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# Cefepime versus carbapenem for treating complicated urinary tract infection caused by cefoxitin-nonsusceptible ESCPM organisms: a multicenter, real-world study

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## Abstract

**Background** This investigation aimed to compare the efficacy of cefepime and carbapenem for complicated urinary tract infection (cUTI) caused by presumptive AmpC β-lactamase-producing *Enterobacter spp.*, *Serratia marcescens*, *Citrobacter freundii*, *Providencia spp.*, and *Morganella morganii* (ESCPM).

**Methods** Data of 458 individuals with cUTI caused by cefoxitin-nonsusceptible [minimum inhibitory concentration (MIC) > 8 μg/mL] and cefepime-susceptible (MIC ≤ 2 μg/mL) ESCPM was acquired from four Chinese hospitals between 2010 and 2022 and were reviewed retrospectively.

**Results** 125 and 333 patients received cefepime and carbapenems, respectively, as antimicrobial therapy. The 28-day treatment failure rate was 15.7% (72/458). The following factors were identified as independent predictors for 28-day therapy: age, cefepime MIC = 2 μg/mL, immunocompromised status, infection source control, appropriate empirical therapy, and days from illness onset to active therapy. In patients who required cefepime MIC ≤ 1 μg/mL, a multivariate logistic model indicated that cefepime was linked with a similar risk of 28-day treatment failure [*odd ratio* (*OR*) 1.791, *95% confidence interval* (*CI*) 0.600–5.350, $p = 0.296$] compared with carbapenems after controlling these predictors. Compared with individuals with cefoxitin-nonsusceptible ESCPM, those with isolates of cefepime (MIC = 2 μg/mL) had an enhanced risk of 28-day treatment failure (*OR* = 2.579, *95% CI* = 1.012–6.572, $p = 0.047$). A propensity score for treatment analysis validated this relationship.

**Conclusions** The cefepime and carbapenem had comparable efficacy for treating cUTI caused by cefoxitin-nonsusceptible ESCPM organisms with cefepime MIC ≤ 1 μg/mL, whereas carbapenems are potentially more effective for isolates with cefepime MIC = 2 μg/mL.

**Keywords** Cefepime, Carbapenem, Complicated urinary tract infection (cUTI), AmpC β-lactamase, ESCPM, Cefoxitin-nonsusceptible, Cefepime-susceptible

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## Background

The urinary tract frequently acquires life-threatening infections, an essential cause of sepsis in hospitalized individuals, including those in emergency departments and intensive care units [1]. Urosepsis causes 20–40% mortality in critically ill individuals [1]. Complicated urinary tract infection (cUTI) affects the lower or upper urinary tract, usually in immunosuppressed patients or those with a functional or structural abnormality that inhibits urine flow. With the increasing population age, advances in medical technology, wide use of immunosuppressants, and invasive medical procedures, the incidence of cUTI is surgery and causes a considerable disease burden globally [2]. However, its treatment is becoming increasingly challenging due to its extending antimicrobial resistance [1–2].

Enterobacterales are the most frequent cUTI-causing pathogens, and various members of this order, including *Enterobacter spp.*, *Serratia marcescens*, *Citrobacter freundii*, *Providencia spp.*, and *Morganella morganii* (ESCPM) chromosomally encoded and inducible AmpC β-lactamase genes [3]. ESCPM exposure to specific β-lactam antibiotics, even if they are initially susceptible in vitro, promotes AmpC gene expression, causing clinical treatment failure [3–4]. Carbapenems are used to treat AmpC-producing Enterobacterales due to high resistance to AmpC β-lactamase hydrolysis because of the stable acyl-enzyme complex formation [3]. However, because of increasing carbapenem-resistant organisms, non-carbapenem treatment avenues require elucidation. Cefepime is a fourth-generation cephalosporin and a weak AmpC inducer. In-vitro investigations have indicated that cefepime, unlike other cephalosporins, has maintained its antibacterial potential against AmpC-producing organismsm [3]. The Infectious Diseases Society of America recommends cefepime as a replacement to carbapenems for treating infections of organisms that may produce substantial AmpC under the influence of cefepime (MIC ≤ 2 μg/mL) [3]. Many AmpC-producing Enterobacterales with extended-spectrum beta-lactamases (ESBLs) have recently been identified worldwide [5–6]. Wang et al. [5] reported that urinary AmpC-producing *Enterobacteriaceae* with ESBL co-production accounted for 34.4% in China. A study from Sri Lanka showed that the incidence of ESBL + AmpC co-producing *Enterobacterales* extracted from the community- and hospital-acquired UTIs was 12% and 18%, respectively [6]. Usually, the MICs of cefepime for ESBLs producing *Enterobacterales* are increased than non-producers and fall within the dose-dependent susceptibility or resistance range [7]. However, some isolates susceptible to cefepime are also ESBL producers. The Surveillance of Multicenter Antimicrobial Resistance in Taiwan (SMART) in 2007 indicated that the cefepime susceptibility rate in ESBL-inducing isolates according to CLSI criteria (MIC ≤ 2 μg/mL) was 56.7–71.4% [8]. However, cefepime's effectiveness for treating infection caused by AmpC-producing Enterobacterales isolates with potential ESBL co-production remains unclear.

Currently, routine identification techniques for AmpC β-lactamase–producing isolates are not performed in clinical laboratories. That cefoxitin (MIC > 8 μg/mL) non-susceptible isolates are often used as a phenotypic criterion for presumptive AmpC production in these ESCPM species [9]. This is a multicenter, real-world investigation that compares the efficacy of cefepime and carbapenems against cUTI caused by ESCPM organisms which were non-susceptible to cefoxitin and susceptible to cefepime (MIC ≤ 2 μg/mL).

## Methods

### Patients selection and study design

The medical records of individuals who enrolled at four Chinese teaching hospitals from January 1, 2010, through Dec 31, 2022, were retrospectively analyzed (Supplementary material 1). Those with ESCPM-positive urine cultures, which were also cefoxitin-nonsusceptible (MIC > 8 μg/mL) and cefepime-susceptible (MIC ≤ 2 μg/mL), were selected for this investigation. Individuals who (1) were < 14 years old, under 14 patients were admitted to pediatric units in China; (2) had asymptomatic bacteriuria or uncomplicated UTIs; (3) died within 48 h after the definitive antimicrobial therapy was initiated; (4) had co-infections with non-ESCPM species; and (5) received definitive treatment regimens other than carbapenems or cefepime, were excluded from this investigation. The acquired data were analyzed by a two-level review method, and a third investigator resolved any disagreements related to data interpretation. The investigation followed STROBE recommendations (https://www.equator-network.org/reporting-guidelines/strobe/).

