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ORIGINAL RESEARCH

Clinical Characteristics, Prognosis and Treatment of Bloodstream Infections with *Enterobacter Cloacae* Complex in a Chinese Tertiary Hospital: A Retrospective Study

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Objective: This research aimed to analyze the clinical characteristics, prognosis, and antimicrobial treatment of bloodstream infections (BSI) caused by *Enterobacter cloacae* complex (ECC).

Methods: The clinical data of patients with bloodstream infections caused by *Enterobacter cloacae* complex from April 2017 to June 2023 were collected retrospectively. These data were then analyzed in subgroups based on the detection results of extended-spectrum β-lactamase (ESBL), 30-day mortality, and the type of antimicrobial agent used (β-lactam/β-lactamase inhibitor combinations (BLICs) or carbapenems).

Results: The proportion of ESBL-producing *Enterobacter cloacae* complex was 32.5% (37/114). Meanwhile, ICU admission, receiving surgical treatment within 3 months, and biliary tract infection were identified as risk factors for ESBL-producing ECC-BSI. Additionally, immunocompromised status and Sequential Organ Failure Assessment (SOFA) score ≥ 6.0 were identified as independent risk factors of 30-day mortality in patients with ECC-BSI (n = 108). Further analysis in BSI patients caused by non-ESBL-producing ECC revealed that patients treated with BLICs (n = 45) had lower SOFA scores and lower incidence of hypoproteinemia and sepsis compared with patients treated with carbapenems (n = 20). Moreover, in non-ESBL-producing ECC-BSI patients, the univariate Cox regression analysis indicated a significantly lower 30-day mortality rate in patients treated with BLICs compared to those treated with carbapenems (hazard ratios (HR) [95% CI] 0.190 [0.055–0.662], $P = 0.009$; adjusted HR [95% CI] 0.106 [0.013–0.863], $P = 0.036$).

Conclusion: This study investigated the factors influencing the susceptibility to infection by ESBL-producing strains and risk factors for 30-day mortality in ECC-BSI patients. The results revealed that ESBL-negative ECC-BSI patients treated with BLICs exhibited significantly lower 30-day mortality compared to those treated with carbapenems. BLICs were found to be more effective in ECC-BSI patients with milder disease (ESBL-negative and SOFA ≤6.0).

Keywords: *Enterobacter cloacae* complex, extended-spectrum β-lactamase, bloodstream infection, risk factors, β-lactam/β- lactamase inhibitor combinations, carbapenems

Introduction

Enterobacter cloacae (*E. cloacae*) complex (ECC), mainly including *Enterobacter cloacae*, *Enterobacter asburiae*, *Enterobacter hormaechei*, *Enterobacter kobei*, *Enterobacter ludwigii*, and *Enterobacter nimipressuralis*, is an important

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group of opportunistic pathogens.[1] These may cause hospital-acquired infections such as pneumonia, urinary tract infection, intraabdominal infection, and bloodstream infections (BSI).[2–5] Research indicated that the *E. cloacae* complex is widely distributed in both the natural environment and the human gastrointestinal tract. Meanwhile, *E. cloacae* complex ranks as the third most commonly isolated bacterium within the *Enterobacterales* family, following *Escherichia coli* and *Klebsiella pneumoniae*, particularly in the context of nosocomial infection.[1,3] Moreover, *E. cloacae* complex bloodstream infections (ECC-BSI) commonly occur in hospitalized and debilitated patients, resulting in crude mortality rates ranging from 15.1% to 33.3%.[6–10] Consequently, ECC-BSI has emerged as a significant menace to global public health.

In recent years, the escalating and indiscriminate use of extended-spectrum antibiotics has resulted in a rise in the resistance rate of *E. cloacae* complex to β-lactam antibiotics. Subsequently, extended-spectrum β-lactamase (ESBL) and carbapenem-resistant (CR) strains have rapidly developed. Specifically, the drug resistance mechanism of the *E. cloacae* complex primarily involves the production of diverse drug-resistant enzymes, such as ESBLs, carbapenemases, and AmpC enzymes, leading to drug inactivation through hydrolysis. Resistance in these bacteria is also mediated by high expression of bacterial efflux pumps, decreased expression or loss of membrane pore proteins ompF and ompC, and alteration of drug binding sites.[1,11,12] Notably, ESBL-producing *Enterobacterales* were classified as one of the most significant pathogens in the World Health Organization's list of priority pathogens.[13,14] A nationwide survey conducted in China revealed that the prevalence of ESBL-producing *Enterobacterales* was as high as 40.6%.[14]

Surveillance data collected on a global scale indicated that the prevalence of extended-spectrum β-lactamase-producing *E. cloacae* complex (ESBL producing-ECC) infection has reached alarming levels, with rates as high as 28.6% in Asia[15] and 47.6% in Africa[16] over the past decade. The resistance of ECC to β-lactam antibiotics poses a significant challenge to clinical anti-infective treatment. Additionally, ECC negatively impacts patient safety and prognosis, while also imposing a substantial economic burden on both society and individuals. However, the risk factors and outcomes associated with ESBL-producing ECC bloodstream infections remain uncertain.

Therefore, this study primarily aimed to examine the risk factors associated with bloodstream infections caused by ESBL-producing ECC. In parallel, the risk factors contributing to 30-day mortality in ECC-BSI patients were explored. Furthermore, the efficacy of β-lactam/β-lactamase inhibitor combinations (BLICs) and carbapenem antibiotics in treating ECC-BSI was assessed based on the specific antimicrobial drug types. The ultimate goal of this research was to provide a reference for the clinical diagnosis, treatment, and judicious use of antibiotics in ECC-BSI patients.

Materials and Methods

Study Design and Setting

This retrospective study was conducted at the Second Affiliated Hospital of Nanchang University, a tertiary university hospital in Jiangxi Province, China, from April 2017 to June 2023. The study excluded pregnant women, individuals with missing key data, patients who died within 48 hours after ECC-BSI onset, individuals under 18 years of age, and patients with polymicrobial bacteremia. The analysis only included the initial episode of ECC-BSI for each patient. Moreover, to investigate antibiotic treatment strategies for ECC-BSI, this study included adult patients (age ≥ 18) who were diagnosed with ECC-BSI and received active carbapenems (carbapenem treatment regimen, CTG) or β-lactam/β-lactamase inhibitor combinations (Cefoperazone/sulbactam or Piperacillin/tazobactam, BLICs treatment regimen, BTG) for at least 50% of the total duration of therapy (Figure 1).

