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Original Article

Propensity-matched analysis of the impact of extended-spectrum β-lactamase production on adults with community-onset *Escherichia coli*, *Klebsiella* species, and *Proteus mirabilis* bacteremia

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Abstract *Background:* The presence of extended-spectrum β-lactamase (ESBL) in *Escherichia coli*, *Klebsiella* species, and *Proteus mirabilis* (EKP) is of great microbiological and clinical importance. The study dealing with the direct impact of ESBL producers on the outcome of patients with community-onset bacteremia is lacking.
Methods: Adults with community-onset EKP bacteremia were recruited retrospectively during a 6-year period. ESBL producers were determined according to ESBL phenotype. ESBL patients were compared on a 1:2 basis with non-ESBL patients by using propensity-score matching (PSM) calculated based on independent predictors of 28-day mortality.

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Results: Of the 1141 eligible adult patients, 65 (5.7%) caused by ESBL producers. Significant differences between the two groups were discovered in the proportions of patients with critical illness (a Pitt bacteremia score $\geq$ 4) at bacteremia onset, inappropriate empirical antibiotic therapy, bacteremia because of urosepsis and pneumonia, and several comorbidities. In a PSM analysis after controlling for six independent predictors—critical illness at bacteremia onset, underlying fatal comorbidities (McCabe classification), inappropriate empirical antibiotic therapy, comorbidities with liver cirrhosis, bacteremia because of urosepsis and pneumonia—a appropriate matching between two groups (ESBL group, 60 patients; non-ESBL group, 120) were observed in age, causative microorganism, bacteremia severity, major comorbidities, comorbidity severity, and major bacteremia source. Consequently, a strong relationship between ESBL producers and poor prognosis was highlighted.
Conclusions: The adverse influence of ESBL producers on clinical outcomes was presented with respect to adults with community-onset EKP bacteremia. Establishing a predictive scoring algorithm for identifying patients at risk of ESBL-producer infections is crucial.

Introduction

Bacteremia is a life-threatening condition that is associated with significant healthcare costs and high mortality rates.[1] Enterobacteriaceae, particularly *Klebsiella pneumoniae* and *Escherichia coli*, are the leading cause of community-onset bacteremia.[2,3] The presence of extended-spectrum β-lactamase (ESBL) in the Enterobacteriaceae family is of great microbiological and clinical importance.[4] In past years, ESBL enzymes have spread from hospital to community environments, and infections caused by ESBL-producing microorganisms are an important public health issue.[4–6] Additionally, the incidence of community-onset bacteremia caused by ESBL producers has increased worldwide.[5,6]

The adverse impact of ESBL producers on patients with hospital- or healthcare facility-onset bacteremia has been documented.[4,7] Research has investigated and compared community-onset bacteremia caused by non-ESBL producers, despite findings indicating the dissimilar clinical characteristics and outcomes of patients with community-onset bacteremia caused by ESBL producers.[8,9] Although previous reports have found the difference of bacteremia severity and patient demography between the patients infected by ESBL producers and those by non-ESBL producers to be significant, demonstrating the direct influence of ESBL producers on patient prognosis is difficult. Therefore, we analyzed the impact of ESBL-producing isolates on the outcome of bacteremic patient after controlling for baseline patient characteristics and bacteremia severity by using a propensity-matched analysis (PSM).

Methods

Study design and population

A retrospective, cohort study was conducted at an emergency department (ED) of medical center in southern Taiwan, between January 2008 and December 2013. The study hospital, National Cheng Kung University Hospital, is a 1200-bed, university-affiliated medical center with an annual ED census of approximate 70,000 patients. The hospital institutional review board approved the study, which was reported by the format recommended by STROBE (Strengthening the Reporting of Observational Studies in Epidemiology), and partial clinical information in this study cohort has been published.[10,11]

Study protocol

Bacterial growth in blood cultures from adults sampled in the ED during the study period was screened in a computer database. Patients caused by bacteremic isolates of *E. coli*, *Klebsiella* species, and *Proteus mirabilis* (EKP) were included. Clinical information on eligible adults was retrieved from medical records by using a predetermined case record form including demographic data, initial syndromes, vital signs, bacteremia severity, comorbidities, comorbidity severity, duration and type of antimicrobial agents, bacteremia source, length of hospitalization, and clinical outcome. The study excluded any patients with hospital-onset bacteremia, those with polymicrobial bacteremia, those lacking clinical information from chart records, and those diagnosed with bacteremia prior to visiting the ED. The medical records of eligible patients were reviewed for the preceding clinical information by two of the authors. If any discrepancies were found, both authors examined the medical records together. In cases with multiple bacteremic episodes, only the patient's first episode was included. Adults with bacteremia caused by ESBL producers were assigned to the ESBL group; otherwise, they were assigned to the non-ESBL group.

