Ceftazidime/avibactam-based versus polymyxin B-based therapeutic regimens for the treatment of carbapenem-resistant Klebsiella pneumoniae infection in critically ill patients: a retrospective cohort study

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Research Article

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Abstract

Background: Considering the importance of ceftazidime/avibactam (CAZ/AVI) and polymyxin B (PMB) in treating carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infection, it is essential to evaluate the efficacy and safety of these agents and provide appropriate medical advice to clinical specialists.

Methods: We conducted a retrospective cohort study in two Chinese tertiary hospitals for critically ill patients with CRKP infection who received at least 24-hour CAZ/AVI-based or PMB-based treatment. A binary logistic model and a Cox proportional hazards regression model were constructed to analyze variables that could potentially affect 30-day microbiological eradication and all-cause mortality, respectively.

Results: From January 2019 to December 2021, 164 eligible patients were divided into CAZ/AVI and PMB cohorts. A notably lower 30-day mortality rate (35.4% vs 69.5%, $P < 0.001$) and a higher 30-day microbiological eradication rate (80.5% vs 32.9%, $P < 0.001$) were observed for patients receiving CAZ/AVI-based treatment, compared with cases in PMB group. A longer antimicrobial treatment duration (> 7 days) could also significantly decrease the mortality rate and increase the microbiological eradication rate. Female patients had a higher survival rate than male. Age over 65 years, sepsis, Continuous Renal Replacement Therapy (CRRT) and organ transplantation were identified as negative factors on survival. In the subgroup analysis, we found that CAZ/AVI combined with tigecycline (Hazard ratio, 0.267; 95% Confidence Interval, 0.077-0.921; $P = 0.037$) or amikacin (Hazard ratio, 0.105; 95% Confidence Interval, 0.014-0.766; $P = 0.026$) could effectively lower mortality. According to safety evaluation results, potential hepatic enzymes elevation was associated with CAZ/AVI-based treatment, while renal impairment was probably related to PMB-based treatment.

Conclusions: CAZ/AVI was more effective than PMB in treating CRKP infected patients. Tigecycline and amikacin were proved to be beneficial as concomitant agents in combination with CAZ/AVI. A treatment period lasting over 7 days was recommended. Although clinical safety of these two agents could be ensured because the severity level and incidence of adverse effects were relatively low, hepatoxicity of CAZ/AVI and nephrotoxicity of PMB should be monitored carefully. Further well-designed studies should be performed to verify our conclusion.

Introduction

In the last few decades, Carbapenem-resistant *Enterobacteriaceae* (CREs) have been regarded as one of fatal medical threats to the public health based on World Health Organization priority list of antibiotic-resistant bacteria, which could cause a variety of intractable infections, such as pneumonia, bloodstream infections and urinary tract infections[1, 2]. Carbapenem-resistant *Klebsiella pneumoniae* (CRKP), the most common pathogens amidst the various strains of CREs, is considered as a nationwide clinical therapeutic challenge in China[3, 4]. According to the corresponding statistics from China Antimicrobial

Surveillance Network, a rapidly increasing incidence and prevalence rates of CRKP infection has been observed from 2.9% in 2005 to 25% in 2021[5].

Only few available antimicrobial agents show adequate clinical efficacy treating CRKP infection due to its multi-drug resistance, such as aminoglycosides, carbapenems, tigecycline and fosfomycin. Therefore, combination treatments are widely accepted by clinicians to utilized synergies to achieve bactericidal effects against CRKP[2, 6, 7].

Moreover, some novel antimicrobial agents have been developed for the sake of overcoming the treating dilemma of CRKP infection in recent years. It is acknowledged that ceftazidime/avibactam (CAZ/AVI) and polymyxins [polymyxin B (PMB) & colistin] reveal their own antibacterial effects as the first-line agents against CRKP infection[2, 6, 7]. As far as we know, clinical studies about comparing clinical efficacy between CAZ/AVI and polymyxins-based therapeutic regimens are still rare. Shields *et al*. found that CAZ/AVI treatment had a significantly higher clinical success and survival rates than other antimicrobial drug regimens when treating CRKP bacteremia, including colistin treatment[8]. In Fang *et al*.'s article, Patients who received CAZ/AVI treatment had significantly lower rates of 28-day mortality (8.1 vs 29.5%, $P = 0.013$), higher microbiological eradication and 28-day clinical success[5]. Consequently, it is worthwhile conducting several further clinical investigations to provide sufficient evidence for making guidance on treatment of CRKP infection with CAZ/AVI and PMB-based therapeutic regimens.

In terms of our previous study, we have found that using combination treatment scheme of CAZ/AVI with carbapenems, fosfomycin, or tigecycline could significantly decrease the mortality of critically ill patients with CRKP infection[9]. However, PMB-based treatment regimen had not been evaluated. Hence, we perform the current study to compare the clinical efficacy and safety of treating CRKP infection in critical ill patients between CAZ/AVI-based and PMB-based regimen.

Methods

Study design and participants

This retrospective cohort study was performed at two tertiary hospitals in China, which based upon the ethical standards of the Declaration of Helsinki 1964 and its later amendments or comparable ethical standards. Our study was approved by the Institutional Review Board of Huashan Hospital Affiliated to Fudan University and Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. All complete data were extracted respectively from the electronic medical record information system in each hospital without direct interference with the enrolled participants.

Adult patients (age ≥ 18 years) who admitted to the intensive care unit (ICU) from January 2019 to October 2021 and received at least one dose of CZA/AVI or PMB with verified CRKP infections (based on microbiological culture test) and documented susceptibility testing results were enrolled in our study. The exclusion criteria were as follows: (1) patients who received CAZ/AVI-based or PMB-based treatment for less than 24 hours or died within this period; and (2) patients with missing data.

Antibiotic dosing regimens

CAZ/AVI-based therapy was considered as an antimicrobial treatment with CAZ/AVI and any other antibiotics except for PMB. Correspondingly, PMB-based therapy was classified as an antimicrobial treatment with PMB and any other antibiotics except for CAZ/AVI. Combination therapy was defined as using any other anti-CRKP agents accompanied with CZA-AVI or PMB at the onset of CAZ/AVI or PMB treatment, respectively. The selection of concomitant antibiotics and the duration of CAZ/AVI-based and PMB-based therapy were both at the discretion of the clinicians.

As for the dose regimen of CAZ/AVI, a 2.5 g fixed dose was administered every 8 hours with a 2-hour infusion time. Dose adjustment was in accordance with patients' creatinine clearance (CrCl) level. Patients who underwent Continuous Renal Replacement Therapy (CRRT) received a standard dosing regimen regardless of the different modes of CRRT[10].

