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ORIGINAL RESEARCH

Impact of Immunosuppressed Status on Prognosis of Carbapenem-Resistant Organisms Bloodstream Infections

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ABSTRACT

Introduction: The impact of immunosuppression on prognosis of carbapenem-resistant organism (CRO) bloodstream infection (BSI) remains unclear. The aim of this study was to clarify the relationship between immunosuppression and mortality of CRO-BSI and to identify the risk factors associated with mortality in immunosuppressed patients.

Methods: This retrospective study included 279 patients with CRO-BSI from January 2018 to March 2023. Clinical characteristics and outcomes were compared between the immunosuppressed and immunocompetent patients. The relationship between immunosuppression and 30-day mortality after BSI onset was assessed through logistic-regression analysis, propensity score matching (PSM) and inverse probability of treatment weighting (IPTW). Factors associated with mortality in immunosuppressed patients were analyzed using multivariable logistic regression analysis.

Results: A total of 88 immunocompetent and 191 immunosuppressed patients were included, with 30-day all-cause mortality of 58.8%. Although the 30-day mortality in immunosuppressed patients was significantly higher than in immunocompetent patients (46.6% vs. 64.4%, $P=0.007$), immunosuppression was not an independent risk factor for mortality in multivariate logistic regression analysis (odds ratio [OR] 3.53, 95% confidence interval [CI] 0.74–18.89; $P=0.123$), PSM (OR 1.38, 95% CI 0.60–3.18; $P=0.449$,) or IPTW (OR 1.40, 95% CI 0.58–3.36; $P=0.447$). For patients with CRO-BSI, regardless of immune status, appropriate antibiotic therapy was associated with decreased 30-day mortality, while Charlson comorbidity index (CCI), intensive care unit (ICU)-acquired infection and thrombocytopenia at CRO-BSI onset were associated with increased mortality.

Conclusion: Despite the high mortality rate of CRO-BSI, immunosuppression did not affect the mortality. Appropriate antibiotic therapy is

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crucial for improving the prognosis of CRO-BSI, regardless of the immune status.

Keywords: Carbapenem-resistant organisms (CROs); Immunosuppressed; Bloodstream infection (BSI); Mortality; Antimicrobial therapy

Key Summary Points

Why carry out this study?

Carbapenem-resistant organism (CRO) infections are associated with high mortality and substantial costs, and immunosuppressed patients are special populations deserving particular attention because of their vulnerability.

This study compared the characteristics of immunosuppressed patients with the immunocompetent and aimed to determine whether immunosuppression was an independent risk factor for mortality in CRO bloodstream infection (BSI).

What was learned from the study?

Although the 30-day mortality in immunosuppressed patients was significantly higher compared with immunocompetent patients, immunosuppression was not an independent risk factor in CRO bloodstream infections.

Appropriate antibiotic therapy was crucial for improving the prognosis of CRO-BSI, in both overall and immunosuppressed patients.

For patients with CRO-BSI, regardless of immune status, Charlson comorbidity index (CCI), intensive care unit (ICU)-acquired infection and thrombocytopenia at CRO-BSI onset were associated with increased mortality.

INTRODUCTION

Antimicrobial resistance is universally recognized as one of the most serious public health challenges of the twenty-first century [1]. According to the latest data, the additional cost caused by a single episode of carbapenem-resistant organism (CRO) bacteremia was $72,051 [2], significantly higher than that of other multidrug-resistant organisms. CRO infection has also been reported to be associated with increased mortality [3], exceeding 50% in cases of bloodstream infections (BSI) [4, 5]. Immunosuppressed individuals are prone to hospitalization because of their underlying diseases, and they often receive broad-spectrum antibiotic treatment, thus increasing the risk for developing multidrug-resistant bacteria [6]. Many studies have shown that immunosuppression is related to a higher incidence of infection with multidrug-resistant pathogens, including CRO [7–9].

Immunosuppressed status has been shown to have a close relationship with poor clinical prognosis [10]. Previous studies identified immunosuppression as an independent risk factor for mortality in CRO carriers and infections [3, 11]. However, few have focused on CRO-BSI in immunosuppressed patients. The relationship between immunosuppression and mortality in cases of CRO-BSI, as well as the factors affecting the mortality of immunosuppressed patients, remains unclear.

Focused on CRO-BSI, this retrospective study aimed to describe the characteristics and outcomes of immunosuppressed patients compared with the immunocompetent to identify whether the immunosuppression was an independent risk factor for mortality and to analyze the predictors for mortality in immunosuppressed patients.

