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Clinical efficacy and risk factors of colistin sulfate in the treatment of carbapenem-resistant Gram-negative bacilli infections: A retrospective study

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ABSTRACT

Objective: Infections caused by carbapenem-resistant Gram-negative bacilli (CR-GNB) have become a global public health concern because of their high incidence and mortality. Although intravenous colistin sulfate has been widely used for the treatment of CR-GNB infections, systematic evaluations of its clinical efficacy and safety remain limited. This study aims to evaluate the clinical efficacy and safety of colistin sulfate in the treatment of CR-GNB infections and to analyze factors associated with therapeutic efficacy and prognosis, thereby providing evidence for rational clinical use and improved patient outcomes.

Methods: Clinical data of patients from the Third Xiangya Hospital of Central South University who received intravenous colistin sulfate for CR-GNB infections between July 2020 and March 2023 were retrospectively collected, including demographic characteristics, infection-related information (infection sites, pathogens, and antimicrobial susceptibility results), concomitant medications (drug type, dosage, and treatment duration), laboratory findings, and patient outcomes. The clinical efficacy and safety of colistin sulfate for CR-GNB infections were evaluated, and the 30-day all-cause mortality and microbiological eradication rate were analyzed. Multivariable Logistic regression analysis was performed to identify independent risk factors affecting the clinical efficacy of colistin sulfate treatment and to construct a predictive model. The predictive performance of the model was assessed using the area under the receiver operating characteristic curve (AUROC). Kaplan-Meier curves and Cox regression models were used to analyze factors associated with 30-day all-cause mortality.

Results: A total of 112 patients with CR-GNB infections were included. Among them,

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85.7% were admitted to the intensive care unit (ICU), 67.9% received mechanical ventilation, and 51.8% required vasopressor support. The lung was the most common site of infection (81.3%), followed by bloodstream infection (17.0%). The predominant pathogens were *Klebsiella pneumoniae* (69.6%) and *Acinetobacter baumannii* (60.7%), and 72 (64.3%) patients were infected with 2 or more pathogens. All patients received combination therapy with colistin sulfate, most commonly in combination with carbapenems (75.0%). After treatment, the overall clinical response rate was 67.0%, the microbiological eradication rate was 48.8%, and the 30-day all-cause mortality rate was 28.6%. The clinical response rates and 30-day all-cause mortality rates were generally similar among different combination regimens. Colistin sulfate combined with carbapenems achieved the highest clinical response rate (56/84, 66.7%), whereas colistin sulfate combined with ceftazidime-avibactam showed the lowest clinical response rate (9/17, 52.9%) but the lowest 30-day all-cause mortality rate (4/17, 23.5%). In addition, 16 (16/90, 17.8%) patients developed acute kidney injury during treatment, and 16 (16/112, 14.3%) patients developed colistin resistance among CR-GNB isolates during hospitalization. The multivariate Logistic regression model was established as follows: *Y* (clinical efficacy)=2.174−0.031×(age)−1.510×(mechanical ventilation)−1.720×(continuous renal replacement therapy)+0.004×(platelet count)+1.908×(treatment duration≥7 d). The AUROC was 0.840 (95% *CI* 0.761 to 0.919), indicating good predictive performance, and the calibration curve showed good model fit (Hosmer-Lemeshow χ^2=5.909, *P*=0.657). Cox regression analysis demonstrated that a higher baseline platelet count (adjusted *HR*=0.99, 95% *CI* 0.99 to 1.00, *P*=0.029) and treatment duration ≥7 d (adjusted *HR*=0.31, 95% *CI* 0.11 to 0.90, *P*=0.031) were independently associated with lower 30-day all-cause mortality.

Conclusion: Colistin sulfate is effective in the treatment of CR-GNB infections. Treatment duration ≥7 d is an independent factor associated with improved clinical efficacy and survival. During adequate treatment courses, the emergence of colistin resistance should be closely monitored, and combination regimens should be selected according to antimicrobial susceptibility results.

KEY WORDS colistin sulfate; carbapenem-resistant Gram-negative bacilli; clinical efficacy; 30-day all-cause mortality; risk factors

硫酸黏菌素治疗碳青霉烯类耐药革兰氏阴性杆菌感染的临床疗效与危险因素分析：一项回顾性研究

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［摘 要］**目的：**碳青霉烯类耐药革兰氏阴性杆菌(carbapenem-resistant Gram-negative bacilli，CR-GNB)感染因高发生率与高病死率，已成为全球性公共卫生问题。注射用硫酸黏菌素虽已广泛用于CR-GNB感染的治疗，但其临床疗效与安全性的系统评价仍有限。本研究旨在评估硫酸黏菌素治疗CR-GNB感染的临床疗效及安全性，并分析影响疗效与预后的相关因素，以期为临床合理用药、改善患者结局提供依据。**方法：**回顾性收集2020年7月至2023年3月

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期间静脉使用硫酸黏菌素治疗CR-GNB感染患者的临床资料，包括人口学特征、感染情况(感染部位、病原体及药敏结果)、合并用药(种类、剂量、疗程)、实验室检查结果及患者预后。评估硫酸黏菌素对CR-GNB感染的临床疗效及安全性，并分析30 d全因死亡率、微生物清除率。采用多变量Logistic回归分析影响硫酸黏菌素治疗CR-GNB感染临床疗效的独立危险因素并构建预测模型，运用受试者操作特征曲线下面积评估模型的预测性能，采用Kaplan-Meier曲线和Cox回归模型分析30 d全因死亡率的影响因素。**结果：**共纳入112例CR-GNB感染患者，其中85.7%的患者入住ICU，67.9%的患者使用呼吸机辅助通气，51.8%的患者使用血管活性药物支持治疗。感染部位以肺部为主(81.3%)，其次为血流感染(17.0%)；病原体以肺炎克雷伯菌(69.6%)和鲍曼不动杆菌(60.7%)为主，72例(64.3%)患者感染2种及以上病原体。所有患者均采用硫酸黏菌素联合治疗方案，联合药物以碳青霉烯类药物为主(75.0%)。经治疗后，患者的总体临床有效率为67.0%、微生物根除率为48.8%、30 d全因死亡率为28.6%。不同联合治疗方案的临床有效率和30 d全因死亡率接近，其中硫酸黏菌素联合碳青霉烯类药物治疗方案的临床有效率最高(56/84，66.7%)；硫酸黏菌素联合头孢他啶阿维巴坦治疗方案的临床有效率最低(9/17，52.9%)，但该联合方案30 d全因死亡率最低(4/17，23.5%)。此外，16例(16/90，17.8%)患者用药期间发生急性肾损伤，16例(16/112，14.3%)患者在住院期间出现CR-GNB对黏菌素耐药性进展。多因素Logistic回归模型公式为*Y*(临床疗效)=2.174−0.031×(年龄)−1.510×(呼吸机辅助通气)−1.720×(连续性肾脏替代治疗)+0.004×(血小板计数)+1.908×(治疗时间≥7 d)。受试者操作特征曲线下面积为0.840(95% *CI* 0.761~0.919)，提示预测模型预测性能较好，且校正曲线图与模型拟合较好(Hosmer Lemeshow χ^2=5.909，*P*=0.657)。Cox回归分析显示，较高的基线血小板计数(校正后*HR*=0.99，95% *CI* 0.99~1.00，*P*=0.029)和用药时间≥7 d(校正后*HR*=0.31，95% *CI* 0.11~0.90，*P*=0.031)与较低的30 d全因死亡率独立相关。**结论：**硫酸黏菌素治疗CR-GNB感染有效。用药时间≥7 d是临床有效性与生存的独立保护因素。在足疗程用药过程中应密切监测硫酸黏菌素的耐药性进展，并根据药敏结果选择联合用药方案。