Data Collection

All data were collected from the laboratory information system (LIS) and hospital information system (HIS) of our hospital, including the demographic characteristics, the season of onset, inpatient department information, antimicrobial agent history, microbiological data, invasive procedures, potential diseases and complications, antibiotic usage, disease severity, antimicrobial therapy data, and clinical outcomes. To evaluate the severity of the condition, the age-adjusted Charlson Comorbidity Index (aCCI), Pitt bacteremia score, and Sequential Organ Failure Assessment (SOFA) score were calculated at the onset of bloodstream infections (BSI).

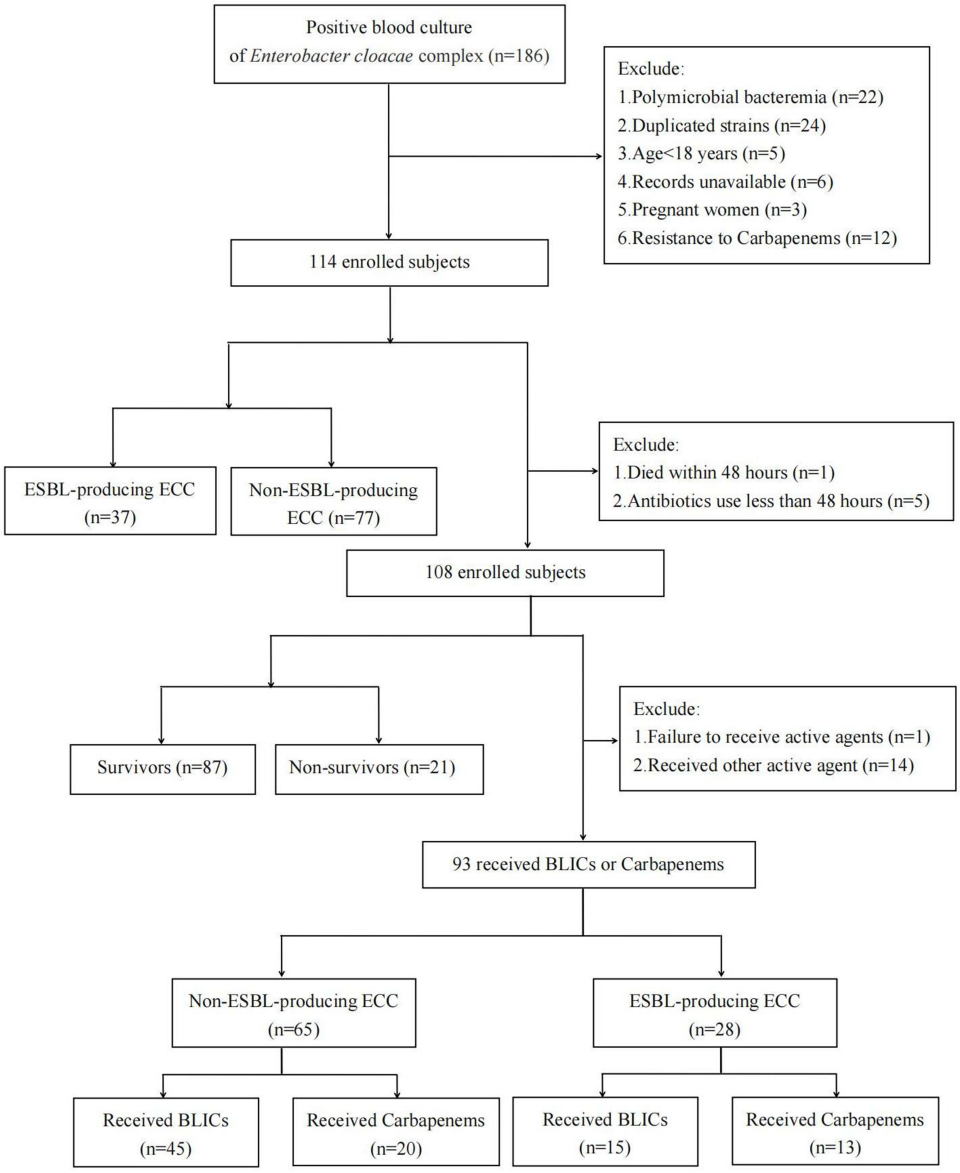

Figure 1 Case identification flow chart.

Definitions and Outcomes

Bloodstream infection (BSI) was defined by the presence of positive blood cultures in a patient exhibiting signs of systemic infection. BSI was classified as either secondary to a known source or primary in nature (without identified origin).[17] Cases in which the initial culture-positive sample was procured more than 48 hours after admission to the hospital or within 48 hours after discharge were classified as nosocomial infections. Other patients were categorized as community-acquired infections.[18] Patients were considered to be immunocompromised status if they met any of the following criteria: post-transplant status, chronic glucocorticoid administration, cancer chemotherapy, disease-modifying drug use, or biological immune modulator use.[19] Treatment failure was defined as the occurrence of infection, recurrence, or progression of disease following a period of two weeks of antimicrobial therapy.[20] The primary outcome was 30-day mortality, and the secondary outcome was 14-day treatment failure.

Microbiological Analysis

E. cloacae complex isolates were identified using the VITEK 2 Compact system (bioMérieux, France) or MALDI-TOF MS (bioMérieux, France). The VITEK-2 Compact AST-GN16 (bioMérieux) or Kirby-Bauer test was employed to determine

in vitro antimicrobial susceptibilities. Drug sensitivities were interpreted based on the standards set by the Clinical and Laboratory Standards Institute (CLSI, 2017–2023). Subsequently, *E. cloacae* complex isolates that exhibited resistance to one or more third-generation cephalosporins were screened for ESBL production using the combination disc-diffusion test (CDDT) in accordance with CLSI criteria, utilizing cefotaxime and ceftazidime alone or in combination with clavulanic acid.

Statistical Analysis

The data analysis was conducted using SPSS v26.0 (SPSS Inc.). The normally distributed data were presented as mean ± standard deviation (SD), while continuous data not conforming to a normal distribution were expressed as median and interquartile range (IQR). Categorical variables were represented by accumulated frequencies and percentages. To compare groups, the Mann–Whitney *U*-test or Student's *t*-test was used for continuous variables, while the chi-square test or Fisher's exact test was employed for categorical variables. In addition, logistic regression analysis was performed to determine the independent risk factors for ESBL-producing ECC bloodstream infection and to assess risk factors for 30-day mortality in patients with ECC-BSI. The comparative effectiveness of BLICs and carbapenem treatment was evaluated through propensity score matching (PSM) using 1:1 nearest-neighbor matching without replacement, with a caliper length of 0.2, and Cox regression analysis. All statistical *P*-values were two-tailed, and those < 0.05 were considered statistically significant.

