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ORIGINAL RESEARCH

A Retrospective Analysis of Risk Factors and Patient Outcomes of Bloodstream Infection with Extended-Spectrum β-Lactamase-Producing *Escherichia coli* in a Chinese Tertiary Hospital

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Yanping Xiao*
Yaping Hang*
Yanhui Chen
Xueyao Fang
Xingwei Cao
Xiaoyan Hu
Hong Luo
Hongying Zhu
Wu Zhu
Qiaoshi Zhong
Longhua Hu

Jiangxi Provincial Key Laboratory of Medicine, Clinical Laboratory of the Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, People's Republic of China

*These authors contributed equally to this work

Objective: The present study assessed risk factors and patient outcomes of bloodstream infection (BSI) caused by extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* (*E. coli*).

Methods: A retrospective study was performed to analyze risk factors and patient outcomes of BSI caused by extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL-EC) in one Chinese tertiary hospital over a 7.5-year period. The clinical characteristics of patients infected with ESBL-producing and non-ESBL-producing *E. coli* were compared. Predictors of 30-day mortality in patients with *E. coli* BSI were also identified in our study.

Results: The results of drug sensitivity showed that quinolones, aminoglycosides, *β*-lactam/*β*-lactamase inhibitor combinations (BLICs) and trimethoprim/sulfamethoxazole exhibited significant differences between the ESBL and non-ESBL groups. Of the 963 patients with *E. coli* BSI, 57.6% developed ESBL-EC. Multivariate analysis showed that biliary tract infection (BTI) [P<0.001,OR (95% CI):1.798 (1.334–2.425)], urinary tract obstructive disease [P=0.001,OR (95% CI):2.106 (1.366–3.248)], surgery within 3 months [P=0.002,OR (95% CI):1.591 (1.178–2.147)], hospitalization within 3 months [P<0.001,OR (95% CI):2.075 (1.579–2.725)], ICU admission [P=0.011,OR (95% CI):1.684 (1.124–2.522)] and history of cephalosporin use [P=0.006,OR (95% CI):3.097 (1.392–6.891)] were statistically significant. In mortality analysis, aCCI>2 [P=0.016,OR (95% CI): 2.453 (1.179–5.103)], gastrointestinal catheterization [P=0.004, OR (95% CI): 2.525 (1.333–4.782)] were significantly associated with 30-day mortality. According to Kaplan-Meier survival analysis, we found that in SOFA<2 group and SOFA≥2 group, the mortality rate of patients treated with BLICs were lower than that of carbapenems (P<0.05).

Conclusion: This study showed that BTI, urinary tract obstructive disease, surgery within 3 months, hospitalization within 3 months, ICU admission and cephalosporin exposure were independent risk factors for the emergence of ESBL-EC BSI. Analysis of risk factors for 30-day mortality revealed that the factors independently associated with a higher risk of mortality were aCCI>2, gastrointestinal catheterization. Compared to carbapenems, the BLICs had preferable effect to treat patients with ESBL-EC BSI. Notably, patients with severe illness were inlcined to use carbapenems, which affected the analysis results. Therefore, we suggest that BLICs could be recommended to treat mild patients with ESBL-EC bacteremia.

Keywords: *Escherichia coli*, extended-spectrum beta-lactamase, bloodstream infection, risk factors, carbapenems

Correspondence: Qiaoshi Zhong; Longhua Hu
Email zhong20000947@sina.com; longhuahu@163.com

Introduction

Escherichia coli (*E. coli*) is one of the most common microorganisms causing intra-abdominal, urinary system and bloodstream infection (BSI).[1,2] According to the data of the European Antimicrobial Resistance Surveillance Network from 2002 to 2009, *E. coli* is the distinctly dominant BSI-causing pathogen. In South Korea, surveillance network data in 2016–2017 showed that *E. coli* was the predominant pathogenic bacteria. A Belgian study in 2000–2014 also showed a gradual increase in *E. coli* infections.[3–5] There is no doubt that *E. coli* infection has become a major health crisis attracting worldwide attention.

