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RESEARCH

# Multicenter study on clinical outcomes and poor prognostic factors in patients with *Klebsiella pneumoniae* bacteremia receiving cefoperazone/sulbactam treatment

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## Abstract

**Background** Infections caused by *Klebsiella pneumoniae* are common and result in high mortality rates. In vitro studies demonstrated the potency of cefoperazone/sulbactam (CPZ/SUL) against *Klebsiella pneumoniae*. However, the clinical efficacy of CPZ/SUL for the treatment of *K. pneumoniae* bacteremia has not been studied.

**Objectives** This study aimed to associate the clinical outcomes of patients with bacteremia with the minimal inhibitory concentrations (MICs) of CPZ/SUL against the causative *K. pneumoniae* isolates.

**Methods** This multicenter, retrospective study was conducted in Taiwan between July 2017 and April 2021. Patients with *K. pneumoniae* bacteremia treated with CPZ/SUL were enrolled in this study. CPZ/SUL MICs were determined using the agar dilution method. Data on the patients' clinical outcomes and characteristics were collected and analyzed.

**Results** In total, 201 patients were enrolled. Among the causative *K. pneumoniae* isolates, 180 (89.5%) were susceptible to CPZ/SUL. Most patients ($n = 156$, 77.6%) had favorable outcomes. The 30-day mortality rate was 11.9% ($n = 24$). Multivariate risk analyses showed that higher APACHE II score (Odds Ratio [OR], 1.14; Confidence Interval [CI], 1.07–1.21; $p < 0.001$), metastatic tumors (OR, 5.76; CI, 2.31–14.40; $p < 0.001$), and causative *K. pneumoniae* CPZ/SUL MICs > 16 μg/ml (OR, 4.30; CI, 1.50–12.27; $p = 0.006$) were independently associated with unfavorable outcomes.

**Conclusion** Patients with *K. pneumoniae* bacteremia treated with CPZ/SUL at a ratio 1:1 had favorable outcomes when the CPZ/SUL MICs were ≤ 16 μg/ml. Patients with higher APACHE II scores and metastatic tumors had unfavorable outcomes.

**Keywords** Bacteremia · Breakpoint · Cefoperazone · *Klebsiella pneumoniae* · Minimal inhibitory concentration · Outcome · Sulbactam

## Introduction

*Klebsiella pneumoniae* is a common and life-threatening community-acquired, healthcare-associated, and hospital-acquired pathogen. *K. pneumoniae* can cause pneumonia, urinary tract infections, intra-abdominal infections, liver abscesses, bacteremia, and other invasive infections [1–3]. The mortality rates of patients with *K. pneumoniae* bacteremia differed from 20 to 50%, depending on the infected population, and the rates became higher when the severity of the infection increased and the presence of carbapenem resistances [4–6]. The emergence of extended-spectrum β-lactamase (ESBL)-producing *K. pneumoniae* during the past decades has hindered the treatment of these infections and further limited available drug choices for antimicrobial therapy [7–9]. Adequate treatment of patients infected with this problematic pathogen is a major concern to physicians.

Cefoperazone (CPZ) is a third-generation cephalosporin that is active against the most commonly encountered gram-negative bacteria (GNB) [10–12], but not ESBL-producing GNB. The inclusion of sulbactam (SUL), a penicillanic

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acid sulfone with activity against Ambler class A enzymes, broadened the antimicrobial spectrum of CPZ [13, 14].

Over the past, the emergence of ESBL-producing *K. pneumoniae* has caused a serious clinical burden [7–9]. The Taiwan Surveillance of Antimicrobial Resistance program conducted from 2002 to 2012 reported that the prevalence of ESBL-producing *K. pneumoniae* increased from 4.8 to 11.9% in Taiwan [15]. According to the SENTRY antimicrobial surveillance program data, the prevalence of multidrug-resistant (MDR) *Enterobacterales*-associated bloodstream infections increased from 6.2 to 15.8% between 1997 and 2016 [9].

