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ORIGINAL RESEARCH

Combination Therapy of Ceftazidime/Avibactam for the Treatment of Patients Infected with Carbapenem-Resistant *Klebsiella pneumoniae*: A Multicenter Retrospective Study

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ABSTRACT

Introduction: This study aimed to evaluate the different efficacies between monotherapy and combination therapy with ceftazidime/avibactam (CAZ/AVI) in treating carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infection.
Methods: We retrospectively analyzed observational multicenter data from 38 hospitals in China. Multivariate regression analysis was used to explore the association between combination therapy with CAZ/AVI and in-hospital mortality. Propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) were performed to validate our findings.
Results: A total of 132 eligible patients were divided into CAZ/AVI combination therapy (n = 43) and monotherapy (n = 89) cohorts. Multivariate logistic regression showed that there was no statistically significant relationship between combination therapy and a lower risk of in-hospital mortality [odds ratio (OR) 0.907, 95% confidence interval (CI) 0.329–2.498, p = 0.850]. In the subgroup of critical patients who were in the intensive care unit (ICU) (OR 0.943, 95% CI 0.221–4.033,

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$p = 0.937$) or with sequential organ failure assessment (SOFA) ≥ 3 (OR 0.733, 95% CI 0.191–2.808, $p = 0.650$), CAZ/AVI combination therapy was not a lower risk factor for in-hospital mortality. Moreover, in the subgroup of patients using CAZ/AVI plus tigecycline (accounting for 46.5% in the combination therapy) compared with CAZ/AVI monotherapy, there was no statistical difference between the two groups in in-hospital mortality, nor in the subgroup of patients with CRKP-associated pneumonia.

Conclusion: Combination therapy (or CAZ/AVI combined with tigecycline) and monotherapy with CAZ/AVI had similar prognoses in patients with only CRKP infection (or CRKP-associated pneumonia), as well as in critically ill patients. Larger randomized controlled trials are warranted to confirm these findings.

Keywords: Ceftazidime/avibactam; Carbapenem-resistant *Klebsiella pneumoniae*; Tigecycline; Pneumonia; Combination therapy

Key Summary Points

Why carry out the study?

The efficacy of combination therapy of ceftazidime/avibactam for the treatment of patients infected with carbapenem-resistant *Klebsiella pneumoniae* remains unclear.

What was learned from the study?

There was no statistical difference in hospital mortality between the combination therapy group and monotherapy group in patients with carbapenem-resistant *K. pneumoniae*-associated infection.

Combination therapy and monotherapy with CAZ/AVI had similar prognoses in patients with only carbapenem-resistant *K. pneumoniae*-associated infection. Larger randomized controlled trials are needed to confirm conclusions.

INTRODUCTION

Carbapenem-resistant Enterobacteriaceae (CRE) are commonly encountered pathogenic bacteria in clinical practice. Resistance of CRE to multiple antibiotics poses a significant challenge for clinical management. Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is the most common type of CRE [1], with a mortality rate of 19–43% [2, 3], and severely impacts human health. The selection of antibiotics for CRKP is limited, with older antibiotics such as tigecycline, polymyxin, and amikacin available. However, the use of these antibiotics is challenging for CRKP treatment as a result of unstable drug concentrations or kidney toxicity [4].

Ceftazidime/avibactam (CAZ/AVI) is a novel antibiotic [5] that has shown good therapeutic efficacy in the treatment of CRKP infections in various sites, such as the lungs and abdominal cavity [6, 7]. In recent years, CAZ/AVI has been increasingly used in clinical practice. However, as CAZ/AVI is a relatively new antibiotic, there are limited clinical studies on its use as a monotherapy or in combination with other drugs for the treatment of CRKP infections. Currently, there is controversy regarding the efficacy of CAZ/AVI in combination with other antibiotics for the treatment of CRKP infections, as well as when and how to use such combinations. Therefore, there is an urgent need for clinical trials to explore the rational application of CAZ/AVI in the treatment of CRKP infections.

