Ceftazidime-avibactam in combination with *in vitro* non-susceptible antimicrobials versus ceftazidime-avibactam in monotherapy in critically ill patients with carbapenem-resistant *Klebsiella pneumoniae* infection

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**Research**

**Keywords:** Ceftazidime-avibactam, Carbapenem-resistant Klebsiella pneumoniae, Combination therapy, critically ill patients, Mortality.
Abstract

Background: There is no clinical study investigating if using CAZ-AVI combination schemes with an *in vitro* non-susceptible antimicrobial could be superior to CAZ-AVI monotherapy against CRKP clinically.

Methods: We performed a retrospective, cohort study at two tertiary hospitals in China for patients with CRKP infection who treated by CAZ-AVI at least 72 hours. A Cox-proportional hazards regression model was set up to evaluate covariates which potentially affected 30-day mortality.

Results: Sixty-two patients were eligible in our study, 41 (66.1%) received CZA-AVI combination therapy and 21 (33.9%) received CZA-AVI monotherapy. The overall 30-day mortality was 33.9% (21 patients): 24.4% (10/41) and 47.6% (11/21), \( P = 0.028 \), in combination and monotherapy groups, respectively. Combination therapy was significantly associated with lower 30-day mortality (HR 0.167, 95%CI 0.060-0.465, \( P = 0.001 \)), while higher APACHE II score, use of vasoactive drug and comorbidity of organ transplantation were considered as factors on increasing mortality. The propensity score showed no significant alteration with other variables after adding it into the final model. In the subgroup analysis, the protective effect revealed when combination with carbapenems, tigecycline or fosfomycin were applied, and in the following subgroups of patients: with sepsis, with CrCl > 50 mL/min, stayed in ICU \( \leq 30 \) days or underwent mechanical ventilation.

Conclusions: CAZ-AVI combination with another in vitro non-susceptible antimicrobial, especially carbapenems, fosfomycin and tigecycline, could significantly decrease 30-day mortality rate for critically ill patients with CRKP infection. Further investigation should be carried out to confirm this conclusion and find out the autot antimicrobials in CAZ-AVI combination schemes.

Introduction

As an urgent medical crisis, antimicrobial resistance has become one of biggest worldwide threats to public health in the last few decades mainly due to inappropriate use of antibiotics. The emergence of carbapenem-resistant gram-negative pathogens, especially carbapenem-resistant *Klebsiella pneumoniae* (CRKP), pose a tough clinical therapeutic challenge since carbapenems have been regarded as highly effective antimicrobial agents to treat a series of severe multidrug-resistant bacterial infections[1, 2]. CRKP infection is endemic in China with high probability of occurrence and prevalence, which indicated that improving CRKP infection control and treatment levels was urgent and essential in nationwide medical institutions[3].

When it comes to treatment of CRKP, combination therapy is considered as the prior choice for CRKP infection treatment because of its contribution to lower mortality rates, instead of monotherapy. Unfortunately, there are only few available antimicrobial agents for clinical use. Tigecycline, fosfomycin, aztreonam, polymyxins and aminoglycosides are the mainstays of CRKP treatments. In some cases, high-dose and prolonged-infusion of carbapenems or double-carbapenems therapy could also be applied as therapeutic options. It is urgent to develop other effective drugs against CRKP infection[4, 5]. New
antibiotics like plazomicin, eravacycline, meropenem-vaborbacatam and ceftazidime-avibactam (CAZ-AVI) have been proved as great complements for CRKP infection treatment[6].

CAZ-AVI, a novel combination of cephalosporin and β-lactamase inhibitor, was first approved for treatment of complicated intra-abdominal infections and complicated urinary tract infections by U.S. Food and Drug Administration in February 2015[7]. In China, CAZ-AVI has been of great concern for its confirmed clinical efficacy against CRKP infection by inhibiting the activities of extended-spectrum β-lactamase (ESBL), AmpC-producing β-lactamase, Klebsiella pneumoniae carbapenemase (KPC) and OXA-48 carbapenemase since its initial marketing in September 2019 [8–11].

