a major global health challenge, associated with limited therapeutic alternatives and elevated mortality rates. This study aimed to evaluate factors linked to mortality in bloodstream infections (BSI) caused by CR-GNB and to compare the effectiveness of various treatment modalities.
Materials and Methods: We conducted a single-center, retrospective cohort study of all consecutive patients with hospital-acquired CR-GNB BSI treated in the intensive care unit (ICU) of a 1010-bed tertiary university hospital between 2019 and 2022. Demographic characteristics, severity scores, invasive procedures, antibiotic regimens, and 28-day mortality outcomes were collected.
Results: A total of 156 patients met the inclusion criteria. The mean age was 68.6±15.8 years, and 91 (58.3%) were male. The overall 28-day mortality rate was 52.5**%.** Mortality was significantly higher among patients who underwent mechanical ventilation (p<0.001) or central venous catheterization (p=0.005) and among those with solid organ malignancy (p<0.001), hematologic malignancy (p<0.001), or immunosuppressive therapy (p=0.024). Independent predictors of mortality included Charlson Comorbidity Index [odds ratio (OR), 1.55; 95% confidence interval (CI), 1.22-1.97; p<0.001], septic shock (OR, 6; 95% CI, 1.74-21.18; p=0.05), total parenteral nutrition (TPN) (OR, 202.7; 95% CI, 13.5-3036.9; p<0.001), length of ICU stay prior to bacteremia diagnosis (OR, 0.95; 95% CI, 0.91-0.99; p=0.04), and receipt of effective treatment based on antibiogram results (OR, 0.06; 95% CI, 0.01-0.34; p=0.002). Mortality did not differ remarkably between patients receiving combination therapy and those receiving monotherapy, nor between those who received appropriate empiric therapy and those who did not.
Conclusion: Where feasible, invasive procedures such as central venous catheterization and mechanical ventilation should be minimized. TPN should be reserved for cases where alternative nutritional support is not possible. Mortality was reduced by the administration of effective therapy guided by antibiogram results. Given the scarcity of effective agents, the development of new antibiotics remains an urgent priority.
Keywords: Carbapenem-resistant Gram-negative bacteria, bloodstream infections, mortality, intensive care unit, antibiogram-guided therapy

Öz
Giriş
Karbapenem dirençli Gram-negatif bakteriler (KD-GNB), sınırlı tedavi alternatifleri ve yüksek ölüm oranları ile önemli bir küresel zorluk teşkil etmektedir. Bu çalışma, KD-GNB'lerin neden olduğu kan dolaşımı enfeksiyonlarında (KDİ) ölüme bağlı faktörleri değerlendirmeyi ve çeşitli tedavi yöntemlerinin etkinliğini karşılaştırmayı amaçlamıştır.
Gereç ve Yöntem: Bu çalışma, 2019'dan 2022'ye kadar 1010 yataklı bir üçüncül düzey üniversite hastanesinin yoğun bakım ünitesinde tedavi edilen hastane kaynaklı KD-GNB KDİ olan ardışık tüm hastaları içeren tek merkezli, retrospektif bir kohort analizidir. Demografik veriler, şiddet skorları, invaziv işlemler, antibiyotik tedavisi ve hastanın 28 günlük mortalite sonuçları kaydedilmiştir.
Bulgular: Çalışmanın kriterlerini karşılayan toplam 156 hasta dahil edildi. Hastaların ortalama yaşı 68,6±15,8 yıl idi. Yirmi sekiz günlük kümülatif mortalite oranı %52,5'ti. Mekanik ventilasyon (p<0,001), santral venöz kateterizasyon (p=0,005), solid organ malignitesi (p<0,001), hematolojik malignite (p<0,001) ve immünsüpresif ilaç kullanımı (p=0,024) mortalite gelişen grupta anlamlı derecede daha

