Heliyon 10 (2024) e35757

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Ceftazidime-avibactam: Combination therapy versus monotherapy in the challenge of pneumonia caused by carbapenem-resistant *Klebsiella pneumoniae*

Chang-wei Liu [a,b], Qiang Chen [c,d], Nan Ding [e,**], Li-fen Hu [c,d,*]

[a] *Department of Pharmacy, The First Affiliated Hospital of Anhui Medical University, Hefei, PR China*
[b] *The Grade 3 Pharmaceutical Chemistry Laboratory of State Administration of Traditional Chinese Medicine, The First Affiliated Hospital of Anhui Medical University, Hefei, PR China*
[c] *Department of Infectious Diseases, The First Affiliated Hospital of Anhui Medical University, Hefei, PR China*
[d] *Anhui Center for Surveillance of Bacterial Resistance, Hefei, PR China*
[e] *Department of Pharmacy, Shanghai Changhai Hospital, The First Affiliated Hospital of Naval Medical University, Shanghai, PR China*

ARTICLE INFO

Keywords:
Ceftazidime-avibactam
Monotherapy
Combination therapy
Pneumonia
Carbapenem-resistant *Klebsiella pneumoniae*

ABSTRACT

This research focused on evaluating the clinical results of patients suffering from pneumonia caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP), who received treatment with either ceftazidime–avibactam (CZA) alone or in combination with other antibiotics. From January 2020 to December 2023, we retrospectively analyzed CRKP-related pneumonia patients treated in two Chinese tertiary hospitals. Mortality was measured at 14 and 30 days as the primary outcome. Secondary outcomes included the 14-day microbiological cure rate and the 14-day clinical cure rate. Factors contributing to clinical failure were evaluated via both univariate analysis and multivariate logistic regression. To account for confounding factors, propensity score matching (PSM) was utilized. Among the 195 patients with CRKP infections, 103 (52.8 %) received CZA combination therapy, and 92 (47.2 %) patients received CZA monotherapy. The combination therapy group exhibited superior clinical and microbiological cure rates compared to the monotherapy group, with a 14-day clinical cure rate of 60.1 % vs. 45.7 % ($P = 0.042$) and a 14-day microbiological cure rate of 72.8 % vs. 58.6 % ($P = 0.038$), respectively. Combination therapy reduced mortality rates at 14 days (7.8 % vs. 17.4 %, $P = 0.041$), but not at 30 days (14.6 % vs. 25.0 %, $P = 0.066$). Even after using PSM, the group treated with the CZA combination continued to had a lower mortality rate at 14 days (5.9 % vs. 17.6 %, $P = 0.039$). The 14-day clinical cure rate for the combination therapy group was 63.2 %, and the 14-day microbial cure rate was 77.9 %. Both of these statistics were notably greater than those observed in the monotherapy group. Furthermore, the multivariate logistic regression model indicated a significant link between combination therapy and a decrease in clinical failure. Carbapenems were noted to be the most effective class of concomitant agents. Our findings indicate that patients with pneumonia due to CRKP benefit from combination treatment of CZA rather than monotherapy; administering

* Corresponding author. Department of Infectious Diseases, the First Affiliated Hospital of Anhui Medical University, Jixi Road 218, Hefei, PR China.
** Corresponding author. Department of Pharmacy, Shanghai Changhai Hospital, the First Affiliated Hospital of Naval Medical University, Changhai Road 168, Shanghai, PR China.
E-mail addresses: 609123572@qq.com (N. Ding), hulifen@ahmu.edu.cn (L.-f. Hu).

https://doi.org/10.1016/j.heliyon.2024.e35757
Received 5 May 2024; Received in revised form 1 August 2024; Accepted 2 August 2024
Available online 3 August 2024

carbapenem in combination with CZA in the early stages could provide considerable survival benefits.

1. Introduction

In recent years, the global public health problem of antibiotic-resistant infections has become increasingly prevalent, especially nosocomial infections such as carbapenem-resistant *Klebsiella pneumoniae* (CRKP) [1]. CRKP is known as a “nightmare bacterium” due to its high mortality rate of 40–60 % [2,3]. Treatment options for CRKP are limited and typically include colistin, tigecycline, aminoglycosides, carbapenems, or combination therapy [4]. However, toxicity or ineffectiveness limits the clinical use of these drugs. Research on mortality among patients subjected to different treatment regimens has shown that mortality can reach 57 % for colistin alone, 80 % for tigecycline alone, 64 % for colistin-tigecycline, and 67 % for combination therapy with colistin and carbapenems [5,6]. Accordingly, identifying novel antibacterial drugs against these resistant bacteria is imperative.