It is acknowledged that selection of anti-CRKP agents depends on infectious severity, patients’ clinical information, and most importantly, in vitro susceptibility result[6]. In view of therapeutic difficulty, clinicians usually tend to prescribe CAZ-AVI in combination with another susceptible (if any) antimicrobial agent for eradicating CRKP. Although several in vitro studies have proved that using CAZ-AVI in combination with an extra anti-CRKP agent was synergistic against CRKP[12, 13], no differences in mortality and microbiological cure rates were observed for patients receiving CAZ combination therapy or CAZ monotherapy in both studies of Onorato L et al.[14] and Fiore M et al.[15]. What’s more, there is also no clinical study investigating if using CAZ-AVI combination schemes with an in vitro non-susceptible antimicrobial drug could have a better clinical effectiveness than CAZ-AVI monotherapy for treating CRKP infection.

Therefore, this study primarily aimed to find out if CAZ-AVI in combination with an in vitro non-susceptible antibiotic is superior to CAZ-AVI monotherapy against CRKP infection in critical ill patients based on addressing potential indication bias.

**Methods**

**Study design and participants**

We conducted a retrospective, cohort study at two tertiary hospitals in Shanghai, China. This study was approved by Institutional Review Board from Huashan and Ruijin hospital and performed by the ethical standards of the Declaration of Helsinki 1964 and its later amendments or comparable ethical standards. All data in this study were extracted from the electronic medical record information system in each hospital.

All participators with aged ≥ 18 years admitted intensive care unit (ICU) from January 2019 to December 2020, who suffered from documented CRKP infections (according to microbiological culture tests) with susceptibility testing results and received at least one dose of CAZ-AVI infusion for treatment were included in our cohort. Patients were excluded when they met any one of following exclusion criteria: (1) patients received previous CAZ-AVI treatment before current study beginning; (2) patients received CAZ-AVI treatment duration < 72 hours or died within this period; (3) a CAZ-AVI-resistant pathogen was isolated from patients; (4) patients received CAZ-AVI accompanied with a second in vitro susceptible agent as
combination therapy, according to the susceptibility testing result; and (5) patients with any missing data. If patients underwent more than one treatment with CAZ-AVI, only the first course was taken into consideration in our study.

**CAZ-AVI dosing regimen**

CAZ-AVI treatment duration was at the discretion of clinicians. A fixed dose of 2.5 g CAZ-AVI was administered every 8 hours with 2-hour infusion time. Dose adjustment was applied for patients with moderate or severe renal impairment, namely creatinine clearance (CrCl) ≤ 50 mL/min. Dose adjustment details were all listed in Table 1. Patients who underwent any mode of continuous renal replacement therapy (CRRT) received a usual dosage regimen with 2.5 g q8h (infusion time ≥ 2 h) because of limited clinical evidence[16].

| CrCl (ml/min) | Dose  | Dosing Interval | Infusion time |
|--------------|-------|----------------|--------------|
| 31 ~ 50      | 1.25 g| every 8 hours  | ≥ 2 hours    |
| 16 ~ 30      | 0.94 g| every 12 hours | ≥ 2 hours    |
| 6 ~ 15       | 0.94 g| every 24 hours | ≥ 2 hours    |
| ≤ 5          | 0.94 g| every 48 hours | ≥ 2 hours    |

**Study objectives, definitions and variables**

The primary outcome of our study was 30-day mortality. Combination therapy was considered as prescribing a non-susceptible anti-CRKP agent accompanied with CAZ-AVI within 48 hours of starting CAZ-AVI treatment and maintaining therapeutic duration of at least 72 hours.

Variables which were possibly associated with 30-day mortality included age; sex; weight; site of infection (defined in accordance with Centers for Disease Control and Prevention (CDC) criteria[17]); sepsis when starting CAZ-AVI therapy (identified by Sequential Organ Failure Assessment (SOFA) score of 2 points and more[18]); polymicrobial infections; Acute Physiology and Chronic Health Evaluation II (APACHE II) scores at the onset of CAZ-AVI therapy[19]; CrCl (calculated by Cockcroft-Gault formula[20]) at the beginning of CAZ-AVI therapy; CRRT within duration of CAZ-AVI therapy; length of ICU stay before starting CAZ-AVI therapy; concomitant use of vasoactive drugs and mechanical ventilation with the initiation of CAZ-AVI therapy; Charlson comorbidity index (CCI) score[21] and comorbidities; time to start CAZ-AVI therapy and CAZ-AVI treatment duration.

