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ORIGINAL RESEARCH

Treatment with Ceftazidime-Avibactam for Lower Respiratory Tract Infections Caused by the Multidrug-Resistant Gram-Negative Bacteria in the Intensive Care Unit

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Purpose: Ceftazidime avibactam (CAZ-AVI) is recommended for treating severe infections caused by multidrug-resistant gram-negative bacteria (MDR-GNB). However, there are few real-world studies on the use of CAZ-AVI to treat lower respiratory tract infections (LRTIs) caused by MDR-GNBs in intensive care units (ICUs). This study aimed to evaluate the clinical characteristics of patients with LRTIs caused by MDR-GNB who were treated with CAZ-AVI in the ICU, and to investigate the independent risk factors for mortality.

Patients and Methods: This single-center retrospective study included patients with LRTIs treated with CAZ-AVI in the respiratory ICU of a tertiary hospital in Anhui Province between December 2022 and November 2024. The primary outcomes were 28-day survival and independent risk factors for all-cause mortality.

Results: A total of 71 patients were enrolled in the study and 56.3% (40/71) had 28-day survival outcomes. The Acute Physiology and Chronic Health Evaluation (APACHE) II score (odds ratio [OR]: 1.144, 95% confidence interval [CI]: 1.012–1.293, p=0.032), coinfection with *Aspergillus* (OR: 42.753, 95% CI: 2.324–786.555, p=0.011), and days of CAZ-AVI (OR: 0.851, 95% CI: 0.734–0.986, p=0.032) were independent risk factors for 28-day all-cause mortality. Kaplan-Meier analysis demonstrated prolonged CAZ-AVI therapy (>10 days) improved survival (p<0.001), APACHE II scores >24 correlated with increased 28-day mortality (p=0.0048), and *Aspergillus* coinfection significantly reduced survival rates (p=0.001). We also constructed a nomogram for predicting the risk of death in ICU patients treated with CAZ-AVI for LRTIs, with good discrimination and calibration.

Conclusion: CAZ-AVI can be used to treat LRTIs caused by MDR-GNB in the ICU. Higher APACHE II scores and coinfection with Aspergillus were associated with 28-day mortality, whereas a longer course of therapy was a protective factor. The nomogram can help clinicians predict CAZ-AVI outcomes.

Keywords: lower respiratory tract infections, multidrug-resistant gram-negative bacteria, ceftazidime avibactam, 28-day mortality, nomogram

Introduction

Lower respiratory tract infections (LRTIs) include acute bronchitis, pneumonia, and acute exacerbation of chronic lung disease.[1] It is a major cause of morbidity and mortality worldwide. The Global Burden of Disease Study 2021 reported a global incidence of 344 million lower respiratory tract infections and 2.18 million deaths.[2] Pathogenic organisms admitted to the intensive care unit (ICU) for LRTIs are predominantly gram-negative bacteria,[3] especially in patients with

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chronic lung disease and comorbid sepsis.[4,5] Increasing drug resistance poses an important challenge for the effective treatment of infections.[6,7] It was also independently associated with a higher risk of mortality.[8] The most common carbapenem-resistant gram-negative bacteria were *Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae*, or *Acinetobacter baumannii*.[9,10] These bacteria are prone to developing resistance to antimicrobial drugs through several mechanisms, such as increasing efflux pumps, altering drug- binding sites, decreasing the permeability of the bacterial outer membrane, and producing degradative enzymes. Combination regimens based on drugs such as carbapenems, mucins, tigecycline, and fosfomycin have long been the treatment of choice for infections caused by severe multidrug-resistant gram-negative bacteria (MDR-GNB).[11] However, the use of several new drugs in recent years has broken through the limitations of traditional combination therapies.[12]

Ceftazidime avibactam (CAZ-AVI) exhibits excellent in vitro activity against many gram-negative pathogens.[13] Avibactam protects ceftazidime from degradation by inhibiting Ambler class A and C enzymes and certain class D carbapenemases produced by MDR-GNBs. Guidelines recommend CAZ-AVI for treating serious infections caused by carbapenem-resistant Enterobacteriaceae.[14] Since the introduction of CAZ-AVI in China, several observational studies have explored its efficacy and clinical characteristics.[15–18] These studies did not target infections at a single site but mostly covered infections at various sites throughout the body. Moreover, few real-world studies have investigated the use of CAZ-AVI in ICU patients with LRTIs caused by MDR-GNB.

This study aimed to investigate the clinical characteristics of CAZ-AVI treatment in patients admitted to the ICU with MDR-GNB infections of the lower respiratory tract. We also explored independent risk factors for 28-day mortality. These findings may support the use of CAZ-AVI in the management of severe LRTIs caused by MDR-GNB, particularly in critically ill patients.

Materials and Methods

Study Design and Patients

This was a single-center retrospective study of patients with LRTIs who were treated with CAZ-AVI between December 2022 and November 2024 in the respiratory ICU of a tertiary hospital in Anhui, China. This study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of the Anhui Chest Hospital (Ethics No. KJ2024-082) and was eligible for the informed consent waiver because the study was retrospective. To ensure the confidentiality of patient data, strict data protection measures have been implemented. All data collected and analyzed have been anonymized. This commitment fully protects patients' privacy rights throughout the study.

Inclusion criteria were (1) age ≥18 years, (2) patients with LRTIs admitted to the ICU, and (3) ≥24 hours of treatment with CAZ-AVI for lower respiratory tract MDR-GNB infections. The exclusion criteria were: (1) age <18 years, (2) non-ICU patients, (3) non-lower respiratory tract infections, (4) treatment with CAZ-AVI for less than 24 hours, (5) incomplete medical records during treatment, and (6) patients with unclear outcomes.

