ORIGINAL RESEARCH

Risk Factors for Mortality and Outcomes in Hematological Malignancy Patients with Carbapenem-Resistant *Klebsiella pneumoniae* Bloodstream Infections

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Background: This study aimed to identify risk factors for mortality and outcomes in hematological malignancy (HM) patients with bloodstream infection (BSI) caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP).

Methods: A retrospective study was conducted at a tertiary teaching hospital in Henan Province, China, between January 2018 and December 2021. All BSIs caused by CRKP in hospitalized HM patients were identified. Data on patient demographics, disease, laboratory tests, treatment regimens, outcomes of infection, and the antimicrobial susceptibility of each isolate were collected from medical records.

Results: A total of 129 patients with CRKP BSI were included in the study, and the 28-day mortality rate was 80.6% (104/129). In Cox analysis an absolute neutrophil count < 500 at discharge (hazard ratio [HR] 6.386, 95% confidence interval [CI] 3.074–13.266, $p < 0.001$), intensive care unit admission (HR 1.834, 95% CI 1.065–3.157, $p = 0.029$), and higher Pitt bacteremia score (HR 1.185, 95% CI 1.118–1.255, $p < 0.001$) were independent risk factors associated with 28-day mortality. Survival curve analysis indicated that compared with ceftazidime-avibactam-based therapy, both polymyxin b (HR 8.175, 95% CI 1.099–60.804, $p = 0.040$) and tigecycline (HR 14.527, 95% CI 2.000–105.541, $p = 0.008$) were associated with a higher risk of mortality.

Conclusion: In HM patients CRKP BSI resulted in high mortality. Intensive care unit admission, higher Pitt bacteremia score, and absolute neutrophil count < 500 at discharge were independently associated with higher mortality. Early initiation of new agents such as ceftazidime-avibactam may improve outcomes.

Keywords: bloodstream infection, carbapenem-resistant *Klebsiella pneumonia*, hematological malignancy, risk factor

Introduction

Carbapenem-resistant Enterobacteriaceae (CRE), especially *Klebsiella pneumonia* (*KP*), has emerged as a global threat over the past decade. According to data from the China Antimicrobial Surveillance Network, *KP* resistance to meropenem and imipenem increased to 25.0% and 26.3% in 2018 respectively from 3.0% and 2.9% in 2005, and the resistance rate increased by more than 8 times.[1] Due to primary immunodeficiency, neutropenia caused by hematopoietic stem cell transplantation or chemotherapy, and frequent exposure to broad-spectrum antibiotics, patients with a hematological malignancy (HM) appear to be at higher risk of carbapenem-resistant *KP* (CRKP) infection.[2–5]

The mortality rate of CRKP bloodstream infection (BSI) is > 50% worldwide, higher than that of other Gram-negative BSIs in patients with HM.[6–8] Trecarichi et al[9] conducted a prospective cohort study of 278 episodes of *KP* BSI in 13 Italian hematological units. They reported 21-day mortality rates of 52.2% in patients with CRKP BSI, and 14.5%

in patients with carbapenem-susceptible *KP* (CSKP) BSI. Therefore, it is necessary to identify patients with CRKP early and accurately. However, studies on risk factors for mortality in HM patients with CRKP BSI have yielded inconsistent results. Septic shock, acute respiratory failure, inadequate initial antimicrobial therapy, rectal CRKP colonization, severe neutropenia, and invasive mechanical ventilation are reportedly independently associated with mortality.[9,10] Considering the poor outcomes of HM patients with CRKP BSI, early initiation of an active therapy is critical. Nevertheless, antimicrobial therapy has largely relied on the use of older agents such as polymyxins, tigecycline, aminoglycosides, and fosfomycin, which have a high risk of toxicity and poor efficacy.[11,12]

The aim of the current study was to identify risk factors for mortality and outcomes in HM patients with CRKP BSIs.