Food and Drug Administration (FDA) approved ceftazidime–avibactam (CZA) in 2015 for the treatment of hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), complicated intra-abdominal infections (cIAIs) and complicated urinary tract infections (cUTIs) [7]. Studies conducted in the US and in European countries have shown that CZA is effective against CRKP in vitro, suggesting that CZA could be a viable alternative treatment option for CRKP infection [8,9]. However, whether CZA should be used alone or in combination remains controversial. According to some studies, CZA alone or in combination with other drugs had no effect on death rates [10,11]. The Infectious Diseases Society of America (IDSA) advised using CZA by itself for treating CRE infections in their guideline documengt [8,9,12]. However, due to the challenge of treating infections from carbapenem-resistant bacteria, CZA is frequently employed alongside other antibiotics in medical settings. An analysis of 62 cases of CRKP was conducted, the group receiving combination therapy had a 30-day mortality rate of 24.4 %, whereas the group receiving monotherapy had a much higher mortality rate of 47.6 % ($P = 0.028$). The study was revealed that the use of combination therapy significantly reduced 30-day mortality, confirming its greater benefit for critically ill patients. In addition, several studies have shown that between 3.7 % and 8.1 % of patients infected with CRE and treated with CZA develop resistance during or after treatment [4], and CZA combination regimens may prevent the emergence of resistance to CZA.

There has been a long debate about the use of combination regimens to treat CRKP infections. We performed a comparative study on the effectiveness of CZA alone versus in combination for treating pneumonia caused by CRKP. The objective was to evaluate the relative merits and demerits of the two treatments. In addition, we analyzed the independent factors linked to clinical failure.

2. Methods

2.1. Patient sample and study Design

From January 2020 to December 2023, we carried out a retrospective, multicenter and observational cohort study at the First Affiliated Hospital of Anhui Medical University, a 4990-bed tertiary teaching hospital in Hefei, Anhui, China, and Changhai Hospital of the Second Military Medical University, a 2700-bed tertiary teaching hospital in Shanghai. Among our cohort were patients aged ≥18 years who had documented monomicrobial pneumonia caused by CRKP and whose susceptibility testing results were available. These patients had received at least 48 h of treatment with CZA infusion. Patients were excluded if their infection diagnosis did not include a diagnosis of pneumonia., if they had a treatment duration of less than 48 h, if they previously received CZA treatment, or if they had concomitant or polymicrobial infections that were not properly treated. In the event that a patient experienced multiple episodes of CRKP infection, only the initial episode was included in the dataset. Following the principles of the Helsinki Declaration, the Research Ethics Committee at the First Affiliated Hospital of Anhui Medical University granted approval for this study (Approval Number Quick-PJ 2022-02-10).

2.2. Definition

The American Thoracic Society (ATS) and IDSA guidelines classify both VAP and HAP as forms of pneumonia [13]. The Acute Physiology and Chronic Health Evaluation II (APACHE II) is a tool that can evaluate the seriousness of infection [14]. Hospital-acquired infections refer to infections acquired by the patient in the hospital, including infections occurring during hospitalization and those acquired in the hospital after discharge, and do not include infections that began before admission or were present on admission [15]. A treatment regimen involving CZA alone was regarded as monotherapy. CZA combined with another antimicrobial agent was considered combination therapy. Within 14 and 30 days after the infection, mortality rates were determined as deaths from any cause occurring within 14 and 30 days, respectively. Additionally, the terms "14-day microbiological cure" and "14-day clinical cure" refer to events occurring within 14 days after treatment initiation with CZA. Clinical failure was defined as persistent infection-related symptoms or signs, death or relapse. No recurrence, survival or improvement in clinical signs or symptoms was considered clinical success. The absence of the previous pathogen from cultures after treatment was defined as a microbiological cure.

2.3. Microbiology and ceftazidime-avibactam dosing regimen

Microbiological specimens were taken from bronchoalveolar lavage fluid (BALF), blood, urine or drainage fluid. For patients with only pneumonia, reliable sputum specimens were helpful for microbiological diagnosis. The Clinical and Laboratory Standards Institute (CLSI) guidelines were followed for susceptibility testing. *Klebsiella pneumoniae* was deemed resistant to meropenem or imipenem if the MIC exceeded 4 mg/mL [16]. The antimicrobial agents tested against the strains obtained included imipenem, meropenem, ceftazidime, gentamicin, levofloxacin, aztreonam, amikacin, fosfomycin, tigecycline, and CZA. Furthermore, a polymerase chain reaction (PCR) test was utilized to detect the carbapenemase genes in CRKP isolates, including blaKPC, blaNDM, blaOXA-48, blaVIM, and blaIMP [17].

Patients received 2.5 g of CZA intravenously every 8 h over a 2-h period. The dosage was adjusted according to kidney function [18]. Given the scarcity of clinical data, standard dosages were administered to patients undergoing continuous renal replacement therapy (CRRT) to guarantee effective treatment [19].

2.4. Statistical analysis

A study revealed that the 30-day mortality rate for severely ill patients with CRKP infection was 33.9 % overall, 24.4 % for those given combination therapy, and 47.6 % for those on monotherapy [4]. Given mortality rates of 24.4 % and 47.6 %, and assuming an alpha level of 0.05, a power of 80 %, and a beta of 0.2, a minimum of 134 samples was required. Categorical data are presented as n (%), and differences were assessed via Pearson's chi-square test or Fisher's exact test. Continuous data are displayed as the mean ± SEM or the median with interquartile ranges (IQRs), and their significance was assessed via the Mann-Whitney *U* test or the *t*-test. A backward stepwise approach was utilized for multivariate logistic regression, incorporating covariates that had a *P* value less than 0.10 in the univariate analysis. To account for confounding factors, this research utilized a propensity score matching(PSM)technique. Utilizing a caliper width of 0.02 and a one-to-one nearest neighbor matching technique, the propensity score was determined using a logistic regression model. All statistical analyses were conducted using IBM SPSS Statistics version 25.0. A P value < 0.05 was deemed to indicate statistical significance.