**Microbiology**

All pathogens’ isolation and antimicrobial susceptibility test (except CAZ-AVI) were carried out by Vitek 2 Compact system (bioMérieux, Inc). Susceptibility of CAZ-AVI was determined by disk-diffusion method.
(Kirby-Bauer Method). The diameter of inhibition zone for CAZ-AVI $\geq 21$mm and $\leq 20$mm represented susceptible and resistant, respectively. Clinical and Laboratory Standards Institute (CLSI) criteria 2019 was performed as the evaluation standard of breakpoints to interpret all antibiotics susceptibility testing result.

**Statistical analysis**

All statistical analyses were performed by SPSS (version 26.0, Chicago, IL, USA).

Each variable was assessed by bivariate analysis about 30-day mortality. Shapiro-Wilk test was carried out to verifying the normality of distribution about variables separately. The chi-square test or Fisher’s exact test were applied for analyzing categorical variables as well as calculating $P$-value, while the Student’s t-test or Mann-Whitney U test were implemented to analyze continuous variables and calculate $P$-value. Any Variable with a $P$-value $\leq 0.20$ would be selected to execute a forward stepwise selection for building a Cox-proportional hazards regression model. Covariates with $P$-values $\leq 0.10$ were remained in the model.

For the sake of adjusting for confounding by indication, comparison of variables between Combination therapy and monotherapy was performed at first. Variables with $P$-values $\leq 0.20$ were included in the Cox-proportional hazards regression model for 30-day mortality, while only those with $P$-values $\leq 0.10$ would be maintained in this model. Moreover, a propensity score was calculated by the logistic regression model covered the aforementioned variables with $P$-values $\leq 0.10$ and examined in the final model.

The proportional hazard assumption was assessed graphically by the plot of log[-log(survival)] versus log(time). Collinearity between covariates was checked as well. Tests for interactions were not conducted. All tests were two-tailed, and $P$-values $\leq 0.05$ were considered as statistically significant.

**Results**

From January 2019 to December 2020, a total of 62 eligible patients were included in our study eventually (Fig. 1). Among these 62 patients, their mean age was 60.9 ± 17.1 years and their mean weight was 66.3 ± 13.5 kg. Forty-seven (75.8%) patients were male. As for the primary infection site, twenty-five patients (40.3%) were identified as respiratory infection, as well as 9 for bloodstream infection (14.5%), 12 for abdominal infection (19.4%), 11 for urinary tract infection (17.7%) and 5 for other infections (8.1%). In addition, 40 patients (64.5%) and 12 (19.4%) patients suffered from sepsis and polymicrobial infection, respectively. The APACHE II score at the onset of CAZ-AVI therapy was 17.5 (Interquartile Range [IQR], 14.8–20).

According to the CAZ-AVI dosing regimen, 12 patients (19.4%) received dose adjustment when starting CAZ-AVI therapy due to their lower CrCl level without CRRT treatment. The median average CAZ-AVI treatment duration was 14 days (IQR, 10–14).
The overall 30-day mortality was 33.9% (21 patients) and the median time of death was 14 days (IQR, 9.5–22.5). There were 41 (66.1%) patients received CZA-AVI combination therapy as well as 21 (33.9%) with CZA-AVI monotherapy. Dosing regimens of combined antimicrobial agents were described in Table 2. The 30-day mortality for patients in combination therapy and monotherapy groups were 24.4% (10/41) and 47.6% (11/21), \( P = 0.028 \), respectively. The mortality rates for patients receiving combination therapy and monotherapy were 9.3/1000 patient days and 24.9/1000 patient days, \( P = 0.014 \) (Log Rank, Fig. 2), respectively.