Materials and Methods

Study Design and Patients

This retrospective study was conducted at the First Affiliated Hospital of Zhengzhou University in Zhengzhou, Henan Province, China. All episodes of BSI caused by CRKP that occurred between January 2018 and December 2021 in hospitalized HM patients were identified. The characteristics collected from the hospital electronic medical records system included patient demographics, disease, laboratory data, treatment regimens, outcome of infection, and antimicrobial susceptibilities of each isolate. In patients with recurrent infections, only the first episode was included in the analysis. Patients aged < 18 years were excluded from the study. The primary outcome was 28-day mortality after BSI onset. The study was reviewed and approved by the Research Ethics Committee of the First Affiliated Hospital of Zhengzhou University (2022-KY-0306-002). Because patient data were analyzed anonymously and confidentiality was maintained, the requirement for patient consent was waived. The study was conducted in accordance with the Declaration of Helsinki.

Definitions

The following terms were defined prior to data analysis. CRKP BSI was defined as an infection with a positive blood culture for CRKP. BSI onset was defined as the collection date of the first positive blood culture. Neutropenia and severe neutropenia were respectively defined as absolute neutrophil counts (ANCs) < 500 cells/mm^3 and < 100 cells/mm^3. Carbapenem exposure was defined as any carbapenem administered within 30 days before BSI. Appropriate early antimicrobial treatment was defined as the administration of active agents during the first 72 h of BSI onset. Pitt bacteremia score (PBS) was calculated within 48 h of the day of the first positive blood culture, and the highest score was recorded. Septic shock was defined as sepsis associated with hypotension and perfusion abnormalities refractory to organ dysfunction.[13]

Antibiotic Susceptibility Test

CRKP refers to *KP* isolates that were resistant to at least one carbapenem. The VITEK 2 Compact system (bioMérieux, Marcy l'Etoile, France) and the Phoenix100 automated system (Becton Dickinson, Spark, MD, USA) were used for isolate identification. The results were interpreted in accordance with the Clinical and Laboratory Standards Institute Document M100 edition (2020). For colistin, the results were interpreted in accordance with European Committee on Antimicrobial Susceptibility Testing clinical breakpoints (version 6.0). The combined modified carbapenem inactivation method and EDTA-CIM was used for phenotypic detection of carbapenemase-producing Enterobacteriaceae.

Statistical Analysis

Continuous variables with normal distributions are presented as means ± the standard deviation (SD), and those with non-normal distributions are presented as medians and interquartile ranges. Categorical variables are presented as frequencies and proportions. Cox regression analysis was conducted to identify independent risk factors for 28-day mortality. Variables with *p* values < 0.01 in univariate analysis were included in the Cox regression model. Optimal cutoffs for continuous variables were evaluated using receiver operating characteristic (ROC) curve analysis. The

Kaplan–Meier method was used for survival analysis. All statistical analyses were performed using SPSS version 26.0 for Windows.

Results

Patient Characteristics

The clinical characteristics of 129 HM patients with CRKP BSI are summarized in Table 1. The average age of the population was 46.1 ± 13.8 years, and 65.9% of the patients were male. Seventy-seven patients were diagnosed with acute myeloid leukemia, which accounted for the majority (59.7%) of HM. At the onset of BSI, 10 (7.8%) patients had hematopoietic stem cell transplantation, 120 (93%) had neutropenia, and 98 (76%) had severe neutropenia. Only 31

Table 1 Clinical Characteristics of 129 Patients with CRKP Bloodstream Infection Carbapenem-Resistant *Klebsiella Pneumonia*

