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ORIGINAL RESEARCH

# Clinical Efficacy and Safety of Omadacycline Versus Tigecycline in Treating Severe Pneumonia Caused by Carbapenem-Resistant Gram-Negative Bacilli: A Retrospective Cohort Study

Ye Zhang[1], Fei Wang[2], Min Wang[1], Wenhui Xu[3], Aiping Wang[3], Yueping Ding[2]

[1]Department of Pharmacy, The Second Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, Zhejiang, People's Republic of China; [2]Department of Intensive Care Unit, The Second Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, Zhejiang, People's Republic of China; [3]Department of Emergency Medicine, Hospital of Traditional Chinese Medicine of Songyang, Songyang, Zhejiang, People's Republic of China

Correspondence: Yueping Ding, The Second Affiliated Hospital of Zhejiang Chinese Medical University, 318 Chaowang Road, Hangzhou, Zhejiang, People's Republic of China, Email Dingyp0424@zcmu.edu.cn



**Objective:** To investigate the clinical efficacy and safety of intravenous omadacycline compared to intravenous tigecycline in patients with severe pneumonia caused by carbapenem-resistant gram-negative bacilli (CRGNB), and to explore the factors influencing 28-day all-cause mortality.

**Methods:** Our retrospective analysis was conducted on adult patients with CRGNB-associated severe pneumonia who received intravenous omadacycline or tigecycline for at least 72 hours in the intensive care unit (ICU) between April 1, 2023, and March 31, 2025. The primary outcome was 28-day all-cause mortality, while secondary endpoints included clinical efficacy and microbiological clearance rates. Safety was also assessed. Logistic regression analysis was used to identify factors associated with 28-day all-cause mortality.

**Results:** A total of 80 patients with CRGNB-associated severe pneumonia were enrolled, including 43 in the omadacycline group and 37 in the tigecycline group. Compared with the tigecycline group, there was no statistically significant difference in 28-day mortality ($\chi^2 = 2.882$, $p = 0.090$) or microbiological clearance rate (58.14% vs 48.65%, $p = 0.501$) in the omadacycline group. However, the omadacycline group showed a significantly higher clinical efficacy rate (72.09% vs 43.24%, $p = 0.012$) and a markedly lower incidence of adverse events (4.65% vs 24.32%, $p = 0.020$). Multivariate logistic regression analysis revealed that combination therapy with β-lactams was an independent predictor of reduced 28-day mortality, whereas central venous catheterization and baseline C-reactive protein (CRP) levels were independently associated with increased 28-day mortality.

**Conclusion:** Our study found that omadacycline is comparable to tigecycline in clinical effectiveness for the treatment of CRGNB-associated severe pneumonia, while exhibiting a better safety profile. Novel tetracyclines may be used in combination with β-lactams for the treatment of severe pneumonia caused by CRGNB.

**Keywords:** omadacycline, tigecycline, carbapenem-resistant gram-negative bacilli, severe pneumonia, 28-day mortality

## Introduction

Severe pneumonia is a potentially fatal lung infection that frequently necessitates intensive care unit (ICU) hospitalization due to complications such as shock or the need for mechanical ventilation. Critically ill patients already in the ICU are also prone to developing severe pneumonia, which carries a high mortality rate.[1] Pneumonia in critically ill patients includes community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP).[2] Previous data indicate that inpatients with severe CAP admitted to the ICU have an in-hospital mortality rate of 17%, with a one-year mortality rate reaching almost 50%. Patients admitted to the ICU later tend to have higher mortality rates compared to those admitted earlier.[3] In ICU patients, the mortality rates for VAP and mechanically

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ventilated HAP are as high as 28%.[2] Severe pneumonia can be attributable to not only by conventional bacterial pathogens, including *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*, but also by multidrug-resistant (MDR) bacteria.[1,4] In recent years, the emergence of carbapenem-resistant gram-negative bacilli (CRGNB) has posed significant challenges for clinical treatment. It is estimated that globally, approximately 1.3 million deaths were caused by drug-resistant infections in 2019, with projections suggesting this number could surpass 10 million annually by 2050.[5] The World Health Organization's (WHO) Bacterial Priority Pathogens List (BPPL) in 2024 classifies carbapenem-resistant *Enterobacterales* (CRE) and carbapenem-resistant *Acinetobacter baumannii* (CRAB) as "critical priority" pathogens.[6] According to the China Antimicrobial Surveillance Network, the prevalence of CRGNB infections in China has been steadily rising. Clinically, *Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii*, and *Pseudomonas aeruginosa* consistently rank among the top five bacterial isolates recovered from hospital settings nationwide. The infection rate of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) increased from 3% in 2005 to 23.1% in 2021, accounting for 60–90% of CRE infections. Concurrently, the prevalence of CRAB surged from 31.0% in 2005 to 71.5% in 2021.[7]

