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ORIGINAL RESEARCH

A Visualized Mortality Prediction Score Model in Hematological Malignancies Patients with Carbapenem-Resistant Organisms Bloodstream Infection

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Background: Bloodstream infection (BSI) due to carbapenem-resistant organisms (CROs) has emerged as a worldwide problem associated with high mortality. This study aimed to evaluate the risk factors associated with mortality in HM patients with CROs BSI and to establish a scoring model for early mortality prediction.

Methods: We conducted a retrospective cohort study at our hematological department from January 2018 to December 2021, including all HM patients with CROs BSI. The outcome measured was death within 30-day of BSI onset. Survivor and non-survivor subgroups were compared to identify predictors of mortality. Univariate and multivariate Cox regression analyses were used to identify prognostic risk factors and develop a nomogram.

Results: In total, 150 HM patients were included in the study showing an overall 30-day mortality rate of 56%. *Klebsiella pneumonia* was the dominant episode. Cox regression analysis showed that pre-infection length of stay was >14 days (score 41), Pitt score >4 (score 100), mucositis (score 41), CAR (The ratio of C-reactive protein to albumin) >8.8 (score 57), early definitive therapy (score 44), and long-duration (score 78) were positive independent risk predictors associated with 30-day mortality, all of which were selected into the nomogram. Furthermore, all patients were divided into the high-risk group (≥160 points) or the low-risk group based on the prediction score model. The mortality of the high-risk group was 8 times more than the low-risk group. Kaplan-Meier analysis showed that empirical polymyxin B therapy was associated with a lower 30-day mortality rate, which was identified as a good prognostic factor in the high-risk group. In comparison, empirical carbapenems and tigecycline were poor prognostic factors in a low-risk group.

Conclusion: Our score model can accurately predict 30-day mortality in HM patients with CROs BSI. Early administration of CROs-targeted therapy in the high-risk group is strongly recommended to decrease mortality.

Keywords: carbapenem-resistant organisms, predictive model, nomogram, hematological malignancies, bloodstream infection

Introduction

In recent years, carbapenem-resistant organisms (CROs) infections have become a major global public health problem which is associated with increased mortality up to 50%, prolonged the hospital stay and additional medical costs.[1–6] The hematological malignancies (HM) patients and the recipients of hematopoietic stem cell transplant (HSCT) might be particularly vulnerable to CROs infection. Because of intensive myelosuppressive or immunosuppressive-induced gastrointestinal mucositis, prolonged

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hospitalizations and neutropenia, and frequent use of broad-spectrum antibacterial agents.[7] Especially, mucositis induced by chemotherapy promotes bacteria to penetrate through a mucosal barrier into the bloodstream to increase the incidence of CROs bloodstream infection (BSI).[5,8] The course of CROs BSI in HM patients is usually abrupt and rapidly develops into shock, disseminated intravascular coagulation (DIC), and multiple organ dysfunction.[9] High in-hospital mortality rate (65–100%) for CROs has been found in these highly immunocompromised population.[7,10–13] Accurate identification of predictors associated with mortality in BSI patients is critical for early clinical interventions and, thus, improving clinical outcomes.

In this study, we collected the clinical data of 150 HM patients with CROs BSI and compared the clinical characteristics, laboratory tests, and treatment to explore the risk factors for the prognosis. The objective of this study is to established a visualized mortality prediction score model to produce forecasts of mortality in HM patients with CROs BSI and provide a reference for early clinical diagnosis and treatment.

Subjects and Methods

Study Design and Subjects

This study retrospectively reviewed the clinical and microbiological data of inpatient HM patients with CROs BSI from January 2018 to December 2021 in Wuhan Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. We recorded the demographic and clinical variables of patients diagnosed with CROs BSI. Exclusion criteria were age < 18 years and patients with polymicrobial bacteria including methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE) infections, or invasive fungal disease. Recurrent infections were excluded, and only the first CROs BSI episode per patient was included in our analysis. A retrospective cohort study design was employed. The outcome measure was death within 30 days of the first positive blood culture. Survivor and non-survivor subgroups were compared to identify the predictors of mortality. A Cox proportional hazard model was used to analyze the survival data and determine significant risk factors to develop a prediction model. This model was used to create a nomogram for predicting the survival rate of patients for up to 30 days.

The study was approved by the research ethics committee of Union Hospital. Written informed consent was waived due to the anonymized retrospective nature of the analysis.

Data Collection

Demographic and clinical data include gender, age, primary disease status, pre-infection length of stay, HSCT, hypoalbuminemia, mucositis, laboratory findings, empirical antimicrobial use in the 30 days before infection, Pitt bacteremia score at BSI onset, previous history of CROs colonization within 30 days before BSI onset, invasive devices (mechanical ventilation, sputum suction, bladder catheterization) and antimicrobial treatment and outcome. The primary outcome was all-cause 30-day mortality. For statistical purposes, patients discharged as terminally ill (life expectancy <1 week, as estimated by the attending physician) were considered to have died at the time of hospital discharge.[14]

Bacterial Identification and Drug Sensitivity Test

The isolation and identification of pathogenic bacteria were carried out strictly following the relevant provisions of the National Clinical Laboratory Procedures. Vitek® 2 automated system (France Biomerieux) and matrix-assisted laser-desorption ionization time-of-flight mass spectrometry (Bruker Daltonics Inc., Billerica, Massachusetts) were used to bacterial identification and drug sensitivity tests.[15] The identification of drug resistance both by disk diffusion method (K-B method) and broth microdilution (BMD), BMD was used to determine MICs. For tigecycline and colistin, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint was used, the rest of antibiotics were interpreted according to the standard of the CLSI document.[16,17]

Related Definition

The CROs BSI was defined as a BSI documented by blood culture positivity (at least 1 specimen) for a CROs strain and clinical signs of systemic inflammatory response syndrome.[18]

Previous CROs colonization was defined as patients with CROs isolated from the rectal swab without symptoms and signs of invasive infection.