The CPZ/SUL combination is active against many MDR GNBs, including ESBL-producing *Enterobacterales*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* [16, 17]. CPZ/SUL is effective against MDR GNBs that cause febrile neutropenia, intra-abdominal infections, community-acquired pneumonia, and hospital-acquired pneumonia [12, 18–22]. However, there are no available minimal inhibitory concentration (MIC) interpretation breakpoints for the CPZ/SUL combination according to the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [23, 24]. In Taiwan, antimicrobial susceptibility test reports for CPZ/SUL are generated by automated testing using a 2:1 ratio of CPZ to SUL, and the results are interpreted using the CLSI breakpoints for cefoperazone against *Enterobacterales*. Studies have reported that CPZ/SUL administered at a 1:1 ratio has superior antibacterial activities against ESBL-producing *K. pneumoniae* and most MDR GNB compared with the 2:1 ratio [25, 26]. A recent study revealed an 82.7% clinical success rate in treating bacteremia caused by ESBL-producing *Enterobacterales* with 1:1 CPZ/SUL [27].

We conducted a multicenter, retrospective study to correlate the MIC values of a 1:1 ratio of CPZ/SUL against *K. pneumoniae* and the clinical outcomes of patients with *K. pneumoniae* bacteremia.

## Materials and methods

### Study design and patients

This multicenter study was conducted between July 2017 and September 2022 at eight medical centers located in different parts of Taiwan, including Southern Taiwan (Chi Mei Medical Center [CMMC], Kaohsiung Chang-Guan Memorial Hospital [KCGMH], and Kaohsiung Medical University Hospital [KMUH]), Central Taiwan (China Medical University Hospital [CMUH] and Taichung Veterans General Hospital [TCVGH]), and Northern Taiwan (Linkou Chang Gung Memorial Hospital [LCGMH], Tri-Service General Hospital [TSGH], and Taipei Veterans General Hospital [TVGH]).

The enrolled patients were > 20 years of age had monomicrobial bacteremia caused by *K. pneumoniae* and were initially treated using antimicrobial monotherapy with a 1:1 ratio of CPZ/SUL within 24 h of bacteremia onset with treatment lasting for more than 72 h. The onset of bacteremia was defined as the date of index blood culture collected [25, 28]. CPZ/SUL was given intravenously every 12 h at a standard dosage of 2/2 g, with dosage modification as the manufacturer's guidelines, according to the estimated creatinine clearance using the Cockroft–Gault equation [29]. Patients receiving additional antimicrobial therapies exceeding 48 h were excluded, except those treatments were targeting GPCs, virus or fungi. This study was approved by the Institutional Review Board (IRB) of the TSGH (No. 1-106-05-116) and the IRBs of all other participating hospitals.

### Antimicrobial susceptibility test

The antimicrobial MICs (μg/ml) were determined using the agar dilution method in accordance with CLSI recommendations [23]. The 1:1 combination ratio was used [25]. CPZ/SUL powder was purchased from TTY Biopharm (Taipei, Taiwan).

### Variable definition and assessment of the treatment efficacy

The Charlson Comorbidity Index [30] was used to assess comorbidities. Immunosuppressant therapy indicated those patient receiving prednisolone for at least10mg per day (or equivalent potency agents) from 2 days before bacteremia onset till 30 days post the event. The Acute Physiology and Chronic Health Evaluation II (APACHE II) [31] was used to assess disease severity. The source of bacteremia was classified as respiratory tract infection/pneumonia, urinary tract infection, soft-tissue infections, intraabdominal infection, or primary bloodstream infection, according to the definitions of the Centers for Disease Control and Prevention [32]. Clinical outcomes were assessed at 30 days. The clinical outcomes were recorded and divided into four categories: cure, improvement, lack of efficacy, and death. A cure was defined as the absence of symptoms and signs of infection without the requirement for additional antibiotic therapy and a negative result in the subsequent blood culture within a week of the onset of bacteremia. Improvement indicated that the symptoms and signs subsided with or without laboratory improvement, based on clinical judgment, and further antibiotic treatment was required. Lack of efficacy was defined as clinical progression or persistent bacteremia at the end of CPZ/SUL treatment [33]. Regarding the correlation

between treatment efficacy and the MICs of CPZ/SUL, cure and improvement were defined as favorable outcomes. In contrast, a lack of efficacy and death were defined as unfavorable outcomes.