The investigations' primary outcomes were 14- and 28-day definitive antimicrobial therapy failure, where failure meant death or the incidence of untreated signs/symptoms, leading to a change in antimicrobial regimens. The secondary outcomes involved 14- and 28-day treatment reactions, defined by improvements in the patient's signs/symptoms assessed by the physician or laboratory tests. Repeated negative urine culture results indicated microbiologic eradication. Relapse was described by recurrent UTIs by the same pathogen with similar susceptibility assessed by urine culture.

The Ethics Committee of Nanjing Lishui People's Hospital approved this study (No.2022SQ009). Given the retrospective nature of the study, the Ethics Committee of Nanjing Lishui People's Hospital determined that an informed consent was not necessary.

### Microbiological analyses

Using Vitek 2 (bioMérieux, Marcy l'Etoile, France) platform and MALDI-TOF mass spectrometry (MALDI Biotyper, Bruker Daltonics GmbH, Leipzig, Germany, or Vitek-MS, bioMérieux), the microbial isolates were identified. Antibiotic susceptibility was assessed by following standard hospital methods, with most tests being carried out via the Vitek 2 system. The interpretation of susceptibility was performed in accordance with the 2022 CLSI recommendations.

#### *Definitions*

The UTIs were confirmed by a positive urine culture test with at least one UTI symptom (costovertebral angle or suprapubic tenderness, urinary urgency or frequency, general weakness, fever, dysuria, or hematuria) [10]. The midstream or Foley samples' positive urine culture threshold was $\geq 10^5$ colony-forming units (cfu)/mL, whereas the threshold for the samples of nephrostomy, suprapubic puncture, and simple catheterization was $\geq 10^3$ cfu/mL [10]. Individuals were considered positive for cUTIs if they were male, had structural deformities, had comorbid diabetes, and were immunocompromised (i.e. were solid organ transplant recipients, had active malignancies, were diagnosed with primary immunodeficiency, received immunosuppressive treatment, had a history of splenectomy, with a CD4 + T cell count < 200 /mL or < 14% cells, infected with HIV, or a history of hematopoietic stem cell transplantation) [11]. The individual was confirmed with septic shock if they needed vasopressors for maintaining ≥ 65 mmHg mean arterial pressure despite adequate resuscitation volume with ≥ 2 mmol/L serum lactate levels [10]. Infection source control included obstructions relief interventions, catheter removal/exchange, and abscesses or contaminated urine drainage facilitation [10]. Empirical therapy comprised the administration of antimicrobial drugs before urine culture, and the definitive therapy included antimicrobial treatments after the susceptibility testing [10]. An appropriate regimen comprised at least one disease-causing bacteria-sensitive drug during in-vitro susceptibility assessment; other regimens were considered inappropriate [10].

### Data collection

Patients' empirical, demographics, clinical outcomes, comorbidities (Supplementary material 2), definitive antimicrobial treatment (only first-course), and microbiological data were collected retrospectively from their medical records.

### Statistical measurements

The normally distributed data were assessed by the Kolmogorov-Smirnov test. The normal and non-normal data were depicted as means ± standard deviation (SD) and median (interquartile range). For assessing continuous data, Mann-Whitney U and Student's t-tests were carried out, and for categorical data, Fisher's exact and Chi-square tests were conducted. A two-tailed $P < 0.05$ was deemed significant. SPSS 22.0 (IBM NY, USA) was utilized for all the assessments. No power measurements were conducted, and all cases which met the criteria for inclusion were added in this investigation.

With the help of univariate analyses, patients' baseline characteristics which they experienced or not in 30-day treatment failure, were compared. For variables with $P < 0.01$, the backward stepwise multivariate logistic regression model (Model-1) was applied to assess independent 28-day treatment failure predictors. The relative carbapenem and cefepime efficacy was identified by determining independent risk factors as confounding variables during Model-1.

Furthermore, to minimize the influence of confounding variables, the approach of propensity score (PS) weighting was applied. With the help of a multivariate logistic regression model, PS values for each patient's suitability for carbapenem treatment were identified. Covariates included age, participating hospitals, sex, nosocomial UTI, comorbidities (diabetes mellitus, asthma, chronic obstructive pulmonary, chronic kidney, cerebrovascular, cardiovascular, and chronic liver diseases), secondary bacteremia, immunocompromised status, causative pathogens, appropriate empirical therapy, indwelling urinary catheter, cefepime MIC = 2 μg/mL, infection source control, septic shock, active therapy duration, and days from illness onset to active therapy. Weighted PS (WPS) values were assessed as follows: WPS = Pt/PS for patients receiving carbapenems as definitive therapy, and WTPS = (1-Pt)/(1-PS) for those receiving cefepime as definitive therapy, where Pt = the fraction number of patients who received carbapenems treatment from the total number of patients [12]. The impacts of various definitive therapies on clinical outcome factors were assessed after WPS values adjustment in a multivariate model (Model 2).

## Results

### Patient overview

A total of 821 hospitalized patients had positive for ESCPM organisms in urine culture; 458 of these were susceptible to cefepime (MIC ≤ 2 μg/mL) and non-susceptible to cefoxitin (MIC > 8 μg/mL) and were included in the research (Fig. 1). Of these 458 cases, 35.2% (116/458) were positive for *Enterobacter cloacae*, 24.0% (110/458) for *Klebsiella aerogenes*, 19.4% (89/458) for *Serratia marcescens*, 12.0% (55/458) for *Citrobacter freundii*, 7.0% (32/458) for *Morganella morganii*, and 2.4% (11/458) for *Providencia spp.* Overall, 31.2% (143/458) of isolates had a cefepime MIC = 2 μg/mL (Table 1). A total

