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Original Article

Resistance profile and clinical outcomes of Xuebijing injection combined with antibiotics for carbapenem-resistant Pseudomonas aeruginosa infection: a single-center retrospective cohort study

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Abstract: Objective: To examine the resistance profile of carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) and to evaluate the clinical efficacy of Xuebijing injection (XBJ) combined with antibiotics versus antibiotics alone. Methods: This single-center retrospective cohort study included 295 hospitalized patients with microbiologically confirmed CRPA infection between January 2019 and June 2024. Patients received either antibiotics alone (control group, n=141) or XBJ plus antibiotics (combination group, n=154). The primary outcome was 28-day all-cause mortality. Inverse probability of treatment weighting (IPTW) was applied to balance baseline covariates. Logistic and Cox regression models were performed to evaluate the association between combination therapy and 28-day mortality. Results: After IPTW adjustment, all covariates achieved satisfactory balance (standardized mean differences <0.10). Compared with control group, the combination group showed significantly higher clinical response rate (OR=1.705, 95% CI: 1.039-2.798, P=0.035) and bacterial eradication rate (OR=1.758, 95% CI: 1.097-2.817, P=0.019), as well as a lower risk of escalation of anti-infective therapy (OR=0.529, 95% CI: 0.302-0.925, P=0.026). The duration of hospital stay and ICU stay were numerically shorter in the combination group, though differences were not significant (both P>0.05). After IPTW adjustment, no significant difference was observed in 28-day mortality between the two groups (16.85% vs 22.72%, P=0.207); however, multivariable Logistic regression identified combination therapy as an independent protective factor for 28-day mortality (OR=0.250, 95% CI: 0.071-0.873, P=0.030). Older age, higher APACHE II scores, bloodstream infection, and absence of targeted antimicrobial therapy were independently associated with increased mortality risk. Sensitivity analyses confirmed model robustness. Subgroup analysis suggested greater benefit in patients with APACHE II score <20. Conclusion: XBJ combined with antibiotics improved infection control outcomes in patients with CRPA infections, with more evident benefits observed among patients with lower disease severity. The effect of this combination therapy on 28-day mortality requires further validation in multicenter prospective studies.

Keywords: Carbapenem-resistant Pseudomonas aeruginosa, Pseudomonas aeruginosa infection, Xuebijing injection, propensity score weighting, 28-day mortality

Introduction

Pseudomonas aeruginosa (CRPA) is a major opportunistic pathogen responsible for hospital-acquired and severe infections, causing a variety of clinical syndromes, such as pulmonary infections, bloodstream infections, urinary tract infections, and intra-abdominal infections [1, 2]. This bacterium has strong adaptability to environmental stressors through multiple mechanisms, including virulence regulation, biofilm formation, intrinsic and acquired antimicrobial resistant, and genetic plasticity. Over the years, *P. aeruginosa* has become one of the major pathogens of concern in the prevention and treatment of Gram-negative infections [3]. Studies investigating the global burden of antimicrobial resistance have shown the continuous evolution of this pathogen, with bacterial resistance emerging as a serious threat to public health. Moreover, P. aeruginosa remains a contributor to healthcare-associated

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infections. Recent reviews have indicated that its extensive genome and remarkable genetic plasticity facilitate rapid alterations in resistance profiles under antimicrobial pressure, thereby increasing the difficulty in clinical management [4, 5].

Due to the widespread use of carbapenems, carbapenem-resistant CRPA has become one of the most challenging resistance phenotypes encountered in clinical practice [3]. Current evidence suggests that CRPA development is usually not attributable to a single mechanism, but results from the combined effects of multiple factors, including loss or downregulation of OprD porins, overexpression of efflux pumps, AmpC β-lactamase derepression, and production of carbapenemases or metallo-β-lactamases [6]. As a result, patients with CRPA infection often experience failure of empiric therapy, limited options for targeted treatment, and an increased risk of adverse clinical outcomes. Recent retrospective studies on *P. aeruginosa* bloodstream infections have shown that antimicrobial management strategies are closely associated with clinical outcomes, including 30-day mortality, and that treatment optimization is particularly important in patients infected with CRPA [7].

In recent years, substantial progress has been made in the treatment of resistant *P. aeruginosa infections*. Several reviews and meta-analyses have indicated that novel antimicrobial agents, including ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/relebactam, and cefiderocol, provide additional therapeutic options for resistant infections. However, their clinical application remains limited by factors such as drug accessibility, susceptibility matching, emergence of resistance, and variable efficacy across different infection sites [3, 4]. Systematic reviews have also highlighted substantial heterogeneity regarding the optimal monotherapy regimen, timing of empiric therapy, and comparative benefits among different novel β-lactam agents. Real-world cohort studies further indicate that *P. aeruginosa* bloodstream infections are associated with high risks of recurrence and mortality. Therefore, the use of novel antimicrobial agents alone may not fully address the complexity of CRPA infections in real-world clinical scenarios [8-10].

In this context, strategies aimed at improving host inflammatory responses, infection control, and clinical outcomes in addition to standard antimicrobial therapy are of considerable clinical interest. An integrated intervention model combining traditional Chinese medicine (TCM) and antibiotics has been widely applied in the management of infectious diseases in China. Among TCM preparations, Xuebijing injection (XBJ) is one of the most extensively studied intravenous formulations for severe infections, with potential effects on modulating inflammatory responses, immune function, and the internal physiological environment. However, high-quality clinical evidence regarding its application in patients with CRPA infection remains insufficient, especially studies that systematically integrating pathogen resistance profiles with real-world clinical outcomes. Therefore, this study aimed to characterize the antimicrobial resistance profile of CRPA isolates and compare the clinical efficacy of XBJ combined with antibiotics versus antibiotics alone, providing further evidence for optimizing the management of CRPA infections [10-12].

Materials and methods

Study design and sample size calculation

This single-center retrospective cohort study included patients with microbiologically confirmed carbapenem-resistant CRPA infection who were hospitalized between January 2019 and June 2024. The primary outcome was 28-day mortality, and clinical outcomes were compared between patients receiving TCM-plus-antibiotic therapy and those receiving antibiotic therapy alone.

Sample size was estimated using two approaches. First, the sample size was calculated based on the single proportion estimation formula: $N = Z^2 \times [P \times (1 - P)]/E^2$. With a two-sided α of 0.05, Z was set at 1.96. Based on previous studies reporting short-term mortality among patients with severe CRPA or drug-resistant *P. aeruginosa* infection, the 28-day mortality rate was estimated to be approximately 20-30% [11, 12]. In this study, P=0.25 and an allowable error of E=0.05 were used, yielding a minimum estimated sample size of approximately 288 cases. Considering about 10% potential of missing or invalid data, the recommended sample size was approximately 317 cases.

Second, because Cox proportional hazards regression analysis was also planned, the sam-

ple size for survival analysis was further estimated using the Schoenfeld formula. Assuming a two-sided α of 0.05 and a statistical power of 80%, and referring to the reported potential effect of XBJ on 28-day mortality in severe infection [13, 14], a hazard ratio (HR) of approximately 0.65 was assumed, requiring approximately 42 events. Based on an estimated event rate of 25%, the required total sample size was approximately 169 patients; after accounting for 10% potential attrition, approximately 186 cases would be required. Overall, the actual inclusion of 295 patients was considered adequate for the primary statistical analyses, including survival analysis and multivariable regression models.

Inclusion and exclusion criteria

Inclusion criteria: 1) Age ≥18 years; 2) Diagnosis of *P. aeruginosa* infection during hospitalization based on clinical manifestations, imaging findings, and microbiological evidence, with anti-microbial susceptibility testing indicating resistance to carbapenems (detailed pathogen identification and susceptibility testing methods are described in "Measurement Methods"); 3) Completion of anti-infective treatment with clear classification into the antibiotic-alone group or XBJ-plus-antibiotic group; and 4) Availability of relatively complete medical records, laboratory data, microbiological information, and follow-up outcomes.

Exclusion criteria: 1) Mixed infection with other major pathogens during the same infectious episode, making it difficult to determine *P. aeruginosa* as the primary pathogen; 2) Hospitalization duration <48 hours or self-discharge shortly after diagnosis; 3) Missing key variables, including the primary exposure, primary outcome, or core covariates; 4) Repeated hospitalizations, in which case only the first eligible infectious episode was retained; or 5) Pregnancy or lactation.

This study was approved by the Ethics Committee of the Second People's Hospital of Lanzhou City. Because this was a retrospective observational study that did not alter routine diagnostic or therapeutic procedures, the requirement for written informed consent was waived.

Criteria for infection diagnosis

To improve diagnostic accuracy and minimize misclassification of colonization as infection, strict criteria were applied for defining CRPA infection. Cases were included if they met one of the following criteria: Pulmonary infection: fever or abnormal white blood cell count (WBC), new or progressive pulmonary infiltrates on imaging, positive CRPA culture from respiratory specimens, and initiation of anti-infective therapy by the attending physician; Bloodstream infection: at least one positive blood culture for CRPA accompanied by clinical manifestation suggestive of infection; Urinary tract infection: positive urine culture for CRPA accompanied by urinary symptoms or laboratory evidence of inflammation; Intra-abdominal infection or drainage-related infection: positive CRPA culture from sterile body fluids or drainage specimens accompanied by clinical evidence of infection. Positive cultures without clinical evidence of infection were excluded and considered contamination.

Clinical data collection

Clinical data were extracted from the hospital electronic medical record system, laboratory information system, microbiology information system, and medical record database. All extracted data were independently reviewed and verified by two investigators to ensure accuracy and completeness. The collected information included: 1) Demographic details, including age and sex; 2) Hospitalization- and disease severity-related data, including ICU admission, duration of ICU stay, total length of hospital stay, mechanical ventilation, and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score; 3) Comorbidities and host-related factors, including diabetes, chronic kidney disease (CKD), malignancy, and immunosuppression; 4) Infection-related clinical features, including infection site, specimen source, carbapenem exposure within 30 days before infection, and receipt of targeted antimicrobial therapy; 5) Inflammatory biomarkers, including white blood cell count (WBC), C-reactive protein (CRP), procalcitonin (PCT); 6) Antimicrobial susceptibility profiles, such as resistance to imipenem, meropenem, piperacillin/tazobactam, ceftazidime, cefepime, aztreonam, ciprofloxacin, levofloxacin, amikacin, and polymyxin B;

and 7) Clinical outcomes and treatment process indicators, including clinical response, bacterial eradication, escalation of anti-infective regimen, and 28-day mortality.