Neutropenia was defined as neutrophil cells <500 per microlitre of blood.

The ratio of C-reactive protein to albumin (CAR) was calculated using C-reactive protein (CRP) and albumin concentrations.

Antimicrobial exposure was defined as the use of antibiotics for more than 72 hours before CROs BSI.

Appropriate empirical therapy was defined as administering in vitro active antimicrobials against the isolates within 24 h of infection onset and at least 48 h.[19]

Definitive therapy referred to antimicrobial therapy after the susceptibility testing results were available, defined as appropriate therapy if at least one in vitro active antimicrobial was administered within 7 days of infection and for at least 48 h, or as inappropriate therapy if these criteria were not met.[19] Early definitive therapy was considered to administer an in vitro active antimicrobial within 72 h of infection onset.

Long-duration treatment was defined as receiving antimicrobial treatment ≥10 days.

Statistical Analysis

Original data were expressed as number and percentage (n [%]), mean ± standard deviation, and median (interquartile range) due to the different shapes of continuous data collected. We compared patients' demographic and clinical variables using the chi-square test and Fisher's exact test. All laboratory indexes were converted to categorical variables according to the reference range, or the cut-off values of the above-combined indexes were identified by X-tile software. We used Kaplan–Meier curves for subgroup analysis. A Cox proportional hazard model was used to determine risk factors for mortality. The variables with $P < 0.05$ in univariate analysis were incorporated into the Cox proportional hazard model for multivariate analysis. We attempted to establish a parsimonious prediction model based on risk factors at the onset.

The candidate risk factors were included in the Cox proportional hazard model. The models were checked by a variance inflation factor (VIF) and C-index. All analyses were performed by R statistical software 4.0.1. A two-sided $P < 0.05$ indicated that the difference was statistically significant

Study Results

Microbiological Characteristics

The flow procedure is shown in Figure 1A. 453 HM patients with positive Gram-negative BSI were first included in this study, and 303 patients were classified into the *Carbapenem-sensitive organisms* (CSOs) BSI group and finally excluded from our study. The data from the remaining 150 patients were further analyzed, and the top three predominant pathogens of CROs BSI were *Klebsiella pneumoniae* (48.0%), and *Pseudomonas aeruginosa* (15.3%), *Escherichia coli* (14.0%), and *Acinetobacter baumannii* (14.0%). The other strains were *Enterobacter cloacae* (4.0%), *Klebsiella oxytoca* (2.3%), *Salmonella Dublin* (0.6%), *Enterobacter polymeris* (0.6%), *Aeromonas hydrophila* (0.6%) and *Aeromonas sobria* (0.6%) (Figure 1B).

Baseline and Treatment Characteristics

150 patients with BSI caused by CROs were observed during the study period. As shown in Table 1, 59.3% (n=89) of the patients were males. In terms of disease distribution, acute myelocytic leukemia (AML) was the predominant primary disease (n=62, 41.3%). Bacterial classification included CRE (n=106, 70.7%), CARA (n=23, 15.3%), and CRAB (n=21, 14.0%). At the time of diagnosis, 30% of the patients presented with septic shock. Additionally, patients who died had worse clinical and laboratory indicators (higher temperature/CRP/procalcitonin (PCT) and lower neutrophil/hemoglobin/platelet count), while patients who survived had a longer length of antibiotic therapy ($p<0.05$). A total of 39.3% (n=59) of the patients accepted appropriate empirical therapy, and 54.7% (n=82) of the patients accepted early definitive therapy.

Risk Factors of Mortality

The univariate analysis results indicated the variables associated with mortality as follows: age, pre-infection length of stay >14 days, primary disease status, Pitt score >4, mucositis, laboratory findings including CAR >8.8, PCT >11.74 ug/L, HB <82 G/L,