Table 2
Concomitant antimicrobial agents in CAZ-AVI combination therapy scheme

| Antimicrobial agents | n = 41 | Dose regimen | 30-day mortality n = 10 (24.4%) |
|----------------------|--------|--------------|---------------------------------|
| Meropenem            | 11 (26.8) | 1 for 500 mg qd | 3 (27.3) |
|                      |         | 1 for 500 mg q12 |                      |
|                      |         | 1 for 1000 mg q12h |                    |
|                      |         | 8 for 1000 mg q8h |                      |
| Imipenem             | 3 (7.3)  | 2 for 1000 mg q8h | 1 (33.3) |
|                      |         | 1 for 1000 mg q6h |                      |
| Tigecycline\( ^a \)  | 9 (22.0) | 9 for 50 mg q12h | 3 (33.3) |
| Amikacin             | 10 (24.4) | 1 for 600 mg qd | 1 (10) |
|                      |         | 3 for 800 mg qd |                  |
|                      |         | 4 for 1000 mg qd |                |
|                      |         | 1 for 1200 mg qd |               |
|                      |         | 1 for 1400 mg qd |              |
| Fosfomycin           | 6 (14.6) | 2 for 4 g q8h | 2 (33.3) |
|                      |         | 4 for 4 g q6h |                      |
| Aztreonam            | 2 (4.9)  | 2 for 2 g q8h | 0 |

\( ^a \) All 9 patients were given first dose tigecycline 100 mg as loading dose.

Table 3 displayed the details of patient characteristics in combination and monotherapy group. Age \( (P = 0.079) \), respiratory infection \( (P = 0.166) \), sepsis \( (P = 0.169) \), length of ICU stay before starting CAZ-AVI therapy \( (P = 0.059) \) and CCI score \( (P = 0.090) \) were chosen for stepwise variables selection in the Cox-proportional hazards regression model and creation of the propensity score.
| Variablea | Combination (n = 41) | Monotherapy (n = 21) | P-value |
|-----------|---------------------|----------------------|---------|
| Age, years | 58.2 ± 18.4 | 66.2 ± 13.2 | 0.079 |
| Sex (male) | 33 (80.5) | 14 (66.7) | 0.229 |
| Weight, kg | 67.8 ± 14.2 | 63.2 ± 11.6 | 0.207 |
| Primary site of infection | | | |
| Primary bloodstream infection | 7 (17.1) | 2 (9.5) | 0.705 |
| Respiratory infection | 14 (34.1) | 11 (52.4) | 0.166 |
| Abdominal infection | 9 (22.0) | 3 (14.3) | 0.735 |
| Urinary tract infection | 7 (17.1) | 4 (19.0) | 1.000 |
| Other infections | | | |
| Sepsis | 24 (58.5) | 16 (76.2) | 0.169 |
| Polymicrobial infection | 9 (22.0) | 3 (14.3) | 0.735 |
| APACHE II score (CAZ-AVI onset) | 18 (14-20.5) | 17 (16–19) | 0.846 |
| CrCl, mL/min | 76.7 (42.5-133.6) | 97.5 (60.0-131.9) | 0.409 |
| CRRT | 4 (9.8) | 2 (9.5) | 1.000 |
| Length of ICU stay before starting CAZ-AVI therapy, days | 17 (8–31) | 32 (9.5–58.5) | 0.059 |
| Vasoactive drug | 24 (58.5) | 13 (61.9) | 0.798 |
| Mechanical ventilation | 26 (63.4) | 13 (61.9) | 0.907 |
| Variablea | Combination (n = 41) | Monotherapy (n = 21) | P-value |
|-----------|---------------------|----------------------|---------|
| Comorbidities | 10 (24.4) | 6 (28.6) | 0.722 |
| Cardiovascular disease | 18 (43.9) | 8 (38.1) | 0.661 |
| Respiratory Disease | 7 (17.1) | 4 (19.0) | 1.000 |
| Central Nervous system disease | 4 (9.8) | 2 (9.5) | 1.000 |
| Autoimmune disease | 13 (31.7) | 7 (33.3) | 0.897 |
| Liver disease | 11 (26.8) | 4 (19.0) | 0.498 |
| Renal insufficiency | 8 (19.5) | 7 (33.3) | 0.229 |
| Diabetes | 6 (14.6) | 4 (19.0) | 0.722 |
| Organ transplantation | 13 (31.7) | 7 (33.3) | 0.897 |