Data Collection and Related Definitions

We collected data from the electronic medical system, including demographic characteristics, comorbidities, laboratory variables, clinical characteristics, infection characteristics, therapeutic characteristics, and 28-day survival outcomes.

Comorbidities included chronic obstructive pulmonary diseases, bronchiectasis, diabetes mellitus, cardiovascular diseases, tumors, and cerebrovascular diseases. After a definitive diagnosis of LRTI was made, we performed a systematic review of each patient's laboratory detection results. In order to assess the severity of the disease more comprehensively, in cases where more than one detection result was present, we chose the worst values as a representative. Clinical characteristics included the use of mechanical ventilation because not all patients were mechanically ventilated. The worst Acute Physiology and Chronic Health Evaluation (APACHE) II score within 48h after the onset of LRTI, the occurrence of septic shock, the incidence of acute kidney injury (AKI) and the length of ICU stay were also included.

Bacterial pathogens were identified using a combination of traditional microbiological techniques and advanced diagnostic methods. MacConkey agar cultured Gram-negative rods. For definitive identification, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) determined the bacterial species. According to the guidelines of the Clinical and Laboratory Standards Institute (CLSI), the minimum inhibitory concentration (MIC) of various antibiotics was determined by broth microdilution method. MIC results were interpreted using established breakpoint criteria for each antibiotic to classify strains as susceptible, intermediate, or resistant. The tested antibiotics included Piperacillin/Tazobactam, Amoxicillin/Clavulanate, Ceftriaxone, Ceftazidime, Imipenem, Meropenem, Amikacin, Ciprofloxacin, Aztreonam, Tetracycline, Tigecycline, Polymyxin B, CAZ-AVI, and Co-trimoxazole. MDR bacteria were defined as those cultured from sputum or bronchoalveolar lavage fluid (BALF) that were resistant to three or more classes of antimicrobial drugs.

Since the research center is a chest hospital that admits tuberculosis and respiratory diseases, the coinfections included *Mycobacterium tuberculosis* and *Aspergillus*. All tuberculosis patients had been diagnosed prior to admission and were receiving standardized therapy, with no history of drug-resistant tuberculosis. Screening for *Aspergillus* infection excluded colonization according to the European Organization for Research and Treatment of Cancer and Mycosis Study Group Education and Research Consortium (EORTC/MSGERC) criteria and the supplementary criteria for Invasive Fungal Disease ICU in Adult Patients (FUNDICU).

Patients with empiric CAZ-AVI use were not included in this study. The use of CAZ-AVI was initiated when MDR-GNB was clearly detected as a pathogen and was susceptible to CAZ-AVI. Only the first instance was included if treatment with CAZ-AVI was used multiple times during hospitalization. Patients with AKI were administered an appropriate dose of the drug according to the manufacturer's instructions. There was no dose adjustment for CAZ-AVI in AKI patients treated with continuous renal replacement therapy. In summary, the therapeutic characteristics included carbapenems before CAZ-AVI, dose reduction of CAZ-AVI, days of CAZ-AVI, and combination therapy (Polymyxin B and Tigecycline).

The primary outcomes of this study were the 28-day all-cause survival rate following CAZ-AVI treatment initiation and the independent risk factors for 28-day all-cause mortality. Patients who discontinued CAZ-AVI treatment due to premature discharge were tracked via telephone interviews to confirm survival status and date of death within 28 days of treatment initiation.

Statistical Analysis

Data were analyzed using SPSS (version 26.0) and R (version 4.4.1). Categorical data were presented in terms of frequencies and percentages, and we applied the Pearson chi-square test to explore the differences between the different groups. We used the mean ± standard deviations to describe normally distributed continuous variables, while we assessed differences using the Student's *t*-test. For non-normally distributed data, we used the median and interquartile range to represent them, and analyzed them using the Mann–Whitney *U*-test.

Potential variables ($p<0.1$) in the univariate logistic regression analyses were added to the multivariate analyses to identify independent risk factors for 28-day mortality. Adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were presented. Then we constructed a visual nomogram based on the independent risk factors for 28-day mortality obtained from the multivariable logistic regression. The performance of the nomogram was assessed using evaluation tools including the area under the receiver operating characteristic (ROC) curve (AUC), Calibration Curve, and Decision Curve Analysis (DCA).

Patients were stratified into two groups according to the independent risk factor levels. We used the median as the cut-off threshold for continuous variables. Survival analysis was performed via the Kaplan-Meier method, with Kaplan-Meier curves generated to visualize 28-day survival outcomes. Between-group differences were statistically assessed using the Log rank test. Statistical significance was set at the two-tailed p-value of less than 0.05.

Results

Baseline Characteristics

Between December 2022 and November 2024, 119 patients with LRTIs were treated with CAZ-AVI at our research center. Of them, 41 non-ICU patients, 4 who had not used CAZ-AVI for more than 24 hours, 1 who used CAZ-AVI for a bloodstream infection, and 2 with unclear outcomes were excluded, resulting in the inclusion of 71 patients (Figure 1).