Bacterial resistance, particularly the emergence of extended-spectrum β-lactamase (ESBL), is an unavoidable and urgent problem worldwide. The emergence of ESBL mediates drug resistance to cephalosporins and greatly increases medical costs. *E. coli* is one of the major species of ESBL-producing family *Enterobacteriaceae*, and studies demonstrated that the infection rate of extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL-EC) is increasing annually.[6,7] In China, the prevalence rate of ESBL-EC is up to 53.6%.[8] ESBL-EC BSI has been increasing sharply, which greatly increases the medical burden. However, risk factors and outcomes associated with ESBL-EC BSI are not well established. The present study investigated the prevalence and some specific risk factors associated with ESBL-EC bacteremia and outcomes of patients infected with *E. coli*.

Materials and Methods

Study Design and Population

This retrospective, case–control study was performed at the Clinical Laboratory of the Second Affiliated Hospital of Nanchang University, which is a tertiary university hospital with 2400 patient beds in Jiangxi, China. We included all people with *E. coli* BSI from January 2012 to June 2019. Only the first bacteremic episode of each patient was included (Figure 1).

Data Collection

All data were collected from electronic medical records, including demographics and health-care history (admission diagnoses, history of chronic illness, antibiotic usage, hospital exposures, mortality, and collection time of first positive blood culture). The age-adjusted Charlson Comorbidity Index (aCCI) and sepsis-related organ failure assessment (SOFA) scores were calculated at the time of BSI onset.

Definitions

E. coli bloodstream infection was defined as at least one positive blood culture together, while presenting the following at least two criteria: 1) body temperature was higher than 38 °C or lower than 36 °C; 2) heart rate exceeded 90 beats per minute; 3) respiratory rate exceeded 20 breaths per minute; 4) the peripheral blood cell count showed an increase above 10×10^9/L or a decrease below 4×10^9/L. Nosocomial infection was defined as an infection that occurred >48h after admission to the hospital. The onset of infection was the time of sample collection. Empirical antibiotic therapy referred to antibiotics chosen after the patient had infection symptoms. Appropriate empirical antibiotic therapy as defined by the antimicrobials is active in vitro.

Antimicrobial Susceptibilities

E. coli isolates were identified using the VITEK 2 Compact system (bioMérieux, France) or MALDI-TOF MS (bioMérieux, France), and antimicrobial susceptibilities were determined in vitro using VITEK-2 Compact AST-GN16 (bioMérieux, France) or a Kirby–Bauer test. Drug sensitivities refer to the Clinical and Laboratory Standards Institute (CLSI) standards. Screening for ESBL production was performed using a combination disc method according to CLSI protocols using cefotaxime and ceftazidime alone or in combination with clavulanic acid.

Statistical Analysis

For categorical variables, the X^2 test or Fisher's exact test was used. In risk factor analysis, candidate variables with a P value <0.1 in a univariate model were included and then further determined in a forward stepwise logistic regression model. We used cox regression analysis to evaluate the survival in patients with bloodstream infection with *E. coli*. The Kaplan–Meier product-limit method was used to estimate the survival distribution function. Nonparametric (log-rank) tests were used to compare survival functions in different groups. All analyses were performed using SPSS (version24.0) software. In all analyses, P values≤0.05 were considered significant.

Results

Microbiological Characteristics of *E.coli*

During the 7.5-year study period, a total of 980 patients with *E. coli* BSIs were included. According to drug