Variable	N = 129
Demographic information	
Age	46.1 ± 13.8
Male sex	85 (65.9)
Patient characteristics	
ANC < 500 (cells/mm^3)	120 (93.0)
ANC < 100 (cells/mm^3)	98 (76.0)
Days of ANC < 500 (cells/mm^3)	11 (7.0–19.0)
ANC < 500 (cells/mm^3) at discharge	98 (76.0)
HSCT	10 (7.8)
Hematological malignancy	
Acute lymphatic leukemia	17 (13.2)
Acute myeloid leukemia	77 (59.7)
Chronic myeloid leukemia	2 (1.6)
Myelodysplastic syndrome	15 (11.6)
Lymphoma	16 (12.4)
Multiple myeloma	2 (1.6)
ICU admission	93 (72.1)
PBS	3 (1.0–6.0)
Renal replacement therapy	4 (3.1)
Mechanical ventilation	70 (54.3)
Septic shock	86 (66.7)
Length of stay in ICU	1 (0–4.0)
Length of hospitalization	25 (18–39)
Length of hospitalization before the onset of BSI	20 (14.5–28.5)
Carbapenem exposure	120 (93.0)
Antimicrobial therapy	
Quinolones	9 (7.0)
TMP/SMX	3 (2.3)
Fosfomycin	11 (8.5)
Aztreonam or β-lactam/β-lactamase inhibitors	17 (13.2)
Aminoglycosides	2 (1.6)
Carbapenems	107 (82.9)
Tigecycline	86 (66.7)
Polymyxin B	30 (23.3)
CAZ/AVI	7 (5.4)
Appropriate early antimicrobial treatment	94 (72.9)

Abbreviations: ANC, absolute neutrophil count; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; TMP/SMX, trimethoprim-sulfamethoxazole; CAZ/AVI, ceftazidime-avibactam; PBS, Pitt bacteremia score.
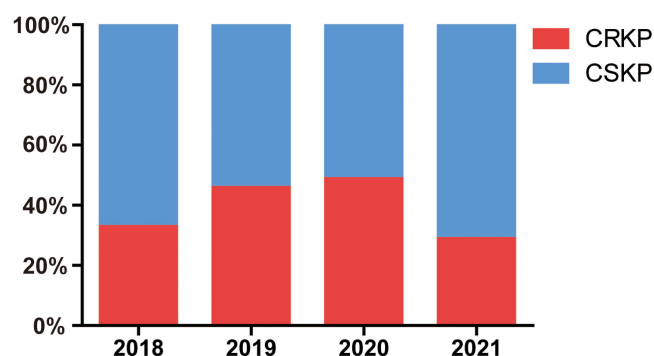
Figure 1 The isolation rate of CRKP during the study period.

(24%) patients with neutropenia had recovered prior to discharge. A total of 93 (72.1%) patients needed to be admitted to the intensive care unit (ICU), 86 (66.7%) patients had septic shock, and 70 (54.3%) patients needed mechanical ventilation. More than 90% of patients had been exposed to carbapenems prior to the onset of BSI, and more than 70% of patients received appropriate early antimicrobial therapy after the onset of BSI. Carbapenems and tigecycline were the most commonly used antimicrobial drugs, with respective frequencies of 82.9% and 66.7%.

Microbiological Characteristics

A total of 129 isolates were identified as CRKP. The isolation rate of CRKP ranged from 28.7% to 48.6% during the study period (Figure 1). Only 22 (17%) of isolates were tested for carbapenemase, and all were *KP* carbapenemase. Colistin and tigecycline were the most active drugs, whereas ciprofloxacin and aztreonam were the least active (Table 2). Ceftazidime-avibactam (CAZ/AVI) susceptibility was not routinely tested at our hospital.

Risk Factors for 28-Day Mortality

The univariate analysis of Cox regression indicated that ANC < 500 at discharge, ICU admission, higher PBS, mechanical ventilation, septic shock, and length of hospitalization were associated with 28-day mortality, whereas CAZ/AVI treatment and appropriate early antimicrobial treatment were significantly associated with survival ($p <$ 0.05). In the multivariate analysis of Cox regression, ANC < 500 at discharge (hazard ratio [HR] 6.386, 95% confidence interval [CI] 3.074–13.266, $p < 0.001$), ICU admission (HR 1.834, 95% CI 1.065–3.157, $p = 0.029$), and higher PBS (HR 1.185, 95% CI 1.118–1.255, $p < 0.001$) were identified as independent risk factors (Table 3). ROC curve analysis indicated that a PBS cut-off of 2 was a good predictor of mortality in HM patients with CRKP BSI, with an area under curve of 0.846 (95% CI 0.772–0903, $p < 0.001$), sensitivity of 72.1%, and specificity of 84% (Figure 2). In Kaplan-Meier curve analysis PBS ≥ 2 was associated with a higher risk of mortality ($p < 0.001$) (Figure 3A).

