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ORIGINAL ARTICLE

Nomogram Based on Clinical Characteristics to Predict 28-Day Mortality Among Patients with CRAB-BSI

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SUMMARY

Background: **The drug resistance of carbapenem-resistant *Acinetobacter baumannii* bloodstream infections (CRAB-BSI), especially hospital-acquired infections, has promoted their rapid and vast spread. It is necessary to use reliable methods to establish better prediction models. According to Cox proportional hazards regression, a nomogram was established.**

Methods: **A retrospective cohort study among patients who were diagnosed with CRAB-BSI was performed from January 2020 to December 2022. Univariate and multivariate Cox proportional hazards regression analyses were used to determine independent prognostic factors regarding CRAB-BSI. Then, nomograms were used to calculate the area under the curve (AUC), C-index, and calibration curve to determine the predictive accuracy and discriminability. Decision curve analysis (DCA) was employed to further confirm the clinical effectiveness of the nomogram.**

Results: **A total of 98 cases were included in the comparison between the 28-day mortality group consisting of 32 patients and the 28-day survival group with 66 patients. The use of cefoperazone-sulbactam was significantly higher among patients who survived than among those who died. Univariable analysis revealed that factors such as primary diagnosis, time to inadequate antimicrobial therapy, and high serum creatinine and procalcitonin (PCT) levels were more prevalent in the mortality group. However, only primary diagnosis, time to inadequate antimicrobial therapy, and high PCT levels emerged as statistically significant risk factors for death in multivariate analysis and were used to construct the nomogram. The nomogram validation exhibited excellent performance.**

Conclusions: **The nomogram was sufficiently accurate to predict the risk and prognostic factors of CRAB-BSI, allowing for individualized clinical decisions for future clinical work. The cefoperazone-sulbactam did have an effect, but more studies are needed to interpret it.**

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KEYWORDS

carbapenem-resistant *Acinetobacter baumannii*, bloodstream infections, nomogram, clinical characteristics, cefoperazone-sulbactam

LIST OF ABBREVIATIONS

CRAB - carbapenem-resistant *Acinetobacter baumannii*
BSI - bloodstream infection
PCT - procalcitonin
ROC curve - receiver operating characteristic curve

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MDR - multi-drug resistant
DALY - disability-adjusted life year
ESCMID - European Society of Clinical Microbiology and Infectious Diseases
ICU - intensive care unit
APACHE-II - Acute Physiology and Chronic Health Evaluation II
SOFA - Sequential Organ Failure Assessment
RCT - randomized controlled trial
OR - odds ratio
CI - confidence interval
ALI - acute lung injury
CRAB-BSI - carbapenem-resistant *Acinetobacter baumannii* bloodstream infection

INTRODUCTION

Among the most common species in sepsis and septic shock is carbapenem-resistant *Acinetobacter baumannii* (CRAB), which is a gram-negative, non-fermentative *A. baumannii* strain. The pathogen exhibits a considerably rapid acquisition of drug resistance, especially in hospital-acquired infections, which fosters its swift and broad dissemination. Consequently, as a major antibiotic-resistant bacterium, CRAB has been demonstrated to be increasingly prevalent worldwide [1-3]. CRAB infections are very difficult to address. Increasingly, the use of invasive procedures, such as central venous catheterization, urinary tract catheterization and mechanical ventilation, has contributed to the spread of CRAB. Coupled with the misuse of glucocorticoids and broad-spectrum antibiotics, CRAB poses a substantial threat in hospitals. This has resulted in an escalating prevalence of bloodstream infections and even outbreaks within health care facilities [5,6]. These pathogens often colonize hospital patients on their external communicating cavities, such as the respiratory tract, skin, gastrointestinal tract, and wounds, ultimately inducing CRAB-BSI that commonly afflicts critically ill patients with venous catheters and abdominal infections. Given their compromised state and weakened immunity, these patients face severe threats to their well-being, with mortality rates exceeding 50% [7,8]. Currently, there are no appropriate or effective treatment options available for patients with CRAB-BSI, excluding ampicillin-sulbactam [8]. However, many controversies surround ampicillin-sulbactam in the global medical community; for example, it increases the risk of drug resistance and is difficult to obtain [9]. In the countries where it can be acquired, cefoperazone-sulbactam could represent an alternative. Notably, there has been a yearly increase in the drug resistance rate for cefoperazone-sulbactam medications. Cefoperazone-sulbactam is the most promising regimen for the treatment of CRAB infections [10,11].

Hence, our study reevaluated and updated the risk factors associated with the prognosis of CRAB-BSI, as this holds significant implications for managing infections and reducing mortality rates. In this study, we conducted a retrospective analysis of the prognostic outcomes for patients with hospital-acquired CRAB-BSI. Additionally, we investigated the therapeutic efficacy of cefoperazone-sulbactam to offer insights that could contribute to minimizing the incidence of CRAB-BSI and associated mortality across the entire hospital.

MATERIALS AND METHODS

Patient population

Between January 2020 and December 2022, patients diagnosed with CRAB-BSI in the Clinical Laboratory Center of the Affiliated Hospital of Guizhou Medical University's microbial culture database were categorized into two groups based on their 28-day prognosis: the survival group and the mortality group. This study was conducted at a 2,025-bed academic tertiary general hospital in southwestern China. The inclusion criteria were as follows: Patients with four collected venous blood samples and a minimum of one positive blood culture indicating CRAB-BSI who also met the diagnostic criteria for bloodstream infections. In cases of multiple positive blood cultures during hospitalization, the medical record at the time of the first positive test was used. The exclusion criteria were as follows: patients with hematological malignancies or instances of contamination or colonization, patients with incomplete medical records, patients aged below 18 years, and pregnant women.