[关键词] 硫酸黏菌素；碳青霉烯耐药革兰阴性杆菌；临床疗效；30 d全因死亡率；危险因素

In recent years, nosocomial infections caused by carbapenem-resistant Gram-negative bacilli (CR-GNB) have become a global concern due to their high mortality and morbidity, particularly among critically ill patients[1-2]. The broad antimicrobial resistance of CR-GNB and the limited treatment options available have led to a resurgence of polymyxins as a last-line therapeutic option (after exhausting effective salvage therapy measures) due to their high sensitivity against CR-GNB in clinical practice[3-4].

Polymyxins are a class of lipopeptide antibiotics approved in the late 1950s[3]. They have a unique mechanism of action in which they interact with phospholipids and lipopolysaccharides (LPS), leading to damage to the outer membrane integrity of Gram-negative bacilli[5]. Currently, 3 intravenous formulations of polymyxins, including polymyxin B, colistin sulfate, and colistin methanesulfonate sodium (CMS), are available for clinical use[6]. Among these, CMS is a pro-drug that is converted into active polymyxin E through the kidneys to exert bactericidal effects, whereas polymyxin B and colistin sulfate act directly without requiring conversion[7-8].

Colistin sulfate, another active form of polymyxin E, has been in widespread use in China since 2019. In 2010, Huang, et al[9] were the first to report that intravenous colistin sulfate was a promising alternative for the treatment of severe infections caused by multidrug-resistant (MDR) Gram-negative bacteria, with a clinical response rate of 73.3% and a microbiological clearance rate of 60% among 15 patients. However, a recent study[10] showed that the clinical efficacy rate was only 41.7% among patients infected with CR-GNB. Another study[11] indicated that among patients infected with CR-GNB, the clinical efficacy rate was 94.4% in the colistin combined therapy group and 73.3% in the monotherapy group, respectively. To date, several studies[9-17] have reported that the clinical efficacy of colistin sulfate varied considerably, ranging from 41.7% to 94.4%, owing to the heterogeneity observed in various factors such as patient inclusion criteria, causative pathogens, infection site, and monotherapy or combined therapy regimens. Overall, studies[9-17] on the clinical efficacy and safety of colistin sulfate were still limited to some extent with relatively small sample sizes. Thus, more research on this topic is needed to optimize the use of colistin sulfate.

In the present study, a real-world retrospective study was conducted to evaluate the efficacy and safety of colistin sulfate in the treatment of CR-GNB

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infections. In addition, the study also aims to identify risk factors associated with favorable response and mortality rates, and to provide a reference for the use of colistin sulfate in clinical practice.

1 Subjects and methods

1.1 Ethics statements

This retrospective study was carried out at the Third Xiangya Hospital of Central South University from July 2020 to March 2023. The research design fully adhered to the Declaration of Helsinki and was approved by the Ethics Committee of the Third Xiangya Hospital of Central South University (Approval number: Quick 23700), and the need for patient consent was waived.

1.2 Study design and patients

Patients meeting all the following criteria were included: 1) Age≥18 years; 2) received intravenous colistin sulfate (Colistin, Asia Pioneer Pharmaceutical Co., Ltd., Shanghai, China) treatment for more than 72 h; 3) had culture-documented evidence of at least 1 CR-GNB infection. The susceptibility of CR-GNB to carbapenems was determined according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines[18]. The exclusion criteria were as follows: 1) A history of intravenous use of polymyxin B or colistin sulfate in the past 14 d; 2) pregnant or lactating women; 3) clinical efficacy could not be evaluated owing to non-infectious factors. Eligibility was determined independently by 2 physicians based on the inclusion and exclusion criteria.

1.3 Data collection

Data were retrieved from the electronic medical records, including demographic data and comorbidities, intensive care unit (ICU) admission, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, clinical features of the infections (including the site of infection, the type of CR-GNB, co-infecting bacteria, and the bacterial susceptibility to colistin), physiological parameters and laboratory indices at the initiation of colistin sulfate, antimicrobial therapy regimens, and the data of colistin sulfate use (including loading dose, maintenance dose, administration route, duration, cumulative dose, etc.), clinical efficacy, and adverse effects. Data were collected for the duration of the hospitalization, and follow-up was completed at day 30 following colistin sulfate initiation, at the time of death, whichever occurred first.

1.4 Outcomes and definitions

The primary endpoints were clinical efficacy and 30-day all-cause mortality. Secondary endpoints included microbiological eradication, development of colistin resistance, and adverse drug reaction (ADR) associated with colistin sulfate. All clinical outcomes were assessed by 1 physician and 1 clinical pharmacist. Discrepancies were resolved by a third investigator.

Clinical efficacy was classified as clinical success (CS) or clinical failure (CF). CS was defined as a composite of survival and either disappearance or improvement of infection-related signs and symptoms at the end of the treatment. CF was defined by any of the following criteria: Death related to infection, hemodynamic instability, deterioration in the SOFA score, persistent fever >38.5 ℃, or worsening biochemical indicators of infection[15].

Thirty-day all-cause mortality was recorded from the start of colistin sulfate treatment, including in-hospital deaths and patients who were discharged after abandonment of treatment.

Microbiological eradication was defined as the absence of original CR-GNB from the same site of infection after the treatment with colistin sulfate. Persistence was defined as the repeat isolation of bacteria on or day 7 after colistin sulfate administration. Indeterminate was defined as absence of bacterial culture after colistin therapy. Microbiological eradication rate was calculated as the number of pathogens eradicated divided by the total number of pathogens that were either eradicated or persisted (cases classified as indeterminate were excluded from the denominator).

Colistin susceptibility was determined per EUCAST guidelines (v13.0, 2023) [18], with a minimum inhibitory concentration (MIC) ≤2 mg/L considered susceptible. Development of colistin resistance was defined as a 4-fold increase in the MIC values of colistin for the same isolate after the initiation of colistin sulfate.

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Antimicrobial susceptibility testing was performed using a VITEK®-2 Compact automated system (bioMérieux, France) with VITEK cards (colistin range: 0.5 to 16 mg/L). According to the EUCAST guideline (v10.0, 2020)[19], ADR associated with colistin sulfate was defined as a noxious response unrelated to the purpose of the treatment, emerged after colistin sulfate use and disappearing upon its discontinuation. According to the prescribing information, ADRs include nephrotoxicity, rash, and neuromuscular blockade. The occurrence of acute kidney injury (AKI) was evaluated using the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria[20], excluding patients who had an estimated glomerular filtration rate [eGFR, calculated by the Chronic Kidney Disease Collaboration (CKD-EPI) equation] ≤15 mL/(min·1.73 m^2) at the initiation of polymyxin therapy, or who had no serum creatinine (SCr) measurement, or who required dialysis or any form of renal replacement therapy at baseline.

