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A retrospective analysis of risk factors and outcomes in patients with extended-spectrum beta-lactamase-producing *Escherichia coli* bloodstream infections

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ABSTRACT

Objective: Risk factors and outcomes associated with extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (*E. coli*) bloodstream infections (BSI) are not yet fully understood.
Methods: This was a retrospective analysis of patients with *E. coli* BSI treated over a 4-year period. The characteristics of bacteremia caused by ESBL-producing versus non-ESBL-producing *E. coli* were compared. Factors influencing mortality were also assessed.
Results: Of 554 eligible patients, 58.9% developed ESBL-producing *E. coli*. Multivariate analysis showed that urinary tract infections, stomach tube catheterization, and prior cephalosporin exposure were independent risk factors for the emergence of ESBL-producing *E. coli* BSI. No significant differences in 30-day mortality were seen in patients with BSI caused by ESBL-producing or non-ESBL-producing *E. coli* (11.1% vs. 9.2%; $P = 0.642$). Factors independently associated with a higher risk of mortality were previous carbapenem exposure, high APACHE II score, and respiratory tract origin.
Conclusions: This study showed that prior UTIs and previous cephalosporin exposure represent significant risk factors for the development of ESBL-producing *E. coli* BSI. Previous carbapenem exposure, high APACHE II score, and a respiratory tract origin were seen to be independent mortality risk factors in patients with *E. coli* BSI.

1. Introduction

Escherichia coli (*E. coli*) is an important cause of community-acquired and hospital-acquired infections, and is the most common cause of Gram-negative bloodstream infections (BSI) [1]. Production of β-lactamase enzymes is the principal mechanism by which Gram-negative bacteria resist the action of β-lactam antibiotics. Infections due to extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae have dramatically increased worldwide, representing a major health crisis. In China, the prevalence of ESBLs has risen by 38.9–55.8% for various clinical isolates of *E. coli* in the past 5 years [2]. Risk factors for ESBL infection include age, comorbidities, recurrent urinary tract infections (UTI), intensive care unit (ICU) stay, previous use of antibiotics, and colonization with ESBL [3–6]. The impact of ESBL-producing *E. coli* bacteremia on mortality is controversial. Some studies have shown that mortality is associated with ESBL production, whereas others have reported increased mortality due to inappropriate antimicrobial therapy [7–10]. In previous retrospective studies, carbapenem regimens were seen to be the most effective for managing ESBL-producing *E. coli* [11], but some studies have suggested that β-lactam-β-lactamase inhibitor (BLBLI) combination regimens could replace carbapenems as the treatment of choice [12,13]. Therefore, this study investigated the prevalence and risk factors for ESBL-producing *E. coli* bacteremia and outcomes in hospitalized patients.

2. Materials and methods

2.1. Subjects and study design

A retrospective cohort study was conducted to evaluate the clinical characteristics and outcomes of patients with *E. coli* bacteremia. The medical records of patients with one or more

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blood cultures positive for *E. coli* hospitalized between January 2013 and December 2016 in a 2500 bed teaching hospital were retrieved. Data from patients with the following characteristics were included in the analysis: (a) a blood culture positive for *E. coli*; (b) clinical manifestations of infection; and (c) hospitalization and a complete clinical data set. Patients aged <16 years and those without complete medical records were excluded. In patients experiencing more than one episode of *E. coli* bacteremia within a 6-month period, only data from the first episode of bacteremia were included. Clinical data were collected through a retrospective review of the electronic medical records, including: patient demographics, clinical and microbiologic data, underlying diseases, possible sources of bacteremia, laboratory data at the time of bacteremia onset, results of antimicrobial susceptibility testing, antibiotic regimen, and other relevant information.

A three-part analysis was conducted (Fig. 1). First, risk factors associated with ESBL-producing *E. coli* infection were evaluated by comparing the ESBL-producing and non-ESBL-producing patient groups (26 patients with carbapenem non-susceptible *E. coli* BSI were excluded). Second, patients were grouped according to their survival status after 30 days of infection (excluding those with a treatment time after BSI <48 h, and those who were untreated) to explore the prognosis of *E. coli* BSI and antibiotic treatment programs. Third, a cohort design study was conducted to assess the risk factors associated with 30-day mortality and treatment among patients with ESBL-producing *E. coli* BSI.

2.2. Definitions and patient assessment

Bacteremia was defined as the isolation of *E. coli* in one or more separately obtained blood cultures, and clinical features compatible with sepsis syndrome. Hospital-acquired bacteremia was defined as a positive blood culture taken from a patient who demonstrated clinical evidence of infection no sooner than 48 h

Fig. 1. Flowchart of the case selection process.
Abbreviations: ESBL, extended-spectrum beta-lactamase; *E. coli*, *Escherichia coli*; BSI, bloodstream infection; CS, carbapenem-susceptible.

after admission. The Charlson index was used to assess the burden of chronic disease [14]. The probable infectious source was determined using CDC/National Healthcare Safety Network (NHSN) surveillance definitions [15]. Steroid therapy was defined as prednisone >20 mg/day or its equivalent administered for ≥7 days. The Acute Physiology and Chronic Health Evaluation (APACHE) II scores and Pitt scores calculated at the time of BSI onset were used to assess illness severity [16]. Antimicrobial drug exposure referred to the use of antibiotics for >72 h 30 days prior to BSI diagnosis. The initial empirical antimicrobial therapy was considered appropriate if the treatment regimen included antibiotics active in vitro, and the dosage and route of administration were in accordance with current medical standards. If the antimicrobial agent was not administered in a timely fashion (within 24 h of the appearance of primary infection symptoms), antimicrobial use was considered inappropriate [17]. All-cause mortality was defined as death from *E. coli* BSI within 14 days, and 30 days of the onset of bacteremia.