METHODS

Design and Setting

This retrospective cohort study was conducted at Peking Union Medical College Hospital, a tertiary care teaching hospital with more than 2000 beds, from 1 January 2018 to 31 March 2023. Patients > 18 years old with positive blood cultures of CRO and meeting the diagnostic criteria for BSI based on Infectious Diseases Society of

America standard were screened from the electronic records in the electronic database [12]. This study only included the first positive sample of each patient. Exclusion criteria included any of the following: patients with key variables unavailable or with bacteria other than CRO or fungi cultured in blood.

We categorized the patients with CRO-BSI into immunosuppressed group and immunocompetent group to compare the clinical characteristics and outcomes. Risk factors associated with 30-day mortality were identified in the overall population and the subgroup of immunosuppressed patients.

Definition

CRO was defined as microorganisms resistant to any of the carbapenems, such as imipenem, meropenem or ertapenem, based on CLSI 2018 breakpoints criteria [13]. BSI referred to at least one detection of pathogenic microorganisms in blood culture. We determined the source of bacteremia based on the criteria of the Center for Disease Control and Prevention [14]. Immunosuppression was defined as: active hematologic malignancy, solid tumor (active or in remission for less than 3 years), autoimmune diseases with long-term (≥ 28 days) use of steroids (≥ 20 mg of prednisone per day or equivalent) or other immunosuppressant drugs, human immunodeficiency virus infection, solid-organ transplant or hematopoietic stem cell transplantation [15]. Bacteremia onset was defined as the day of positive blood culture collection. Thrombocytopenia, neutropenia, lymphopenia and hypoalbuminemia referred to peripheral blood platelet count $< 100 \times 10^9$/l, neutrophils $< 1 \times 10^9$/l, lymphocytes $< 0.5 \times 10^9$/l and albumin < 30 g/l, respectively. Mortality was defined as all-cause mortality, and length of stay indicated length of stay after BSI onset.

Appropriate empirical therapy was defined as administration of at least one antimicrobial in vitro activity against the isolates within 24 h of infection onset and for at least 48 h. Early appropriate therapy and appropriate therapy were defined as administering one or more in vitro active antimicrobials within 3 days and 7 days of infection onset and for at least 48 h, respectively. As for the antimicrobial therapies, monotherapy indicated the application of only one antibiotic which was sensitive in vitro, and combination antimicrobial therapy meant the use of at least two types of active antibiotics with combined application times > 48 h.

Data Collection

We retrospectively reviewed hospital's electronic medical record system and collected the demographic characteristics, comorbidities including Charlson comorbidity index (CCI) and information on immunosuppression [16]. We also recorded laboratory results and disease severity including Pitt bacteremia score [17], intensive care unit (ICU) admission and organ support information on the day onset. In addition, we documented microbiologic data such as infection site, source of infection, species and antibiotic susceptibility results, antimicrobial therapy and outcomes including mortality and length of stay.

Statistical Analysis

We used descriptive analysis to describe each variable. Categorical variables were shown as counts and percentages and were compared by chi-squared test or Fisher's exact test. Continuous variables were presented as the mean ± SD or median with interquartile range (IQR) and were compared by Student's *t*-test or Mann-Whitney *U* test, based on whether the variable conformed to a normal distribution.

In multivariable logistic regression model, we included variables with $P < 0.05$ in the univariable analysis. We used the variance inflation factor (VIF) to check multicollinearity among all variables and considered the model acceptable if VIF values were < 10. Hosmer-Lemeshow test was performed to evaluate the goodness of fit for the logistic regression model. The odds ratios (ORs) and the 95% confidence intervals (CIs) for variables were calculated. To avoid collinearity, we only included appropriate treatment in the multivariate analysis in terms of antimicrobial

treatment. Sensitivity analyses for 30-day mortality were performed in specific subgroups.

We performed propensity score matching (PSM) to reduce bias by adjusting for the following five variables: age, sex, ICU-acquired infection, Pitt bacteremia score and appropriate therapy. PSM was implemented with a nearest-neighbor strategy. Immunosuppressed and immunocompetent patients were paired based on the propensity scores using exact matching with a paired ratio of 1:1 and a caliper size of 0.02. During the process of matching, we lost a considerable number of patients. So, we also performed inverse probability of treatment weighting (IPTW) by using propensity score analysis to estimate the effects on mortality of immunosuppression including all eligible patients.

All statistical analyses were performed using *R* version 4.2.2. $P<0.05$ was considered statistically significant.