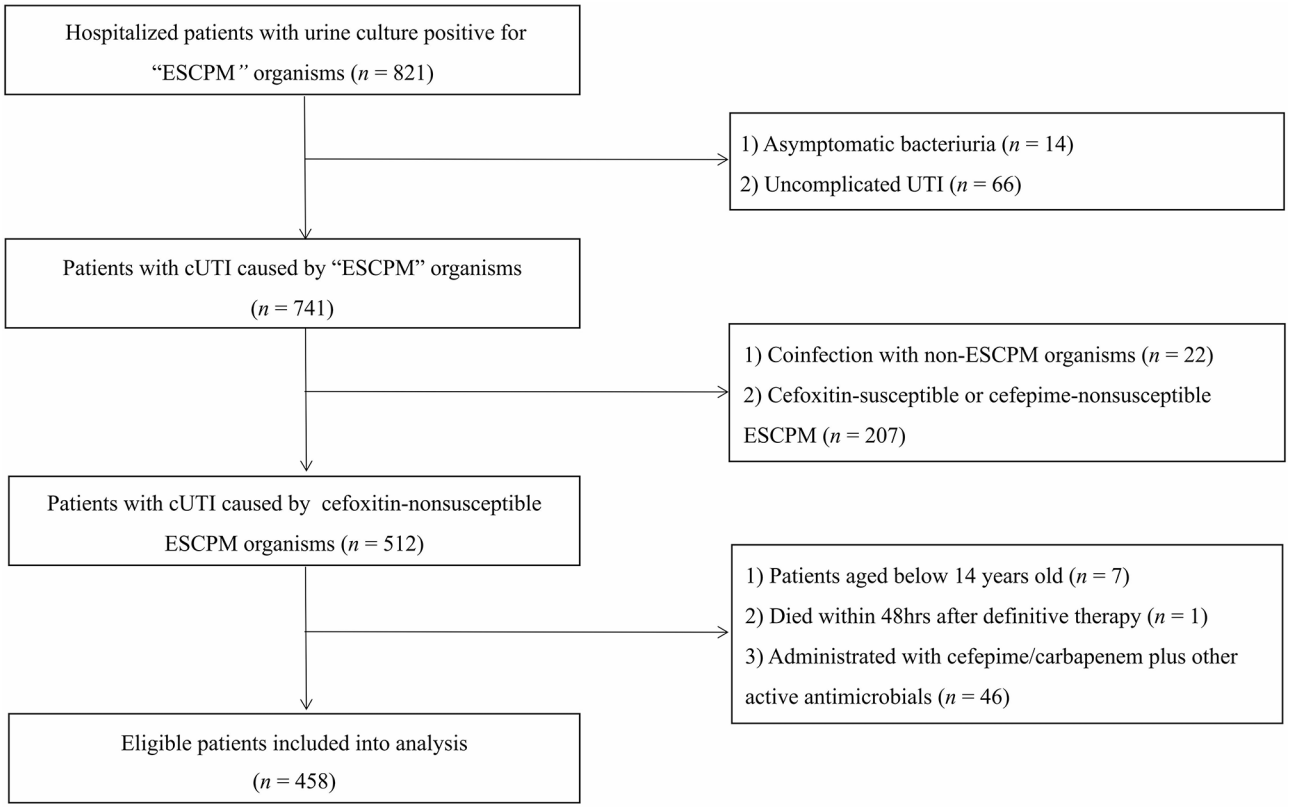


**Fig. 1** Screening algorithm of patients with cUTI caused by cefoxitin-nonsuseptible "ESCPM" organisms. Of the 821 hospitalized patients with positive urine culture results for "ESCPM" organisms screened, 458 non-duplicate cases with cUTI caused by "ESCPM" isolates which were non-susceptible to cefoxitin (MIC > 8 μg/mL) and susceptible to cefepime (MIC ≤ 2 μg/mL) were entered into the final analysis

of 333 patients received cefepime (4 ~ 6 g/day), and 125 patients received carbapenem as definitive antimicrobial therapies, including 56, 51, and 18 patients who received meropenem (3–6 g/day), imipenem (1–2 g/day), and biapenem (0.6–1.2 g/day), respectively. The above antimicrobials were adjusted in cases of renal insufficiency (Table 1).

In the entire cohort, 52.6% of the participants were male with a median age of 67.0 yrs (IQR: 55.0 yrs, 76.0 yrs). The most common comorbidities were cardiovascular disease (52.0%, 238/458), chronic kidney disease (33.8%, 155/458), and diabetes mellitus (27.7%, 127/458). The immunocompromised factors were observed in 38.6% (117/458) of patients. Secondary bacteremia and septic shock occurred in 6.1% (28/458) and 3.3% (15/458) of patients, respectively. 34.3% (157/458) of the participants had indwelling urinary catheters. Appropriate empirical therapy and infection source control was provided to 36.5% (167/458) and 30.1% (138/458) of patients, respectively. The 14-day treatment failure, clinical response, and mortality were 18.1% (83/458), 77.7% (356/458), and 2.6% (12/458), respectively. However, the 28-day treatment failure, clinical response, and mortality were 15.7% (72/458), 84.7% (388/458), and 3.5% (16/458), respectively (Table 1).

### Comparing the clinical features and outcomes between individuals treated with cefepime and carbapenems definitive therapies

In comparison with individuals who received carbapenems, those who received cefepime had less frequent chronic liver disease (4.8% vs. 11.2%, $p = 0.014$), immunosuppression (26.7% vs. 70.4%, $p < 0.001$), secondary bacteremia (4.5% vs. 10.4%, $p = 0.019$) and septic shock (2.1% vs. 6.4%, $p = 0.045$). The number of participants infected with isolates susceptible to cefepime MIC = 2 μg/mL was reduced (24.9% vs. 48.0%, $p < 0.001$) during empirical therapy (44.1% vs. 16.0%, $p < 0.001$). The infection source control (32.7% vs. 23.3%, $p = 0.048$) was increased in the cefepime group than in the carbapenems group. In cefepime-treated patients, the median days from illness onset to active therapy (2.5 days vs. 3.0 days, $p < 0.001$) were less than in carbapenems-treated patients. Overall, treatment failure was lowered by 14 days (15.3% vs. 25.6%, $p = 0.011$) and 28 days (12.9% vs. 23.3%, $p = 0.007$), the 14-day (81.1% vs. 68.8%, $p = 0.005$) and 28-day (87.4% vs. 77.6%, $p = 0.010$) clinical response, and 28-day microbiologic eradication (83.9% vs. 74.4%, $p = 0.023$) were increased in cefepime cohort than in carbapenems therapy cohort (Table 1).