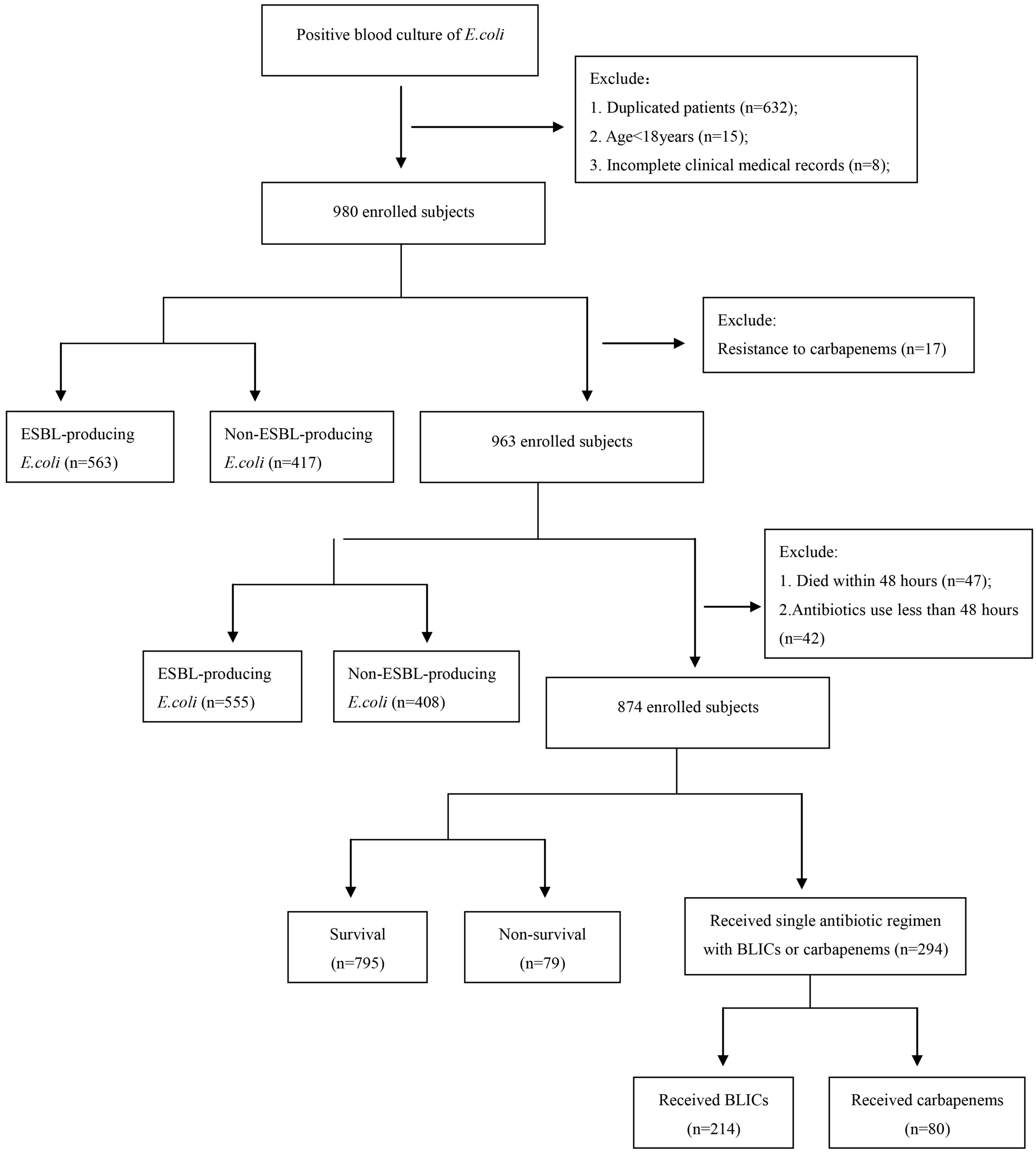

Figure 1 Case identification flow chart.

sensitivity test results, isolates were the highest sensitive to carbapenem, followed by furantoin and piperacillin/tazobactam. Compared the antimicrobial susceptibility profiles, we found that quinolones, aminoglycosides (except amikacin), β-lactam/β-lactamase inhibitor combinations (BLICs) and trimethoprim/sulfamethoxazole showed significant differences between the ESBL and non-ESBL groups. Of these drugs, amoxicillin/clavulanate and piperacillin/tazobactam showed more resistance in the non-ESBL groups. There was no difference between the resistance of carbapenem in ESBL and non-ESBL groups (Table 1).