In the group of PMB based therapy, patients received a loading dose of 2.0-2.5 mg/kg/d and maintenance doses of 1.25–1.5 mg/kg/d every 12 hours. Both loading dose and maintenance dose were calculated based on total body weight (TBW) and administered with at least one-hour infusion time. No renal function-based dose adjustment was performed in our study, even if patients were receiving CRRT [11].

Study objectives and variables

The 30-day mortality rate was classified as primary outcome in the current study, and the 30-day microbiological eradication rate was evaluated to compare the clinical efficacy between CAZ/AVI and PMB-based therapy. Microbiological eradication was determined as the vanishment of CRKP from all subsequent cultures.

Variables that were recorded in our study included age, sex, TBW, site of infection (defined in line with the Centers for Disease Control and Prevention (CDC) criteria[12]); polymicrobial infections; Sequential Organ Failure Assessment (SOFA)[13] and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores at the onset of CAZ/AVI-based or PMB-based treatment[14]; sepsis (identified by SOFA scores ≥ 2[13]) when starting CAZ/AVI-based or PMB-based therapy; CrCl (calculated by Cockcroft-Gault formula[15]) at the beginning of CAZ/AVI-based or PMB-based therapy; CRRT or Extracorporeal Membrane Oxygenation (ECMO) within the duration of CAZ/AVI-based or PMB-based therapy; length of ICU stay before starting antimicrobial therapy; combination therapy and concomitant antibiotics treatment; concomitant use of vasoactive drugs or mechanical ventilation by the start of CAZ/AVI-based or PMB-based therapy; Charlson comorbidity index (CCI) score[16] and comorbidities at admission; CAZ/AVI-based or PMB-based treatment duration.

Microbiology

All pathogen isolation and antimicrobial susceptibility tests, except for CAZ/AVI, were performed by the Vitek 2 Compact system (bioMérieux, Inc.). The susceptibility of CAZ/AVI was determined by the disk-

diffusion method (Kirby-Bauer method). The Clinical and Laboratory Standards Institute (CLSI) criteria 2020 were utilized as the evaluation standard of breakpoints to interpret all antibiotic susceptibility testing results. In addition, carbapenem resistance was defined as the minimum inhibitory concentration (MIC) of imipenem or meropenem was 4 mg/L or over.

Statistical analysis

All statistical analyses were performed with SPSS software (version 26.0, IBM Corp, Armonk, NY, USA). The Shapiro-Wilk test was carried out to validate the normality of the distribution of each variable. As for the categorical variables, the Pearson's chi-square test or Fisher's exact test was utilized for data analyzation and *P*-values calculation. The Student's t-test or Mann-Whitney U test was applied for analyzing continuous variables and calculate *P*-values. To set up a multivariate regression analysis model for investigating the potential risk factors on 30-day microbiological eradication, each variable was evaluated by univariate analysis at first. Variables with their *P*-values ≤ 0.10 were added in the binary logistic regression analysis. The Kaplan-Meier method was chosen to achieve the survival analysis. Any variable with *P*-value ≤ 0.10 was involved in a Cox proportional hazards regression model with a forward stepwise selection for analyzing 30-day mortality, while only those with *P*-values ≤ 0.10 remained in this model. The differences of variables between CAZ/AVI group and PMB group were compared in advance. Variables with *P*-values ≤ 0.20 were included in both binary and Cox proportional hazards regression analysis, with the purpose of adjusting for confounding by indication. Covariates which had their *P*-values ≤ 0.10 were kept in the models. Furthermore, a propensity score for CAZ/AVI group was calculated by a logistic regression model covering the above-mentioned variables with *P*-values ≤ 0.20 and included in these two regression models. The plot of log[-log(survival)] versus log(time) was utilized to evaluate the proportional hazard assumption graphically. The collinearity between covariates was also checked. Tests for interactions were not performed. All tests were two-tailed, and *P*-values ≤ 0.05 were considered statistically significant.

Results

Comparison of efficacy between CAZ/AVI-based and PMB-based therapeutic regimen

From January 2019 to December 2021, 164 eligible patients were inclusive in our study (Fig. 1), while 128 patients were admitted to Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine and 36 were hospitalized in Huashan Hospital Affiliated to Fudan University. Their mean age was 65.4 ± 14.9 and the percentage of patients over 65 accounted for 60.4%. A hundred and five patients (64.0%) were female. The most primary common infection site of these patients was respiratory (56.1%). About 15% and 36% patients suffered from polymicrobial infection and sepsis. Cardiovascular disease (51.2%) and respiratory disease (45.1%) were two major types of comorbidities. Nearly three-quarter (74.4%) patients were treated by CAZ/AVI-based or PMB-based therapeutic regimen with a period of at least 7 days. The antimicrobial susceptibility test results of *Klebsiella pneumoniae* isolates were listed in Table 1.

The *Klebsiella pneumoniae* isolates were highly susceptible to CAZ/AVI, colistin and tigecycline, while amikacin and fosfomycin showed suboptimal antibacterial activities against these isolates.

Table 1
Antimicrobial susceptibility characteristics of *Klebsiella pneumoniae* isolates.

Antimicrobial agent	MIC range	S[a] (%)	I[b](%)	R[c] (%)
CAZ/AVI	< 20 mm–>21 mm	96.3	N/A[d]	3.7
Colistin	0.125–0.5 μg/ml	100	N/A	0
Meropenem	≥ 16 μg/ml	0	0	100
Imipenem	≥ 16 μg/ml	1.2	1.8	97.0
Tigecycline	≤ 0.5 μg/ml	94.5	N/A	5.5
Amikacin	≤ 16–≥64 μg/ml	17.1	6.1	76.8
Fosfomycin	≤ 64–≥256 μg/ml	24.4	18.3	57.3

[a] *S = Susceptible.*

[b] *I = Intermediate.*

[c] *R = Resistant.*

[d] *N/A = Not applicable.*

All patients were divided into two groups by receiving CAZ/AVI-based or PMB-based therapeutic regimen. The number of patients in each group was equal (n = 82). Table 2 displayed the demographic and clinical characteristics of patients in these two aforesaid cohorts, which indicated that there were only minor distinctions between the two groups. The proportion of septic patients in PMB cohort was significantly inferior to the CAZ/AVI cohort (22.0% vs 50%, $P < 0.001$). Patients in CAZ/AVI group had a significantly longer antimicrobial treatment duration than the other group (14 days vs 9 days, $P = 0.001$).

Table 2
Characteristics of patients receiving CAZ/AVI-based and PMB-based therapeutic regimens.