Therapeutic options for CRGNB infections are currently limited, and tetracyclines have shown potential as an effective treatment. Tigecycline, a glycylcycline-class antibiotic, overcomes tetracycline resistance mediated by bacterial efflux pumps and ribosomal protection through the addition of a glycylamido side chain at the C-9 position of minocycline. It demonstrates good activity against CRE and CRAB, with lung concentrations approximately twice those in serum, but shows intrinsic resistance to CRPA. These characteristics support its recommendation for treating pulmonary infections associated with CRE and CRAB.[7,8] However, the progressive increase in minimum inhibitory concentration (MIC) has led to more frequent use of double-dose tigecycline, which correlates with an increased likelihood of adverse events. Omadacycline, a novel member of the aminomethylcycline class of antibiotics, shares structural similarities with tigecycline but differs in that the glycylamido moiety at the C-9 position is replaced by an alkylaminomethyl group. Like tigecycline, omadacycline is approved for the treatment of pneumonia.[9] In vitro studies have shown that omadacycline demonstrates comparable activity against CRAB to tigecycline ($MIC_{90}$ 4 mg/L vs 2 mg/L), and exhibits a susceptibility rate of 75% against CRKP ($MIC_{90}$ = 32 mg/L).[10] Currently, clinical experience with omadacycline for treating severe pneumonia caused by CRGNB remains insufficient. Moreover, due to its relatively recent introduction in China, data on its clinical efficacy and safety compared to tigecycline remain scarce and warrant further investigation. This retrospective study aims to evaluate and compare the clinical effectiveness and safety of omadacycline and tigecycline in treating severe pneumonia caused by CRGNB, and to identify predictors of 28-day mortality, thereby providing reference for therapeutic decision-making in CRGNB-associated severe pneumonia.

# Material and Methods

## Study Design

This was a single-center, retrospective cohort study conducted at the Second Affiliated Hospital of Zhejiang Chinese Medical University in Hangzhou, China, a 1200-bed tertiary teaching hospital. Data were collected from patients admitted to four ICUs between April 1, 2023, and March 31, 2025. The inclusion criteria were as follows: age ≥ 18 years; severe pneumonia caused by CRGNB; and receipt of intravenous omadacycline or tigecycline for at least 72 hours. Exclusion criteria included pregnancy, advanced malignant tumors, and sequential use of both omadacycline and tigecycline within the 28-day period. This study adhered to the ethical standards of the Declaration of Helsinki. The study protocol underwent review and was approved by Ethics Review Committee of The Second Affiliated Hospital of Zhejiang Chinese Medical University (Approval No. ZJTCMU2AE2025R028-IH01). Given that all data were collected retrospectively and did not include any information explicitly refused by patients for use, and considering that patient privacy and personal identifiers were fully protected with no need for follow-up or additional data collection, the Ethics Review Committee granted a waiver of informed consent.

Eligible patients with severe pneumonia were allocated to either the omadacycline group or the tigecycline group. Patients in the omadacycline group received a loading dose of 200 mg intravenously every 24 hours, administered as a 1-hour infusion, followed by a maintenance dose of 100 mg every 24 hours, infused duration of 0.5 hour. In the

tigecycline group, the treatment regimen consisted of an initial loading dose of 100 mg intravenously, followed by a maintenance dose of 50 mg every 12 hours, adjusted according to hepatic function, with an infusion time of 0.5 to 1 hour. The primary outcome was 28-day all-cause mortality following initiation of therapy. Secondary outcomes included clinical efficacy rate, microbiological clearance rate, with safety also evaluated.

## Definition and Data Collection

Severe pneumonia was defined as the presence of either one major criterion or at least three minor criteria. Major criteria: respiratory failure requiring mechanical ventilation; septic shock with need for vasopressors. Minor criteria: core temperature $< 36\,^{\circ}C$; respiratory rate $\geq 30$ breaths/min; $PaO_2/FiO_2$ ratio $\leq 250$; multilobar infiltrates; confusion/disorientation; blood urea nitrogen level $\geq 20$ mg/dl; infection-related white blood cell count $< 4000$ cells/μL; platelet count $< 100{,}000/\mu L$; hypotension requiring aggressive fluid resuscitation.[11] Disease severity was quantified using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Sequential Organ Failure Assessment (SOFA) score, derived from clinical parameters recorded upon admission.[12,13] The observation endpoint was 28 days after the initiation of treatment. Clinical efficacy was defined as improvement or resolution of clinical symptoms during treatment, accompanied by stabilization or normalization of vital signs and inflammatory markers. Clinical failure was defined as the absence of amelioration in both clinical symptoms and inflammatory parameters.[14] Microbiological clearance was defined as the absence of the initially isolated pathogen in two consecutive cultures from the infection site over the treatment period.[14,15] All study data were retrospectively extracted from electronic medical records and included patient demographics, clinical diagnoses, comorbidities, APACHE II and SOFA scores, infection sources, laboratory test results, microbiological culture and antimicrobial susceptibility profiles, CRGNB treatment regimens and duration, 28-day mortality, clinical outcomes, microbiological clearance, and adverse events.

## Microbiology

Gram-negative bacteria were identified using the Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) system in China. Susceptibility to meropenem, imipenem, and tigecycline was tested using broth microdilution or disk diffusion methods. Gram-negative bacteria were classified as CRGNB if they exhibited nonsusceptibility to at least one carbapenem agent. The MIC breakpoints or zone diameters for meropenem and imipenem were interpreted in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines. For tigecycline, MIC breakpoints were interpreted based on criteria from the European Committee on Antimicrobial Susceptibility Testing (EUCAST). There are no standardized testing conditions available for omadacycline susceptibility testing.

## Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics 27 software (IBM Corp., Armonk, N.Y., USA). Continuous variables that followed a normal distribution were presented as mean ± standard deviation (SD) and compared between groups using Student's *t*-test. Non-normally distributed continuous variables were expressed as median (interquartile range, IQR) and analyzed using the Mann–Whitney *U*-test. Categorical variables were summarized as n (%) and compared using the chi-square test or Fisher's exact test. Survival curves were estimated using the Kaplan-Meier method and compared by the Log rank test. Covariates with a p-value of $\leq 0.1$ in univariate analysis were advanced to the logistic regression model. Multivariable logistic regression analysis was performed to identify independent factors associated with 28-day all-cause mortality. Statistical significance was defined as $p < 0.05$.

# Results

## Patients Enrollment

During the study period, a total of 244 ICU patients received treatment with either omadacycline or tigecycline. Among these, 164 patients were excluded: 53 received empirical therapy, 33 did not meet the diagnostic criteria for severe pneumonia, 30 were infected with non-CRGNB pathogens, 20 had a medication duration of less than 72 hours, 19

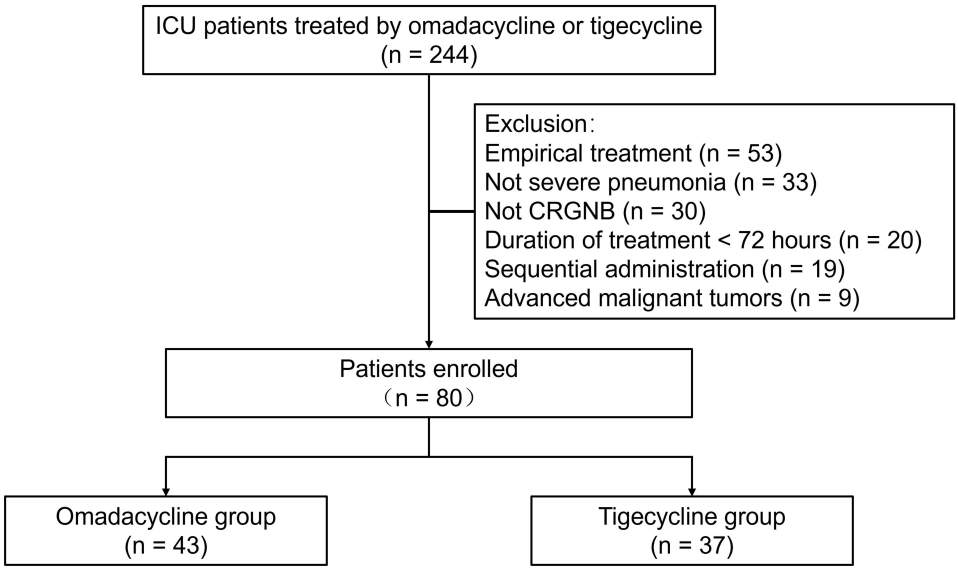


**Figure 1** Patients' flowchart.
**Abbreviation**: CRGNB, carbapenem-resistant gram-negative bacilli.

received sequential treatment with both omadacycline and tigecycline within 28 days, and 9 had a baseline diagnosis of advanced malignant tumors. Ultimately, a total of 80 eligible patients with CRGNB-associated severe pneumonia were enrolled in the analysis. Of these, 43 patients were assigned to the omadacycline group and received intravenous omadacycline, while 37 patients were allocated to the tigecycline group and received intravenous tigecycline. The flowchart of the study is displayed in Figure 1.

A total of 82 CRGNB isolates were identified from sputum or bronchoalveolar lavage fluid samples of 80 patients with severe pneumonia, including 44 isolates in the omadacycline group and 38 in the tigecycline group. The most commonly isolated pathogen was CRKP, followed by CRAB. Other CRE included carbapenem-resistant *Escherichia coli* (CREC), carbapenem-resistant *Serratia marcescens*, and carbapenem-resistant *Enterobacter cloacae*. Two patients had respiratory specimens yielding multiple CRGNB species: one patient grew both CRKP and CRAB, and another grew both CRKP and CREC. All CRGNB strains were resistant to meropenem, and the majority remained susceptible to tigecycline. Data on susceptibility to omadacycline are lacking. No statistically significant differences were revealed in the distribution of pathogens between the two groups. The distribution of Microbiology in CRGNB-associated severe pneumonia patients is summarized in Table 1.

## Baseline Features

We analyzed the demographic and clinical baseline characteristics of the enrolled patients. No statistically significant differences were observed between the omadacycline and tigecycline groups in terms of age, sex, comorbidities, medical interventions, disease severity, laboratory parameters, duration of drug administration, or concomitant medications. Both

**Table 1** Distribution of Microbiology in CRGNB-Associated Severe Pneumonia Patients

| Microbiology, n (%) | Total (n = 82) | Omadacycline (n = 44) | Tigecycline (n = 38) | P-value |
|---|---|---|---|---|
| CRKP | 36(43.90%) | 21(47.73%) | 15(39.47%) | 0.505 |
| CRAB | 42(51.22%) | 20(45.45%) | 22(57.89%) | 0.270 |
| Other CRE | 4(4.88%) | 3(6.82%) | 1(2.63%) | 0.620 |

**Abbreviations**: CRKP, carbapenem-resistant *Klebsiella pneumonia*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant *Enterobacteriales*; Other CRE, carbapenem-resistant *Escherichia coli*, carbapenem-resistant *Serratia marcescens*, carbapenem-resistant *Enterobacter cloacae*.