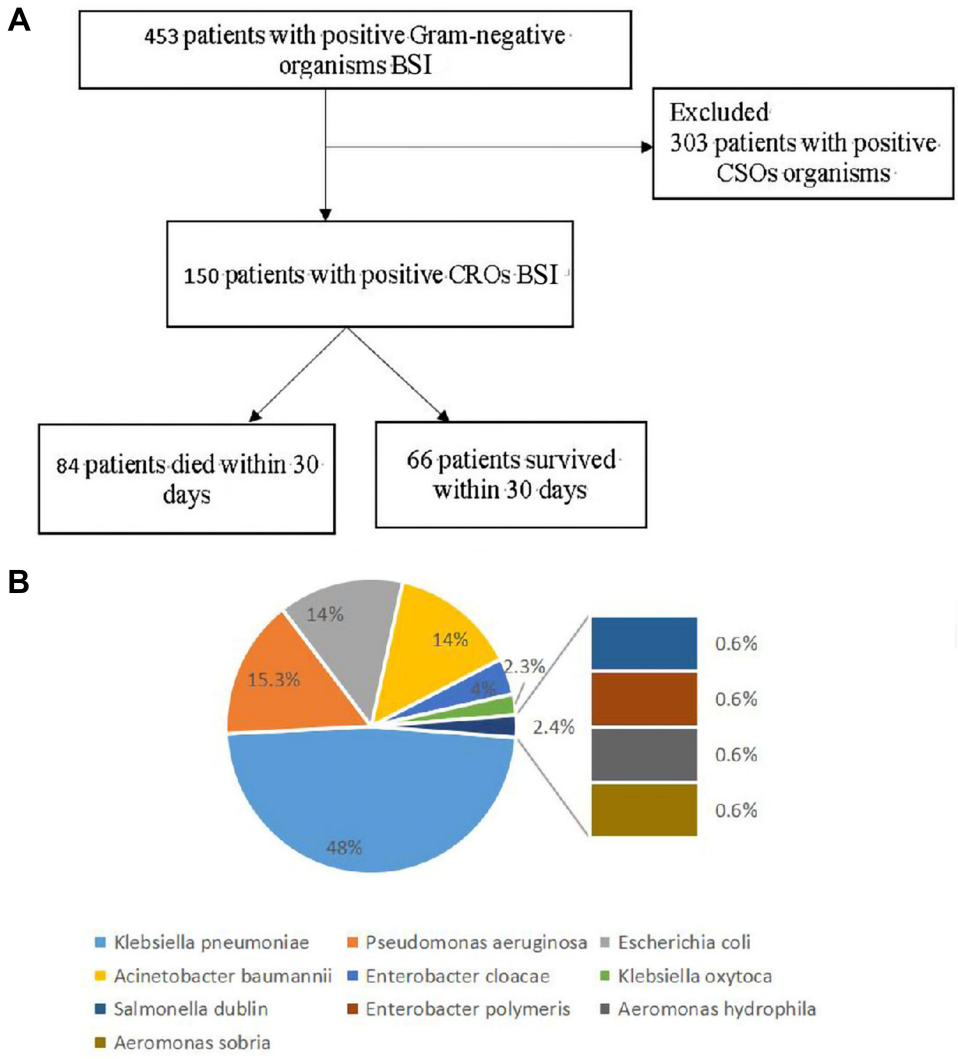

Figure 1 (**A**) Screening algorithm of the HM patients with Carbapenem-resistant Gram-negative organisms Bloodstream infection. In all, 453 hospitalized patients had positive Gram-negative organisms BSI, and a total of 150 eligible, unduplicated cases were recruited into this study. (**B**) Distribution of Carbapenem-resistant Gram-negative bacteria BIS.

PLT <28 G/L, hypoalbuminemia, appropriate empirical therapy, early definitive therapy, long-duration treatment and invasive procedures (sputum suction, bladder catheterization) ($p<0.05$).

The statistically significant risk factors from the univariate analysis above were chosen for further multivariate analysis. Early definitive therapy (HR=0.52; 95% CI, 0.32–0.86), long-duration treatment (HR=0.37; 95% CI, 0.21–0.64) were independent favorable prognostic factors for 30-day mortality, while pre-infection length of stay >14 days (HR=1.80; 95% CI, 1.02–3.17), Pitt score >4 (HR=3.32; 95% CI, 1.02–3.17), mucositis (HR=2.11; 95% CI, 1.20–3.70) and CAR >8.8 (HR=1.80; 95% CI,1.02–3.17) were independent negative prognostic factors for 30-day mortality (Table 2).

Establishment of a Risk Prediction Score Model of 30-Day Mortality in 150 HM Patients with CROs BSI

In addition, we also identified potential predictors with the highest coefficients based on permutation importance using the random forest algorithm. It was found that pre-infection length of stay >14 days (variable importance (VI), 2.12), Pitt score >4 (the most important VI, 16.05), mucositis (VI, 2.56), CAR>8.8 (VI, 3.60), early definitive therapy (VI, 4.39), and long-duration treatment (VI, 11.47) were independent predictors for 30-day mortality (Table 2). Then, the above six

Table 1 Basic Clinical Characteristics of HM Patients with CROs BSI

Metrics	Total (n=150) (%)	Survivor (n=66) (%)	Death (n=84) (%)	Test Quantity (Chi-Square /Fisher's Exact)	*P*
Gender				0.5232	0.4695
Male	89(59.3%)	37 (56.1%)	52 (61.9%)		
Female	61(40.7%)	29 (43.9%)	32 (38.1%)		
Age				3.1293	0.0769
≤45	81 (54.0%)	41 (62.1%)	40 (47.6%)		
>45	69 (46.0%)	25 (37.9%)	44 (52.4%)		
Primary disease				Fisher's exact text	0.0125
AML	62 (41.3%)	31 (47.0%)	31 (37.0%)		
ALL	40 (26.7%)	11 (16.7%)	29 (34.5%)		
Lymphoma	16 (10.7%)	8 (12.1%)	8 (9.5%)		
MDS	12 (8.0%)	3 (4.5%)	9 (10.7%)		
MM	5(3.3%)	3(4.5%)	2(2.3%)		
Others	15 (10.0%)	10 (15.2%)	5 (6.0%)		
Bacterial kinds				2.9779	0.2256
CRE	106 (70.7%)	51 (77.3%)	55 (65.5%)		
CRPA	23 (15.3%)	9 (13.6%)	14 (16.7%)		
CRAB	21 (14.0%)	6 (9.1%)	15 (17.8%)		
Pre-infection length of stay				5.6671	0.0173
≤14d	40 (26.7%)	24 (36.4%)	16 (19.0%)		
>14d	110 (73.3%)	42 (63.6%)	68 (81.0%)		
HSCT				0.8705	0.3508
YES	29 (19.3%)	15 (22.7%)	14 (16.7%)		
NO	121 (80.7%)	51 (77.3%)	70 (83.3%)		
Previous CROs colonization				2.1149	0.4832
YES	68 (45.3%)	33 (50.0%)	35 (41.7%)		
NO	36 (24.0%)	21 (31.8%)	15 (17.9%)		
Unknown	46 (30.7%)	12 (18.2%)	34 (40.4%		
Primary disease remission				4.7639	0.0291
YES	37 (24.7%)	22 (33.3%)	15 (17.9%)		
NO	113 (75.3%)	44 (66.7%)	69 (82.1%)		
Mucositis				4.9526	0.0261
YES	105(70.0%)	40 (60.6%)	65 (77.4%)		
NO	45 (30.0%)	26 (39.4%)	19 (22.6%)		
Disturbance of consciousness				23.0144	<0.0001
YES	52 (34.7%)	9(13.6%)	43 (51.2%)		
NO	98 (65.3%)	57 (86.4%)	41 (48.8%)		
Temperature				20.2649	<0.0001
≤39°C	69 (46.0%)	44 (66.7%)	25 (29.8%)		
>39°C	81 (54.0%)	22 (33.3%)	59 (70.2%)		
CAR				15.2579	<0.0001
≤8.8	123 (82.0%)	62 (93.9%)	61 (72.6%)		
>8.8	27 (18.0%)	4 (6.1%)	23 (27.4%)		
PCT				20.5763	<0.0001
≤11.74 ug/L	100 (66.7%)	57 (86.4%)	43 (48.8%)		
>11.74 ug/L	50 (33.3%)	9 (13.6%)	41 (51.2%)		
Neutrophil count				0.1669	0.6828
≤0.5 g/L	34 (22.7%)	16 (24.2%)	18 (21.4%)		
>0.5 g/L	116 (77.3%)	50 (75.8%)	66 (78.6%)		