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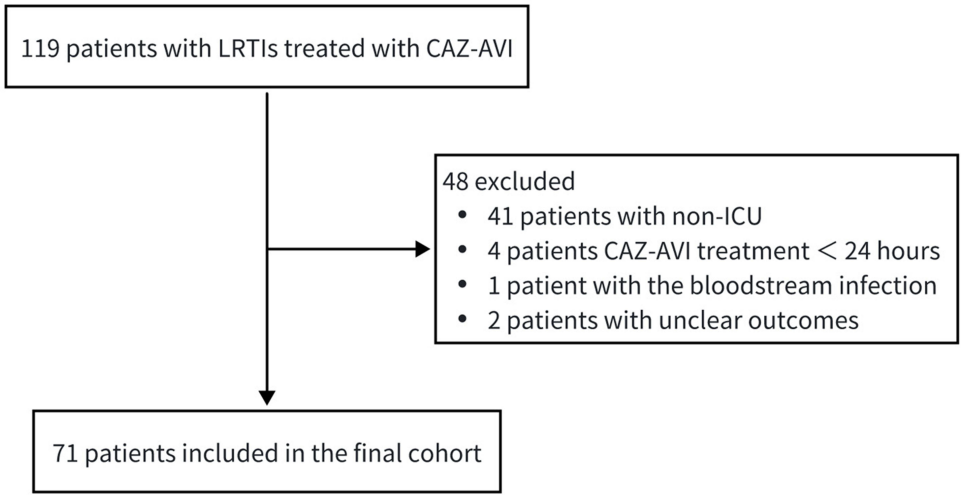

Figure 1 Study flowchart for patient selection.
Abbreviations: LRTIs, lower respiratory tract infections; ICU, intensive care unit; CAZ-AVI, ceftazidime-avibactam.

Table 1 shows the demographic and clinical characteristics of the study population. The mean age of 71 patients was 70.6 ±13.7 years. Majority of the patients were male (58/71, 85.0%). 40 (56.3%) survived 28 days. 28-day all-cause mortality was 43.7% (31/71). There were no statistically significant differences between the 28-day survival and non-survival groups in terms of sex, age, or comorbidities. Regarding laboratory examinations, patients in the non-survival group had a lower arterial oxygen partial pressure (PaO2)/ fraction of inspired oxygen (FiO2) (p=0.014) and lower T-lymphocyte counts (p=0.047). In addition, the duration of mechanical ventilation (p=0.046) and ICU stay (p=0.001) were longer in the survivor group. The mean APACHE II score was 24.2±6.3. The non-survival group had a higher APACHE II score (p=0.001) and a greater percentage of septic shock occurrences (p=0.038). AKI occurred in 26.8% (19/71) of patients in this study. There was no statistically significant difference in the incidence of AKI between the two groups (p=0.144).

Characteristics of Infection and Medication Use

Table 2 presents the characteristics of the study population in terms of infection and medication use. MDR *P. aeruginosa* (n=34, 47.9%), *K. pneumoniae* (n=20, 28.2%), and *Stenotrophomonas maltophilia* (n=28, 39.4%) accounted for the

Table 1 Baseline Characteristics of Patients With LRTIs Treated With CAZ-AVI

Variable	Total (n=71)	28-Day non-survive (n=31)	28-Day Survive (n=40)	*p-value*
Male, n (%)	58(85.0)	24(77.4)	34(81.7)	0.413
Age(years)	70.6±13.7	72.0±15.4	69.6±12.4	0.475
Comorbidities, n (%)				
Chronic obstructive pulmonary	15(21.1)	7(22.6)	8(20.0)	0.792
Bronchiectasis	9(12.7)	5(16.1)	4(10.0)	0.441
Diabetes mellitus	20(28.2)	9(29.0)	11(27.5)	0.887
Cardiovascular disease	34(47.9)	14(45.2)	20(50.0)	0.686
Tumor	27(38.0)	10(32.3)	17(42.5)	0.378
Cerebrovascular disease	23(32.4)	7(22.6)	16(40.0)	0.120

(*Continued*)

Table 1 (Continued).

Variable	Total (n=71)	28-Day non-survive (n=31)	28-Day Survive (n=40)	*p-value*
Laboratory variables at the time of infection				
Neutrophils (10^9/L)	11.5±6.2	12.2±6.2	10.9±6.1	0.353
Lymphocytes (10^9/L)	0.4(0.3–0.8)	0.4(0.3–0.7)	0.5(0.3–0.9)	0.388
Platelet (10^9/L)	184.0±101.2	191.2±113.7	178.5±91.5	0.605
Albumin (g/L)	29.8±4.1	29.1±3.9	30.3±4.2	0.234
Urea nitrogen (mmol/L)	16.6±11.4	17.5±12.7	15.9±10.5	0.550
Creatinine (mmol/L)	94.8±71.0	103.7±82.5	87.9±60.8	0.355
Procalcitonin (ng/mL)	1.0(0.2–3.7)	0.7(0.2–2.0)	1.4(0.2–6.7)	0.410
C-reactive protein (mg/L)	131.6±79.6	138.6±83.4	126.2±77.0	0.518
PaO2/FiO2 (mmHg)	191.1±87.4	162.7±81.4	213.0±86.5	0.014
T lymphocyte counts	400.0±239.1	336.3±179.1	449.4±268.7	0.047
Clinical characteristics				
Mechanical ventilation, n (%)	66(93.0)	29(93.5)	37(92.5)	0.864
Length of MV (hours)	357.9±282.0	284.2±241.6	415.0±300.3	0.046
APACHE II score	24.2±6.3	26.9±6.6	22.2±5.1	0.001
Septic shock, n (%)	27(38.0)	16(51.6)	11(27.5)	0.038
Acute kidney injury, n (%)	19 (26.8)	11 (35.5)	8 (20.0)	0.144
Length of ICU (days)	19.4±13.6	13.6±10.1	24.0±14.3	0.001

Abbreviations: LRTI, lower respiratory tract infection; CAZ-AVI, ceftazidime-avibactam; PaO2, arterial oxygen partial pressure; FiO2, fraction of inspired oxygen; APACHE, Acute Physiology and Chronic Health Evaluation; MV, mechanical ventilation.