Table 1 Antibiotic Resistance of ESBL-Producing *Escherichia coli* versus Non-ESBL-Producing *Escherichia coli*

Antimicrobial	Overall (n=980)	ESBL-Positive *E. coli* (n=563)	ESBL-Negative *E. coli* (n=417)	X^2	P value
Cefoxitin	17.5% (127/724)	17.0% (70/412)	18.3% (57/312)	0.201	0.654
Ciprofloxacin	52.9% (462/874)	70.5% (341/484)	31.0% (121/390)	134.745	<0.001
Levofloxacin	51.0% (499/978)	67.2% (377/561)	29.3% (122/417)	137.818	<0.001
Gentamicin	39.1% (382/977)	45.8% (257/561)	30.0% (125/416)	24.926	<0.001
Amikacin	2.5% (24/974)	3.6% (20/558)	1.0% (4/416)	6.821	0.09
Macrodantin	1.8% (16/891)	2.8% (14/496)	0.5% (2/395)	6.690	0.01
Tobramycin	11.1% (99/893)	15.3% (76/498)	5.8% (23/395)	19.907	<0.001
Meropenem	2.5% (2/81)	3.3% (2/61)	0(0/20)	-	0.565
Imipenem	1.6% (16/974)	1.2% (7/561)	2.2% (9/413)	1.277	0.258
Amoxicillin/clavulanate	16.1% (102/633)	13.1% (45/344)	19.7%(57/289)	5.125	0.024
Piperacillin/Tazobactam	3.1% (30/971)	1.6% (9/558)	5.1% (21/413)	9.510	0.002
Ampicillin/sulbactam	56.1% (143/255)	70.0% (105/150)	36.2% (38/105)	28.665	<0.001
Trimethoprim/sulfamethoxazole	51.1% (499/976)	56.9% (320/562)	43.2% (179/414)	17.914	<0.001

Demographic Characteristics of Patients with *E. coli* BSI

In the 980 patients, 17 cases of carbapenem-resistant *E. coli* BSI were excluded. The median age was 61 years (IQR: 51–72), and the female account for 54.1% (521/963). Nosocomial infection occurred in 49.9% (481/963), and most patients (33.2%) had hypertention, followed by biliary tract infection (BTI) (30.5%). A total of 24.1% (232/963) had antimicrobial exposure within 30 days. Among these patients, the proportion of patients who received BLICs antibiotic treatment was the highest. In all isolates, 57.6% (555/963) isolates were ESBL-producing organisms. All data are shown in Table 2.

Risk Factors for ESBL-Producing *E. coli* BSI

Table 2 shows the risk factors of ESBL-producing *E. coli*. In univariate analysis, female, diabetes, BTI, urinary tract obstructive disease, gastrointestinal catheterization, surgery within 3 months, hospitalization within 3 months, intensive care unit (ICU) admission, history of cephalosporin use and history of BLICs use were incorporated into multivariate analysis. After adjusting the confounding factors via logistics regression analysis, BTI [P<0.001,OR (95% CI):1.798 (1.334–2.425)], urinary tract obstructive disease [P=0.001,OR (95% CI):2.106 (1.366–3.248)], surgery within 3 months [P=0.002,OR (95% CI):1.591 (1.-178–2.147)], hospitalization within 3 months [P<0.001,OR (95% CI):2.075 (1.579–2.725)], ICU admission [P=0.011, OR (95% CI):1.684 (1.124–2.522)] and history of cephalosporin use [P=0.006,OR (95% CI):3.097 (1.392–6.891)] were independent risk factors of ESBL-producing *E. coli* BSI.