Clinical response was defined as a significant improvement in infection-related symptoms, clinical signs, and inflammatory markers compared with baseline after anti-infective treatment, without the need for treatment escalation due to clinical deterioration. Bacterial eradication was defined as negative results on repeat microbiological cultures after treatment. Escalation of anti-infective therapy was defined as modification to a higher-level or broader-spectrum anti-infective regimen due to poor clinical response, infection progression, or antimicrobial susceptibility results indicating insufficient coverage by the initial regimen. Twenty-eight-day mortality was defined as all-cause mortality occurring within 28 days after the diagnosis of infection. For survival analysis, follow-up duration was recorded using survival status variables, and patients who remained alive beyond 28 days were censored at day 28.

Treatment

All patients received standard anti-infective treatment. Empiric anti-infective therapy was usually initiated as early as possible after infection diagnosis or when infection was strongly suspected. The selection of empirical regimens was determined by the attending physician according to infection site, previous antimicrobial exposure, underlying diseases, organ function status, and local antimicrobial resistance patterns. After pathogen identification and antimicrobial susceptibility results became available, treatment regimens were further optimized and adjusted to targeted antimicrobial treatment. The antibiotics used mainly included antipseudomonal β-lactams, β-lactam/β-lactamase inhibitor combinations, aminoglycosides, and polymyxins. Specific drug selection, route of administration, dosing frequency, treatment duration, and the use of combination antibiotic therapy were individualized according to disease severity, renal function, and antimicrobial susceptibility profiles.

The control group received antibiotics alone, whereas the combination group received XBJ in addition to antibiotic therapy. XBJ Injection (manufacturer: Tianjin Chase Sun Pharmaceutical Co., Ltd., Tianjin, China; drug approval number: Guo Yao Zhun Zi Z20040033; specification: 10 mL per vial) was administered at a dose of 100 mL via intravenous infusion every 12 h for 5-7 days, consistent with dosing regimens reported in previous clinical studies [13, 15]. Because this retrospective study spanned the period from January 2019 to June 2024, multiple batches of XBJ were used during the study period. The specific batch numbers for each administration were documented in individual patient medication records and are available upon reasonable request. If syndrome differentiation-based modified herbal decoctions or other TCM preparations were used in routine clinical practice, the composition, dosage, preparation method, route of administration, and treatment duration were supplemented according to the original medical orders.

Measurement methods

All laboratory tests were performed by the hospital laboratory department according to standardized operating procedures. WBC counts were measured using an automated hematology analyzer (Sysmex XN-9000, Sysmex, Japan). CRP levels were measured by chemiluminescent immunoassay using an automated biochemical analyzer (AU5800, Beckman Coulter, Japan). PCT levels were measured by chemiluminescent immunoassay using an automated chemiluminescence analyzer (Cobas e601, Roche Diagnostics, Germany).

Pathogen identification and antimicrobial susceptibility testing were performed by the hospital microbiology laboratory. Bacterial identification was performed using VITEK 2 GN identification cards (bioMérieux, Marcy-l'Étoile, France), and antimicrobial susceptibility testing was performed using VITEK 2 AST-N cards (bioMérieux) on the VITEK 2 Compact automated microbiology system. The results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) criteria applicable during the corresponding study year (CLSI M100, 2019-2024 editions). Carbapenem resistance was defined as resistance to imipenem and/or meropenem per CLSI breakpoints.

Outcome measures

The primary outcome of this study was 28-day all-cause mortality. This endpoint was chosen

because 28-day mortality is one of the most widely used and clinically relevant outcomes in severe infection research and can reasonably reflect short-term prognosis and infection control effectiveness.

Secondary outcomes included: 1) Clinical response; 2) Bacterial eradication rate; 3) Escalation rate of anti-infective regimen; 4) Length of hospital stay; and 5) Length of ICU stay. To ensure consistency in outcome assessment, clinical response and bacterial eradication were evaluated as binary variables according to predefined criteria, whereas hospital length of stay and length of ICU stay were analyzed as continuous variables.

In addition, descriptive analyses of resistance phenotypes against different antimicrobial agents were performed to characterize the antimicrobial resistance spectrum of CRPA isolates. These microbiological findings were used as background information to support the interpretation of clinical outcomes.

Statistical analysis

All statistical analyses were performed using R software (version 4.5.1) and SPSS software (version 27.0). Continuous variables were first tested for distribution. Normally distributed variables were presented as mean ± standard deviation (SD) and compared using the independent-samples *t* test. Non-normally distributed variables were presented as median (interquartile range, IQR) and compared using the Mann-Whitney *U* test. Categorical variables were presented as number (percentage) and compared using the chi-square test or Fisher's exact test, as appropriate.

Given the retrospective observational design and the potential for baseline differences between treatment groups, a propensity score (PS) model was developed. Receipt of XBJ combination therapy was used as the dependent variable, and age, APACHE II score, WBC, CRP, PCT, sex, ICU admission, infection site, mechanical ventilation, diabetes, chronic kidney disease, malignancy, immunosuppression, carbapenem exposure within 30 days before infection, and receipt of targeted antimicrobial therapy were included as covariates in a logistic regression model to estimate PS values. Stabilized inverse probability of treatment weighting (IPTW) was then calculated. To minimize the influence of extreme weights on model stability, stabilized weights were trimmed at the 1st and 99th percentiles. Standardized mean differences (SMDs) were used to assess covariate balance before and after weighting, with SMD <0.10 considered indicative of adequate balance.

Before regression analyses, candidate variables were assessed for pairwise correlations and variance inflation factor (VIF) to identify potential multicollinearity. Least absolute shrinkage and selection operator (LASSO) regression was then performed for variable selection, and the final variables included in the multivariable models were determined based on both statistical results and clinical relevance. Using 28-day mortality as the dependent variable, unweighted and IPTW-weighted univariable and multivariable logistic regression models were constructed. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate the association between TCM combination therapy and short-term mortality. In addition, unweighted and IPTW-weighted Cox proportional hazards regression models were performed to further evaluate the association between treatment strategy and time-to-event mortality outcomes. Hazard ratios (HRs) with 95% CIs were calculated.

The proportional hazards assumption was assessed using Schoenfeld residuals for variables showing significance in univariable analyses and for the final multivariable Cox models. If the proportional hazards assumption was violated, this was reported in the Results section and considered when interpreting Cox model results. To evaluate the robustness of the findings, multiple sensitivity analyses were performed, including stabilized IPTW without trimming, stabilized IPTW with 5-95% trimming, overlap weighting, and doubly robust estimation models. Prespecified subgroup analyses were conducted according to age, APACHE II score, bloodstream infection, mechanical ventilation status, and receipt of targeted antimicrobial therapy. Interaction terms were incorporated into the regression models to calculate *P* values for interaction and evaluate the consistency of treatment effects across subgroups. All statistical tests were two-sided, and P<0.05 was considered statistically significant.

Results

Antimicrobial resistance profile of CRPA isolates

The complete antimicrobial susceptibility profiles of the 295 CRPA isolates, overall and stratified by treatment group, are presented in Table S1. By study definition, all isolates were resistant to imipenem and/or meropenem, with resistance rates of 94.9% for imipenem and 92.9% for meropenem. The isolates exhibited high levels of co-resistance to multiple β-lactam and fluoroquinolone agents. Specifically, resistance rates exceeded 70% for piperacillin/tazobactam (84.1%), ciprofloxacin (78.6%), levofloxacin (76.3%), ceftazidime (73.9%), and cefepime (70.5%). The resistance rate for aztreonam was 66.1%.

Amikacin retained moderate in vitro activity, with a resistance rate of 33.9% and a susceptibility rate of 58.6%. Polymyxin B demonstrated the highest in vitro activity, with a susceptibility rate of 98.3%; resistance was detected in only 1.7% of isolates (5/295). Overall, 94.6% of isolates (279/295) met the criteria for multidrug-resistant (MDR) *P. aeruginosa*, defined as non-susceptibility to at least one antimicrobial agent in ≥3 antimicrobial classes. The resistance profiles were comparable between the control group and the combination group for all tested antimicrobial agents, with no statistically significant differences in resistance rates (all P>0.05).

Baseline characteristics before weighting

Before IPTW adjustment, baseline characteristics of the two groups were generally comparable, although several variables showed imbalance. Among continuous variables, CRP levels differed significantly between the combination group and the control group (P=0.017); however, no significant differences were observed in age (P=0.064), APACHE II score (P=0.683), WBC count (P=0.455), or procalcitonin (P=0.308) between the two groups.

Among categorical variables, the proportion of patients receiving mechanical ventilation differed significantly between the groups (*P*=0.046). No significant differences were observed in sex (*P*=0.717), ICU admission (*P*=0.070), infection site (*P*=0.854), diabetes (*P*=0.696), CKD (*P*=0.823), malignancy (*P*=0.636), immunosuppression (*P*=0.643), carbapenem exposure within 30 days before infection (*P*=0.560), or receipt of targeted antimicrobial therapy (*P*=0.077) (**Table 1**).

Baseline characteristics after weighting

After IPTW adjustment, baseline characteristics between the two groups achieved adequate balance. Among continuous variables, intergroup differences in age, APACHE II score, WBC count, CRP, and PCT levels were minimal, with all SMDs below 0.1. Among categorical variables, the distributions of sex, ICU admission, infection site, mechanical ventilation, diabetes, CKD, malignancy, immunosuppression, prior carbapenem exposure within 30 days, and targeted antimicrobial therapy were also well balanced, with all covariates showing SMDs below 0.1. These findings indicated that IPTW substantially improved baseline comparability between the two groups (**Table 2**; **Figure 2**).

Comparison of clinical outcomes between the two groups before and after IPTW weighting

Before IPTW weighting, the combination group demonstrated significantly higher clinical response and bacterial eradication rates compared with the control group (both *P*=0.004). In addition, the escalation rate of anti-infective regimen was significantly lower in the combination group than that in the control group (*P*=0.026), and 28-day mortality was also lower in the combination group (*P*=0.033). After IPTW adjustment, the combination group continued to show significant advantages in clinical response (*P*=0.035) and bacterial eradication (*P*=0.019). Furthermore, the risk of escalation of anti-infective regimen remained significantly lower in the combination group (*P*=0.026). However, the intergroup difference in 28-day mortality was no longer statistically significant after weighting (*P*=0.207) (**Table 3**).