Results

Demographic and Clinical Characteristics of Patients with Bloodstream Infections Caused by *E. cloacae* Complex

This study included a cohort of 186 patients diagnosed with bloodstream infections caused by the *E. cloacae* complex (ECC-BSI). Following the exclusion of 72 cases, a total of 114 patients with ECC-BSI were included in the analysis (Figure 1). These 114 patients had an average age of 60.5 ± 14.4 years, with males accounting for 68.4% (78/114) of the total patient population. The incidence of nosocomial infection was found to be 70.2% (80/114), with approximately half of the cases (49.1%, 56/114) occurring in summer. The majority of patients presented with malignant tumors (35.1%, 40/114), followed by immunocompromised status (34.2%, 39/114), and hypertension (29.8%, 34/114). Within three months, a notable proportion of individuals (39.5%, 45/114) underwent surgical procedures. Meanwhile, the majority of patients (54.4%, 62/114) received antibiotic treatment with BLICs (Cefoperazone/sulbactam or Piperacillin/tazobactam). Furthermore, the detection rate of ESBL-producing *E. cloacae* complex was 32.5% (Table 1).

Subsequently, the 114 patients were divided into the ESBL-positive (n = 37) and ESBL-negative (n = 77) groups based on the detection results of ESBL enzymes. Table 1 describes the different features of the two groups. Patients in the ESBL-positive group exhibited a higher ratio of admission to the ICU, mechanical ventilation, central venous catheterization, urinary catheterization, and history of surgery within 3 months compared to those in the ESBL-negative group. Additionally, they displayed a higher proportion of immunocompromised status, hypoproteinemia, biliary tract infection, and 30-day mortality, while showing a lower rate of admission to the internal medicine department (all $P < 0.05$).

Moreover, as shown in Table 2, the outcomes of the antimicrobial susceptibility tests revealed that all clinical isolates (n = 114) were sensitive to carbapenems. Subsequently, ECC strains displayed a higher susceptibility towards tigecycline, followed by aminoglycosides and β-lactam/β-lactamase inhibitor combinations (BLICs). Upon comparing the antimicrobial susceptibility profiles, notable differences were observed in quinolones, cephalosporins, aztreonam, cotrimoxazole, and BLICs (Cefoperazone/sulbactam and Piperacillin/tazobactam) between the ESBL-positive ECC and ESBL-negative ECC groups (all $P < 0.05$). Notably, among the aforementioned drugs, quinolones, aztreonam and cephalosporins (all showing an incidence of antibiotic resistance exceeding 50%) exhibited a higher proportion of resistance within the ESBL-positive ECC group.

Risk Factors of Bloodstream Infections Caused by ESBL-Producing *E. Cloacae* Complex

A logistic regression analysis was performed to further determine the risk factors associated with ESBL-producing ECC-BSI. Univariate logistic regression analysis revealed significant associations between ESBL-producing ECC-BSI and

Table 1 Demographic and Clinical Characteristics of Patients with ESBL-Positive and ESBL-Negative *E. cloacae* Complex

Characteristics	Overall (n=114)	ESBL Positive (n=37)	ESBL Negative (n=77)	OR (95% CI)	*P* value
Univariate analysis, N (%)					
Age (years), mean±SD	60.5±14.4	62.6±13.8	59.5±14.7	1.015 (0.987–1.044)	0.286
Sex, N (%)					
Male	78 (68.4%)	28 (75.7%)	50 (64.9%)	1.680 (0.693–4.070)	0.248
Female	36 (31.6%)	9 (24.3%)	27 (35.1%)	–	–
Inpatient department, N (%)					
ICU	26 (22.8%)	15 (40.5%)	11 (14.2%)	4.091 (1.638–10.219)	0.002
Internal Medicine	40 (35.1%)	7 (18.9%)	33 (42.9%)	0.311 (0.122–0.795)	0.012
Surgery Ward	48 (42.1%)	15 (40.5%)	33 (42.9%)	0.909 (0.410–2.016)	0.815
Acquisition, N (%)					
Hospital-acquired	80 (70.2%)	25 (67.6%)	55 (71.4%)	0.833 (0.357–1.945)	0.673
Community-associated	34 (29.8%)	12 (32.4%)	22 (28.6%)	–	–
Season of onset, N (%)					
Winter	9 (7.9%)	4 (10.8%)	5 (6.5%)	1.745 (0.440–6.923)	0.668
Summer	56 (49.1%)	16 (43.2%)	40 (51.9%)	0.705 (0.320–1.552)	0.384
Invasive procedures, N (%)					
Mechanical ventilation	55 (48.2%)	23 (62.2%)	32 (41.6%))	2.310 (1.034–5.164)	0.039
Central venous catheterization	37 (32.5%)	19 (51.4%)	18 (23.4%)	3.460 (1.504–7.960)	0.003
Gastrointestinal catheterization	25 (21.9%)	11 (29.7%)	14 (18.2%)	1.904 (0.765–4.741)	0.163
Urinary catheterization	61 (53.5%)	26 (70.3%)	35 (45.5%)	2.836 (1.230–6.541)	0.013
Indwelling drainage tube	32 (28.1%)	14 (37.8%)	18 (23.4%)	1.995 (0.854–4.661)	0.108
Surgery within 3 months	45 (39.5%)	22 (59.5%)	23 (29.9%)	3.443 (1.520–7.802)	0.003
Underlying disease, N (%)					
Malignant tumors	40 (35.1%)	17 (45.9%)	23 (29.9%)	1.996 (0.888–4.486)	0.092
Immunocompromised status	39 (34.2%)	18 (48.6%)	21 (27.3%)	2.526 (1.116–5.718)	0.024
Hypertension	34 (29.8%)	8 (21.6%)	26 (33.8%)	0.541 (0.217–1.350)	0.185
Hypoproteinemia	31 (27.2%)	15 (40.5%)	16 (20.8%)	2.599 (1.104–6.122)	0.026
Diabetes	26 (22.8%)	5 (13.5%)	21 (27.3%)	0.417 (0.143–1.212)	0.101
Biliary tract infection	23 (20.2%)	16 (43.2%)	7 (9.1%)	7.619 (2.766–20.987)	<0.001
Sepsis	30 (26.3%)	12 (32.4%)	18 (23.4%)	1.573 (0.661–3.745)	0.304
History of antimicrobial treatment within 3 months	40 (35.1%)	14 (37.8%)	26 (33.8%)	1.242 (0.548–2.816)	0.604
Empiric therapy, N (%)					
Carbapenems	33 (28.9%)	13 (35.1%)	20 (26.0%)	1.544 (0.663–3.596)	0.313

(*Continued*)

Table 1 (Continued).