Risk Factors of 30-Day Mortality in Patients with ESBL-Producing *E. coli* BSI

In the risk factor analysis for mortality, 47 patients who died within 48h were excluded, and 42 patients who were treated with antibiotics for less than 48h were excluded. The 30-day mortality rate was 9.0%. In cox regression analysis, adjusting for ESBL production, central venous catheterization, urinary catheterization, nosocomial infection and appropriate empirical antibiotic therapy, aCCI>2 [P=0.016,OR (95% CI): 2.453 (1.179–5.103)], gastrointestinal catheterization [P=0.004,OR (95% CI):2.525 (1.-333–4.782)] were significantly associated with 30-day mortality (Table 3). ESBL-positive *E. coli* did not impact the mortality rate. To evaluate the efficacy of antibiotics in the treatment of ESBL-positive patients, we divided all ESBL-positive patients into SOFA score <2 and SOFA score ≥2 group. According to the therapy of different antibiotics in ESBL-positive patients, a Kaplan-Meier survival analysis is presented in Figure 2.

Discussion

In this study, we retrospectively analyzed the clinical characteristics of ESBL-producing and non-ESBL-producing *E. coli* BSI. We found that ESBL-EC was often more resistant to quinolones, aminoglycosides (except amikacin) and trimethoprim/sulfamethoxazole, which is consistent with other studies.[9–11] The reason may be that plasmids carrying genes encoding ESBL also often carry other drug-resistant genes

Table 2 Demographic and Clinical Characteristics of Patients with ESBL-Positive and ESBL-Negative *Escherichia coli*

Characteristics	ESBL Negative (n=408)	ESBL Positive (n=555)	Univariate Analysis		Multivariate Analysis	
			P value	OR (95% CI)	P value	OR (95% CI)
Female	239	282	0.017	0.730 (0.564–0.945)	Not selected	Not selected
Median age (IQR)	61 (52–72)	61 (50–71)	0.317	0.996 (0.987–1.004)	-	-
Pre-existing medical conditions						
Hypertension	139	181	0.636	0.937 (0.714–1.228)	-	-
Diabetes	85	88	0.047	0.716 (0.515–0.996)	Not selected	Not selected
Biliary tract infection	100	194	0.001	1.655 (1.244–2.201)	<0.001	1.798 (1.334–2.425)
Pancreatitis	17	17	0.363	0.728 (0.367–1.443)	-	-
Liver disease	56	79	0.822	1.043 (0.721–1.509)	-	-
Gastrointestinal disease	41	55	0.943	0.985 (0.643–1.508)	-	-
Urinary tract obstructive disease	37	83	0.007	1.763 (1.169–2.658)	0.001	2.106 (1.366–3.248)
Chronic kidney disease	26	35	0.967	0.989 (0.585–1.671)	-	-
Leukemia	17	13	0.112	0.552 (0.265–1.149)		
Solid tumor	104	124	0.256	0.841 (0.624–1.134)	-	-
Invasive procedure or device						
Central venous catheterization	49	80	0.280	1.234 (0.843–1.806)	-	-
Urinary catheterization	59	101	0.124	1.316 (0.927–1.868)	-	-
Gastrointestinal catheterization	18	47	0.015	2.005 (1.146–3.506)	Not selected	Not selected
Surgery within 3 months	100	190	0.001	1.603 (1.205–2.134)	0.002	1.591 (1.178–2.147)
Hospitalization within 3 months	138	278	<0.001	1.964 (1.508–2.557)	<0.001	2.075 (1.579–2.725)
Nosocomial infection	193	288	0.160	1.202 (0.930–1.552)	-	-
ICU admission	43	91	0.010	1.665 (1.130–2.453)	0.011	1.684 (1.124–2.522)
Antimicrobial exposure within 30 days						
Penicillin	9	12	0.963	0.980 (0.409–2.348)	-	-
Cephalosporin	8	36	0.002	3.468 (1.594–7.544)	0.006	3.097 (1.392–6.891)
BLICs	31	67	0.024	1.670 (1.068–2.609)	Not selected	Not selected
Fluoroquinolone	19	33	0.383	1.294 (0.725–2.311)	-	-
Carbapenem	6	11	0.553	1.355 (0.497–3.694)	-	-

encoding quinolones, aminoglycosides and trimethoprim/sulfamethoxazole.[12]