(*Continued*)

Table 1 (Continued).

Metrics	Total (n=150) (%)	Survivor (n=66) (%)	Death (n=84) (%)	Test Quantity (Chi-Square /Fisher's Exact)	*P*
HB				12.1379	0.0005
≤82 G/L	130 (86.7%)	50 (75.8%)	80 (95.2%)		
>82 G/L	20 (13.3%)	16 (24.2%)	4 (4.8%)		
PLT				3.9686	0.0464
≤28 G/L	126 (84.0%)	51 (77.3%)	75 (89.3%)		
>28 G/L	24 (16.0%)	15 (22.7%)	9 (10.7%)		
Hypoproteinemia				8.3378	0.0039
YES	90 (60.0%)	31 (47.0%)	59 (70.2%)		
NO	60 (40.0%)	35 (53.0%)	25 (29.8%)		
Glucocorticoid				0.0007	0.9789
YES	82 (54.7%)	36 (54.5%)	46 (54.8%)		
NO	68 (45.3%)	30 (45.5%)	38 (45.2%)		
Mechanical ventilation				16.526	<0.0001
YES	29 (19.3%)	3 (4.5%)	26 (41.0%)		
NO	121 (80.7%)	63 (95.5%)	58 (59.0%)		
Others (sputum suction, bladder catheterization)				5.3663	0.0205
YES	54 (36.0%)	17 (25.8%)	37 (44.0%)		
NO	96 (64.0%)	49 (74.2%)	47 (56.0%)		
Comorbidities					
Diabetes	14 (9.3%)	6 (9.1%)	8 (9.5%)	0.008	0.928
CLD	24 (16.0%)	10 (15.2%)	14 (16.7%)	0.063	0.802
CKD	12 (8.0%)	5 (7.6%)	7 (8.4%)	0.029	0.865
AKI	7 (4.7%)	2 (3.0%)	5 (6.0%)	0.205	0.651
Appropriate empirical therapy				9.266	0.0023
YES	59 (39.3%)	35 (53.0%)	24 (28.6%)		
NO	91 (60.7%)	31 (47.0%)	60 (71.4%)		
Early definitive therapy				10.7436	0.0010
YES	82 (54.7%)	46 (69.7%)	36 (42.9%)		
NO	68 (45.3%)	20 (30.3%)	48 (57.1%)		
Total course of antibiotic therapy		16.11±8.681	13.5±8.617	1.83	0.0687

Abbreviations: HMs, hematological malignancies; AML, acute myeloblastic leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; MM, multiple myeloma; HSCT, hematopoietic stem cell transplantation. HSCT, hematopoietic stem cell transplantation. CAR, the ratio of C-reactive protein to albumin. PCT, procalcitonin. HB, hemoglobin. PLT, platelet. CLD, chronic liver disease. CKD, chronic kidney disease. AKI, acute kidney injury.

independent predictors of 30-day mortality were integrated into a 30-day mortality rate estimation nomogram (Figure 2A). The C-index of the nomogram was 0.81 (Table 2). The predictive performance of the nomogram, as measured by AUC value was 0.893, 0.901 and 0.885 for the 7-day,14-day, and 28-day OS, respectively (Figure 2B–D). Our study found that calibration plots showed good agreement between the predictions and actual observations (Figures 2E–G). Internal bootstrap validation is shown in Figure S1A. The nomogram by 1000 times bootstrap showed AUC of 0.889, 0.894, and 0.876 for the 7-day, 14-day, and 28-day OS, respectively, similar to the original prediction model. The Decision curve analysis (DCA) is presented in Figure S1B. In addition, the time-dependent AUC was used to determine whether the AUC or prediction accuracy changed significantly over time (Figure S1C). ROC analysis was conducted to evaluate the prognosis of patients, and the AUC was calculated. X-title software was used to determine the optimal cut-off point with the highest sensitivity and specificity to discriminate between low-risk and high-risk patients. With the threshold score of 160 for the 30-day mortality nomogram, 101 patients with total points ≤160 were defined as

Table 2 Univariate and Multivariate Analysis of Factors Associated with All-Cause 30-Day Mortality of 150 HM Patients with with CROs BSI