This study employed a retrospective design and included patients with CRKP infections who were treated with CAZ/AVI in real-world settings. Notably, this study included a larger number of cases of CAZ/AVI use in respiratory infections compared to previous studies. The study aimed to compare the efficacy of CAZ/AVI as a monotherapy and in combination therapy and to explore the differences in prognosis between the two treatment approaches. Additionally, the study investigated the impact of different sites of infection and the use of different types of antibiotics in combination therapy. The study aimed to provide the

evidence for the development of clinical guidelines for the rational use of CAZ/AVI in the treatment of CRKP infections.

METHODS

Study Design and Patients

This multicenter retrospective study was conducted in 38 hospitals between August 2019 and August 2022 in China. The inclusion criteria included the following: (1) patients were infected with CRKP; and (2) patients who received CAZ/AVI. The exclusion criteria included the following: (1) pathogenic bacteria other than CRKP; (2) the antibiotics were combined with aztreonam or lacked efficiency against gram-negative bacilli (GNB); (3) treatment for fewer than 2 days [8]; and (4) patients who were younger than 14 years of age.

Variables and Definitions

Combination therapy of CAZ/AVI was defined as patients using CAZ/AVI and other anti-GNB antibiotics together for more than 2 days.

Monotherapy of CAZ/AVI was defined as patients only using CAZ/AVI and did not use other anti-GNB antibiotics together for more than 2 days.

Susceptibility tests of antimicrobials were surveyed for determining minimal inhibitory concentrations (MICs) by microdilution test in vitro and were interpreted according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI) [9].

Carbapenem resistance was defined as a MIC $\geq$ 8 μg/mL for meropenem and imipenem, according to the breakpoints of the CLSI.

To assess the incidence of adverse drug events, we calculated the variation in creatinine (maximum minus minimum creatinine within 1 week of antibiotic use).

The primary endpoint was defined as all-cause 30-day mortality. The secondary outcomes included variations in 90-day mortality, microbial cure, variation in creatinine, and length of hospital stay. Data retrieved from the patients' medical records included demographic characteristics, underlying comorbidities, Charlson comorbidity index (CCI) [10], sequential organ failure assessment (SOFA), care in the intensive care unit (ICU), laboratory findings, antibiotic therapy, microbiological data, and follow-up.

Statistical Analysis

Continuous variables are expressed as the median and interquartile range (IQR). Categorical variables are presented as the number and percentage (%). The chi-square test or Fisher's exact test was used to test comparisons between groups for categorical variables. For between-group comparisons of continuous variables, the *t* test or the Mann–Whitney *U* test were used as appropriate. The outcome of mortality was compared between the treatment groups using the logistic regression model in terms of odds ratios (ORs) and 95% confidence intervals (CIs). Subgroup analyses were performed to assess whether the results were robust. Statistical analyses were performed using R software (Comprehensive R Archive Network Project 4.2.2) and SPSS Statistics (version 26.0). A two-tailed p value of < 0.05 was considered statistically significant. Propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) were performed to control for confounding variables [11, 12]. A propensity score for combination therapy was estimated using covariates with $p \leq 0.2$ in the univariate analysis: SOFA, diabetes mellitus, chronic renal disease, shock, white blood cell (WBC) $> 9.5 \times 10^9$/L, and culture from blood (Table S1). One–one nearest neighbor matching with a caliper width of 0.05 was utilized in our study. Standardized mean differences (SMDs) were calculated to assess the availability of the PSM and IPTW. An SMD $\leq$ 10% indicated a good balance between the two groups.

This study was approved by Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College (Protocol No. JS-3029B) and has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki 1964

and its later amendments or comparable ethical standards. Our multicenter study used only one ethics committee; as the content and procedure were based on muticenter research, other hospitals used this common ethics committee.

RESULTS

Patient Cohort and Baseline Characteristics

A total of 829 patients had positive culture results for multidrug-resistant gram-negative bacilli (MDR-GNB). Initially, 132 qualified patients who received CAZ/AVI treatment with CRKP infection were identified, and 89 patients received CAZ/AVI monotherapy (Fig. 1). Baseline characteristics stratified by combination therapy or monotherapy are presented in Table 1. Patients treated with combination therapy or monotherapy had significant differences in SOFA score, diabetes mellitus, chronic renal disease, WBC $> 9.5 \times 10^9$/L, and blood culture ($p < 0.05$). Twenty patients used CAZ/AVI plus tigecycline (accounting for 46.5% in the combination therapy).