Clinical data and definitions

Patient data were obtained from hospital records without requiring additional tests or interventions. This information included demographic information, primary diagnosis upon ICU admission, and comorbidities. For CRAB-BSI cases, researchers gathered data on the pathogen, along with its antibiogram, and the timing of blood culture sampling. Patients were then followed up for 28 days until hospital discharge or death. The 28-day timeframe and time to inadequate antimicrobial therapy were initiated from the blood culture sampling date. The time to inadequate antimicrobial therapy was defined as the period during which antibiotics were altered at least once within 48 hours of obtaining a positive sample.

Microbiological procedures

CRAB was isolated from blood culture specimens of patients and detected by a VITEK2 instrument (Biomerieux, France). The Kirby-Bauer disk diffusion method was used for the drug susceptibility test. Antimicrobial agents included cefoperazone-sulbactam, metal β-lactamase, serine carbapenemase, ceftazidime-avibactam, polymyxin B, ampicillin-sulbactam, amikacin, ampicillin, etc. The antimicrobial disc and MH AGAR used were all products of OXOID Company, UK. *Escherichia coli* ATCC25922 was used as the quality control strain for the drug susceptibility test, and the results

were judged according to the Clinical and Laboratory Standards Institute (CLSI) 2022 standards.

Statistical analysis

In the first part of this study, the test (for measurement data) and the chi-squared (χ^2) test (for count data) were employed to analyze the collected data. The adjustments made to different types of antibiotic agents were examined before and after blood culture. Upon obtaining a positive blood culture result, the Kaplan–Meier method was utilized to compare the survival curve consistency between two groups: patients with cefoperazone-sulbactam and those without.

The second part of the current study was model construction and assessment. By transforming the continuous variables into categorical variables, the optimal cutoff value for the continuous variables was obtained by X-tile [12]. The factors influencing the prognosis of CRAB-BSI were selected by Cox proportional hazards regression. Those with a $p < 0.05$ in univariate analysis were included in multivariate Cox regression analysis. Based on the results of the multivariate analysis, a nomogram was constructed based on 28 days as the endpoint. Then, the goodness-of-fit and discriminative ability of the nomogram were examined with the Akaike information criterion (AIC), Bayesian information criterion (BIC), and concordance index (C-index). Calibration curves were used to evaluate the calibration of the nomogram, and decision curve analysis was performed to evaluate the clinical utility of the nomogram. For internal validation, a calibration curve with 1,000 resamples was drawn using the bootstrap method.

We used R software (version 4.2.3) to analyze the data. Data were analyzed using the rms package and pec package, and survival analysis was performed using the survminer and survival packages in the software ((R Core Team [2013]). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/). All statistical p-values were two-sided, with $p < 0.05$ indicating statistical significance.

RESULTS

Clinical characteristics of patients with CRAB-BSI

Overall, a total of 114 cases of CRAB-BSI were identified from January 2020 to December 2022; three patients were excluded because they were less than 18 years old, and four patients were excluded due to hematologic neoplasms. Additionally, two patients lacked information on 28-day mortality and were excluded. Others were excluded, as shown in Figure 1. Ninety-eight patients with CRAB-BSI were divided into a survival group (n = 66) and a mortality group (n = 32) according to the 28-day prognosis, as shown in Table 1. The age of the two groups was 61.59 ± 15.81 years in the mortality group and 55.86 ± 19.83 years in the survival group. The cost of antibiotics for polymicrobial *A. baumannii* and hospital length of stay (LOS) were higher in the mortality group than in the survival group. In contrast, cefoperazone-sulbactam was more commonly used in the survival group. Notably, the primary admission diagnosis of the mortality group was related to the respiratory system, but that of the survival group was related to the gastrointestinal system. The cutoffs for the following continuous variables were obtained by X-tile: BMI (21, range 16.4 - 37.1), WBC (12.25×10^9/L, range 1.04 - 36.94), PCT (1.89 ng/mL, range 2.07 - 100), serum creatinine (70.52 μmol/L, range 54.62 - 333.43), total bilirubin (8.56 μmol/L, range 3.9 - 357.6), and prealbumin (40 mg/L, range 1 - 290).

Antibiotic regimen

As shown in Table 1, the total cost of the two antibiotic groups was different and needed further analysis. Cefoperazone-sulbactam, meropenem, tigecycline, imipenem, and piperacillin/tazobactam served as the principal anti-infective treatments following admission. Cefoperazone-sulbactam was consistently administered during the three initial antibiotic adjustments prior to blood culture, as illustrated in Figure 2A. Upon obtaining a positive blood culture result, cefoperazone-sulbactam and tigecycline emerged as the primary antibiotics administered for the first and second adjustments, as depicted in Figure 2B. A subgroup analysis demonstrated that patients treated with cefoperazone-sulbactam experienced a higher survival rate after positive blood culture, as shown in Figure 3.