**Table 2** Antibiotic Susceptibility Characteristics of *Klebsiella Pneumonia* Isolates

Antibiotic (N)	S (%)	I (%)	R (%)
Colistin (120)	99.2	NA	0.8
Tigecycline (129)	87.6	3.1	9.3
Trimethoprim-sulfamethoxazole (128)	33.6	NA	66.4
Amikacin (129)	30.2	NA	69.8
Ciprofloxacin (129)	5.4	NA	94.6
Aztreonam (129)	2.3	NA	97.7

Abbreviation: NA, not applicable.

Table 3 Univariate and Multivariate Cox Regression Analysis of Mortality of Patients with Carbapenem-Resistant *Klebsiella Pneumonia* Bloodstream Infection

Variable	Survivors (N = 25)	Non-survivors N = 104	Univariate Analysis		Multivariate Analysis	
			HR (95% CI)	*p* values	HR (95% CI)	*p* values
Demographic information						
Age	44.0 ± 11.8	46.6 ± 14.2	1.008 (0.993–1.023)	0.294		
Male sex	17 (68.0)	68 (65.4)	0.989 (0.660–1.481)	0.957		
Patient characteristics						
ANC < 500 (cells/mm^3)	23 (92.0)	97 (93.3)	1.426 (0.661–3.078)	0.365		
ANC < 100 (cells/mm^3)	19 (76.0)	79 (76.0)	0.999 (0.637–1.568)	0.996		
Days of ANC < 500 (cells/mm^3)	12 (8.0–19.0)	11 (7.0–18.8)	0.993 (0.977–1.011)	0.452		
ANC < 500 (cells/mm^3) at discharge	3 (12.0)	95 (91.3)	8.665 (4.256–17.642)	< 0.001	6.386 (3.074–13.266)	< 0.001
HSCT	5 (20.0)	5 (4.8)	0.499 (0.203–1.227)	0.130		
Hematological malignancy						
Acute lymphatic leukemia	3 (12.0)	14 (13.5)	0.921 (0.524–1.620)	0.776		
Acute myeloid leukemia	17 (68.0)	60 (57.7)	0.786 (0.532–1.160)	0.225		
Chronic myeloid leukemia	0 (0)	2 (1.9)	1.995 (0.489–8.137)	0.336		
Myelodysplastic syndrome	2 (8.0)	13 (12.5)	1.536 (0.858–2.749)	0.149		
Lymphoma	2 (8.0)	14 (13.5)	1.269 (0.723–2.230)	0.407		
Multiple myeloma	1 (4.0)	1 (1.0)	0.559 (0.078–4.008)	0.562		
ICU admission	7 (28.0)	86 (82.7)	3.338 (1.984–5.618)	< 0.001	1.834 (1.065–3.157)	0.029
PBS	1 (0–1.0)	4 (1.0–6.8)	1.223 (1.169–1.301)	< 0.001	1.185 (1.118–1.255)	< 0.001
RRT	0 (0)	4 (3.8)	1.879 (0.689–5.129)	0.218		
Mechanical ventilation	0 (0)	70 (67.3)	3.494 (2.255–5.412)	< 0.001		
Septic shock	4 (16.0)	82 (78.8)	3.680 (2.256–6.002)	< 0.001		
ICU LOS	0 (0–4.0)	1.0 (1.0–4.0)	0.998 (0.981–1.015)	0.836		
Length of hospitalization	41 (27.5–51.0)	23 (18.0–35.0)	0.978 (0.965–0.991)	0.001		
Length of hospitalization before the onset of BSI	22 (10.0–27.0)	19.5 (15.0–30.0)	1.007 (0.995–1.020)	0.229		
Carbapenem exposure	23 (92.0)	97 (93.3)	1.115 (0.518–2.402)	0.781		
Antimicrobial therapy						
Quinolones	3 (12.0)	6 (5.8)	0.614 (0.269–1.401)	0.247		
TMP/SMX	2 (8.0)	1 (1.0)	0.280 (0.039–2.010)	0.206		
Fosfomycin	0 (0)	11 (10.6)	1.542 (0.821–2.894)	0.178		
Aztreonam or β-lactam/β-lactamase inhibitors	5 (20.0)	12 (11.5)	0.821 (0.449–1.500)	0.521		
Aminoglycosides	1 (4.0)	1 (1.0)	0.379 (0.053–2.721)	0.335		
Carbapenems	18 (72.0)	89 (85.6)	1.456 (0.841–2.522)	0.180		
Tigecycline	17 (68.0)	69 (66.3)	0.802 (0.533–1.206)	0.289		
Polymyxin B	8 (32.0)	22 (21.2)	0.637 (0.397–1.021)	0.061		
CAZ/AVI	6 (24.0)	1 (1.0)	0.085 (0.012–0.608)	0.014		
Appropriate early antimicrobial treatment	21 (84.0)	73 (70.2)	0.553 (0.361–0.846)	0.006		