### Statistical analyses

Descriptive statistics were used to present the demographic characteristics of enrolled patients. The demographic characteristics of the two groups (MIC ≤ 16 and MIC > 16) were compared using the Fisher's exact test for categorical variables. Continuous variables are presented as the mean ± standard deviation and compared using Student's t-test. Statistical significance was set at $p < 0.05$. A multivariate analysis was performed for all variables that were statistically significant in the univariate analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) and *p*-values were calculated. All statistical analyses were performed using SPSS version 20 (IBM Corp., Armonk, NY, USA).

## Results

During the study period, 201 patients with *K. pneumoniae* bacteremia were enrolled based on the patient selection criteria (Fig. 1). The patient demographic data were presented in Table 1. The majority of patients were male. The most prevalent comorbidities included diabetes mellitus, impaired liver function, and impaired renal function. The primary cause of bacteremia was intra-abdominal infection, followed by primary bacteremia, respiratory tract infection, and urinary tract infections. Antimicrobial susceptibility results for *K. pneumoniae* are detailed in Table 2.

The MIC of CPZ alone and the 1:1 combination of CPZ/SUL against *K. pneumoniae* are shown in Table 3. The MIC ranges and $MIC_{50}$ values for CPZ and CPZ/SUL were similar. However, the $MIC_{90}$ values were lower for CPZ/SUL ($MIC_{90}$: 32 ug/ml) than for CPZ ($MIC_{90}$: >64 ug/ml) alone. Among the 201 isolates, 180 (89.55%) were susceptible, six (2.99%) were intermediate, and 15 (7.46%) were resistant to CPZ/SUL. For isolates that were not susceptible to CPZ, the addition of SUL restored the susceptibility rate from 0 to 53.33% and reduced the resistance rate from 82.22 to 33.33% (Table 3). Distribution of the cefoperazone/sulbactam MIC values among those *K. pneumoniae* isolates were showed in Fig. 2. Most of those *K. pneumoniae* isolates in this study exhibited MIC values of less than 8 µg/ml (< 8 µg/ml, $n = 157$, 78.11%) (Fig. 2).

Outcome evaluations revealed that 77.61% exhibited favorable outcomes (cure and improvement) and 22.39% showed unfavorable outcomes (death and lack of treatment efficacy). (Table 1). The clinical outcomes correlated with CPZ/SUL MIC values were showed in Fig. 2. As the MIC value increased, the rate of favorable outcomes decreased, and the 30-days mortality rate increased.

Comparing the patient characteristics and outcomes in causative *K. pneumoniae* isolates with CPZ/SUL MIC ≤ 16 µg/ml and > 16 µg/ml in Table 1, we observed