Construction of the nomogram

Based on potential prognostic predictors obtained by univariate and multivariate Cox regression, we estimated a risk prediction nomogram model for CRAB-BSI. The univariate regression analysis showed that the influencing factors included primary diagnosis, time to inadequate antimicrobial therapy, serum creatinine, PCT, and cefoperazone-sulbactam. While other variables were considered potentially relevant, none of them were statistically significant (Table 2). Those factors were included in multivariate Cox regression analysis, showing that primary diagnosis, time to inadequate antimicrobial therapy, PCT, and cefoperazone-sulbactam were still statistically significant risk factors (primary diagnosis, $p < 0.001$, HR = 4.907, 95% CI: 1.988 - 12.113; time to inadequate antimicrobial therapy, $p < 0.010$, HR = 2.649, 95% CI: 1.255 - 5.591; PCT, $p < 0.030$, HR = 2.683, 95% CI: 1.092 - 6.592; SCF, $p < 0.038$, HR = 0.424, 95% CI: 0.188 - 0.956) (Figure 4 and Table 2). Then, incorporating the above prognostic markers in the multivariate Cox model, a nomogram was constructed for CRAB-BSI (Figure 5). The nomogram obviously suggested that the primary diagnosis played a key role as an indispensable predictor, in addition to time to inadequate antimicrobial therapy and PCT. Each prognostic portion on the nomogram had a risk point that could be established by drawing a line vertically from its corresponding value to an axis

Table 1. Characteristics of participating population with CRAB-BSI.

Parameters		Mortality group (n = 32)	Survival group (n = 66)	p-value
Gender (%)	female	11 (34.4%)	18 (27.3%)	0.47
	male	21 (65.6%)	48 (72.7%)	
Age (years)		57.4 (39.0, 72.0)	63 (50.5, 74.7)	0.157
Body Mass Index (kg/m^2)		23.5 (20.9, 27.2)	24.3 (21.8. 26.0)	0.704
Temperature (℃)		36.8 (36.3, 40.0)	36.7 (36.5, 37.0)	0.441
CCI		3 (1, 4)	2 (0, 4)	0.585
Type of admission				0.565
ICU		25 (78.1%)	48 (72.7%)	
Non-ICU		7 (21.9%)	18 (27.3%)	
Primary diagnosis				
Digestive system disease		1 (3.1%)	21 (31.8%)	0.018
Respiratory system disease		11 (34.4%)	9 (13.6%)	
Nervous system disease		9 (28.1%)	14 (21.2%)	
Urinary system disease		1 (3.1%)	0 (0.0%)	
Circulation system disease		5 (16.5%)	9 (13.6%)	
Infection		2 (6.3%)	4 (6.1%)	
Other		3 (9.4%)	9 (13.6%)	
Time & Cost				
Hospital LOS (days)		39 (26.7, 60.0)	19 (11.25, 23.0)	0.001
Total cost in hospital (RMB)		311,181.0 (183,466.7, 494,463.0)	179,150 (119,949.5, 254,126.7)	0.67
Cost in antibiotic (RMB)		37,433.5 (18,594.0, 66,993.2)	13,808 (7,320.5, 30,582.5)	0.001
Focus of infection				
Lung		25 (78.1%)	44 (66.7%)	0.244
Other		7 (21.9%)	22 (33.3%)	
Site of colonization				
Sputum		15 (46.9%)	37 (56.1%)	0.652
Other		5 (15.6%)	10 (15.2%)	
Antimicrobial susceptibility test				
Tigecycline		2 (6.3%)	6 (9.1%)	0.86
Polymyxins		8 (25.0%)	15 (22.7%)	0.824
Ampicillin/sulbactam		30 (93.8%)	60 (90.9%)	0.61
Levofloxacin		30 (93.8%)	62 (93.9%)	0.738
Amikacin		28 (87.5%)	57 (86.4%）	0.204
Source control		26 (81.3%)	41 (62.1%)	0.056
Use of antibiotics				
Tigecycline		14 (43.8%)	32 (48.5%)	0.66
Cefoperazone-sulbactam		9 (20.9%)	34 (79.1%)	0.029
Meropenem		3 (9.4%)	18 (27.3%)	0.078

Results are presented as the median (25th - 75th percentiles) for quantitative variables and patient number (column proportion) for qualitative variables.
CRAB - carbapenem-resistant *Acinetobacter baumannii*, BSI - bloodstream infection, CCI - Charlson comorbidity index, LOS - length of stay.

Table 2. Univariate and multivariate Cox proportional hazards regression analysis for CRAB-BSI.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Gender (female vs. male)	0.840	0.410 - 1.700	0.650			
ICU	1.100	0.320 - 3.500	0.093			
BMI (≥ 21 vs. < 21)	0.540	0.270 - 1.100	0.087			
Central venous catheter	2.000	0.700 - 12.000	0.140			
Mechanical ventilation	1.700	0.710 - 3.800	0.240			
CRRT	0.720	0.340 - 1.500	0.390			
WBC (≥ 12.25 vs. < 12.25; 10^9/L)	1.400	0.690 - 2.800	0.360			
Primary diagnosis	4.800	2.000 - 12.000	0.001	4.907	1.988 - 12.113	0.001
Time to inadequate antimicrobial therapy	2.200	1.100 - 4.500	0.027	2.649	1.255 - 5.591	0.010
PCT (≥ 1.89 vs. < 1.89; ng/mL)	49.000	6.700 - 360.00	0.001	2.683	1.092 - 6.592	0.030
Serum creatinine (≥ 70.52 vs. < 70.52; µmoI/L)	4.200	1.900 - 9.000	0.001	1.488	0.658 - 3.365	0.339
Total bilirubin (≥ 8.56 vs. < 8.56; µmol/L)	1.300	0.520 - 3.500	0.540			
SCF	0.410	0.190 - 0.880	0.023	0.424	0.188 - 0.956	0.038
Prealbumin (≥ 40 vs. < 40; mg/L)	0.450	0.170 - 1.200	0.099			
CCI	2.500	0.880 - 7.200	0.084			

CRAB - carbapenem-resistant *Acinetobacter baumannii*, BSI - bloodstream infection, CCI - Charlson comorbidity index, BMI - body mass index, ICU - intensive care unit.