yüksekti. Charlson Komorbidite İndeksi [olasılık oranı (OR): 1,55, %95 güven aralığı (GA): 1,22-1,97, p<0,001], septik şok (OR: 6, %95 GA: 1,74-21,18, p=0,05), total parenteral nutrisyon (TPN) (OR: 202,7, %95 GA: 13,5-3036,9, p<0,001), bakteriyemi öncesi yoğun bakım ünitesinde kalış günü (OR: 0,95, %95 CI: 0,91-0,99, p=0,04) ve antibiyogram sonuçlarına göre etkili tedavi alma (OR: 0,06, %95 GA: 0,01-0,34, p=0,002) mortalite ile ilişkili bağımsız faktörler olarak belirlenmiştir. Kombinasyon tedavisi ile monoterapi arasında mortalitede önemli bir fark kaydedilmedi. Ampirik tedavinin uygun bir şekilde başlanması, ölüm oranlarında belirgin bir fark yaratmamıştır.
Sonuç: İnvaziv yöntemler, santral venöz kateterizasyon ve mekanik ventilasyon dahil, mümkün olan en büyük ölçüde minimize edilmelidir. Alternatif beslenme yöntemleri mevcut olmadığı durumda TPN düşünülmelidir. Antibiyogram sonuçlarına göre yönlendirilen etkili tedavi uygulaması, ölüm oranlarını azaltmıştır.
Anahtar Kelimeler: Gram-negatif bakteriler, mortalite, yoğun bakım enfeksiyonları, karbapenem dirençli enterobacterales

Introduction
Infections are a common problem among patients in intensive care units (ICUs), contributing substantially to morbidity, mortality, and healthcare costs. In Türkiye and worldwide, the incidence of healthcare-associated infections caused by carbapenem-resistant enteric bacteria has been increasing[1]. According to the US Centers for Disease Control and Prevention's (CDC) Antibiotic Resistance Threats Report, more than 2.8 million antibiotic-resistant infections occur annually in the United States, leading to over 35,000 deaths. A considerable portion of this burden is attributable to multidrug-resistant (MDR) Gram-negative pathogens[2].

In 2024, the World Health Organization (WHO) updated its bacterial priority pathogen list, highlighting microorganisms that necessitate the research and development of novel antibiotics. These include carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant Enterobacterales, and third-generation cephalosporin-resistant Enterobacterales [3]. Infections caused by these pathogens are associated with high mortality rates. Prolonged hospitalization, the use of broad-spectrum antibiotics, central venous catheterization, intubation, immunosuppression, and severe comorbidities are recognized risk factors for mortality [4].

The current recommendation for managing carbapenem-resistant Enterobacterales bloodstream infections (CRE-BSI) is the use of next-generation β-lactam/β-lactamase inhibitors (BLBLIs). In cases involving metallo-β-lactamase (MBL) production, either the combination of ceftazidime–avibactam with aztreonam or cefiderocol monotherapy is advised. For CRAB, high-dose ampicillin–sulbactam in combination therapy is suggested as an alternative option [5]. In Turkey, however, ceftazidime–avibactam is the only available agent in this novel BLB1 class, and its use is restricted to select patients under specific reimbursement criteria.
This study aimed to evaluate mortality rates and risk factors associated with death in hospital-acquired BSI caused by carbapenem-resistant Gram-negative bacteria (CR-GNB) in the ICU and compare the effectiveness of different treatment regimens.

Materials and Methods
Study Design
This was a single-center, retrospective cohort study conducted at a 1010-bed tertiary care academic hospital. We included patients admitted to the ICU between January 2019 and January 2022 with CR-GNB bacteremia.

Patient Inclusion
Eligible participants were adult patients (≥18 years) admitted to the ICU during the study period. Only the initial episodes of monomicrobial bacteremia associated with clinical signs and symptoms of infection were analyzed. Additional inclusion criteria were (1) hospitalization in the ICU for at least 48 hours; (2) detection of CR-GNB in blood cultures; (3) fulfillment of healthcare-associated infection criteria; (4) a minimum of 48 hours of follow-up after initiation of treatment.

Exclusion of Patients
Patients were excluded if they were aged less than 18 years, if blood cultures were obtained within 48 hours of hospitalization, or if positive culture results were not accompanied by clinical manifestations of bacteremia.

Data Collection
The following data were extracted from medical records: demographic characteristics, Charlson Comorbidity Index (CCI), Acute Physiology and Chronic Health Evaluation II (APACHE II) score on the first day of ICU admission, and Pittsburgh Bacteremia Score (PBS) at the time of blood culture collection. Information was also collected on invasive procedures, primary cause of ICU admission, nutritional status, pathogens isolated from blood cultures, sources of bacteremia, antibiotic treatment details (monotherapy vs. combination therapy), delay in initiation of optimal therapy, presence of septic shock, ICU length of stay before bacteremia onset, and 28-day mortality.