Table 2 Infection and Medication Characteristics of Patients With LRTIs Treated With CAZ-AVI

Variable	Total (n=71)	28 Days Non-Survive (n=31)	28 Days Survive (n=40)	*p-value*
Pathogenic microorganism, n (%)				
Pseudomonas aeruginosa	34(47.9)	16(51.6)	18(45.0)	0.580
Klebsiella pneumoniae	20(28.2)	5(16.1)	15(37.5)	0.047
Escherichia coli	6(8.5)	1(3.2)	5(12.5)	0.163
Stenotrophomonas maltophilia	28(39.4)	11(35.5)	17(42.5)	0.549
Enterobacter cloacae	4(5.6)	1(3.2)	3(7.5)	0.439
Serratia marcescens	2(2.8)	2(6.5)	0(0)	0.103
Achromobacter xylosoxidans	4(5.6)	1(3.2)	3(7.5)	0.439
Mixed infection, n (%)	15(21.1)	5(16.1)	10(25.0)	0.364

(*Continued*)

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Table 2 (Continued).

Variable	Total (n=71)	28 Days Non-Survive (n=31)	28 Days Survive (n=40)	*p-value*
Coinfection, n (%)				
Mycobacterium tuberculosis	18(25.4)	10(32.3)	8(20.0)	0.239
Aspergillus	10(14.1)	9(29.0)	1(2.5)	0.001
Medication characteristics, n (%)				
Carbapenems before CAZ-AVI	36(50.7)	15(48.4)	21(52.5)	0.731
Dose reduction of CAZ-AVI	14(19.7)	10(32.3)	4(10.0)	0.019
Days of CAZ-AVI	10.2±4.7	8.4±4.1	11.5±4.7	0.006
Combination therapy	18(25.4)	6(19.4)	12(30.0)	0.306
Polymyxin B	8(11.3)	2(6.5)	6(15.0)	0.259
Tigecycline	7(9.9)	1(3.2)	6(15.0)	0.099

highest percentage of infections. Mixed infections accounted for 21.1% (15/71) of patients. There was no statistically significant difference between the survival and non-survival groups in terms of pathogenic distribution.

Mycobacterium tuberculosis coinfection was also not significantly different between the two groups (p=0.239). *Aspergillus* coinfection was more frequent in the non-survival group (p=0.001). In this study, there were 10 patients with coinfections of *Aspergillus*, of whom 2 were on immunosuppressive drugs after solid organ transplantation, 6 patients were on long-term use of corticosteroids at a therapeutic dose of ≥0.3 mg/kg within the last 60 days, 2 had a diagnosis of lung cancer, and 1 of them had a history of recent chemotherapy. These patients met both the host factor criteria defined by the EORTC/MSGERC and FUNDICU criteria. In combination with the clinical features and the detection of *Aspergillus* in sputum or BALF, they can be classified as "probable" invasive aspergillosis.

Prior to using CAZ-AVI, patients received empiric therapy with carbapenems or non-carbapenem antibiotics, with the former accounting for 50.7% (36/71). Most non-survivors had a reduced CAZ-AVI dose (p=0.019), while survivors were treated with CAZ-AVI for a longer duration (p=0.006). The mean duration of CAZ-AVI use was 10.2±4.7 days. Combination therapy showed no statistically significant difference between the two groups (p=0.306). We also observed the use of CAZ-AVI in combination with Co-trimoxazole in the therapeutic modality of *Stenotrophomonas maltophilia*. This group of strains may be susceptible to Co-trimoxazole, and the use of CAZ-AVI is intended to cover mixed infections.

The results of antibiotic susceptibility testing of all strains are shown in Figure 2, indicating that all strains were susceptible to CAZ-AVI. The table of antibiotic susceptibility results by different MDR-GNB is provided in Table S1; Supplement 1. The results show that 100% (98/98) of the strains were susceptible to CAZ-AVI, followed by Polymyxin B (56.9%) and Amikacin (34.7%). Most strains exhibited resistance to Amoxicillin/Clavulanate (89.8%), Imipenem (84.7%), and Meropenem (81.6%). Figure S1; Supplement 2 demonstrates the MIC distribution of CAZ-AVI, with most MIC values centered on 8 mg/L.

Independent Risk Factors for 28-Day All-Cause Mortality

Table 3 shows the results of the univariate and multivariate regression analyses and provides a detailed summary of the ORs and 95% CIs. Firstly, univariate logistic regression analysis was used to screen 5 statistically significant variables: T lymphocyte counts, APACHE II score, coinfection with *Aspergillus*, dose reduction of CAZ-AVI, and days of CAZ-AVI. Further multivariate regression analysis of these five variables showed that APACHE II score, coinfection with *Aspergillus*, and days of CAZ-AVI were independent risk factors for 28-day all-cause mortality in patients. For each point increase in the APACHE II score, the risk of death increased by 1.144 (OR: 1.144, 95% CI: 1.012–1.293, p=0.032).