Variable[a]	CAZ/AVI (n = 82)	PMB (n = 82)	*P*-value
Age, years	63.2 ± 17.0	67.5 ± 12.3	0.173
Sex (Female)	56 (68.3)	49 (59.8)	0.255
TBW, kg	65.2 ± 13.8	64.1 ± 13.2	0.586
Primary site of infection	10 (12.2)	12 (14.6)	0.647
Primary bloodstream infection	38 (46.3)	54 (65.9)	0.012
Respiratory infection	17 (20.7)	12 (14.6)	0.306
Abdominal infection	12 (14.6)	3 (3.7)	0.027
Urinary tract infection	5 (6.1)	1 (1.2)	0.210
Other infections			
Sepsis	41 (50)	18 (22.0)	< 0.001
Polymicrobial infection	16 (19.5)	9 (11.0)	0.128
APACHE II score (antimicrobial treatment onset)	16.5 (14–19)	16.5 (14–19)	0.895
CrCl, mL/min	76.7 (46.4-119.8)	56.8 (39.0-95.1)	0.039
CRRT	11 (13.4)	21 (25.6)	0.049
ECMO	1 (1.2)	1 (1.2)	1.000
Length of ICU stay before starting antimicrobial therapy, days	23 (11.8–53.3)	35.5 (21.5–54.8)	0.017
Vasoactive drugs	46 (56.1)	42 (51.2)	0.531
Mechanical ventilation	54 (65.9)	51 (62.2)	0.625

Variable[a]	CAZ/AVI (n = 82)	PMB (n = 82)	*P*-value
Comorbidities	28 (34.1)	56 (68.3)	< 0.001
Cardiovascular disease	38 (46.3)	36 (43.9)	0.754
Respiratory disease	17 (20.7)	21 (25.6)	0.459
Central nervous system disease	9 (11.0)	6 (7.3)	0.416
Autoimmune disease	25 (30.5)	19 (23.2)	0.290
Liver disease	22 (26.8)	30 (36.6)	0.179
Renal insufficiency	18 (22.0)	21 (25.6)	0.582
Diabetes	10 (12.2)	5 (6.1)	0.176
Organ transplantation	25 (30.5)	10 (12.2)	0.004
Neoplasia			
CCI score	4 (3–6)	5 (3.8-6)	0.223
Antimicrobial treatment duration, days	14 (10–14)	9 (6-14.3)	0.001
Antimicrobial combination therapy	49 (59.8)	60 (73.2)	0.069

[a] All data are exhibited as number (%), mean ± standard deviation (SD) or median (P_{25}-P_{75}).

There were 59.8% and 73.2% of cases receiving antimicrobial combination therapy in CAZ/AVI and PMB cohort. The antimicrobial therapy information was listed entirely in Table 3. Carbapenems, tigecycline, amikacin and fosfomycin were the main concomitant drugs of combination therapy in each group. Intragroup data analysis indicated that combination therapy was superior to monotherapy in CAZ/AVI cohort because of its higher 30-day microbiological eradication and lower 30-day mortality rate. However, there was nearly no difference in mortality between combination therapy and monotherapy in PMB cohort, while monotherapy even had a higher microbiological eradication rate than combination therapy.

Table 3
Antimicrobial treatment options for patients receiving CAZ/AVI-based or PMB-based therapeutic regimens

Antimicrobial treatment option	CAZ/AVI group			PMB group		
	n = 82	30-day microbiological eradication	30-day mortality	n = 82	30-day microbiological eradication	30-day mortality
Monotherapy	33	22 (66.7)	17 (51.5)	22	8 (36.4)	16 (69.6)
Combination therapy	49	44 (89.8)	12 (24.5)	60	19 (31.7)	41 (68.3)
Carbapenems	17	14 (82.4)	5 (29.4)	19	6 (31.6)	11 (57.9)
Tigecycline	11	11 (100)	3 (27.3)	11	4 (36.4)	8 (72.7)
Amikacin	11	11 (100)	1 (9.1)	15	7 (46.7)	11 (73.3)
Fosfomycin	7	5 (71.4)	3 (42.9)	10	0 (0)	9 (90)
Aztreonam	2	2 (100)	0 (0)	0	-	-
Other Drugs	1	1 (100)	0 (0)	5	2 (40)	2 (40)
Minocycline	1	1 (100)	0 (0)	3	1 (33.3)	1 (33.3)
Moxifloxacin	0	-	-	1	1 (100)	0 (0)
SMZ/TMP[a]	0	-	-	1	0 (0)	1 (100)

[a] *SMZ/TMP = sulfamethoxazole/trimethoprim.*

The comparison of microbiological eradication rate between these two cohorts was described graphically in Fig. 2. The 14-day microbiological eradication rate in CAZ/AVI group was significantly higher than PMB group (51.2% vs 26.8%, $P = 0.001$). The 30-day microbiological eradication rate was 80.5% for patients treated with CAZ/AVI-base therapy, and 32.9% for patients in PMB cohort ($P < 0.001$).

According to the result of survival analysis (Fig. 3), the 30-day all-cause mortality rate in CAZ/AVI group was significantly lower than that in PMB group, (35.4% vs 69.5%, log-rank, $P < 0.001$). The mortality rate for patients receiving CAZ/AVI-based and PMB-based therapeutic regimen were 14.2/1000 patient-days and 42.6/1000 patient-days ($P < 0.001$), respectively.

Risk factors for 30-day microbiologic eradication in critically ill patients with CRKP infection

The microbiological eradication rate on 30 days was 80.5% for CAZ/AVI group and 32.9% for PMB group, respectively. In our study, univariate and multivariable analyses were applied to ascertain potential risk factors of 30-day microbiological eradication. All enrolled participants were classified into success and failure groups, which depended on their 30-day bacterial eradication status. Table 4 summarized the details of demographic and clinical characteristics for patients in these two groups. Variables with their *P*-values ≤ 0.10, including Sex (Female), comorbidity of cardiovascular disease and neoplasia, antimicrobial treatment duration (> 7 days) and CAZ/AVI-based therapeutic regimen were chosen in the next step of multivariate analysis. After covariates forward stepwise selection and adjustment of the propensity score, the eventual results of binary logistic regression analysis showed that the antimicrobial treatment duration of more than 7 days (Odds Ratio, 4.375; 95% Confidence Interval, 1.824–10.496; $P < 0.001$) and CAZ/AVI-based therapeutic regimen (Odds Ratio, 6.392; 95% Confidence Interval, 3.037–13.457; $P < 0.001$) were identified as merely two independent factors relating to a lower rate of 30-day microbiological eradication (Table 5). What's more, the propensity score had not made any significant alteration with the results of the other variables in the binary logistic regression model.