Definition of Terms
BSI, carbapenem resistance, and nosocomial infection were defined according to the CDC criteria [6]. BSI is characterized by a positive blood culture for specified pathogens obtained ≥48 hours after hospital admission. The PBS was used to evaluate the immediate severity of illness and predicts mortality in patients with BSI. All parameters were assessed on the day of the initial positive blood culture or within the preceding 48 hours, and the highest score during this period was recorded. Scoring was given as follows:

• **Temperature:** 35.1–36°C or 39–39.9°C = 1 point; ≤35°C or ≥40°C = 2 points
• **Blood pressure:** A rapid decline in systolic pressure >30 mmHg or diastolic pressure >20 mmHg, systolic pressure <90 mmHg, or the need for intravenous vasopressors = 2 points.
• **Mechanical ventilation:** 2 points
• **Cardiac arrest:** 4 points
• **Mental Status:** Alert, 0; disoriented, 1; stuporous, 2; comatose, 4 [7].

Monotherapy was defined as the administration of a single *in vitro*–active antibiotic, whereas combination therapy was defined as the concurrent administration of at least one *in vitro*–active antibiotic. The onset of bacteremia was defined as the date of blood culture collection. Antibiotic therapy was considered appropriate if it included at least one active agent at an adequate dosage. Empirical treatment was defined as antimicrobial therapy initiated before antibiotic susceptibility results were available, whereas definitive treatment was therapy initiated after susceptibility testing. Delay in optimal treatment was defined as the interval between blood culture collection and the initiation of appropriate therapy according to antibiogram results. Septic shock was defined as a serum lactate level > 2 mmol/L despite adequate fluid resuscitation, together with the need for vasopressors to maintain a mean arterial pressure < 65 mmHg [8].

Identification and Antimicrobial Susceptibility Testing of Strains

Blood cultures were processed in the clinical microbiology laboratory using the BACTEC FX automated blood culture system (Becton Dickinson, USA). From 2019 to 2021, bacterial identification and antimicrobial susceptibility testing were performed with the BD Phoenix M50 system (Becton Dickinson, USA). From 2021 onward, identification was conducted using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS; Bruker, Germany), whereas susceptibility testing was continued with the BD Phoenix M50 system. Colistin susceptibility was assessed using automated methods. Antimicrobial susceptibility results for isolates were interpreted according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria, using either the Kirby–Bauer disk diffusion method or the BD Phoenix automated system.

Statistical Analysis

The Shapiro–Wilk test was used to evaluate the normality of continuous variables. Continuous variables were compared between groups using the Mann–Whitney U test when the data are not normally distributed, whereas categorical variables were compared using the chi-squared test, for which Pearson, Yates' continuity correction, Fisher's exact, and Monte Carlo exact tests were applied as appropriate. The two-proportion z-test was used to compare chi-squared subcategories. Backward stepwise logistic regression analysis was performed to calculate odds ratios (ORs) with 95% confidence intervals (CIs). A two-tailed p-value < 0.05 was considered statistically significant. Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

Ethics Approval

The study protocol was reviewed and approved by the Eskişehir Osmangazi University Non-interventional Clinical Research Ethics Committee (approval number: 29, dated: 26.04.2022).

RESULTS

Description of the Cohort

A total of 871 cases of Gram-negative bacteremia were identified. The majority (n = 715, 82.1%) were excluded for multiple reasons. A total of 156 patients (17.9%) were included in the final analysis (Figure 1).

Clinical Characteristics and Mortality Risk Factors

The study cohort comprised 156 patients who met the inclusion criteria, with a mean age of 68.6 ± 15.8 years; 91 (58.3%) were male. **By day 28, 82 patients (52.5%) had died.**

Compared with the survivors, nonsurvivors were considerably older **(p=0.03)** and had higher CCI scores (p = 0.001) and PBS (p < 0.001). No significant difference was observed in the APACHE II score at admission. The prevalence of COVID-19 was remarkably higher among nonsurvivors (p = 0.012) (Table 1).

Statistically significant differences were also noted in the distribution of solid versus hematologic malignancies (p < 0.001) and in the use of immunosuppressive drugs (p = 0.024) (Table 2).