Neoplasia

| Variable | Combination | Monotherapy | P-value |
|----------|-------------|-------------|---------|
| CCI score | 4 (3–5) | 4 (3.5-6) | 0.090 |
| CAZ-AVI treatment duration, days | 14 (12–14) | 14 (10–14) | 0.299 |

*All data are exhibited as number (%), mean ± SD or median (P25-P75).*

Table 4 showed us the bivariate analysis results for 30-day mortality. Other infections (P = 0.157), polymicrobial infection (P = 0.195), APACHE II score at the onset of CAZ-AVI therapy (P = 0.032), CrCl (P = 0.076), vasoactive drug (P < 0.001), mechanical ventilation (P = 0.008), cardiovascular disease (P = 0.028), respiratory disease (P = 0.082), liver disease (P = 0.111), organ transplantation (P < 0.001), neoplasia (P = 0.111) and combination therapy (P = 0.028) were also included in Cox regression model for stepwise variables selection.
Table 4
Potential risk factors for 30-day mortality in patients treated with CAZ-AVI

| Variable                        | 30-day Mortality | \( P \) value |
|---------------------------------|------------------|---------------|
|                                | Survival (n = 41) | Death (n = 21) |
| Age, years                      | 57.9 ± 17.2      | 66.7 ± 15.8   | 0.055 |
| Sex (male)                      | 31 (75.6)        | 16 (76.2)     | 0.960 |
| Weight, kg                      | 66.2 ± 13.8      | 66.4 ± 13.1   | 0.949 |
| Primary site of infection       |                  |               | 0.705 |
| Primary bloodstream infection   | 7 (17.1)         | 2 (9.5)       | 0.053 |
| Respiratory infection           | 13 (31.7)        | 12 (57.1)     | 0.053 |
| Abdominal infection             | 7 (17.1)         | 5 (23.8)      | 0.520 |
| Urinary tract infection         | 9 (22.0)         | 2 (9.5)       | 0.305 |
| Sepsis                          | 22 (53.7)        | 18 (85.7)     | 0.014 |
| Polymicrobial infection         | 10 (24.4)        | 2 (9.5)       | 0.195 |
| APACHE II score (CAZ-AVI onset) | 16 (14-19.5)     | 18 (17–21)    | 0.032 |
| CrCl, mL/min                    | 100.2 (55.3–142.0) | 61.4 (33.8–108.7) | 0.076 |
| CRRT                            | 3 (7.3)          | 3 (14.3)      | 0.398 |
| Length of ICU stay before starting CAZ-AVI therapy, days | 21 (7.5–33.5) | 23 (13-51.5) | 0.198 |
| Vasoactive drug                 | 17 (41.5)        | 20 (95.2)     | < 0.001 |
| Mechanical ventilation          | 21 (51.2)        | 18 (85.7)     | 0.008 |
| Variablea | 30-day Mortality |   |   |
|-----------|------------------|--|--|
|           | Survival (n = 41) | Death (n = 21) | P-value |
| Comorbidities | 7 (17.1) | 9 (42.9) | 0.028 |
| Cardiovascular disease | 14 (34.1) | 12 (57.1) | 0.082 |
| Respiratory disease | 8 (19.5) | 3 (14.3) | 0.735 |
| Central Nervous system disease | 5 (12.2) | 1 (4.8) | 0.654 |
| Autoimmune disease | 16 (39.0) | 4 (19.0) | 0.111 |
| Liver disease | 9 (22.0) | 6 (28.6) | 0.565 |
| Renal insufficiency | 9 (22.0) | 6 (28.6) | 0.565 |
| Diabetes | 1 (2.4) | 9 (42.9) | < 0.001 |
| Organ transplantation | 16 (39.0) | 4 (19.0) | 0.111 |
| Neoplasia |   |   |   |
| CCI score | 4 (3–5) | 4 (3.5–5) | 0.311 |
| Combination therapy | 31 (75.6) | 10 (47.6) | 0.028 |
| CAZ-AVI treatment duration, days | 14 (12–14) | 14 (9.5–18) | 0.704 |

All data are exhibited as number (%), mean ± SD or median (P_{25–P_{75}}).