Comparison of Outcomes Between Combination Therapy and Monotherapy

In the multivariate analysis, combination therapy was not associated with a decreased risk of in-hospital mortality (OR 0.907, 95% CI 0.329–2.498; $p = 0.850$) (Table S2). The prognosis and creatinine variation did not differ between the two groups (Table 2). There were no differences between the combination therapy and monotherapy in-hospital mortality in different culture sites ($p > 0.05$) and different type of combined drugs (Table 3). We did not find significant differences in the days of using various combinations between the groups of survivor and non-survivor ($p > 0.05$) (Table 3).

PSM and IPTW

After PSM, 32 pairs of combination therapy and monotherapy were matched (Table 1). In Table S3, the SMDs indicated a generally favorable between-group balance after the PSM and IPTW procedure. After PSM, there were no significant differences in microbial cure/mortality between the combination therapy and monotherapy (Table 2). We observed that combination therapy was not an independent factor for in-hospital mortality according to the PSM (OR 0.429; 95% CI 0.115–1.602; $p = 0.208$) and IPTW (OR 1.122; 95% CI 0.792–1.589; $p = 0.517$) procedures (Fig. 2).

Subgroup Analysis

The results of the subgroup analyses showed that there were no interactions between combination therapy and in-hospital mortality in the subgroups of age, CCI, SOFA, ICU, and culture of lung and blood, indicating that these results are comparable for all populations (Fig. 3). Numbers described in Fig. 3 are based on the whole cohort not on the PSM matched group. In the subgroup of patients who received combined tigecycline when compared with monotherapy, monotherapy was not a risk factor for in-hospital mortality (OR 1.233, 95% CI 0.361–4.212, $p = 0.738$). In the subgroup of patients with CRKP-associated pneumonia who had combined therapy with tigecycline when compared with monotherapy, monotherapy was not related to in-hospital mortality (OR 4.200, 95% CI 0.793–22.255, $p = 0.092$).

DISCUSSION

This study focused specifically on the therapeutic efficacy of CAZ/AVI in the treatment of CRKP infections. Compared to other studies, this study excluded patients with concomitant infections with other pathogenic bacteria and cases where antifungal or anti-gram-positive bacterial drugs were also used to reduce bias. In our study, we excluded the cases that used aztreonam to avoid bias from the insensitivity of CAZ/AVI to metalloenzyme. In this study, the PSM and IPTW methods were employed to achieve balance between the baseline characteristics of the two groups receiving monotherapy and combination therapy, respectively, to