The incidence of mechanical ventilation (p < 0.001), central venous catheterization (p = 0.005), admission with respiratory distress (p < 0.05), and receipt of total parenteral nutrition (TPN) (p < 0.05) was remarkably higher among nonsurvivors (Tables 2-3). In contrast, survivors were more likely to have undergone tracheostomy (p = 0.03), surgical intervention within the previous 3 months (p = 0.02), trauma (p = 0.03), or were receiving oral nutrition (p < 0.05) (Tables 2-3). At the time of blood culture collection, the proportion of patients in septic shock was significantly higher in the nonsurvivor group (p < 0.001) (Table 1). No marked difference in mortality was observed across the microorganisms isolated from blood cultures (p = 0.57) (Table 4).

Mortality Rates Based on Antimicrobial Therapy

The effect of antibiotic regimens on mortality was evaluated. Patients received meropenem, imipenem, piperacillin–tazobactam, third-generation cephalosporins, or combinations with colistin, aminoglycoside, or fosfomycin. Five patients received ceftazidime–avibactam monotherapy. After 28 days, no statistically significant differences were observed in the antibiotics administered between survivors and nonsurvivors (Table 5).

Similarly, no statistically significant differences were noted between monotherapy and combination therapy. Neither the postponement of optimal treatment nor the initiation of appropriate empiric therapy influenced mortality rates. However, the proportion of patients who received effective treatment according to antibiogram results was markedly higher in the survivor group (p<0.001) (Table 5).

Backward stepwise logistic regression was used to identify independent risk factors for mortality. Collinearity testing revealed a correlation between the PBS and septic shock; therefore, PBS was excluded from the model. Variables that were statistically significant in the univariate analysis (Table 6) were included in the initial model and subsequently analyzed by backward stepwise regression. The multivariate analysis demonstrated that higher **CCI scores** (**OR, 1.55; 95% CI, 1.22–1.97; p < 0.001), the presence of septic shock (OR, 6.00;**

95% CI, 1.74–21.18; p = 0.05), and TPN feeding (OR, 202.7; 95% CI, 13.5–3036.9; p < 0.001) were associated with increased mortality. In contrast, a longer duration of ICU stay before the onset of bacteremia (OR, 0.95; 95% CI, 0.91–0.99; p = 0.04) and receipt of effective treatment based on antibiogram results (OR, 0.06; 95% CI, 0.01–0.34; p = 0.002) were protective factors.

Discussion

CR-GNB infections are associated with high treatment failure rates and elevated mortality, largely owing to limited antibiotic options and restricted global access to novel agents. Patients with CR-GNB BSIs in the ICU face particularly poor prognoses [9]. In the present study, the 28-day mortality rate was 52.5%, which is higher than the 32% and 45% rates reported in previous studies [10, 11]. Age was an important determinant of the outcome, as the mean age was markedly higher among nonsurvivors. Prior research has also identified advanced age—specifically >55 years—as an independent risk factor for mortality in CR-GNB BSI [11]. Consistent with earlier findings, our multivariate analysis demonstrated that higher CCI scores were independently associated with increased risk of death, with each unit increase in CCI conferring a **1.55-fold** rise in mortality risk. A comparable study also reported that a CCI score ≥2 was an independent predictor of 28-day mortality [12]. Additionally, the **PBS was markedly higher in the nonsurvivor group, further supporting its prognostic relevance.** In a study investigating mortality predictors in patients with CRE-BSI, the PBS was also found to be markedly higher among nonsurvivors [13], consistent with our findings. Although prior research has demonstrated an association between APACHE II scores and mortality risk [14], our analysis did not identify APACHE II as an independent predictor.

Furthermore, the proportion of patients with solid organ and hematologic malignancies receiving immunosuppressive therapy was remarkably higher in the nonsurvivor group. This observation aligns with the findings by Shi et al., who reported that solid organ tumors were independent risk factors for mortality in CRE-BSI [15].