Variable	Univariate HR (95% CI)	P	Multivariate HR (95% CI)	p	c-Index	Vif	Nomo Score
Gender	1.2 (0.751–1.81)	0.4910			0.81		
Age	1.6 (1.01–2.39)	0.0433					
Primary disease remission	0.51 (0.29–0.887)	0.0172					
Pre-infection length of stay>14 days	1.8 (1.03–3.06)	0.0395	1.80 (1.02–3.17)	0.0419		1.076959	0/41
HSCT	0.71 (0.401–1.27)	0.2480					
Pitt score>4	5.9 (3.78–9.28)	8.17E-15	3.32 (1.02–3.17)	0		1.491147	0/100
Mucositis	1.7 (1.01–2.82)	0.0450	2.11 (1.2–3.7)	0.0094		1.207350	0/41
CAR>8.8	3 (1.87–4.96)	7.03E-06	1.80 (1.02–3.17)	0.0426		1.38889	0/57
PCT	2.7 (1.73–4.12)	8.83E-06					
Neutrophil count	0.68 (0.248–1.85)	0.4450					
HB	4.3 (1.57–11.7)	0.00451					
PLT	2 (1–4.01)	0.0488					
Glucocorticoid	1 (0.666–1.57)	0.9140					
Exposure to antimicrobial (≤ 30d)							
Empirical using carbapenems	1.6 (1.05–2.48)	0.0297					
Empirical using tigecycline	2.1 (1.35–3.24)	9E-04					
Empirical using polymyxin B	0.35 (0.15–0.80)	0.0132					
Appropriate empirical therapy	2 (1.22–3.14)	0.00561					
Early definitive therapy	0.52 (0.326–0.817)	0.00475	0.52 (0.32–0.86)	0.0103		1.149479	0/44
Carbapenems-based combination therapy	1.1 (0.704–1.67)	0.716					
Tigecycline-based combination therapy	1.1 (0.749–1.76)	0.524					
Polymyxin B-based combination therapy	0.74 (0.457–1.21)	0.231					
Long-duration	0.28 (0.171–0.473)	1.18E-06	0.37 (0.21–0.64)	4.00E-04		1.160608	0/78
Others (sputum suction, bladder catheterization)	1.6 (1.05–2.49)	0.0295					

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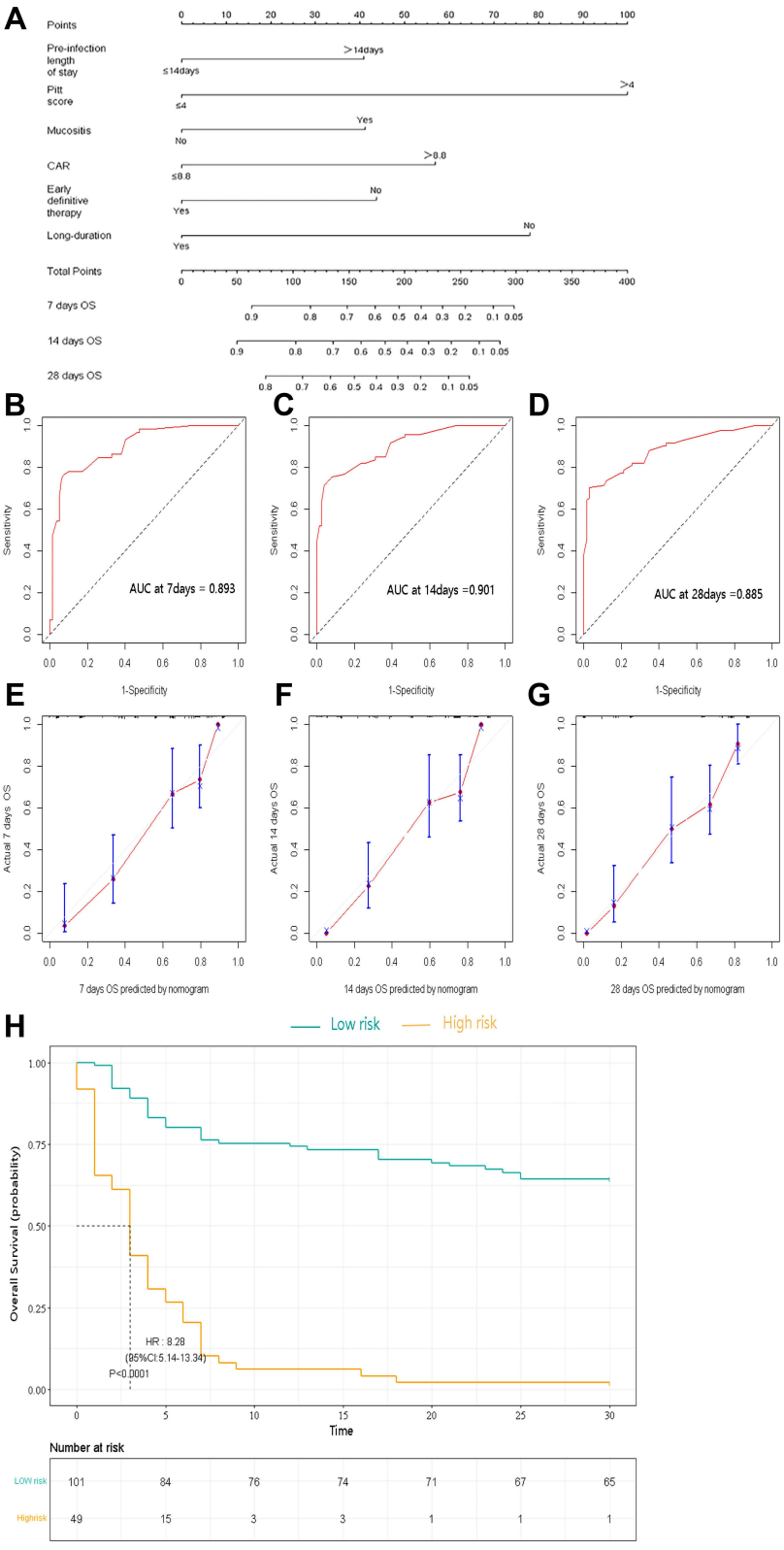