Regarding length of hospital stay, patients in the combination group had a numerically shorter duration of hospitalization than those in the control group; however, the difference was not statistically significant either before weighting (22.21 ± 8.40 vs. 25.01 ± 11.30 days, P=0.086) or after IPTW adjustment (22.22 ± 8.04 vs. 25.02 ± 10.86 days; β=-2.796, 95%

Table 1. Baseline characteristics of patients in the control group and combination group before weighting

Variable	Overall	Control group	Combination group	Statistic	*P* value
Age (years)	61.79 ± 13.66	63.33 ± 13.78	60.38 ± 13.45	1.862	0.064
APACHE II score	16.52 ± 6.36	16.68 ± 6.57	16.38 ± 6.18	0.409	0.683
White blood cell count (×10^9/L)	14.09 ± 4.38	13.89 ± 4.04	14.27 ± 4.67	-0.749	0.455
CRP (mg/L)	114.90 ± 50.77	122.31 ± 53.35	108.11 ± 47.46	2.407	0.017
PCT (ng/mL)	3.77 ± 2.44	3.92 ± 2.50	3.63 ± 2.38	1.021	0.308
Sex				0.131	0.717
Male	181 (61.36%)	85 (60.28%)	96 (62.34%)		
Female	114 (38.64%)	56 (39.72%)	58 (37.66%)		
ICU admission				3.292	0.07
Yes	149 (50.51%)	79 (56.03%)	70 (45.45%)		
No	146 (49.49%)	62 (43.97%)	84 (54.55%)		
Infection site				1.341	0.854
Pulmonary infection	158 (53.56%)	80 (56.74%)	78 (50.65%)		
Bloodstream infection	51 (17.29%)	23 (16.31%)	28 (18.18%)		
Urinary tract infection	34 (11.53%)	15 (10.64%)	19 (12.34%)		
Intra-abdominal/drainage-related infection	32 (10.85%)	15 (10.64%)	17 (11.04%)		
Other-site infection	20 (6.78%)	8 (5.67%)	12 (7.79%)		
Mechanical ventilation				3.998	0.046
Yes	139 (47.12%)	75 (53.19%)	64 (41.56%)		
No	156 (52.88%)	66 (46.81%)	90 (58.44%)		
Diabetes				0.153	0.696
Yes	89 (30.17%)	41 (29.08%)	48 (31.17%)		
No	206 (69.83%)	100 (70.92%)	106 (68.83%)		
Chronic kidney disease				0.05	0.823
Yes	57 (19.32%)	28 (19.86%)	29 (18.83%)		
No	238 (80.68%)	113 (80.14%)	125 (81.17%)		
Malignancy				0.224	0.636
Yes	41 (13.90%)	21 (14.89%)	20 (12.99%)		
No	254 (86.10%)	120 (85.11%)	134 (87.01%)		
Immunosuppression				0.214	0.643
Yes	37 (12.54%)	19 (13.48%)	18 (11.69%)		
No	258 (87.46%)	122 (86.52%)	136 (88.31%)		
Prior carbapenem exposure within 30 days				0.34	0.56
Yes	179 (60.68%)	88 (62.41%)	91 (59.09%)		
No	116 (39.32%)	53 (37.59%)	63 (40.91%)		
Targeted antimicrobial therapy				3.129	0.077
Yes	201 (68.14%)	89 (63.12%)	112 (72.73%)		
No	94 (31.86%)	52 (36.88%)	42 (27.27%)		

Notes: APACHE II, Acute Physiology and Chronic Health Evaluation II; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; ICU, intensive care unit.

CI: -5.868 to 0.277, P=0.077). Similarly, ICU length of stay was numerically shorter in the combination group before weighting (10.84 ± 5.82 vs. 12.39 ± 5.49 days, P=0.098) and after weighting (10.85 ± 5.83 vs. 12.34 ± 5.25 days; β=-1.486, 95% CI: -3.285 to 0.312, P=0.107), though the differences remained statistically nonsignificant (**Table 3**).

Table 2. Baseline characteristics of patients in the control group and combination group after IPTW weighting

Variable	Weighted overall	Weighted control group	Weighted combination group	SMD
Age (years)	61.58 ± 13.60	61.54 ± 14.12	61.62 ± 13.11	0.006
APACHE II score	16.52 ± 6.38	16.57 ± 6.54	16.48 ± 6.22	0.015
White blood cell count ($\times 10^9$/L)	14.06 ± 4.38	14.07 ± 4.11	14.05 ± 4.62	0.004
CRP (mg/L)	115.72 ± 49.92	116.29 ± 50.91	115.20 ± 48.99	0.022
PCT (ng/mL)	3.76 ± 2.43	3.75 ± 2.48	3.77 ± 2.39	0.011
Sex				0.029
Male	178.86 (60.85%)	86.08 (61.38%)	92.78 (60.37%)	0.021
Female	115.05 (39.15%)	54.15 (38.62%)	60.90 (39.63%)	0.021
ICU admission				
Yes	149.87 (50.99%)	71.69 (51.13%)	78.18 (50.87%)	0.005
No	144.04 (49.01%)	68.54 (48.87%)	75.50 (49.13%)	0.005
Infection site				
Pulmonary infection	159.26 (54.19%)	76.48 (54.53%)	82.78 (53.87%)	0.013
Bloodstream infection	49.91 (16.98%)	23.20 (16.54%)	26.72 (17.39%)	0.023
Urinary tract infection	33.75 (11.48%)	16.25 (11.59%)	17.50 (11.38%)	0.006
Intra-abdominal/drainage-related infection	31.12 (10.59%)	14.95 (10.66%)	16.17 (10.52%)	0.005
Other-site infection	19.87 (6.76%)	9.36 (6.67%)	10.51 (6.84%)	0.007
Mechanical ventilation				
Yes	136.76 (46.53%)	65.79 (46.91%)	70.97 (46.18%)	0.015
No	157.15 (53.47%)	74.45 (53.09%)	82.71 (53.82%)	0.015
Diabetes				
Yes	85.65 (29.14%)	40.51 (28.89%)	45.15 (29.38%)	0.011
No	208.26 (70.86%)	99.72 (71.11%)	108.53 (70.62%)	0.011
Chronic kidney disease				
Yes	55.79 (18.98%)	26.20 (18.69%)	29.59 (19.25%)	0.014
No	238.12 (81.02%)	114.03 (81.31%)	124.09 (80.75%)	0.014
Malignancy				
Yes	41.97 (14.28%)	19.45 (13.87%)	22.52 (14.65%)	0.022
No	251.94 (85.72%)	120.78 (86.13%)	131.16 (85.35%)	0.022
Immunosuppression				
Yes	38.34 (13.04%)	17.94 (12.79%)	20.40 (13.27%)	0.014
No	255.57 (86.96%)	122.29 (87.21%)	133.28 (86.73%)	0.014
Prior carbapenem exposure within 30 days				
Yes	174.78 (59.47%)	83.31 (59.41%)	91.47 (59.52%)	0.002
No	119.13 (40.53%)	56.92 (40.59%)	62.21 (40.48%)	0.002
Targeted antimicrobial therapy				
Yes	200.98 (68.38%)	96.27 (68.65%)	104.71 (68.14%)	0.011
No	92.93 (31.62%)	43.96 (31.35%)	48.97 (31.86%)	0.011

Notes: IPTW, inverse probability of treatment weighting; SMD, standardized mean difference; APACHE II, Acute Physiology and Chronic Health Evaluation II; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; ICU, intensive care unit.

Definitions and coding of variables included in the analysis

To ensure the standardization and reproducibility of the statistical analyses, all variables included in this study, including treatment grouping variables, baseline characteristics, infection-related indicators, antimicrobial susceptibility results, clinical outcome variables, survival analysis variables, propensity score

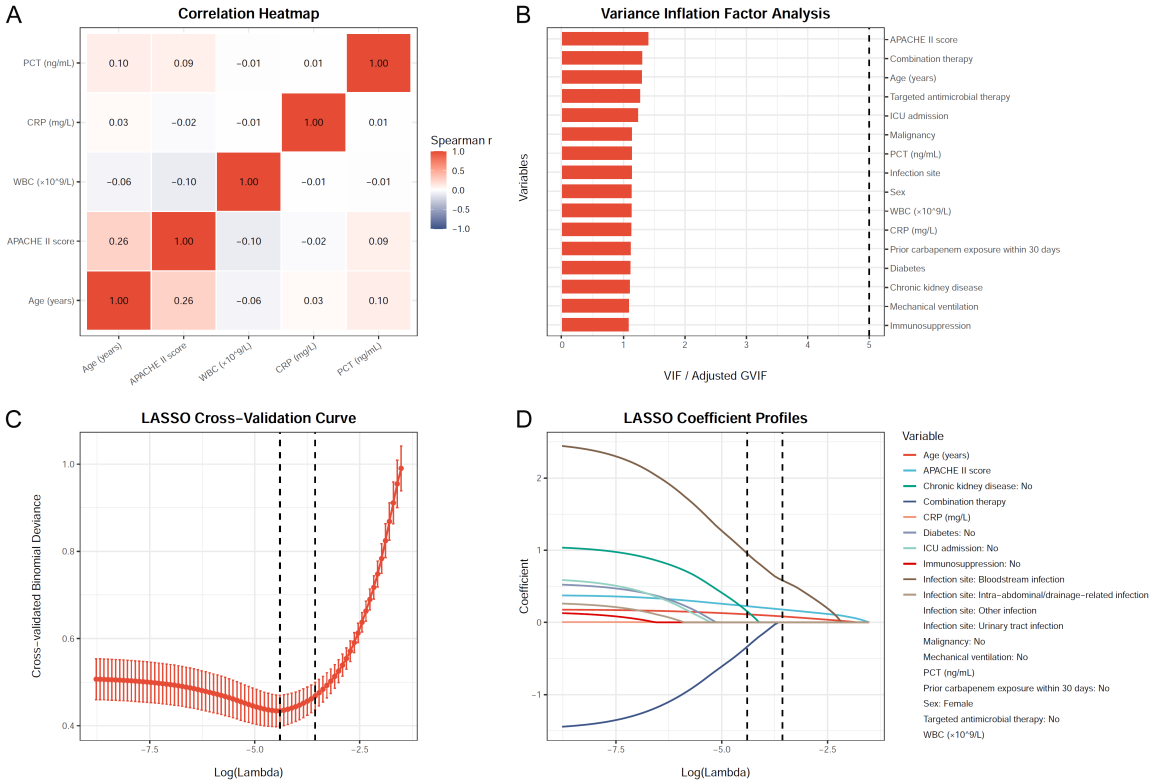


Figure 1. Variable screening before multivariable regression analysis. A. Spearman correlation heatmap of continuous candidate variables. B. Variance inflation factor analysis of candidate variables. C. LASSO cross-validation curve for variable selection. D. LASSO coefficient profiles of candidate variables. Notes: LASSO, least absolute shrinkage and selection operator; VIF, variance inflation factor; GVIF, generalized variance inflation factor; APACHE II, Acute Physiology and Chronic Health Evaluation II; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; ICU, intensive care unit.

weighting variables, and subgroup analysis variables, were predefined and uniformly coded. Continuous variables were entered as original numeric values, whereas categorical variables were incorporated according to predefined coding schemes. The primary outcome variable, weighting-related variables, and subgroup analysis variables were standardized to support subsequent IPTW analyses, logistic regression models, Cox regression models, sensitivity analyses, and subgroup analyses (**Table 4**).