2.3. Microbiological tests

The identification and antimicrobial susceptibility of *E. coli* were determined using the Vitek2 system (bioMérieux, Marcy-l' Etoile, France). ESBL production was determined using a double-disk potentiation test with ceftazidime, ceftazidime-clavulanic acid and cefotaxime, cefotaxime-clavulanic acid, or using the ESBL-positive results of the VITEK-2 N131. According to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) standards (2015), carbapenem non-susceptibility was defined as a minimum inhibitory concentration (MIC) of ≥2 mg/L for imipenem or meropenem, or an MIC of ≥1 mg/L for ertapenem [18].

2.4. Statistical analysis

To evaluate continuous variables, Student's *t*-test (for normally distributed variables) or the Mann-Whitney U test (for variables that did not have normal distribution) was used. Categorical variables were analyzed by the χ^2 or two-tailed Fisher exact test when appropriate. For continuous variables, results were expressed as mean ± standard deviation (S.D.) or median (interquartile range [IQR]), and categorical variables using percentages of the group from which they were derived. The strength of all associations was assessed using odds ratios (ORs) and 95% confidence intervals (CIs). Two-tailed tests were used to determine statistical significance. For the multivariate analysis, binary logistic regression (forward: condition) was used to identify independent predictors, and variables with a *P*-value ≤0.05 in the univariate analysis were incorporated with a stepwise approach. The Kaplan–Meier product limit method was used to estimate the survival distribution function; nonparametric (log-rank and Wilcoxon) tests were used to compare survival functions in different groups. In all analyses, *P*-values ≤0.05 were considered to be significant. All statistical analyses were carried out using SPSS version 23.0.

3. Results

3.1. Demographic and clinical characteristics

During the 4-year study period, 580 patients with *E. coli* BSI were enrolled, 57.6% of whom (334 of 580) developed ESBL-producing strains. The current study showed the detection of ESBL-producing *E. coli* to be high throughout the study period (65.6% in 2013 and 53.4% in 2016). The drug sensitivity of patients with *E. coli* bacteremia between January 2013 and December 2016 is presented in Fig. S1, showing the highest sensitivity to imipenem, ertapenem and amikacin, followed by nitrofurantoin and piperacillin/tazobactam. There were 24 patients with carbapenem-resistant *E. coli* and two with carbapenem-intermediate *E. coli*; 23.1% (6 of 26) were New Delhi metallo-β-lactamase (NDM)-5 and 7.7% were NDM-1, and there was one case of NDM-16 and one of *Klebsiella pneumoniae* carbapenemase (KPC), all of which were excluded.

Table 1 shows the demographic and clinical characteristics of the remaining 554 patients. Bacteremias were largely hospital associated: 62.4% occurred >48 h after admission, and the median time to ESBL-producing *E. coli* BSI diagnosis was 5 days (IQR 1–14 days). Regarding the probable infectious source of *E. coli* BSI, intra-abdominal infection was most common and reported in 49.8% of patients (276 of 554), followed by respiratory tract infection in 21.3% (118 of 554) and UTI in 17.9% (99 of 554). The male:female ratio, mean age, underlying disease, leukocyte count, and illness severity did not differ between the ESBL-producing and non-ESBL-producing *E. coli* bacteremia groups.

3.2. Risk factors associated with the development of ESBL-producing E. coli BSI

Univariate analysis showed that, in comparison with patients with non-ESBL-producing *E. coli*, those with ESBL-producing *E. coli* were more likely to: show the urinary tract as the primary site of *E. coli* BSI, have undergone a nonsurgical invasive procedure (including urinary catheterization and stomach tube insertion), and have had prior exposure to antimicrobial therapy in the past 30 days and previous cephalosporin exposure.

Multivariate analysis showed that UTI as the primary site of *E. coli* BSI (OR 1.986; $P = 0.005$), stomach tube catheterization (OR 2.318; $P = 0.027$), and prior treatment with cephalosporins in the 30 days prior to BSI (OR 3.025; $P = 0.003$) were independent risk factors for the emergence of ESBL-producing *E. coli* BSI (Table 1).

3.3. Risk factors for 30-day mortality in patients with E. coli BSI

Of 554 patients, 41 were excluded from the analysis because they received <48 h of antimicrobial therapy, and nine cases were excluded due to early death. Table 2 shows the predictors of 30-day mortality for patients with *E. coli* BSI included in the study. Fig. S2 shows that there was no significant difference in mortality between patients in the ESBL (33 of 298) and non-ESBL (19 of 206) groups ($\chi^2 = 0.216$; $P = 0.642$). In the multivariate analysis (Table 2), factors independently associated with a higher risk of *E. coli* 30-day mortality were respiratory tract origin (OR 2.050; $P = 0.031$), prior use of carbapenem in the 30 days prior to BSI (OR 3.491; $P = 0.003$), and high APACHE II score (OR 1.149; $P < 0.001$). Therefore, patients were divided into two groups according to carbapenem use prior to BSI. This analysis showed a higher in-hospital infection rate in the carbapenem use group (n = 29 vs. n = 9 in the no-carbapenem group; $P = 0.038$) and a longer median time before infection (8 vs. 3 days, respectively; $P = 0.024$). Meanwhile, there were no significant differences in 30-day mortality among *E. coli* BSI patients who received appropriate empirical treatment vs. inappropriate empirical treatment ($\chi^2 = 0.973$; $P = 0.324$). A total of 298 ESBL-producing *E. coli* BSI patients were included in this analysis, and the 30-day all-cause mortality was 11.1%. The main characteristics of the ESBL-producing *E. coli* BSI survivor and non-survivor subgroups are shown in Table 3.