Table 3. The AIC, BIC and C-index of prognostic factors and nomogram for prediction CRAB-BSI.

	C-index	p-value	AIC	BIC
PCT	0.671	< 0.001	269.380	270.846
Time to inadequate antimicrobial therapy	0.649	< 0.001	272.696	274.161
Primary diagnosis	0.665	< 0.001	267.638	269.103
Nomogram	0.787	< 0.001	249.740	254.137

CRRT - continuous renal replacement therapy, WBC - white blood cell, PCT - procalcitonin, SCF - cefoperazone-sulbactam, BSI - bloodstream infection, C-index - concordance index, 95% CI - 95% confidence interval, AIC - Akaike Information Criterion, BIC - Bayesian Information Criterion.
p-values are calculated based on normal approximation using function rcorrp.cens in Hmisc package.

marked “points” directly upward. After obtaining the three predictor “points”, the total score obtained by adding individual “points” drew a vertical line directly downward at the risk line to determine the probability of death from CRAB-BSI.

Nomogram validation

The goodness-of-fit and discrimination of the nomogram were examined by using the AIC, BIC, and C-index, as shown in Table 3. From these results, the values of the AIC and BIC of the nomogram were lower than the others (AIC: 249.740 < 267.638 < 269.380 < 272.696; BIC: 254.137 < 269.103 < 270.846 < 274.161), and the value of the C-index was higher in the nomogram (0.787 > 0.671 > 0.665 > 0.649), meaning that the nomogram had a better goodness-of-fit in the prediction. The nomogram's bootstrap-corrected C-index was greater than the other values (Figure 6). According to time-dependent C-index analysis, the nomogram model also showed good predictive accuracy in clinical outcome prediction for CRAB-BSI compared with every individual prognostic marker. A similar result was also revealed by internal validation using the bootstrap resampling technique (Figure 6).

Regarding the net benefit and predictive capacity of the nomogram, decision curve analysis (DCA), and the cali-

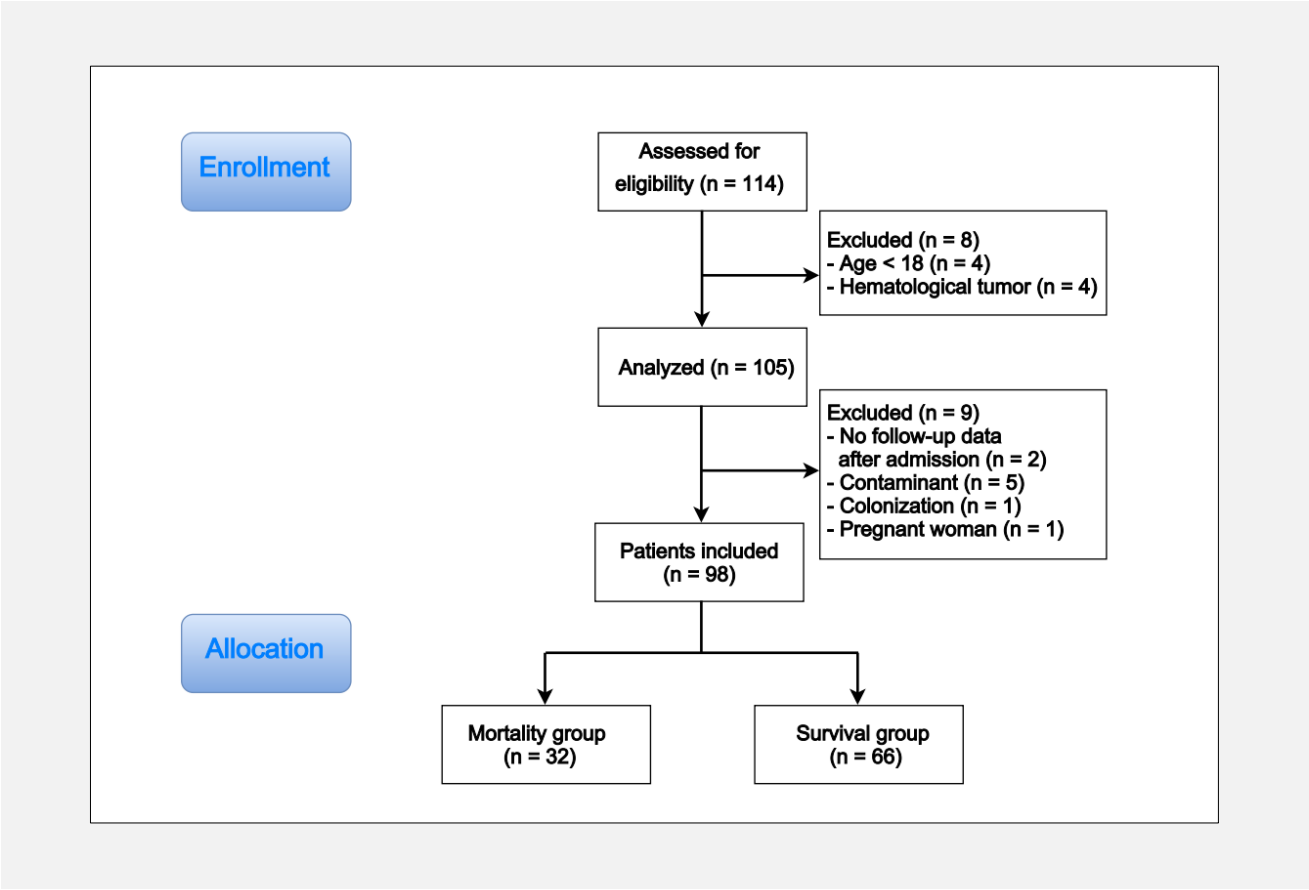

Figure 1. Flowchart of inclusion and patients distribution.