3. Results

3.1. Baseline characteristics

Throughout the study, 279 individuals with CZA were assessed, and 195 of whom satisfied the inclusion requirements. A total of 153 patients (78.5 %) were male. Most infections (168/195, 86.2 %) were hospital acquired. More than 60 % (123/195, 63.1 %) received their diagnosis during their stay in the intensive care unit (ICU). In Fig. 1, we can see that, the remaining 84 patients were excluded due to having previously been treated with CZA before the current study began (n = 20), a duration of CZA treatment <48 h (n = 8), lack of pneumonia (n = 35), or the presence of polymicrobial or concomitant infections that were not properly treated (n = 21). An average of 57.7 years of age was reported among the 195 patients. Regarding the type of pharmacotherapy, ninety-two patients received CZA monotherapy, and one hundred and three patients received CZA alongside other medications. Table 1 shows the

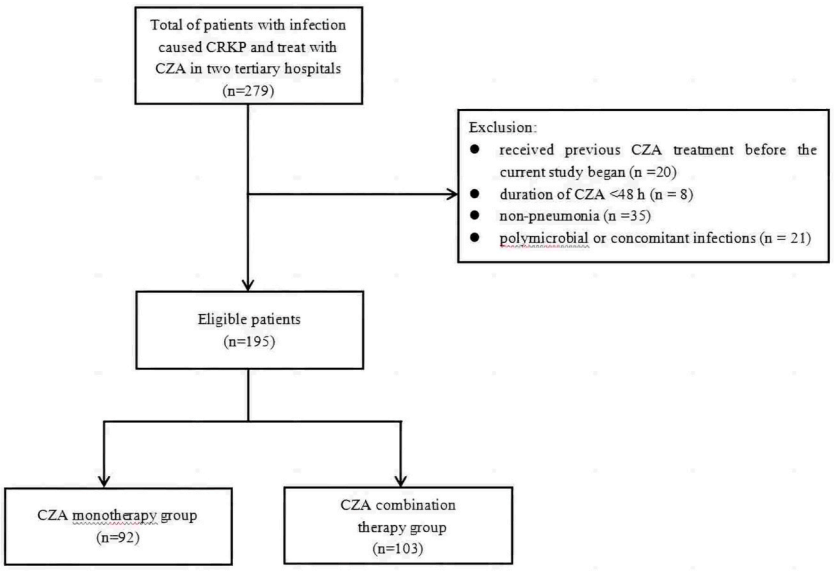

Fig. 1. Study flow chart of the sample size calculation. CRKP, carbapenem-resistant Klebsiella pneumoniae; CZA, ceftazidime/avibactam.

Table 1
Baseline Characteristics and Outcomes of patients receiving CZA monotherapy and combination antimicrobial treatment.