Ethics

The retrospective study was approved by the Ethics Committee of Peking Union Medical College Hospital (K23C3906) and was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. As this was a retrospective study, informed consent was waived.

RESULTS

Patient Characteristics

Characteristics of All Patients

A total of 334 episodes of 317 patients were screened, and finally 279 patients were included in the study, among whom 88 (31.5%) were immunocompetent and 191 (68.5%) were immunosuppressed (Fig. 1). Patients were mostly male (63.4%), with a median age of 61 (IQR 49–70) years. Hospital- and ICU-acquired infections accounted for 90.7% and 45.5%, respectively. Carbapenem-resistant *Acinetobacter baumannii* (CRAB) accounted for the highest proportion of 42.7%, followed by Carbapenem-resistant *Enterobacterales* (CRE) (36.9%). More than half of patients (57.0%) were admitted to ICU on the day of bacteremia, and 60.9% experienced septic shock. The proportions of appropriate empirical therapy and early appropriate therapy were 37.6% and 51.3%, respectively. Most patients (62.0%) received appropriate antimicrobial therapy (Table 1). Regrading the antibiotic susceptibility results of CRO species, 93.1% of all isolates were sensitive to polymyxin, and 68.2% of non-*Pseudomonas aeruginosa* species were sensitive to tigecycline. Except for CRAB, 80.4% of isolates were sensitive to ceftazidime avibactam (Supplementary Material 1).

In terms of outcomes, 3-day, 7-day and 30-day mortality were 30.8%, 40.9% and 58.8%, respectively. The median length of stay after CRO-BSI onset was 29 (IQR 16–49) days.

Characteristics Between Immunocompetent and Immunosuppressed Patients

Compared with the immunocompetent patients, the immunosuppressed patients had higher CCI scores (6 vs. 4, $P=0.001$) and higher proportions of ICU-acquired infections (49.2% vs. 37.5%, $P=0.090$). There was no significant difference in types of bacteria, source of BSI or severity of disease between the two groups. As for laboratory results, patients in the immunosuppressed group had lower lymphocyte (0.35 vs. 0.54×10^9/l, $P<0.001$) and platelet (65 vs. 120×10^9/l, $P<0.001$) values compared with the immunocompetent group.

There was no significant difference in 7-day mortality (33.0% vs. 44.5%, $P=0.091$) and length of stay (30 vs. 29 days, $P=0.524$) between immunocompetent and immunosuppressed populations, but the 30-day mortality rate was significantly higher in the immunosuppressed group (46.6% vs. 64.4%, $P=0.007$). According to the bacterial species, the 30-day mortality rate of CRAB BSI was the highest, reaching 70.6% (84/119), which was significantly higher in the immunosuppressed group (79.1% vs. 48.5%, $P=0.001$). The proportion of patients receiving appropriate therapy was similar between the two groups (61.4% vs. 62.3%, $P=0.986$). There was no significant difference in 30-day mortality between the immunosuppressed group and immunocompetent group in patients receiving