bration curve of the nomogram revealed a better effect of the predictors. DCA is widely used to judge the clinical value of a nomogram. As shown in Figure 7, the nomogram was superior to others and showed a substantial positive net benefit for the risk of mortality, demonstrating its excellent clinical applicability in predicting the survival of CRAB-BSI patients. In conclusion, all results demonstrated that our nomogram for CRAB-BSI patients had good efficiency in predicting survival.

DISCUSSION

To our knowledge, this is the first retrospective investigation to date to construct nomogram models and explore the factors associated with mortality for CRAB-BSI risk. In our study, the efficacy of cefoperazone-sulbactam represented an underappreciated treatment component for CRAB-BSI patients, and primary diagnosis played a pivotal role in the nomogram by using Cox proportional hazards regression. The mortality rate for CRAB-BSI was 32.6%, which aligns with the findings of other research [13]. There is a critical need to identify the reasons for mortality caused by CRAB-BSI. In addition to using cefoperazone-sulbactam, this study also retrospectively analyzed CRAB-BSI patients with clinical characteristics, especially highlighting the antibiotic treatment regimen in which five antimicrobial agents, SCF, MEM, tigecycline, IM/CI, and TZP, are mainly regarded as first-line drugs against CRAB in the hospital. In the process of establishing the nomogram, SCF was discovered to be a protective factor for CRAB-BSI patients, similar to the KM curve results. Eventually, primary diagnosis, PCT, and time to inadequate antimicrobial therapy were used as predictors in the model. The findings are highly important for both preventative efforts and the diagnosis and treatment of CRAB-BSI.

As previously stated, cefoperazone-sulbactam was associated with better clinical outcomes in the KM curve and univariate and multivariate Cox regression analyses. After obtaining positive blood culture results, patients with cefoperazone-sulbactam-treated CRAB had a higher survival rate. Sulbactam, a β-lactamase inhibitor, inhibits penicillin-binding protein 2 to have intrinsic antibacterial properties against *A. baumannii,* which is commercially available in a combined formulation of cefoperazone-sulbactam [14]. The clinical efficacy of

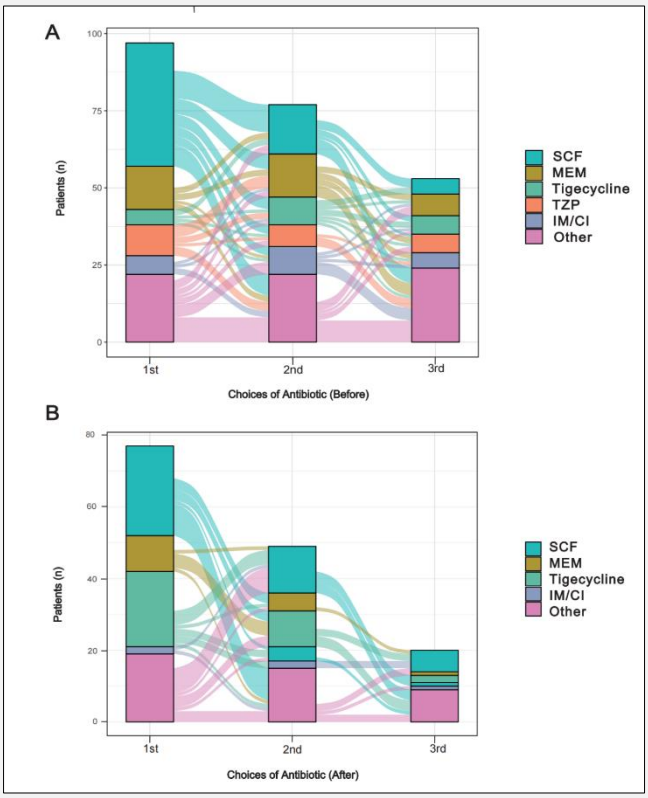

Figure 2. The first three antibiotic regimens were changed before and after the positive blood sample.

Alluvial plot showing the trend for the shift in antibiotic use. SCF - cefoperazone sodium and sulbactam, TZP - piperacillin/tazobactam, MEM - meropenemn, IM/CI - imipenem and cilastatin.