**Table 1** Comparison of clinical characteristics and outcomes between patients received cefepime and carbapenem as definitive therapy

| Variable | Total (*n* = 458) | Cefepime (*n* = 333) | Carbapenem (*n* = 125) | *P* value |
|---|---|---|---|---|
| Male (*n*, %) | 241 (52.6) | 173 (52.0) | 68 (54.4) | 0.640 |
| Age (yrs, median, IQR) | 67.0 (55.0, 76.0) | 67.0 (55.0, 77.0) | 67.0 (54.0, 75.0) | 0.625 |
| Participating hospital (*n*, %) | | | | **0.005** |
| 1 | 130 (28.4) | 94 (28.2) | 36 (28.8) | |
| 2 | 156 (34.1) | 120 (36.0) | 36 (28.8) | |
| 3 | 110 (24.0) | 67 (20.1) | 43 (34.4) | |
| 4 | 62 (13.5) | 52 (15.6) | 10 (8.0) | |
| Comorbidities (*n*, %) | | | | |
| Cardiovascular disease | 238 (52.0) | 167 (50.2) | 71 (56.8) | 0.204 |
| Chronic kidney disease | 155 (33.8) | 114 (34.2) | 41 (32.8) | 0.773 |
| Diabetes mellitus | 127 (27.7) | 85 (25.5) | 42 (33.6) | 0.086 |
| Cerebrovascular disease | 120 (26.2) | 96 (28.2) | 24 (19.2) | **0.037** |
| COPD | 48 (10.5) | 36 (10.8) | 12 (9.6) | 0.706 |
| Chronic liver disease | 30 (6.6) | 16 (4.8) | 14 (11.2) | **0.014** |
| Asthma | 12 (2.6) | 9 (2.7) | 3 (2.4) | 1.000 |
| Immunocompromised status (*n*, %) | 177 (38.6) | 89 (26.7) | 88 (70.4) | **< 0.001** |
| Nosocomial UTI (*n*, %) | 160 (34.9) | 116 (34.8) | 44 (35.2) | 0.942 |
| Indwelling urinary catheter (*n*, %) | 157 (34.3) | 119 (35.7) | 38 (30.4) | 0.284 |
| Secondary bacteremia (*n*, %) | 28 (6.1) | 15 (4.5) | 13 (10.4) | **0.019** |
| Septic shock (*n*, %) | 15 (3.3) | 7 (2.1) | 8 (6.4) | **0.045** |
| Causative pathogens (*n*, %) | | | | 0.893 |
| *Enterobacter cloacae* | 161 (35.2) | 114 (34.2) | 47 (37.6) | |
| *Klebsiella aerogenes* | 110 (24.0) | 79 (23.7) | 31 (24.8) | |
| *Serratia marcescens* | 89 (19.4) | 64 (19.2) | 25 (20.0) | |
| *Citrobacter freundii* | 55 (12.0) | 43 (12.9) | 12 (9.6) | |
| *Morganella morganii* | 32 (7.0) | 25 (7.5) | 7 (5.6) | |
| *Providencia spp.* | 11 (2.4) | 8 (2.4) | 3 (2.4) | |
| Cefepime MIC = 2 ug/mL (*n*, %) | 143 (31.2) | 83 (24.9) | 60 (48.0) | **< 0.001** |
| Appropriate empirical therapy (*n*, %) | 167 (36.5) | 147 (44.1) | 20 (16.0) | **< 0.001** |
| Infection source control (*n*, %) | 138 (30.1) | 109 (32.7) | 29 (23.3) | **0.048** |
| Days from illness onset to active therapy (median, IQR) | 3.0 (3.0, 4.0) | 2.5 (2.0, 3.0) | 3.0 (3.0, 4.0) | **< 0.001** |
| Treatment duration of active therapy (days, median, IQR) | 12.0 (9.0, 16.0) | 12.0 (9.0, 16.0) | 12.0 (9.0, 16.5) | 0.972 |
| Clinical outcomes (*n*, %) | | | | |
| 14-day treatment failure | 83 (18.1) | 51 (15.3) | 32 (25.6) | **0.011** |
| 28-day treatment failure | 72 (15.7) | 43 (12.9) | 29 (23.3) | **0.007** |
| 14-day clinical response | 356 (77.7) | 270 (81.1) | 86 (68.8) | **0.005** |
| 28-day clinical response | 388 (84.7) | 291 (87.4) | 97 (77.6) | **0.010** |
| 14-day mortality | 12 (2.6) | 6 (1.8) | 6 (4.8) | 0.144 |
| 28-day mortality | 16 (3.5) | 9 (2.7) | 7 (5.6) | 0.223 |
| 14-day microbiologic eradiction † | 331/432 (76.6) | 250/318 (78.6) | 81/114 (71.1) | 0.102 |
| 28-day microbiologic eradiction ‡ | 358/440 (81.4) | 271/323 (83.9) | 87/117 (74.4) | **0.023** |
| 14-day relapse † | 11/432 (2.5) | 9/318 (2.8) | 2/114 (1.8) | 0.780 |
| 28-day relapse ‡ | 16/440 (3.6) | 12/323 (3.7) | 4/117 (3.4) | 0.662 |

IQR: interquartile range; COPD: chronic obstructive pulmonary disease; MIC: minimum inhibitory concentration. Immunocompromised status included primary immune deficiency diseases, active malignancy, HIV infection with a CD4 T-lymphocyte count < 200 cells/mL or percentage < 14%, immunosuppressive therapy, solid organ transplantation, hematopoietic stem cell transplantation, splenectomy. The bolded values are *p*-values < 0.05, which represented significant differences between patients treated cefepime and carbapenem as definitive therapy. †: 15 and 11 patients treated with cefepime and carbapenem were not perform repeated urine culture within 14- days after definitive therapy, respectively; ‡: 10 and 8 patients treated with cefepime and carbapenem were not perform repeated urine culture within 28- days after definitive therapy, respectively

**Table 2** Risk factors of 28-day treatment failure in patients with cUTI caused by cefoxitin-nonsuseptible "ESCPM" organisms

| Variable | OR (95% CI) | *P* |
|---|---|---|
| Age | 1.025 (1.003–1.047) | 0.024 |
| Cefepime MIC = 2 ug/mL | 5.982 (3.262–10.969) | < 0.001 |
| Immunocompromised status | 2.476 (1.311–4.677) | 0.005 |
| Infection source control | 0.366 (0.159–0.845) | 0.019 |
| Appropriate empirical therapy | 0.362 (0.160–0.821) | 0.015 |
| Days from illness onset to active therapy | 1.732 (1.196–2.508) | 0.004 |