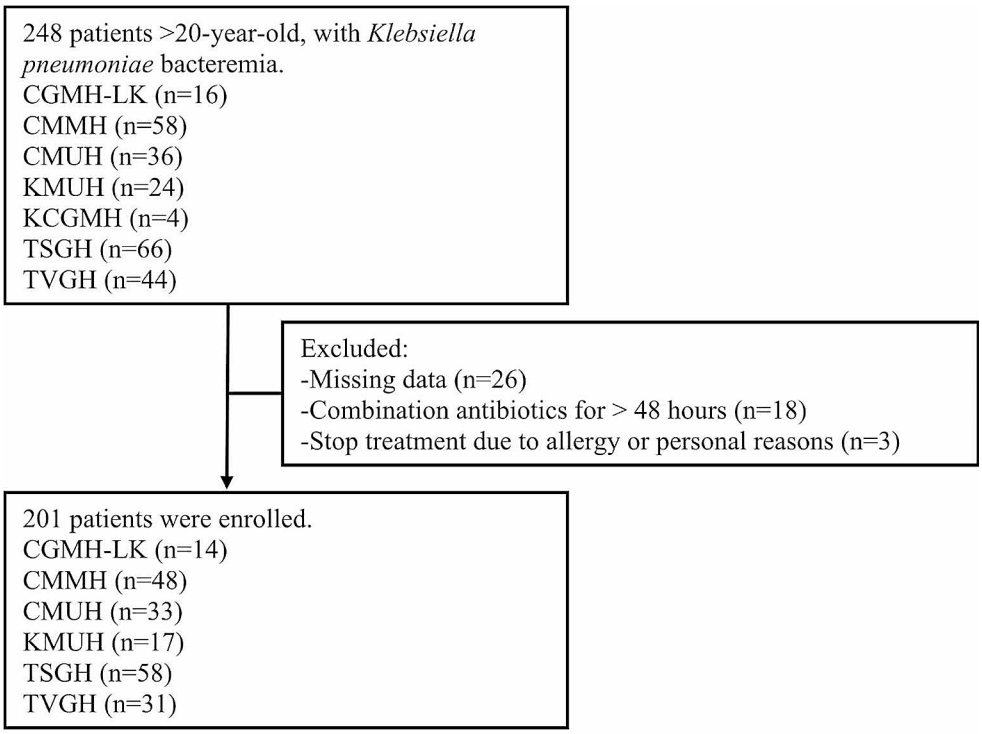


**Fig. 1** Methodology for application of exclusion criteria. CPZ/SUL, cefoperazone/sulbactam; CGMH-LK, Chang Gung Memorial Hospital; CMMH, Chi Mei Medical Hospital; CMUH, China Medical University Hospital; KCGMH, Kaohsiung Chang Gung Memorial Hospital; KMUH, Kaohsiung Medical University Hospital; TSGH Tri-Service General Hospital; TVGH Taipei Veterans General Hospital; TCTVGH, Taichung Veterans General Hospital

**Table 1** Demographic and clinical characteristics of patients with *Klebsiella pneumoniae* bacteremia receiving cefoperazone/sulbactam treatment.*

| | | All | Agar dilution (1:1) MIC | | *p* value |
|---|---|---|---|---|---|
| | | | MIC ≤ 16 | MIC > 16 | |
| Number | | 201 | 180 | 21 | |
| Sex | Male | 124 (61.69) | 111 (61.67) | 13 (61.90) | 0.99 |
| | Female | 77 (38.31) | 69 (38.33) | 8 (38.10) | |
| Age (Mean ± SD) | | 68.78 ± 14.86 | 68.39 ± 15.49 | 72.14 ± 6.57 | 0.06 |
| APACHE II score (Mean ± SD) | | 13.98 ± 6.94 | 13.42 ± 6.88 | 18.76 ± 5.80 | 0.001 |
| Charlson Comorbidity score > 3 | | 156 (77.61) | 137 (76.11) | 19 (90.48) | 0.17 |
| Comorbidities | | | | | |
| Liver function impairment | | 61 (30.35) | 56 (31.11) | 5 (23.81) | 0.62 |
| Renal function impairment | | 41 (20.40) | 31 (17.22) | 10 (47.62) | 0.003 |
| Heart failure | | 15 (7.46) | 15 (8.33) | 0 (0.00) | 0.38 |
| Diabetes mellitus | | 77 (38.31) | 65 (36.11) | 12 (57.14) | 0.10 |
| Neutropenia | | 8 (3.98) | 8 (4.44) | 0 (0.00) | 0.99 |
| Immunosuppressant therapy** | | 14 (6.97) | 10 (5.56) | 4 (19.05) | 0.04 |
| Metastatic tumor | | 35 (17.41) | 33 (18.33) | 2 (9.52) | 0.54 |
| Infection sources | | | | | 0.48 |
| Respiratory tract | | 33 (16.42) | 27 (15.00) | 6 (28.57) | |
| Urinary tract | | 28 (13.93) | 25 (13.89) | 3 (14.29) | |
| Intra-abdomen | | 65 (32.34) | 60 (33.33) | 5 (23.81) | |
| Primary bacteremia | | 64 (31.84) | 57 (31.67) | 7 (33.33) | |
| Others*** | | 11 (5.47) | 11 (6.11) | 0 (0.00) | |
| Outcomes | | | | | 0.001 |
| Favorable | | 156 (77.61) | 146 (81.11) | 10 (47.62) | |
| Cure | | 62 (30.84) | 59 (32.78) | 3 (14.29) | |
| Improvement | | 94 (46.77) | 87 (48.33) | 7 (33.33) | |
| Unfavorable | | 45 (22.39) | 34 (18.89) | 11 (52.38) | |
| Lack of efficacy**** | | 21 (10.45) | 16 (8.89) | 5 (23.81) | |
| Death | | 24 (11.94) | 18 (10.00) | 6 (28.57) | |