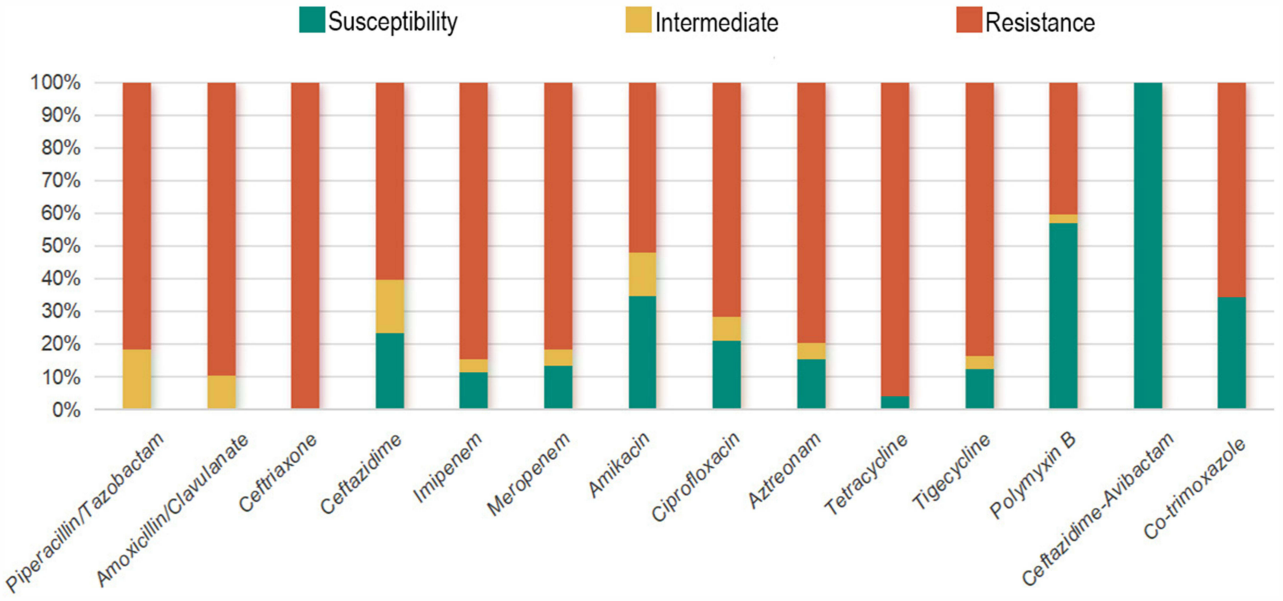

Figure 2 The percentage bar stack plot of antibiotic sensitivity testing results for all strains.

Coinfection with *Aspergillus* increased the risk of death by 42.753-fold (OR: 42.753, 95% CI: 2.324–786.555, p=0.011). The days of CAZ-AVI treatment was a protective factor against mortality (OR: 0.851, 95% CI: 0.734–0.986, p=0.032).

Finally, a nomogram was constructed based on the above three variables (Figure 3). As shown in the nomogram, each factor corresponded to one individual score. The total score corresponded to the probability value at the bottom, which indicated the predicted 28-day risk of death in patients treated with CAZ-AVI.

Table 3 Univariable and Multivariable Logistic Regression of Risk Factors for 28-Day Mortality

Variables	Univariable Logistic Regression		Multivariable Logistic Regression	
	OR (95% CI)	*p-value*	OR (95% CI)	*p-value*
Male	1.653(0.493–5.538)	0.415		
Age	1.013(0.978–1.049)	0.471		
Chronic obstructive pulmonary	1.167(0.372–3.663)	0.792		
Diabetes mellitus	1.079(0.381–3.054)	0.887		
Tumor	0.644(0.242–1.716)	0.379		
Neutrophils	1.038(0.960–1.122)	0.350		
Lymphocytes	0.521(0.187–1.453)	0.213		
Albumin	0.930(0.825–1.048)	0.233		
Procalcitonin	0.999(0.977–1.022)	0.957		
C-reactive protein	1.002(0.996–1.008)	0.512		
T lymphocyte counts	0.998(0.996–1.000)	0.052	0.998(0.995–1.001)	0.127
Mechanical ventilation	1.176(0.184–7.507)	0.864		
APACHE II score	1.153(1.049–1.268)	0.003	1.144(1.012–1.293)	0.032

(*Continued*)

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Table 3 (Continued).

Variables	Univariable Logistic Regression		Multivariable Logistic Regression	
	OR (95% CI)	***p-value***	**OR (95% CI)**	***p-value***
Acute kidney injury	2.200(0.756–6.404)	0.148		
Mixed infection	0.577(0.175–1.906)	0.367		
Mycobacterium tuberculosis	1.905(0.647–5.611)	0.242		
Aspergillus	15.955(1.894–134.397)	0.011	42.753(2.324–786.555)	0.011
Carbapenems before CAZ-AVI	0.848(0.332–2.169)	0.731		
Dose reduction of CAZ-AVI	4.286(1.194–15.389)	0.026	2.178(0.448–1.580)	0.334
Days of CAZ-AVI	0.852(0.755–0.961)	0.009	0.851(0.734–0.986)	0.032
Combination therapy	0.560(0.183–1.714)	0.310		

The ROC curve for the nomogram is shown in Figure 4. The AUC was 0.830, indicating that the nomogram discriminated well between the survivors and non-survivors. Figure S2; Supplement 3 shows that the calibration curve of the nomogram had a good fit with the observed probability curve, suggesting that it could predict the risk of death in patients. Figure S3; Supplement 4 shows the DCA results of the nomogram. The horizontal and vertical axes represent the threshold probability and net benefit, respectively. The black horizontal line represents the net benefit without intervention, and the grey diagonal line represents the net benefit for all patients who received the intervention. The