The use of central venous catheters and mechanical ventilation has consistently been associated with higher mortality rates in patients with CR-GNB BSI [15-17]. In contrast, a history of surgery within 3 months preceding bacteremia, tracheostomy, and trauma has been reported as a protective factor [18-20]. In our study, mechanical ventilation and central venous catheterization were notably more common among nonsurvivors, whereas tracheostomy, recent surgical intervention, and trauma history were more frequently observed in survivors. **TPN emerged as an independent risk factor for mortality, whereas oral feeding was associated with improved survival** [21]**.** The protective effects of trauma and surgery may be attributable to the younger age and lower comorbidity burden in these patients.

Tracheostomy may reduce mortality by lowering the risk of aspiration of secretions, thereby decreasing pulmonary complications.
The multivariate analysis revealed that septic shock increased mortality risk nearly **sixfold**, consistent with previous reports identifying septic shock as a major contributor to adverse outcomes [16, 22].

In contrast, the timely initiation of empiric therapy did not considerably affect mortality rates. Although the empiric treatment group showed a lower mortality rate (19.5% vs. 27%), the difference was not statistically significant. This result may have been influenced by the subsequent administration of appropriate therapy as patients who received effective empirical treatment were often more severely ill. A similar observation has been reported in a previous study [23].

A delay in optimal treatment was not found to affect mortality, though this result warrants careful interpretation. In survivor and nonsurvivor cohorts, the time to initiation of appropriate therapy was relatively prolonged (3.6 days vs. 4.2 days), and the high proportion of patients (78.8%) who ultimately received effective antibiotics may have influenced outcomes. Moreover, the early administration of broad-spectrum antimicrobials in high-risk patients, such as those with sepsis, may not have improved survival outcomes as some patients could have died before antibiogram-guided therapy could take effect, thereby limiting the observable benefit. In contrast, lower-risk patients may have received treatment at a later stage without much impact on outcomes. Our findings align with those of a prospective cohort study that also reported no statistically significant association between delays in optimal therapy and 28-day mortality [24]. However, other studies have shown that timely and appropriate antibiotic administration is associated with reduced mortality [10, 25]. While the indiscriminate use of broad-spectrum antibiotics carries substantial risks, prompt and targeted antimicrobial therapy remains essential for managing hospital-acquired BSI (HA-BSI).

No difference in mortality was observed between patients receiving monotherapy and those receiving combination therapy. **However, the proportion of patients receiving effective treatment based on antibiogram results was remarkably higher among survivors, and this was identified as an independent predictor of survival**. A study evaluating 28-day mortality in CR-GNB BSI similarly reported no marked difference between monotherapy and combination therapy, while demonstrating that inappropriate therapy was associated with increased mortality [9]. Likewise, Zhou et al. found that appropriate treatment reduced mortality, although no survival benefit was observed with combination therapy compared to monotherapy, consistent with our findings [13].

For CRAB infections, however, current recommendations support the use of combination therapy, incorporating at least two agents with confirmed *in vitro* activity, regardless of the susceptibility profile of a single agent. This approach reflects the limited treatment options and the need to maximize therapeutic efficacy against this highly resistant pathogen. Combination therapies incorporating sulbactam–ampicillin, polymyxin B, colistin, and tigecycline are commonly recommended for CRAB infections [26, 27]. In our cohort, *Acinetobacter* spp. was the predominant pathogen, which led to the frequent use of carbapenem-colistin combinations. However, recent guidelines favor use of novel BLBIs as the preferred agents, given the increased mortality and nephrotoxicity associated with use of polymyxin- or aminoglycoside-based regimens when combined with meropenem for the treatment of CRE [28]. In Turkey, reimbursement for ceftazidime–avibactam was only approved 8 months before the end of our study period and was restricted by stringent criteria. Consequently, this agent was administered to only five patients with CR-GNB BSI.

Patients with severe infections caused by CRE that demonstrate *in vitro* susceptibility only to polymyxins, aminoglycosides, tigecycline, or fosfomycin—and in the absence of newer BLBI combinations—should be managed according to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines with a regimen comprising multiple *in vitro*–active agents. However, no specific recommendations for or against particular drug combinations can be made [26].

In our cohort, comparison of different antibiotic regimens revealed no statistically significant differences in mortality. **Receiving effective treatment guided by antibiogram results emerged as an independent factor influencing survival.** Combination therapy was administered with at least one agent demonstrating *in vitro* activity. Owing to high resistance rates, many isolates were susceptible to only a single antibiotic, necessitating monotherapy in such cases. Previous studies on the management of CR-GNB infections have likewise reported no marked differences among treatment protocols [17, 25].