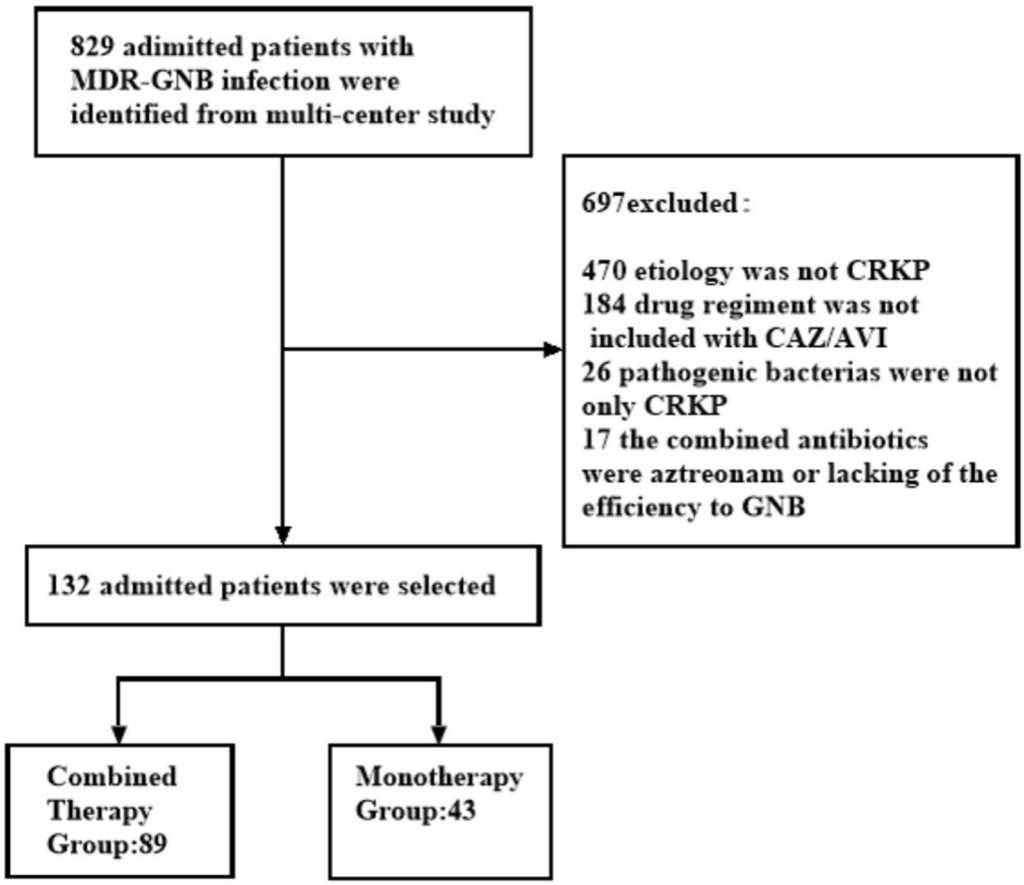

Fig. 1 Flowchart of CAZ/AVI combination therapy or monotherapy for the treatment of CRKP infection. *MDR-GNB* multidrug-resistant gram-negative bacilli, *CRKP* carbapenem-resistant *Klebsiella pneumoniae*, *CAZ/AVI* ceftazidime/avibactam

obtain comparable results. The study found no significant difference in in-hospital mortality, 30-day mortality, or 90-day mortality between patients with CRKP infections receiving monotherapy with CAZ/AVI and those receiving combination therapy. The subgroup analyses further supported the robustness of the results. No differences were found between the two groups in terms of microbiological clearance, a secondary endpoint. The safety analyses also did not reveal any differences in the incidence of elevated serum creatinine between the monotherapy and combination therapy groups.

Previous small-sample studies have suggested that CAZ/AVI monotherapy is not associated with treatment failure in MDR-GNB infections [13]. The recent meta-analysis about CRE (the majority of CRE was CRKP) have showed CAZ/AVI combination therapy and monotherapy have a similar effect on mortality. The results were consistent with ours; our study only focused on CRKP to avoid bias due to other pathogens, and we included more cases than the meta-analysis about in-hospital mortality [14]. For CRKP infections, Jorgensen et al. [15] found no difference in mortality between CAZ/AVI monotherapy and combination therapy, which is similar to the results of this study. However, in recent years, some scholars have proposed that CAZ/AVI combination therapy may be more suitable for severe infections. In this study, patients with concomitant infections with other pathogenic bacteria were excluded, indicating that the overall condition of the patients was relatively mild and less complicated. However, the subgroup analyses based on