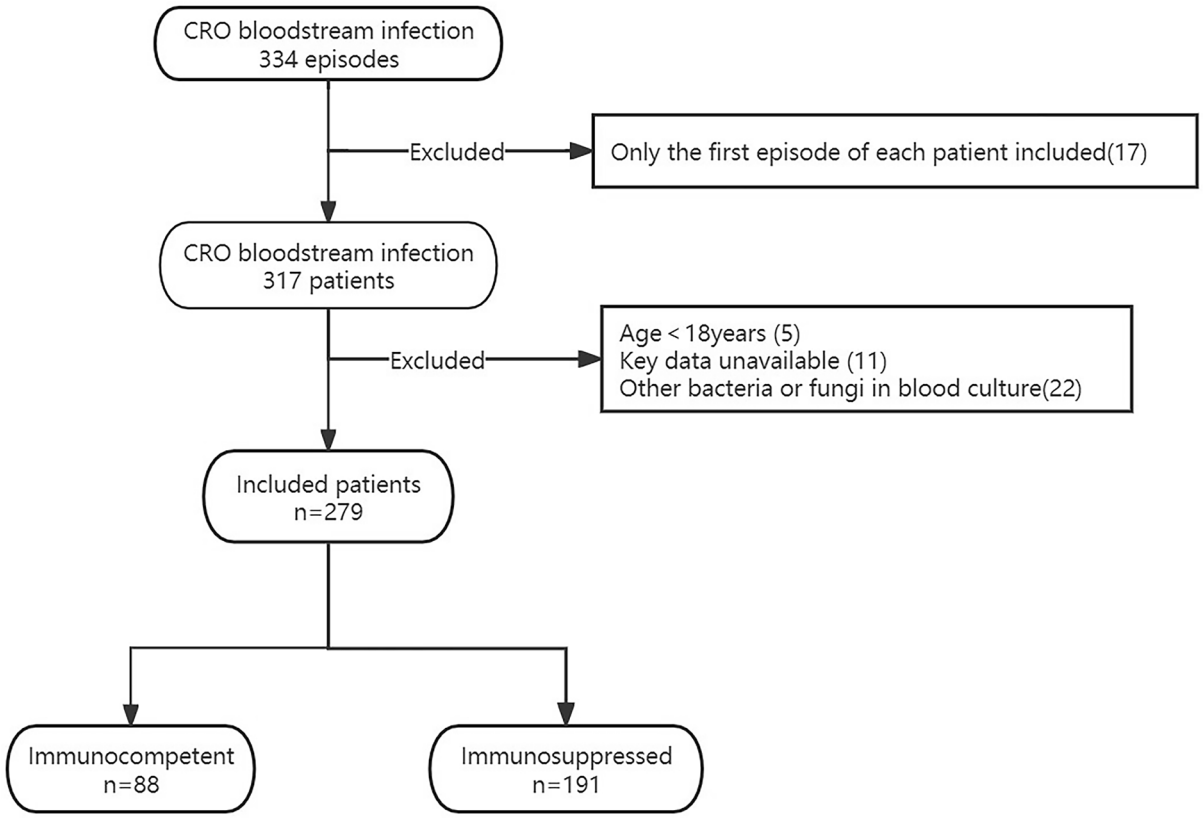

Fig. 1 Flowchart of participants through this study. *CRO* Carbapenem-resistant organisms

either monotherapy (52.1% vs. 38.2%, P=0.183) or combination therapy (54.3% vs. 30.0%, P=0.069).

Immunosuppression Was Not an Independent Risk Factor for 30-Day Mortality

Univariate Analysis and Multivariate Logistic Regression Analysis

A comparison of the survival and non-survival group is shown in Table 1. The proportion of immunosuppressed population in the non-survival group was 75.0% (123/164), while it was only 59.1% (68/115) in the survival group (P = 0.007). The proportion of ICU-acquired infections in the non-survival group was statistically higher (55.5% vs. 31.3%, P < 0.001). For laboratory results, patients in the non-survival group had a higher proportion of lymphopenia (62.8% vs. 46.1%, P = 0.008) and thrombocytopenia (72.6% vs. 40.0%, P < 0.001) compared with the survival group. There was no significant difference in the proportion of appropriate empirical therapy between the survival and non-survival group, but the proportion of early appropriate therapy and appropriate therapy in the non-survival group was significantly lower.

There was no significant difference in 30-day mortality between monotherapy and combination therapy among patients receiving appropriate therapy (47.7% vs. 47.0%, P = 0.929). Active antibiotic treatments for patients with appropriate antimicrobial therapy are shown in Table 2.

Multivariable logistic regression showed that the independent risk factors for 30-day mortality of CRO-BSI included CCI (OR 1.23, 95% CI 1.06–1.44), ICU-acquired infection (OR 2.59, 95% CI 1.12–6.13) and thrombocytopenia (OR 4.09, 95% CI 1.85–9.34), while appropriate

Table 1 Comparison of clinical characteristics between survivors and non-survivors in 30 days with CRO bloodstream infections