Variable screening before multivariable regression analysis

Before inclusion in the multivariable models, candidate variables were evaluated using correlation analysis, multicollinearity assessment, and LASSO regression-based variable selection. Spearman correlation analysis showed generally weak correlations among continuous variables, and no highly correlated variable pairs were identified (all $|r|<0.7$), indicating the absence of evident correlation clustering among candidate variables (**Figure 1A**). VIF analysis further showed that all variables had VIF or adjusted generalized VIF (GVIF) values below the predefined threshold, indicating no evident multicollinearity and supporting the inclusion of these variables in subsequent selection procedures (**Figure 1B**). LASSO logistic regression was subsequently performed for dimensionality reduction and variable selection. Under the lambda.min criterion, 11 variables were selected, whereas 6 variables were selected under the lambda.1se criterion. Because treatment group represented the primary exposure variable of interest in this study but was not retained in the lambda.1se model, variables selected under the lambda.min criterion were included in subsequent multivariable regression analyses (**Figure 1C**, **1D**).

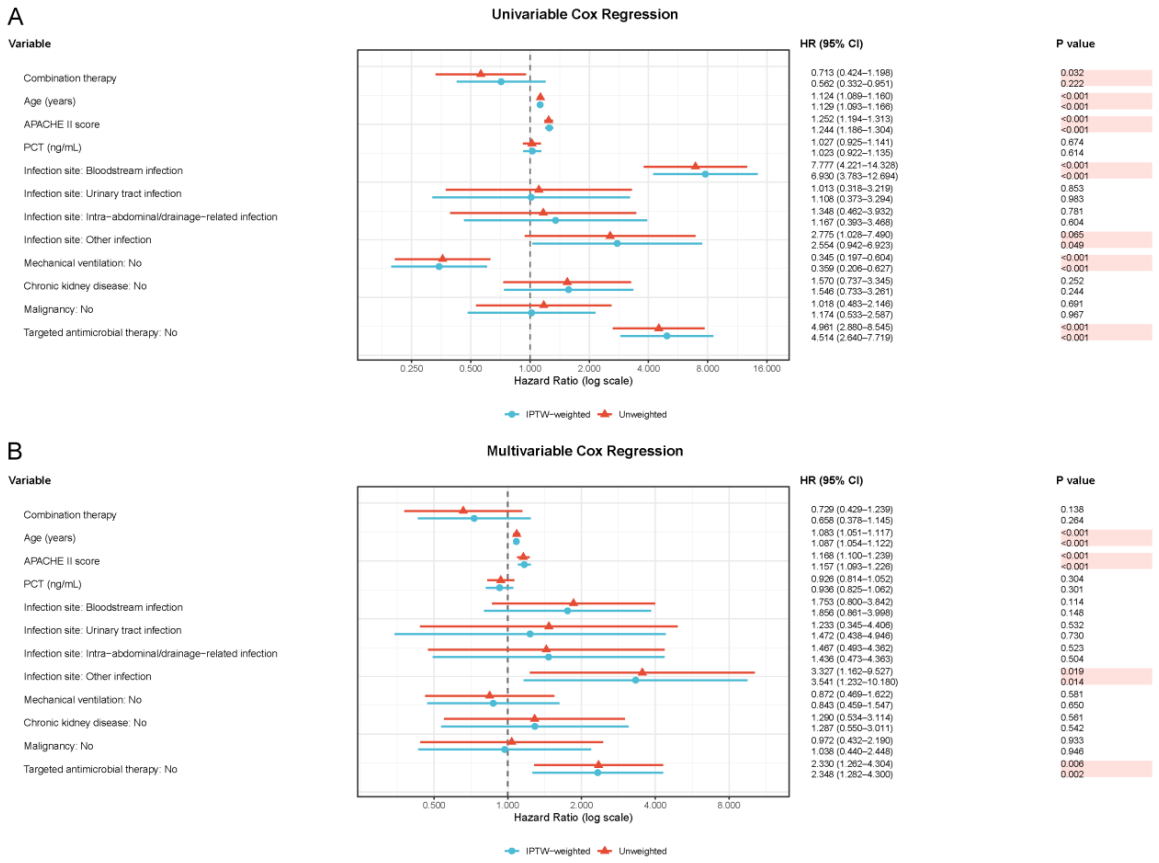


Figure 2. Univariable and multivariable Cox regression analyses of factors associated with 28-day mortality before and after IPTW weighting. A. Univariable Cox regression analyses before and after IPTW weighting. B. Multivariable Cox regression analyses before and after IPTW weighting. Notes: HR, hazard ratio; CI, confidence interval; IPTW, inverse probability of treatment weighting; APACHE II, Acute Physiology and Chronic Health Evaluation II; PCT, procalcitonin.

Logistic regression analysis of factors associated with 28-day mortality before weighting

In the unweighted univariable logistic regression analysis, XBJ combination therapy (P=0.034), age (P<0.001), APACHE II score (P<0.001), bloodstream infection (P<0.001), mechanical ventilation (P<0.001), and absence of targeted antimicrobial therapy (P<0.001) were all significantly associated with 28-day mortality. After further adjustment in the multivariable logistic regression model, XBJ combination therapy remained an independent protective factor for 28-day mortality (P=0.043). Meanwhile, age (P<0.001), APACHE II score (P<0.001), bloodstream infection (P=0.008), and absence of targeted antimicrobial therapy (P<0.001) remained independently associated with mortality.

In contrast, PCT (univariable P=0.702; multivariable P=0.237), urinary tract infection (univariable P=0.865; multivariable P=0.633), intra-abdominal/drainage-related infection (univariable P=0.775; multivariable P=0.903), other infection (univariable P=0.078; multivariable P=0.079), mechanical ventilation (multivariable P=0.278), CKD (univariable P=0.238; multivariable P=0.182), and malignancy (univariable P=0.654; multivariable P=0.222) were not significantly associated with 28-day mortality in the multivariable model (**Table 5**).

Logistic regression analysis of factors associated with 28-day mortality after IPTW weighting

In the IPTW-weighted univariable Logistic regression analysis, age (P<0.001), APACHE II score (P<0.001), bloodstream infection (P<0.001), mechanical ventilation (P<0.001), and absence of targeted antimicrobial therapy (P<0.001) were significantly associated with 28-day mortality, whereas combination therapy did not show statistical significance in the

Table 3. Comparison of clinical outcomes between the control group and combination group before and after IPTW weighting

Outcome	Control group before weighting	Combination group before weighting	Statistic before weighting	*P* value before weighting	Control group after IPTW	Combination group after IPTW	IPTW OR	IPTW 95% CI	IPTW *P* value
Clinical response (effective)	83 (58.87%)	115 (74.68%)	8.337	0.004	87.12 (62.13%)	113.20 (73.66%)	1.705	1.039-2.798	0.035
Bacterial eradication	72 (51.06%)	104 (67.53%)	8.295	0.004	74.50 (53.12%)	102.32 (66.58%)	1.758	1.097-2.817	0.019
Escalation of anti-infective regimen	40 (28.37%)	27 (17.53%)	4.924	0.026	39.18 (27.94%)	26.14 (17.01%)	0.529	0.302-0.925	0.026
28-day mortality	35 (24.82%)	23 (14.94%)	4.556	0.033	31.86 (22.72%)	25.89 (16.85%)	0.689	0.387-1.229	0.207
Length of hospital stay (d)	25.01 ± 11.30	22.21 ± 8.40	1.728	0.086	25.02 ± 10.86	22.22 ± 8.04	-2.796†	-5.868-0.277	0.077
ICU length of stay (d)	12.39 ± 5.49	10.84 ± 5.82	1.667	0.098	12.34 ± 5.25	10.85 ± 5.83	-1.486†	-3.285-0.312	0.107

Notes: IPTW, inverse probability of treatment weighting; OR, odds ratio; CI, confidence interval. †For length of hospital stay and ICU length of stay, IPTW effect is expressed as β coefficient (mean difference) from weighted linear regression, not OR.

Table 4. Definitions and coding of variables included in the analysis

Variable	Coding/Definition
Treatment group	type: C = control group (antibiotic therapy alone), P = combination group (XBJ combined with antibiotic therapy); for modeling, group_num: C = 0, P = 1
Age (years)	Continuous variable, entered as the actual value
Sex	Male = 1, Female = 2; converted to Male/Female in analysis
APACHE II score	Continuous variable, entered as the actual value
WBC ($\times 10^9$/L)	Continuous variable, entered as the actual value
CRP (mg/L)	Continuous variable, entered as the actual value
PCT (ng/mL)	Continuous variable, entered as the actual value
Length of hospital stay	Continuous variable, entered as the actual value
ICU length of stay	Continuous variable, entered as the actual value
ICU admission	Yes = 1, No = 2; converted to Yes/No in analysis
Mechanical ventilation	Yes = 1, No = 2; converted to Yes/No in analysis
Diabetes	Yes = 1, No = 2; converted to Yes/No in analysis
Chronic kidney disease	Yes = 1, No = 2; converted to Yes/No in analysis
Malignancy	Yes = 1, No = 2; converted to Yes/No in analysis
Immunosuppression	Yes = 1, No = 2; converted to Yes/No in analysis
Prior carbapenem exposure within 30 days	Yes = 1, No = 2; converted to Yes/No in analysis
Targeted antimicrobial therapy	Yes = 1, No = 2; converted to Yes/No in analysis
Infection site	Pulmonary infection = 1, bloodstream infection = 2, urinary tract infection = 3, intra-abdominal/drainage-related infection = 4, other-site infection = 5
Isolate source	Respiratory specimen (sputum/BALF) = 1, blood = 2, urine = 3, wound/drainage fluid = 4, ascitic fluid/bile = 5

Imipenem resistance	Resistant = 1, non-resistant = 2
Meropenem resistance	Resistant = 1, non-resistant = 2
Piperacillin/tazobactam resistance	Resistant = 1, non-resistant = 2
Ceftazidime resistance	Resistant = 1, non-resistant = 2
Cefepime resistance	Resistant = 1, non-resistant = 2
Aztreonam resistance	Resistant = 1, non-resistant = 2
Ciprofloxacin resistance	Resistant = 1, non-resistant = 2
Levofloxacin resistance	Resistant = 1, non-resistant = 2
Amikacin resistance	Resistant = 1, non-resistant = 2
Polymyxin B resistance	Resistant = 1, non-resistant = 2
Clinical response	Effective = 1, ineffective = 2
Bacterial eradication	Yes = 1, No = 2
Escalation of anti-infective regimen	Yes = 1, No = 2
28-day outcome	Death = 1, survival = 2
28-day mortality event	death28: death = 1, survival = 0
Survival time	Follow-up time recorded using the “survival status” variable; values beyond 28 days were truncated at 28 days
Propensity score	ps: probability of receiving combination therapy estimated by Logistic regression
Stabilized weight	sw: combination group = P(T = 1)/PS, control group = P(T = 0)/(1-PS)
Trimmed stabilized weight	sw_trim_1_99: stabilized weight trimmed at the 1st and 99th percentiles
Age subgroup	<65 vs ≥65
APACHE II subgroup	<20 vs ≥20
Bloodstream infection subgroup	Yes = infection site was bloodstream infection; No = non-bloodstream infection
Mechanical ventilation subgroup	Yes/No
Targeted antimicrobial therapy subgroup	Yes/No

Notes: APACHE II, Acute Physiology and Chronic Health Evaluation II; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; ICU, intensive care unit; BALF, bronchoalveolar lavage fluid; PS, propensity score; IPTW, inverse probability of treatment weighting.