Multivariate analysis results were listed detailedly in Table 5. Combination therapy was significantly associated with lower 30-day mortality (HR 0.167, 95%CI 0.060–0.465, P = 0.001), while higher APACHE II score at the onset of CAZ-AVI therapy, use of vasoactive drug and comorbidity of organ transplantation were considered as the factors on increasing 30-day mortality. Moreover, the propensity score showed no significant alteration with the results of other variables in the Cox regression model.
Table 5
Cox-proportional hazards regression model for 30-day mortality\textsuperscript{a}

| Variable\textsuperscript{b}                  | HR   | 95\% CI       | \(P\)-value |
|---------------------------------------------|------|---------------|-------------|
| Combination therapy                         | 0.167| 0.060–0.465   | 0.001       |
| APACHE II score (CAZ-AVI onset)             | 1.180| 1.027–1.356   | 0.019       |
| Vasoactive drug                             | 14.732| 1.881-115.407| 0.010       |
| Organ transplantation                       | 3.817| 1.475–9.881   | 0.006       |

\textsuperscript{a} A propensity score for prescribing combination therapy included age, respiratory infection, sepsis, length of ICU stay before starting CAZ-AVI therapy and CCI score in a logistic regression model using a Likelihood Ratio (LR) forward stepwise method (Hosmer-Lemeshow goodness-of-fit test: \(\chi^2\)-square = 7.478; \(P = 0.486\)). The propensity score that was included in the final Cox-proportional hazards regression model showed no significant alteration with the results of other variables (\(P = 0.926\)).

\textsuperscript{b} Age, sepsis, respiratory infection, length of ICU stay before starting CAZ-AVI therapy, CCI score in Table 1 and other infections, polymicrobial infection, CrCl, mechanical ventilation, cardiovascular disease, respiratory Disease, liver disease, neoplasia in Table 2 were all checked but excluded finally in the Cox-proportional hazards regression model because the \(P\)-value > 0.10 for each aforementioned variable.

\textsuperscript{c} \(HR = \) Hazard ratio.

\textsuperscript{d} CI= confidence interval.

Subgroup Analysis

CAZ-AVI combination therapy could be conductive to lower 30-day mortality when patients received carbapenems, tigecycline and fosfomycin as another concomitant agent, compared with CAZ-AVI monotherapy. Furthermore, combination therapy was a protective factor in the subgroup of patients with sepsis or CrCl > 50 mL/min. Patients stayed in ICU \(\leq 30\) days or underwent mechanical ventilation when starting CAZ-AVI therapy were also benefited from CAZ-AVI combination therapy for decreased mortality as well (Table 6).
Table 6
Hazard ratio of CAZ-AVI combination therapy and 30-day mortality according in the subgroup analysis.

| Subgroup                                      | n   | HR<sup>b</sup> | 95% CI<sup>c</sup> | P-value |
|-----------------------------------------------|-----|----------------|---------------------|---------|
| Combination with carbapenem<sup>d</sup>       | 35  | 0.222          | 0.053–0.938         | 0.041   |
| Combination with tigecycline                  | 30  | 0.220          | 0.052–0.936         | 0.040   |
| Combination with fosfomycin                   | 27  | 0.101          | 0.016–0.638         | 0.015   |
| Sepsis                                        | 40  | 0.136          | 0.039–0.474         | 0.002   |
| CrCl > 50mL/min                                | 45  | 0.219          | 0.065–0.741         | 0.015   |
| ICU stay before starting CAZ-AVI therapy ≤ 30d | 41  | 0.139          | 0.036–0.542         | 0.004   |
| Mechanical ventilation                        | 39  | 0.214          | 0.066–0.686         | 0.010   |

<sup>a</sup>Adjusted for APACHE II score (CAZ-AVI onset), vasoactive drug and organ transplantation.

<sup>b</sup>HR = Hazard ratio.

<sup>c</sup>CI = confidence interval.

<sup>d</sup>Eleven patients received meropenem and three patients received imipenem.