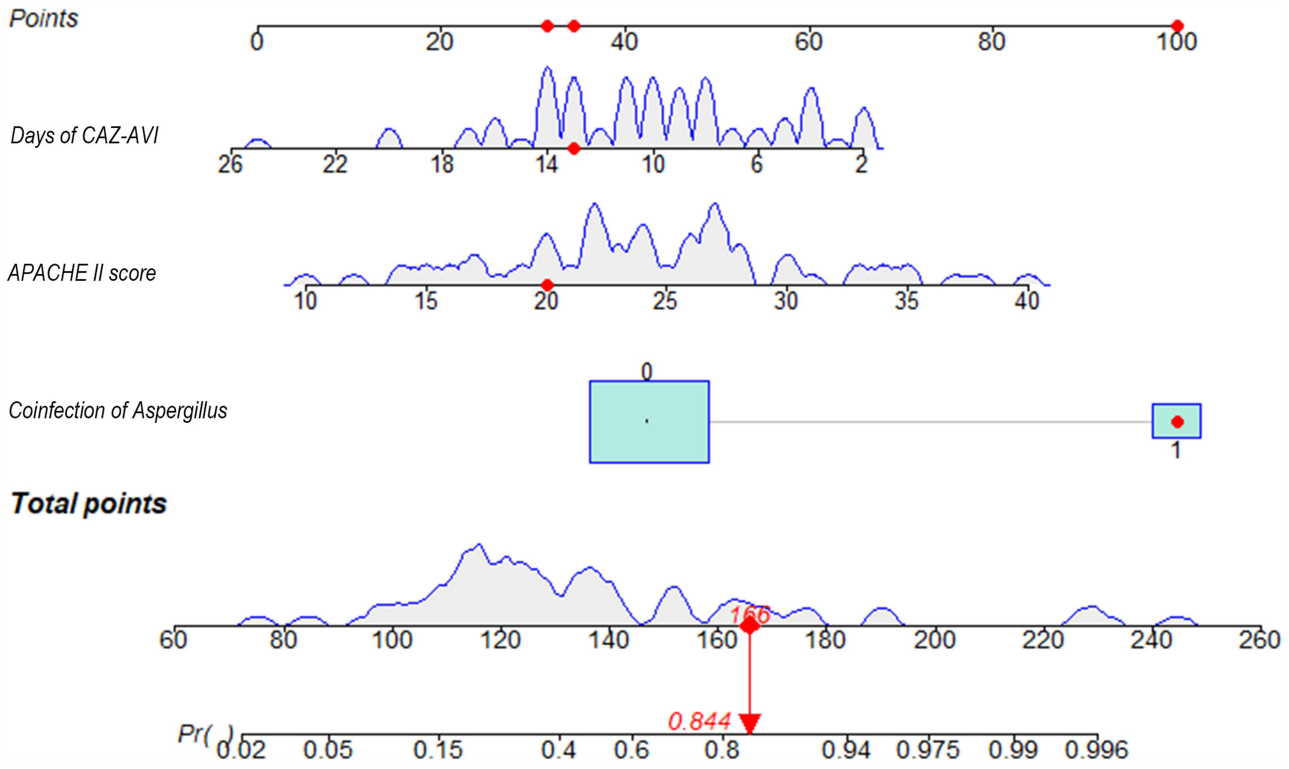

Figure 3 The nomogram used to predict the 28-day mortality risk in ICU patients with multidrug-resistant gram-negative bacterial lower respiratory tract infections treated with ceftazidime avibactam.

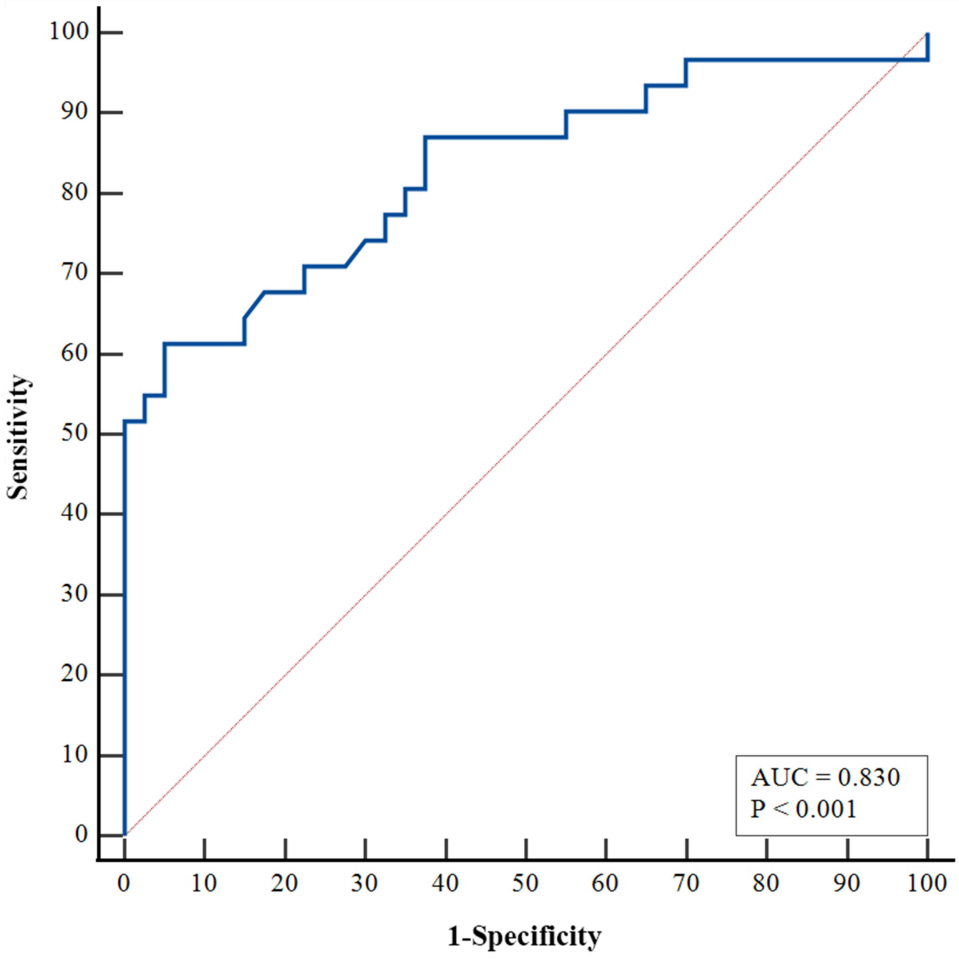

Figure 4 The ROC curve of the nomogram.

red curve was above the two reference lines, indicating that there was a significant net benefit across most of the threshold probability range, suggesting that this nomogram has a certain value for clinical application.

Kaplan-Meier analysis revealed that prolonged CAZ-AVI therapy (>10 days) significantly improved 28-day survival (p<0.001) (Figure 5A), while higher APACHE II scores (>24) correlated with increased 28-day mortality (p=0.0048) (Figure 5B). Additionally, *Aspergillus* coinfection markedly reduced 28-day survival rates (p=0.001) (Figure 5C).