3.4. Antibiotic treatment and outcome of patients with ESBL-producing versus non-ESBL-producing E. coli bacteremia

As shown in Table 2, carbapenem (n = 319, 63.3%), BLBLIs (n = 218, 43.3%), and quinolones (n = 76, 15.1%) were the most commonly used antimicrobials in patients with *E. coli* bacteremia. Patients with ESBL-producing *E. coli* bacteremia were less

Table 1
Clinical and demographic characteristics of patients with bloodstream infections caused by *Escherichia coli*.

	Univariate analysis			Multivariable analysis			
	Non-ESBL-producing *E. coli* (n = 228)	ESBL-producing *E. coli* (n = 326)	*P*-values	*P*-values	OR	95% CI for OR	
						Lower	Upper
Demographic							
Gender, male, n (%)	125 (54.8)	178 (54.6)	0.959				
Mean age, years (IQR)	61 (47–71)	61 (49–71)					
Time before bacteremia, days (IQR)	4 (0–13)	5 (1–14)	0.293				
Pre-existing medical conditions							
Hypertension	64 (28.1)	89 (27.3)	0.842				
Diabetes mellitus	37 (16.3)	49 (15.0)	0.685				
Pulmonary disease	2 (0.9)	6 (1.8)	0.481				
Cardiovascular disease	4 (1.8)	9 (2.8)	0.441				
Hepatic disease	65 (28.5)	87 (26.7)	0.636				
Urinary system diseases	21 (9.2)	41 (12.6)	0.216				
Nervous system diseases	7 (3.1)	10 (3.1)	0.999				
Hematologic system diseases	44 (19.3)	48 (14.7)	0.155				
Solid tumor	44 (19.3)	67 (20.6)	0.717				
Median Charlson comorbidity index (IQR)	2 (0–2)	2 (0–2)	0.455				
Likely source of bacteremia							
Catheter-related	16 (7.0)	13 (4.0)	0.115				
Pneumonia	55 (24.1)	63 (19.3)	0.175				
Intra-abdominal	119 (52.5)	157 (48.2)	0.35				
Urinary tract	29 (12.7)	70 (21.5)	0.008	0.005	1.986	1.233	3.197
Intracranial infection	1 (0.4)	5 (1.5)	0.409				
Mixed infection	17 (7.5)	27 (8.3)	0.723				
Cutaneous infection	7 (3.1)	11 (3.4)	0.843				
Intestinal infection	6 (2.6)	10 (3.1)	0.763				
Primary bloodstream infection	23 (10.1)	34 (10.4)	0.896				
Hospital-acquired infection	138 (60.5)	208 (63.8)	0.433				
Prior hospitalization[a]	84 (56.4)	132 (60.6)	0.425				
Prior ICU stay[b]	14 (6.1)	28 (8.6)	0.284				
Prior surgery[b]	37 (16.2)	73 (22.4)	0.073				
Prior invasive procedure or devices[b]	55 (24.1)	99 (30.4)	0.106				
Mechanical ventilation	9 (3.9)	12 (3.7)	0.872				
Central venous catheterization	24 (10.5)	51 (15.6)	0.083				
Stomach tube catheterization	10 (4.4)	35 (10.7)	0.007	0.027	2.318	1.103	4.874
Urinary catheterization	20 (8.8)	48 (14.7)	0.036				
Percutaneous tube	7 (3.1)	25 (7.7)	0.022				
Prior chemotherapy or radiotherapy[b]	43 (18.9)	48 (14.7)	0.196				
Prior corticosteroid use[b]	21 (9.2)	36 (11.0)	0.485				
Prior immunosuppressant use[b]	8 (3.5)	20 (6.1)	0.165				
Use of antibiotics within 30 days prior to BSI[b]	77 (33.8)	155 (47.5)	0.001				
Cephalosporin	10 (4.4)	43 (13.2)	0.001	0.003	3.025	1.468	6.231
BLBLI	32 (14.0)	69 (21.2)	0.032				
Sulbactam and cefoperazone	8 (3.5)	36 (11.0)	0.001				
Cefotaxime sodium/sulbactam	1 (0.4)	9 (2.8)	0.09				
Piperacillin and tazobactam	25 (11.0)	28 (8.6)	0.349				
Tigecycline	2 (0.9)	4 (1.2)	>0.050				
Carbapenem	20 (8.8)	23 (7.1)	0.457				
Aminoglycosides	1 (0.4)	2 (0.6)	0.783				
Fluoroquinolone	31 (13.6)	44 (13.5)	0.973				
Sulfamethoxazole	4 (1.8)	8 (2.5)	0.795				
Laboratory examination							
Neutropenia	41 (18.0)	49 (15.0)	0.354				
Serum albumin <30 g/L	70 (31.5)	105 (32.9)	0.735				
Severity of illness at time of BSI							
Mean APACHE II score (IQR)	9 (6–12)	9 (6–13)	0.434				
Mean Pitt score (IQR)	1 (0–2)	0 (0–2)	0.359				