Table 4
Potential risk factors for 30-day microbiological eradication in patients receiving CAZ/AVI- or PMB-based therapeutic regimens.

Variable[a]	30-day microbiological eradication		*P*-value
	Success (n = 93)	Failure (n = 71)	
Age, years	64.4 ± 16.7	66.7 ± 12.2	0.328
Sex (Female)	65 (69.9)	40 (56.3)	0.073
TBW, kg	64.8 ± 14.0	64.5 ± 12.9	0.887
Primary site of infection	13 (14.0)	9 (12.7)	0.808
Primary bloodstream infection	50 (53.8)	42 (59.2)	0.491
Respiratory infection	14 (15.1)	15 (21.1)	0.312
Abdominal infection	11 (11.8)	4 (5.6)	0.173
Urinary tract infection	5 (5.4)	1 (1.4)	0.236
Other infections			
Sepsis	37 (39.8)	22 (31.0)	0.245
Polymicrobial infection	13 (14.0)	12 (16.9)	0.606
APACHE II score (antimicrobial treatment onset)	16 (14–19)	17 (14–19)	0.975
CrCl, mL/min	67.0 (41.1-110.5)	61.5 (41.0-121.5)	0.828
CRRT	15 (16.1)	17 (23.9)	0.194
ECMO	1 (1.1)	1 (1.4)	1.000
Length of ICU stay before starting antimicrobial therapy, days	30 (15-61.5)	33 (20–50)	0.960
Vasoactive drugs	49 (52.7)	39 (54.9)	0.775
Mechanical ventilation	59 (63.4)	46 (64.8)	0.859

Variable[a]	30-day microbiological eradication		*P*-value
	Success (n = 93)	Failure (n = 71)	
Comorbidities	40 (43.0)	44 (62.0)	0.016
Cardiovascular disease	43 (46.2)	31 (43.7)	0.743
Respiratory disease	21 (22.6)	17 (23.9)	0.838
Central nervous system disease	7 (7.5)	8 (11.3)	0.410
Autoimmune disease	24 (25.8)	20 (28.2)	0.735
Liver disease	29 (31.2)	23 (32.4)	0.869
Renal insufficiency	26 (28.0)	13 (18.3)	0.150
Diabetes	9 (9.7)	6 (8.5)	0.787
Organ transplantation	25 (26.9)	10 (14.1)	0.047
Neoplasia			
CCI score	5 (3–6)	4 (3–6)	0.860
Antimicrobial treatment duration (> 7 days)	83 (89.2)	39 (54.9)	< 0.001
CAZ/AVI-based therapeutic regimens	66 (71.0)	16 (22.5)	< 0.001
Antimicrobial combination therapy	63 (67.7)	46 (64.8)	0.691
All data are exhibited as number (%), mean ± SD or median (P_{25}-P_{75}).			

Table 5
Binary logistic regression analysis of potential risk factors for 30-day microbiological eradication.

Variable	Without/With propensity score adjustment[a]		
	OR[b]	95% CI[c]	P-value
Antimicrobial treatment duration (> 7 days)	4.375	1.824–10.496	< 0.001
CAZ/AVI-based therapeutic regimens	6.392	3.037–13.457	< 0.001

[a] The propensity score that was included in the binary logistic regression model showed no significant alteration with the results of other variables (P = 0.393).

[b] OR = Odds Ratio.

[c] CI = Confidence Interval.

Risk factors for 30-day all-cause mortality in critically ill patients with CRKP infection

As the primary outcome of the current study, the 30-day all-cause mortality was analyzed among all critically ill patients with CRKP infection. These patients were divided into survival and death group based on their 30-day survival status. Table 6 exhibited demographic and clinical characteristics for grouped patients. The 30-day mortality rate was 52.4% (78/164) for all eligible patients.

Table 6
Potential risk factors for 30-day mortality in patients receiving CAZ/AVI-based or PMB-based therapeutic regimens.

Variable[a]	30-day mortality		*P*-value
	Survival (n = 78)	Death (n = 86)	
Age (> 65 years)	40 (51.3)	59 (68.6)	0.024
Sex (Female)	56 (71.8)	49 (57.0)	0.048
TBW, kg	64.9 ± 13.6	64.4 ± 13.5	0.792
Primary site of infection	11 (14.1)	11 (12.8)	0.806
Primary bloodstream infection	41 (52.6)	51 (59.3)	0.385
Respiratory infection	11 (14.1)	18 (20.9)	0.252
Abdominal infection	10 (12.8)	5 (5.8)	0.120
Urinary tract infection	5 (6.4)	1 (1.2)	0.103
Other infections			
Sepsis	26 (33.3)	33 (38.4)	0.502
Polymicrobial infection	15 (19.2)	10 (11.6)	0.176
APACHE II score (antimicrobial treatment onset)	15 (14–19)	17 (14.8–19)	0.072
CrCl, mL/min	83.6 (49.2-116.4)	55.8 (33.5–96.9)	0.007
CRRT	9 (11.5)	23 (26.7)	0.013
ECMO	1 (1.3)	1 (1.2)	1.000
Length of ICU stay before starting antimicrobial therapy, days	30 (15-63.8)	29.5 (18-52.3)	0.678
Vasoactive drugs	38 (48.7)	50 (58.1)	0.227
Mechanical ventilation	47 (60.3)	58 (67.4)	0.338

Variable[a]	30-day mortality		*P*-value
	Survival (n = 78)	Death (n = 86)	
Comorbidities	32 (41.0)	52 (60.5)	0.013
Cardiovascular disease	33 (42.3)	41 (47.7)	0.490
Respiratory disease	21 (26.9)	17 (19.8)	0.278
Central nervous system disease	6 (7.7)	9 (10.5)	0.538
Autoimmune disease	21 (26.9)	23 (26.7)	0.979
Liver disease	22 (28.2)	30 (34.9)	0.359
Renal insufficiency	19 (24.4)	20 (23.3)	0.868
Diabetes	1 (1.3)	14 (16.3)	0.001
Organ transplantation	22 (28.2)	13 (15.1)	0.041
Neoplasia			
CCI score	4 (3–6)	5 (4–6)	0.206
Antimicrobial treatment duration (> 7 days)	71 (91.0)	51 (59.3)	< 0.001
CAZ/AVI-based therapeutic regimens	53 (67.9)	29 (33.7)	< 0.001
Antimicrobial combination therapy	56 (71.8)	53 (61.6)	0.168
All data are exhibited as number (%), mean ± SD or median (P_{25}-P_{75}).			