	Total (*n* = 279)	**Survivors (*n* = 115)**	**Non-survivors (*n* = 164)**	***P***
Age (years)	61 (49, 70)	59 (44, 70)	62 (52, 70)	0.098
Male	177 (63.4)	79 (68.7)	98 (59.8)	0.162
Comorbidities				
CCI (points)	5 (3, 7)	4 (3, 6)	6 (4, 8)	< 0.001
Diabetes mellitus	76 (27.2)	27 (23.5)	49 (29.9)	0.296
COPD	12 (4.3)	3 (2.6)	9 (5.5)	0.386
Congestive heart failure	15 (5.4)	4 (3.5)	11 (6.7)	0.364
Liver cirrhosis	5 (1.8)	2 (1.7)	3 (1.8)	1.00
CKD with regular dialysis	10 (3.6)	3 (2.6)	7 (4.3)	0.684
Immunosuppression	191 (68.5)	68 (59.1)	123 (75.0)	0.007
Types of immunosuppression				0.001
Autoimmune disease	43 (15.4)	9 (13.2)	34 (27.6)	
Solid tumor	47 (16.8)	27 (39.7)	20 (16.3)	
Hematologic malignancy	58 (20.8)	15 (22.1)	43 (35.0)	
Others	43 (15.4)	17 (25.0)	26 (21.1)	
ICU-acquired infection	127 (45.5)	36 (31.3)	91 (55.5)	< 0.001
Hospital-acquired infection	253 (90.7)	100 (87.0)	153 (93.3)	0.113
Microbiologic data				
Blood culture time to positivity (h)	13 (10, 16)	14 (11, 18)	12 (10, 15)	0.001
Types of bacteria				< 0.001
Acinetobacter baumannii	119 (42.7)	35 (30.4)	84 (51.2)	
Enterobacterales [a]	103 (36.9)	44 (38.3)	59 (36.0)	
Pseudomonas aeruginosa	33 (11.8)	20 (17.4)	13 (7.9)	
Others[b]	24 (8.6)	16 (13.9)	8 (4.9)	
Source of infection				< 0.001
Pulmonary	150 (53.8)	43 (37.4)	107 (65.2)	
Intra-abdominal	70 (25.1)	42 (36.5)	28 (17.1)	
Catheter-related	8 (2.9)	3 (2.6)	5 (3.0)	
Others	28 (10.0)	15 (13.0)	13 (7.9)	
Unknown	23 (8.2)	12 (10.4)	11 (6.7)	

Table 1 continued

	Total ($n = 279$)	Survivors ($n = 115$)	Non-survivors ($n = 164$)	*P*
Disease severity on the day of bacteremia				
ICU admission	159 (57.0)	49 (42.6)	110 (67.1)	< 0.001
Pitt bacteremia score (points)	4 (1.5, 6)	2 (1, 4)	4.5 (4, 7)	< 0.001
Septic shock	170 (60.9)	43 (37.4)	127 (77.4)	< 0.001
Invasive mechanical ventilation	167 (59.9)	47 (40.9)	120 (73.2)	< 0.001
CRRT	66 (23.7)	20 (17.4)	46 (28.0)	0.055
Antimicrobial treatments				
Appropriate empirical therapy[c]	105 (37.6)	52 (45.2)	53 (32.3)	0.039
Early appropriate therapy[d]	143 (51.3)	71 (61.7)	72 (43.9)	0.005
Appropriate therapy[e]	173 (62.0)	91 (79.1)	82 (50.0)	< 0.001
Monotherapy	107 (38.4)	56 (48.7)	51 (31.1)	0.929
Combination therapy	66 (23.7)	35 (30.4)	31 (18.9)	0.929

Data are presented as *n* (%) or median (IQR). *CCI* Charlson comorbidity index, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *CRO* carbapenem-resistant organisms, *CRRT* continuous renal replacement therapy, *ICU* intensive care unit

[a]Including 76 *Klebsiella pneumoniae*, 14 *Escherichia coli*, 6 *Enterobacter cloacae*, 4 *Enterobacter aerogen*, 1 *Citrobacter braakii*, 1 *Enterobacter hormaechei* and 1 *Enterobacter asburiae*

[b]Including 10 *Aeromonas*, 6 *Burkholederia cenocepacia*, 3 *Moraxella osloensis*, 2 *Ralstonia mannitolilytica*, 1 *Brevundimonas*, 1 *Flavobacterium indologenes* and 1 *Vibrio cincinnatiensis*

[c]Appropriate empirical therapy was defined as administering in vitro active antimicrobials against the isolates within 24 h of infection onset and for at least 48 h

[d]Early appropriate therapy indicated administering one or more in vitro active antimicrobials within 72 h of infection onset and for at least 48 h

[e]Appropriate therapy was defined as administering one or more in vitro active antimicrobials within 7 days of infection onset and for at least 48 h

therapy (OR 0.27, 95% CI 0.12–0.62) was associated with decreased mortality (Table 3). Immunosuppression was not an independent risk factor associated with 30-day mortality of CRO-BSI (OR 1.14, 95% CI 0.48–2.66).

Sensitivity Analysis

We conducted two additional sensitivity analyses to explore the impact of immunosuppression on the mortality of CRO-BSI and obtained consistent results. Immunosuppression was not an independent risk factor for 30-day mortality in either sensitivity analysis: one excluding patients with solid tumors featuring the lowest mortality rate (OR 2.21, 95% CI 0.84–5.91; *P* 0.109) and the other considering only patients with hematologic malignancies as the immunosuppressed population (OR 3.53, 95% CI 0.74–18.89; *P* 0.123).