Characteristics	Overall (n=114)	ESBL Positive (n=37)	ESBL Negative (n=77)	OR (95% CI)	*P* value
Cephalosporins	13 (11.4%)	6 (16.2%)	7 (9.1%)	1.935 (0.601–6.233)	0.262
Aminoglycosides	2 (1.8%)	1 (2.7%)	1 (1.3%)	2.111 (0.128–34.718)	0.820
Fluoroquinolones	4 (3.5%)	1 (2.7%)	3 (3.9%)	0.685 (0.069–6.820)	0.826
BLICs	62 (54.4%)	16 (43.2%)	46 (59.7%)	0.513 (0.232–1.136)	0.098
Outcomes, N (%)					
14-day treatment failure	33 (28.9%)	13 (35.1%)	20 (26.0%)	1.544 (0.663–3.596)	0.313
30-day mortality	22 (19.3%)	12 (32.4%)	10 (13.0%)	3.216 (1.235–8.371)	0.014
Multivariate analysis					
ICU				4.680 (1.170–18.719)	0.029
Internal Medicine				0.886 (0.233–3.364)	0.858
Mechanical ventilation				0.296 (0.073–1.199)	0.088
Central venous catheterization				2.398 (0.721–7.969)	0.154
Urinary catheterization				1.138 (0.325–3.979)	0.840
Surgery within 3 months				5.565 (1.554–19.925)	0.008
Immunocompromised status				1.046 (0.325–3.367)	0.940
Hypoproteinemia				0.920 (0.288–2.939)	0.888
Biliary tract infection				5.030 (1.336–18.942)	0.017
30-day mortality				1.967 (0.429–9.017)	0.384

Abbreviations: ESBL, extended-spectrum β-lactamase; BLICs, β-lactam/β-lactamase inhibitor combinations; ICU, intensive care unit.

Table 2 Antibiotic Resistance of ESBL-Producing *E. cloacae* Complex versus Non-ESBL-Producing *E. cloacae* Complex

Antibacterial Drugs	Total (n=114)	ESBL-Positive ECC (n=37)	ESBL-Negative ECC (n=77)	*P* value
Amikacin (37 vs 77)*	4 (3.5%)	2 (5.4%)	2 (2.6%)	0.826
Gentamicin (31 vs 51)*	9 (11.0%)	6 (19.4%)	3 (5.9%)	0.056
Tobramycin (35 vs 75)*	9 (8.2%)	5 (14.3%)	4 (5.3%)	0.242
Ciprofloxacin (35 vs 75)*	24 (21.8%)	18 (51.4%)	6 (8.0%)	<0.001
Levofloxacin (37 vs 77)*	29 (25.4%)	20 (54.1%)	9 (11.7%)	<0.001
Aztreonam (37 vs 77)*	43 (37.7%)	36 (97.3%)	7 (9.1%)	<0.001
Ceftriaxone (37 vs 77)*	45 (39.5%)	37 (100%)	8 (10.4%)	<0.001
Ceftazidime (31 vs 60)*	34 (37.4%)	31 (100%)	3 (5.0%)	<0.001
Tigecycline (37 vs 77)*	3 (2.6%)	2 (5.4%)	1 (1.3%)	0.511

(*Continued*)

Table 2 (Continued).

Antibacterial Drugs	Total (n=114)	ESBL-Positive ECC (n=37)	ESBL-Negative ECC (n=77)	*P* value
Cotrimoxazole (37 vs 77)*	17 (14.9%)	10 (27.0%)	7 (9.1%)	0.012
Cefoperazone/sulbactam (26 vs 51)*	8 (10.4%)	6 (23.1%)	2 (3.9%)	0.023
Piperacillin/tazobactam (37 vs 77)*	13 (11.4%)	9 (24.3%)	4 (5.2%)	0.007

Notes: *The figures in parentheses were the total numbers of *E. cloacae* complex used for antimicrobial susceptibility testing in both groups.

various factors, including ICU admission, internal medicine admission, mechanical ventilation, central venous catheterization, urinary catheterization, recent surgery within 3 months, immunocompromised status, hypoproteinemia, and biliary tract infection (Table 1). Confounding variables were adjusted for, and the multivariate logistic regression analysis revealed that ICU admission [$P = 0.029$; odds ratio, OR (95% CI): 4.680 (1.170, 18.719)], surgery within 3 months [$P = 0.008$; OR (95% CI): 5.565 (1.554, 19.925)], and biliary tract infection [$P = 0.017$; OR (95% CI): 5.030 (1.336, 18.942)] were independent risk factors for ESBL-producing ECC-BSI (Table 1).

Risk Factors Associated with 30-Day Mortality in Patients with ECC-BSI

Next, the risk factors for 30-d mortality were analyzed. One patient who died within 48 h and 5 patients who received antibiotics for less than 48 h were excluded (Figure 1). The all-cause mortality rate within 30 days among the remaining patients was 19.4% (21/108). Subsequent analyses revealed that the non-survival group (n = 21) exhibited a higher proportion of ICU admissions, onset during the summer, mechanical ventilation, immunosuppressed status, hypoproteinemia, and carbapenem antibiotics therapy compared to the survival group (n = 87). In contrast, the non-survival group showed a lower proportion of patients who received BLIC (Cefoperazone/sulbactam or Piperacillin/tazobactam) therapy (all $P < 0.05$). Furthermore, regarding the severity of the disease, the Pitt scores and SOFA scores exhibited a statistically significant elevation in the non-survival group compared to the survival group (all $P < 0.05$) (Table 3). In addition, the findings of the multivariate logistic regression analysis revealed a significant association between the immunocompromised status [$P = 0.010$, OR (95% CI): 7.559 (1.622,35.233)], SOFA ≥ 6.0 [$P = 0.045$, OR (95% CI): 4.943 (1.038, 23.538)], and the 30-day mortality in patients with ECC-BSI (Table 3).