MIC, mimimal inhibitory concentration

* Data are n (%) unless otherwise stated

** Immunosuppressant therapy: patients receiving prednisolone for at least10mg per day (or equivalent potency agents) from 2 days before bacteremia onset till 30 days post the event

*** Others, other infection sources, six cases of catheter-related blood stream infection (CRBSI) and five cases of soft tissue or wound infection

**** Lack of efficacy was defined as clinical progression or persistent bacteremia at the end of CPZ/SUL treatment

**Table 2** The antimicrobial susceptibilities of 201 *Klebsiella pneumoniae* isolates

| Antimicrobial agents | Susceptibility (*n*/*N*) % | | |
|---|---|---|---|
| | S | I | *R* |
| Amikacin | 95.02 | 1.49 | 3.48 |
| Gentamicin | 76.12 | 5.97 | 17.91 |
| Ampicillin | 0.00 | 0.00 | 100.00 |
| Piperacillin/Tazobactam | 74.63 | 7.46 | 17.91 |
| Cefazolin | 34.33 | 27.36 | 38.31 |
| Ceftriaxone | 68.66 | 0.99 | 30.35 |
| Ceftazidime | 65.67 | 4.48 | 29.85 |
| Cefepime | 83.08 | 1.00 | 15.92 |
| Ciprofloxacin | 67.66 | 6.47 | 25.87 |
| Levofloxacin | 73.13 | 3.48 | 23.38 |
| Imipenem | 90.05 | 1.99 | 7.96 |
| Ertapenem | 90.05 | 2.99 | 6.96 |
| Tigecycline | 89.55 | 5.97 | 4.48 |
| Trimethoprim/sulfamethoxazole | 58.71 | 0.00 | 41.29 |

that unfavorable outcomes were more frequent in those with MIC > 16 μg/ml than those with MIC ≤ 16 μg/ml. Those infected by isolates with MIC > 16 μg/ml had a higher APACHE II scores and higher prevalence of impaired renal function. There were no significant differences in sex, age, or source of infection between the two groups.

Logistic regression analysis of the prognostic factors for unfavorable outcomes was shown in Table 4. Comparing the two groups, patients with higher APACHE II score (mean ± standard deviation, 12.74 ± 6.35 vs. 18.27 ± 7.18 points; $p < 0.001$), metastatic tumors ($n = 19$, 12.18% vs. $n = 16$, 35.56%; $p < 0.001$), and infection by *K. pneumoniae* isolates with CPZ/SUL MIC > 16 μg/ml ($n = 10$, 6.41% vs. $n = 11$, 24.44%; $p = 0.001$) were associated with a higher risk of unfavorable outcomes in univariate analysis. In multivariate analysis, patients with a higher APACHE II score (OR, 1.14; 95% CI, 1.07–1.21; $p < 0.001$), metastatic tumors (OR, 5.76; CI, 2.31–14.40; $p < 0.001$), and infection by *K. pneumoniae* isolates with CPZ/SUL MIC > 16 μg/ml (OR, 4.30; CI, 1.50–12.27; $p = 0.006$) were independently associated with unfavorable outcomes.

## Discussion

This is the first multicenter study to investigate the effects of CPZ/SUL therapy in patients with *K. pneumoniae* bacteremia and to provide reference clinical breakpoints and prognostic factors for outcomes. The correlation analysis of