Table 1 General information before and after PSM

Characteristics	Before PSM			After PSM		
	Monotherapy (n = 89)	Combined therapy (n = 43)	p value	Monotherapy (n = 32)	Combined therapy (n = 32)	p value
Age (years)	58 (49, 69)	59 (46, 75)	0.803	57 (51, 69)	54 (42, 72)	0.493
Gender female, n (%)	23 (25.8)	9 (20.9)	0.537	9 (28.1)	7 (21.9)	0.564
CCI score	1 (0, 2)	1 (0, 2)	0.683	1 (0, 2.5)	1 (0, 2)	0.650
SOFA score	3 (1, 5)	3 (2, 6)	0.098	3 (2, 5.5)	3.5 (1.5, 6)	0.882
Diabetes mellitus, n (%)	13 (14.6)	12 (27.9)	0.068	8 (25)	6 (18.8)	0.545
Myocardial infarction, n (%)	10 (11.2)	5 (11.6)	0.947	5 (15.6)	3 (9.4)	0.705
Congestive heart failure, n (%)	5 (5.6)	3 (7.0)	1.000	3 (9.4)	2 (6.3)	1.000
Chronic pulmonary disease, n (%)	10 (11.2)	6 (14)	0.654	3 (9.4)	4 (12.5)	1.000
Liver disease, n (%)	13 (14.6)	6 (14)	0.920	3 (9.4)	4 (12.5)	1.000
Chronic renal disease, n (%)	5 (5.6)	6 (14)	0.104	3 (9.4)	2 (6.3)	1.000
Cancer, n (%)	15 (16.9)	7 (16.3)	0.934	7 (21.9)	5 (15.6)	0.522
MV, n (%)	8 (9.0)	5 (11.6)	0.633	3 (9.4)	3 (9.4)	1.000
CRRT, n (%)	7 (7.9)	5 (11.6)	0.481	7 (21.9)	5 (15.6)	1.000
Shock, n (%)	3 (3.4)	4 (9.3)	0.312	1 (3.1)	1 (3.1)	1.000
ICU, n (%)	51 (57.3)	20 (46.5)	0.244	17 (53.1)	14 (43.8)	0.453
WBC ($> 9.5 \times 10^9$ /L), n (%)	76 (85.4)	32 (74.4)	0.125	24 (75)	26 (81.3)	0.545
CRP ($>$ 100 mg/L), n (%)	60 (67.4)	30 (69.8)	0.786	24 (75)	23 (71.9)	0.777
Platelet ($< 100 \times 10^9$ / L), n (%)	23 (25.8)	15 (34.9)	0.282	11 (34.4)	9 (28.1)	0.590
TBIL ($>$ 17.1 μmol/L), n (%)	58 (65.2)	31 (72.1)	0.426	23 (71.9)	23 (71.9)	1.000
Creatinine ($>$ 133 μmol/L), n (%)	30 (33.7)	17 (39.5)	0.512	11 (34.4)	13 (40.6)	0.606
Culture of blood, n (%)	12 (13.5)	12 (27.9)	0.044	3 (9.4)	7 (21.9)	0.302
Culture site			0.310			0.816
More than one culture site	12 (13.5)	2 (4.7)		7 (21.9)	2 (6.3)	

Table 1 continued

Characteristics	Before PSM			After PSM		
	Monotherapy (n = 89)	Combined therapy (n = 43)	p value	Monotherapy (n = 32)	Combined therapy (n = 32)	p value
Sputum or BALF	48 (53.9)	22 (51.2)		19 (59.4)	17 (53.1)	
Peripheral blood	12 (13.5)	12 (27.9)		3 (9.4)	7 (21.9)	
Hydrothorax and ascites	5 (5.6)	2 (4.7)		1 (3.1)	2 (6.3)	
Midstream urine	3 (3.4)	0 (0)		2 (6.3)	0 (0)	
Cerebrospinal fluid	3 (3.4)	2 (4.7)		0 (0)	2 (6.3)	
Others	6 (6.7)	3 (7.0)		0 (0)	2 (6.3)	
Combined drug						
More than one combined drug	–	8 (18.6)		–	6 (18.8)	
Tigecycline	–	20 (46.5)		–	15 (46.9)	
Polymyxin	–	2 (0.05)		–	1 (3.1)	
Carbapenems	–	5 (11.6)		–	4 (12.5)	
Amikacin/quinolone/ others	–	8 (18.6)		–	6 (18.8)	

Continuous variables are expressed as the median and interquartile range (IQR). Categorical variables are presented as the number and percentage (%)

PSM propensity score matching, *CCI* Charlson comorbidity index, *SOFA* sequential organ failure assessment, *MV* mechanical ventilation, *CRRT* continuous renal replacement therapy, *ICU* intensive care unit, *WBC* white blood cell, *CRP* C-reactive protein, *TBIL* total bilirubin, *BALF* bronchoalveolar lavage fluid, *CAZ/AVI* ceftazidime/avibactam