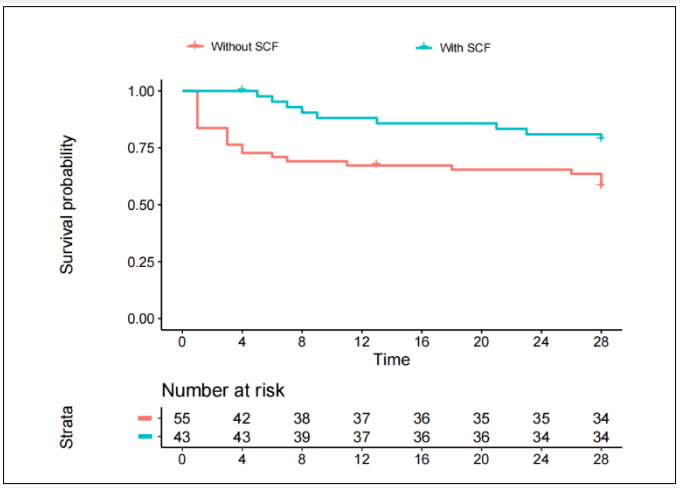

Figure 3. Kaplan-Meier estimates of 28-day survival in patients with SCF and without SCF.

SCF - cefoperazone sodium and sulbactam.

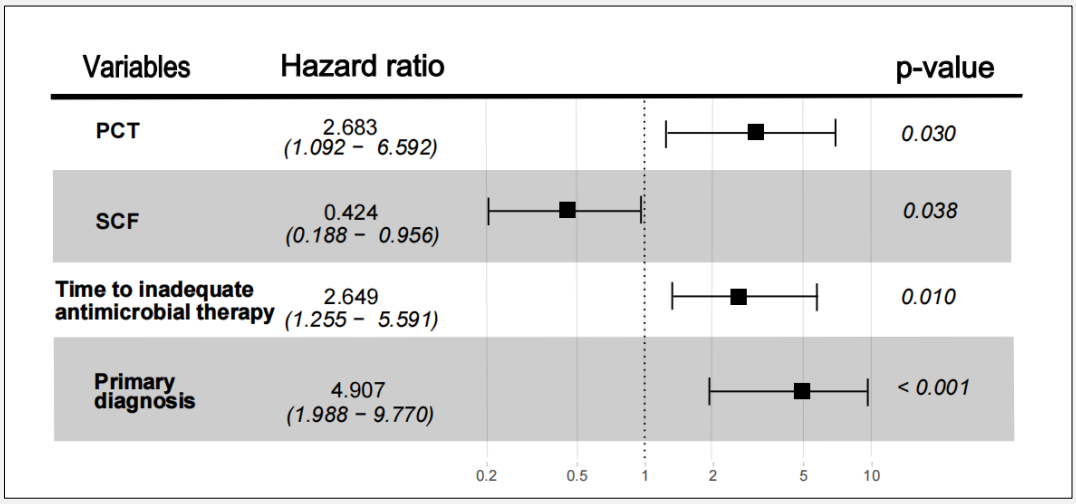

Figure 4. The HR and 95% CI of four independent prognostic factors for CRAB-BSI.

PCT - procalcitonin, SCF - cefoperazone sodium and sulbactam.

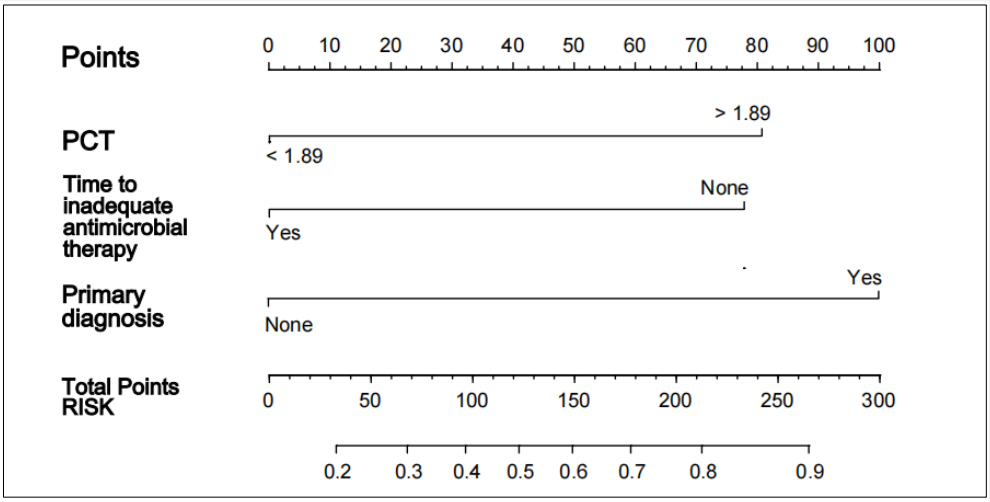

Figure 5. Nomogram based on PCT, time to inadequate antimicrobial therapy, primary diagnosis. The nomogram was used by summing the points identified on the points scale for each prognostic factor.

PCT - procalcitonin.

cefoperazone-sulbactam has been demonstrated in other studies [17,18]. As is well known, this bacterium has an exceptional capacity to acquire and evolve a variety of cell mechanisms that confer resistance to almost all antimicrobial drugs relevant to *Acinetobacter* infections [17]. Few novel antimicrobial drugs are effective against *A. baumannii*, although new drugs are being developed for gram-negative bacteria [10]. The rate of resistance to cefoperazone sodium has been rising in recent years, and hospital monitoring has shown the same