Characteristic	Total (n = 195)	Monotherapy (n = 92)	Combination (n = 103)	*P*-value
Age year, mean ± SD	57.7 ± 17.8	59.6 ± 17.9	56.2 ± 17.6	0.182
Male sex,n (%)	153(78.5)	71(77.2)	82(79.6)	0.679
Weight, kg, mean ± SD	65.4 ± 13.7	64.6 ± 12.5	66 ± 14.6	0.493
BMI, kg/m^2, mean ± SD	22.9 ± 4.1	22.8 ± 3.9	23.1 ± 4.3	0.663
Comorbidities,n (%)	87(44.6)	47(51.1)	40(38.8)	0.086
Cardiovascular disease	43(22.1)	20(21.7)	23(22.3)	0.921
Diabetes mellitus	45(23.1)	17(18.5)	25(24.3)	0.326
Organ transplantation	23(11.8)	8(8.7)	15(14.4)	0.205
Surgery cancer	31(15.9)	16(17.4)	15(14.6)	0.590
Others	26(13.3)	13(14.1)	13(12.6)	0.757
Types of infections,n (%)	76(38.9)	47(51.5)	29(28.2)	0.001
Pneumonia	67(34.4)	23(25.0)	44(42.7)	0.009
Pneumonia + BSIs	19(9.7)	11(11.9)	8(7.8)	0.325
Pneumonia + UTIs	38(19.5)	14(15.2)	24(23.3)	0.155
Pneumonia + IAIs				
APACHE II score at infection onset, median (IQR)	13(11–16)	14(10–16)	12(10–16)	0.257
Laboratory results at infection onset, median (IQR)	10.5(6.2–15.4)	10.4(5.7–14.5)	10.7(7.3–16.4)	0.195
WBC count, $x10^9$/L	8.9(5.1–14.0)	8.5(3.9–12.9)	9.4(6.3–15.1)	0.113
Neutrophils count, $x10^9$/L	136(65.0–204)	145(75.5–205)	128(47–195)	0.193
Platelet count,$x10^9$/L	2.1(0.5–10.4)	1.31(0.2–4.0)	2.9(0.8–16.9)	**< 0.001**
PCT, ng/mL	74.3(25.6–146.5)	70.8(21.1–130.0)	81.4(26.5–172.4)	0.252
C-reactive Protein (mg/L)	109(51–257)	104(51.3–250.3)	114.0(50.7–269)	0.366
Creatinine, μmol/L				
Clinical characteristics at infection onset,n (%)	108(55.4)	46(50.0)	62(60.2)	0.153
Temperature >38 °C	83(42.6)	34(36.9)	49(47.6)	0.134
Pulse >110 bpm				
Clinical status at start of CZA treatment,n (%)	123(63.1)	56(60.9)	67(65.0)	0.546
Mechanical ventilation	59(30.1)	27(29.3)	32(31.1)	0.794
Vasopressor support	71(36.4)	36(39.1)	35(33.9)	0.456
Unconscious				
CZA treatment	1(1–4)	2(1–4)	1(1–4)	0.239
Time from positive culture to CZA initiation(days),median (IQR)	8(5–13)	8.5(5.3–13.8)	8(5–13)	0.497
Days of CZA treatment, median (IQR)	150(76.9)	70(76.1)	80(77.7)	0.793
Received standard CZA dose,n (%)				
Relapse, n (%)	26(13.3)	16(17.4)	10(9.7)	0.115
CRRT,n (%)	56(28.7)	18(19.6)	38(36.9)	0.008
Length of ICU stay time, median (IQR)	14(1–30)	12.5(1–35.8)	15(2–28)	0.845
Length of hospital time, median (IQR)	38(25–60)	36.5(24.5–59)	38(26–60)	0.689
14-day clinical cure,n (%)	104(53.3)	42(45.7)	62(60.1)	**0.042**
14-day microbiological cure,n (%)	129(66.2)	54(58.6)	75(72.8)	**0.038**
14-day mortality,n (%)	24(12.3)	16(17.4)	8(7.8)	**0.041**
30-day mortality,n (%)	38(19.5)	23(25.0)	15(14.6)	0.066

Notes:Bold values indicated that these variables were significant in univariate analysis ($P < 0.05$).
CZA, ceftazidime-avibactam; IQR, Interquartile Range; BMI, Body Mass Index; APACHE II, Acute Physiology and Chronic Health Evaluation II; BSIs, bloodstream infections; UTIs, urinary tract infections; IAIs, Intra-abdominal infections; WBC, White Blood Cells; CRRT, continuous renal replacement therapy. ICU, Intensive Care Unit.

characteristics of patients who received combination and monotherapy with CZA. In the combination group, procalcitonin (PCT) was significantly elevated compared with that in the monotherapy group ($P < 0.001$), as was the incidence of CRRT (36.9 % vs. 19.6 %, $P = 0.008$). With respect to the infection site, in the overall study cohort, 76 patients had only pneumonia (38.9 %), 67 patients (34.4 %) had pneumonia complicated with bloodstream infections (BSIs), 19 patients (9.7 %) had pneumonia complicated with UTIs, and 38 patients (19.5 %) had pneumonia complicated with IAIs. In the monotherapy group, pneumonia was more frequent than in the combination group (51.5 % vs. 28.2 %, $P = 0.001$), whereas both pneumonia and BSI were more prevalent in the combination group (42.7 % vs. 25.0 %, $P = 0.009$). Additionally, no significant differences were found between the groups in terms of the proportion of patients with comorbidities, the use of mechanical ventilation, the APACHE II score and the use of vasopressor support.

3.2. Antimicrobial susceptibility

The antimicrobial susceptibility of isolates is displayed in Table S1. Every isolate examined showed susceptibility to tigecycline and CZA, whereas 91 isolates (46.7%) were responsive to aztreonam and 83 isolates (42.8%) were responsive to amikacin. However, the resistance rates of CRKP strains to cephalosporin, gentamicin and quinolones were higher. Due to the limitation of conditions, only a portion of the strains were tested for CRKP resistance genes, with 82 KPC-producing strains and 8 NDM-producing strains being detected.

3.3. Treatment characteristics

According to Table 1, the median duration from infection to CZA initiation was similar between the two groups: 2 (1–4) versus 1 (1–4) days ($P = 0.239$). The duration of CZA treatment was similar: 8.5 (5.3–13.8) versus 8 (5–13) days ($P = 0.497$). There were no notabledistinctions observed between the two groups in any of these parameters. One hundred and fifty patients (76.9 %) received the standard dose of CZA (2.5 g every 8 h) throughout treatment, including 80 (77.7 %) in the combination therapy group and 70 (76.1 %) in the CZA monotherapy group ($P = 0.793$). Patients with decreased renal function received CZA at adjusted doses. Both the monotherapy and combination therapy groups experienced similar hospital stays (36.5 vs. 38 days, respectively; $P = 0.689$). A comparison of the success rates of different antibiotics in combination therapy is provided in Table S2. The most common combination agents were carbapenem in 58 patients, tigecycline in 16 patients, amikacin in 10 patients, and aztreonam in 6 patients. Carbapenem, with a success rate of 82.8% (48/58), was the most successful treatment for pneumonia caused by CRKP, while tigecycline, amikacin and aztreonam had success rates of 56.3% (9/16), 50% (5/10) and 66.7% (6/18) respectively; The differences among these groups were statistically significant ($\chi2=11.372$, $P<0.05$). In terms of clinical failure reduction, carbapenems was recognized as the most effective concomitant agent.