Propensity Score Matching and Inverse Probability of Treatment Weighting

The PSM resulted in 58 immunosuppressed patients matched to 58 immunocompetent

Table 2 Active antibiotic treatments for patients with appropriate antimicrobial therapy[a]

	Total ($n = 173$)	Survivors ($n = 91$)	Non-survivors ($n = 82$)	*P*
Polymyxin B-based therapy	54 (31.2)	25 (27.5)	29 (35.4)	0.263
Polymyxin B	18 (10.4)	8 (8.8)	10 (12.2)	
Polymyxin B + tigecycline/minocycline	31 (17.9)	14 (15.4)	17 (20.7)	
Polymyxin B + CAZ-AVI	2 (1.2)	2 (2.2)	0	
Polymyxin B + other antibiotics	3 (1.7)	1 (1.1)	2 (2.4)	
CAZ-AVI-based therapy	16 (9.2)	7 (7.7)	9 (11.0)	0.457
CAZ-AVI	8 (4.6)	3 (3.3)	5 (6.1)	
CAZ-AVI + tigecycline/minocycline	6 (3.5)	2 (2.2)	4 (4.9)	
Tigecycline/minocycline-based therapy	96 (55.5)	44 (48.4)	52 (63.4)	0.047
Tigecycline/minocycline	46 (26.6)	20 (22.0)	26 (31.7)	
Tigecycline/minocycline + amikacin	7 (4.0)	6 (6.6)	1 (1.2)	
Tigecycline/minocycline + β-lactams/β-lactamase inhibitor[b]	4 (2.3)	1 (1.1)	3 (3.7)	
Tigecycline/minocycline + other antibiotics	2 (1.2)	1 (1.1)	1 (1.2)	
Other antibiotic-based therapy	46 (26.6)	33 (36.3)	13 (15.9)	0.002
Carbapenem	13 (7.5)	12 (13.2)	1 (1.2)	
Other β-lactams/β-lactamase inhibitor	13 (7.5)	7 (7.7)	6 (7.3)	
Amikacin	6 (3.5)	3 (3.3)	3 (3.7)	
Amikacin-based combination therapy	7 (4.0)	5 (5.5)	2 (2.4)	
Other monotherapy	3 (1.7)	3 (3.3)	0	
Other combination therapy	4 (2.3)	3 (3.3)	1 (1.2)	

Data are presented as *n* (%). CAZ-AVI = ceftazidime-avibactam

[a]Appropriate therapy was defined as administering one or more in vitro active antimicrobials within 7 days of infection onset and for at least 48 h

[b]β-Lactams/β-lactamase inhibitors except CAZ-AVI

patients. More participants were immunosuppressed; thus, 133 immunosuppressed patients were unmatched in contrast to 30 immunocompetent patients. Then, IPTW assessed from patients with all covariate data was included in the propensity analysis ($n = 279$). The results showed that immunosuppression was not an independent risk factor associated with 30-day mortality in CRO-BSI in either the PSM cohort (OR 1.38, 95% CI 0.60–3.18; *P* 0.449) or IPTW cohort (OR 1.40, 95% CI 0.58–3.36; *P* 0.447).

Risk Factors for 30-Day Mortality in Immunosuppressed Patients

In immunosuppressed patients, the 30-day mortality was 64.4% (123/164). The CCI (6 vs.

Table 3 Multivariate logistic regression analysis for risk factors of 30-day mortality in patients with CRO bloodstream infections

Risk factor[a]	*OR (95% CI)*	*P*
CCI	1.23 (1.06, 1.44)	0.009
ICU-acquired infection	2.59 (1.12, 6.13)	0.027
Thrombocytopenia[b]	4.09 (1.85, 9.34)	0.001
Appropriate therapy[c]	0.27 (0.12, 0.62)	0.002

CCI Charlson comorbidity index, *CI* confidence interval, *CRO* carbapenem-resistant organisms, *ICU* intensive care unit, *OR* odds ratio, *VIF* variance inflation factor

[a]Variables in this model included CCI, ICU-acquired infection, immunosuppression, blood culture time to positivity (hours), types of bacteria, source of infection, lymphopenia, thrombocytopenia, Pitt bacteremia score, septic shock, invasive mechanical ventilation and appropriate therapy. The *P* value for the Hosmer-Lemeshow test was 0.444, and the VIF values of all variables in this logistic regression model were < 5

[b]Thrombocytopenia refers to peripheral blood platelet count < 100×10^9/l

[c]Appropriate therapy was defined as administering one or more in vitro active antimicrobials within 7 days of infection onset and for at least 48 h

5, $P<0.001$) and Pitt bacteremia score (4 vs. 1, $P<0.001$) were statistically higher, and the blood culture time to positivity was significantly lower in the non-survival group (12 vs. 13.5 h, $P=0.009$). More patients in the survival group received appropriate therapy (82.4% vs. 51.2%, $P<0.001$) (Supplementary Material 2).