Abbreviations: ANC, absolute neutrophil count; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; PBS, Pitt bacteremia score; RRT, renal replacement therapy; LOS, length of stay; BSI, bloodstream infection; CAZ/AVI, ceftazidime-avibactam; TMP/SMX, trimethoprim -sulfamethoxazole; CAZ/AVI, ceftazidime-avibacta.

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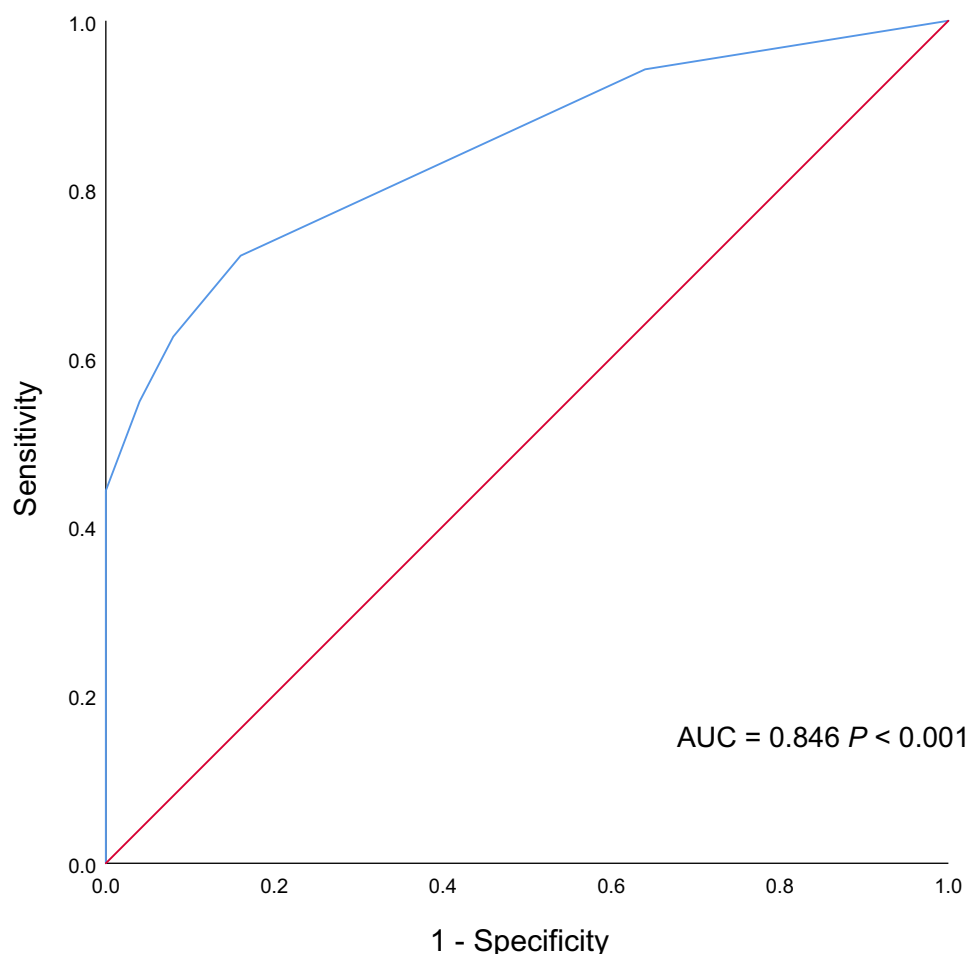
Figure 2 Receiver operating characteristic (ROC) curve of Pitt bacteremia score (PBS).