**Table 2** Baseline Characteristics of Enrolled Patients

| | Total (n = 80) | Omadacycline (n = 43) | Tigecycline (n = 37) | P-value |
|---|---|---|---|---|
| **Population Characteristics** | | | | |
| Age, mean years ± SD | 80±13 | 81±14 | 79±12 | 0.584 |
| Man, n (%) | 55(68.75%) | 27(62.79%) | 28(75.68%) | 0.237 |
| **Comorbidities, n (%)** | | | | |
| Hypertension | 55(68.75%) | 29(67.44%) | 26(70.27%) | 0.814 |
| Diabetes | 42(52.50%) | 26(60.47%) | 16(43.24%) | 0.178 |
| Cerebrovascular disease | 42(52.50%) | 26(60.47%) | 16(43.24%) | 0.178 |
| Chronic kidney disease | 14(17.50%) | 8(18.60%) | 6(16.22%) | 1.000 |
| Chronic pulmonary disease | 11(13.75%) | 6(13.95%) | 5(13.51%) | 1.000 |
| Coronary Heart Disease | 19(23.75%) | 12(27.91%) | 7(18.92%) | 0.433 |
| Heart failure | 49(61.25%) | 28(65.12%) | 21(56.76%) | 0.495 |
| Autoimmune disease | 1(1.25%) | 1(2.33%) | 0(0.00%) | 1.000 |
| **Medical Intervention, n (%)** | | | | |
| Invasive mechanical ventilation | 64(80.00%) | 38(88.37%) | 26(70.27%) | 0.054 |
| Non-invasive mechanical ventilation | 8(10.00%) | 2(4.65%) | 6(16.22%) | 0.135 |
| CRRT | 6(7.50%) | 3(6.98%) | 3(8.11%) | 1.000 |
| Central venous catheterization | 48(60.00%) | 26(60.47%) | 22(59.46%) | 1.000 |
| Urinary catheter or Vesicostomy | 78(97.50%) | 42(97.67%) | 36(97.30%) | 1.000 |
| Nasogastric tube or Nasoenteric tube | 75(93.75%) | 41(95.35%) | 34(91.89%) | 0.658 |
| Gastrostomy tube | 4(5.00%) | 2(4.65%) | 2(5.41%) | 1.000 |
| **Disease Severity, mean ± SD** | | | | |
| APACHE II score | 20±5 | 20±6 | 20±5 | 0.762 |
| SOFA score | 6±2 | 6±2 | 7±3 | 0.554 |
| **Laboratory tests, mean ± SD** | | | | |
| Body temperature, °C | 37.4±0.7 | 37.4±0.7 | 37.4±0.7 | 0.885 |
| White blood cells, $\times 10^9$/L | 11.48±7.23 | 11.80±8.65 | 11.10±5.22 | 0.668 |
| Platelet, $\times 10^9$/L | 213.58±100.94 | 226.19±104.59 | 198.92±95.85 | 0.231 |
| C-reactive protein, mg/L | 90.84±60.91 | 79.50±52.01 | 104.01±68.21 | 0.072 |
| Procalcitonin, ng/mL | 2.32±6.21 | 3.21±8.19 | 1.28±2.10 | 0.141 |
| Alanine aminotransferase, U/L | 33.71±55.91 | 34.91±70.77 | 32.32±31.85 | 0.838 |
| Total bilirubin, μmol/L | 12.00±6.02 | 10.77±4.50 | 13.42±7.21 | 0.057 |
| Creatinine, μmol/L | 129.92±103.57 | 138.18±118.67 | 120.32±83.25 | 0.445 |
| **Drug administration, mean ± SD** | | | | |
| Duration, days | 11±6 | 12±6 | 10±5 | 0.059 |
| **Concomitant medication, n (%)** | | | | |
| Carbapenems | 28(35.00%) | 14(32.56%) | 14(37.84%) | 0.646 |
| β-lactams | 33(41.25%) | 17(39.53%) | 16(43.24%) | 0.821 |
| Polymyxin B | 5(6.25%) | 3(6.98%) | 2(5.41%) | 1.000 |
| Fluoroquinolones | 2(2.50%) | 1(2.33%) | 1(2.70%) | 1.000 |
| Nebulized aminoglycosides | 6(7.50%) | 5(11.63%) | 1(2.70%) | 0.209 |
| β-lactams and polymyxin B | 1(1.25%) | 0(0.00%) | 1(2.70%) | 0.462 |
| Monotherapy | 5(6.25%) | 3(6.98%) | 2(5.41%) | 1.000 |

**Abbreviations**: CRRT, continuous renal replacement therapy; Carbapenems, meropenem, imipenem/cilastatin; β-Lactams, piperacillin/tazobactam, cefoperazone/sulbactam, ceftazidime/avibactam, ceftazidime; Fluoroquinolones, levofloxacin; Aminoglycosides, amikacin.

groups most commonly used β-lactams as combination therapy in managing CRGNB-associated severe pneumonia. The baseline characteristics of the enrolled patients are presented in Table 2.