Table 3 Analysis of Risk Factors for 30-Day Mortality in Patients with *E. cloacae* Complex Bloodstream Infection

Characteristics	Overall (n=108)	Non-Survivors (n=21)	Survivors (n=87)	OR (95% CI)	*P* value
Univariate analysis, N (%)					
Age (years), mean±SD	60.3±14.5	63.8±13.0	59.5±14.7	1.022 (0.987–1.058)	0.229
Sex, N (%)					
Male	74 (68.5%)	13 (61.9%)	61 (70.1%)	0.693 (0.257–1.870)	0.467
Female	34 (31.5%)	8 (38.1%)	26 (29.9%)	–	–
Inpatient department, N (%)					
ICU	24 (22.2%)	12 (57.1%)	12 (13.8%)	8.333 (2.894–23.993)	<0.001
Internal Medicine	39 (36.1%)	4 (19.1%)	35 (40.2%)	0.350 (0.108–1.127)	0.119
Surgery Ward	45 (41.7%)	5 (23.8%)	40 (46.0%)	0.367 (0.124–1.091)	0.064

(*Continued*)

Table 3 (Continued).

Characteristics	Overall (n=108)	Non-Survivors (n=21)	Survivors (n=87)	OR (95% CI)	*P* value
Acquisition, N (%)					
Hospital-acquired	75 (69.4%)	16 (76.2%)	59 (67.8%)	1.519 (0.505–4.564)	0.455
Community-associated	33 (30.6%)	5 (23.8%)	28 (32.2%)	–	–
Season of onset, N (%)					
Winter	8 (7.4%)	3 (14.3%)	7 (8.0%)	1.905 (0.449–8.087)	0.641
Summer	50 (46.3%)	5 (23.8%)	45 (51.7%)	0.292 (0.098–0.866)	0.021
Invasive procedures, N (%)					
Mechanical ventilation	54 (50.0%)	16 (76.2%)	38 (43.7%)	4.126 (1.387–12.272)	0.008
Central venous catheterization	36 (33.3%)	10 (47.6%)	26 (29.9%)	2.133 (0.807–5.636)	0.122
Gastrointestinal catheterization	25 (23.1%)	8 (38.1%)	17 (19.5%)	2.534 (0.907–7.083)	0.070
Urinary catheterization	61 (56.5%)	15 (71.4%)	46 (52.9%)	2.228 (0.791–6.280)	0.124
Indwelling drainage tube	30 (27.8%)	8 (38.1%)	22 (25.3%)	1.818 (0.666–4.966)	0.240
Surgery within 3 months	45 (41.7%)	8 (38.1%)	37 (42.5%)	0.832 (0.313–2.211)	0.712
Underlying disease, N (%)					
Malignant tumors	40 (37.0%)	10 (47.6%)	30 (34.5%)	1.727 (0.659–4.528)	0.263
Immunocompromised status	37 (34.3%)	17 (81.0%)	20 (23.0%)	14.238 (4.296–47.186)	<0.001
Hypertension	33 (30.6%)	7 (33.3%)	26 (30.0%)	1.173 (0.424–3.243)	0.758
Hypoproteinemia	30 (27.8%)	10 (47.6%)	20 (23.0%)	3.045 (1.130–8.207)	0.024
Diabetes	26 (24.1%)	3 (14.3%)	23 (26.4%)	0.464 (0.125–1.722)	0.376
Biliary tract infection	21 (19.4%)	7 (33.3%)	14 (16.1%)	2.607 (0.892–7.620)	0.073
Sepsis	30 (27.8%)	9 (42.9%)	21 (24.1%)	2.357 (0.872–6.369)	0.086
History of antimicrobial treatment within 3 months	37 (34.3%)	10 (47.6%)	27 (31.0%)	2.020 (0.766–5.326)	0.151
Empiric therapy, N (%)					
Carbapenems	33 (30.6%)	13 (61.9%)	20 (23.0%)	5.444 (1.978–14.983)	0.001
Cephalosporins	9 (8.3%)	0 (0)	9 (10.3%)	1.269 (1.146–1.406)	0.201
Aminoglycosides	1 (0.9%)	0 (0)	1 (1.1%)	1.244 (1.133–1.366)	>0.999
Fluoroquinolones	4 (3.7%)	1 (4.8%)	3 (3.4%)	1.400 (0.138–14.176)	0.721
BLICs	61 (56.5%)	7 (33.3%)	54 (62.1%)	0.306 (0.112–0.835)	0.017
Bacterial type, N (%)					
ESBL-producing *E. cloacae* complex	33 (30.6%)	11 (52.4%)	22 (25.3%)	3.250 (1.216–8.689)	0.016
Severity of condition, median (IQR)					
aCCI score	6 (4, 7)	7 (4.5, 8.5)	6 (4, 7)	1.278 (0.997–1.638)	0.053

(*Continued*)

Table 3 (Continued).

Characteristics	Overall (n=108)	Non-Survivors (n=21)	Survivors (n=87)	OR (95% CI)	*P* value
SOFA score	4 (3, 6)	7 (6, 8)	3 (2, 5)	1.965 (1.468–2.632)	<0.001
Pitt score	3 (2, 4)	4 (3, 4.5)	3 (2, 4)	2.600 (1.533–4.408)	<0.001
Length of hospital stay (IQR)	20 (12.25, 31)	14 (7, 36)	20 (12, 31)	0.998 (0.972–1.024)	0.339
Multivariate analysis					
ICU				2.321 (0.450–11.978)	0.315
Summer				0.359 (0.084–1.536)	0.167
Mechanical ventilation				2.426 (0.505–11.641)	0.268
Immunocompromised status				7.559 (1.622–35.233)	0.010
Hypoproteinemia				0.587 (0.110–3.119)	0.532
Carbapenems				3.783 (0.276–51.931)	0.320
BLICs				1.390 (0.090–21.433)	0.813
SOFA score ≥ 6				4.943 (1.038–23.538)	0.045
Pitt score				1.611 (0.344–7.543)	0.545
ESBL-producing *E. cloacae* complex				1.591 (0.373–6.781)	0.530

Abbreviations: aCCI, age-adjusted Charlson Comorbidity Index; SOFA, Sequential Organ Failure Assessment; Pitt score, Pitt bacteremia score.