Data are expressed as n (%) unless otherwise stated.
Abbreviations: ESBL, extended-spectrum beta-lactamase; APACHE, Acute Physiology and Chronic Health Evaluation; BSI, bloodstream infection; ICU, intensive care unit; IQR, interquartile range; S.D., standard deviation; BLBLI, β-lactam-β-lactamase inhibitor.
[a] During the 3 months preceding BSI onset.
[b] During the 30 days preceding BSI onset.

frequently treated with adequate empirical antibiotic therapy compared with controls (90.9% vs. 98.1% adequacy, respectively; $P = 0.001$), and a similar level of carbapenem use was seen vs. the non-ESBL-producing *E. coli* group (62.4% vs. 61.2%; $P = 0.776$). No significant differences in definitive treatment regimens were seen between the ESBL-producing and non-ESBL-producing *E. coli* BSI groups (97.3% vs. 99.5%; $P = 0.136$). When the patients' drug susceptibility results became available, medication was adjusted in 81 patients. Among these, 28 patients with non-ESBL-producing *E. coli* (13.6%) received an alternative treatment plan, compared with 54 patients (18.1%) with ESBL-producing *E. coli*. Of them, most patients were altered from BLBLI to carbapenems. A single antibiotic regimen with BLBLIs (n = 81) or carbapenem (n = 161) resulted in no differences in 30-day and 14-day mortality between

Table 2
Analysis of risk factors for 30-day mortality in patients with *Escherichia coli* bloodstream infections (n = 504).

	Univariate analysis			Multivariable analysis			
	Survivors (n = 452)	Non-survivors (n = 52)	*P*-values	*P*-values	OR	95% CI for OR	
						Lower	Upper
Demographic							
Male	247 (54.6)	32 (61.5)	0.344				
Mean age, years (IQR)	61 (49–71)	62 (47–73)	0.816				
Duration before bacteremia, days (IQR)	3 (0–13)	7 (0–19)	0.294				
Duration after bacteremia, days (IQR)	13 (8–23)	12 (6–18)	0.034				
Pre-existing medical conditions							
Hypertension	119 (26.3)	14 (26.9)	0.926				
Diabetes mellitus	71 (15.7)	4 (7.8)	0.135				
Pulmonary disease	5 (1.1)	2 (3.8)	0.33				
Cardiovascular disease	10 (2.2)	2 (3.8)	0.801				
Hepatic disease	117 (25.9)	20 (38.5)	0.054				
Urinary system diseases	49 (10.8)	4 (7.7)	0.483				
Nervous system diseases	14 (3.1)	1 (1.9)	0.967				
Hematologic system diseases	76 (16.8)	1 (21.2)	0.433				
Solid tumor	86 (19.0)	13 (25.0)	0.305				
Comorbid conditions							
Median Charlson comorbidity index (IQR)	2 (0–2)	2 (1–2.8)	0.056				
Charlson comorbidity index (≥3)	74 (16.4)	13 (25.0)	0.119				
Likely source of bacteremia							
Catheter-related	25 (5.5)	0 (0)	0.161				
Pneumonia	83 (18.4)	21 (40.4)	<0.001	0.031	2.05	1.069	3.929
Intra-abdominal	229 (50.7)	29 (55.8)	0.485				
Urinary tract	83 (18.4)	8 (15.4)	0.597				
Intracranial infection	4 (0.9)	1 (1.9)	0.421				
Mixed infection	32 (7.1)	9 (17.3)	0.022				
Cutaneous infection	15 (3.3)	1 (1.9)	0.9				
Intestinal infection	10 (2.2)	2 (3.8)	0.801				
Primary bloodstream infection	49 (10.8)	2 (3.8)	0.113				
ESBL-producing *E. coli*	265 (58.6)	33 (63.5)	0.502				
Hospital-acquired infection	269 (59.5)	36 (69.2)	0.175				
Prior hospitalization[a]	164 (56.7)	32 (68.1)	0.144				
Prior ICU stay[b]	32 (7.1)	6 (11.5)	0.381				
Prior surgery[b]	88 (19.5)	14 (26.9)	0.205				
Invasive procedure or devices[b]	111 (24.6)	18 (34.6)	0.116				
Mechanical ventilation	15 (3.3)	3 (5.8)	0.612				
Central venous catheterization	25 (5.5)	5 (9.6)	0.385				
Urinary catheterization	49 (10.8)	9 (17.3)	0.166				
Stomach tube catheterization	36 (8.0)	7 (13.5)	0.279				
Percutaneous tube	25 (5.5)	3 (5.8)	>0.050				
Invasive procedure or devices after BSI	79 (17.2)	13 (20.6)	0.509				
Prior hemodialysis[b]	10 (2.2)	1 (1.9)	>0.050				
Prior chemotherapy or radiotherapy[b]	75 (16.6)	12 (23.1)	0.241				
Prior corticosteroid use[b]	43 (9.5)	6 (11.5)	0.641				
Prior immunosuppressant use[b]	20 (4.4)	3 (5.8)	0.929				
Hemodialysis after BSI	13 (2.9)	2 (3.8)	>0.050				
Corticosteroid use after BSI	61 (13.5)	10 (19.2)	0.26				
Immunosuppressant use after BSI	25 (5.5)	5 (9.6)	0.385				
Antibiotic therapy in the 30 days prior to BSI[b]	179 (39.6)	31 (59.6)	0.006				
Cephalosporin	46 (10.2)	3 (5.8)	0.31				
BLBLI	77 (17.0)	11 (21.2)	0.459				
Sulbactam and cefoperazone	30 (6.6)	8 (15.4)	0.047				
Cefotaxime sodium/sulbactam	8 (1.8)	2 (3.8)	0.623				
Piperacillin and tazobactam	42 (9.3)	2 (3.8)	0.29				
Tigecycline	4 (0.9)	2 (3.8)	0.234				
Carbapenem	27 (6.0)	11 (21.2)	<0.001	0.003	3.491	1.514	8.047
Aminoglycosides	2 (0.4)	1 (1.9)	0.279				
Fluoroquinolone	57 (12.6)	10 (19.2)	0.183				
Compound sulfamethoxazole	8 (1.8)	2 (3.8)	0.623				
Laboratory examination							
Neutropenia	74 (16.4)	10 (19.2)	0.6				
Serum albumin <30 g/L	134 (30.3)	22 (43.1)	0.062				
Severity of illness at time of BSI							
Mean APACHE II score (IQR)	9 (6–11.0)	12.5 (9.3–16.0)	<0.001	<0.001	1.149	1.083	1.219
Total antimicrobial after BSI							
Appropriate empirical treatment	426 (94.5)	47 (90.4)	0.387				
Appropriate definitive treatment	444 (98.4)	51 (98.1)	>0.050				
Cephalosporin	41 (9.1)	4 (7.7)	0.942				
BLBLI	199 (44.0)	19 (36.5)	0.302				
Tigecycline	22 (4.9)	9 (17.3)	0.001				
<0.2 g/day	18 (4.0)	8 (15.4)					
≥0.2 g/day	4 (0.9)	1 (1.9)					