Therapy and Outcomes

The overall 14-day mortality rate was 77.5% (100/129), and the 28-day mortality rate was 80.6% (104/129). Among patients who received active drugs as targeted therapy, 30 received polymyxin b-based therapy, 86 received tigecycline-based therapy, one received levofloxacin, and seven patients received CAZ/AVI-based therapy which was considered a potential therapeutic alternative. Survival curve analysis indicated that compared with CAZ/AVI-based therapy, both polymyxin b (HR 8.175, 95% CI 1.099–60.804, p = 0.040) and tigecycline (HR 14.527, 95% CI 2.000–105.541, p = 0.008) were associated with a higher risk of mortality (Figure 3B).

Discussion

CRKP is an emerging global health problem and poses a significant risk to immunocompromised patients. Few studies conducted in HM patients with carbapenem-resistant Gram-negative bacteria (including *KP*) BSI have reported independent risk factors for mortality, such as septic shock, acute respiratory failure, inadequate initial antimicrobial therapy, CRKP isolation, Acute Physiology and Chronic Health Evaluation score, prolonged neutropenia, and treatment with one active drug.[9,14–17] In the current study ICU admission, higher PBS, and ANC < 500 at discharge were associated with 28-day mortality. It is not surprising that ICU admission was a risk factor for mortality, and previous studies have suggested that ICU admission increased the risk of mortality in general populations infected with CRKP.[18,19] Mechanical ventilation and septic shock requiring vasopressors were the two most common indications for ICU admission in the current study, and they were also identified as independent predictors of mortality in HM patients in previous studies.[20–25] Liu et al[26] conducted a retrospective chart review of 121 sequential ICU admissions with HM over a 5-year period, with