SOFA score, ICU admission, and shock did not find any differences between monotherapy and combination therapy for patients with severe disease, although the number of cases in this subgroup was relatively small. Overall, this study did not find any benefit of CAZ/AVI combination therapy for CRKP infections or severe CRKP infections. Studies on severe GNB infections have suggested that CAZ/AVI combination therapy is not associated with higher clinical and microbiological responses [16]. However, Zheng et al. [17] found that combination therapy with CAZ/AVI and other antimicrobial agents improved the 30-day prognosis of patients with severe disease. Zheng et al. did not separate the use of CAZ/AVI in combination with other drugs or in concomitant infections with other microorganisms, which may have biased their results. Therefore, we speculate that CAZ/AVI monotherapy may be sufficient for the treatment of CRKP infections.

CAZ/AVI is commonly used in the treatment of CRKP infections in the lungs [15]. In this study, respiratory infections were the most common indication for CAZ/AVI use, which differs from the findings of a large-sample study by Tumbarello et al. [18], where bloodstream infections were the most common indication. This study did not find any statistically significant differences in prognosis between monotherapy and combination therapy with

Table 2 Results for the primary and secondary outcome

Characteristics	Before PSM			After PSM		
	Monotherapy (n = 89)	Combined therapy (n = 43)	p value	Monotherapy (n = 32)	Combined therapy (n = 32)	p value
LOS	37 (25, 56)	34 (22, 63)	0.900	37 (26, 56)	35.5 (25, 64)	0.963
Days of using CAZ/AVI	11 (7,14)	10 (7,14)	0.760	11 (7, 13)	10 (7, 14)	0.779
Creatinine variation	61.5 (27, 190)	97 (57, 197)	0.096	98.5 (27, 206.4)	93.8 (51, 171.8)	0.657
Microbial cure, n (%)	42 (47.2)	18 (41.9)	0.564	13 (40.6)	13 (40.6)	1.000
In-hospital mortality, n (%)	15 (16.9)	8 (18.6)	0.804	8 (25)	4 (12.5)	0.337
30-day mortality, n (%)	7 (7.9)	5 (11.6)	0.481	2 (6.3)	3 (9.4)	1.000
90-day mortality, n (%)	13 (14.6)	8 (18.6)	0.556	7 (21.9)	4 (12.5)	0.508

Continuous variables are expressed as the median and interquartile range (IQR). Categorical variables are presented as the number and percentage (%)

PSM propensity score matching, *LOS* length of stay, *CAZ/AVI* ceftazidime/avibactam

CAZ/AVI for pulmonary CRKP infections, which may be due to the favorable tissue distribution of CAZ/AVI in airway epithelial cells [19], consistent with the results of Tumbarello et al. The use of CAZ/AVI in bloodstream infections was found to be associated with better prognosis [20]. This study did not find any statistically significant differences in prognosis between monotherapy and combination therapy with CAZ/AVI for bloodstream CRKP infections, and recent studies have not found any significant effects of CAZ/AVI combination therapy on the prognosis of bloodstream CRKP infections [21]. Recent small-sample case studies have suggested that CAZ/AVI combination therapy is an effective treatment for central nervous system CRKP infections [22]. In our study, no deaths were reported for either monotherapy or combination therapy for CRKP infections in cerebrospinal fluid, making further research difficult. This suggests that combination therapy with CAZ/AVI may be beneficial for CRKP infections in special sites.