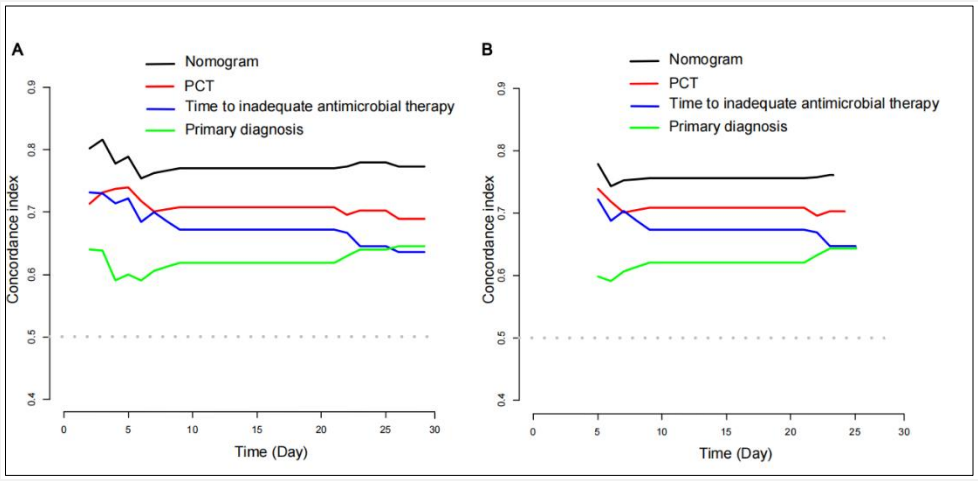

Figure 6. Time-dependent C-index of nomogram compared with PCT, time to inadequate antimicrobial therapy. Primary diagnosis for CRAB-BSI (A) and internally validated with using a bootstrap resampling method (B).

PCT - procalcitonin.

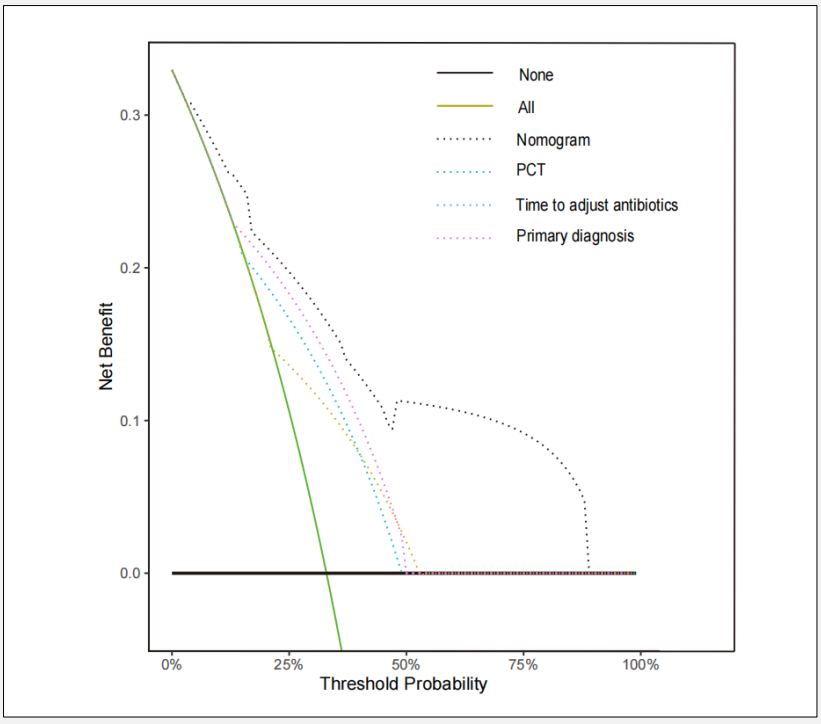

Figure 7. Decision curve analysis of nomogram compared with PCT, time to adjust antibiotics, underlying disease for CRAB-BSI.

The thick grey line is the net benefit for a strategy of treating all men, the thick black line is the net benefit of treating no men. The y-axis indicates the overall net benefit, which is calculated by summing the benefits (true positive results) and subtracting the harms (false positive results).

result. Presently, similar to the results above, the current guidelines do not indicate any single agent or combination therapy as superior against sulbactam resistance [18]. In the KM curve, patients who received cefoperazone-sulbactam had a higher 28-day survival rate than those who did not receive cefoperazone-sulbactam. This suggests that cefoperazone-sulbactam with monotherapy or combination therapy may have a greater effect than other therapies. In a retrospective analysis and review of all *A. baumannii* clinical isolates for patients with the same drug, 77% of the patients (27/35) presented successful clinical efficacy [19]. Therefore, one of the few antimicrobial compounds that is now regarded as a viable solution to treat MDRAB infections is sulbactam [20]. The reason why sulbactam has the best evidence is probably due to its ability to saturate penicillin-binding proteins 1 and 3 when given in high doses, including ampicillin-sulbactam and cefoperazone-sulbactam [21]. As a result, sulbactam-based combinations are becoming more popular as alternative therapies. In actual clinical work, clinicians frequently select antibiotics based on the patient's evolving condition. For instance, even when blood culture drug sensitivity results indicate cefoperazone-sulbactam resistance, clinicians may still opt for combination therapy with cefoperazone-sulbactam. Nonetheless, there are no clinical outcomes to support the results in randomized clinical trials. Other observational studies evaluated the role of combination therapy versus monotherapy for the treatment of CRAB infections with different results because there is heterogeneity in terms of antibiotics, dosages, and type of primary diagnosis, which may make the interpretation of a few of these studies difficult [22-24].