OR: odd ratio; CI: confidence interval

### Identification of 28-day treatment failure risk factors

When compared with 28-day treatment failure, successful treatment individuals were younger (median, 66.0 yrs vs. 71.0 yrs, $p = 0.005$), had less immunocompromised factors (33.2% vs. 68.1%, $p < 0.001$), and were infected with cefepime MIC = 2 μg/mL susceptible organisms (16.6% vs. 68.1%, $p < 0.001$). The occurence of nosocomial UTI (45.8% vs. 32.9%, $p = 0.035$), secondary bacteremia (13.9% vs. 4.7%, $p = 0.006$), septic shock (9.7% vs. 2.1%, $p = 0.003$) were increased whereas appropriate empirical therapy (13.9% vs. 40.7%, $p < 0.001$) and infection source control (11.1% vs. 33.7%, $p < 0.001$) were decreased in 28-day treatment failure patients than those without 28-day treatment failure. Furthermore, the median duration from illness onset to active therapy (3.0 days vs. 2.5 days, $p < 0.001$) was also prolonged in 28-day treatment failure patients (Supplementary material 3).

According to the multivariate logistic regression analysis, age [*odd ration* (*OR*) 1.025, *95% confidence interval* (*CI*) 1.003–1.047, $p = 0.024$], cefepime MIC = 2 μg/mL (*OR* 5.982, *95% CI* 3.262–10.969, $p < 0.001$), immunocompromised status (*OR* 2.476, *95% CI* 1.311–4.677, $p = 0.005$), infection source control (*OR* 0.366, *95% CI* 0.159–0.845, $p = 0.019$), appropriate empirical therapy (*OR* 0.362, *95% CI* 0.160–0.821, $p = 0.015$) and days from illness onset to active therapy (*OR* 1.732, *95% CI* 1.196–2.508, $p = 0.004$) independently predicted 28-day therapy failure in cefoxitin-nonsusceptible and cefepime-susceptible ESCPM caused cUTI patients (Table 2).

### The efficacy of definitive regimens in individuals with cUTI caused by cefepime susceptible organisms (MIC ≤ 1 μg/mL)

In individuals with cUTI caused by cefepime susceptible organisms (MIC ≤ 1 μg/mL), after control for age, appropriate empirical therapy, immunocompromised status, and infection source control, and days from illness onset to active therapy, Model-1 indicated that cefepime therapy resulted in comparable 14-day (*OR* 1.256, *95% CI* 0.469–3.364, $p = 0.650$) and 28-day (*OR* 1.791, *95% CI* 0.600–5.350, $p = 0.296$) treatment failure, 14-day (*OR* 0.619, *95% CI* 0.223–1.716, $p = 0.356$) and 28-day (*OR* 0.525, *95% CI* 0.163–1.688, $p = 0.280$) clinical response, 14-day (*OR* 0.543, *95% CI* 0.236–1.547, $p = 0.150$) and 28-day (*OR* 1.590, *95% CI* 0.245–10.298, $p = 0.627$) mortality, 14-day (*OR* 0.772, *95% CI* 0.351–1.679, $p = 0.519$) and 28-day (*OR* 0.563, *95% CI* 0.208–1.522, $p = 0.257$) microbiologic eradication, 14-day ($p > 0.999$) and 28-day (*OR* 1.685, *95% CI* 0.165–17.237, $p = 0.660$) relapse compared with carbapenems definitive therapy. Similar associations were also confirmed by a multivariate logistic regression model after control for WTPS (Model 2) (Table 3; Fig. 2).

### The efficacy of definitive regimens in individuals with cUTI caused by cefepime susceptible organisms (MIC = 2 μg/mL)

According to Model 1, in individuals with cUTI caused by cefepime MIC = 2 μg/mL susceptible organisms, after adjusting age, appropriate empirical therapy and infection source control, immunocompromised status, and days from illness onset to active therapy, the definitive cefepime therapy revealed an increased risk of 14-day

**Table 3** The efficacy of definitive regimens in individuals with cUTI caused by cefepime susceptible organisms (MIC ≤ 1 ug/mL)

| Outcomes | Group | | Model 1* | | Model 2# | |
|---|---|---|---|---|---|---|
| | Carbapenem (*n* = 65) | Cefepime (*n* = 250) | OR (95% CI) | *P* | OR (95% CI) | *P* |
| 14-day treatment failure | 8 (12.3) | 19 (7.6) | 1.256 (0.469–3.364) | 0.650 | 0.944 (0.367–2.452) | 0.914 |
| 28-day treatment failure | 6 (9.2) | 17 (6.8) | 1.791 (0.600–5.350) | 0.296 | 1.826 (0.603–5.531) | 0.287 |
| 14-day clinical response | 58 (89.0) | 230 (92.0) | 0.619 (0.223–1.716) | 0.356 | 0.830 (0.312–2.207) | 0.708 |
| 28-day clinical response | 60 (92.3) | 234 (93.6) | 0.525 (0.163–1.688) | 0.280 | 0.489 (0.151–1.582) | 0.233 |
| 14-day mortality | 2 (3.1) | 2 (0.8) | 0.604 (0.067–5.425) | 0.653 | 0.442 (0.045–4.298) | 0.482 |
| 28-day mortality | 2 (3.1) | 4 (1.6) | 1.590 (0.245–10.298) | 0.627 | 1.294 (0.173–9.676) | 0.802 |
| 14-day microbiologic eradiction † | 47/59 (79.7) | 205/241 (85.1) | 0.543 (0.236–1.547) | 0.150 | 0.772 (0.351–1.679) | 0.519 |
| 28-day microbiologic eradiction ‡ | 53 (88.3) | 219/244 (89.8) | 0.563 (0.208–1.522) | 0.257 | 0.521 (0.196–1.383) | 0.191 |
| 14-day relapse † | 0/59 (0) | 5/241 (2.1) | —— | NS | —— | NS |
| 28-day relapse ‡ | 1/60 (1.7) | 6/244 (2.5) | 1.685 (0.165–17.237) | 0.660 | 3.290 (0.339–31.912) | 0.304 |

Model 1*: adjusted by age, cefepime MIC = 2 ug/mL, immunocompromised status, infection source control, appropriate empirical therapy and days from illness onset to active therapy; Model 2#: adjusted by WTPs. †: 6 and 9 patients treated with carbapenem and cefepime were not performed repeated urine culture within 14-days after definitive therapy, respectively; ‡: 5 and 6 patients treated with carbapenem and cefepime were not performed repeated urine culture within 28-days after definitive therapy, respectively. NS: not significant