## Primary Outcome

The primary clinical outcome was evaluated at 28 days following the initiation of omadacycline or tigecycline therapy in all patients with CRGNB-associated severe pneumonia. The 28-day mortality rates were 16.28% (7/43) in the

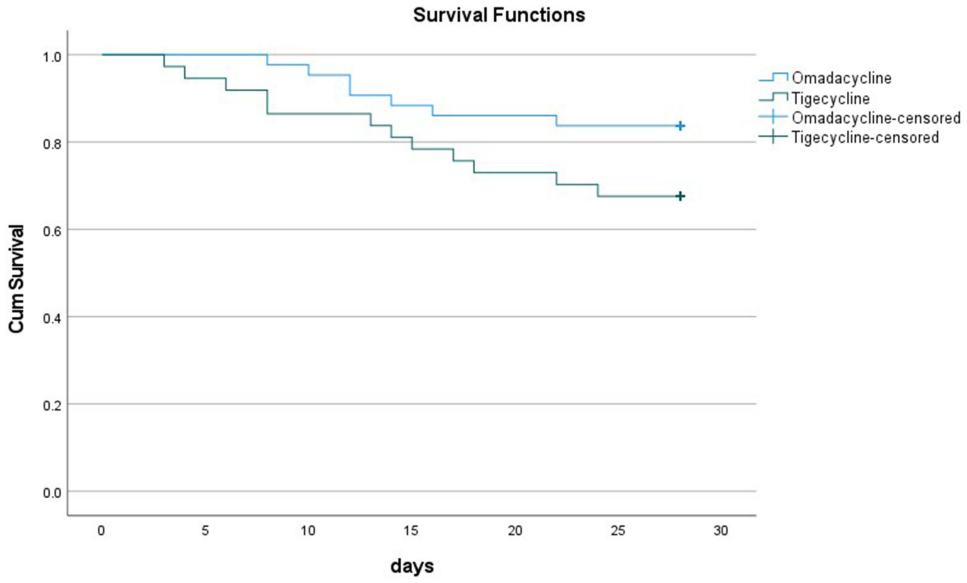


**Figure 2** Comparison of Kaplan-Meier survival curves.

omadacycline group and 32.43% (12/37) in the tigecycline group. Survival analysis demonstrated no statistically significant difference in 28-day mortality between the two groups ($\chi^2$ = 2.882, p = 0.090). Comparison of Kaplan-Meier survival curves is shown in Figure 2.

## Secondary Outcome

The overall clinical efficacy rate was 58.75% (47/80), and the overall microbiological clearance rate was 53.75% (43/80). As shown in Table 3, the clinical efficacy rates in the omadacycline and tigecycline groups were 72.09% and 43.24%, respectively, showing a statistically significant difference between the two groups (p = 0.012). However, no significant difference was observed in microbiological clearance rates between the groups (58.14% vs 48.65%, p = 0.501).

## Factors Associated with 28-Day All-Cause Mortality

We analyzed a total of 80 patients with CRGNB-associated severe pneumonia. Based on their outcomes at 28 days, these patients were categorized into the survivor group and the non-survivor group. The overall 28-day all-cause mortality rate was 23.75% (19/80). Table 4 summarizes the univariate analysis of demographic and clinical characteristics associated

**Table 3** Clinical Efficacy and Microbiological Clearance Rates

| Secondary Outcome, n (%) | Total (n = 80) | Omadacycline (n = 43) | Tigecycline (n = 37) | P-value |
|---|---|---|---|---|
| Clinical efficacy rates | 47(58.75%) | 31(72.09%) | 16(43.24%) | 0.012 |
| Microbiological clearance rates | 43(53.75%) | 25(58.14%) | 18(48.65%) | 0.501 |

**Table 4** Univariate Analysis of Factors Associated with 28-Day All-Cause Mortality

| | Total (n = 80) | Survivor (n = 61) | Non-survivor (n = 19) | P-value |
|---|---|---|---|---|
| **Population Characteristics** | | | | |
| Age, mean years ± SD | 80±13 | 81±14 | 77±12 | 0.346 |
| Man, n (%) | 55(68.75%) | 43(70.49%) | 12(63.16%) | 0.579 |

(*Continued*)