A

B
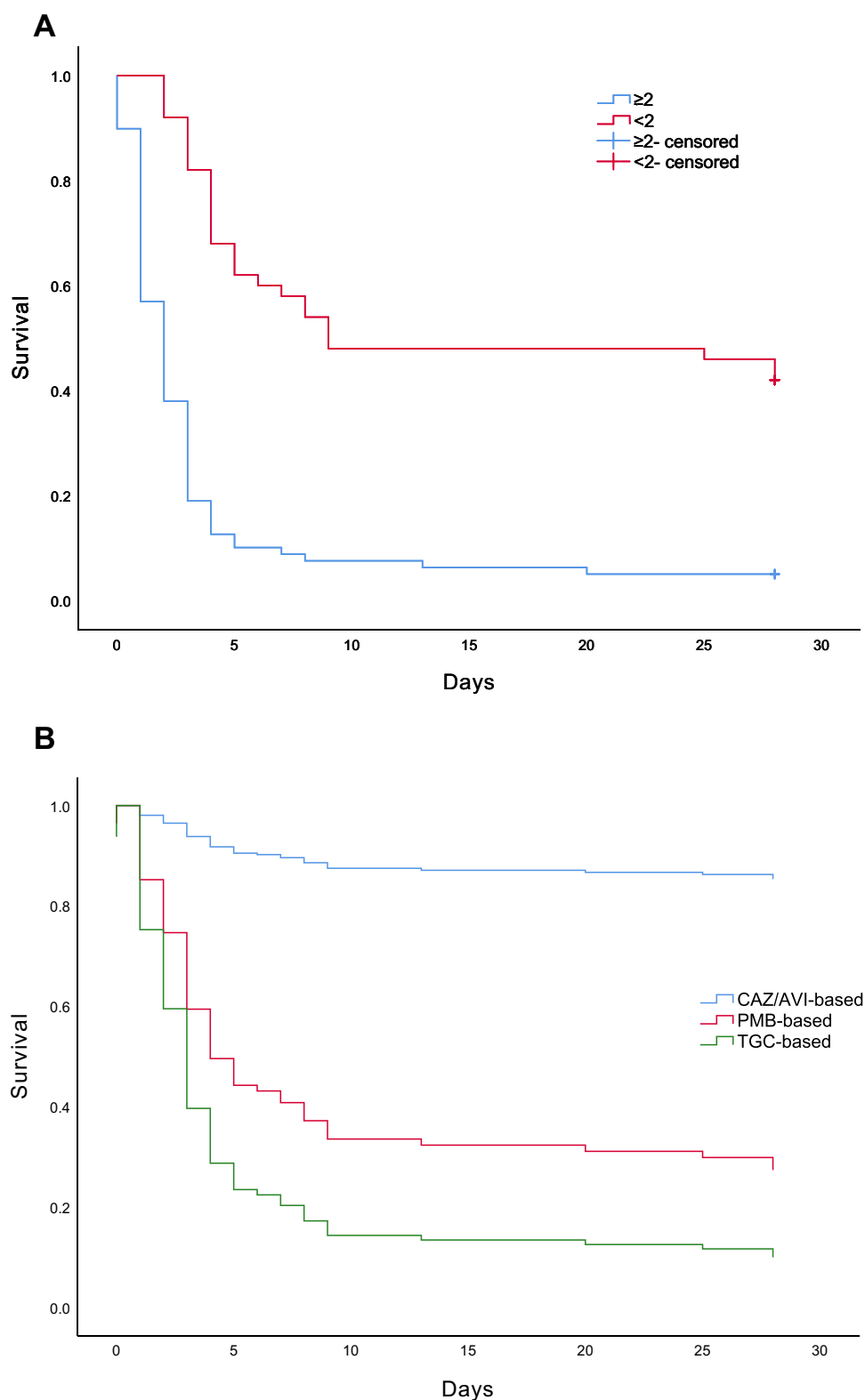
Figure 3 Kaplan-Meier survival estimates among patients with (**A**) PBS≥2 and PBS<2, (**B**) different antimicrobial regimen.

a 1-month mortality rate of 85.9%. In the present study more than 70% of patients were admitted to ICU, with a mortality rate of 92.4%, slightly higher than that reported by Liu et al,[26] which could be related to the fact that all our patients were infected with CRKP.

The PBS is a severity of acute illness index widely used in infectious disease research, with a score ≥ 4 commonly used as an indicator of critical illness and increased risk of mortality.[27–30] In recent studies higher PBS was an independent risk factor for mortality in CRE BSI, as well as in CRKP BSI, confirming the value of the PBS in such infections.[31–36] However, reports on the use of PBS in HM patients with CRKP BSI are scarce. In the current study higher PBS was independently associated with mortality. Consistent with this finding, higher PBS has been associated with increased risk of mortality in HM patients with BSI.[10] In the present study a PBS cutoff of 2 was a better predictor than the scores of 3 or 4 reported in previous studies, which could be a result of differences in patient characteristics.[10,33,37] Overall, all these findings validated the predictive significance of the severity of illness with respect to mortality in HM patients with CRKP BSI.