Table 2
Baseline Characteristics and Outcomes of patients receiving CZA monotherapy and combination antimicrobial treatment After Adjustment.

Characteristic	Total (n = 136)	Monotherapy (n = 68)	Combination (n = 68)	*P*-value
Age year, mean ± SD	58.5 ± 18.5	58.8 ± 19.1	58.1 ± 17.9	0.825
Male sex,n (%)	107(78.7)	52(76.5)	55(80.9)	0.530
Weight, kg, mean ± SD	64.7 ± 11.8	63.9 ± 12.8	65.5 ± 10.8	0.455
BMI, kg/m^2, mean ± SD	22.8 ± 3.8	22.6 ± 4.0	22.9 ± 3.5	0.626
Comorbidities,n (%)	62(45.6)	31(45.6)	31(45.6)	1.000
Cardiovascular disease	20(14.7)	9(13.2)	11(16.2)	0.628
Diabetes mellitus	28(20.6)	13(19.1)	15(22.1)	0.671
Organ transplantation	12(8.8)	5(7.4)	7(10.3)	0.545
Surgery cancer	20(14.7)	12(17.6)	8(11.8)	0.333
Others	19(13.9)	11(16.2)	8(11.8)	0.458
Types of infections,n (%)	60(44.1)	32(47.1)	28(41.2)	0.490
Pneumonia	36(26.5)	19(27.9)	17(25)	0.697
Pneumonia + BSIs	12(8.8)	7(10.3)	5(7.4)	0.545
Pneumonia + UTIs	22(16.2)	9(13.2)	13(19.1)	0.352
Pneumonia + IAIs				
APACHE II score at infection onset, median (IQR)	13(11–16)	11(10–16)	12(10–16)	0.357
Laboratory results at infection onset, median (IQR)	10.2(6.2–15.4)	10.1(5.7–14.1)	11(7.3–16.1)	0.149
WBC count, x10^9/L	8.6(4.9–13.5)	8.3(3.9–11.8)	9.5(6.3–14.7)	0.089
Neutrophils count, x10^9/L	137(71.3–222)	136(72.8–222)	141.5(67.3–226.5)	0.915
Platelet count,x10^9/L	2.0(0.5–8.4)	2.0(0.2–4.4)	1.8(0.63–12.2)	0.226
Procalcitonin, ng/mL	74.3(21.7–143.3)	75.3(25.5–133.3)	70.7(20–153)	1.000
C-reactive Protein (mg/L)	87(50.2–242)	88(51.3–241.8)	82.9(50–242)	0.823
Creatinine, μmol/L				
Clinical characteristics at infection onset,n (%)	77(56.6)	34(50)	43(63.2)	0.119
Temperature >38 °C	53(38.9)	23(33.8)	30(44.1)	0.218
Pulse >110 bpm				
Clinical status at start of CZA treatment,n (%)	81(59.6)	40(58.8)	41(60.3)	0.861
Mechanical ventilation	41(30.1)	21(30.9)	20(29.4)	0.852
Vasopressor support	48(35.3)	24(35.3)	24(35.3)	1.000
Unconscious				
CZA treatment	1(1–4)	2(1–4)	1(1–4)	0.365
Time from positive culture to CZA initiation(days),median (IQR)	8(5–13)	7(5–13.8)	8.5(5.3–13)	0.664
Days of CZA treatment, median (IQR)	107(78.7)	54(79.4)	53(77.9)	0.834
Received standard CZA dose,n (%)				
Relapse, n (%)	12(8.8)	7(10.3)	5(7.4)	0.545
CRRT,n (%)	35(25.7)	16(23.5)	19(27.9)	0.556
Length of ICU stay time, median (IQR)	14.5(1–29.8)	10(1–33.8)	16(2.5–28)	0.497
Length of hospital time, median (IQR)	37.5(25.3–61.5)	36(23.3–59.8)	40(27.3–62.8)	0.398
14-day clinical cure,n (%)	73(53.7)	30(44.1))	43(63.2)	**0.025**
14-day microbiological cure,n (%)	90(66.2)	37(54.4)	53(77.9)	**0.004**
14-day mortality,n (%)	16(11.8)	12(17.6))	4(5.9)	**0.039**
30-day mortality,n (%)	27(19.9)	16(23.5)	11(16.2)	0.281

Notes: Bold values indicated that these variables were significant in univariate analysis ($P < 0.05$).
CZA, ceftazidime-avibactam; IQR, Interquartile Range; BMI, Body Mass Index; APACHE II, Acute Physiology and Chronic Health Evaluation II; BSIs, bloodstream infections; UTIs, urinary tract infections; IAIs, Intra-abdominal infections; WBC, White Blood Cells; CRRT, continuous renal replacement therapy. ICU, Intensive Care Unit.