Discussion

As the first novel antibiotics coming to market against CRKP, CZA-AVI was highly concerned by clinicians and pharmacists. Although the rapid developing resistance of CAZ-AVI was reported in some cases by several studies<sup>22–25</sup>, it was still considered as a first-line anti-CRKP agent due to its superiority to the current polymyxin-based therapy in both efficacy and safety<sup>26, 27</sup>. However, it was remained unclear if CAZ-AVI should be used as monotherapy or in combination with other agents in the article from Jason et al.<sup>28</sup> Therefore, we performed a study to made the comparison with CAZ-AVI combination therapy and CAZ-AVI monotherapy for the patients with CRKP infections for the first time.

In our study, we found that CAZ-AVI in combination with another in vitro non-susceptible antimicrobial could significantly lower the 30-day mortality for the patients with CRKP infection. Taking developing resistance of few therapeutic drugs against CRKP into consideration, this was a highly inspired conclusion because the CAZ-AVI combination therapy did not depend on the susceptibility of other antimicrobials revealed and sufficient clinical efficacy at the same time.

Furthermore, carbapenems, tigecycline and fosfomycin were recognized as the effective concomitant agents to decrease 30-day mortality by subgroup analysis. This indicated that CAZ-AVI in combination
with fosfomycin could be a potential therapeutic scheme to treat CRKP infection, which was consistent with the conclusion in Ojdana et al’s *in vitro* study that CAZ-AVI combined with fosfomycin could enhance antibacterial activity against carbapenemase-producing *Klebsiella pneumoniae*.[13]

As another combined drugs with CAZ-AVI, tigecycline was proved clinically effective on patients with CRKP infection in our study, while unsatisfactory results were described by Ojdana *et al.*[13] and Gaibani *et al.*[29] that only 5% and 8% isolates of carbapenemase-producing *Klebsiella pneumoniae* were received synergistic effect of these two agents, respectively. Nevertheless, these two aforesaid studies were both *in vitro* and lack of clinical isolates to verify credibility of their conclusions. Besides, a clinical case had been reported that CAZ-AVI plus tigecycline successfully cured a 61-year old man with intra-abdominal carbapenemase-producing *Klebsiella pneumoniae* infection[30]. We still believed that CAZ-AVI plus tigecycline might be another meaningful therapeutic combination against CRKP based upon the above reasons.

We also found that carbapenems (meropenem and imipenem) played a crucial role in combination therapy with CAZ-AVI as a protective factor on 30-day mortality. Ertapenem was not included in our study since it was only applied to dual carbapenem treatment as an anti-CRKP combination partner[31]. Gaibani *et al.*’s study[29] suggested that the combination of CAZ-AVI and imipenem could be a therapeutic option against CRKP. Mikhail *et al.* evaluated the synergistic activity of CAZ-AVI and other antimicrobials. Their data revealed that the use of CAZ-AVI in combination with meropenem had potential synergy to treat Multidrug-Resistant *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*[12]. Although this treatment scheme was rare in clinical practice because CAZ-AVI and carbapenems were both β-lactam antibiotics, it might be similarly resultful in consideration of enhancing efficacy about double carbapenem therapy as a rescue strategy for the treatment of CRKP[32–34]. Further investigation should be carried out to find out possible mechanisms of increasing anti-CRKP activity between CAZ-AVI with carbapenems and which carbapenem was the optimum choice in clinical practice, as well as the appropriate dose regimen.

What’s more, we could not neglect two other kinds of anti-CRKP agents, namely aztreonam and polymyxins (polymyxin B and colistin). Combination of CAZ-AVI and aztreonam had been already reported as a promising treatment option against carbapenemase-producing pathogens, especially metallo-beta-lactamase-producing gram-negative bacteria[35–38]. Polymyxins (polymyxin B and colistin) were addressed as the last resort antibiotics to treat CRKP infection before CAZ-AVI coming into clinical practice[1, 39–41]. However, combination with CAZ-AVI and polymyxins was not found in any clinical studies. In our study, aztreonam and polymyxins were not evaluated as *in vitro* non-susceptible antibiotics with CAZ-AVI because aztreonam resistance was only emerged in 5 patients who received CAZ-AVI less than 72 hours and no isolate was found resistant to polymyxin B and colistin in our study. These two agents should be included in our further studies.