Table 5. Univariable and multivariable logistic regression analyses of factors associated with 28-day mortality before weighting

Variable	Univariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
Combination therapy	0.532 (0.296-0.955)	0.034	0.279 (0.081-0.960)	0.043
Age (years)	1.156 (1.109-1.205)	<0.001	1.183 (1.106-1.265)	<0.001
APACHE II score	1.354 (1.251-1.465)	<0.001	1.406 (1.233-1.605)	<0.001
PCT (ng/mL)	1.023 (0.910-1.150)	0.702	0.877 (0.705-1.090)	0.237
Infection site: Bloodstream infection	10.097 (4.786-21.303)	<0.001	8.634 (1.768-42.174)	0.008
Infection site: Urinary tract infection	1.106 (0.347-3.522)	0.865	1.575 (0.244-10.159)	0.633
Infection site: Intra-abdominal/drainage-related infection	1.185 (0.371-3.788)	0.775	1.107 (0.217-5.632)	0.903
Infection site: Other infection	2.765 (0.893-8.561)	0.078	4.746 (0.835-26.959)	0.079
Mechanical ventilation: No	0.323 (0.175-0.596)	<0.001	0.551 (0.188-1.617)	0.278
Chronic kidney disease: No	1.629 (0.725-3.661)	0.238	2.707 (0.628-11.672)	0.182
Malignancy: No	1.220 (0.511-2.911)	0.654	2.773 (0.540-14.255)	0.222
Targeted antimicrobial therapy: No	5.564 (3.015-10.268)	<0.001	8.209 (2.572-26.201)	<0.001

Notes: OR, odds ratio; CI, confidence interval; APACHE II, Acute Physiology and Chronic Health Evaluation II; PCT, procalcitonin.

Table 6. Univariable and multivariable logistic regression analyses of factors associated with 28-day mortality after IPTW weighting

Variable	Univariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
Combination therapy	0.689 (0.387-1.229)	0.207	0.250 (0.071-0.873)	0.03
Age (years)	1.151 (1.105-1.198)	<0.001	1.196 (1.112-1.286)	<0.001
APACHE II score	1.380 (1.270-1.500)	<0.001	1.453 (1.254-1.684)	<0.001
PCT (ng/mL)	1.031 (0.916-1.159)	0.615	0.842 (0.670-1.059)	0.141
Infection site: Bloodstream infection	11.734 (5.492-25.075)	<0.001	11.595 (2.130-63.113)	0.005
Infection site: Urinary tract infection	1.007 (0.297-3.416)	0.991	1.292 (0.168-9.939)	0.805
Infection site: Intra-abdominal/drainage-related infection	1.371 (0.435-4.318)	0.59	1.015 (0.198-5.193)	0.986
Infection site: Other infection	3.036 (0.983-9.383)	0.054	4.587 (0.765-27.513)	0.096
Mechanical ventilation: No	0.306 (0.165-0.567)	<0.001	0.545 (0.180-1.646)	0.282
Chronic kidney disease: No	1.646 (0.725-3.739)	0.233	2.834 (0.607-13.242)	0.185
Malignancy: No	1.042 (0.454-2.389)	0.923	2.793 (0.517-15.079)	0.232
Targeted antimicrobial therapy: No	6.258 (3.363-11.643)	<0.001	10.241 (2.945-35.610)	<0.001

Notes: OR, odds ratio; CI, confidence interval; APACHE II, Acute Physiology and Chronic Health Evaluation II; PCT, procalcitonin; IPTW, inverse probability of treatment weighting.

univariable analysis (*P*=0.207). After further adjustment in the multivariable Logistic regression model, combination therapy became an independent protective factor for 28-day mortality (*P*=0.030). At the same time, age (*P*< 0.001), APACHE II score (*P*<0.001), bloodstream infection (*P*=0.005), and absence of targeted antimicrobial therapy (*P*<0.001) remained independently associated with mortality.

PCT (univariable *P*=0.615; multivariable *P*= 0.141), urinary tract infection (univariable *P*= 0.991; multivariable *P*=0.805), intra-abdominal/drainage-related infection (univariable *P*= 0.590; multivariable *P*=0.986), other infection (univariable *P*=0.054; multivariable *P*=0.096), mechanical ventilation (multivariable *P*=0.282), CKD (univariable *P*=0.233; multivariable *P*= 0.185), and malignancy (univariable *P*=0.923; multivariable *P*=0.232) were not significantly associated with 28-day mortality in the multivariable model (**Table 6**).

Cox regression analyses of factors associated with 28-day mortality before and after IPTW weighting

In the unweighted univariable Cox regression analysis, XBJ combination therapy (*P*=0.032),

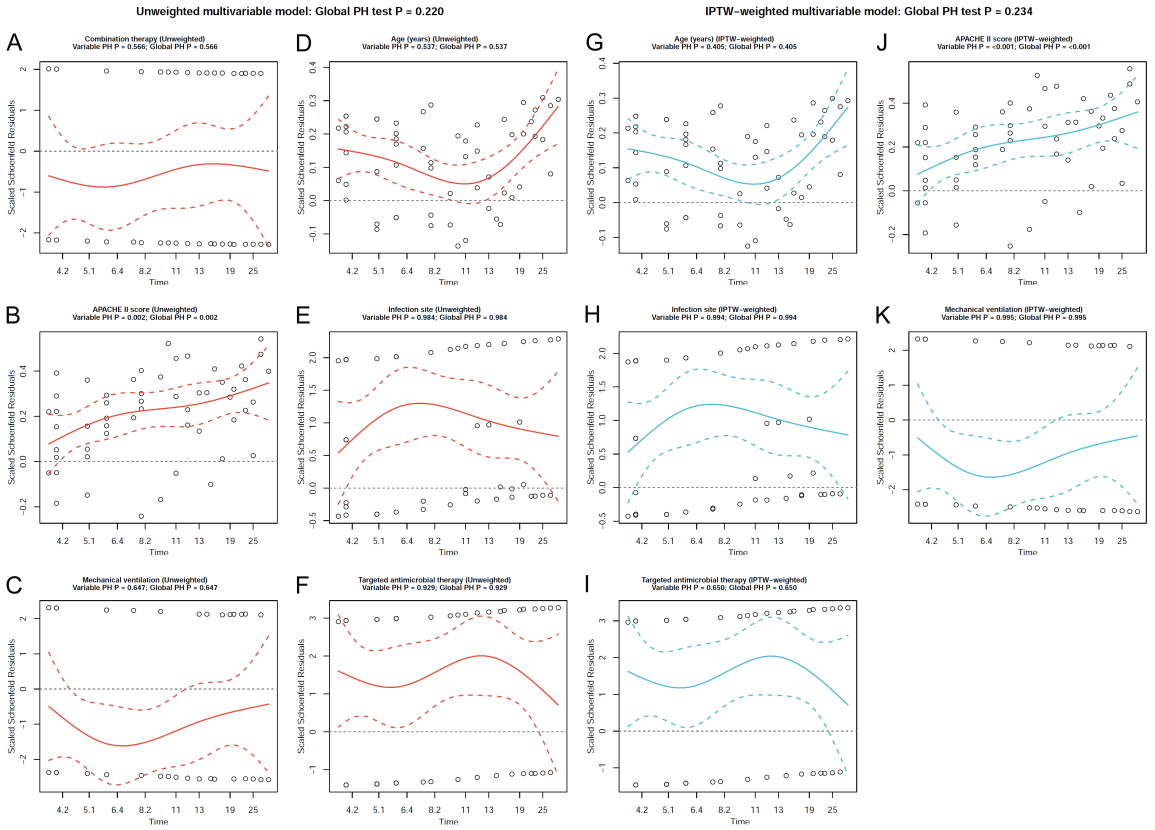


Figure 3. Assessment of proportional hazards assumption for significant variables in Cox regression analyses. A-F. Schoenfeld residual plots of significant variables from the unweighted univariable Cox regression analyses. G-K. Schoenfeld residual plots of significant variables from the IPTW-weighted univariable Cox regression analyses. The global proportional hazards test results of the multivariable Cox models are presented above each panel group. Notes: PH, proportional hazards; IPTW, inverse probability of treatment weighting; APACHE II, Acute Physiology and Chronic Health Evaluation II.

age (P<0.001), APACHE II score (P<0.001), bloodstream infection (P<0.001), mechanical ventilation (P<0.001), and absence of targeted antimicrobial therapy (P<0.001) were all significantly associated with 28-day mortality.

After IPTW weighting, age (P<0.001), APACHE II score (P<0.001), bloodstream infection (P< 0.001), other infection (P=0.049), mechanical ventilation (P<0.001), and absence of targeted antimicrobial therapy (P<0.001) remained significantly associated with 28-day mortality, whereas XBJ combination therapy was not significant in the weighted univariable Cox analysis (P=0.222).

In the multivariable Cox regression analysis, the unweighted model demonstrated that age (P<0.001), APACHE II score (P<0.001), other infection (P=0.019), and absence of targeted antimicrobial therapy (P=0.006) were independently associated with 28-day mortality. After IPTW weighting, these associations remained consistent, with age (P<0.001), APACHE II score (P<0.001), other infection (P=0.014), and absence of targeted antimicrobial therapy (P=0.002) remaining as independent factors associated with 28-day mortality.

However, XBJ combination therapy, PCT, bloodstream infection, urinary tract infection, intra-abdominal/drainage-related infection, mechanical ventilation, CKD, and malignancy were not significantly associated with mortality in either the unweighted or IPTW-weighted multivariable Cox models (all P>0.05) (**Figure 2**).