1.5 Statistical analysis

All statistical analyses were conducted using R software (version 4.2.2). Normally distributed continuous variables were presented as mean±standard deviation (*SD*), and non-normally distributed variables as median (25th percentile, 75th percentile). Between-group comparisons were performed using Student's *t*-test for normally distributed data and the Mann-Whitney *U* test for non-normally distributed data. Categorical variables were presented as number and percentage and compared using χ^2 test or Fisher exact test. Variables with a $P<0.1$ were included in a multivariate Logistic regression model to identify independent factors related to clinical efficacy, and a Cox regression model for 30-day all-cause mortality. Variables were assessed for potential confounding and collinearity, and a forward stepwise method was employed to select the final predictors. Additionally, the discriminatory power of the final Logistic regression model was evaluated using the area under the receiver operating characteristic curve (AUROC), and the goodness of fit was assessed using the Hosmer-Lemeshow test. Kaplan-Meier survival curves were generated to illustrate survival probability within 30 d, and were compared between groups using the log-rank test. All tests were 2-tailed, and $P<0.05$ was considered statistically significant.

2 Results

2.1 Clinical characteristics of patients

Table 1 shows the demographic and clinical information of 112 patients enrolled. The median age was 66.0 (51.0, 74.0) years, and 87 (77.7%) patients were male. The APACHE II score and SOFA score were 15.0 (11.8, 22.8) and 7.0 (4.0, 11.0), respectively. Among these patients, 76 (67.9%) received mechanical ventilation, 36 (32.1%) had septic shock, and 96 (85.7%) were admitted to the ICU. Moreover, vasopressors were administered to 58 (51.8%) patients, and glucocorticoids to 40 (35.7%) patients. The most common underlying disease was cardiovascular disease (61.6%), followed by chronic liver disease (46.4%) and hypertension (38.4%).

Among all patients, 20 (17.9%) had more than 2 infection sites caused by CR-GNB. The most common infection site was the lung (81.3%), followed by bloodstream (17.0%), abdomen (12.5%), graft (6.3%), skin and soft tissue (5.4%), and urinary system (4.5%). In this study, 164 CR-GNB isolates were recovered, including *Klebsiella pneumoniae* (*K. pneumoniae*) from 78 (69.6%) patients and *Acinetobacter baumannii* (*A. baumannii*) from 68 (60.7%) patients. Supplementary Table 1 details the specific infection sites and causative pathogens (https://doi.org/10.57760/sciencedb.xbyxb.00156). Moreover, Gram-positive aerobes, fungi, and viruses were isolated from 22 (19.6%) patients, 22 (19.6%) patients, and 14 (12.5%) patients, respectively. Seventy-two (64.3%) patients were infected with 2 or more pathogens (Table 2).

Regarding antibiotic treatment, 34 (30.4%) patients received colistin sulfate before the results of the CR-GNB culture were available. Before colistin sulfate use, most patients had previously received intravenous antimicrobial therapy: Eighty-four (75.0%) patients had received carbapenems, 17 (15.2%) patients tigecycline, and 5 (4.5%) ceftazidime/avibactam. A loading dose of colistin sulfate was given to only 44 (39.3%) patients, and 53 (47.3%) patients received nebulized colistin. The daily maintenance doses of colistin sulfate ranged from 1.0 to 3.0 MU. All patients received colistin-based combination therapy; 75.0% of patients received concomitant carbapenems, followed by cefoperazone/sulbactam

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(19.6%), ceftazidime/avibactam (15.2%), and tigecycline (14.3%). The treatment duration of colistin sulfate was 9.0 (6.0, 13.3) days, and the cumulative intravenous dose was 14.3 (9.9, 21.0) MU (Table 3).

Table 1 Characteristics for the 112 patients with CR-GNB infection

Variables	Values	Variables	Values
Age/years	66.0(51.0, 74.0)	Concomitant vasopressors/[No.(%)]	58(51.8)
Male/[No.(%)]	87(77.7)	Concomitant glucocorticoids/[No.(%)]	40(35.7)
Disease severity		Underlying diseases/[No.(%)]	
APACHE II score	15.0(11.8, 22.8)	Cardiovascular disease	69(61.6)
SOFA score	7.0(4.0, 11.0)	Chronic liver disease	52(46.4)
Mechanical ventilation/[No.(%)]	76(67.9)	Hypertension	43(38.4)
ICU admission/[No.(%)]	96(85.7)	Diabetes mellitus	29(25.9)
Surgery/[No.(%)]	39(34.8)	Chronic pulmonary disease	27(24.1)
Hypoalbuminemia (<30 g/L)/[No.(%)]	81(72.3)	Solid organ transplantation	18(16.1)
Severely immunocompromised status*/[No.(%)]	22(19.6)	Chronic kidney disease	19(17.0)
Septic shock /[No.(%)]	36(32.1)	Tumor	20(17.9)
CRRT/[No.(%)]	18(16.1)	Trauma	10(8.9)

Non-normally distributed variables are presented as median (25th percentile, 75th percentile). Categorical variables are presented as number and percentage. CR-GNB: Carbapenem-resistant Gram-negative bacilli; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; ICU: Intensive care unit; CRRT: Continuous renal replacement therapy. *Severely immunocompromised status is defined as meeting any of the following criteria: Neutropenia (absolute neutrophil count <500 cells/μL), leukemia, lymphoma, human immunodeficiency virus infection with $CD4^+$ T cell count <200 cells/μL, solid organ or hematopoietic stem cell transplantation, cytotoxic chemotherapy, or steroid use (prednisone equivalent >15 mg/d for >2 weeks).

Table 2 Infection characteristics and pathogenic features of 112 patients with CR-GNB infection

Variables	No.(%)	Variables	No.(%)
CR-GNB infection sites		Patients infected with ≥2 CR-GNB	24(21.4)
Lung	91(81.3)	Patients with CR-GNB infection and other pathogens	
Bloodstream	19(17.0)	Gram-positive aerobes	22(19.6)
Abdomen	14(12.5)	Fungus	22(19.6)
Graft	7(6.3)	Virus	14(12.5)
Skin and soft tissue	6(5.4)	Patients infected with ≥2 types of pathogen	72(64.3)
Urinary tract	5(4.5)	Colistin MIC distribution for CR-GNB*	
Patients with ≥2 infection sites by CR-GNB	20(17.9)	MIC≤0.5 mg/L	95(57.9)
Patients with CR-GNB infection		MIC=1 mg/L	10(6.1)
Klebsiella pneumoniae	78(69.6)	MIC=2 mg/L	38(23.2)
Acinetobacter baumannii	68(60.7)	MIC=4 mg/L	2(1.2)
Pseudomonas aeruginosa	11(9.8)	MIC=8 mg/L	1(0.6)
Acinetobacter pittii	3(2.7)	MIC=16 mg/L	5(3.0)
Others	4(3.6)	Unknown†	13(7.9)

*CR-GNB is identified from clinical specimens. Isolates of the same pathogen from the same infection site with identical antimicrobial susceptibility profiles are counted as one pathogen; isolates differing in species, infection site, or antimicrobial susceptibility profile are considered distinct pathogens. A total of 164 CR-GNB isolates were included in the analysis. †Colistin susceptibility is reported as susceptible without a specific MIC value. MIC: Minimum inhibitory concentration.