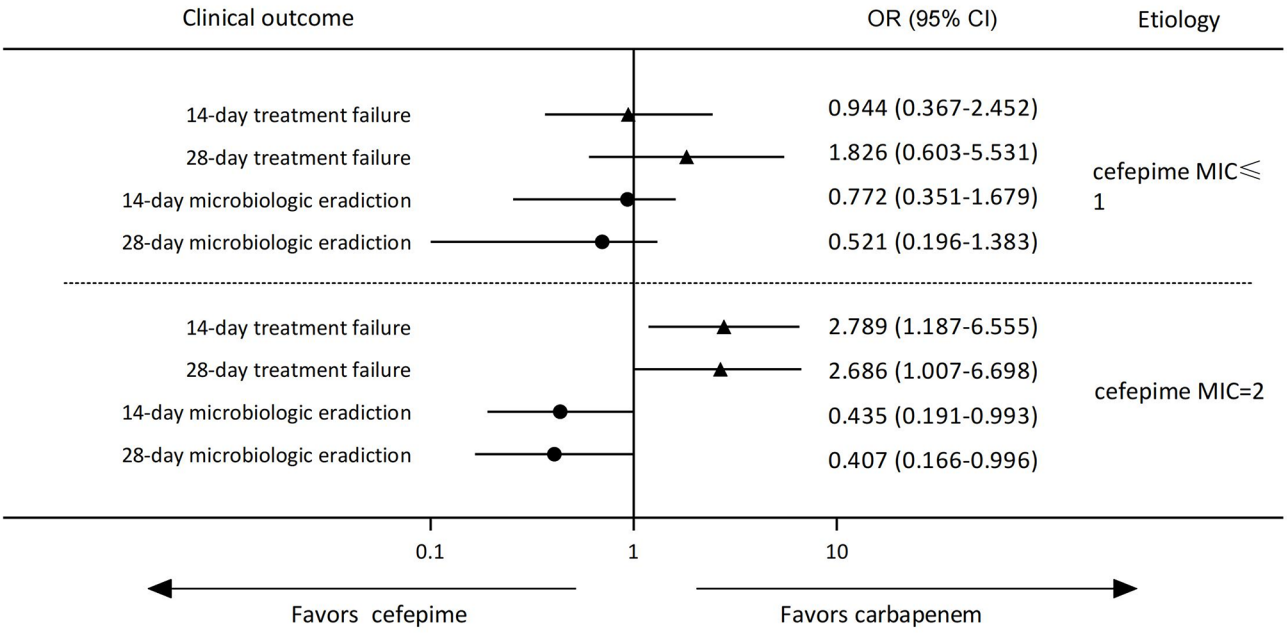


**Fig. 2** The impact of cefepime and carbapenem as definitive antimicrobial regimens on clinical outcomes by propensity score for treatment analysis. Among patients with cUTI caused by organisms with cefepime MIC ≤ 1 ug/mL, cefepime was associated with similar risks of 14-day and 28-day treatment failure, 14-day and 28-day microbiologic eradiction compared with carbapenem; while in patients with cUTI caused by organisms with cefepime MIC = 2 ug/mL, after control for WTPs, cefepime was associated with increased risks of 14-day and 28-day treatment failure, and decreased risks of 14-day and 28-day microbiologic eradiction

**Table 4** The efficacy of definitive regimens in individuals with cUTI caused by cefepime susceptible organisms (MIC = 2 ug/mL)

| Outcomes | Group | | Model 1* | | Model 2⁑ | |
|---|---|---|---|---|---|---|
| | Carbapenem (*n* = 60) | Cefepime (*n* = 83) | OR (95% CI) | *P* | OR (95% CI) | *P* |
| 14-day treatment failure | 24 (40.0) | 32 (38.6) | 3.157 (1.261–7.907) | 0.014 | 2.789 (1.187–6.555) | 0.019 |
| 28-day treatment failure | 23 (38.3) | 26 (31.3) | 2.579 (1.012–6.572) | 0.047 | 2.686 (1.007–6.698) | 0.034 |
| 14-day clinical response | 28 (46.7) | 40 (48.2) | 0.297 (0.117–0.754) | 0.011 | 0.434 (0.193–0.977) | 0.044 |
| 28-day clinical response | 37 (61.7) | 57 (68.7) | 0.388 (0.152–0.989) | 0.047 | 0.372 (0.149–0.928) | 0.034 |
| 14-day mortality | 4 (6.7) | 4 (4.8) | 1.353 (0.275–6.657) | 0.710 | 4.212 (0.641–27.657) | 0.134 |
| 28-day mortality | 5 (8.3) | 5 (6.2) | 1.333 (0.306–5.781) | 0.704 | 4.482 (0.801–25.068) | 0.088 |
| 14-day microbiologic eradiction † | 34/55 (61.8) | 45/77 (58.4) | 0.243 (0.092–0.644) | 0.004 | 0.435 (0.191–0.993) | 0.048 |
| 28-day microbiologic eradiction ‡ | 34/57 (59.6) | 52/79 (65.8) | 0.358 (0.138–0.929) | 0.035 | 0.407 (0.166–0.996) | 0.049 |
| 14-day relapse † | 2/55 (3.6) | 4/77 (5.2) | 1.607 (0.234–11.040) | 0.629 | 1.592 (0.242–10.686) | 0.629 |
| 28-day relapse ‡ | 3/57 (5.3) | 6/79 (7.6) | 1.664 (0.343–8.072) | 0.527 | 1.537 (0.325–7.281) | 0.588 |

Model 1*: adjusted by age, cefepime MIC = 2 ug/mL, immunocompromised status, infection source control, appropriate empirical therapy and days from illness onset to active therapy; Model 2⁑: adjusted by WTPs. †: 5 and 6 patients treated with carbapenem and cefepime were not performed repeated urine culture within 14-days after definitive therapy, respectively; ‡: 3 and 4 patients treated with carbapenem and cefepime were not performed repeated urine culture within 28-days after definitive therapy, respectively

(*OR* 3.157, *95% CI* 1.261–7.907, $p = 0.014$) and 28-day (*OR* 2.579, *95% CI* 1.012–6.572, $p = 0.047$) treatment failure, reduced risks of 14-day (*OR* 0.297, *95% CI* 0.117–0.754, $p = 0.011$) and 28-day clinical response (*OR* 0.297, *95% CI* 0.152–0.989, $p = 0.047$), 14-day (*OR* 0.243, *95% CI* 0.092–0.644, $p = 0.004$) and 28-day (*OR* 0.358, *95% CI* 0.138–0.929, $p = 0.035$) microbiologic eradication than carbapenems treatment. However, 14-day (*OR* 1.353, *95% CI* 0.275–6.657, $p = 0.710$) and 28-day (*OR* 1.333, *95% CI* 0.306–5.781, $p = 0.704$) mortality, 14-day (*OR* 1.607, *95% CI* 0.234–11.040, $p = 0.629$) and 28-day relapse (*OR* 1.664, *95% CI* 0.343–8.072, $p = 0.527$) had similar risks (Table 4). After WTPS control, Model 2 confirmed this relationships (Table 4; Fig. 2).