Our study found that BTI was an independent risk factor for ESBL-EC BSI. Gut luminal bile has anti-inflammatory, endotoxin-binding, bacteriostatic, mucosal-trophic, epithelial tight-junction maintaining, and gut motility-regulating effects.[13] BTI could lead to the deficiency of intestinal bile, resulting in excessive growth of intestinal flora, translocation of microflora and entry of endotoxin into the portal vein and systemic circulatory system.[14,15] Studies also found that intestinal microbiota imbalance led to a large number of pathogen colonization, which caused the spread of drug resistance genes (including genes encoding ESBL).[16,17] This pathway is likely the major reason for the increase of ESBL caused by BTI. Besides, most of these patients underwent biliary stent implantation. Invasive treatment leads to damage to the intestinal mucosal epithelium and results in bacterial translocation, which may also be another reason for the increase of ESBL.[18] Obstructive diseases of the urinary system were also an important risk factor for ESBL-EC BSI. Urinary tract infections are the major sources of bacteremia, and *E. coli* is the most common bacteria isolated from urine specimens.[19,20] In recent years, antibiotic-resistant *E. coli* in urinary tract infections is increasing, predominantly ESBL-EC.[21] Therefore, we need to be highly vigilant for serious bloodstream infections caused by urinary tract infection bacteria entering the bloodstream.

Exposure to cephalosporins, hospitalization and surgical history was closely related to the production of ESBL, which suggests that recent medical treatment behavior may accelerate the spread of ESBL. We speculated that the spread of ESBL was closely related to the relevant medical institutions, and many asymptomatic patients may become carriers and disseminators of ESBL for the related health-care behavior. ICU admission was also a risk factor for ESBL-EC

Table 3 Analysis of Risk Factors for 30-Day Mortality in Patients with *Escherichia coli* Bloodstream Infections

Characteristics	Survival (n=795)	Nonsurvival (n=79)	Multivariate Analysis	
			P value	**OR (95% CI)**
aCCI score>2	623	71	0.016	2.453 (1.179–5.103)
ESBL-producing *E. coli*	463	45	0.671	Not selected
Central venous catheterization	101	13	0.719	Not selected
Urinary catheterization	120	21	0.070	Not selected
Gastrointestinal catheterization	47	11	0.004	2.525 (1.333–4.782)
Nosocomial infection	391	41	0.846	Not selected
Appropriate empirical antibiotic therapy	715	72	0.840	Not selected

BSI. We speculated that patients admitted to ICU use a variety of antibiotics for a long time, which caused the increase in the horizontal transfer of ESBL genes.[22]

According to multivariate analysis, aCCI>2 and gastrointestinal catheterization were relatedly associated with day 30 mortality. Research demonstrated that enteral nutrition significantly reduced the infection rate and mortality of patients compared with parenteral nutrition.[23,24] Our data showed that most of the patients who underwent gastrointestinal catheterization were in critical condition. Therefore, it is reasonable to assume that the increased mortality in patients with gastrointestinal catheterization was more likely associated with their own underlying diseases. The production of ESBL did not affect the 30-day mortality of patients.

Many studies confirmed that carbapenem was effective or an optimal scheme for treating ESBL-EC.[25,26] However, carbapenem resistance has increased gradually. Studies found that BLICs, especially novel BLICs, have shown excellent in vitro susceptibilities to ESBL-EC.[27] Treatment of ESBL-producing strains with BLICs could alleviate potential antibiotic selective pressure and resistance of carbapenems. We estimated the single antibiotic regimen with BLICs or carbapenems in 30-day mortality. Among the patients isolated with ESBL-positive strains, a total of 294 patients received BLICs or carbapenems alone, of which 214 received BLICs and others received carbapenems. In SOFA score <2 group and SOFA score ≥2 group, the mortality rate of patients receiving BLICs all showed lower than that of patients received carbapenems (Figure 2). BLICs had preferable effect to mild-severity patients. But it does not means carbapenems were ineffective. In fact, carbapenems were part of antibiotic therapy for severe gram-negative infections and might therefore just indicate patients with a higher grade of severity of illness and, thus, increased mortality (Table 4). Furthermore, our study was a single-center retrospective analysis, which means that selection bias and sample size would impact our results.