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Table 3 Antimicrobial treatment regimens of 112 patients with CR-GNB infection

Variables	Values
Preemptive therapy*/[No.(%)]	34(30.4)
Previous use of carbapenems/[No.(%)]	84(75.0)
Previous use of tigecycline/[No.(%)]	17(15.2)
Previous use of ceftazidime/avibactam/[No.(%)]	5(4.5)
Loading dose of colistin/[No.(%)]	44(39.3)
Maintenance dose of colistin†//[No.(%)]	
3.0 MU/d	2(1.8)
2.0 MU/d	23(20.5)
1.5 MU/d	81(72.3)
1.0 MU/d	19(17.0)
Cumulative intravenous dose of colistin/MU	14.3(9.9, 21.0)
Treatment duration of colistin/d	9.0(6.0, 13.3)
Nebulized colistin/[No.(%)]	53(47.3)
Therapy regimens/[No.(%)]	
Colistin+carbapenems	84(75.0)
Colistin+cefoperazone/sulbactam	22(19.6)
Colistin+ceftazidime/avibactam	17(15.2)
Colistin+tigecycline	16(14.3)
Colistin+piperacillin/tazobactam or levofloxacin	2(1.8)
Three-drug regimen‡	10(8.0)

Non-normally distributed variables are presented as median (25th percentile, 75th percentile). Categorical variables are presented as number and percentage. *Colistin sulfate is administered before the results of the CR-GNB culture are available. † A total of 13 patients received multiple maintenance doses and were counted in each applicable category: Two patients in both the 2.0 and 1.5 MU/d groups, and 11 in both the 1.5 and the 1.0 MU/d groups. ‡A three-drug regimen is defined as colistin combined with carbapenems plus one additional antimicrobial agent, which may be cefoperazone/sulbactam, ceftazidime/avibactam, tigecycline, piperacillin/tazobactam, or levofloxacin. MU: Million units

2.2 Therapeutic efficacy

The overall rate of clinical favorable response was 67.0% (Table 4). Compared with the CF group, patients in the CS group had significantly lower 30-day all-cause mortality (17.8% vs 48.7%, $P<0.001$; Supplementary Table 2, https://doi.org/10.57760/sciencedb.xbyxb.00156). Among the 7 patients with graft infection, the clinical favorable response rate was 71.4%, which was higher than the rates observed for pulmonary infection (61/91, 67.0%), urinary system infection (3/5, 60.0%), bloodstream infection (11/19, 52.6%), skin and soft tissue infection (3/6, 50.0%), and abdomen infection (6/14, 42.9%) (Figure 1A). No significant differences in clinical favorable response rates were observed among groups based on infection site (Figure 1A), pathogenic bacteria (Figure 1B), or combination therapy regimens (all $P>0.05$, Figure 1C). Moreover, the clinical favorable response rate was 67.2% in patients infected with *K. pneumoniae*, slightly higher than the rate of 64.5% in patients infected with *A. baumannii* (Figure 1B; Supplementary Table 3, https://doi.org/10.57760/sciencedb.xbyxb.00156). In addition, patients infected with *K. pneumoniae* of an MIC ≤0.5 mg/L showed a superior response rate (72.5%) compared with those infected with *K. pneumoniae* with an MIC of 2 mg/L (57.1%) (Supplementary Table 3, https://doi.org/10.57760/sciencedb.xbyxb.00156). Three-drug regimens (colistin combined with carbapenems plus 1 additional antimicrobial agent, including cefoperazone/sulbactam, ceftazidime/avibactam, tigecycline, piperacillin/tazobactam, or levofloxacin) showed slightly lower clinical efficacy than colistin combined with carbapenems or cefoperazone/sulbactam (Figure 1C).

Univariate analysis was performed to identify risk factors associated with a clinical favorable response rate. Our results showed that 15 variables were significantly associated with clinical efficacy, including age, APACHE II score, SOFA score, septic shock, receipt of surgery, mechanical ventilation or continuous renal replacement therapy (CRRT), elevated alanine aminotransferase, platelet count, prothrombin time activity, prothrombin time, international normalized ratio, concomitant use of vasopressors, and cumulative dose and treatment duration of colistin ($P<0.05$, Table 5). A multivariate Logistic regression model was then developed using 18 variables ($P<0.10$) to predict a favorable clinical response rate. Age (adjusted *OR*=0.97, 95% *CI* 0.94 to 1.00, $P=0.047$), mechanical ventilation (adjusted *OR*=0.22, 95% *CI* 0.06 to 0.68, $P=0.012$), CRRT (adjusted *OR*=0.18, 95% *CI* 0.04 to 0.69, $P=0.015$), and treatment duration ≥7 d (adjusted *OR*=6.74, 95% *CI* 2.49 to 20.29, $P<0.001$) were identified as independent factors associated with a favorable clinical response (Table 5). The final regression model equation (log odds of favorable response) was as follows: $Y=2.174-0.031\times$

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(age)−1.510×(mechanical ventilation)−1.720×(CRRT)+0.004×(platelet count)+1.908×(treatment duration ≥7 d).

The receiver operating characteristic (ROC) curve (Figure 2A) demonstrated an area under the curve (AUC) of 0.840 (95% *CI* 0.761 to 0.919), with a sensitivity of 76.7% and a specificity of 79.5% at the optimal cutoff value. Additionally, the calibration curve (Figure 2B) showed good model fit (Hosmer Lemeshow χ^2=5.909, *P*=0.657).

Table 4 Antimicrobial efficacy and safety of 112 patients with CR-GNB infection

Variables	Values	Variables	Values
Efficacy		Safety	
Clinical efficacy/[No.(%)]	75(67.0)	Development of resistance/[No.(%)]	16(14.3)
Microbiological eradication*/[No.(%)]	59(48.8)	AKI†/[No.(%)]	16(17.8)
Microbiological removal time/d	7.0(4.0, 10.0)	Time to AKI/days	6.0(2.8, 8.0)
30-day all-cause mortality/[No.(%)]	32(28.6)	Severity of AKI by RIFLE criteria/[No.(%)]	
Length of hospital stay/d	28.0(19.8, 46.0)	Risk	7(7.8)
Length of ICU stay/d	19.7(8.0, 29.2)	Injury	8(8.9)
Length of mechanical ventilation/d	7.6(0.5, 16.9)	Failure	1(1.1)

Non-normally distributed variables are presented as median (25th percentile, 75th percentile). Categorical variables are presented as number and percentage. *Microbiological eradication is assessed at the end of treatment based on follow-up bacterial culture results. Isolates with an indeterminate response (i.e., no repeat bacterial culture after treatment) are excluded. Among the 164 CR-GNB isolates, 43 were excluded due to lack of follow-up culture, leaving 121 isolates for the evaluation of microbiological eradication. †Among the 112 patients, 2 were excluded due to missing serum creatinine measurements, and 20 were excluded because they required renal replacement therapy before initiation of colistin sulfate, leaving 90 patients for the analysis of AKI. AKI is defined as a serum creatinine increase >1.5 fold or an eGFR decrease >25% from baseline within 7 days according to the RIFLE criteria. AKI: Acute kidney injury; eGFR: Estimated glomerular filtration rate; RIFLE: Risk, injury, failure, loss of kidney function, and end-stage kidney disease.