## Discussion

In this multicenter, real-world study, the comprehensive analysis revealed that cefepime MIC was an independent predictor for treatment failure and an essential variable for cefepime treatment efficacy. When treating cUTI caused by ESCPM susceptible to cefepime MIC ≤ 1 μg/mL, the effectiveness of cefepime and carbapenems were

comparable; however, carbapenems was more potent than cefepime against cUTI caused by susceptible to cefepime MIC = 2 μg/mL.

Consistent with the literature, in China, *Enterobacter cloacae*, *Klebsiella aerogenes*, and *Serratia marcescens*-are the most frequent *Enterobacteriaceae* species causing UTI following *E. coli* and *Klebsiella pneumoniae* [5–6, 13–14]. In Spain, *Enterobacter cloacae* and *Klebsiella aerogenes* accounted for more than half of UTIs caused by ESCPM, and > 80% of invasive infections are because of *Enterobacteriaceae* expressing AmpC β-lactamases [13]. Lena Herrmann et al. [14] revealed that *Enterobacter cloacae*, *Klebsiella aerogenes*, and *Serratia marcescensare* were also the top three potential AmpC β-lactamase-producing *Enterobacterale*-causing bloodstream infections (BSI).

This investigation revealed that the 28-day treatment failure rate was 15.7%, and the patients who lacked a positive clinical response or died were 15.3% and 3.5%, respectively, consistent with the literature [15–16]. Host-specific variables, medical interventions, and complications are all associated with outcomes of infections caused by ESCPM, including cUTIs [17]. Here, 38.6% of the individuals were immunocompromised, and immunocompromised status was determined as an independent treatment failure predictor. Even after appropriate antibiotic therapy, immunocompromised individuals suffered more from prolonged symptoms and increased mortality rates than immunocompetent individuals [18]. Increased age is linked with decreased immunity and important organ function and is an independent infectious disease risk factor [19]. In this investigation, many cUTI cases were secondary to indwelling urinary catheters or urinary obstruction, suggesting that appropriate source control efforts, including catheter removal/replacement, urinary drainage, or lithangiuria removal, are essential. Appropriate empirical therapy produces better outcomes for severe infections [20]. Furthermore, it was indicated that the prolonged duration from illness onset to active therapy was associated with enhanced treatment failure, suggesting the importance of prompt treatment against cUTI caused by AmpC β-lactamase-producing ESCPM species.

The literature indicates that carbapenems can treat infections caused by AmpC β-lactamase-inducing organisms. However, the cefepimes' role, a poor stimulator of and relatively more stable to AmpC β-lactamase, remains unclear. Much research indicates that cefepime is more appropriate for treating infections caused by AmpC β-lactamase-inducing ESCPM bacteria. Pranita D. Tamma et al. [15] retrospectively reviewed 399 invasive infectious cases caused by ESCPM species, and 24% had confirmed infections caused by AmpC β-lactamase-producing organisms. No substantial difference was identified in 30-day mortality or length of hospitalization between patients treated with cefepime and meropenem. In the retrospective study by Tan and his colleagues [16], cefepime had comparable efficacy for 30-day mortality (OR = 0.65, 95% CI = 0.12–3.55) in patients with BSI caused by ESCPM than those treated with a carbapenem, although they did not perform AmpC screening test for the isolates included. Markus Hilty et al. [21] also observed that cefepime and carbapenems had similar favorable outcomes (88.9% vs. 92.3%) of treatment against *Enterobacter cloacae* bacteremia. However, different susceptible breakpoints for cefepime (e.g., cefepime MIC ≤ 8 μg/mL [15], ≤ 2 μg/mL [16], or ≤ 1 μg/mL [21]) were used in each study, some even lacked the susceptibility to cefepime [22]. Here, cefepime MIC was identified as an independent positive clinical response predictor and was associated with the efficacy of cefepime for treating cUTI caused by ESCPM.

In the past decades, the emergence of ESBL in *Enterobacterales* species has become a growing threat to public health globally. Although the most common ESBL-producing *Enterobacterales* are *E.coli* and *K. pneumoniae*, the prevalence of ESBL in ESCPM organisms has been increasing in recent years, particularly in South-East Asia. Eric Farfour et al. retrospectively assessed the incidence of antimicrobial resistance in *Enterobacterales* isolated from urinary tract samples from 26 French clinical laboratories. They found that the overall rate of ESBL-producing *Enterobacterales* isolates was 6.7%, while *E. cloacae* in 18.9% *and C. freundii* in 5.9% [23]. In the USA, 10.1% of *E. cloacae* isolated from BSI patients harbored ESBL genes [24]. A prospective Korean study indicated that 10% of AmpC β-lactamase-producing *Enterobacteriaceae* produced ESBL, and the positive rate of phenotypical ESBL-test in *Enterobacter spp.*, *S. marcescens*, and *C. freundii* was 12.8%, 12.4%, 4.9%, respectively [25]. The China Antimicrobial Resistance Surveillance Trial (CARST) Program revealed the rates of ceftriaxone-resistance in BSI-causing *E. cloacae* were 49.15–72.4% between 2011 and 2020 [26]. Similarly, the prospective multicenter study performed in China by Jingjing Quan [27] and Kai Zhou et al. [28] reported that the prevalence of ESBL-positive *K. aerogenes* and *Enterobacter cloacae* were 13.0% and 29.0%, respectively. Much clinical evidence suggests cefepime as a suboptimal choice against infections caused by ESBL-producing *Enterobacterales* than carbapenems. In a randomized trial of UTIs (by ESBL-producing *Enterobacterales*) patients, the treatment failure rate for cefepime was increased than ertapenem [29]. Wang et al. [30] performed a propensity score-match research on 17 and 51 patients receiving empiric cefepime and carbapenem therapies, respectively, for ESBL bacteremia. Carbapenem had a 2.87 times increased survival rate than cefepime therapy. In

some previous studies, the coexistence of ESBL + AmpC has been described below 5% [15, 21]. Thus, the different conclusions between this study and others might reflect the geographical and chronological differences in ESBL prevalence in ESCPM organisms.