Neutropenia is a common adverse effect of chemotherapy or hematopoietic stem cell transplantation in HM patients. Neutropenic HM patients with intestinal mucositis, central venous catheter, and gastrointestinal bacterial colonization are at high risk of BSI due to immunosuppression. In previous studies neutropenia and HM were independent risk factors for CRKP BSI.[3,10,14,38] In addition, neutropenia is associated with the risk of mortality. Li et al[39] identified neutropenia as an independent predictor of mortality in CRE BSI patients. Moreover, in the neutropenic patients with hematological diseases, unresolved neutropenia (> 14 days) was an independent predictor of death.[16,17] Consistent with these findings, in the current study ANC < 500 at discharge was an independent risk factor for mortality in HM patients with CRKP BSI. Neutrophils are essential in the acute inflammatory response, as well as host defenses against bacterial infections. Neutropenia reduces the inflammatory response to developing infections, which promotes bacterial growth and invasion. The majority of patients in the present study had neutropenia or severe neutropenia at BSI onset, and remained unrecovered from neutropenia at discharge, resulting in a poor outcome. Therefore neutropenic patients require more attention, and new treatment strategies are urgently needed for these patients.

The most effective treatment strategy for CRKP BSI remains controversial. Polymyxins, tigecycline, and aminoglycosides were the most regularly used antibiotics, with at least one of them active in vitro. Tigecycline and polymyxin b are the two most commonly used active drugs at our center, but in the current study neither significantly affected patient outcome in univariate analysis, which was consistent with previous studies. In retrospective studies tigecycline has exhibited poor efficacy in patients with CRKP BSI, possibly due to suboptimal doses and blood concentrations.[36,38] In addition, in a systematic review of 3195 CRKP-infected patients there were no statistically significant differences in the pooled likelihood of mortality between combination-containing and combination-sparing regimens of polymyxins, tigecycline, aminoglycosides, and carbapenems.[40] In the present study CAZ/AVI-based therapy was associated with a lower risk of mortality than polymyxin b. Similar findings were obtained in the CRACKLE study, in which using CAZ/AVI was associated with lower all-cause hospital mortality and better benefit-risk outcomes than colistin.[41] Furthermore, several previous retrospective studies have supported the superiority of CAZ/AVI in the treatment of CRKP infection.[42–44] Given the modest number of patients who received CAZ in the current study, the efficacy of CAZ/AVI in patients with CRKP BSI needs to be confirmed in larger-scale trials.

The mortality rate of CRE BSI in immunocompromised hosts is surprisingly high, ranging from 45% to 100% in HM patients,[9,10,14,45,46] 25% to 82% in solid organ transplant recipients,[47–49] and 63.7% to 72.7% in solid tumor patients.[50,51] There was a high mortality rate in the present study (80.6%). The high proportion of patients with shock, acute myeloid leukemia, neutropenia, and ICU admission, and the low number of patients receiving active antibiotics such as polymyxin, aminoglycosides, and CAZ/AVI as targeted treatment may be the key reasons for the high mortality rate. The majority of patients died within 14 days. Preemptive detection of CRKP colonization, early identification of at-risk patients, and initiation of antibiotics active against CRKP isolates including new drugs such as CAZ/AVI may help to reduce mortality in patients with HM.[52,53]

The current study had several limitations. It was conducted in a hospital with a high prevalence of CRKP, and only included HM patients. The findings may not be applicable to other settings or patients. Furthermore, not all patients underwent phenotypic screening and detection. Lastly, the small number of patients in the study may have influenced the capacity of the analysis to identify risk factors and outcomes.

Conclusions

HM patients with CRKP BSI exhibited a high mortality rate. ICU admission, higher PBS, and ANC < 500 at discharge were independently associated with higher mortality. Early initiation of new agents such as CAZ/AVI may improve outcomes in these patients.

Abbreviations

ANC, absolute neutrophil count; BSI, bloodstream infection; CAZ/AVI, ceftazidime/avibactam; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; HM, hematological malignancy; *KP, Klebsiella pneumoniae*; PBS, Pitt bacteremia score; ROC, receiver operating characteristic; SD, standard deviation.

Data Sharing Statement

All data analyzed during this study are included in this published article.

Consent for Publication

Not applicable.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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