The result of Cox proportional hazards regression analysis was itemized in Table 7. Female gender, receiving antimicrobial treatment in a duration of over 7 days or employing CAZ/AVI therapeutic regimen were significantly associated with lower 30-day mortality rates for critically ill patients with CRKP infection. On the contrary, a higher age (> 65 years), application of CRRT, concurrent septic status and comorbidity of organ transplantation were identified as the independently negative factors on patients' 30-day survival. At last, the propensity score adjustment had not changed the consequences of this Cox regression model.

Table 7
Cox proportional hazards regression analysis of potential risk factors for 30-day mortality.

Variable	Without/With propensity score adjustment[a]		
	HR[b]	95% CI[c]	P-value
Age (> 65 years)	2.038	1.263–3.286	0.004
CRRT	1.786	1.087–2.932	0.022
Sepsis	1.868	1.127–3.097	0.015
Organ Transplantation	4.660	2.390–9.088	< 0.001
Sex (Female)	0.628	0.397–0.995	0.047
Antimicrobial treatment duration (> 7 days)	0.171	0.104–0.281	< 0.001
CAZ/AVI-based therapeutic regimens	0.391	0.236–0.648	< 0.001

[a] The propensity score that was included in the Cox-proportional hazards regression model showed no significant alteration with the results of other variables (P = 0.475).

[b] HR = Hazard Ratio

[c] CI= Confidence Interval.

Subgroup analysis to find out CAZ/AVI-based therapeutic schemes

Taking the data of Table 2 into consideration, we could make an initial deduction that CAZ/AVI-based therapy could probably be conducive to lower mortality rate, compared to PMB-based therapy. Thus, further subgroup analysis was conducted to find out appropriate CAZ/AVI-based therapy schemes for further investigation. As a result, CAZ/AVI-base therapeutic regimen could be beneficial to reduce the 30-day mortality rate significantly when tigecycline ($P = 0.037$) or amikacin ($P = 0.026$) was prescribed as another concomitant agent with CAZ/AVI. (Table 8).

Table 8
Hazard ratio of CAZ/AVI-based therapeutic regimens and 30-day mortality according in the subgroup analysis.

Subgroup[a]	n	HR[b]	95% CI[c]	*P*-value
CAZ/AVI + carbapenem[d]	99	0.585	0.325–1.053	0.074
CAZ/AVI + tigecycline	93	0.267	0.077–0.921	0.037
CAZ/AVI + amikacin	93	0.105	0.014–0.766	0.026
CAZ/AVI + fosfomycin	89	0.299	0.077–1.160	0.081
CAZ/AVI monotherapy	115	0.591	0.332–1.054	0.075

[a] Adjusted for age (> 65 years), CRRT, sepsis, organ transplantation, sex (Female), antimicrobial treatment duration (> 7 days).

[b] HR = Hazard ratio.

[c] CI= Confidence Interval.

[d] Fourteen patients received meropenem and three patients received imipenem.

Safety evaluation between CAZ/AVI-based and PMB-based therapeutic regimen

The clinical safety of CAZ/AVI-based and PMB-based therapy was evaluated by laboratory parameters in three aspects in Table 9, including liver function [alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil)], kidney function [CrCl, blood urea nitrogen (BUN)] and coagulation function [activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen (Fib)]. Significantly elevated ALT and AST were observed after CAZ/AVI-based treatment. Differences in the CrCl and BUN values before and after treatment in the PMB group were all statistically significant. No significantly alteration was identified for all three coagulation parameters in both cohorts.

Table 9
Comparison of safety between CAZ/AVI group and PMB group with different types of laboratory parameters.

Group	Laboratory parameters	Before Treatment	After Treatment	*P*-value
CAZ/AVI	ALT (U/L)	23 (14-30.3)	28.5 (17.8–45)	< 0.001
	AST (U/L)	29.5 (21.5–44.3)	34 (22.5–73.8)	0.035
	TBil (μmol/L)	15.9 (12.7–21.3)	17.5 (10.5–27.7)	0.487
	CrCl (mL/min)	76.7 (46.4-119.8)	80.0 (41.6-120.7)	0.310
	BUN (mmol/L)	8.6 (6.1–13.1)	11.9 (6.3–26.0)	0.013
	APTT (s)	32.5 (28.9–39.0)	32.2 (28.1–36.9)	0.240
	PT (s)	13.6 (12.7–15.5)	14.2 (12.3–17.2)	0.085
	Fib (g/L)	2.8 (2.1–3.6)	3.3 (2.3–4.7)	0.112
PMB	ALT (U/L)	17 (10–41)	19 (12.5–34)	0.683
	AST (U/L)	28 (18.5–56)	28 (19-69.5)	0.431
	TBil (μmol/L)	14.8 (11.3–25.7)	18.4 (11.1–46.1)	0.062
	CrCl (mL/min)	56.8 (39.0-95.1)	48.3 (30.9–70.6)	< 0.001
	BUN (mmol/L)	13.4 (7.3–26.0)	7.2 (4.1–11.5)	< 0.001
	APTT (s)	31.0 (28.3–34.3)	32.2 (28.7–35.5)	0.482
	PT (s)	13.4 (12.2–15.3)	13.8 (12.1–16.7)	0.235
	Fib (g/L)	3.5 (2.8–4.4)	3.6 (3.0-4.4)	0.434
Statistical methods: Wilcoxon rank sum test				

The Adverse Events (AEs) was also collected in the current study. Diarrhea was the main AEs recorded in both cohorts. There were 17.1% (14/82) of patients suffering from diarrhea during the CZA/AVI treatment period, while 12.2% (10/82) of cases had diarrhea in the PMB group ($P = 0.377$). In addition, it must be stressed that seven and two patients developed acute kidney injury and *Clostridium difficile* infection (CDI) when they received PMB-based therapeutic regimes respectively, while only one patient was observed CDI occurring in CAZ/AVI group.

Discussion

Nowadays, when it comes to the available antimicrobial agents against CRKP infection, no one could deny the fact that both CAZ/AVI and PMB are the mainstays of effective pharmacotherapeutic schemes for CRKP infected patients. Several *in vitro* and *in vivo* studies have discussed the effectiveness of CAZ/AVI and PMB in CRKP treatment. As an illustration, a multicenter study carried out by King *et al.*

described that CAZ/AVI was a reliable treatment option for patients with CRE (mainly CRKP) infections because of better clinical outcomes but no significant difference was observed between combination therapy or monotherapy in hospital mortality[17]. Liang *et al*. suggested that using PMB-based combination therapy within 48h of bacteremia onset could notably improve the probability of bacterial clearance and 30-day survival rate for patients with CRKP bloodstream infection[18]. A meta-analysis performed by Hou *et al*. concluded that PMB-based combination therapy was associated with significantly lower mortality than PMB-based monotherapy when treating CRKP infection, especially in combination with carbapenems and tigecycline[19].