**Table 4** (Continued).

| | Total (n = 80) | Survivor (n = 61) | Non-survivor (n = 19) | P-value |
|---|---|---|---|---|
| **Comorbidities, n (%)** | | | | |
| Hypertension | 55(68.75%) | 43(70.49%) | 12(63.16%) | 0.579 |
| Diabetes | 42(52.50%) | 35(57.38%) | 7(36.84%) | 0.188 |
| Cerebrovascular disease | 42(52.50%) | 35(57.38%) | 7(36.84%) | 0.188 |
| Chronic kidney disease | 14(17.50%) | 9(14.75%) | 5(26.32%) | 0.302 |
| Chronic pulmonary disease | 11(13.75%) | 9(14.75%) | 2(10.53%) | 1.000 |
| Coronary Heart Disease | 19(23.75%) | 16(26.23%) | 3(15.79%) | 0.538 |
| Heart failure | 49(61.25%) | 36(59.02%) | 13(68.42%) | 0.592 |
| Autoimmune disease | 1(1.25%) | 1(1.64%) | 0(0.00%) | 1.000 |
| **Medical Intervention, n (%)** | | | | |
| Invasive mechanical ventilation | 64(80.00%) | 48(78.69%) | 16(84.21%) | 0.750 |
| Non-invasive mechanical ventilation | 8(10.00%) | 6(9.84%) | 2(10.53%) | 1.000 |
| CRRT | 6(7.50%) | 2(3.28%) | 4(21.05%) | 0.026 |
| Central venous catheterization | 48(60.00%) | 30(49.18%) | 18(94.74%) | <0.001 |
| Urinary catheter or Vesicostomy | 78(97.50%) | 60(98.36%) | 18(94.74%) | 0.421 |
| Nasogastric tube or Nasoenteric tube | 75(93.75%) | 58(95.08%) | 17(89.47%) | 0.588 |
| Gastrostomy tube | 4(5.00%) | 3(4.92%) | 1(5.26%) | 1.000 |
| **Disease Severity, mean ± SD** | | | | |
| APACHE II score | 20±5 | 19±5 | 23±6 | 0.002 |
| SOFA score | 6±2 | 6±2 | 8±3 | <0.001 |
| **Laboratory tests, mean ± SD** | | | | |
| Body temperature, °C | 37.4±0.7 | 37.4±0.6 | 37.4±0.9 | 0.698 |
| White blood cells, $\times 10^9$/L | 11.48±7.23 | 10.91±7.12 | 13.31±7.49 | 0.210 |
| Platelet, $\times 10^9$/L | 213.58±100.94 | 219.61±93.57 | 194.21±122.53 | 0.341 |
| C-reactive protein, mg/L | 90.84±60.91 | 82.16±60.04 | 118.70±56.48 | 0.021 |
| Procalcitonin, ng/mL | 2.32±6.21 | 2.02±6.59 | 3.28±4.78 | 0.444 |
| Alanine aminotransferase, U/L | 33.71±55.91 | 25.98±29.99 | 58.53±99.36 | 0.175 |
| Total bilirubin, μmol/L | 12.00±6.02 | 12.00±5.94 | 11.97±6.44 | 0.984 |
| Creatinine, μmol/L | 129.92±103.57 | 116.19±83.54 | 174.01±145.33 | 0.113 |
| **Drug administration, mean ± SD** | | | | |
| Duration, days | 11±6 | 11±6 | 9±5 | 0.192 |
| **Concomitant medication, n (%)** | | | | |
| Carbapenems | 28(35.00%) | 16(26.23%) | 12(63.16%) | 0.005 |
| β-lactams | 33(41.25%) | 31(50.82%) | 3(15.79%) | 0.009 |
| Polymyxin B | 5(6.25%) | 4(6.56%) | 1(5.26%) | 1.000 |
| Fluoroquinolones | 2(2.50%) | 1(1.64%) | 1(5.26%) | 0.416 |
| Nebulized aminoglycosides | 6(7.50%) | 6(9.84%) | 0(0.00%) | 0.327 |
| β-lactams and polymyxin B | 1(1.25%) | 0(0.00%) | 1(5.26%) | 0.235 |
| Monotherapy | 5(6.25%) | 4(6.56%) | 1(5.26%) | 1.000 |

**Abbreviations**: CRRT, continuous renal replacement therapy; Carbapenems, meropenem, imipenem/cilastatin; β-Lactams, piperacillin/tazobactam, cefoperazone/sulbactam, ceftazidime/avibactam, ceftazidime; Fluoroquinolones, levofloxacin; Aminoglycosides, amikacin.

with 28-day all-cause mortality. Statistically significant differences between the two groups were found for the following variables: undergoing continuous renal replacement therapy (CRRT); central venous catheterization; APACHE II score; SOFA score; baseline C-reactive protein (CRP) level; combination therapy with carbapenems and combination therapy with β-lactams.

We further conducted logistic regression analysis on variables with $p < 0.1$ and present the results in Table 5. The results revealed that undergoing CRRT, presence of central venous catheter, APACHE II score, SOFA score, baseline CRP level, and combination therapy with carbapenems were linked to higher 28-day mortality. Conversely, combination therapy with β-lactams was linked to a lower risk of 28-day mortality. The multivariate regression analysis demonstrated that combination

**Table 5** Univariate Logistic Regression Analysis of 28-Day All-Cause Mortality

| Variable | Survivor (n = 61) | Non-survivor (n = 19) | P-value | OR | 95% CI |
|---|---|---|---|---|---|
| CRRT, n (%) | 2(3.28%) | 4(21.05%) | 0.024 | 7.867 | 1.314–47.093 |
| Central venous catheterization, n (%) | 30(49.18%) | 18(94.74%) | 0.006 | 18.600 | 2.335–148.184 |
| APACHE II score, mean ± SD | 19±5 | 23±6 | 0.004 | 1.182 | 1.056–1.323 |
| SOFA score, mean ± SD | 6±2 | 8±3 | <0.001 | 1.642 | 1.246–2.164 |
| Baseline CRP levels (mg/L), mean ± SD | 82.16±60.04 | 118.70±56.48 | 0.026 | 1.010 | 1.001–1.018 |
| Combined carbapenems, n (%) | 16(26.23%) | 12(63.16%) | 0.005 | 4.821 | 1.616–14.381 |
| Combined β-lactams, n (%) | 31(50.82%) | 3(15.79%) | 0.016 | 0.194 | 0.051–0.734 |

**Abbreviations**: CRRT, continuous renal replacement therapy; CRP: C-reactive protein; Carbapenems, meropenem, imipenem/cilastatin; β-Lactams, piperacillin/tazobactam, cefoperazone/sulbactam, ceftazidime/avibactam, ceftazidime; Fluoroquinolones, levofloxacin; Aminoglycosides, amikacin.