Study Limitations

This study has several limitations. First, carbapenem resistance genes were not analyzed, and colistin resistance was assessed only with automated systems. **Second, restricting the cohort to initial monomicrobial BSIs improved statistical independence but limited the evaluation of recurrent infections, cumulative risk, and treatment failure.**

Conclusion

This study identified key mortality risk factors in patients with BSIs caused by WHO-designated priority pathogens. **CCI, septic shock, TPN, duration of ICU stay prior to bacteremia, and receipt of effective treatment based on antibiogram results were independent predictors of mortality.** No specific antibiotic regimen demonstrated superiority, and **no difference in mortality was observed between monotherapy and combination therapy.** Our findings emphasize the importance of minimizing invasive procedures and ensuring timely access to antibiogram-guided therapy to reduce mortality. **TPN was associated with increased mortality and should be used with caution.** The growing prevalence of antibiotic resistance and the need for alternative therapies highlight the critical importance of access to novel antimicrobial agents.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the Eskişehir Osmangazi University Non-interventional Clinical Research Ethics Committee (approval number: 29, dated: 26.04.2022).

Informed Consent: Because of the retrospective design, informed consent was not obtained from the patients.

Footnotes

Authorship Contributions B.A.Ö., N.E., E.D.K., S.N.A., H.K., B.Y.,
Surgical and Medical Practices:
Concept:
Design:
Data Collection or Processing:
Analysis or Interpretation:
Literature Search:
Writing:

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Table 1. Demographic and clinical characteristics of the study cohort

	Nonsurvivors (n = 82)	Survivors (n = 74)	Total	p
Sex, male	47 (57.3%)	44 (59.5%)	91 (58.3%)	0.786
Age Mean±SD	70.9 ± 15.4	66.1 ± 16	68.6 ± 15.8	**0.03**
CCI Mean±SD	6 ± 2.7	4.4 ± 2.7	5.2 ± 2.8	**0.001**
APACHE II Median (IQR)	17 (11–25)	15 (9–21)		**0.17**
PBS Mean±SD	6.6 ± 2.8	4.3 ± 2.8	5.5 ± 3	**< 0.001**
COVID-19 (+)	33 (40.2%)	16 (21.6%)	49 (31.4%)	**0.012**
Septic shock	45 (%54.9)	10 (%13.5)	55 (%35.2)	**< 0.001**
Day of ICU stay before onset of bacteremia Mean ± SD	14.9 ± 12.56	21.66 ± 19.2	18.1 ± 16.3	**0.01**
Day of hospitalization before onset of bacteremia Mean ± SD	19.82 ± 14.78	25.72 ± 20.97	22.6 ±18.17	0.102

Abbreviations: CCI, Charlson Comorbidity Index; PBS Pittsburgh Bacteremia Score; APACHE II, Acute Physiology and Chronic Health Evaluation II

Table 2. Comorbidities and use of invasive procedures or devices

	Nonsurvivors (n = 82)	Survivors (n = 74)	Total	p
Comorbidities				
Chronic renal failure	5 (6.1%)	5 (6.8%)	10 (6.4%)	1
Renal replacement therapy	3 (3.7%)	3 (4.1%)	6 (3.8%)	1
Diabetes mellitus	29 (35.4%)	25 (33.8%)	54 (34.6%)	0.83
Hypertension	41 (50%)	36 (48.6%)	77 (49.4%)	0.86
COPD	13 (15.9%)	12 (16.2%)	25 (%16)	1
Chronic liver disease	1 (1.2%)	2 (2.7%)	3 (1.9%)	0.6
Cardiovascular disease	24 (29.3%)	21 (28.4%)	45 (28.8%)	1
Cerebrovascular disease	14 (17.1%)	17 (23%)	31 (19.9%)	0.47
Dementia	13 (15.9%)	9 (12.2%)	22 (14.1%)	0.66
Solid organ tumor	25 (30.5%)	7 (9.5%)	32 (20.5%)	< 0.001
Hematologic malignancy	6 (7.3%)	0 (0%)	6 (3.8%)	< 0.001
Immunosuppressive drug use **	23 (28%)	9 (12.2%)	32 (20.5%)	0.024
Invasive procedures or devices				
Mechanical ventilation	63 (76.8%)	41 (55.4%)	104 (66.7%)	< 0.001
Tracheostomy	13 (15.9%)	23 (31.1%)	36 (23.1%)	0.03
Chest tube	4 (4.9%)	7 (9.5%)	11 (7.1%)	0.42
Central venous catheterization	57 (69.5%)	35 (47.3%)	92 (59%)	0.005
Urinary catheterization	81 (98.8%)	73 (98.6%)	154 (98.7%)	0.72
Nasogastric tube	48 (58.5%)	35 (47.3%)	83 (53.2%)	0.16
Percutaneous endoscopic gastrostomy	8 (9.8%)	11 (14.9%)	19 (12.2%)	0.46
Surgical intervention in the last 3 months	23 (28%)	34 (45.9%)	57 (36.5%)	0.02
Trauma	6 (7.3%)	15 (20.3%)	21 (13.5%)	0.03