Regarding the comparison between CAZ/AVI and PMB, Fang *et al.* had drawn a conclusion that CAZ/AVI-based therapy was more effective than PMB-based therapy in treating CRKP infection by implementing a retrospective analysis to compare the efficacy between these two therapies[5]. Chen *et al.* also established a nomogram to predict the mortality risk for adult patients with CRKP infection, which presented that using CAZ/AVI could significantly improve treatment effectiveness against CRKP, while PMB could not bring about similar effect statistically[20]. Nevertheless, suitable therapeutic combined agents with CAZ/AVI remain unclear. Safety evaluation of CAZ/AVI and PMB should also be performed ulteriorly. It is reasonable for us to design a novel clinical trial to make a comprehensive analysis about effectiveness and safety of CAZ/AVI-based and PMB-based therapeutic schemes.

In our study, we have evaluated the 30-day all-cause mortality as primary outcome of clinical efficacy between these two therapies. Patients with a higher age (> 65 years), suffering from sepsis, receiving CRRT during antimicrobial treatment or having comorbidity of organ transplantation had a significantly higher risk of death. It is worthwhile mentioning that CRRT is a negative factor on survival in our study, which is contrary to our knowledge that CRRT is widely used in critically ill patients since it plays a crucial role in elimination of inflammatory mediators and continuous control of hemodynamic and electrolytical stability *in vivo*. This phenomenon might have possible causes in two aspects. On the one hand, survival patients have a better renal function than dead patients according to the comparison result of CrCl, which are related to a lower demand on CRRT. On the other hand, some clinical studies indicate that CRRT could not effectively lower mortality for infected or septic patients. A retrospective study with the joint model conducted by Wang *et al.* proved that CRRT use were not associated with the 28-day survival of patients with sepsis-induced acute kidney injury[21]. Ren *et al.* had constructed a nomogram prediction model to evaluate the in-hospital mortality for patients with sepsis and lung function in ICU, which figured out that CRRT use could be an obstructive factor on the survival of eligible patients[22]. Regarding the controversy over CRRT in current study, we should put a great emphasis on kidney function to exclude the interference of utilizing CRRT in our further studies.

A comparatively longer period (> 7 days) of antimicrobial treatment, CAZ/AVI-based therapeutic schemes and female gender were significantly decreasing mortality for CRKP infected patients in the present study. Clinical panelists suggest that appropriate treatment courses of CRKP infection should be determined by patients' immune status, general response to therapy, and the control of infection source since there is no consensus on the exact number of days as the duration of CRKP treatment[23]. Zhou *et al*. had

investigated patients with bloodstream infection whose causative pathogen was predominantly CRKP (85.6%) to discover the potential risk factors for mortality. Their research revealed that a short duration of antimicrobial therapy from 4 to 9 days would significantly increase the mortality, which provided a strongly support for our result[24]. We advocate that 7-day above antimicrobial treatment period would have a positive correlation with survival rate for CRKP infected patients.

The gender differences are evidently important for patients with infection and sepsis, which is attributed to sex hormones specifically. Septic female patients may have a survival benefit in comparison with male patients due to the salutary effects of estrogen on releasing cytokines which could improve the positive immune response and restoring organ function after sepsis. The immunosuppressive role of testosterone is also associated with the higher mortality rate for male patients with infection[25–27]. This gender-dependent differences was also existed in our study as well. It is meaningful to investigate the mortality risk by using clinically accurate preclinical models that reflecting sex differences in our further research.

CAZ/AVI-based therapy was proved to be apparently effective on treating CRKP patients in the current study, not only improving survival rate but increasing bacterial clearance rate as well, compared with PMB-based therapy. Quite a few studies demonstrat that CAZ/AVI was of great value in treating CRKP infection. CAZ/AVI therapy was more clinically advantageous than other antibiotics to decrease 30-day mortality for patients with CRKP infection, according to Gu *et al.*'s study[28]. Chen *et al.* analyzed CRKP infected patients after liver transplantation retrospectively and summarized that no matter CAZ/AVI-based combination therapy or monotherapy, promising clinical efficacy and safety were revealed in treating severe CRKP infections[29].

Given the favorable performance of CAZ/AVI therapy in lowering 30-day mortality, we also carried out the subgroup analysis in CAZ/AVI group to investigate whether various CAZ/AVI-based therapeutic schemes could be beneficial for patients with CRKP infection. According to the result from subgroup analysis, those who received CAZ/AVI combining with another anti-CRKP agent including carbapenems (meropenem and imipenem), tigecycline, amikacin and fosfomycin, or CAZ/AVI monotherapy could improve 30-day survival rate. We have recognized that CAZ/AVI combination therapies with tigecycline or amikacin showed notable differences in lowering 30-day mortality, compared to other therapeutic schemes. In our previous study, we have discovered that carbapenems, tigecycline and fosfomycin in combination with CAZ/AVI could significantly improve survival rate for patients with CRKP infection, even these agents were resistant to the CRKP isolates[9].

Tigecycline was identified as a notably effective combined agent in our both studies. Amikacin was also regarded as another potentially useful concomitant drug in CAZ/AVI combination therapy. Ojdana *et al.* undertook one *in vitro* research to explore the synergy of antibiotics combination against CRKP. They found that combination with CAZ/AVI and tigecycline was capable of exerting synergistic effect against KPC- and OXA-48-producing *Klebsiella pneumoniae*[30]. Another *in vitro* time-kill experiment demonstrated that combinations of CZA/AVI with both tigecycline and amikacin exhibited better antimicrobial effects than monotherapy[31]. Tigecycline and amikacin could enhance the therapeutic

efficiency against CRKP in terms of Chen *et al.*'s study[20]. To sum it up, these two antibiotics are widely approved as instrumental drugs in CAZ/AVI combination therapeutic regimens against CRKP infection by clinicians and researchers. This could provide adequate clinical evidence for supporting our conclusion.

We also assessed the 30-day microbiological eradication rate as secondary outcome of the current study. The result from our study showed that those who received CAZ/AVI-based antimicrobial therapy would have a significantly higher probability of CRKP clearance than PMB-based antimicrobial therapy *in vivo*, which was consistent with the conclusion of Fang *et al.*'s article[5]. The antimicrobial treatment lasting longer than 7 days was another independently advantageous factor on increasing bacterial clearance rate for critically ill CRKP infected patients, which revalidated that adequate anti-infective treatment period is essential for clinical success. In addition, combination therapy had a better effect on bacterial clearance than monotherapy in CAZ/AVI group, while the opposite conclusion could be acquired in PMB group.