Figure 2 (**A**) A nomogram predicts the 7-day,14-day, and 28-day OS in 150 HM patients with CROs BSI. (**B**–**D**) The AUC of the nomogram for the 7-day,14-day, and 28-day OS. (**E**–**G**) The calibration curves for predicting the 7-day,14-day, and 28-day OS. (**H**) Kaplan-Meier survival curves of 30-day mortality. The diagonal gray lines could help to judge the agreement between predictions and actual observations in the AUC and calibration curves. The dotted lines drawn on the Kaplan–Meier curves were used to reveal the median survival time of patients when 50% of patients had the event. The data in the tables showed the number at risk and a cumulative number of events at specific time points.

the low-risk group, and 49 patients>160 were defined as the high-risk group. The 30-day mortality of HM patients with CROs BSI in the high-risk group was significantly higher than that in the low-risk group (all patients: 33% vs 67%, $p < 0.0001$; HR: 8.28, 95% CI: 5.14–13.34) (Figures 2H).

Effect of Different Empirical Antimicrobial Regimens on Different Risk Population

Different antimicrobial therapy had different effects on treatment outcomes, but the optimal antimicrobial therapy for CROs BSI has not been determined. Kaplan–Meier analysis showed that the patients who received empirical carbapenems and empirical tigecycline had poor prognostic (p=0.0297/p<0.0001) (Figure 3A and B), while the patients who received empirical polymyxin B had good prognostic (p=0.0132) (Figure 3C).

According to our novel risk predictive score model, we further evaluated the effect of empiric antimicrobial regimens on different risk populations. In the low-risk group, the patients who received empirical carbapenems and empirical tigecycline had poor prognostic (p=0.0298/p=0.0336) (Figure 3D and E), and there was no difference in 30-day mortality among patients who received empirical polymyxin B (p=0.3672) (Figure 3F). In the high-risk group, there was no difference in 30-day mortality among patients who received empirical carbapenems and empirical tigecycline (p=0.6191/p = 0.0506) (Figure 3G and H), while the patients who received empirical polymyxin B had good prognosis (p=0.0082) (Figure 3I). Therefore, polymyxin B-based therapy should be selected as early as possible in the patients in high-risk groups.

We further assessed the effects of combinational therapy. There was no difference in 30-day mortality among 60 patients who received the carbapenem-based combination therapy (p=0.1177) (Figure 3K). The patients who received tigecycline-based combination therapy had a 30-day dead benefit (p=0.0176) (Figure 3L). The patients who received polymyxin B-based combination therapy had a 30-day survival benefit (p=0.0017) (Figure 3M).

Discussion

Risk factors for CROs infection in HM patients include: CROs colonization, previous CROs infections, previous use of carbapenems, enzyme inhibitor compound agents, quinolones, aminoglycosides and cephalosporins, elderly patients, ICU admission, prolonged neutropenia (≥7d).[20–22] Previous studies have reported that multiple clinical factors, including underlying medical conditions, previous antibiotic exposure, and severity of bacteremia, were independently associated with poor outcomes in patients with BSI.[23,24] CROs BSI is associated with high mortality in HM patients with immunodeficiency, and many factors could affect the prognosis of patients, including septic shock, the severity of illness, pathogen characteristics, and the late onset of empirical antibiotic therapy.[25,26] The current retrospective study found that pre-infection length of stay >14 days, Pitt score >4, mucositis, CAR >8.8, early definitive therapy, and long-duration treatment were independent predictors for 30-day mortality. A score of ≥160 suggests that HM patients with CROs BSI will have higher 30-day mortality. The results suggest that high-risk group patients had approximately 8 times the odds of dying within 30 days compared to patients in the low-risk group after accounting for the severity of illness on day 1 of bacteremia.

PCT is a commonly used inflammation-related biomarker for the diagnosis of bacterial infections. However, it has limited significance for diagnosing BSI in neutropenia patients since they have an impaired capacity for generating PCT compared with nonneutropenic patients.[27] CRP is one of the acute-phase proteins released in inflammation. It is used for the diagnosis and follow-up of sepsis and for determining treatment efficacy.[28,29] Prat et al[30] found that CRP was more sensitive than PCT to predict bacteremia in patients with febrile neutropenia. Albumin is a negative acute-phase reactant. In critical care, the hypoalbuminemia grade correlates with infection-triggered inflammation.[31] Using a ratio between CRP and albumin would provide a variable capable of merging the information provided by CRP and albumin into an index that correlated positively with infection, ie, a higher ratio indicates higher inflammatory status.[32] CAR has also been shown to correlate with infection severity, a useful score based on inflammation and nutrition, reflecting not only systemic inflammation status but also nutritional status.[33] CAR has recently been a prognostic marker for various solid tumors and chronic lymphocytic leukemia (CLL).[34–36] Ranzani et al[37] reported that on admission to the hospital, the CAR >2 showed the greatest sensitivity and specificity in predicting mortality at 90 days among patients with severe sepsis or septic shock. A retrospective cohort study showed CAR > 5.09 had the best sensitivity and specificity in predicting 180-day mortality in patients with severe sepsis and septic shock.[38] Our study revealed an association of CAR > 8.8 with higher mortality, which might also reflect the severity of