3.4. Outcomes

As shown in Table 1, the 14-day mortality rate for the combination treatment group was 7.8 %, which is notably less than the 17.4 % observed in the monotherapy group ($P = 0.041$). However, when the 30-day mortality rates were examined, the two groups showed no notable disparity (14.6 % vs. 25 %, $P = 0.066$). Nevertheless, these two groups had significant differences in 14-day clinical cure rates (60.1 % vs. 45.7 %, $P = 0.042$). Additionally, the CZA combination therapy group had a greater microbiological cure rate than the monotherapy group (72.8 % vs. 58.6 %, $P = 0.038$). Our analysis, which accounted for variables using the PSM method, revealed that the 14-day mortality rate was significantly lower in the CZA combination therapy groups compared to the CZA monotherapy groups. (Table 2). In addition, when compared to the monotherapy group, the combination therapy group had a greater microbiological cure rate (77.9 % vs. 55.4 %, P = 0.004), as well as a greater clinical cure rate (63.2 % vs. 44.1 %, P = 0.025); both groups had similar 30-day mortality rates.

Table 3 displays the single-variable analyses of the elements associated with clinical failure. Notable differences were found in age ($P < 0.001$), diabetes mellitus presence ($P = 0.04$), history of organ transplantation status ($P < 0.001$), cancer diagnosis ($P = 0.01$), platelet count ($P < 0.001$), use of mechanical ventilation ($P < 0.001$), consciousness state ($P < 0.001$), duration of CZA therapy ($P < 0.001$), combination treatments ($P = 0.04$), hospital stay length ($P = 0.01$), and ICU stay duration ($P = 0.01$). Table 4 shows the multivariate logistic regression model analysis. Platelet count, unconscious status and combination therapy were significantly associated with clinical failure. According to Table 5, after adjusting with PSM, unconsciousness (odds ratio, 3.958; 95 % confidence interval, 1.632–9.599; $P = 0.002$) and duration of hospital stay (odds ratio, 2.608; 95 % confidence interval, 1.145–5.943; $P = 0.023$) were found to be independent indicators of clinical failure, whereas combination therapy (odds ratio, 0.436; 95 % confidence interval, 0.191–0.992; $P = 0.048$) was identified as an independent predictor of clinical success.

Table 3
Comparison of Clinical Characteristics Between Clinical Success and Failure in patients treated with CZA therapy.

Variable	Total (n = 195)	Success (n = 104)	Failure (n = 91)	P-value
Age year, mean ± SD	57.7 ± 17.8	53.5 ± 17.6	62.6 ± 16.9	**< 0.001**
Male sex,n (%)	153(78.5)	78(75)	75(82.4)	0.209
Weight, kg, mean ± SD	65.4 ± 13.7	64.3 ± 11.6	66.6 ± 15.6	0.250
BMI, kg/m^2, mean ± SD	22.9 ± 4.1	22.7 ± 3.5	23.2 ± 4.7	0.429
Comorbidities,n (%)	87(44.6)	42(40.4)	45(49.5)	0.204
Cardiovascular disease	43(22.1)	17(16.3)	26(28.6)	**0.040**
Diabetes mellitus	45(23.1)	37(35.6)	8(8.8)	**< 0.001**
Organ transplantation	23(11.8)	13(12.5)	10(10.9)	0.744
Surgery cancer	31(15.9))	13(12.5)	18(19.8)	0.165
Others	26(13.3)	13(12.5)	13(14.3)	0.714
Types of infections,n (%)	76(38.9)	34(32.7)	42(46.2)	0.054
Pneumonia	67(34.4)	36(34.6)	31(34.1)	0.936
Pneumonia + BSIs	19(9.7)	12(11.5)	7(7.7)	0.366
Pneumonia + UTIs	38(19.5)	20(19.2)	18(19.8)	0.923
Pneumonia + IAIs				
APACHE II score at infection onset, median (IQR)	13(11–16)	12(10.0–15.5)	15(12.0–17.0)	0.185
Laboratory results at infection onset, median (IQR)	10.5(6.2–15.4)	9.5(6.2–15.6)	11.5(6.2–14.6)	0.732
WBC count, x10^9/L	8.9(5.1–14.0)	8.3(4.7–14.9)	9.4(5.2–12.2)	0.994
Neutrophils count, x10^9/L	136(65.0–204)	169(91.3–220.8)	85((46–175)	**< 0.001**
Platelet count,x10^9/L	2.1(0.5–10.4)	1.3(0.2–9.6)	2.4(0.7–11.3)	0.163
Procalcitonin, ng/mL	74.3(25.6–146.5)	53.8(18.5–132.6)	82.2(51–150.3)	0.054
C-reactive Protein (mg/L)	109(51–257)	134.7(47.8–300.2)	100(52–198.3)	0.340
Creatinine, μmol/L				
Clinical characteristics at infection onset,n (%)	108(55.4)	53(50.9)	55(60.4)	0.184
Temperature >38 °C	83(42.6)	43(41.3)	40(43.9)	0.713
Pulse >110 bpm				
Clinical status at start of CZA treatment,n (%)	123(63.1)	59(56.7)	64(70.3)	0.050
Mechanical ventilation	59(30.1)	15(14.4)	44(48.4)	**< 0.001**
Vasopressor support	71(36.4)	22(21.2)	49(53.8)	**< 0.001**
Unconscious				
CZA treatment	1(1–4)	1(1–4)	1(1–3)	0.809
Time from positive culture to CZA initiation(days),median (IQR)	8(5–13)	10(6.3–14)	7(4–11)	**< 0.001**
Days of CZA treatment, median (IQR)	150(76.9)	75(72.1)	75(82.4)	0.088
Received standard CZA dose,n (%)				
Relapse, n (%)	26(13.3)	10(9.6)	16(17.6)	0.103
Combination,n (%)	103(52.8)	62(59.6)	41(45.1)	**0.042**
CRRT,n (%)	56(28.7)	27(25.9)	29(31.9)	0.363
Length of ICU stay time, median (IQR)	14(1–30)	8(1–28)	17(7–31)	**0.010**
Length of hospital time, median (IQR)	38(25–60)	45(27–62.8)	33(21–56)	**0.010**