Table 2 (*Continued*)

	Univariate analysis			Multivariable analysis			
	Survivors (n = 452)	Non-survivors (n = 52)	*P*-values	*P*-values	OR	95% CI for OR	
						Lower	Upper
Carbapenem	281 (62.2)	38 (73.1)	0.122				
Aminoglycosides	28 (6.2)	5 (9.6)	0.517				
Fluoroquinolone	76 (16.8)	5 (9.6)	0.181				

Data are expressed as n (%) unless otherwise stated.
Abbreviations: ESBL, extended-spectrum beta-lactamase; APACHE, Acute Physiology and Chronic Health Evaluation; BSI, bloodstream infection; ICU, intensive care unit; IQR, interquartile range; S.D., standard deviation; BLBLI, β-lactam-β-lactamase inhibitor; *E. coli*, *Escherichia coli*.
[a] During the 3 months preceding BSI onset.
[b] During the 30 days preceding BSI onset.

Table 3
Univariate analysis of risk factors for 30-day mortality in patients with ESBL-producing *Escherichia coli* bloodstream infections (n = 298).

	Survivor (n = 265)	Non-survivor (n = 33)	*P*-values
Sulfamethoxazole			
Gender, male, n (%)	148 (55.8)	18 (54.5)	0.887
Mean age, years (IQR)	60 (49–70)	66 (53–78)	0.105
Duration before bacteremia, days (IQR)	4 (1–14)	7 (1–20)	0.45
Duration after bacteremia, days (IQR)	13 (9–24)	14 (7–19)	0.277
Pre-existing medical conditions			
Hypertension	66 (24.9)	12 (36.4)	0.158
Diabetes mellitus	39 (14.7)	2 (6.1)	0.274
Pulmonary disease	3 (1.1)	2 (6.1)	0.096
Cardiovascular disease	6 (2.3)	2 (6.1)	0.483
Hepatic disease	72 (27.2)	10 (30.3)	0.704
Urinary system diseases	31 (11.7)	4 (12.1)	>0.050
Nervous system diseases	8 (3.0)	1 (3.0)	>0.050
Hematologic system diseases	39 (14.7)	5 (15.2)	>0.050
Solid tumor	53 (20.0)	8 (24.2)	0.733
Comorbid conditions			
Median Charlson comorbidity index (IQR)	2 (0–2)	2 (1–2)	0.08
Charlson comorbidity score (≥3)	44 (16.6)	7 (21.2)	0.507
Likely source of bacteremia			
Catheter-related	11 (4.2)	0 (0)	0.482
Pneumonia	42 (15.8)	12 (36.4)	0.004
Intra-abdominal	131 (49.4)	18 (54.5)	0.58
Urinary tract	58 (21.9)	7 (21.2)	0.929
Intracranial infection	3 (1.1)	1 (3.0)	0.376
Mixed infection	19 (7.2)	5 (15.2)	0.211
Cutaneous infection	10 (3.8)	1 (3.0)	>0.050
Intestinal infection	6 (2.3)	1 (3.0)	>0.050
Primary bloodstream infection	30 (11.3)	1 (3.0)	0.243
Hospital-acquired infection	163 (61.5)	22 (66.7)	0.565
Prior hospitalization[a]	99 (58.2)	22 (71.0)	0.183
Prior ICU stay[b]	22 (8.3)	4 (12.1)	0.685
Prior surgery[b]	61 (23.0)	7 (21.2)	0.816
Invasive procedure or devices[b]	68 (25.7)	15 (45.5)	0.017
Mechanical ventilation	8 (3.0)	2 (6.1)	0.687
Central venous catheterization	15 (5.7)	3 (9.1)	0.695
Urinary catheterization	35 (13.2)	7 (21.2)	0.327
Stomach tube catheterization	28 (10.6)	5 (15.2)	0.619
Percutaneous tube	22 (8.3)	2 (6.1)	0.915
Invasive procedure or devices after BSI	43 (16.2)	6 (18.2)	0.775
Prior hemodialysis[b]	3 (1.1)	1 (3.0)	0.376
Prior chemotherapy or radiotherapy[b]	37 (14.0)	8 (24.2)	0.194
Prior corticosteroid use[b]	26 (9.8)	3 (9.1)	>0.050
Prior immunosuppressant use[b]	14 (5.3)	2 (6.1)	>0.050
Hemodialysis after BSI	5 (1.9)	2 (6.1)	0.377
Corticosteroid use after BSI	35 (13.2)	8 (24.2)	0.15
Immunosuppressant use after BSI	18 (6.8)	3 (9.1)	0.9
Prior receipt of antibiotics in the 30 days prior to BSI[b]	120 (45.3)	21 (63.6)	0.046
Cephalosporin	38 (14.3)	3 (9.1)	0.577
BLBLIs	53 (20.0)	8 (24.2)	0.569
Cefoperazone/sulbactam	26 (9.8)	6 (18.2)	0.243
Cefotaxime sodium/sulbactam	7 (2.6)	2 (6.1)	0.587
Piperacillin/tazobactam	23 (8.7)	0 (0)	0.157
Tigecycline	3 (1.1)	1 (3.0)	0.376
Carbapenem	15 (5.7)	5 (15.2)	0.092
Aminoglycosides	2 (0.8)	0 (0)	>0.050
Fluoroquinolone	34 (12.8)	6 (18.2)	0.562
Compound sulfamethoxazole	5 (1.9)	1 (3.0)	>0.050
Laboratory examination			