2.3 Microbiological eradication

Among the 164 CR-GNB isolates, 95 (57.9%) had a colistin MIC ≤0.5 mg/L; the MIC was 1 mg/L in 10 (6.1%), 2 mg/L in 38 (23.2%), and ≥4 mg/L in 8 (4.9%) (Table 2). The overall rate of microbiological eradication was 48.8%, with a microbiological removal time of 7.0 (4.0, 10.0) days (Table 4). Moreover, *K. pneumoniae* had the highest microbiological eradication rate of 56.7%, followed by *A. baumannii* with the microbiological eradication rate of 42.9% (Supplementary Table 1, https://doi.org/10.57760/sciencedb.xbyxb.00156). Additionally, microbiological eradication was achieved in 90.0% of patients with bloodstream infection and in 41.9% of those with pulmonary infection, with median times to eradication of 6 (4.0, 7.0) days and 7.5 (4.8, 10.5) days, respectively (Supplementary Table 1, https://doi.org/10.57760/sciencedb.xbyxb.00156). In this study, it was noted that higher rates of microbiological eradication for *K. pneumoniae* were linked to lower colistin MIC. Specifically, eradication rates were 64.1% for colistin MIC ≤0.5 mg/L and 50.0% for MIC value =2 mg/L. However, this association was not observed among *A. baumannii*. For *A. baumannii*, microbiological eradication rates were seemingly not correlated with baseline colistin MIC values (Supplementary Table 3, https://doi.org/10.57760/sciencedb.xbyxb.00156).

2.4 Mortality

Thirty-two patients died within 30 d, with an overall 30-day all-cause mortality of 28.6% (Table 4). The Kaplan-Meier analysis of 30-day survival (Figure 3) revealed several significant associations. Patients aged ≥ 65 years exhibited notably shorter survival times compared to their younger counterparts (log-rank test *P*=0.050). Additionally, ICU admission correlated with shorter survival times compared to those without ICU admission (log-rank test *P*=0.048), as did underlying comorbidities such as chronic pulmonary disease (log-

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rank test P=0.031), cardiovascular disease (log-rank test P=0.050), or septic shock (log-rank test P=0.001), which were also associated with shorter survival times. Moreover, patients treated with mechanical ventilation (log-rank test P=0.026), CRRT (log-rank test P=0.004), vasopressors (log-rank test P<0.001), or previous tigecycline treatment (log-rank test P=0.041) experienced shorter survival times compared to untreated counterparts. Similarly, patients with platelet count below 100×10^9/L (log-rank test P<0.001) and treatment duration less than 7 d (log-rank test P=0.004) exhibited shortened survival times.

Supplementary Table 4 (https://doi.org/10.57760/sciencedb.xbyxb.00156) shows the univariate analysis for 30-day all-cause mortality. The Cox multivariate analysis revealed that higher platelet count (adjusted HR=0.99, 95% CI 0.99 to 1.00, P=0.029) and treatment duration ≥7 d (adjusted HR=0.31, 95% CI 0.11 to 0.90, P=0.031) were independently associated with lower 30-day all-cause mortality (Table 6).

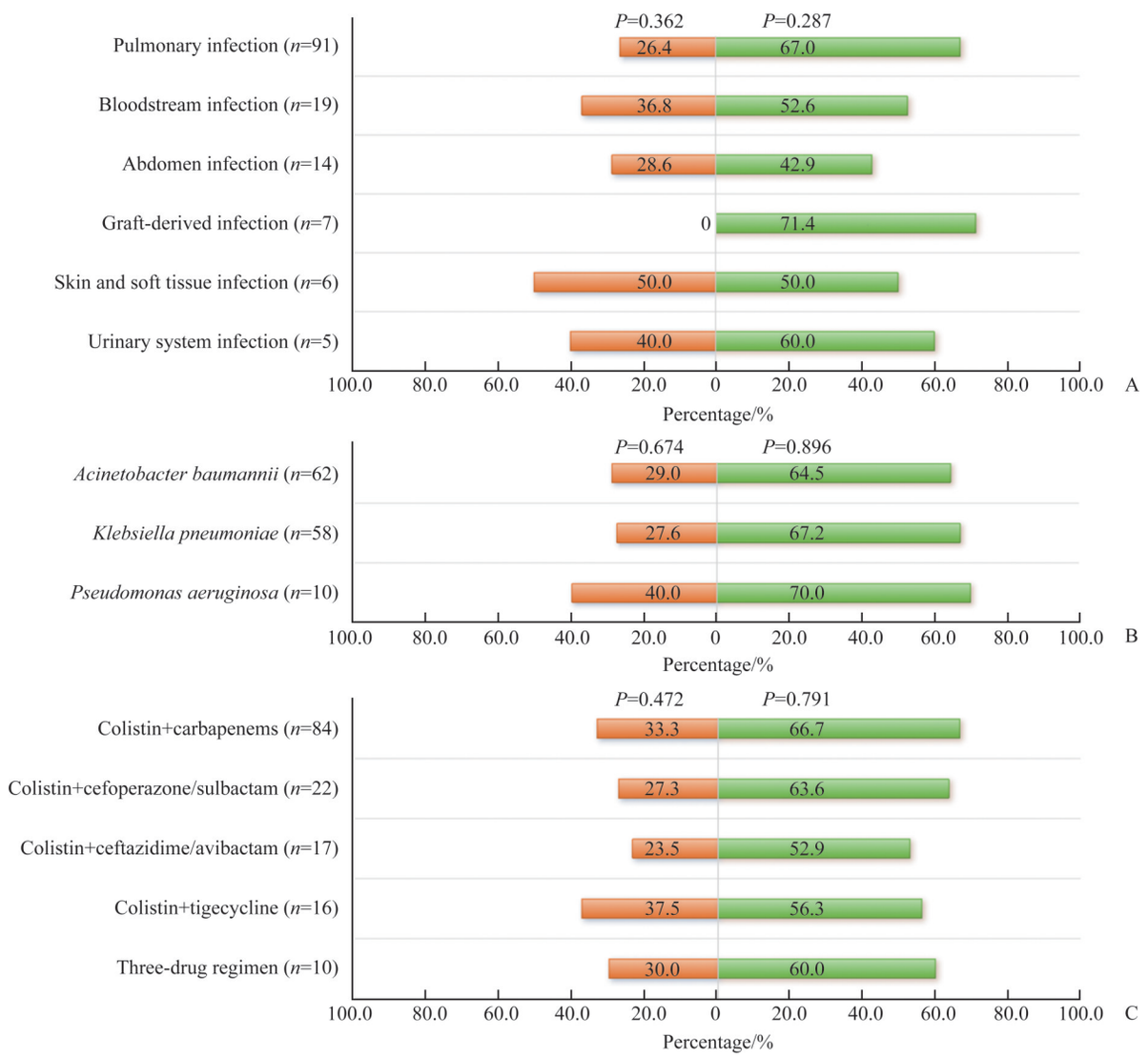


Figure 1 Thirty-day all-cause mortality and clinical favorable response rates in patients with CR-GNB infections, stratified by infection site (A), causative pathogen (B), and antimicrobial therapy regimen (C)

Orange bars indicate 30-day all-cause mortality, while green bars indicate clinical favorable response rates. Comparisons of categorical variables among multiple groups were performed using Fisher's exact test. No statistically significant differences were observed in either mortality or clinical favorable response rates among the subgroups. CR-GNB: Carbapenem-resistant Gram-negative bacillus.