Additionally, we further refined the types of antibiotics used in combination therapy to identify potential combination therapy regimens that may be suitable for CRKP infections. In vitro studies have shown that amikacin has a synergistic effect, while tigecycline and colistin have partial synergistic effects [23]. However, neither this study nor previous studies found any significant effects of combination therapy on prognosis, which may be due to the various factors that influence the clinical use of antibiotics, which are different from the results of laboratory experiments. In this study, tigecycline was the most commonly used antibiotic in combination therapy. The comparison of combination therapy with tigecycline and CAZ/AVI with monotherapy did not reveal any differences in prognosis, consistent with the results of other studies. In recent studies on bloodstream infections caused by KPC-KP, no improvement in the effectiveness of monotherapy was found with the addition of polymyxin B [21]. Zhuang et al. found that

Table 3 Combination therapy versus monotherapy in-hospital mortality in different culture sites and combined drugs

	Survivor group (combination therapy/monotherapy)	Non-survivor group (combination therapy/monotherapy)	*p* value
Culture site			
More than one culture site (*n*)	2/10	0/2	–
Sputum or BALF (*n*)	16/42	6/6	0.128
Peripheral blood (*n*)	11/9	1/3	0.584
Hydrothorax and ascites (*n*)	1/2	1/3	1.000
Midstream urine (*n*)	0/3	0/0	–
Cerebrospinal fluid (*n*)	2/3	0/0	–
Others (*n*)	3/5	0/1	–
Combined drug/monotherapy			
More than one combined drug (*n*)	5/74	3/15	0.335
Days of using more than one combined drug (days)	9 (7, 11)	7 (3.5, 13)	0.786
Tigecycline (*n*)	16/74	4/15	0.993
Days of using tigecycline (days)	17.5 (11, 19)	9 (7.5, 13.5)	0.116
Polymyxin (*n*)	2/74	0/15	–
Days of using polymyxin (days)	6.5 (4, 9)	–	–
Carbapenems (*n*)	5/74	0/15	–
Days of using carbapenems (days)	14 (11, 18)	–	–
Amikacin or quinolone or others (*n*)	7/74	1/15	1.000
Days of using amikacin or quinolone or others (days)	9 (9, 14)	7 (7, 7)	0.264

Continuous variables of the days of using various combinations are expressed as the median and interquartile range (IQR)
BALF bronchoalveolar lavage fluid, *n* number of the cases

CAZ/AVI in combination with carbapenems was associated with microbiological clearance in carbapenem-resistant GNB infections but did not find any association with clinical prognosis [24], and this needs to be further refined to CRKP infections. Nevertheless, as the number of cases included in this study and other previous studies is still limited, this area warrants further large-scale research for validation.

In recent years, an increasing number of new drugs have been developed. Combination therapy may have led to adverse drug reactions, and the results of our research suggest that caution should be exercised in evaluating the use of combination therapy with CAZ/AVI in clinical practice.

The limitations of this study were as follows. First, some subcenters had missing details about

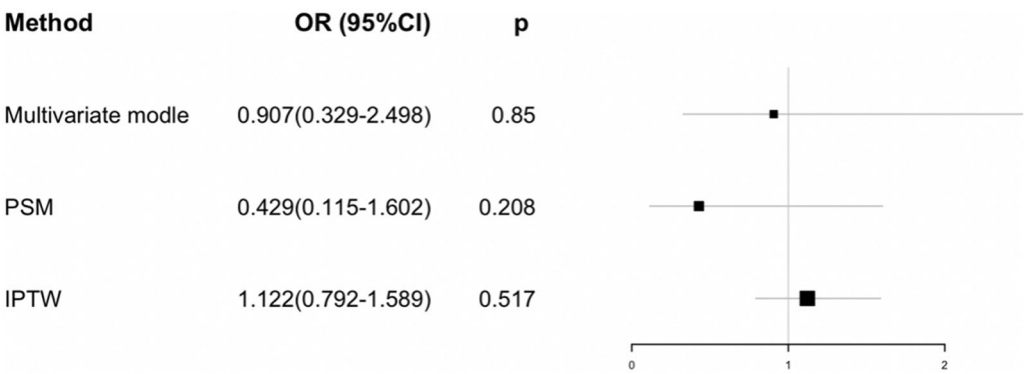

Fig. 2 Association between combined therapy and in-hospital mortality. The odds ratios and 95% confidence intervals in both cohorts were calculated according to the method of covariate adjustment. *OR* odds ratios, *CI* confidence intervals, *PSM* propensity score matching, *IPTW* inverse probability of treatment weight