Assessment of the proportional hazards assumption of the cox regression models

To evaluate the validity of the Cox proportional hazards models, Schoenfeld residual tests and

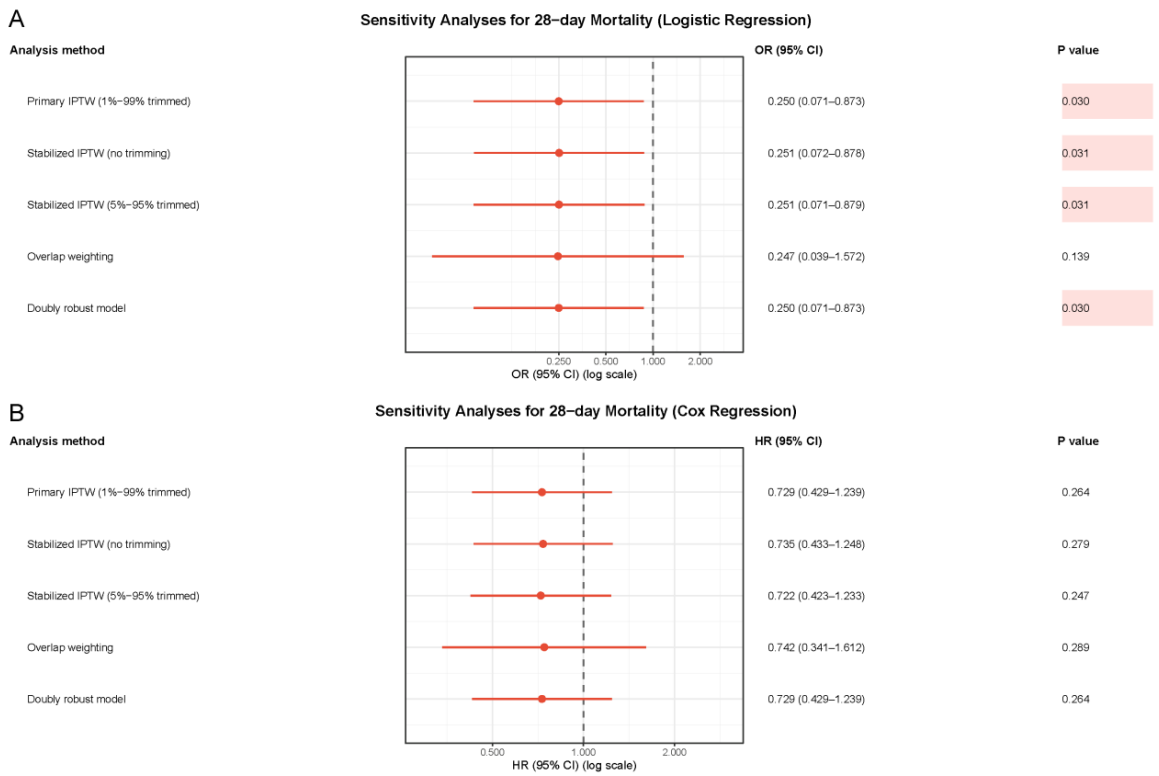


Figure 4. Sensitivity analyses for 28-day mortality under different weighting strategies. A. Sensitivity analyses of 28-day mortality using logistic regression under different weighting strategies. B. Sensitivity analyses of 28-day mortality using Cox regression under different weighting strategies. Notes: OR, odds ratio; HR, hazard ratio; CI, confidence interval; IPTW, inverse probability of treatment weighting.

graphical assessments were performed for significant covariates. The results showed that, in both the unweighted and IPTW-weighted models, the global test for the proportional hazards assumption in the multivariable Cox regression model was not statistically significant, indicating that the models overall satisfied the proportional hazards assumption.

At the individual covariate level, the APACHE II score violated the proportional hazards assumption in both the unweighted and IPTW-weighted models (both $P<0.001$), whereas no significant violations were observed for the remaining covariates. Visual inspection of Schoenfeld residual plots also showed that, except for APACHE II score, the smoothed curves of other variables remained relatively stable over time, further supporting the applicability of the proportional hazards assumption for most covariates (**Figure 3**).

Sensitivity analyses for 28-day mortality

To assess the robustness of the primary findings, sensitivity analyses were further conducted using alternative weighting approaches. For logistic regression analyses of 28-day mortality, XBJ combination therapy consistently showed a protective association across the primary IPTW model, stabilized IPTW without trimming, stabilized IPTW with 5-95% trimming, and doubly robust models, with consistent effect directions (all $P=0.030$ or 0.031). In the overlap weighting analysis, the direction of association remained consistent, although the difference did not reach statistical significance ($P=0.139$).

In contrast, Cox regression-based sensitivity analyses showed that, regardless of the weighting method used, no significant association was observed between combination therapy and the time-risk of 28-day mortality, and the directions of the effect estimates were generally consistent across models (all $P>0.05$). Overall, the logistic regression findings were relatively stable across different weighting strategies, whereas the Cox regression analyses consistently demonstrated a nonsignificant trend, indicating the overall robustness of the study conclusions (**Figure 4**).

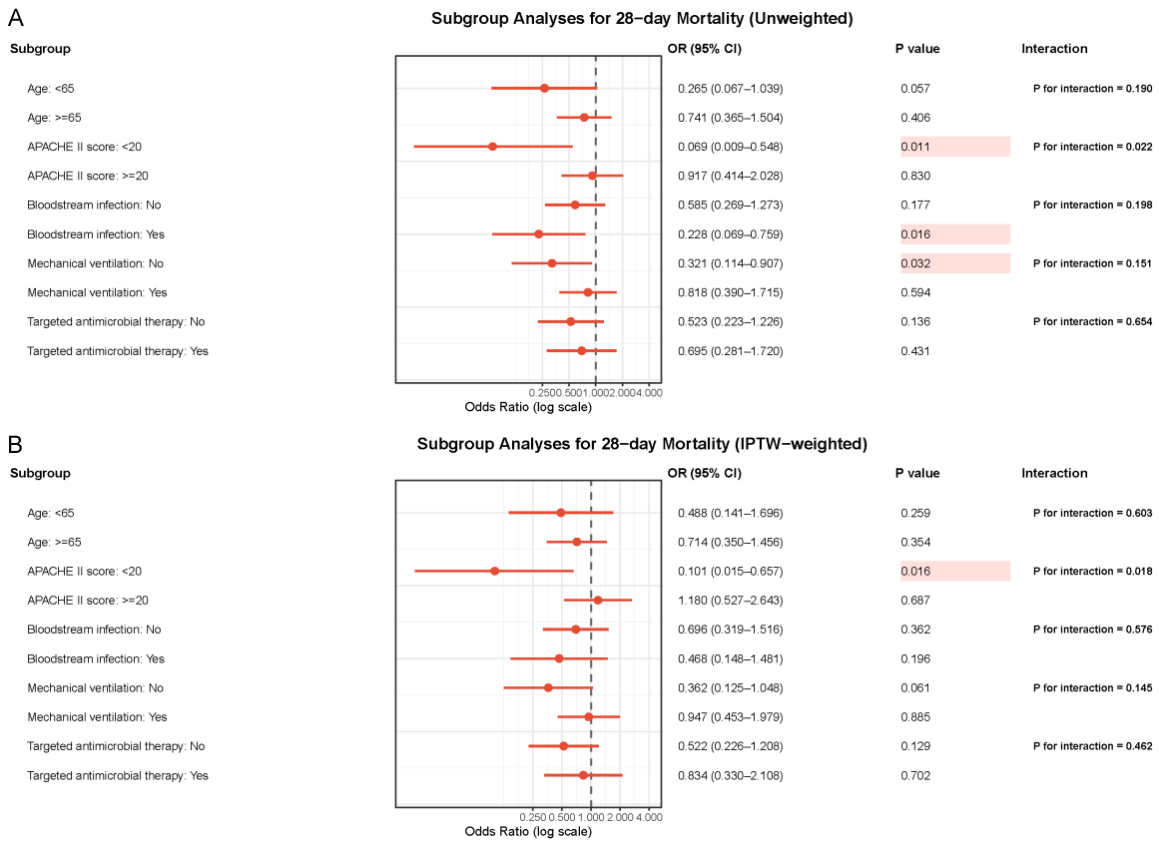


Figure 5. Subgroup analyses for 28-day mortality in unweighted and IPTW-weighted cohorts. A. Subgroup analyses for 28-day mortality in the unweighted cohort. B. Subgroup analyses for 28-day mortality in the IPTW-weighted cohort. Notes: OR, odds ratio; CI, confidence interval; IPTW, inverse probability of treatment weighting; APACHE II, Acute Physiology and Chronic Health Evaluation II.

Subgroup analyses for 28-day mortality

Prespecified subgroup analyses were further performed to evaluate the association between TCM-plus-antibiotic therapy and 28-day mortality across clinically relevant subgroups. In the unweighted analysis, combination therapy was significantly associated with reduced 28-day mortality among patients with APACHE II score <20 (P=0.011), bloodstream infection (P=0.016), and without mechanical ventilation (P=0.032). However, no significant associations were observed across subgroups stratified by age, targeted antimicrobial therapy, or other evaluated factors (all P>0.05). Interaction analyses demonstrated that only APACHE II score showed a statistically significant interaction with treatment effect (P for interaction=0.022), suggesting that baseline disease severity may modify the association between combination therapy and mortality.

After IPTW adjustment, XBJ combination therapy remained significantly associated with lower 28-day mortality only in patients with APACHE II score <20 (P=0.016), whereas no significant differences were observed in the remaining subgroups (all P>0.05). Consistently, the weighted interaction analysis identified a significant interaction only for APACHE II score (P for interaction=0.018), whereas the interaction effects for age, bloodstream infection, mechanical ventilation, and targeted antimicrobial therapy were not statistically significant (all P>0.05). Overall, the benefit of XBJ combination therapy appeared to be more pronounced among patients with lower disease severity, whereas no significant heterogeneity of treatment effect was observed across other subgroups (**Figure 5**).

Discussion

This study systematically evaluated the clinical efficacy of XBJ combined with antibiotics in patients with CRPA infections and interpreted the findings in the context of antimicrobial

resistance characteristics. The results showed that, compared with antibiotic therapy alone, combination therapy demonstrated consistent advantages across several infection-control-related outcomes, including higher clinical response and bacterial eradication rates, as well as a lower rate of escalation of anti-infective regimen. However, for the 28-day all-cause mortality, the effect of combination therapy was not entirely consistent across various statistical models, suggesting that its impact on short-term survival remains uncertain. Previous studies have shown that the clinical benefits of XBJ in patients with sepsis are not always consistently reflected in all mortality endpoints but are more often observed in inflammation control, organ protection, and overall disease improvement [14, 15]. The present findings do not necessarily indicate a contradiction; rather, they suggest that the benefits of XBJ combination therapy may be more evident in infection control and clinical improvement, whereas its effect on mortality may be relatively limited and sensitive to model specification.