The safety analysis of corresponding laboratory parameters and AEs was conducted to verify the safety of these two therapeutic schemes as well. Generally speaking, we could conclude that safety could be ensured if patients receive CAZ/AVI or PMB therapeutic regimens since diarrhea was the most common AEs during the treatment period in both cohorts and no severe AE was observed in the present study. Only one case with CDI was observed in CAZ/AVI group in our study. It was quite credible since long-term utilization of broad-spectrum antibiotics could possibly affect the function of gastrointestinal tract, which might cause intestinal flora disorder and antibiotic-associated diarrhea, including CDI[32, 33]. A large study about safety evaluation of CAZ/AVI with the pooled data from seven phase II and III clinical studies elaborated that the incidence of CAZ/AVI-induced diarrhea varied from 3.1–15.4%, which was similar with our result[34].

Significant augmentation of AST and ALT values were found during CAZ/AVI treatment period in our study. This could be attributed to ceftazidime-induced transient elevations in hepatic enzymes[35–37]. Increasing ALT and AST were two of common abnormality in hepatic laboratory parameters when patients used CAZ/AVI based on the statistical data from Cheng *et al.*'s study[34]. Taking the high incidence rate into account, CAZ/AVI-associated hepatoxicity is included in pharmacovigilance surveillance as a vital potential risk. We should attach great importance to monitoring when using CAZ/AVI-based therapeutic treatment, especially in combination with drugs having verified hepatoxicity.

It is inevitable to discuss the controversy of the predominant AE of PMB, namely PMB-associated nephrotoxicity[38]. Polymyxin-associated acute kidney injury (AKI) has a high incidence ranging from 10–60%, which is mainly ascribed to receipt of concomitant nephrotoxic agents and selection of inappropriate dose regimens[11, 39, 40]. However, clinical specialists recommend that there is no need for adjusting daily maintenance doses of PMB if patients suffer from renal impairment because PMB is principally eliminated by non-renal mechanisms, which do not depend on CrCl, in view of the results from several clinical pharmacokinetic studies[41–43]. According to the analysis result of corresponding laboratory parameters in kidney function, we could not ignore the potential renal impairment in PMB

group at all, since there were 8.5% of cases occurring AKI during PMB treatment duration, as well as the significantly decline of CrCl and BUN after PMB-based treatment. Hence, it is necessary to be cautious of PMB-induced AKI, especially for patients with existed renal impairment.

As far as we are concerned, the current study achieves both clinical efficacy and safety comparison between CAZ/AVI-based and PMB-based therapeutic regimen in critically ill CRKP infected patients for the first time. We have already tried out utmost controlling the potential for indication bias for this study. On the one hand, variables which related to the potential difference between CAZ/AVI-based and PMB-based treatment were all evaluated in the multivariate model. On the other hand, the propensity scores were calculated and incorporated into regression analysis, which did not alter any variable in the final multivariate and Cox regression models. In summary, we maintained that our study was convincing because the indication bias could barely affect our investigation result.

The current study had some limitations. First of all, our investigation was a retrospective observational cohort study with insufficient participants, which could not exclude the indication biases. More well-designed clinical trials with a larger number of eligible patients should be performed to validate our conclusion in the future. Secondly, genotypic identification of carbapenemases for all clinical isolates of CRKP was not realized in the present study because of lacking essential equipment and experiment reagents. Thirdly, therapeutic drug monitoring (TDM) was not utilized to evaluate PMB serum concentration, which might cause treatment failure or increasing the risk of AKI due to subtherapeutic or excessive dose, respectively. Last but not the least, we should not neglect the fact that triple or more antimicrobial agents' therapy could probably be effective against CRKP infection, which were not investigated for both CAZ/AVI-based and PMB-based regimens in our study.

Conclusions

In conclusion, our study showed that CZA/AVI-based therapeutic regimen was superior to PMB-based therapeutic regimen in descending all-cause mortality and ascending the microbiological eradication rate for critically ill patients with CRKP infection. Especially, using tigecycline or amikacin as the combined agents in CAZ/AVI therapy could significantly lower the mortality risk. Patients would be benefited from a longer antimicrobial treatment duration (> 7 days) as well. Considering the severity and occurrence of AEs, clinical safety could be guaranteed for those who receive CAZ/AVI or PMB therapeutic regimens in general. However, Clinicians and pharmacists should still pay more attention to the hepatoxicity of CAZ/AVI and nephrotoxicity of PMB when treating CRKP infection. Further large-scale prospective studies should be designed to explore the efficacy and safety between these two agents thoroughly.

Abbreviations

AEs: Adverse Events; ALT: alanine transaminase; AKI: acute kidney injury; APACHE II: Acute Physiology and Chronic Health Evaluation II; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CAZ/AVI: ceftazidime/avibactam; CCI: Charlson comorbidity

index; CDC: Centers for Disease Control and Prevention; CDI: Clostridium difficile infection; CI: Confidence Interval; CLSI: Clinical and Laboratory Standards Institute; CrCl: creatinine clearance; CRE: carbapenem-resistant Enterobacteriaceae; CRKP: carbapenem-resistant Klebsiella pneumoniae; CRRT: Continuous Renal Replacement Therapy; ECMO: Extracorporeal Membrane Oxygenation; Fib: fibrinogen; HR: Hazard Ratio; I: Intermediate; ICU: intensive care unit; MIC: minimum inhibitory concentration; N/A: Not applicable; OR: Odds Ratio; PMB: polymyxin B; PT: prothrombin time; R: Resistant; S: Susceptible; SD: standard deviation; SOFA: Sequential Organ Failure Assessment; SMZ/TMP: sulfamethoxazole/trimethoprim; TBil: total bilirubin; TBW: total body weight; TDM: therapeutic drug monitoring.

Declarations

Ethics approval and consent to participate

The institutional review board of each participating hospital approved the study using data collected for routine clinical practice and waived the requirement for informed consent. This study has been performed in accordance with the ethical standards laid down in “Declaration of Helsinki 1964” and its later amendments or comparable ethical standards.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

All authors declare that they have no conflict of interest in this study and the findings specified in this paper.

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Authors’ contributions

Guanhao Zheng, Jiaqi Cai, Juan He and Xiaolan Bian conceived and designed this study. Guanhao Zheng, Liang Zhang, Dayu Chen, Linyu Wang, Yusi Qiu, Han Deng and Hao Bai collected the information in the case, and contributed to the acquisition, analysis, and interpretation of the data. Guanhao Zheng, Jiaqi Cai, Liang Zhang, Juan He and Xiaolan Bian wrote and revised the manuscript. All authors read and approved the final manuscript.