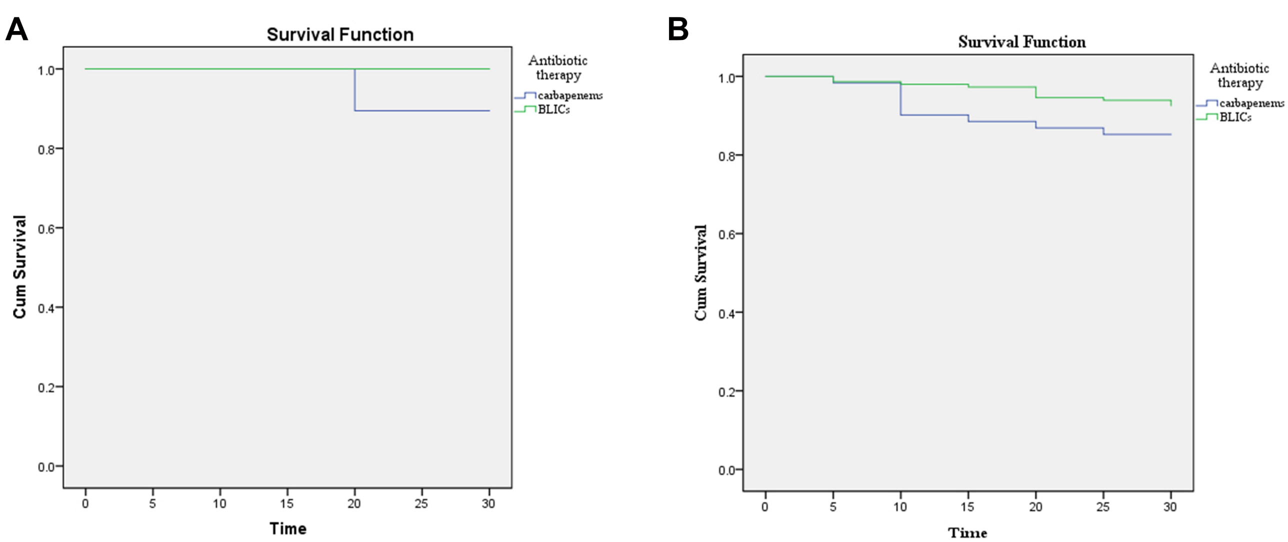

Figure 2 Kaplan–Meier 30-day survival estimates: (**A**) patients (SOFA score <2) treat with carbapenem and BLICs antibiotics (p=0.008); (**B**) patients (SOFA score≥2) treated with carbapenem and noncarbapenem antibiotics (p=0.044).

Table 4 The Patients Treated with Single Regimens in Different SOFA Score Groups

SOFA Score	Total	Received BLICs		Received Carbapenems	
		Survival	Nonsurvival	Survival	Nonsurvival
<2	85	98.5%(64/65)	1.5%(1/65)	90%(18/20)	10%(2/20)
2–6	135	95.2%(99/104)	4.8%(5/104)	96.8%(30/31)	3.2%(1/31)
7–9	43	90%(27/30)	10%(3/30)	76.9%(10/13)	23.1%(3/13)
≥10	31	86.7%(13/15)	13.3%(2/15)	62.5%(10/16)	37.5%(6/16)

In conclusion, this study found that BTI, urinary tract obstructive disease, surgery within 3 months, hospitalization within 3 months, ICU admission and exposure to cephalosporin were independent risk factors of ESBL-EC BSI. In patients with BSI of *E.coli*, aCCI score >2 and indwelling gastrointestinal tube were important risk factors for 30-day mortality. Moreover, BLICs could recommended to treat mild-severity patients.

Data Sharing Statement

All the data are from the database of the second affiliated Hospital of Nanchang University. The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

Ethics Statement

Informed consent was acquired from each participant included in the study. This study was approved by the Second Affiliated Hospital of Nanchang University Medical Research Ethics Committee (No. Review-2011-011).

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Disclosure

The authors have no conflicts of interest to disclose.

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