Discussion

CAZ-AVI is more effective than other conventional drugs in the treatment of MDR-GNB-induced infections, including the treatment of immunocompromised patients, as well as salvage therapy.[14,19–22] Previous studies included bloodstream, abdominal, and urinary tract infections, in addition to pulmonary infections.[23–26] The clinical characteristics of the infection sites were also analyzed. However, few clinical studies have specifically focused on patients with MDR-GNB infections of the lower respiratory tract using CAZ-AVI. We collected and analyzed the clinical data of 71 patients who received CAZ-AVI for the treatment of MDR-GNB infection of the lower respiratory tract in the ICU. The results showed a 28-day survival rate of 56.3%, which was consistent with previous reports.[27] Spanish scholars conducted an observational study to analyze the factors influencing the efficacy of CAZ-AVI in the treatment of KPC-producing *K. pneumoniae* infections. They found that pneumonia was associated with 14-day clinical failure.[28] Maria et al found that death occurred most frequently in patients with gram-negative bacterial infections treated with CAZ-AVI who had pneumonia (p=0.009) or mechanical ventilation (p=0.049).[29] Based on these previous findings, the reason for the differences in survival rates in our study may be the site of infection in the study population.

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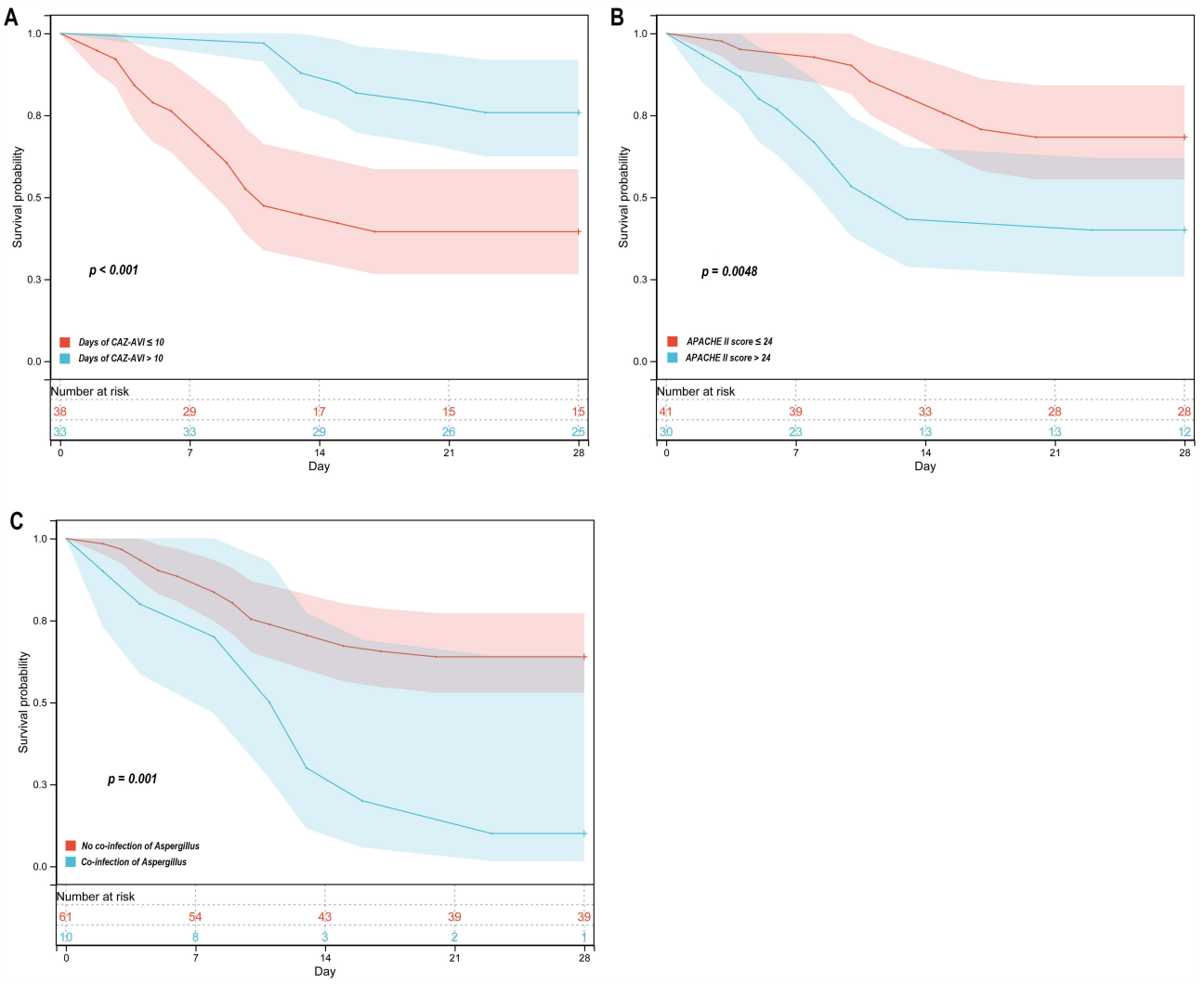

Figure 5 Kaplan–Meier curves for 28-day mortality. (**A**) Survival for patients stratified by days of CAZ-AVI. (**B**) Survival for patients stratified by APACHE II score. (**C**) Survival for *Aspergillus* coinfection.