The Effect of Antimicrobial Regimens on 14-Day Treatment Failure and 30-Day Mortality in Patients with ECC-BSI

Among the participants, 1 patient was excluded due to failing to receive the required active agents, and 14 patients were excluded for receiving other active agents. The efficacy of the two antibiotic (BLICs or Carbapenems) regimens was further assessed in the remaining 93 patients with ECC-BSI (Figure 1). Next, the ESBL-positive (n = 65) and the ESBL-negative group (n = 28) were divided into 2 subgroups, namely the carbapenem treatment regimen group and the BLIC treatment regimen group.

As shown in Table 4, among patients with ESBL-negative ECC-BSI, patients who received a carbapenem treatment regimen (CTG, n = 20) were compared with those who received a BLIC treatment regimen (BTG, n = 45). The BTG group exhibited a lower SOFA score, as well as a lower incidence of sepsis and hypoproteinemia (all $P < 0.05$). Following propensity score matching (PSM), the 14-day treatment failure rate in the BTG group (23.1%, 3/13) was slightly lower than in the CTG group (53.8%, 7/13). However, these differences showed no statistical significance in the univariate Cox regression analysis ($P = 0.079$) and the multivariate Cox regression analysis ($P = 0.140$). Furthermore, after PSM, the 30-day mortality in the BTG group (7.7%, 1/13) was lower than that in the CTG group (53.8%, 7/13). In the univariate analysis, these rates showed significant differences (HR [95% CI] 0.106 [0.013–0.863], $P = 0.036$), but the multivariate analysis revealed that the difference was not significant (HR [95% CI] 0.064 [0.002–1.983], $P = 0.117$) (Table 5). Notably, within the cohort of 45 patients who underwent treatment with BLICs, the optimal cutoff value for the SOFA score was determined to be 6.0. Subsequent analysis indicated that patients with SOFA score ≤ 6 (n = 40) exhibited a 30-day mortality rate of 2.5%, a statistically significant decrease compared to patients with SOFA scores > 6.0 (n = 5, 2.5% vs 40.0%, $P = 0.029$).

Nonetheless, in patients with ESBL-positive ECC-BSI, no significant difference in 30-day mortality and 14-day treatment failure rates was observed between the BTG (n = 15) and CTG (n = 13) groups before and after PSM (Table 4 and Table 5). This may be attributed to due to the limited sample size.

Table 4 Characteristics of Patients Treated with BLICs or Carbapenems

Variable	Non-ESBL-producing *E. cloacae* complex (n=65)							ESBL-producing *E. cloacae* complex (n=28)						
	Total n=65	Before PSM			After PSM			Total n=28	Before PSM			After PSM		
		BLICs n=45	Carbapenems n=20	*P* value	BLICs n=13	Carbapenems n=13	*P* value		BLICs n=15	Carbapenems n=13	*P* value	BLICs n=8	Carbapenems n=8	*P* value
Age(years), mean±SD	60.7±14.1	61.5±13.2	58.9±16.2	0.495	58.8±14.5	61.2±11.7	0.649	62.4±14.4	61.3±15.8	63.7±13.3	0.675	58.9±17.9	58.4±8.7	0.944
Sex, N (%)														
Male	44 (67.7)	30 (66.7)	14 (70.0)	0.791	9 (69.2)	8 (61.5)	>0.999	21 (75.0)	13 (86.7)	8 (61.5)	0.198	7 (87.5)	6 (75.0)	>0.999
Female	21 (32.3)	15 (33.3)	6 (30.0)		4 (30.8)	5 (38.5)		7 (25.0)	2 (13.3)	5 (38.5)		1 (12.5)	2 (25.0)	
Acquisition, N (%)														
Hospital-acquired	45 (69.2)	32 (71.1)	13 (65.0)	0.622	9 (69.2)	8 (61.5)	>0.999	18 (64.3)	10 (66.7)	8 (61.5)	>0.999	6 (75.0)	5 (62.5)	>0.999
Community-associated	20 (30.8)	13 (28.9)	7 (35.0)		4 (30.8)	5 (38.5)		10 (35.7)	5 (33.3)	5 (38.5)		2 (25.0)	3 (37.5)	
Length, median (IQR)														
Length of hospital stay	17 (11, 29.5)	16 (11, 24.5)	22 (11.5, 34.5)	0.277	17 (11.5, 25.5)	14 (8.5, 28.5)	0.817	21.5 (13, 47)	22 (13, 46)	21 (13, 54.5)	0.817	35 (22.5, 73.5)	21 (10, 55.5)	0.293
Severity of condition, median (IQR)														
aCCI score	6 (4, 7)	6 (4, 7)	6 (5, 7)	0.442	6 (3.5, 8.5)	6 (4.5, 7)	0.979	6 (4, 8)	6 (5, 7)	6 (3.5, 9)	0.963	6 (5, 8)	4 (3, 9)	0.560
Pitt score	3 (2, 4)	3 (2, 4)	3.5 (2.5, 4)	0.080	3 (3,4)	3 (2.5, 4.5)	0.807	3 (2, 4)	3 (2, 4)	4 (2, 4)	0.569	3.5 (3, 4)	4 (2, 5)	>0.999
SOFA score	3 (2.5, 6.5)	3 (2, 4)	7 (3.3, 8)	0.005	4 (3, 7.5)	7 (2.5, 8)	0.604	5 (4, 7)	5 (4, 6)	6 (4, 7)	0.225	5.5 (4, 7.5)	6 (3, 8)	0.873
Underlying disease, N (%)														
Malignant tumors	26 (40.0)	18 (40.0)	8 (40.0)	>0.999	5 (38.5)	4 (30.8)	>0.999	12 (42.9)	8 (53.3)	4 (30.8)	0.276	3 (37.5)	4 (50.0)	>0.999
Immunocompromised status	20 (30.8)	12 (26.7)	8 (40.0)	0.282	4 (30.8)	6 (46.2)	0.688	13 (46.4)	6 (40.0)	7 (53.8)	0.705	4 (50.0)	4(50.0)	>0.999
Hypertension	24 (36.9)	17 (37.8)	7 (35.0)	0.830	7 (53.8)	6 (46.2)	>0.999	6 (21.4)	2 (13.3)	4 (30.8)	0.372	2 (25.0)	3 (37.5)	>0.999
Diabetes	19 (29.2)	15 (33.3)	4 (20.0)	0.426	5 (38.5)	4 (30.8)	>0.999	4 (14.3)	2 (13.3)	2 (15.4)	>0.999	2 (25.0)	1 (12.5)	>0.999
Hypoproteinemia	17 (26.2)	8 (17.8)	9 (45.0)	0.021	3 (23.1)	7 (53.8)	0.226	12 (42.9)	5 (33.3)	7 (53.8)	0.445	4 (50.0)	4 (50.0)	>0.999
Sepsis	14 (21.5)	5 (11.1)	9 (45.0)	0.002	3 (23.1)	6 (46.2)	0.411	10 (35.7)	4 (26.7)	6 (46.2)	0.433	4 (50.0)	4 (50.0)	>0.999

Abbreviation: PSM, Propensity Score Matching.