In the current study, CAZ-AVI combination therapy was also beneficial to patients with sepsis or receiving mechanical ventilation, which implied us that combination therapy was reasonable for treating critical ill
patients with CRKP infection, especially for patients stayed in ICU less than 30 days when starting using CZA-AVI. Combination therapy also showed protective effect on mortality for patients with CrCl > 50 mL/min, who received non-adjusted dose of CAZ-AVI during treatment duration. It might be concluded that higher dose of CAZ-AVI could effectively lower mortality. However, current CAZ-AVI dosage regimen had been verified by population pharmacokinetic models that high probability of target attainment (> 95%) was observed in patients with various CrCl levels, except for patients with CrCl between 8 to 15 mL/min, according to the research from Das et al.[42]. Hence, we maintained that the lower mortality could not simply attribute to using non-adjusted dose of CAZ-AVI. Renal insuficiency should be considered as a rational factor on poor outcome for critically ill patients[43].

We had tried our best to control the potential for confounding bias by indication in this study. We used a multivariate model to evaluate all possibly associated variables with combination therapy by forward stepwise selection and include the propensity scores which creating by these same variables. Although Age, sepsis, respiratory infection, length of ICU stay before starting CAZ-AVI therapy, CCI score were included for evaluation in the multivariate model, none of these variables were remained in the nal model. In addition, the propensity score was included without any significant alteration with other variables in the nal Cox-proportional hazards regression model. Consequently, we thought that indication bias could barely affect our study results.

The current study still had some limitations. Firstly, it was a retrospective cohort study with a small sample size. Well-design prospective studies or randomized control trials with more participators should be designed for further investigation. Secondly, carbapenemase detection tests like Carba NP (CNP) test or modified carbapenem inactivation method (mCIM), were not performed to in our study due to lack of necessary devices and reagents in clinical laboratory. Last but not the least, only dual agents’ combination was evaluated in our study, triple or more drugs combination schemes should be applied in our future study.

Conclusions

In conclusion, our study showed that CZA-AVI in combination with another in vitro non-susceptible antimicrobial, especially carbapenems, fosfomycin and tigecycline, could significantly lower the mortality risk in critically ill patients with CRKP infection. Further well-designed prospective studies should be performed to verify if CZA-AVI combination therapy could be beneficial to all patients suffering CRKP infection and find out the optimum CZA-AVI combining scheme.

Abbreviations

CRKP: carbapenem-resistant Klebsiella pneumoniae; CAZ-AVI: ceftazidime-avibactam; ESBL: extended-spectrum β-lactamase; KPC: Klebsiella pneumoniae carbapenemase; ICU: intensive care unit; CrCl: creatinine clearance; CRRT: continuous renal replacement therapy; CDC: Centers for Disease Control and Prevention; SOFA: Sequential Organ Failure Assessment; APACHE II: Acute Physiology and Chronic Health
Declarations

Ethics approval and informed consent to participate

This study was approved by Huashan and Ruijin Hospital Institutional Review Board and has been performed in accordance with the ethical standards laid down in “Declaration of Helsinki 1964” and its later amendments or comparable ethical standards. Written informed consent was obtained from individual or guardian participants.

Consent to publication

Not applicable.

Availability of data and materials

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

Conflicts of interest

All authors declared no conflict of interest in this study or the findings specified in this paper.

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Authors’ contributions

GZ, JH, LZ, ZY and XB conceived and designed this study. GZ, JZ, BW, JC, LW, KH and YZ collected the information in the case, and contributed to the acquisition, analysis, and interpretation of the data. GZ, JZ, BW, LZ and JH wrote and revised the manuscript. All authors read and approved the final manuscript.

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Figures
Figure 1

Study design.
Figure 2

Survival curves of critically ill patients with CAZ-AVI combination therapy (CAZ-AVI and another in vitro non-susceptible antimicrobial) (solid line) and CAZ-AVI monotherapy (dashed line) for treating CRKP infection. The mortality rates were 9.3/1000 patient days in combination therapy group and 24.9/1000 patient days in monotherapy group, P=0.014.