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Table 5 Results of univariate analysis and multivariate Logistic regression analysis for clinical favorable response

Variables	Clinical success (n=73)	Clinical failure (n=39)	P*	β	Adjusted OR (95% CI)	P†
Intercept				2.174	8.79(0.71 to 151.11)	0.107
Age/years	62.0(48.0, 72.0)	71.0(54.5, 79.0)	0.035	−0.031	0.97(0.94 to 1.00)	0.047
APACHE II score	14.0(10.0, 20.0)	20.0(14.0, 26.0)	0.002			
SOFA score	7.0(4.0, 9.0)	9(6.0, 15.5)	0.005			
Mechanical ventilation	42(57.5)	34(87.2)	0.003	−1.510	0.22(0.06 to 0.68)	0.012
Surgery	32(43.8)	7(17.9)	0.011			
Septic shock	16(21.9)	20(51.3)	0.003			
CRRT	7(9.6)	12(30.8)	0.005	−1.720	0.18(0.04 to 0.69)	0.015
eGFR/[mL·min^{-1}·(1.73 m^2)$^{-1}$]‡	91.5(34.3, 109.8)	63.3(26.5, 90.8)	0.061			
Alanine transaminase/(U·L^{-1})	45(20, 94)	22(13, 43.5)	0.008			
Platelet count/(×10^9·L^{-1})	204(107, 298)	121(74, 194)	0.014	0.004	1.00(1.00 to 1.01)	0.115
Prothrombin time activity/%	77.1±20.0	67.5±22.6	0.029			
Prothrombin time/s	13.2(12.2, 14.5)	14.5(12.8, 16.1)	0.009			
INR	1.12(1.02, 1.28)	1.28(1.09, 1.4)	0.010			
CR-GNB abdomen infection	6(8.2)	8(20.5)	0.076			
Colistin MIC=1 mg/L	3(4.1)	4(10.3)	0.089			
Cumulative dose of colistin/MU	16.0(11.0, 22.0)	12.0(7.8, 18.8)	0.016			
Concomitant vasopressors	31(42.5)	27(69.2)	0.012			
Treatment duration≥7 d	57(78.1)	17(43.6)	<0.001	1.908	6.74(2.49 to 20.29)	<0.001

Normally distributed continuous variables are presented as mean±standard deviation, and non-normally distributed variables as median (25th percentile, 75th percentile). *Univariate analysis. †Multivariate Logistic regression analysis. ‡eGFR calculated by Chronic Kidney Disease Collaboration equation. INR: International normalized ratio.

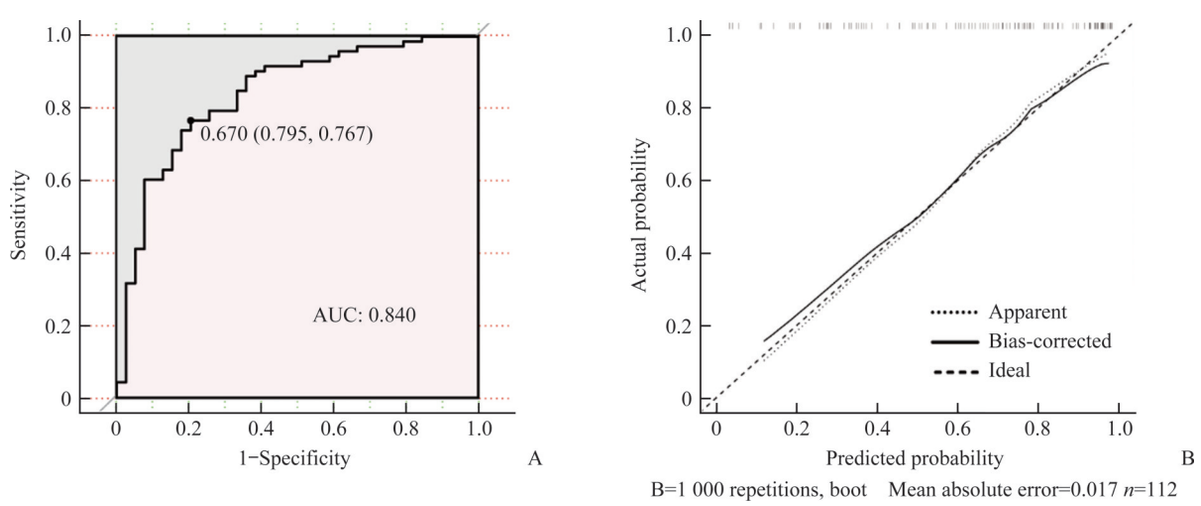


Figure 2 Receiver operating characteristic curve of the Logistic regression model for favorable clinical response (A) and the calibration curve of binary Logistic regression (B)

AUC: Area under the curve.