Table 5 Outcome of Patients Treated with BLICs or Carbapenems

Groups	Outcomes	BLICs		Carbapenems		Univariate analysis		Multivariate analysis	
		N/T (%)	Adjusted N/T (%)	N/T (%)	Adjusted N/T (%)	HR (95% CI), *P*	Adjusted HR (95% CI), *P*	HR (95% CI), *P*	Adjusted HR (95% CI), *P*
Non-ESBL-producing *E. cloacae* complex (n=65)	14-day treatment failure	13/45 (28.9)	3/13 (23.1)	7/20 (35.0)	7/13 (53.8)	0.665 (0.265–1.670), 0.386	0.296 (0.076–1.152), 0.079	1.338 (0.464–3.862), 0.590	0.155 (0.013–1.840), 0.140
	30-day mortality	3/45 (6.7)	1/13 (7.7)	7/20 (35.0)	7/13 (53.8)	0.190 (0.055–0.662), 0.009	0.106 (0.013–0.863), 0.036	0.624 (0.118–3.293), 0.579	0.064 (0.002–1.983), 0.117
ESBL-producing *E. cloacae* complex (n=28)	14-day treatment failure	6/15 (40.0)	4/8 (50.0)	4/13 (30.8)	4/8 (50.0)	1.058 (0.298–3.757), 0.930	0.862 (0.214–3.472), 0.835	1.665 (0.373–7.428), 0.504	0.447 (0.023–8.519), 0.592
	30-day mortality	4/15 (26.7)	4/8 (50.0)	6/13 (46.2)	4/8 (50.0)	0.483 (0.136–1.715), 0.260	0.862 (0.214–3.472), 0.835	0.377 (0.066–2.149), 0.272	0.447 (0.023–8.519), 0.592

Abbreviations: N, number; T, total number; CI, confidence interval; HR, hazard ratio.

Discussion

Bloodstream infections caused by ESBL-producing *Enterobacterales* pose a significant global public health concern and are associated with unfavorable prognosis and elevated mortality rates.[21] This study provided a comprehensive overview of the clinical characteristics of bloodstream infections caused by ESBL-producing and non-ESBL-producing *E. cloacae* complex, while also identifying risk factors for ESBL-producing ECC-BSI (ICU admission, surgery within 3 months, and biliary tract infection). Furthermore, this study confirmed that immunocompromised status and high SOFA score (≥ 6.0) were risk factors for 30-day mortality in patients with ECC-BSI. Finally, the study evaluated the treatment effect of BLICs (Cefoperazone/sulbactam or Piperacillin/tazobactam) and carbapenems in patients with ECC-BSI. In ESBL-negative ECC-BSI patients, although the multivariate Cox regression analyses did not yield statistically significant results, the univariate Cox regression analyses revealed that patients who received BLICs exhibited a more favorable prognosis compared to those treated with carbapenems.

This study revealed that patients admitted to the ICU and with a history of surgery within 3 months were more likely to develop ESBL-producing *Enterobacter cloacae* complex bloodstream infections. The above finding may be attributed to the following reasons. 1) Patients admitted to the ICU typically exhibit critical conditions, necessitating frequent invasive procedures or surgeries, and have been exposed to multiple antimicrobial agents, thereby increasing the probability of ESBL-producing ECC infection.[6] 2) Additionally, repeated exposure of *E. cloacae* complex to antimicrobial agents tends to suppress or eliminate susceptible strains, promoting the proliferation of resistant strains, and facilitating the dissemination of ESBL-producing *E. cloacae* complex strains.[22] Hence, preventive and control measures for nosocomial infections should be implemented, and guidelines for invasive procedures should be strictly followed to mitigate the dissemination of ESBL-producing *E. cloacae* complex.

Moreover, patients with biliary tract infections were found to be at increased risk of ESBL-producing ECC-BSI. Intestinal bile plays a crucial role in various physiological processes and exhibits various functions such as anti-inflammatory, bacteriostatic, endotoxin-binding, and mucosal-trophic functions.[23] The occurrence of bile tract infection in patients can lead to a deficiency in intestinal bile. A significant proportion of these patients undergo biliary stenting, which often damages the intestinal mucosal epithelium. Consequently, intestinal bacteria are translocated, allowing bacterial endotoxins to enter the systemic circulation via the portal vein, ultimately leading to the development of bacteremia.[24] Furthermore, research conducted in Thailand revealed that an aberration in the gut microbiota resulted in a substantial proliferation of ESBL-producing *Enterobacterales*, thereby facilitating the dissemination of bacterial resistance genes and giving rise to severe infections.[25] Collectively, these findings offer reasonable interpretations for our observation.

In addition, the ESBL-producing *E. cloacae* complex exhibited a higher level of resistance towards cephalosporins, aztreonam, and quinolones (Table 2), aligning with previous research findings.[7–9] This phenomenon can potentially be attributed to the presence of plasmids in *E. cloacae* complex strains, which harbor ESBL genes along with resistance genes encoding cephalosporins, aztreonam, and quinolones.[26]

Regrettably, despite previous studies[6,7,27] suggesting a strong association between indwelling drainage tube, central venous catheter, urinary catheter, and mechanical ventilation with the occurrence of ECC-BSI, our study findings indicated that invasive procedures did not independently contribute to the risk of ESBL-producing ECC-BSI. This discrepancy may be attributed to the simultaneous presence of multiple invasive devices in most patients during their hospitalization, leading to interference and weakened mutual influence among these factors. In parallel, prior studies[28,29] have reported a correlation between antibiotic exposure and ESBL-producing *Enterobacterales* infection or colonization. However, the current study did not yield similar findings, which could potentially be due to the restricted sample size. Further research with larger sample sizes is necessary to confirm this finding.