**Table 6** Multivariable Logistic Regression Analysis of 28-Day All-Cause Mortality

| Variable | P-value | OR | 95% CI |
|---|---|---|---|
| CRRT, n (%) | 0.934 | 0.894 | 0.064–12.561 |
| Central venous catheterization, n (%) | 0.021 | 14.058 | 1.493–132.326 |
| APACHE II score, mean ± SD | 0.909 | 0.989 | 0.811–1.206 |
| SOFA score, mean ± SD | 0.060 | 1.554 | 0.982–2.459 |
| Baseline CRP levels (mg/L), mean ± SD | 0.016 | 1.016 | 1.003–1.030 |
| Combined carbapenems, n (%) | 0.912 | 0.901 | 0.144–5.653 |
| Combined β-lactams, n (%) | 0.045 | 0.085 | 0.008–0.946 |

**Abbreviations**: CRRT, continuous renal replacement therapy; CRP, C-reactive protein; Carbapenems, meropenem, imipenem/cilastatin; β-Lactams, piperacillin/tazobactam, cefoperazone/sulbactam, ceftazidime/avibactam, ceftazidime; Fluoroquinolones, levofloxacin; Aminoglycosides, amikacin.

with β-lactams was a predictor of reduced 28-day mortality (OR = 0.085, 95% CI 0.008–0.946, p = 0.045), whereas central venous catheterization (OR = 14.058, 95% CI 1.493–132.326, p = 0.021) and baseline CRP levels (OR = 1.016, 95% CI 1.003–1.030, p = 0.016) were independent predictors of increased mortality. Detailed results are provided in Table 6.

## Safety Assessment

We evaluated the safety of study medications in all 80 enrolled patients. As shown in Table 7, the overall adverse events (AEs) included diarrhea, thrombocytopenia or pancytopenia, and elevated bilirubin or liver enzymes. The incidence of AEs was 4.65% (2/43) in the omadacycline group and 24.32% (9/37) in the tigecycline group, which indicates a significant intergroup difference (p = 0.020). The main difference in AEs between the two groups was gastrointestinal symptoms, particularly a significantly higher incidence of diarrhea in the tigecycline group (p = 0.008). All AEs resolved after discontinuation of the study drugs in both groups.

**Table 7** Incidence of Adverse Events

| Adverse Events, n (%) | Total (n = 80) | Omadacycline (n = 43) | Tigecycline (n = 37) | P-value |
|---|---|---|---|---|
| Overall adverse events | 11(13.75%) | 2(4.65%) | 9(24.32%) | 0.020 |
| Diarrhea | 6(7.50%) | 0(0.00%) | 6(16.22%) | 0.008 |
| Thrombocytopenia or pancytopenia | 3(3.75%) | 1(2.33%) | 2(5.41%) | 0.593 |
| Elevated bilirubin | 1(1.25%) | 0(0.00%) | 1(2.70%) | 0.462 |
| Elevated ALT | 1(1.25%) | 1(2.33%) | 0(0.00%) | 1.000 |

**Abbreviation**: ALT, alanine aminotransferase.

## Discussion

The emergence and spread of CRGNB represent a significant public health concern. CRGNB-associated severe pneumonia presents a particularly challenging clinical problem. A study based on 94,888 clinical isolates collected between 2000 and 2017 revealed that 41% of patients from whom CRGNB was isolated were hospitalized in the ICU, with the most common source of culture specimens being the respiratory tract (53%). Importantly, both mortality and disease burden were significantly increased.[16] Treatment options for CRGNB infections are extremely limited. Novel tetracyclines, which overcome the most common resistance mechanisms associated with traditional tetracyclines, have emerged as a crucial therapeutic option for managing CRGNB infections.[17] Previous studies have reported that tigecycline plasma concentrations are positively correlated with the administered dose. Clinical efficacy is likely influenced by the MIC of the causative pathogen. Although increasing the dose of tigecycline may enhance clinical success rates, dose-limiting AEs can occur, leading to reduced patient tolerance and an increased likelihood of treatment discontinuation.[18,19] Omadacycline and tigecycline are both third-generation novel tetracyclines with comparable and favorable tissue penetration. However, omadacycline demonstrates approximately threefold higher systemic exposure in plasma, epithelial lining fluid (ELF), and alveolar cells (AC) compared to tigecycline. Moreover, its concentration in AC is markedly higher than that in plasma or ELF.[20] Omadacycline is available in both intravenous and oral formulations, whereas tigecycline is only available as an intravenous agent. A real-world study demonstrated that oral omadacycline achieved a clinical success rate of 66.7% (6/9) in treating MDR or extensively drug-resistant (XDR) gram-negative bacterial infections. Specifically, the success rates were 80.0% (4/5) for bone/joint infections, 33.3% (1/3) for intra-abdominal infections, and 100% (1/1) for VAP.[21] In addition, a case report has documented the effective management of complicated acute bacterial skin and skin structure infections caused by carbapenem-resistant *Enterobacter cloacae* through oral administration of omadacycline.[22] To date, there is a paucity of studies evaluating the efficacy of omadacycline for treating severe pneumonia caused by CRGNB. Chinese researchers have conducted studies on the efficacy and safety of omadacycline versus tigecycline for treating CRAB pneumonia in ICU patients; however, additional clinical data are still required. In our study, we enrolled 80 patients with CRGNB-associated severe pneumonia. Of these, 90.00% (72/80) were receiving mechanical ventilation, and 80.00% (64/80) had either endotracheal intubation or tracheostomy. Both drugs were administered intravenously. No significant differences were noted between the omadacycline and tigecycline groups in terms of 28-day mortality (16.28% vs 32.43%, $p = 0.090$) or microbial clearance rates (58.14% vs 48.65%, $p = 0.501$). Notably, the clinical efficacy rate was significantly higher in the omadacycline group (72.09% vs 43.24%, $p = 0.012$). Based on primary outcomes, we conclude that omadacycline exhibits non-inferior clinical efficacy compared to tigecycline in the treatment of CRGNB-associated severe pneumonia.