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Figures

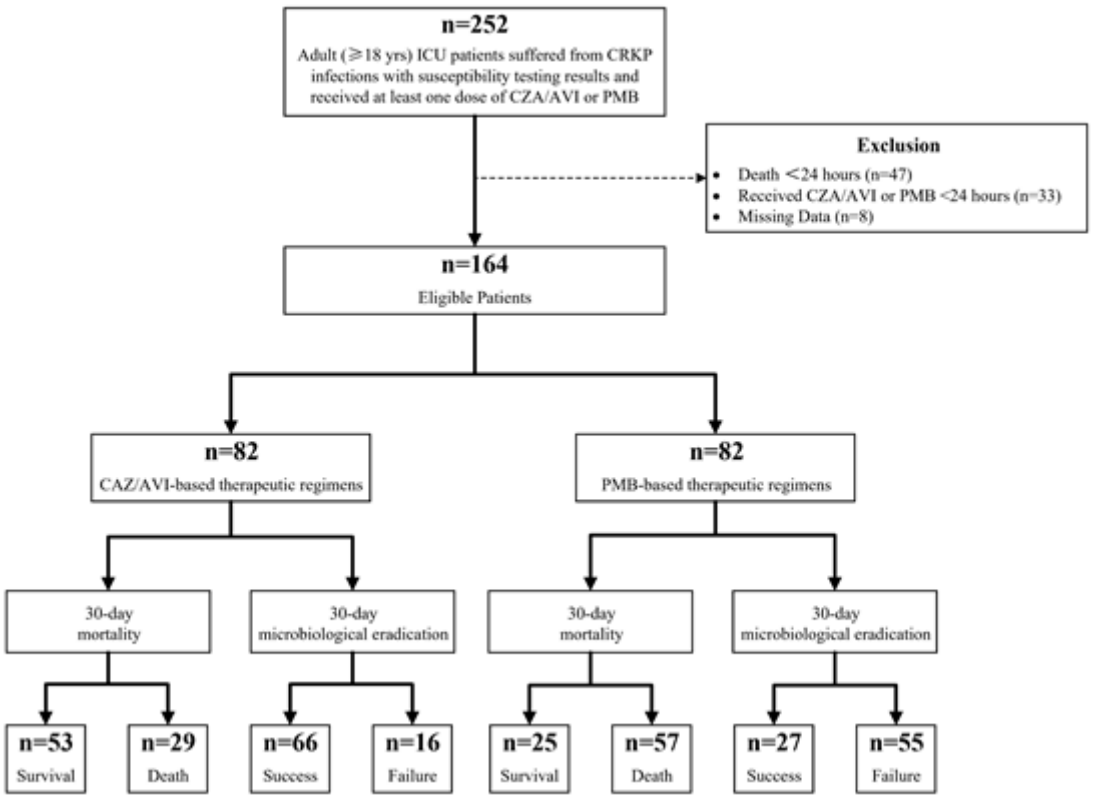

Figure 1

Study design.

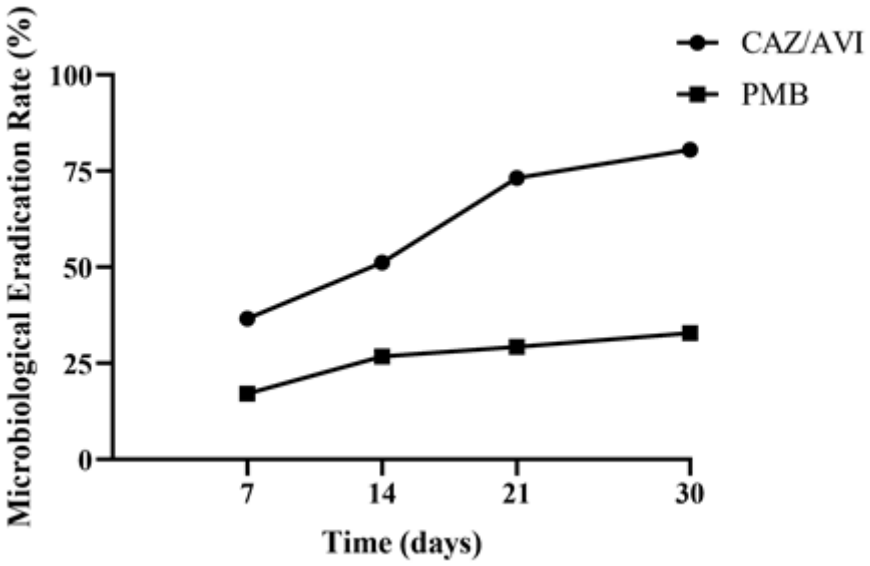

Figure 2

Comparison of microbiological eradication rate in 7, 14, 21 and 30 days between CAZ/AVI and PMB cohorts.

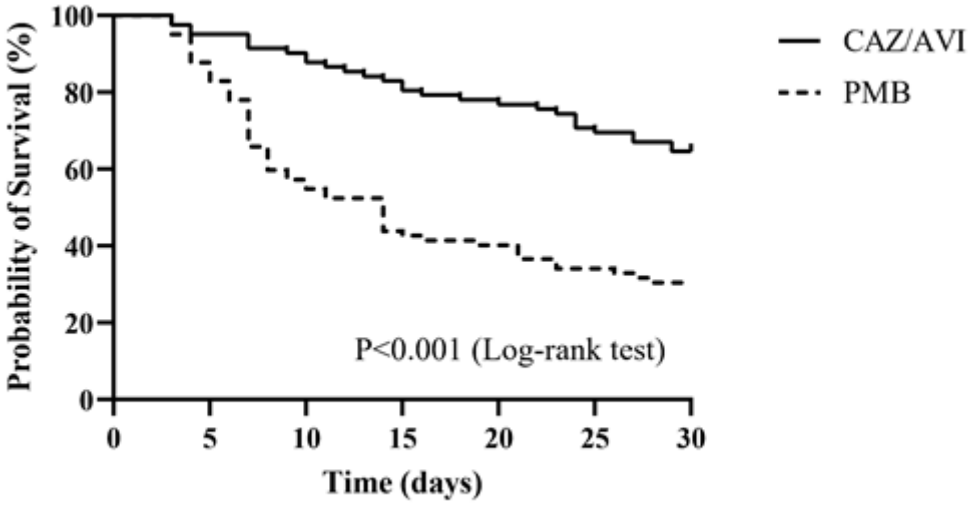

Figure 3

Survival curves of critically ill patients with CRKP infection receiving CAZ/AVI-based and PMB-based therapeutic regimens.