In the present study, CRPA isolates exhibited a pronounced MDR phenotype. Resistance rates exceeded 70% for most β-lactam and fluoroquinolone agents, including piperacillin/tazobactam, ceftazidime, cefepime, ciprofloxacin, and levofloxacin, whereas only amikacin (susceptibility rate: 58.6%) and polymyxin B (susceptibility rate: 98.3%) retained substantial in vitro activity (Table S1). This resistance profile is consistent with the current understanding that CRPA resistance arises from the accumulation of multiple mechanisms, including outer membrane permeability alterations, efflux pump overexpression, AmpC β-lactamase derepression, and production of carbapenemases or metallo-β-lactamases. Reyes et al. [11] reported in the global POP cohort that CRPA isolates showed high co-resistance rates to antipseudomonal β-lactams and fluoroquinolones, with substantial geographic variation but consistently high MDR prevalence. Falcone et al. [16] emphasized that CRPA isolates are heterogeneous in terms of resistance mechanisms and susceptibility profiles, highlighting the importance of individualized antimicrobial selection based on specific resistance characteristics. In a nationwide genomic surveillance study of CRPA in Japan, Yano et al. [17] reported that most CRPA isolates did not harbor carbapenemase genes but were instead associated with oprD inactivation and mutations in efflux pump regulatory genes. Chotimakorn et al. [18] further reported that upregulation of the MexAB-OprM efflux pump, reduced expression of OprD, metallo-β-lactamase production, and AmpC overexpression are common contributors to CRPA resistance. The phenotypic resistance pattern observed in the present cohort, particularly the high levels of co-resistance to piperacillin/tazobactam, ceftazidime, and cefepime, is consistent with these findings. However, based solely on antimicrobial susceptibility profiles, the specific molecular mechanisms underlying resistance in this population cannot be directly determined. Further genomic studies are required to clarify the relative contribution of OprD loss, efflux pump dysregulation, AmpC overexpression, and carbapenemase production. Overall, CRPA resistance is not driven by a single mechanism but rather results from multiple resistance pathways, leading to complex resistance phenotypes. This complexity substantially reduces available treatment options, increases the risk of empiric treatment failure, and presents significant challenges for clinical management [3, 4, 16].

In addition to the resistance mechanisms described above, the clinical complexity and therapeutic challenges associated with CRPA infections are further compounded by the unique pathogenic features of *P. aeruginosa*, including biofilm formation, virulence factor expression, and efflux pump systems, which contribute to both antimicrobial resistance and pathogenicity. Biofilm production protects bacteria from antimicrobial penetration and host immune clearance, thereby promoting persistent colonization, reducing bacterial eradication, and increasing the risk of recurrent infection, particularly in pulmonary infections, catheter-associated infections, and chronic wounds [16, 18]. The virulence repertoire of *P. aeruginosa*, including exotoxins, elastases, pyocyanin, and the quorum-sensing regulatory networks, contributes to tissue damage and excessive host inflammatory responses [18]. Furthermore, efflux pumps such as MexAB-OprM not only mediate resistance to multiple antimicrobial classes but also participate in biofilm formation and virulence regulation [17, 18]. Collectively, these pathogen-related factors indicate that CRPA

treatment failure cannot be attributed solely to inadequate antimicrobial selection or resistance mechanisms detected by conventional susceptibility testing. Instead, clinical outcomes are determined by a complex interplay among antimicrobial resistance phenotypes, biofilm-protected bacterial niches, virulence-driven tissue injury, and dysregulated host inflammatory responses. This perspective provides a rationale for exploring adjunctive therapeutic strategies aimed at modulating host responses and the infection microenvironment rather than relying exclusively on direct antimicrobial activity.

Within this context, antimicrobial therapy alone may be insufficient to substantially improve outcomes in patients with CRPA infections. Previous studies have indicated that although novel antipseudomonal agents, including ceftolozane/tazobactam, ceftazidime/avibactam, and cefiderocol, have increasingly been introduced into clinical practice in recent years, real-world studies have not consistently demonstrated superior mortality or clinical cure outcomes among these agents [19]. Perez et al. [20] demonstrated that despite continued advances in antimicrobial therapy for severe multidrug-resistant Gram-negative infections, treatment success remains highly relied on pathogen characteristics, infection site, host factors, and antimicrobial accessibility. Chinese guidelines for carbapenem-resistant Gram-negative bacilli likewise recommend individualized treatment strategies for CRPA infections based on infection site, susceptibility profiles, and underlying resistance mechanisms [21]. Therefore, investigating adjunctive host-modulating strategies in combination with antimicrobial therapy may have important clinical implications.

The present study showed that XBJ combined with antibiotics significantly improved clinical response and bacterial eradication rates and reduced the need for escalation of anti-infective therapy, with these findings remaining consistent before and after IPTW weighting. In a randomized controlled trial of severe community-acquired pneumonia, Song et al. [15] reported that XBJ significantly improved clinical outcomes compared with placebo. The EXIT-SEP randomized clinical trial further provided evidence from a broader sepsis population, with Liu et al. [13] reporting that XBJ was associated with a significant reduction in 28-day mortality. In a retrospective study involving patients with severe infection and sepsis, Gong et al. [14] found that XBJ combined with carbapenems did not significantly reduce 14-day mortality but improved CRP, PCT, and renal function-related parameters. These findings are highly consistent with the present study, in which XBJ combination therapy appeared to provide greater benefits in infection control rather than demonstrating a consistent effect on short-term mortality. Collectively, evidence from randomized controlled trials [13, 15], real-world studies, and the present investigation suggest that XBJ may confer clinical benefits in severe infections; however, the specific manifestations of these benefits may vary according to patient population, disease spectrum, baseline severity, and endpoint selection.

Mechanistically, the potential benefits of XBJ combination therapy may primarily involve host-level modulation. Previous studies have shown that XBJ exerts multi-target effects, including anti-inflammatory activity, immune regulation, and improvement of coagulation abnormalities and organ dysfunction [22]. Yang et al. [23] reported in a sepsis-associated acute lung injury model that XBJ alleviated pulmonary inflammation and reduced acute lung injury by promoting ferroptosis in proinflammatory CCR2hi monocytes. Another study showed that XBJ may ameliorate endothelial inflammatory activation and coagulation imbalance through inhibition of the ACLY/MYB/RIG-I axis, thereby improving sepsis-associated lung injury [24]. Although these experimental and translational findings cannot directly establish a causal relationship between XBJ administration and clinical outcomes in patients with CRPA infection, they provide potential biological support for the improved clinical response and bacterial eradication rates observed in the present study. These findings suggest that the major benefit of XBJ combination therapy may not be through replacing antimicrobial agents or exerting direct antibacterial activity, but rather through modulation of the host inflammatory environment and optimization of the overall infection-response process.

It is important to emphasize that the present study did not perform in vitro experiments eval-

uating the direct antibacterial activity of XBJ against CRPA, such as minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC), time-kill kinetics, or biofilm formation and eradication assays. Likewise, the effects of XBJ on CRPA virulence factor expression, quorum-sensing systems, or efflux pump activity were not investigated. Therefore, the higher bacterial eradication rate observed in the combination group should not be interpreted as evidence of direct bactericidal or antibiofilm activity of XBJ against CRPA. A more plausible interpretation is that XBJ may enhance the effectiveness of concomitant antimicrobial therapy through host-response modulation, including attenuation of excessive inflammatory responses, regulation of immune function, and improvement of organ dysfunction, thereby indirectly facilitating bacterial clearance. Whether XBJ exerts direct antibacterial, antibiofilm, or antivirulence effects against CRPA remains unclear and requires further investigation using dedicated in vitro and in vivo experimental models.

However, compared with infection-control-related outcomes, the association between XBJ combination therapy and 28-day mortality was less consistent, and this represents an important consideration in the interpretation of the present findings. In the IPTW-weighted crude comparison, the difference in 28-day mortality between the two groups did not reach statistical significance. Nevertheless, after further adjustment for key prognostic factors in the multivariable logistic regression, XBJ combination therapy emerged as an independent protective factor, with a stronger effect estimate. This discrepancy highlights that mortality outcomes are jointly influenced by multiple factors. Previous studies have shown that in patients with CRPA or broader *P. aeruginosa* infections, factors such as age, disease severity, sepsis/septic shock status, infection site, and timely administration of effective antimicrobial therapy often exert a more direct influence on short-term mortality than any single treatment measure [18, 25, 26]. Therefore, although IPTW can reduce baseline imbalance between treatment groups, changes in effect estimates after further adjustment for prognostic variables are possible, particularly in studies with limited sample size and event numbers. These findings indicate that the association between combination therapy and mortality may be influenced by model specification and should therefore be interpreted cautiously.

In addition, this study identified an inconsistency between logistic regression and Cox proportional hazards models regarding mortality outcomes. Logistic regression mainly evaluates death at a predefined time point (day 28), whereas the Cox model assesses the instantaneous risk of mortality over the follow-up period. Therefore, these two models address different but complementary research questions. Previous studies have shown that 30-day mortality associated with CRPA-related infection varies substantially according to infection site, with patients with bloodstream infection generally experiencing a higher mortality risk than those with respiratory, urinary tract, or wound-related infections [11]. Falcone et al. [12] further reported in a nationwide study that CRPA infection was significantly associated with increased 30-day mortality among patients with bloodstream infections caused by carbapenem-resistant Gram-negative bacilli, whereas early appropriate antimicrobial therapy was associated with improved outcomes. Therefore, if an intervention mainly improves infection-control efficiency and reduces the probability of death at a fixed time point among selected patients, but does not substantially modify the timing or distribution of mortality events over time, logistic regression may detect an association while Cox analysis may not. In addition, the violation of the proportional hazards assumption by APACHE II score in this study further weakened the interpretability of the standard Cox model for time-dependent mortality risk estimation. Therefore, the mortality findings of this study may be more appropriately interpreted based on fixed-time-point binary analysis, whereas the time-to-event analyses should be interpreted as supplementary evidence.