In clinical practice, tigecycline-based combination therapy is one of the treatment options for CRGNB pulmonary infections.[7] However, the majority of evidence supporting the synergistic effects of such combination therapies originates from in vitro or animal studies. One study indicated that among MDR gram-negative pathogens, the combination of tigecycline with polymyxins (colistin or polymyxin B) is the most extensively investigated and has demonstrated synergistic activity.[23] Compared to monotherapy, the combination of tigecycline and aminoglycosides has shown synergistic effects in vitro against carbapenemase-producing (including KPC and NDM-1) *Klebsiella pneumoniae*, potentially reducing the development of tigecycline resistance.[24] Studies on omadacycline have also yielded similar results. Against carbapenem-nonsusceptible *Acinetobacter baumannii*, omadacycline in combination with sulbactam exhibited the highest synergy rate and bactericidal activity (80%), followed by omadacycline plus amikacin or polymyxin B (both at 30%).[25] Another in vitro susceptibility test indicated that the combination of omadacycline and polymyxin B exerts a robust synergistic activity against KPC-producing CRKP.[26] In our study, multivariate logistic regression analysis revealed that combination therapy with β-lactams was an independent predictor of reduced 28-day mortality in patients with CRGNB-associated severe pneumonia (OR = 0.085, 95% CI 0.008–0.946, $p = 0.045$). Among the 33 cases treated with a combination of omadacycline or tigecycline and β-lactams, 69.70% (23/33) received cefoperazone/sulbactam, and 18.18% (6/33) received piperacillin/tazobactam. Of note, 93.94% (31/33) of the patients survived. Given that novel tetracyclines exhibit intrinsic resistance to *Pseudomonas aeruginosa* and are therefore not used for CRPA infections, they may be used in conjunction with β-lactams to treat severe pneumonia attributable to CRE or CRAB.

Tigecycline treatment is frequently linked to mild to moderate gastrointestinal AEs, including diarrhea, nausea, and vomiting. At the higher dose (200 mg/day), the incidence of these AEs increases, with diarrhea, nausea, and vomiting reported at 14.3% vs 2.8%, 8.6% vs 2.8%, and 5.7% vs 2.8%, respectively.[27,28] Data from a real-world cohort of 973 patients showed that 5.7% (55/973) developed tigecycline-associated liver injury, predominantly of the cholestatic type (41/55). The incidence was significantly higher with high maintenance dose regimens (100 mg) and treatment durations exceeding 14 days compared to the standard dose and conventional treatment duration.[29] A retrospective study involving 373 patients revealed an incidence of thrombocytopenia at 12.3%, with tigecycline treatment for ≥7 days emerging as a significant independent risk factor.[30] Another study found that patients receiving high-dose tigecycline experienced a more pronounced reduction in fibrinogen levels compared to those in the standard-dose group.[19] Tetracyclines exhibit a similar pattern of AEs. Despite these commonalities, the safety profile of omadacycline has not yet been fully characterized. Clinical trials have reported gastrointestinal disturbances, as well as elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.[31,32] Research data from healthy volunteers indicated a lower incidence of AEs in the omadacycline group compared to the tigecycline group. The most notable difference between the two groups was observed in the incidence of nausea, which was 2.4% versus 47.6%.[20] Similar results were observed in our study. The overall incidence of AEs differed significantly between the two groups, with a lower rate observed in the omadacycline group (4.65%) compared to the tigecycline group (24.32%) ($p = 0.020$). Most notably, diarrhea occurred exclusively in the tigecycline group (16.22% vs 0.00%, $p = 0.008$). We observed that the AEs associated with omadacycline were primarily characterized by thrombocytopenia and elevated ALT. These results suggest that omadacycline may provide a safer therapeutic option than tigecycline for the management of severe pneumonia caused by CRGNB.

This study has several limitations that should be acknowledged. Firstly, the relatively small sample size and the retrospective design of the analysis may introduce potential confounding factors, which could limit the generalizability of the findings. Secondly, tigecycline was administered at standard doses without therapeutic drug monitoring (TDM), which limits our ability to assess the relationship between dosage and efficacy. Future research should involve larger-scale, prospective, randomized controlled trials with more comprehensive clinical data to further evaluate and validate the differences in efficacy and safety between omadacycline and tigecycline, thereby providing robust evidence to guide therapeutic decisions and ultimately improve patient outcomes.

## Conclusion

In summary, our study indicates that omadacycline provides comparable clinical efficacy to tigecycline in treating severe pneumonia caused by CRGNB, while exhibiting a more favorable safety profile. Furthermore, novel tetracyclines may be used in combination with β-lactams for the treatment of severe pneumonia caused by CRGNB. Additionally, central venous catheterization and elevated baseline CRP levels were associated with increased 28-day mortality. These findings warrant further validation through larger, well-designed randomized controlled trials.

## Data Sharing Statement

Data will be made available on request.

## Ethical Approval

The study protocol was approved by the Ethics Review Committee of The Second Affiliated Hospital of Zhejiang Chinese Medical University (Approval No. ZJTCMU2AE2025R028-IH01).

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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