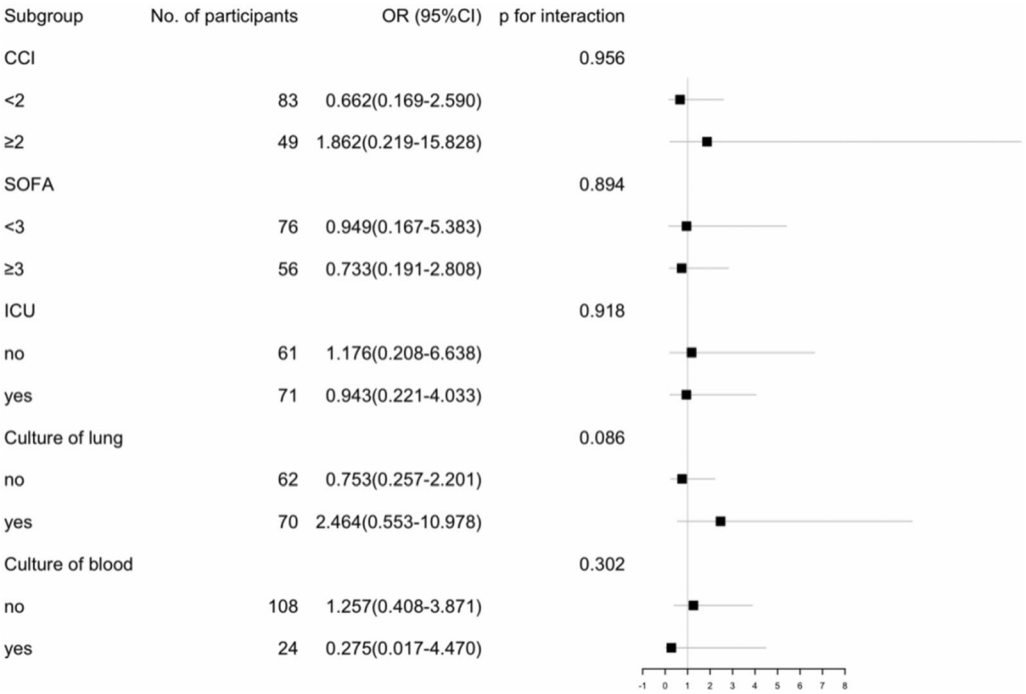

Fig. 3 Subgroup analysis of the association between combined therapy (comparing monotherapy) and in-hospital mortality. *OR* odds ratio, *CI* confidence interval, *CCI* Charlson comorbidity index, *SOFA* sequential organ failure assessment, *ICU* intensive care unit

whether follow-up cultures were performed after positive cultures and the infusion duration of antibiotics. Second, our study was a retrospective study with a limited number of patients who met the inclusion criteria. Finally, the number of combination partners for CAZ-AVI except for tigecycline was limited and the size of the subgroups was small. Hence, further larger clinical studies are needed to validate our research results.

CONCLUSION

This study found that there was no statistical difference in prognosis between monotherapy and combination therapy (tigecycline accounted for most of the data) with CAZ/AVI in patients with CRKP infections, including those with severe infections. In addition, no statistical differences were observed when comparing the use of monotherapy and combination therapy for CRKP infections in different sites (lungs accounted for most of the data). Therefore, monotherapy may be used for the treatment of patients with only CRKP infections. However, larger randomized controlled trials are needed to confirm these conclusions.

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Author Contributions. JL and LZ acquired the data, drafted and revised the manuscript. ZYL designed the study, provided supervision and critically revised the manuscript. All authors approve the final version of the manuscript and agree to be accountable for all aspects of the study.

Disclosures. All authors (Jing Lin, Li Zhang, Menglan Zhou, Xiaotong Tian, Jialong Chen, Minya Lu, Zhengyin Liu) have nothing to disclose.

Ethical Approval. This study was approved by Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College (Protocol No. JS-3029B) and has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki 1964 and its later amendments or comparable ethical standards. Our multicenter study used only one ethics committee; as the content and procedure were based on muticenter research, other hospitals used this common ethics committee.

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

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