Table 3 (*Continued*)

	Survivor (n = 265)	Non-survivor (n = 33)	*P*-values
Neutropenia	37 (14.0)	6 (18.2)	0.698
Serum albumin <30 g/L	80 (30.9)	15 (45.5)	0.093
Severity of illness at time of BSI			
Mean APACHE II score (IQR)	9 (6–11)	12 (10–16.5)	<0.001
Antimicrobial after BSI			
Appropriate empirical treatment	243 (91.7)	28 (84.8)	0.331
Appropriate definitive treatment	258 (97.4)	32 (97.0)	>0.050
Cephalosporin	22 (8.3)	1 (3.0)	0.469
BLBLI	117 (44.2)	13 (39.4)	0.603
Tigecycline	12 (4.5)	7 (21.2)	0.001
<0.2 g/day	12(4.5)	6 (18.2)	
≥0.2 g/day	0 (5.7)	1 (3.0)	
Carbapenem	42 (15.8)	4 (12.1)	0.576
Aminoglycosides	61 (23.0)	13 (39.4)	0.04
Fluoroquinolone	78 (29.4)	15 (45.5)	0.061
Total antimicrobial regimen after BSI			
Cephalosporin	9 (3.4)	1 (3.0)	>0.050
Sulbenicillin	2 (0.8)	0 (0)	>0.050
BLBLI	78 (29.4)	9 (27.3)	0.797
Cefoperazone/sulbactam	43 (16.2)	5 (15.2)	0.874
Piperacillin/tazobactam	35 (13.2)	4 (12.1)	>0.050
Carbapenem	164 (61.9)	22 (66.7)	0.593
Carbapenem monotherapy	142 (53.6)	19 (57.6)	0.664
Carbapenem combination therapy	22 (8.3)	3 (9.1)	>0.050
Fluoroquinolone	15 (5.7)	1 (3.0)	0.824
Fluoroquinolone monotherapy	6 (2.3)	0 (0)	0.829
Fluoroquinolone combination therapy	9 (3.4)	1 (3.0)	>0.050
Aminoglycosides	9 (3.4)	0 (0)	0.592
Aminoglycoside monotherapy	3 (1.1)	0 (0)	>0.050
Aminoglycoside combination therapy	6 (2.3)	0 (0)	0.829
Tigecycline	5 (1.9)	6 (18.2)	<0.001
Tigecycline monotherapy	1 (0.4)	0 (0)	>0.050
Tigecycline combination therapy	4 (1.5)	6 (18.2)	<0.001

Data are expressed as numbers (%) unless otherwise stated.
Abbreviations: ESBL, extended-spectrum beta-lactamase; APACHE, Acute Physiology and Chronic Health Evaluation; BSI, bloodstream infection; ICU, intensive care unit; IQR, interquartile range; S.D., standard deviation; BLBLI, β-lactam-β-lactamase inhibitor; *E. coli*, *Escherichia coli*.
[a] During the 3 months preceding BSI onset.
[b] During the 30 days preceding BSI onset.

the two groups (Fig. S3). For patients with APACHE II scores ≥12 at the onset of bacteremia, the 14-day mortality rate of patients receiving BLBLIs was higher than that of patients receiving carbapenems (45.3% vs. 7.7%; Fig. 2C).

4. Discussion

The clinical isolate rate of Enterobacteriaceae is high, with *E. coli* and Klebsiella bacteria (primarily *Klebsiella pneumoniae*) ranking first and second in clinical isolates of Gram-negative bacteria in hospitalized patients in China. Production of ESBLs is the primary mechanism of drug resistance in these bacteria. Data from the CHINET Antimicrobial Resistance Surveillance Program showed that the detection rate of ESBL-producing *E. coli* in China increased from 38.9% in 2005 to 55.8% in 2014, which is similar to that seen in other countries [2,19]. Previous studies have shown that ESBL-producing *E. coli* is primarily derived from UTIs, whereas the current study showed abdominal infection to be the primary origin; this may be related to the high number of patients with hepatobiliary surgery in the current hospital [20].