Further analysis revealed a 30-day mortality rate of 19.4% in patients with ECC-BSI, which aligned with previously reported rates ranging from 15.1% to 33.3%.[7,8] The multivariate logistic regression analysis demonstrated that being immunocompromised was an independent risk factor for 30-day mortality in patients with ECC-BSI, which was also consistent with findings from a previous study conducted in four teaching hospitals in China.[30] Meanwhile, a retrospective observational cohort study on adults indicated that the immunocompromised status was the primary factor associated with persistent Gram-Negative strains bloodstream infections.[31] Immunocompromised individuals frequently necessitate extended hospitalization periods and undergo numerous invasive interventions, thereby raising their susceptibility to bacterial infections. Furthermore, they are more vulnerable to infections compared to immunocompetent patients, consequently leading to elevated mortality rates.

In addition, a higher SOFA score (≥ 6.0) was an independent risk factor for 30-day mortality in patients with ECC-BSI. This finding was confirmed by a previous study, which demonstrated a significant association between elevated SOFA scores and the prognosis of patients with hospital-acquired bacteremic pneumonia caused by *Klebsiella pneumoniae* and *Escherichia coli*.[32] Indeed, patients with elevated SOFA scores exhibit increased disease severity, heightened susceptibility to infection by multidrug-resistant bacteria, and a greater propensity for developing sepsis or multiple organ failure during an episode of bacteremia. These changes ultimately lead to elevated mortality rates, providing a plausible explanation for our finding. Notably, the univariate logistic regression analysis revealed a significant disparity in mortality rates between ESBL positive and ESBL negative *E. cloacae* complex isolates ($P = 0.016$). However, the production of ESBL was not identified as an independent risk factor for 30-day mortality in patients with ECC-BSI, which may be attributed to the limited sample size and needs to be interpreted with caution.

At present, carbapenems are frequently employed in the treatment of ESBL-producing ECC-BSI.[33] A multicenter retrospective study demonstrated that the use of carbapenems as an initial antimicrobial regimen was effective in improving the prognosis of patients with ESBL-producing ECC-BSI.[34] Alarmingly, the detection rate of ESBL-producing *E. cloacae* complex has shown a significant surge, resulting in an increase in the consumption of carbapenem antibiotics, which further heightened antibiotic selection pressure and has expedited the dissemination of carbapenem-resistant *E. cloacae* complex.[35] As another key antibiotic used in the treatment of ECC-BSI, the efficacy of BLICs in managing *E. cloacae* complex bloodstream infections compared to carbapenems remains controversial.

After adjusting for potential confounding factors, the ESBL-negative ECC-BSI patients showed lower 30-day mortality in the BTG group compared to the CTG group (univariate Cox regression analysis), although this difference did not reach statistical significance in the multivariate Cox regression analysis. Notably, the lack of statistical significance does not imply the ineffectiveness of carbapenems. In our study, patients receiving carbapenem treatment exhibited higher disease severity (Table 4), suggesting that the disparity in 30-day mortality may be attributed to the severity of the infection rather than the diminished efficacy of carbapenems. Carbapenems remain the antibiotic of first choice for the treatment of severe *Enterobacterales* bloodstream infections, in particular ESBL-producing strains.[36,37] Maroun[38] et al conducted a study that demonstrated the absence of a statistically significant disparity in mortality when comparing BLICs to carbapenems as the ultimate or initial treatment for ESBL-producing *Enterobacterales* bloodstream infections. Another meta-analysis conducted in China reported BLICs to be effective in the treatment of ESBL-producing

Enterobacterales bloodstream infections and represented a valid alternative to reduce the use of carbapenems.[21] Additionally, a literature review conducted in Spanish indicated that carbapenems should be the primary choice of treatment for ESBL-producing ECC-BSI infections in severe and immunocompromised patients. However, alternative antibacterial drugs may be considered for less severe infections.[26] These findings aligned with the results of our study, which confirmed that BLICs demonstrated a favorable impact on milder BSI (ESBL-negative and SOFA score ≤ 6.0) caused by *E. cloacae* complex.

Limitations

Nevertheless, the limitations of this research should be acknowledged. First, this was a single-center retrospective study, which inherently restricts the number of included cases and could affect the accuracy of the statistical analysis. Second, despite our efforts to mitigate selection bias and potential confounders through PSM and multivariate analysis, some bias may have been introduced from nonmatched confounding factors. Third, this study assessed the efficacy of BLICs by specifically focusing on two antibiotics, namely Cefoperazone/sulbactam and Piperacillin/tazobactam. Other antibiotics were not included as these two antibiotics are the most commonly used in our hospital, and only a very small number of cases (fewer than 5) involved other classes of BLICs. Fourth, this research revealed that previous surgical treatment within a 3-month period was identified as a risk factor for ESBL-positive *Enterobacter cloacae* complex infection; still, further categorization of the specific types of surgeries was not possible due to the limited number of patients who had undergone surgical procedures. However, further investigation into the specific types of surgery that could increase the risk of ESBL-positive *Enterobacter cloacae* complex bloodstream infection is crucial for the advancement of our research. This will be the focus of our next study, and we hope that larger prospective studies will be conducted to comprehensively address this important issue. Fifth, this study did not evaluate clinical isolates for AmpC enzyme as this assay has not yet been introduced in our laboratory, which requires a prospective study for further investigation. Lastly, our study solely focused on *E. cloacae* complex, and the generalizability of the findings to other *Enterobacterales* remains unknown.

Conclusion

In summary, this study identified the susceptibility factors for infection by ESBL-producing ECC strains and the risk factors for 30-day mortality in patients with ECC-BSI. Furthermore, ESBL-negative ECC-BSI patients treated with BLICs exhibited a better prognosis than those treated with carbapenems. Based on our findings, the use of BLICs should be considered for patients with less severe bloodstream infections (ESBL-negative and SOFA ≤6.0) caused by *E. cloacae* complex, which will aid in mitigating the development of antimicrobial resistance by rationalizing the use of antibiotics.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

Informed consent was acquired from each participant included in the study. This study conformed to the guidelines of the Helsinki Declaration. Ethics approval was obtained by the Research Ethics Committee of the Second Affiliated Hospital of Nanchang University.

Consent for Publication

Written informed consent for publication was obtained from all participants.

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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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Disclosure

The authors report no conflicts of interest in this work.

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