The apparent divergence between the consistent improvements in infection-control-related outcomes (clinical response, bacterial eradication, and lower escalation rates) and the less consistent mortality benefit warrants careful interpretation. In severe infection research, intermediate outcomes such as clinical response and bacterial eradication primarily reflect the

effects of anti-infective treatment at the pathogen clearance and acute inflammatory response levels - domains in which XBJ, through its anti-inflammatory and immunomodulatory properties, may exert relatively direct and measurable effects. In contrast, 28-day all-cause mortality is a complex clinical endpoint influenced not only by infection control but also by baseline physiological reserve, pre-existing organ dysfunction, comorbidity burden, and subsequent complications that may occur independently of the initial infection. Yuan et al. [25] demonstrated that, in patients with *P. aeruginosa* bloodstream infection, age, active hematological disease, elevated PCT, glucocorticoid use, and septic shock were all independently associated with 28-day mortality, highlighting the substantial contribution of host-related factors. Dong et al. [27] further confirmed that sepsis or septic shock at infection onset was a powerful independent predictor of mortality in patients with CRPA bloodstream infection. In broader populations with *P. aeruginosa* infection, host-related variables, including malignancy, respiratory failure, hemodynamic instability, and renal replacement therapy, have been shown to exert greater influence on short-term survival than pathogen- or treatment-related factors [26]. Thus, in a cohort such as the one in the present study, where patients exhibited considerable heterogeneity in baseline disease severity, comorbid conditions, and infection sites, the effect of a single adjunctive therapy on mortality may be attenuated by the dominant prognostic influence of host-related factors. This does not diminish the clinical relevance of improvements in infection-control outcomes; rather, it underscores that reduction in morbidity, including fewer treatment escalations and improved bacterial clearance, may represent meaningful therapeutic benefits even in the absence of a statistically significant mortality reduction, particularly in studies with limited event numbers. Consequently, the potential value of XBJ combination therapy should be evaluated across a spectrum of clinically relevant outcomes rather than being assessed solely through the perspective of mortality.

The association between receipt of targeted antimicrobial therapy and reduced mortality risk has important clinical implications. Previous studies conducted by Chotimakorn et al. [18] and Falcone et al. [12] demonstrated that patients with CRPA infection may achieve improved 30-day survival when effective antimicrobial therapy is appropriately administered. In particular, early appropriate therapy has been identified as an important protective factor in bloodstream infections. Reynolds et al. [28] further emphasized in their review that, for *P. aeruginosa* infections, early microbiological sampling, initiation of effective antimicrobial therapy, and prompt optimization of treatment regimens based on susceptibility results are critical components of successful management. These findings are consistent with the current findings and further support that timely and appropriate targeted antimicrobial therapy remains a key determinant of clinical outcomes in patients with CRPA infection, independent of whether XBJ combination therapy is administered.

Subgroup analyses further suggested that the potential benefit of combination therapy may be more evident in patients with lower APACHE II scores. Previous studies have indicated that therapeutic interventions are more likely to influence outcomes during earlier stages of infection, before the development of irreversible organ dysfunction [13, 14]. Consistent with these observations, the present findings suggest that in patients with relatively milder disease and preserved physiological reserve, XBJ combined with antibiotics may have greater potential to improve clinical outcomes through modulation of inflammatory responses, support of organ function, and enhancement of infection-control efficiency. In contrast, in patients with severe disease or established multiple organ dysfunction, the incremental benefit of an adjunctive therapeutic strategy may be limited. However, this finding should be considered exploratory because of the limited subgroup sample size. Therefore, it should be regarded primarily as a hypothesis-generating observation requiring validation in future prospective studies rather than definitive evidence.

From a broader epidemiological perspective, the clinical significance of CRPA infection extends beyond antimicrobial resistance itself and reflects a substantial disease burden and marked adverse outcomes. Previous studies have shown substantial geographic variation in

CRPA prevalence, carbapenemase distribution, and mortality rates across different infection sites and regions [11]. Surveillance data have also shown the persistent global emergence of CRPA and difficult-to-treat resistance phenotypes, highlighting the importance of continuous epidemiological monitoring and treatment strategies tailored to local resistance patterns [29]. These data support the broader clinical context of the present study, emphasizing that CRPA infection represents not merely a microbiological challenge but a multifaceted clinical problem involving antimicrobial resistance spectrum, host-related factors, healthcare environments, and treatment accessibility.

The findings of this study, interpreted in the context of existing evidence, offer several preliminary considerations for clinical practice. First, in CRPA-infected patients with moderate disease severity (APACHE II score <20) who have relatively preserved organ function, adjunctive XBJ therapy at the evaluated dose (100 mL intravenously every 12 h for 5-7 days) may be considered in addition to standard antimicrobial therapy, as this subgroup appeared to derive greater benefits in infection-control-related outcomes and potentially short-term prognosis. Second, because the clinical benefits of XBJ were primarily manifested in improved clinical response and bacterial eradication rather than a consistent reduction in mortality, XBJ should be considered an adjunctive host-modulating intervention rather than a substitute for effective antimicrobial therapy. Timely initiation of appropriate targeted antimicrobial treatment, guided by local resistance patterns, infection site, and susceptibility results, should remain the therapeutic priority; XBJ should not delay or replace the administration of effective antimicrobial agents. Third, the absence of significant mortality benefit in patients with higher disease severity (APACHE II score ≥20) suggests that the incremental effect of a single adjunctive immunomodulatory intervention may be limited after advanced organ dysfunction has developed. Therefore, clinical decision-making in this population should carefully balance potential benefits against the limited supporting evidence. Fourth, the decision to administer XBJ should be individualized, taking into account infection site (the benefit appeared consistent across pulmonary, bloodstream, and other sources), the patient's inflammatory status, and local formulary availability. Finally, given the single-center retrospective design, heterogeneity in real-world antimicrobial regimens, and the exclusive evaluation of XBJ as the TCM intervention, these clinical implications should be regarded as preliminary and hypothesis-generating. Further validation through multicenter, prospective, and ideally randomized controlled trials is required before XBJ can be incorporated into standardized treatment recommendations for CRPA infection.

This study has several strengths. First, it was based on a real-world cohort of hospitalized patients and incorporated comprehensive clinical information, reflecting practical CRPA management in routine clinical settings. Second, multiple analytical approaches, including IPTW, logistic regression, Cox regression, and sensitivity analyses, were used to estimate treatment effects from different perspectives, strengthening the comprehensiveness of the interpretation. Third, the study evaluated not only clinical outcomes but also the antimicrobial resistance characteristics of CRPA isolates. Previous studies have established that CRPA resistance mechanisms are intricate and that the interaction between specific resistance mechanisms and susceptibility to novel antimicrobial agents is not always straightforward [16]. Consequently, integrating resistance profiles into the interpretation of treatment efficacy provides important clinical and microbiological context.

There are several limitations to this study. First, as a single-center retrospective study, selection bias and residual confounding cannot be completely excluded. Although IPTW and multivariable regression analyses were applied to adjust for measured confounders, the influence of unmeasured variables may still remain. In addition, some clinical outcomes, including clinical response and escalation of anti-infective regimen, were relatively subjective endpoints and may have been influenced by physician judgement and treatment decisions. Microbiological eradication assessment relied on repeat cultures, and variations in the timing and frequency of specimen collection may have introduced potential bias. Furthermore, heterogeneity in real-world antimicrobial regimens, including differences in drug selec-

tion, dosage, and treatment duration, may have influenced the observed effects of combination regimen. Although XBJ was the primary TCM intervention evaluated in this study, concomitant use of other herbal preparations in clinical practice may have introduced additional treatment heterogeneity.

Second, the present study did not perform molecular characterization of CRPA resistance mechanisms, including *oprD* inactivation, AmpC overexpression, carbapenemase gene detection, or MexAB-OprM efflux pump expression. In addition, biofilm formation capacity, virulence factor profiles, and quorum-sensing activity of clinical isolates were not evaluated. Consequently, the potential associations between specific CRPA resistance or virulence phenotypes and clinical response to XBJ combination therapy could not be evaluated. Future studies incorporating genomic resistance profiling, biofilm and virulence phenotyping, and in vitro evaluation of XBJ effects on MIC, MBC, biofilm formation and eradication, as well as virulence factor expression are warranted. Such studies may help clarify whether XBJ exhibits direct antibacterial or antibiofilm activity and to identify CRPA subgroups that may derive greater benefit from combination therapy.

Third, the number of 28-day mortality events in this study was relatively limited, which may have reduced the statistical power and stability of multivariable regression and subgroup analyses. Moreover, the violation of the proportional hazards assumption by APACHE II score in the Cox model further limited the robustness and interpretation of the time-to-event analysis. Finally, the findings of the present study are specific to XBJ and should not be directly extrapolated to other TCM preparations, given the substantial heterogeneity in composition and pharmacological profiles among different TCM formulations. Accordingly, the current findings should be interpreted as real-world evidence suggesting the potential clinical value of XBJ combination therapy, rather than definitive proof of a mortality benefit.

Conclusion

This study demonstrated that XBJ combined with antibiotics was associated with improved infection control in patients with CRPA infection, as reflected by higher clinical response and bacterial eradication rates and a reduced need of escalation of anti-infective regimen. However, the association between XBJ combination therapy and 28-day mortality was not fully consistent across different statistical models, suggesting that evidence supporting a survival benefit remains insufficient. Future multicenter, large-scale, and prospective studies are warranted to validate the clinical effects of XBJ combination therapy in CRPA infection and to identify patient populations most likely to derive benefit.

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Disclosure of conflict of interest

None.

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Table S1. Antimicrobial susceptibility profile of CRPA isolates overall and by treatment group

Antimicrobial agent	Overall (N = 295) R/I/S	Overall %R	Control (n = 141) R/I/S	Control %R	Combination (n = 154) R/I/S	Combination %R	*P* value*
Imipenem	280/5/10	94.9	134/2/5	95	146/3/5	94.8	0.93
Meropenem	274/8/13	92.9	131/4/6	92.9	143/4/7	92.9	0.988
Piperacillin/tazobactam	248/20/27	84.1	119/9/13	84.4	129/11/14	83.8	0.883
Ceftazidime	218/28/49	73.9	105/13/23	74.5	113/15/26	73.4	0.832
Cefepime	208/26/61	70.5	100/12/29	70.9	108/14/32	70.1	0.881
Aztreonam	195/32/68	66.1	94/15/32	66.7	101/17/36	65.6	0.845
Ciprofloxacin	232/16/47	78.6	112/7/22	79.4	120/9/25	77.9	0.753
Levofloxacin	225/18/52	76.3	108/9/24	76.6	117/9/28	76	0.9
Amikacin	100/22/173	33.9	48/11/82	34	52/11/91	33.8	0.96
Polymyxin B	5/0/290	1.7	2/0/139	1.4	3/0/151	1.9	1.000**

Notes: Susceptibility testing was performed using the VITEK 2 Compact automated microbiology system with AST-N cards (bioMérieux, Marcy-l'Étoile, France). Results were interpreted according to CLSI M100 criteria (editions 2019-2024). By inclusion criteria, all isolates were resistant to imipenem and/or meropenem. CRPA = carbapenem-resistant Pseudomonas aeruginosa; R = resistant; I = intermediate; S = susceptible. **P* values for comparison of resistance rates between groups (chi-square test or Fisher's exact test). ***Fisher's exact test.