Abbreviations: COPD, chronic obstructive pulmonary disease; **, use of corticosteroids (prednisone equivalent > 20 mg/day for ≥14 days) or other recognized immunosuppressive therapy

Table 3. Primary cause of ICU admission, nutritional status, and prior location before ICU admission

	Nonsurvivors (n = 82)	**Survivors (n = 74)**	**Total**	**Comparison of ratios ****	**p-value***
Primary cause of ICU admission					
Respiratory distress	53 (64.6%)	33 (44.6%)	86 (55.1%)	**< 0.05**	**0.028**
Trauma	4 (4.9%)	16 (21.7%)	20(12.9%)	**< 0.05**	

GCD	14 (17.1%)	10 (13.5%)	24 (15.4%)	> 0.05	
Post-res.	5 (6.1%)	8 (10.8%)	13 (8.3%)	> 0.05	
Surgery	4 (4.9%)	4 (5.4%)	8 (5.1%)	> 0.05	
Sepsis	2 (2.4%)	3 (4.1%)	5 (3.2%)	> 0.05	
Nutritional status					
NG	44 (53.7%)	35 (47.3%)	79 (50.6%)	> 0.05	
PEG	5 (6.1%)	11 (14.9%)	16 (10.3%)	> 0.05	
TPN	20 (24.4%)	2 (2.7%)	22 (14.1%)	**< 0.05**	**< 0.001**
Oral	10 (12.2%)	26 (35.1%)	36 (23.1%)	**< 0.05**	
Enteral + TPN	3 (3.7%)	0	3 (1.9%)	> 0.05	
Place of stay before the ICU					
Community	33 (40.2%)	50 (67.6%)	83 (%53.2)	**< 0.05**	
Nursing home	1 (1.4%)	0	1 (0.6%)	> 0.05	**< 0.001**
Hospital service	49 (59.9%)	23 (31.2%)	72 (46.3%)	**< 0.05**	

*, Monte Carlo chi-square exact test; **, two-proportion z-test; Abbreviations: GCD, general condition disorder; Post-res., post-cardiopulmonary resuscitation ICU admission; NG, nasogastric catheter; PEG, percutaneous endoscopic gastrostomy, TPN, total parenteral nutrition

Table 4. Microorganisms isolated and source of bacteremia

Microorganisms isolated	Nonsurvivors (n = 82)	Survivors (n = 74)	Total	p
Acinetobacter spp.	49 (59.7%)	42 (56.7%)	91 (58.3%)	
Klebsiella spp.	19 (23.1%)	18 (24.3%)	37 (23.7%)	
Pseudomonas spp.	7 (8.5%)	5 (6.7%)	12 (7.6%)	
Proteus mirabilis	2 (2.4%)	5 (6.7%)	7 (4.4%)	
Escherichia coli	1 (1.2%)	2 (2.7%)	3 (1.9%)	
Others	4 (4.8%)	2 (2.7%)	6 (3.8%)	
				0.57
Bacteremia source				
Primary	19 (23.2%)	15 (20.3%)	34 (21.8%)	
Respiratory system	51 (62.2%)	46 (62.2%)	97 (62.2%)	
Urinary system	4 (4.9%)	1 (1.4%)	5 (3.2%)	
Central venous catheter	5 (6.1%)	6 (8.1%)	11 (7.1%)	
Intra-abdominal infection	2 (2.4%)	2 (2.7%)	4 (2.6%)	
Others	1 (1.2%)	4 (5.4%)	5 (3.2%)	
				0.7