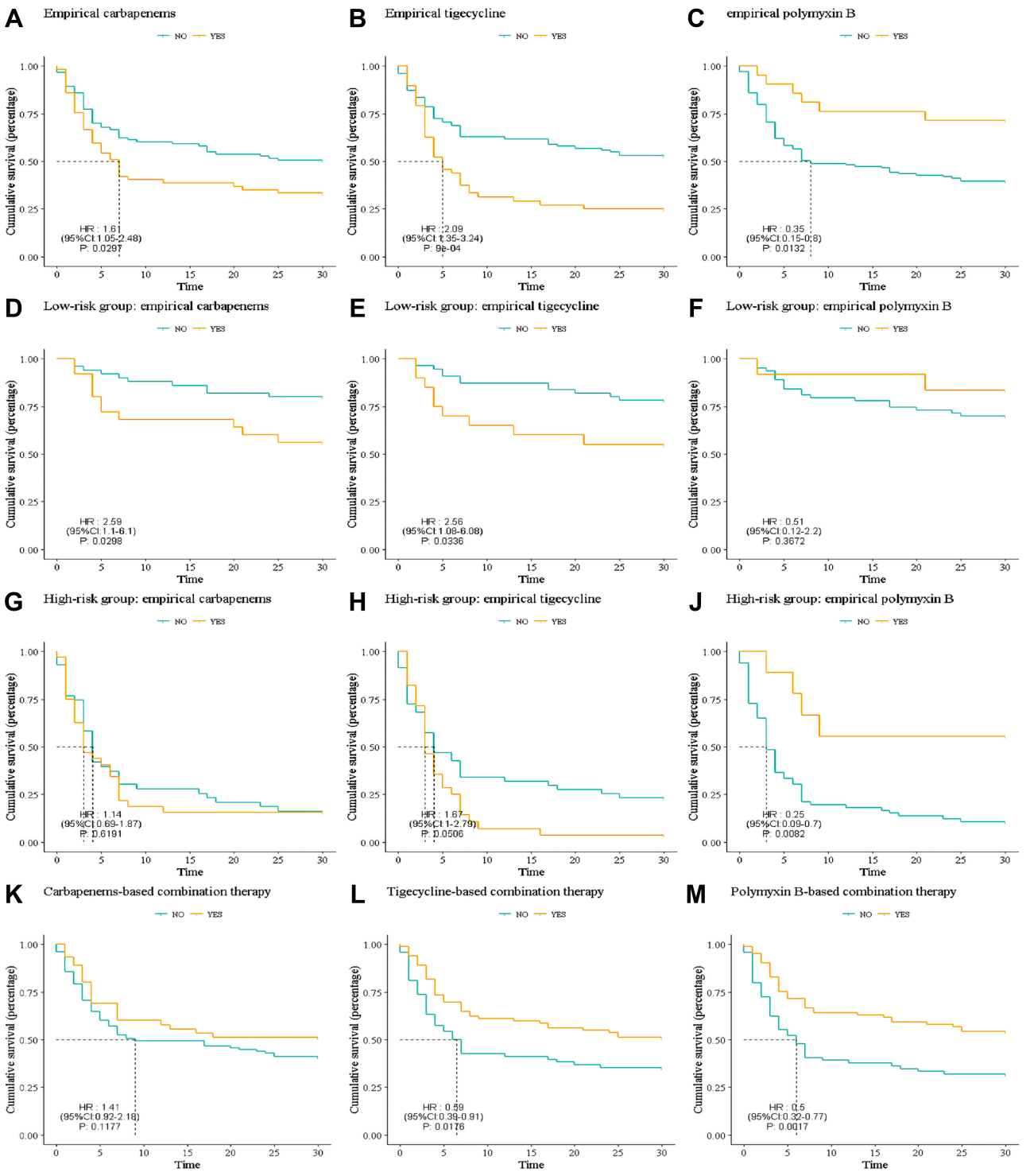

Figure 3 Kaplan–Meier curves showing the impact of different antimicrobial treatments. (**A**–**C**) The patients who received empirical carbapenems and empirical tigecycline had a 30-day poor prognostic, while the patients who received empirical polymyxin B had a 30-day survival benefit. (**D**–**F**) In the low-risk group, the patients who received empirical carbapenems and empirical tigecycline had a 30-day poor prognostic, and there was no difference in 30-day mortality among patients who received empirical polymyxin B. (**G**–**I**) In the high-risk group, there was no difference in 30-day mortality among patients who received empirical carbapenems and empirical tigecycline, while the patients who received empirical polymyxin B had a 30-day survival benefit.(**K**–**M**) The patients who received the carbapenem-based combination therapy had no difference in 30-day mortality. The patients who received tigecycline-based combination therapy had a 30-day dead benefit, and the patients who received polymyxin B-based combination therapy had a 30-day survival benefit.

deaths caused by CROs BSI. Additional prospective studies with larger populations involving multiple centers are necessary to accurately evaluate the significance of CAR as a predictor of mortality.