Notes: Bold values indicated that these variables were significant in univariate and multivariate analysis (P < 0.05).
CZA, ceftazidime/avibactam; OR, odds ratio; CI, confifidence interval; IQR, Interquartile Range; BMI, Body Mass Index; APACHE II, Acute Physiology and Chronic Health Evaluation II; BSIs, bloodstream infections; UTIs, urinary tract infections; IAIs, Intra-abdominal infections; WBC, White Blood Cells; CRRT, continuous renal replacement therapy. ICU, Intensive Care Unit.

Table 4
Multivariate Logistic Regression Analysis of Variables Associated with clinical failure.

Variable	Univariate Analysis		Multivariate Analysis	
	P-value	OR (95 % CI)	P-value	OR (95 % CI)
Age	0.013	2.059(1.162–3.647)	–	–
Diabetes mellitus	0.042	2.047(1.026–4.084)	–	–
Organ transplantation	< < 0.001	0.198(0.086–0.457)	–	–
Platelet count	< 0.001	3.327(1.823–6.073)	< 0.001	3.711(1.814–7.592)
Vasopressor support	0.051	1.808(0.998–3.274)	–	–
Unconscious	< 0.001	4.348(2.326–8.129)	0.004	3.031(1.419–6.475)
Days of CZA Treatment	0.004	2.316(1.302–4.119)	–	–
Combination	0.043	0.800(0.019–1.181)	0.030	0.14(0.076–0.526)
Length of ICU stay time	0.017	2.003(1.131–3.549)	–	–
Length of hospital time	0.013	0.483(0.273–0.856)	–	–

CZA, ceftazidime/avibactam; OR, odds ratio; CI, confifidence interval; ICU, Intensive Care Unit.

Table 5
Multivariate logistic regression analysis of variables associated with clinical failure after adjustment.

Variable	Univariate Analysis		Multivariate Analysis	
	P-value	OR (95 % CI)	P-value	OR (95 % CI)
Organ transplantation	0.002	0.187(0.066–0.529)	–	–
Pneumonia	0.033	2.119(1.064–4.222)	–	–
Platelet count	0.006	2.778(1.343–5.744)	–	–
Unconscious	< 0.001	5.769(2.648–12.570)	0.002	3.958(1.632–9.599)
Days of CZA Treatment	0.016	2.409(1.180–4.917)	–	–
Combination	0.001	0.315(0.156–0.636)2.179(1.096–4.331)	0.048	0.436(0.191–0.992)2.608(1.145–5.943)
Length of hospital time	0.026		0.023	

CZA, ceftazidime/avibactam; OR, odds ratio; CI, confifidence interval.

4. Discussion

CZA, a novel antibiotic used to treat bacteria that are carbapenem-resistant, is considered superior to current therapies in terms of safety and efficacy, especially against CRKP [20–22]. Researchers indicated a 30-day mortality rate of 25 % for patients receiving CZA treatment [23], which aligns closely with our study's 19.5 % mortality rate within the same period. CZA was confirmed to have a beneficial effect on CRKP. However, the effectiveness of CZA by itself or alongside other substances remains unclear at present [24]. Studies have shown that in vitro combinations of CZA with carbapenems, colistin and tigecycline can produce synergistic effects against carbapenem-resistant organisms [25]. According to a retrospective cohort study, patients who received CZA monotherapy exhibited a notably higher 30-day mortality rate compared to patients received combination therapy that included CZA [4]. As far as we known, our research compares the clinical results of CZA monotherapy and combination therapy for treating pneumonia due to CRKP for the first time. We revealed that the combination of CZA and another antimicrobial successfully reduced 14-day mortality rate in patients suffering from pneumonia caused by CRKP infection. Even after the adjustment of PSM, CZA combination therapy significantly improved both clinical and microbiological cure rates at 14 days compared with monotherapy. Moreover, according to the multivariate analysis, combination therapy significantly reduced clinical failure.

In our study, the CZA combination therapy and monotherapy groups had similar 30-day mortality rates before and after adjusting for confounders, which may be due to numerous reasons. First, even after overcoming CRKP infection, severely ill patients face a significant risk of contracting further hospital-acquired infections, which increases the 30-day mortality rate. Second, most of our patients have comorbidities such as cancer, cardiovascular disease and previous surgery. The early effects may not be obvious, but a longer hospital stay increases the risk of death from complications.