**Table 3** The minimal inhibitory concentrations and the susceptibilities of cefoperazone alone and in combination with sulbactam (1:1) against *Klebsiella pneumoniae* isolates

| *K. pneumoniae* ($n=201$) | MIC (ug/ml) | | | Susceptibility [%($n$)][a] | | |
|---|---|---|---|---|---|---|
| | $MIC_{50}$ | $MIC_{90}$ | MIC range | S | I | *R* |
| CPZ | 0.25 | > 64 | 0.0625 ~ > 64 | 77.61% (156) | 3.98% (8) | 18.41% (37) |
| CPZ/SUL | 0.25 | 32 | 0.0625 ~ > 64 | 89.55% (180) | 2.99% (6) | 7.46% (15) |
| CPZnS K. pneumoniae ($n=45$) | MIC (ug/ml) | | | Susceptibility [%($n$)][a] | | |
| | $MIC_{50}$ | $MIC_{90}$ | MIC range | S | I | *R* |
| CPZ | > 64 | > 64 | 32 ~ > 64 | 0.00% (0) | 17.78% (8) | 82.22% (37) |
| CPZ/SUL | 16 | > 64 | 2 ~ > 64 | 53.33% (24) | 13.33% (6) | 33.33% (15) |

[a]The susceptibility breakpoints were adapted from Clinical and Laboratory Standards Institute 2019 for cefoperzaone against *Enterobacterales*: S, MIC ≤ 16 mg/L; I, MIC = 32 mg/L; R, MIC ≥ 64 mg

CPZnS, cefoperazone-non-susceptible; CPZ, cefoperazone; SUL, sulbactam; CPZ/SUL, cefoperazone/sulbactam; MIC, minimal inhibitory concentration

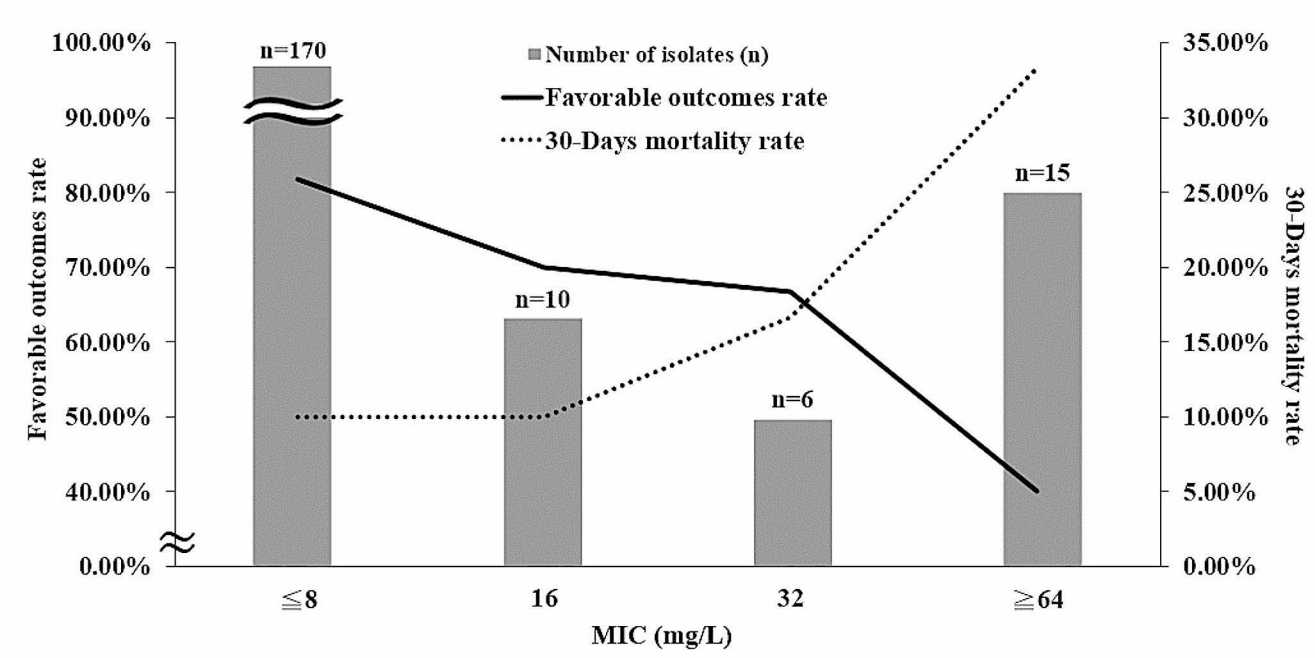


**Fig. 2** Distribution of the cefoperazone/sulbactam minimum inhibitory concentration (MIC) values and clinical outcomes correlated with cefoperazone/sulbactam minimum MIC values among the 201 *Klebsiella pneumoniae* isolates

the MIC values of CPZ/SUL against *K. pneumoniae* with the clinical outcomes revealed that most patients (81.1%) infected by isolates with MIC ≤ 16 μg/ml had favorable outcomes. MIC values > 16 μg/ml were independently associated with unfavorable outcomes. In addition, higher APACHE II scores and metastatic tumors were associated with unfavorable outcomes in patients with *K. pneumoniae* bacteremia.