In addition to cefoperazone-sulbactam, tigecycline was one of the most commonly used antibiotics when clinicians obtained positive blood samples, and as shown in the Sankey diagram (Figure 2), the number of antibiotic (after) uses of tigecycline increased. One of the few remaining treatments for CRAB is tigecycline, which is a relatively new drug [25]. The efficacy of tigecycline in the treatment of CRAB bacteremia still needs to be further evaluated [26]. The proportion of patients with other drugs continued to increase over time regardless of admission or after obtaining a positive CRAB sample, demonstrating that CRAB-BSI still presents a problem due to the paucity of available and effective treatments. Primary diagnosis is also one of the most important factors that determine the prognosis of patients. This finding was consistent with that of a multicenter study (EUROBACT-2) in Europe [4]. However, due to individual variability, the prognostic models in other AB and MDRAB studies did not discuss heterogeneity [33, 34]. The reason why clinical doctors need to pay attention to this is that patients with CRAB-BSI are always diagnosed with sepsis or even septic shock, particularly in the ICU. Sepsis is now mainly considered a highly heterogeneous disease, and its heterogeneity is still not clearly defined. Thus, the primary diagnosis may be an important source of heterogeneity. The primary diagnosis had a significant effect in different groups, but the proportion of respiratory system disease in people who experienced 28-day mortality was higher than that in those who survived at 28 days (Table 1). Nevertheless, CRAB is not explicitly directly associated with respiratory system disease. The mechanism of ALI, a severe respiratory system disease, is related to gut microbiota-derived succinate [29]. The 28-day mortality of ARDS is high and even greater than 40% with severe ARDS [30]. Therefore, the mortality rate of acute lung injury caused by sepsis is relatively high, which may explain the relatively high proportion of respiratory system disease in the mortality group. Instead, the proportion of digestive system disease was lower in the 28-day mortality group. For this result, we thought the role of digestive system disease was an underestimate because there is still no reliable tool to assess gastrointestinal dysfunction rapidly in the hospital [31]. Enteric infections are the primary contributors to the incidence, death, and DALYs lost in the burden of digestive diseases [30]. Digestive disease as a primary diagnosis in our study was less common; more resources and effort are needed to explain this.

We found that PCT > 1.89 ng/mL and time to inadequate antimicrobial therapy were two independent risk factors for CRAB-BSI. Procalcitonin (PCT), a precursor substance of calcitonin, is a hormone secreted by C cells in thyroid tissue to maintain calcium homeostasis in the healthy body, but PCT increases in amount due to hepatocyte and adipocyte release during sepsis [32,33]. A study among immunosuppressed patients with carbapenem-resistant gram-negative bacterial bloodstream infections also found that increased PCT levels were associated with mortality [34]. In addition, a systematic review and meta-analysis showed that increased PCT levels detected in early stages can be useful to diagnose sepsis or septic shock [35]. However, several of the included studies in the meta-analysis had substantial heterogeneity because of the potential sepsis subgroup. There is a similar phenomenon in which the PCT concentration in the case of gram-negative bacilli is significantly higher than that of gram-positive bacilli, anaerobes, non-fermentative bacteria, and fungi, also explaining why the source of heterogeneity may come from different pathogens [35-38]. For inadequate antimicrobial therapy, there are not many choices. According to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines, there is a limited range of preferred antibiotics for patients presenting with sulbactam-resistant CRAB, and high-dose tigecycline and colistin are not advised [18]. Second, regarding the pathogenicity of *A. baumannii*, it was thought that its pathogenicity was weak, and even positive blood culture results did not need active treatment. However, this viewpoint has long been controversial. This study identified that the time taken to adjust antibiotics constituted an independent risk factor for mortality, elevating the risk of death by a factor of 2.649

(range from 1.255 to 5.591). This finding underscores the necessity for clinicians to maintain heightened vigilance when patients present positive blood culture results.

The strengths of this study include clarification of the reasons why the risk factors for CRAB-BSI in this paper differ from those in other studies and the evidence of the effect of cefoperazone-sulbactam. We believe that the difference between the risk factors studied proves that understanding the subphenotypes of sepsis is key to developing more accurate predictive models. Based on the genomic data of blood leukocytes and the differences in pathogenicity of different pathogens, it is possible to construct a special and specific sepsis subtype to reduce the heterogeneity between homogeneous clinical studies and make study results more reliable [39]. It is surprising that cefoperazone-sulbactam seems to provide the best evidence for initial use in patients with CRAB-BSI. However, more research is needed to determine its effectiveness as well as adverse effects. However, the present study has several limitations. First, as a retrospective study, several confounding factors could not be controlled for. There was an enormous difference between the two groups in the diagnosis of patients at admission. Compared with the survival group, the mortality group had a higher proportion of respiratory system diseases and a lower proportion of digestive system diseases. The prognosis of respiratory system diseases is often worse than that of digestive system diseases, and this difference may have contributed to bias in this study. Second, because this was an observational study, it could not control for heterogeneity in antibiotic regimens. Therefore, high-quality RCTs are needed to further verify the results of this paper.

CONCLUSION

Our findings revealed that primary diagnosis, time to inadequate antimicrobial therapy, and procalcitonin (PCT) > 1.89 ng/mL were independent risk factors for death from CRAB-BSI. Evidence was found for the initial use of cefoperazone-sulbactam in CRAB-BSI patients. This study provides a nomogram for CRAB-BSI with good performance that is able to predict mortality in future clinical work.

Ethics Statement:

This study was reviewed and approved by the ethics committees of the Affiliated Hospital of Guizhou Medical University. Informed consent was not required because the medical records and patient information were anonymously reviewed and collected in this observational study.

Availability of Data and Materials:

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of Interest:

The authors declare that there are no conflicts of interest.

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