Results of multivariable logistic regression analysis showed that the independent risk factors for mortality in CRO-BSI included CCI (OR 1.45, 95% CI 1.16–1.88), glucocorticoid use (OR 15.78, 95% CI 2.32–152.12), ICU-acquired infection (OR 7.15, 95% CI 1.96–31.15), thrombocytopenia (OR 4.33, 95% CI 1.18–17.32) and Pitt bacteremia score (OR 1.51, 95% CI 1.16–2.09), while appropriate therapy (OR 0.10, 95% CI 0.02–0.42) was associated with decreased mortality (Table 4).

No specific type of immunosuppression was an independent risk factor for 30-day mortality among immunosuppressed patients.

Table 4 Multivariate logistic regression analysis for risk factors of 30-day mortality in immunosuppressed patients with CRO bloodstream infections

Risk factor[a]	*OR (95% CI)*	*P*
CCI	1.45 (1.16, 1.88)	0.002
Glucocorticoid use	15.78 (2.32, 152.12)	0.008
ICU-acquired infection	7.15 (1.96, 31.15)	0.005
Thrombocytopenia[b]	4.33 (1.18, 17.32)	0.030
Pitt bacteremia score	1.51 (1.16, 2.09)	0.005
Appropriate therapy[c]	0.10 (0.02, 0.42)	0.003

CCI Charlson comorbidity index, *CI* confidence interval, *CRO* carbapenem-resistant organisms, *ICU* intensive care unit, *OR* odds ratio, *VIF* variance inflation factor

[a]Variables in this model for immunosuppressed patients included CCI, glucocorticoid use, ICU-acquired infection, blood culture time to positivity (hours), types of immunosuppression, types of bacteria, source of infection, lymphopenia, thrombocytopenia and appropriate therapy. The *P* value for the Hosmer-Lemeshow test was 0.477, and the VIF values of all variables were < 5

[b]Thrombocytopenia referred to peripheral blood platelet count < 100×10^9/l

[c]Appropriate therapy was defined as administering one or more in vitro active antimicrobials within 7 days of infection onset and for at least 48 h

Among patients receiving appropriate antimicrobial treatment, 30-day mortality between monotherapy and combination therapy did not show a significant difference (52.1% vs. 54.3%, $P=0.807$).

DISCUSSION

Focused on CRO-BSI, this study showed that there was no significant difference in the types of bacteria, source of bacteremia, severity of the disease and proportion of appropriate therapy between immunosuppressed and immunocompetent patients. Although the 30-day mortality was significantly higher in the immunosuppressed patients than immunocompetent ones, immunosuppression was not an independent

risk factor associated with 30-day mortality. The factors associated with prognosis in immunosuppressed patients included CCI, glucocorticoid use, ICU-acquired infection, thrombocytopenia, Pitt bacteremia score and appropriate therapy.

To date, many studies have been concerned with different microbial infections in immunosuppressed patients. However, the populations of those studies were patients with several certain types of immunosuppression, or the researchers focused on specific microbial infections in diverse types of immunosuppression [18–21]. Studies on CRO-BSI in the overall immunosuppressed patients and their comparison with immunocompetent populations are still rare. Compared with immunocompetent patients, this study described the clinical characteristics of immunosuppressed patients with CRO-BSI and identified that immunosuppression was not an independent predictor of mortality.

There is no consistent conclusion on whether immunosuppression is associated with death in sepsis-related studies [22, 23]. In a large study of extremely drug-resistant organism infections in ICU patients, immunosuppression was identified as an independent risk factor associated with 7-, 15- and 30-day mortality [9]. Rivera-Villegas and colleagues also suggested immunosuppression as an independent risk factor for mortality in CRO infections [3]. However, neither of these studies limited the site of infection, with BSI accounting for only 10–35%. However, BSI presented the highest severity and mortality rate among various infections, which requires special attention and research. In this study focused on CRO-BSI, we used several methods (such as multivariate analysis, PSM and IPTW) and conducted sensitivity analysis considering the lowest mortality in patients with solid tumors and hematology malignancy as a classic immunosuppressed population to control bias and adjust confounding factors and then reached the same conclusion. Our results showed that immunosuppression was not an independent risk factor for death in CRO-BSI.