The major mechanism underlying third-generation cephalosporin resistance in *K. pneumoniae* in Taiwan and worldwide is the presence of ESBL genes [34, 35]. The consumption of carbapenems has increased, which has promoted the spread of carbapenem-resistant *K. pneumoniae* [36, 37]. Therefore, CPZ/SUL may offer a valuable carbapenem-sparing alternative for effectively covering ESBL producers, which is important in antimicrobial stewardship [27]. However, in areas where the prevalence of carbapenem resistance is significant, the empirical use of CPZ/SUL should be approached with caution [38, 39].

The addition of SUL effectively restored the efficacy of CPZ from 77.6 to 89.6%. Even in isolates that were not susceptible to CPZ, the addition of SUL to CPZ restored antimicrobial susceptibility from 0 to 53% in the current study (Table 3). In most previous studies, the ratio of CPZ to SUL was 2:1 [40–43]. Recent studies have established that CPZ/SUL ratio of 2:1 and 1:1 significantly increased the efficacy against ESBL strains and MDR GNB compared with CPZ alone [25]. Moreover, CPZ/SUL at a 1:1 ratio produced better activity against MDR GNB than that at a 2:1 ratio [26].

**Table 4** Univariate and multivariate logistic analyses of factors associated with unfavorable outcomes in patients with *Klebsiella pneumoniae* bacteremia.*

| | | Univariant analysis | | | | Multivariant analysis | |
|---|---|---|---|---|---|---|---|
| | | Favorable outcomes | unfavorable outcomes | OR (95%CI) | *p* value | OR (95%CI) | *p* value |
| Number | | 156 | 45 | | | | |
| Sex | Male (n, %) | 96 (61.54) | 28 (62.22) | 1.03 (0.52–2.04) | 0.93 | 0.81 (0.35–1.90) | 0.63 |
| | Female (n, %) | 60 (38.46) | 17 (37.78) | | | | |
| Age (Mean ± SD) | | 68.52 ± 15.48 | 69.69 ± 15.00 | 1.01 (0.98–1.03) | 0.64 | 0.99 (0.95–1.02) | 0.45 |
| APACHE II score (Mean ± SD) | | 12.74 ± 6.35 | 18.27 ± 7.18 | 1.12 (1.07–1.18) | **< 0.001** | 1.14 (1.07–1.21) | **0.002** |
| Charlson Co-morbidities score > 3 (n, %) | | 117 (75.00) | 39 (86.67) | 2.17 (0.85–5.51) | 0.10 | 1.02 (0.83–1.02) | 0.83 |
| Co-morbidities (n, %) | | | | | | | |
| Liver function impairment | | 45 (28.85) | 16 (35.56) | 1.36 (0.68–2.75) | 0.39 | | |
| Renal function impairment | | 33 (21.15) | 8 (17.78) | 0.81 (0.34–1.90) | 0.62 | | |
| Heart failure | | 12 (7.69) | 3 (6.67) | 0.86 (0.23–3.18) | 0.82 | | |
| Diabetes mellitus | | 55 (35.26) | 22 (48.89) | 1.76 (0.90–3.43) | 0.10 | | |
| Neutropenia | | 7 (4.49) | 1 (2.22) | 0.49 (0.06–4.04) | 0.50 | | |
| Immunosuppressant therapy** | | 12 (7.69) | 2 (4.44) | 0.56 (0.12–2.59) | 0.46 | | |
| Metastatic tumor | | 19 (12.18) | 16 (35.56) | 3.98 (1.83–8.65) | **< 0.001** | 5.15 (1.10-24.06) | **0.03** |
| Infection sources (n, %) | | | | | | | |
| Respiratory tract | | 18 (11.54) | 15 (33.33) | 2.98 (1.20–7.36) | 0.02 | 1.67 (0.58–4.81) | 0.34 |
| Urinary tract | | 23 (14.74) | 5 (11.11) | 0.78 (0.25–2.41) | 0.78 | 0.61 (0.17–2.18) | 0.45 |
| Intra-abdomen | | 58 (37.18) | 7 (15.56) | 0.43 (0.16–1.15) | 0.09 | 0.40 (0.13–1.23) | 0.11 |
| Primary bacteremia (Ref.) | | 50 (32.05) | 14 (31.11) | 1 | - | 1 | - |
| Others*** | | 7 (4.49) | 4 (8.89) | 2.04 (0.52–7.98) | 0.31 | 2.63 (0.54–12.83) | 0.23 |
| MIC > 16 ug/ml | | 10 (6.41) | 11 (24.44) | 4.72 (1.86–12.02) | **0.001** | 4.37 (1.49–12.83) | **0.007** |