In our study, an early definitive therapy (≤72h) and long-duration treatment (≥10 days) were independent favorable prognostic factors for 30-day mortality. Similarly, Wasan Katip et al found that patients who received long course of colistin therapy (≥14 days) had presented greater clinical and microbiological responses and lower 30-day mortality.[39] Timely and appropriate antimicrobial therapy is critically important for treating patients with BSI.[40,41] Delayed administration of definitive antibiotic therapy is associated with high mortality rates in patients with bacteremia and sepsis,[42–44] and the probability of death increases with the number of hours of delay of antibiotic administration.[44] Previous studies have shown that more rapid completion of a 3-h bundle of sepsis care and rapid administration of antibiotics was associated with lower risk-adjusted in-hospital mortality.[40] Falcone et al suggested that appropriate antibiotic therapy was preferably initiated within the first 24-h after collection of the blood culture. Conversely, the risk of death progressively increased when appropriate antibiotic therapy was started 24–48 h (mortality rate 37.5%), 48–72 h (mortality rate 57.1%), and > 72 h (mortality rate 66.7%) from the index blood culture collection.[45] However, the average time to obtain a blood culture result requires at least 24–48 hours.[6,39] Recently, new laboratory methods for more rapid bacterial identification and antibiotic resistance, including NTS and carba have been developed and allow early administration of targeted definite antimicrobial treatment, thus potentially improving clinical outcomes.[46]

Appropriate empirical therapy is key to decreasing mortality.[47,48] In our study, patients treated with appropriate empirical therapy had a better prognosis than those treated with inappropriate empirical therapy, similar to those reported in other studies.[49] However, the optimal antimicrobial treatment for CROs BSI has not been determined. According to current guidelines,[50] patients in our study received standard dose tigecycline (SDT) during empirical therapy of infection and once patients with a definitive diagnosis of CROs BSI, high dose tigecycline (HDT) were used. In our study, in all patients and those in the low-risk group, the empirical use of tigecycline was associated with higher mortality. Tigecycline is a bacteriostatic rather than bactericidal agent, which may limit its effectiveness in immunocompromised patients, and is not active against Pseudomonas aeruginosa.[51] The US Food and Drug Administration (FDA) has approved its use for complicated intra-abdominal infections, skin and skin structure infections, and community-acquired pneumonia.[52] However, tigecycline's role in treating BSI is controversial because of its low serum concentration with standard dosing.[53,54] In a non-comparative study, tigecycline appeared to be safe and efficacious in patients with difficult-to-treat serious infections caused by resistant Gram-negative organisms, the clinical cure rate was 72.2%, and the microbiological eradication rate was 66.7%.[55] However, in some randomized trials, tigecycline increased mortality risk and clinical failure.[56,57] The excess risk of death in the subset of tigecycline patients with BSI might be attributed to the persistence of bacteremia owing to low tigecycline serum concentrations, higher bacterial load in patients with primary bacteremia and/or insufficient dose.[58] Besides, tigecycline is associated with a higher frequency of adverse events, especially vomiting, nausea, and acute pancreatitis,[59,60] indicating that surveillance of adverse events from the digestive system is needed during treatment.

Our study found that the empirical use of polymyxin B was associated with survival benefits in all patients and those in the high-risk group. Polymyxin B is an antibiotic of the polymyxin family that demonstrated good results in the past decade for the treatment of multidrug-resistant (MDR) Gram-negative bacteria (GNB).[61,62] In addition to the direct antibacterial activity, polymyxin B has potent anti-endotoxin activity.[63] It has been the preferred agent in many hospitals in China based on its superior PK characteristics and decreased potential to cause nephrotoxicity.[64] A retrospective study from China showed that for patients with carbapenem-resistant Klebsiella pneumonia BSI, irrespective of drug dosage and treatment duration, the early use of polymyxin B could effectively eliminate bacteria, improving 30-day and overall mortality.[65] A more recent Japanese multicentre study showed that polymyxin B treatment of sepsis in 354 patients significantly reduced all-cause mortality.[66] Our results suggest that polymyxin B-based therapy should be used as a first-line agent for the high-risk population in HM patients with CROs BSI. Some studies have found that combination antimicrobial therapy is preferred to monotherapy, particularly in severely ill patients.[67–69] In our study, not only empirical using polymyxin B, but also, combination therapy based on polymyxin B had a 30-day survival benefit, which was similar to previous reports.[25,68] Previous study showed the survival rate of patients in the LD colistin methane sulfonate (CMS) group was 1.7 times (adjusted HR) of those in the non-LD group (p=0.006), but renal function should be closely monitored in view of severe nephrotoxicity caused by polymyxin B.[70] Likewise, LD polymyxin B were used

in our study. Notably, an increasing number of novel potent molecules are being developed for CRO therapy, such as the novel β-lactam/β-lactamase inhibitor combinations, ceftazidime/avibactam, meropenem/vaborbactam, and imipenem/cilastatin/relebactam.[71–75] Their role in the treatment of high-risk population should be furtherly studied.

This study has existing limitations, including its retrospective, observational design. First, we did not identify the enzyme type of the CROs strain, and the specific carbapenemases (KPC, OXA, etc.) were not identified in our studied population. Second, an external validation cohort is needed to assess its discriminatory ability and goodness of fit. Additionally, a limited number of samples were included. Large sample data and randomized controlled studies are needed to study the clinical characteristics and different antimicrobial therapeutic effects on patients with CROs BSI. Finally, it needs to be confirmed whether the established score model is reproducible through relevant prospective studies. In summary, Patients can be divided into low- and high-risk groups based on our mortality prediction score model. Therefore, in high-risk group, the early administration of proper CROs-targeted therapy is strongly recommended to decrease their mortality, especially polymyxin B-based combination therapy. On the contrary, for those patients with low-risk mortality, common treatment and close monitor might be enough. Taken together, our study contribute to the improvement of clinicians' awareness about rational timing of treatment and precision drug selection, which can avoid antibiotic abuse, lower bacterial resistance rate and decrease healthcare costs.

Ethics Statements

The study was approved by the Union Hospital ethics committee for health research. Written informed consent was waived by the Union Hospital ethics committee for research in health due to the anonymized retrospective nature of the analysis. And this study followed the guidelines outlined in the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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