However, ESBL phenotypic confirmation has not been routinely performed in clinics since 2010. Cefepime MIC was linked with the existence of the ESBL gene in some *Enterobacterales* species. Dariusz Hareza et al. [31] assessed 77 *Enterobacter cloacae*, *Klebsiella aerogenes*, and *Citrobacter freundii* isolated from blood cultures from 3 hospitals in the United States. The prevalence of ESBL genes was mostly identified in cefepime susceptible organisms MIC ≥ 16 μg/mL (67%), 18% in MIC = 2 μg/mL, and only 3% in MIC ≤ 1 μg/mL. In Taiwan, an observational study indicated that in 36 patients with *E. cloacae* bacteremia susceptible to cefepime (MIC = 4–8 μg/mL), 89% of isolates had the ESBL gene, substantially more than the 44% of ESBL observed in isolates susceptible to cefepime (MICs ≤ 2 μg/mL) [8]. In the susceptible isolates, the incidence of ESBL genes stratified by cefepime MIC was as follows: MIC = 2 μg/mL (55%) and MIC < 1 μg/mL (3.1%) [8]. In the study by Choi SH et al. [25], the cefepime MIC ≥ 1 μg/ml had the highest sensitivity (0.84) and specificity (0.87) to screen an ESBL-producer-among-AmpC β-lactamase producing *Enterobacteriaceae*. It is suggested by experts that the cefepime MIC breakpoint should be ≤ 1 μg/mL to "provide more confidence that an isolate is not co-producing an ESBL" [32]. Thus, the co-occurrence rate of ESBL would influencen the treatment failure rate observed with cefepime MIC = 2 μg/mL.

Moreover, clinical cefepime therapy success has been correlated with the percentage of time that serum antibiotic concentration exceeds the MIC (%T > MIC) for the infecting organism [33]. The current cefepime recommended dose (4–6 g/day) has the greatest probability of achieving pharmacodynamics targets against fully susceptible *Enterobacteriaceae* (MIC ≤ 1 μg/mL) isolates, specifically against the infections with enhanced bacterial inoculum, called the "inoculum effect" (marked increase in MIC with enhanced inoculum) [33]. In a retrospective study of 178 patients with monomicrobial bacteremia caused by ESBL-producing *Escherichia cloacae*, the multivariable analysis revealed that cefepime therapy was independently linked to substandard outcomes. Substantially increased clinical and microbiological failure and sepsis-related mortality were observed with cefepime MIC ≤ 1 μg/mL than MIC of 2–8 μg/mL [34]. Therefore, a subgroup analysis based on cefepime MIC might explain the discrepant conclusions of this study. Compared with randomized controlled trials (RCTs), observational studies have an increased risk of selection bias, and various confounding factors may influence the results. Two approaches were utilized to minimize possible confounding factors to reduce such bias in this investigation. Both these strategies yielded results that validated the relationship of selected definitive antimicrobial regimens with treatment failure rates with different cefepime MIC subgroups, and yielded similar OR values, thus strengthening these conclusions.

The limitations of this investigation include the following. (1) Since it is a retrospective study, it has a certain selection bias, such as potential changes in treatment guidelines and trends in antimicrobial resistance over time. Despite controlling potential confounders, the study cannot fully control the impact of known and unknown imbalances between groups. (2) Cefoxitin-non-susceptibility was utilized for AmpC production. Even though a genetic protocol might be more accurate, cefoxitin-non-susceptibility is fairly specific, sensitive, and practical. (3) ESBL levels are not routinely assessed in Chinese microbiology laboratories. The actual prevalence of ESBL in this study is yet to be discovered. As there are regional differences in ESBL prevalence, our results must be validated in other countries. (4) Other factors may also have influenced the relative efficacy of the selected antimicrobial regimens, including the dosing or effusion duration for these drugs [35]. Cefepimes' high doses (i.e., 2 g every 8 h) and prolonged effusion (> 3 h) may be more effective against isolates with MIC > 1 μg/mL [36]. As data on effusion duration couldn't be retrieved due to the retrospective design, it was impossible to analyze the effect of these variables on study outcomes. The side effects, to better inform clinical decision-making, could also not reliably be evaluated given the retrospective study design.

## Conclusions

In summary, this investigation revealed that carbapenems and cefepime have comparable efficacy against cUTI caused by cefoxitin-nonsusceptible ESCPM organisms with cefepime MIC ≤ 1 μg/mL in China. While carbapenems might be potentially more effective against causative pathogens with cefepime MIC = 2 μg/mL with a high ESBL prevalence. However, further RCT-based analyses from more regions and countries are essential to validate these findings prior to their clinical application.

### Abbreviations

| | |
|---|---|
| ESCPM | Enterobacter spp., serratia marcescens, citrobacter freundii, providencia spp., and morganella morganii |
| cUTI | Complicated urinary tract infection |
| MIC | Minimum inhibitory concentration |
| OR | Odd ratio |
| CI | Confidence interval |
| ESBL | Extended-spectrum beta-lactamase |

## Supplementary Information

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Supplementary Material 1

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**Author contributions**
LC: conception, design, data collection, data analysis, manuscript writing, manuscript revision, and supervision; JH: conception, design, data collection; XP H: conception, design, data collection, data analysis, manuscript revision. All authors reviewed the manuscript.

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

## Declarations

**Ethics approval and consent to participate**
The Ethics Committee of Nanjing Lishui People's Hospital approved this study (No.2022SQ009). Given the retrospective nature of the study, the Ethics Committee of Nanjing Lishui People's Hospital determined that an informed consent was not necessary. This study used data collected from patient records while maintaining patient anonymity. No administrative permissions were required to access the raw data. The study was carried out in accordance with the Declaration of Helsinki.

**Consent for publication**
NA.

**Competing interests**
The authors declare no competing interests.

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