In agreement with previous studies, multivariate analysis of risk factors for ESBL-producing *E. coli* in the current study showed that UTI was an independent risk factor, with 13.5% of patients having a history of urinary catheterization. As *E. coli* is an opportunistic bacterial infection, an invasive procedure will disrupt the mucosa and facilitate entry of bacteria into the bloodstream [21,22]. Wiener et al. reported that the widespread use of third-generation cephalosporins promoted plasmid-mediated dissemination of ESBL-producing strains [21]. Other studies have found that cephalosporins and quinolones are easy to screen for resistant strains producing ESBLs, and suggest that limiting the use of these two drugs can significantly reduce the proportion of strains producing ESBLs. The current study also found that cephalosporin use in the 30 days prior to infection was an independent risk factor for the emergence of ESBL-producing *E. coli* BSI. Therefore, patients with BSI and a history of cephalosporin use have a high risk of infection with ESBL-producing strains. Therefore, use of a drug that covers ESBL-producing strains is recommended as empirical therapy [23].

Regarding the prognosis of patients with *E. coli* BSI: previous studies have shown 30-day mortality to be 10–35%, which is generally lower than that seen in patients with *Klebsiella pneumoniae* BSI. In the current study, patients with *E. coli* BSI exhibited a 30-day overall mortality rate of 10.3%, which is similar to previous reports [6,24]. ESBL accounted for 56.8% of patients with community infection and 60.7% of patients with nosocomial infection. There was no significant difference in the 30-day mortality rate between the community and nosocomial infection groups. Many previous studies have shown that the mortality rate in patients with ESBL-producing *E. coli* BSI is significantly higher than that in patients with non-ESBL-producing *E. coli* BSI [9].

At the same time, many reports have suggested that inadequate empirical antibiotic therapy is a risk factor for death, but in the present study, no significant difference was seen. This observation may be related to the high use of BLBLIs or carbapenem in the current hospital as empirical treatment for ESBL-producing *E. coli* BSI and the adequacy of this treatment being high (with the resistance rate being 9.1%) [25–27]. In agreement with previous