A number of studies have shown that inappropriate antibiotics are associated with increased mortality in CRO-BSI [3, 24, 25]. Previous studies found that the patients who received inappropriate antibiotic therapy demonstrated close to a two- to threefold higher rate of death [26, 27]. Appropriate antibiotic treatment would be more crucial in immunosuppressed populations. Micozzi and colleagues found that 80% of fatal CRO-BSI in hematologic patients occurred on inappropriate therapy, and initial adequate antibiotic therapy was the single independent protective factor against death [28]. This study also demonstrated that appropriate antimicrobial therapy was associated with decreased mortality in CRO-BSI patients regardless of overall or immunosuppressed patients.

Regarding antimicrobial-resistant bacterial infections, clinicians will be most interested in whether combination therapy can improve prognosis. There is currently no consensus based on existing research results. Kim and colleagues suggested that combination therapy had no significant effect on mortality compared with monotherapy [29]. However, several studies suggested combination therapy for CRO infection [25, 30, 31], and combination antibiotic therapy showed a lower mortality rate independently compared with monotherapy, whether empirical or definitive [32]. As for immunosuppressed patients, previous study found that appropriate combination therapy led to decreased mortality [29]. Our study showed that, among patients receiving monotherapy, there was no significant difference in 30-day mortality between immunosuppressed and immunocompetent patients, neither for combination therapy. Furthermore, among patients receiving appropriate antimicrobial treatments, combination antimicrobial therapy showed no significant effect on 30-day mortality compared with monotherapy, regardless of overall population or immunosuppressed patients.

Different types of immunosuppression may have an effect on different mortality. Tolsma et al. [33] included diverse immunosuppressed patients diagnosed with sepsis and found that AIDS, nonneutropenic solid tumor, nonneutropenic hematologic malignancies and all-cause neutropenia were independently associated with death, while inflammatory or immune disorder, solid organ transplant and primary immunodeficiency were not. Another study showed that only patients with solid tumors exhibited higher mortality rates compared to

other immunosuppressed patients in septic shock [34]. However, in this study focused on CRO-BSI, we also included various immunosuppressed patients, and no specific type of immunosuppression was an independent risk factor for 30-day mortality in CRO-BSI.

Our study had some limitations. First, our study was a single-center study, which may have affected its generalizability. However, we included multiple types of immunosuppressed populations without any being predominant. In addition, we only used common types of disease to classify the immunosuppressed populations and used lymphocyte count to reflect the degree of immunosuppression rather than more precise immune markers because of the retrospective nature of this study.

CONCLUSION

Focused on CRO-BSI, this study revealed that there was no significant difference in types of bacteria, source of bacteremia, severity of the disease and proportion of appropriate therapy in immunosuppressed patients compared to immunocompetent population. Though the 30-day mortality of CRO-BSI was significantly higher in the immunosuppressed patients than immunocompetent ones, immunosuppression was not an independent risk factor for mortality. For patients with CRO-BSI, regardless of immune status, CCI, ICU-acquired infection and thrombocytopenia at CRO-BSI onset were associated with increased mortality, while appropriate antibiotic therapy was associated with decreased 30-day mortality. Besides, among patients receiving appropriate antimicrobial therapy, there was no significance difference in 30-day mortality between monotherapy and combination antimicrobial therapy in both the overall population and immunosuppressed patients.

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Author Contributions. Bin Du, Jin-Min Peng and Yuan-Yuan Li designed the study. Yuan-Yuan Li, Yan-Chen, Yuan-Yuan Li and Shan Li were in charge of data collection. Ran An, Xiao-Yun Hu, Wei Jiang, Chun-Yao Wang, Run Dong and Qi-Wen Yang interpreted the clinical data. Yuan-Yuan Li and Yan-Chen performed the statistical analyses. Jin-Min Peng, Bin Du and Li Weng directed the writing and revised the first version of the manuscript. The first draft of the manuscript was written by Yuan-Yuan Li, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Yuan-Yuan Li, Yan Chen, Shan Li, Yuan-Yuan Li, Ran An, Xiao-Yun Hu, Wei Jiang, Chun-Yao Wang, Run Dong, Qi-Wen Yang, Li Weng, Jin-Min Peng and Bin Du declare that they have no conflicts of interest regarding this work.

Ethical Approval. This study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments and was approved by the Ethics Committee of Peking Union Medical College Hospital (no. K23C3906).

Informed consent was waived because this is a retrospective study.

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