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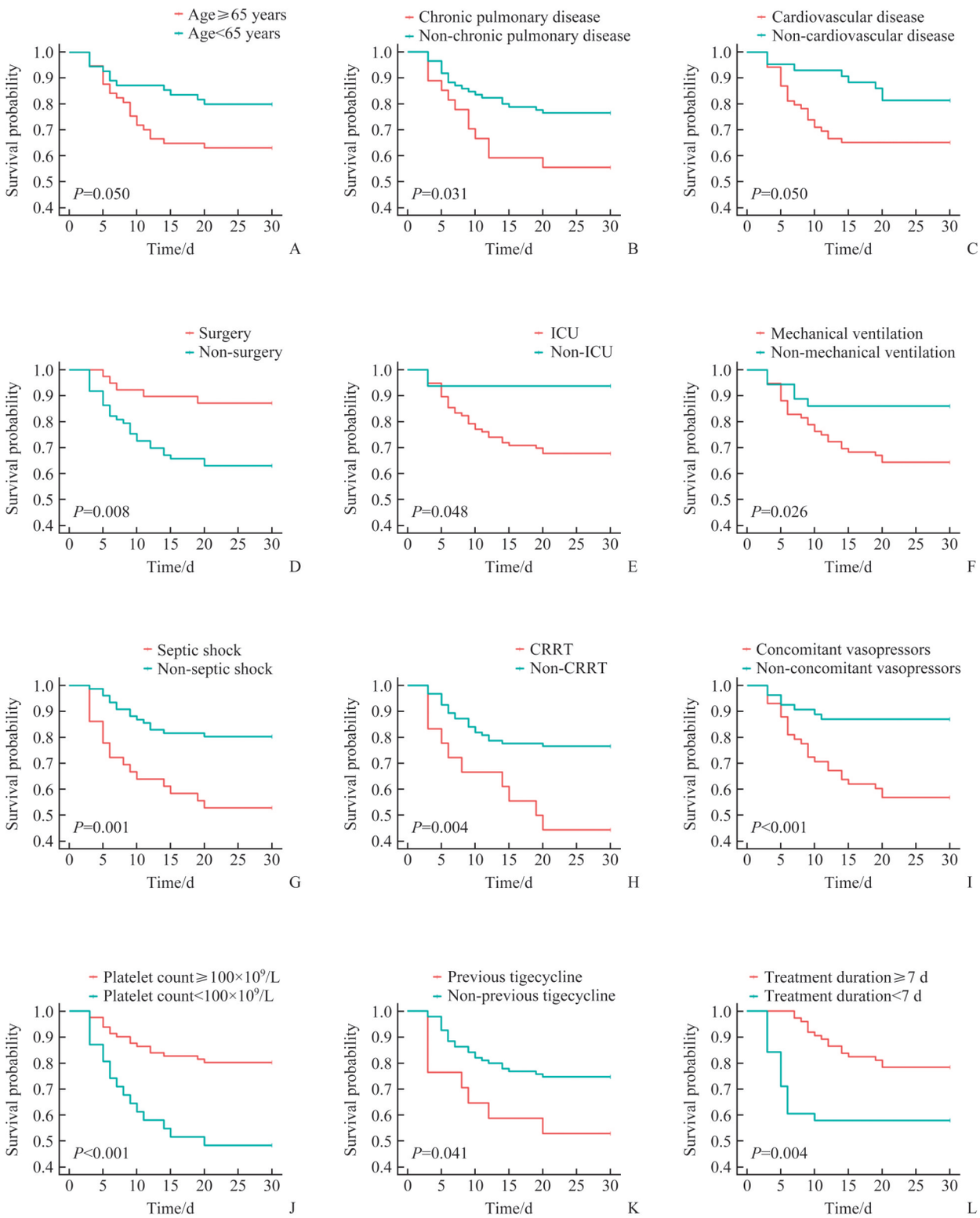


Figure 3 Kaplan-Meier curves for all-cause 30-day mortality

A: Age ≥65 years vs age <65 years. B: Chronic pulmonary disease vs non-chronic pulmonary disease. C: Cardiovascular disease vs non-cardiovascular disease. D: Surgery vs non-surgery. E: ICU admission vs without ICU admission. F: Mechanical ventilation vs non-mechanical ventilation. G: Septic shock vs non-septic shock. H: CRRT vs non-CRRT. I: Concomitant vasopressors vs non-concomitant vasopressors. J: Platelet count ≥100×10^9/L vs platelet count <100×10^9/L. K: Previous tigecycline vs non-previous tigecycline. L: Treatment duration ≥7 d vs treatment duration <7 d.

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Table 6 Results of univariate analysis and Cox regression analysis for 30-day all-cause mortality

Variables	Survival (*n*=80)	Death (*n*=32)	*P**	Adjusted *HR* (95% *CI*)	*P*†
Age/years	63.0(48.0, 72.3)	70.0(55.0, 77.5)	0.071		
SOFA score	7.0(4, 9)	9.0(5.8, 14.5)	0.024		
Mechanical ventilation	49(61.3)	27(84.4)	0.032		
ICU admission	65(81.3)	31(96.9)	0.037		
Surgery	34(42.5)	5(15.6)	0.013		
Sepsis shock	19(23.8)	17(53.1)	0.005		
CRRT	8(10.0)	10(31.3)	0.013		
Total bilirubin/(μmol·L^{-1})	12.9(8.7, 23.8)	15.6(11.0, 47.1)	0.072		
Direct bilirubin/(μmol·L^{-1})	6.4(3.7, 13.8)	8.6(5.3, 26.2)	0.076		
Prothrombin time activity/%	76.5±22.2	66.7±17.5	0.015		
Prothrombin time/s	13.3(12.4, 14.7)	14.4(13.0, 15.7)	0.069		
INR	1.1(1.0, 1.3)	1.3(1.1, 1.4)	0.043		
APTT/s	33.0(28.5, 39.4)	37.9(32.0, 44.0)	0.031		
Previous use of tigecycline	9(11.3)	8(25.0)	0.083		
Platelet count/(×10^{9}·L^{-1})	192.0(115.5, 299.3)	100.0(66.3, 220.3)	0.005	0.99(0.99 to 1.00)	0.029
Maintenance dose of colistin/MU	1.5(1.5, 1.5)	1.5(1.5, 2.0)	0.079		
Cumulative dose of colistin/MU	16.0(10.5, 22.1)	11.8(7.9, 18.41)	0.013		
Concomitant vasopressor	33(41.3)	25(78.1)	<0.001		
Colistin+carbapenems	56(70.0)	28(87.5)	0.091		
Treatment duration ≥7 d	58(72.5)	16(50.0)	0.040	0.31(0.11 to 0.90)	0.031

Normally distributed continuous variables are presented as mean±standard deviation, and non-normally distributed variables as median (25th percentile, 75th percentile). Categorical variables are presented as number and percentage. *Univariate analysis. †Cox regression analysis. APTT: Activated partial thromboplastin time.

2.5 Safety

Among the 112 patients, 2 were excluded due to missing serum creatinine measurements, and 20 were excluded because they required renal replacement therapy before initiation of colistin sulfate, leaving 90 patients for the analysis of AKI. Among the remaining 90 patients, 16 (17.8%) presented with some degree of renal impairment [7 (7.8%) patients were classified as risk degree, 8 (8.9%) patients as injury degree, and 1 (1.1%) patient as failure degree]. The time for AKI onset was 6.0 (2.8, 8.0) days (Table 4). There was no significant difference in AKI prevalence between the CS group and the CF group (*P*=0.132; Supplementary Table 2, https://doi. org/10.57760/sciencedb. xbyxb. 00156), nor between the survival group and the death group (*P*=0.699; Supplementary Table 4, https://doi.org/10.57760/sciencedb. xbyxb.00156).

A total of 16 isolates exhibited at least a 4-fold increase in colistin MIC from baseline (i. e., 11 for *K. pneumoniae*, 3 for *A. baumannii*, 1 for *P. aeruginosa,* and 1 for *E. aerogenes*). Among these 16 isolates, 11 isolates had an MIC value exceeding 4 mg/L, meeting resistance criteria for colistin (Supplementary Table 5, https://doi.org/10.57760/sciencedb.xbyxb.00156).

3 Discussion

This retrospective study investigated the efficacy and safety of colistin sulfate using clinical data from 112 critically ill patients infected with CR-GNB. Based on the recommended dose of 1.0 to 1.5 MU per day, the rates of clinical favorable response, microbiological eradication, and 30-day all-cause mortality were 67.0%, 48.8% and 28.6%, respectively. These rates indicated lower effectiveness than those reported in previous studies by Wu, et al[17] (74.6%, 72.6%, and 22.9%, respectively) and Hao, et al[11] (94.4%, 74.1%, and 11.5%, respectively), and were partially similar to the studies by Jin, et al[12] (58%, 40%, and 44%, respectively) and Lu, et al[13] (53.8%, 49.1%, and 27.7%, respectively), although the mortality rate in the Jin, et

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al[12] study was higher.