The most clinically meaningful combination of drugs remains unknown. Carbapenems and tigecycline have been identified as the most commonly used concomitant agents in combination therapies. CZA and meropenem combined appeared to have a synergistic effect in treating multidrug-resistant *K. pneumoniae* [26]. Gaibani et al. suggested that CZA and imipenem could be therapeutic options for treating CRKP [27]. The potential mechanisms for enhancing the anti-CRKP activity of CZA and carbapenem should be further investigated. Regarding tigecycline, Ojdana et al. reported that CZA/tigecycline had synergistic effects on only 5 % of CRKP isolates, but this study was performed in vitro, and this conclusion needs to be confirmed by clinical studies [28]. Combining CZA and amikacin may be effective for CRKP infection because of its ability to prevent the development of CZA resistance and potential synergistic effects [29]. However, amikacin is not the preferred choice for treating pneumonia. In our study, the main agents used in combination therapy were carbapenems, tigecycline and amikacin. Carbapenems have been recognized as effective combination agents for decreasing clinical failure. Moreover, combination therapies have the potential to reduce the occurrence of CRKP resistance to CZA and the recurrence of CRE infection [30].

Timely and effective antibiotic therapy for CRKP infection is key to reduce the mortality rate of severely ill patients. A previous

study reported that antibiotic therapy administered within 48 h reduced the 30-day mortality rate and was inversely related to overall mortality [31]. Similarly, Jorgense et al. demonstrated that clinical failure rates in MDR-GNB-infected patients were decreased with prompt initiation of CZA administration within 48 h [32]. Almost all patients included in our study were administered CZA treatment at a median of 24 h after positive culture, and the time from infection to the initiation of CZA was similar. Therefore, promptly administering appropriate antibiotics, such as CZA, following blood culture collection is imperative to improve the outcomes of patients infected with CRE.

Carbapenemase production is the primary resistance mechanism that enables CRKP to resist carbapenems. These enzymes encompass class A β-lactamases like KPC, class B metal-β-lactamases such as NDM and IMP, and class D β-lactamases incluing OXA. The most prevalent carbapenemase type in China is KPC, according to previous epidemiological studies [15]. The NDM gene and the IMP gene are the main genotypes reported in Asia and Europe, of which IMP-4 was circulating in China [33]. Changes in the number of drug-resistant bacteria from 2010 to 2014 in China showed that the number of IMP-4 isolates decreased annually, while the number of NDM-1 isolates increased and dominated infections in pediatric patients [34]. The OXA enzyme is common in *Acinetobacter baumannii* and relatively rare in *Klebsiella pneumoniae*, except for the OXA-48 enzyme [35]. Among the 90 strains tested in our study, 82 were KPC-producing strains, and 8 were NDM-producing strains. This finding demonstrates that KPC is the predominant CRKP carbapenemase gene in our area, aligning with the molecular patterns of CRKP identified in most areas of China. The detection of the NDM type in adult patients in our study may indicate the horizontal transfer and cloning transmission ability of the carbapenemase gene of CRKP, which allows CRKP to be spread among different clinical departments in hospitals [36]. CZA was insensitive to NDM-producing CRKP but regained sensitivity when combined with aztreonam [37], suggesting that synergistic effects may increase cumulative antibacterial activity when CZA regimens are combined with antibiotics with different mechanisms of action.

We should acknowledge some limitations of this study. First, CZA has only been marketed in China since 2019, leading to a limited sample size. Moreover, differences in the mechanisms of resistance among CRKP isolates might influence the efficacy of CZA, but we did not detect the carbapenemase gene in all CRKP isolates.

5. Conclusion

This study revealed for the first time that combining CZA with other treatments is more effective than using it alone for patients with pneumonia caused by CRKP. Administering a combination of CZA at an early stage for a sufficient duration can produce a positive clinical outcome. However, further prospective studies involving larger sample sizes are needed to investigate the clinical effectiveness of CZA combined with other antimicrobial drugs or with CZA alone for treating carbapenem-resistant infections.

Ethical approval

The Ethics Committee of the First Affiliated Hospital of Anhui Medical University granted approval for this retrospective cohort study. Because it was retrospective and anonymous, informed consent was not required from the study participants.

Funding

Funding for this research was provided by the Clinical Research Project of the First Affiliated Hospital of Anhui Medical University (LCYJ2021YB005) and the 2021 Outstanding Young Talents Project in Colleges and Universities in 2021(gxyq2021172).

Availability of data and materials

The study data have not been stored in a publicly accessible repository.You can obtain the information by contacting the corresponding author with a valid request.

CRediT authorship contribution statement

Chang-wei Liu: Writing – original draft, Investigation, Formal analysis, Data curation. **Qiang Chen:** Investigation, Data curation. **Nan Ding:** Supervision, Software, Methodology. **Li-fen Hu:** Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Li-fen Hu reports financial support was provided by The First Affiliated Hospital of Anhui Medical University Clinical Research Project. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:mmcdoino

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