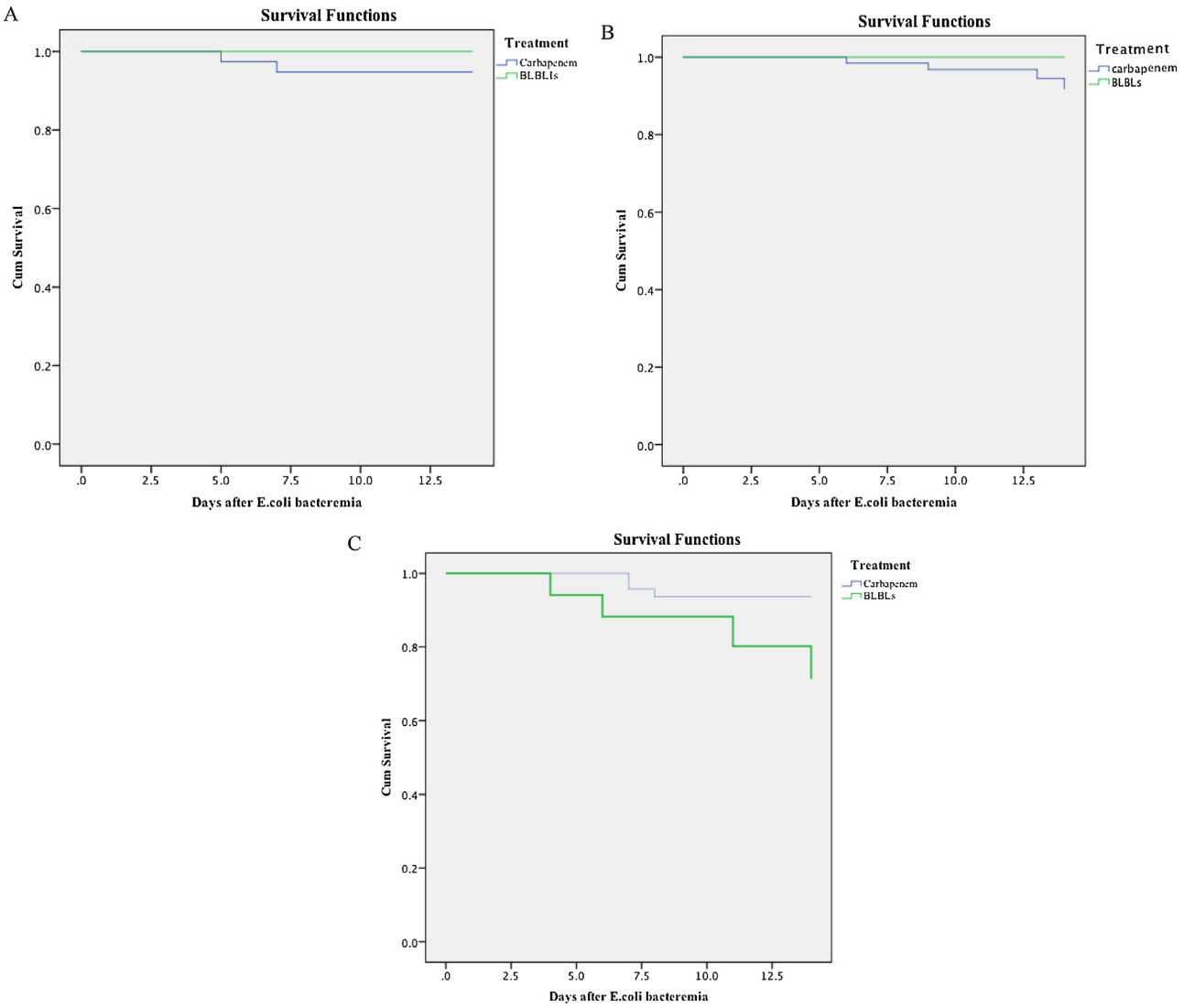

Fig. 2. Kaplan–Meier 14-day survival estimates: (A) *Escherichia coli* bloodstream infection patients (APACHE II score <6) treated with carbapenem and β-lactam-β-lactamase inhibitor (BLBLI) combination antibiotics ($P = 0.338$); (B) *Escherichia coli* bloodstream infection patients (APACHE II score 6–12) treated with carbapenem and BLBLIs ($P = 0.129$); (C) *Escherichia coli* bloodstream infection patients (APACHE II score >12) treated with carbapenem and BLBLIs ($P = 0.035$).

studies, patients with severe disease and high APACHE II scores at the time of BSI had a higher mortality rate. Multivariate analysis found that carbapenem use in the 30 days prior to BSI was an independent risk factor for *E. coli* 30-day mortality, which has not been previously reported. In addition, in the targeted drug regimen after *E. coli* BSI, 18 patients were treated with tigecycline, including 16 patients receiving a dosage of 50 mg every 12 h and two patients receiving a dose of 100 mg every 12 h. This study demonstrated significantly higher mortality rates in the tigecycline group than in other antibiotics group (38.9% vs. 9.3%; $P = 0.001$), which may be related to the severity of their condition and lower concentrations of tigecycline in the blood. This phenomenon has also been reported in previous studies of *Klebsiella pneumoniae* BSI at the current hospital [28].

In China, antimicrobial therapy primarily comprises piperacillin and tazobactam or cefoperazone and sulbactam, which may suggest that BLBLIs can still be used as empirical treatment for ESBL-producing strains. At present, the efficacy of BLBLIs and carbapenem in the treatment of ESBL-producing *E. coli* BSI remains controversial. Some experts who do not support the use of BLBLIs over carbapenems believe that carbapenems have a greater inhibitory effect on ESBL than BLBLIs and that ESBL-producing strains may have multiple drug-resistance mechanisms [29]. Other experts believe that there is a wealth of data showing that BLBLI treatment is similar to carbapenems in patients with ESBL-producing strains [30–32]. According to a Chinese expert consensus statement [33], BLBLIs are recommended for less severe infections, while carbapenems or high-dose BLBLIs are recommended for patients with severe infections. In a study conducted in China [31], cefoperazone-sulbactam was comparable to imipenem in the treatment of ESBL-producing *E. coli* bacteremia (no deaths reported, clinical success rate 71.4% vs. 87.5%, respectively; $P = 0.677$). However, in a study by Tamma et al. on 331 patients with ESBL-producing *E. coli* bacteremia, 103 (48%) of whom received piperacillin-tazobactam and 110 (52%) of whom received carbapenem, piperacillin-tazobactam increased mortality compared with carbapenem therapy (95% CI 1.07–3.45) [29].

The current study analyzed 298 patients with ESBL-producing *E. coli* BSI, including 81 receiving BLBLI monotherapy (piperacillin/tazobactam, n = 35; cefoperazone/sulbactam, n = 46) and 161 cases receiving carbapenem monotherapy (median APACHE II score, 9). The 30-day and 14-day mortality rates were 8.6% and 11.8%, respectively, with no statistically significant between-group differences. ESBL-producing *E. coli* BSI patients were assessed

for 14-day and 30-day mortality according to the APACHE II score (<6, 6–12, >12). Although no significant differences in 30-day mortality were seen, carbapenem monotherapy in patients with severe disease was seen to be more effective than BLBLI treatment.

In summary, in patients with suspected ESBL-producing *E. coli* BSI, antibiotic therapy can be selected according to the severity of the disease prior to blood culture. BLBLIs can be used as empirical antimicrobial therapy in patients with mild- or moderate-severity disease but carbapenems should be recommended when the condition is severe. Rational selection of antimicrobial regimens is important to slow the spread of carbapenem-resistant Enterobacteriaceae bacteria [34].

This study had several limitations. First, the sample of patients with *E. coli* bacteremia was collected from a single center, and institutional differences in mortality rates and prescribing patterns may affect the application of these results to other institutions. Second, the retrospective study design meant that there was potential for bias and inaccurate data collection. Third, the study was based on the isolation of *E. coli* in blood, but in clinical practice the clinical syndrome is usually known beforehand and risk factors for ESBL-producing *E. coli* might be different according to the type of syndrome.

In conclusion, this study demonstrates that prior UTIs and previous cephalosporin exposure represent significant risk factors for the development of ESBL-producing *E. coli* BSI. There was no significant difference in 30-day mortality in patients with BSI caused by ESBL-producing versus non-ESBL-producing *E. coli*. Previous carbapenem exposure, high APACHE II scores, and a respiratory tract origin are independent mortality risk factors in patients with *E. coli* BSI. It is suggested that BLBLI combinations may be as effective as carbapenem in the treatment of ESBL-producing *E. coli* bacteremia of mild or moderate severity.

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Competing interests

None declared.

Ethical approval

Not required.

Author contributions

YHX and TTX conceived the study. ZZW, QYS, and XLZ were involved in statistical analysis and drafting the manuscript. YZZ and XY participated in the study design and manuscript revision. All authors agree to be accountable for all aspects of the work.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jgar.2018.12.014.

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