Patients with MDR LRTIs and poor outcomes in this study had a higher APACHE II score and incidence of septic shock, which is consistent with the results of previous studies.[18,30] Longer ICU stays and mechanical ventilation in the surviving patients may be related to the effectiveness of anti-infective therapy, as they were treated with CAZ-AVI for a longer period and were predominantly adequate-dose users. *P. aeruginosa* and *K. pneumoniae* are the most common MDR organisms found in the ICU. Serious pulmonary infections caused by these agents are also the main indications for CAZ-AVI.[21] The distribution of pathogens in this study was also characterized. Additionally, other species of MDR bacteria were included, including *S. maltophilia* and *E. coli*. Some patients also had mixed bacterial infections. Studies have shown good in vitro activity of CAZ-AVI against resistant bacteria.[13,31–33] Successful treatments have been reported previously.[34–37]

In this study, we explored the clinical factors associated with poor outcomes in patients with LRTIs caused by MDR-GNBs treated with CAZ-AVI. Our results revealed that APACHE II score and co-infection with Aspergillus were the independent risk factors for all-cause mortality within 28 days, while days of CAZ-AVI was a protective factor. For patients in the ICU, an increased APACHE II score indicated a more severe critical illness status. Additionally, severe organ dysfunction may affect the efficacy of antimicrobials, leading to a cycle of worsening conditions. Our findings are consistent with the results of many previous studies showing that the higher the APACHE II score, the greater the risk of death for patients.[18,38]

Our study also found that *Aspergillus* coinfection significantly increased the mortality risk in patients with MDR bacterial LRTIs. Disruption of bacterial microbiota is a prerequisite for fungal overgrowth.[39] In vitro studies have revealed the molecular mechanisms of the interaction between *A. fumigatus* and bacteria such as *P. aeruginosa*, suggesting that *A. fumigatus* can persist and cause diseases, despite the possible dominance of the bacteria in the competition.[40] Fungi, including *Aspergillus* spp., can interact with bacteria in patients with severe pneumonia.[41] Patients with mixed infections have poor prognosis. The lower respiratory tract *Aspergillus* infection that frequently occurs in the ICU is invasive pulmonary aspergillosis. The isolation of *Aspergillus* from critically ill patients is associated with high mortality rates.[42,43]

This study additionally revealed that a decrease in the treatment sessions was associated with increased mortality. A study by Xiao et al showed that the CAZ-AVI treatment course was an independent risk factor affecting the prognosis of patients with Carbapenem-resistant gram-negative bacillus infections treated with CAZ-AVI.[17] This finding is consistent with the results of our study. Full courses of treatment with CAZ-AVI can increase the survival rate of ICU patients with LRTIs caused by MDR-GNBs.

Nomograms are widely used to predict disease recurrence, prognosis, and therapeutic effects.[44–46] Its strength lies in helping clinicians improve the quality of medical decisions through personalized and visual risk assessments. The developed nomogram predicted mortality risk in ICU patients receiving CAZ-AVI for MDR-GNB-associated LRTIs. Model performance was rigorously assessed through discrimination, calibration, and net clinical benefit analyses, demonstrating favorable predictive accuracy and clinical utility in guiding risk stratification.

This study has made some progress in understanding CAZ-AVI for the treatment of MDR-GNB-associated LRTIs in the ICU. Survival analyses demonstrated that prolonged CAZ-AVI treatment (>10 days) significantly improved prognosis and supported an extended course of therapy in the intensive care setting. The identification of *Aspergillus* coinfection as an independent risk factor for mortality highlights the need for clinical screening for fungal co-pathogens in severe bacterial pneumonia. Additionally, patients with APACHE II score exceeding 24 exhibited markedly reduced survival probabilities, implying that early escalation of monitoring or adjunctive therapies might be warranted in this subgroup. The nomogram's integration of APACHE II thresholds and microbiological factors offered a pragmatic tool for real-time risk assessment in ICU settings.

This study had several limitations. First, because the study was conducted at only one medical center, the results may have been influenced by a specific patient population, limiting the extrapolation and generalizability of the findings. Second, this was a retrospective study; therefore, a potential selection bias may be present. Additionally, the limited sample size and the possibility of mixed infections would increase the risk of bias in the results. Finally, although multivariate regression analyses were conducted to adjust for potential confounders, unrecognized confounders may still exist. Future studies should consider a multicenter, prospective study with a large sample size to further validate the results of this study. Meanwhile, stratified analysis by different pathogens can be considered to further explore the relationship between treatment duration and prognosis.

Conclusion

In this study, we evaluated the clinical characteristics and outcomes of ICU patients with LRTIs caused by MDR-GNB treated with CAZ-AVI. We identified the APACHE II score, coinfection with *Aspergillus*, and days of CAZ-AVI as independent risk factors for 28-day all-cause mortality. Furthermore, we constructed a nomogram to predict the mortality risk of ICU patients treated with CAZ-AVI, thereby assisting clinicians in making personalized risk assessments and medical decisions.

Abbreviations

LRTIs, lower respiratory tract infections; ICU, intensive care unit; MDR-GNB, multidrug-resistant gram-negative bacteria; CAZ-AVI, ceftazidime avibactam; APACHE, Acute Physiology and Chronic Health Evaluation; AKI, acute kidney injury; BALF, bronchoalveolar lavage fluid; ORs, odds ratios; CIs: confidence intervals; ROC, receiver operating characteristic; AUC, area under the receiver operating characteristic curve; DCA, Decision Curve Analysis; PaO2,

arterial oxygen partial pressure; FiO2, fraction of inspired oxygen; CLSI, Clinical and Laboratory Standards Institute; MIC, minimum inhibitory concentration.

Ethical Approval

The study was conducted in accordance with the principles of the Declaration of Helsinki. The Ethics Committee of Anhui Chest Hospital approved the study (Ethics No. KJ2024-082) and agreed to the informed consent waiver because the study was retrospective. To ensure the confidentiality of patient data, strict data protection measures have been implemented. All data collected and analyzed have been anonymized. This commitment fully protects patients' privacy rights throughout the study.

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Author Contributions

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

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Disclosure

The authors report no conflicts of interest in this work.

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