Table 5. Antimicrobial treatments administered

	Nonsurvivors (n = 82)	Survivors (n = 74)	Total	p
Antibiotics				
Meropenem	9 (11%)	3 (4.1%)	12 (7.7%)	
İmipenem	2 (2.4%)	0 (0%)	2 (1.3%)	

Piperacillin–tazobactam	3 (3.7%)	4 (5.4%)	7 (4.5%)	
Third-generation cephalosporin	4 (4.9%)	6 (8.1%)	10 (6.4%)	
Quinolone/TMP-SMX	0 (0%)	1 (1.4%)	1 (0.6%)	
Carbapenem+colistin	35 (42.7%)	37 (50%)	72 (46.2%)	0.235
Carbapenem+AG	11 (13.4%)	15 (20.3%)	26 (16.7%)	
Carbapenem+tigesiklin	5 (6.1%)	3 (4.1%)	8 (5.1%)	
Carbapenem+quinolone/TMP-SMX	5 (6.1%)	0 (%0)	5 (3.2%)	
Ceftazidime–avibactam	2 (2.4%)	3 (4.1%)	5 (3.2%)	
Ceftazidime+AG	2 (2.4%)	1 (1.4%)	3 (1.9%)	
Ceftazidime+colistin	2 (2.4%)	0 (0%)	2 (1.3%)	
Carbapenem+fosfomycin	1 (1.2%)	1 (1.4%)	2 (1.3%)	
Carbapenem+polymyxin B	1 (1.2%)	0	1 (0.6%)	
Total	82 (100%)	74 (100%)	156 (100%)	
Treatment				
Monotherapy	20 (24%)	17 (23%)	37 (23.7%)	0.835
Combination therapy	62 (75.6%)	57 (77%)	119(76.3%)	
Delay in optimal treatment (day) Mean ± SD	3.64 ± 3.25	4.22 ± 3.55	3.96 ± 3.42	0.312
Empirical treatment initiated appropriately	16 (19.5%)	20 (27%)	36 (23.1%)	0.35
Receiving effective treatment	55 (67.1%)	68 (91.9%)	123 (78.8%)	**<0.001**

Abbreviations: AG, aminoglycoside; TMP-SMX, trimethoprim–sulfamethoxazole

Table 6. Univariate and multivariate analyses of factors associated with mortality

	Univariate analysis		**Multivariate analysis**	
	p	**OR (95% CI)**	**p**	**OR (95% CI)**
CCI	< 0.001	1.24 (1.10–1.41)	**< 0.001**	1.55 (1.22–1.97)
COVID-19 (+)	0.01	2.44 (1.2–4.99)		
Septic shock	< 0.001	7.78 (3.51–17.2)	**0.05**	6 (1.74–21.18)
Day of ICU stay before bacteremia	0.015	0.97 (0.94–0.99)	**0.04**	0.95 (0.91–0.99)
Solid organ tumor	0.01	4.69 (1.88–11.7)		
Hematologic malignancy	0.99			

Immunosuppressive drug use **	0.017	2.81 (1.20–6.57)		
Central venous catheterization	0.005	2.54 (1.31–4.89)		
Mechanical ventilation	0.001	4.05 (1.82–8.99)		
Surgical intervention in the last 3 months	0.02	0.45 (0.23–0.89)		
Trauma	0.02	0.31 (0.11–0.84)		
Tracheostomy	0.02	0.41 (0.19–0.9)		
Respiratory distress	0.004	0.1 (0.02–0.49)		
TPN feeding	0.007	7.95 (1.74–36.36)	**<0.001**	202.72 (13.5–3036.9)
Oral feeding	0.007	0.3 (0.13–0.71)		
Place of stay before the ICU, Hospital service	0.003	2.82 (1.43–5.57)		
Place of stay before the ICU, Community	0.06			
Receiving effective treatment	<0,001	0.18 (0.06–0.46)	**0.002**	0.06 (0.01–0.34)

Abbreviations: CCI, Charlson Comorbidity Index; **, use of corticosteroids (prednisone equivalent >20 mg/day for ≥14 days) or other recognized immunosuppressive therapy