MIC, minimal inhibitory concentration

* Data are n (%) unless otherwise stated

** Immunosuppressant therapy: patients receiving prednisolone for at least10mg per day (or equivalent potency agents) from 2 days before bacteremia onset till 30 days post the event

*** Others, other sources, included six cases of catheter-related blood stream infection (CRBSI) and five cases of soft tissue or wound infection

To date, no CLSI clinical breakpoints have been reported for CPZ/SUL in *K. pneumoniae*. The CLSI CPZ breakpoints for *Enterobacterales* (MIC ≤ 16 μg/ml, susceptible; MIC = 32 μg/ml, intermediate; MIC ≥ 64 μg/ml, resistant) [23] are often used to interpret susceptibility results for CPZ/SUL. Despite the emergence of resistance, CPZ/SUL maintains good antimicrobial efficacy. A large-scale study in China from 2010 to 2018 reported susceptibility rates of *K. pneumoniae* to CPZ/SUL (2:1) ranging from 72.1 to 76.9% [44]. In the current study, the susceptibility was even higher (89.6%) when using the 1:1 CPZ: SUL combination. CPZ/SUL MIC > 16 μg/ml was associated with unfavorable outcomes, indicating that patients with bacteremia who were infected with *K. pneumoniae* isolates with MIC > 16 μg/ml should not be treated with CPZ/SUL. In contrast, most patients with CPZ/SUL MIC ≤ 16 μg/ml exhibited favorable outcomes (81.1%), indicating the efficacy of treatment with 1:1 CPZ/SUL.

In the current study, we observed that the APACHE score and the presence of metastatic tumors were significant risk factors for unfavorable outcomes. These findings were consistent with prior investigations on *K. pneumoniae* bacteremia [45, 46]. Therefore, judicious antimicrobial treatment is crucial for patients with such risk factors. When the MICs ≤ 16 μg/ml, CPZ/SUL could be confidently used to treat *K. pneumoniae* bacteremia. It is also important to follow the results of antimicrobial susceptibilities and following antimicrobial stewardship principles.

This study had some limitations. The major limitations are its retrospective design with potential intrinsic selection bias, and the fact that the detailed treatment course cannot be controlled. Further randomized controlled studies are required to confirm these findings. The strengths of this study include the inclusion of a relatively large number of patients from multiple medical centers located in representative regions of Taiwan using stringent inclusion criteria. Our findings provide clinicians with useful information regarding the outcomes and risk factors of patients with *K. pneumoniae* bacteremia treated with CPZ/SUL.

## Conclusion

Patients with *K. pneumoniae* bacteremia treated with CPZ/SUL at a ratio of 1:1 had a favorable outcome when the CPZ/SUL MICs were ≤16 μg/ml. Higher APACHE II scores and metastatic tumors were associated with unfavorable outcomes.

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**Data availability** No datasets were generated or analysed during the current study.

## Declarations

**Ethical approval** The study was approved by the Institutional Review Board of the Tri-Service General Hospital (TSGH IRB No. 1-106-05-116) and the institutional review boards of all other participating hospitals.

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



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