This disparity could be attributed to several factors, including differences in clinical efficacy criteria, causative pathogens, colistin MIC distribution, sites of infection, patients' comorbidities, and the use of combination therapy. Notably, in the present study, 81.3% of patients had pulmonary infections, which was a higher proportion than that in previous studies[10, 12, 17], while only 47.3% of patients received nebulized colistin sulfate. It is known that intravenous infusion of colistin sulfate generally has poor penetration into the lung tissues, potentially resulting in insufficient concentrations to inhibit or kill pathogens in the lungs. Furthermore, our study had a higher percentage of patients co-infected with more than 2 types of CR-GNB or with other pathogens (e. g., Gram-positive aerobes, fungi, or viruses), which also contributed to the lower clinical favorable response rate. We also found a higher MIC value of *K. pneumoniae* was associated with lower clinical efficacy (57.1% for isolates of MIC =2 mg/L vs 72.5% for isolates of MIC ⩽0.5 mg/L) in the present study. This finding was consistent with the previous study[21], indicating limited clinical efficacy of polymyxin-based therapy for isolates with the MIC value of 2 mg/L. Additionally, our study included 46 isolates (46/164) with an MIC value of ⩾2 mg/L, which represents a higher proportion than the range of 0% to 9.1% reported in previous studies[10, 11, 22]. This increase in the proportion of isolates with higher MIC values may have contributed to the lower clinical efficacy observed in our study.

Considering the heterogeneous resistance of polymyxins, combination therapy was recommended to treat CR-GNB infections[23]. In the current study, all patients received colistin sulfate combination regimens with carbapenems, tigecycline, cefoperazone/sulbactam, or ceftazidime/avibactam. No significant clinical efficacy or all-cause mortality rate was observed among different combination therapies. The relatively lowest clinical favorable response rate was observed in patients treated with colistin sulfate combined with ceftazidime/avibactam (52.9%) or tigecycline (56.3%), while those receiving a regimen of colistin sulfate combined with carbapenems had a higher clinical efficacy rate (66.7%). However, in comparison to other combination therapies, colistin sulfate combination with tigecycline had higher 30-day all-cause mortality of 50.0%. These findings supported the viewpoint that meropenem combined with colistin does not improve all-cause mortality in CR-GNB infection[24], and indicated that empirical therapy with carbapenems or tigecycline for CR-GNB infections should be used with caution. Additionally, previous tigecycline treatment was associated with shorter survival times and a higher 30-day all-cause mortality rate (25.0% vs 11.3%, P= 0.083). However, further multivariate Cox regression analysis showed that previous tigecycline treatment was not an independent factor affecting all-cause mortality, a finding that may be confounded by interactions with causative pathogens, concomitant antibiotics, or the MIC values of colistin and tigecycline. Therefore, it is recommended to use appropriate combination regimens based on antimicrobial synergy testing when possible[25].

Similar to other studies[13, 17, 26], our study showed that patients who received colistin for ⩾7 days had a 6-fold higher likelihood of exhibiting a clinical favorable response (adjusted *OR*=6.74, 95% *CI* 2.49 to 20.29, P< 0.001) and lower mortality (adjusted *HR*=0.31, 95% *CI* 0.11 to 0.90, P=0.031). Given the lack of significant difference in AKI prevalence between the CS and CF groups or between the survival and death groups, we do not recommend shortening colistin treatment duration to prevent adverse reactions.

A higher baseline platelet count was also associated with reduced mortality (adjusted *HR*=0.99, 95% *CI* 0.99 to 1.00, P=0.029). Platelet count reflects infection severity and coagulation function; a higher baseline platelet count indicates less severe infection, better organ function, and a lower risk of bleeding or thrombosis, and thus is independently associated with lower 30-day mortality. In contrast, advanced age, the need for mechanical ventilation, and CRRT were independent predictors of clinical failure. A multivariate Logistic regression model was developed to predict favorable clinical response and demonstrated good discrimination and calibration. The AUROC and the calibration plot indicated a good model fit.

In terms of safety, 17.8% of patients experienced

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nephrotoxicity, which was higher than the rates of 7.6% to 9.2% reported in previous studies[13, 17] but lower than the nephrotoxicity rate of 26.8% reported for polymyxin B[27]. No patient developed hepatic dysfunction or skin hyperpigmentation in the current study. Notably, the development of colistin resistance was observed in 16 (14.3%) patients during hospitalization. Recently, colistin resistance among CR-GNB isolates has been increasingly reported, following the resurgence and increased use of colistin in humans or animals, and has been associated with poorer treatment outcomes in CR-GNB infections[28-30]. Low-dose colistin exposure and heteroresistance have been reported as contributing factors to colistin resistance[31]. Therefore, adequate colistin use and surveillance of colistin resistance are warranted.

The current study has several limitations that should be taken into consideration when interpreting the findings. First, it was a retrospective, single-center, real-world study without a control group, which may have introduced various confounding factors. Second, the MIC values were determined using the VITEK 2 automated system, which may cause a 1- to 2-fold bias in colistin MIC measurements[32]. Moreover, genotyping of CR-GNB isolates and antimicrobial synergy testing were not performed; instead, empirical combination therapy was used in clinical practice. Third, colistin sulfate dosing was not optimized based on pharmacokinetic/pharmacodynamic (PK/PD) analysis because therapeutic drug monitoring data were unavailable for most patients. Instead, dosing followed the label instructions, which carries a risk of subtherapeutic exposure in patients with normal renal function (creatinine clearance≥80 mL/min) or those infected with pathogens having an MIC ≥1 mg/L[15-16]. Finally, the relatively limited sample size precluded accurate comparison of clinical efficacy among different pathogen types with varying MIC values. To better evaluate the efficacy and safety of colistin sulfate in clinical practice, larger-scale, multicenter prospective studies are needed.

In conclusion, the present study demonstrated that colistin sulfate is a promising treatment option for severe CR-GNB infections. A treatment duration of ≥7 d is an independent protective factor for a favorable clinical response and is associated with longer survival times. Furthermore, a Logistic regression model (including age, mechanical ventilation, CRRT, platelet count, and treatment duration ≥7 d) was developed to predict favorable clinical response. However, this study did not provide evidence supporting the superiority of any empirical combination therapy regimen over others. Surveillance of colistin resistance is warranted, and larger, multicenter studies are needed to further evaluate its clinical utility.

Contributions: XIE Yueliang Study design, data analysis, and writing of the first draft; JIN Xin Study design, data collection, and writing of the first draft; WANG Hui, YAN Shanshan, and LIANG Junhao Data collection; PENG Yue Study design, revision and proofreading of the manuscript. All authors contributed and approved the submitted version of the manuscript.

Conflict of interest: The authors declare that they have no conflicts of interest to disclose.

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