The overall mortality during the 28 days after ED arrival (bacteremia onset) was referred to as the primary outcome. If patients were discharged within 28 days after ED arrival and were not followed up at our hospital, the required information was retrieved by telephone. Any patients who could not be reached by telephone were excluded.

Microbiological methods and ESBL detection

Blood cultures were incubated in a BACTEC 9240 instrument (Becton Dickinson Diagnostic Systems, Sparks, MD, USA) for 5 days at 35 °C. EKP was then identified using biochemical tests and confirmed with a Vitek system (Biomerieux, Lyon, France) and a GNI card. Bacteremic aerobic isolates in the study period were prospectively collected and antimicrobial susceptibility was determined by the disk diffusion method, based on performance standards of Clinical and Laboratory Standards Institute (CLSI) in 2016.[12] The tested drugs included ampicillin/sulbactam, piperacillin/tazobactam, cefazolin, cefuroxime, cefotaxime, ceftazidime, cefepime, ertapenem, imipenem and levofloxacin (supplemental data). If patient empirically treated by other agents, the susceptibility of the indicated agent was measured. ESBL production was detected by the phenotypic confirmatory test with the cephalosporin-clavulanate combination disks.[13]

Definitions

Community-onset bacteremia indicates that the place of bacteremia onset is the community, which includes long-term health-care facilities, as previously described.[10,11,14] Antibiotic therapy was considered to be appropriate, if the route and dosage of an antimicrobial agent was administered as recommended in the Sanford Guide[15] and bacteremic pathogens were *in vitro* susceptible to the prescribed agent based on the contemporary breakpoints recommended by CLSI.[12] Inappropriate empirical antibiotic therapy was defined as the first dose of appropriate antimicrobial agent was not administered within the first 24 h after blood cultures were drawn.[10,11] The severity of underlying medial illness was stratified according to the McCabe score and categorized as rapidly fatal, ultimately fatal, or nonfatal.[16] The severity of bacteremia at the time of bacteremic onset (during the ED stay) was assessed using a Pitt bacteremia score, a validated scoring system based on vital signs, mental status, mechanical ventilation, and the presence of cardiac arrest.[17] Patients with a high Pitt bacteremia score ($\geq$4) was indicated as the critical illness, whereas those having a low Pitt bacteremia score ($=$0) as the stability.[18] Severe sepsis and septic shock was defined as the previous description.[19]

Malignancy includes both hematological malignancies and solid tumors. The definition of comorbidities was as previously described.[20] The sources of bacteremia were determined clinically based on the presence of an active infection site coincident with bacteremia or the isolation of a microorganism from other clinical specimens prior to or on the same date of bacteremia onset. If the source of bacteremia could not be assigned to a specific site, it was classified as primary bacteremia. Crude mortality was used to define death from all causes, whereas the death of a patient with a clinical course suggestive of persistently active infection without an obvious explanation was referred as sepsis-related mortality.

Data analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS, Chicago, Illinois, USA), Version 20.0. Continuous variables were expressed as the means $\pm$ standard deviations (SDs) and were compared with Student's *t*-test. Categorical variables, expressed as numbers and percentages, were compared using the *Chi*-square test or Fisher's exact test. Independent predictors for mortality were identified using logistic regression analysis. All variables with *P*-values less than 0.1 in the univariate analysis were incorporated into a stepwise, backward logistic regression model. To compare the adverse effect of ESBL-producers on survival rate, Kaplan—Meier plots along with a log-rank test was used. A *P*-value less than 0.05 was considered statistically significant.

The propensity score was calculated using independent predictors of 28-day mortality, which were assessed using a multivariable logistic regression model. The ESBL group was matched on a 1:2 basis with the non-ESBL group and the matching by the closest total scores was done manually based on a tolerance interval approach. As previously described,[21] the matching tolerance was a propensity score difference of 0.2: a patient in the ESBL group was matched to a patient in the non-ESBL group only when the estimated probability of the ESBL group was within 20% of the estimated probability of his or her counterpart who infected by a non-ESBL-producer.

Results

Comparisons of clinical characteristics and severity for ESBL and non-ESBL patients

Of the 1141 EKP linked to community-onset monomicrobial bacteremia, the leading causative microorganism (826 isolates, 72.4%) was *E. coli*, followed by *Klebsiella* species (284, 24.9%) and *P. mirabilis* (31, 2.7%). ESBL producers only accounted for 5.7% (65 isolates). For the total 1141 patients, univariate analyses were used to compare the clinical variables at bacteremia onset and clinical outcome between the ESBL and non-ESBL groups (Table 1), including patient demography, causative microorganism, inappropriate empirical therapy, bacteremia severity, bacteremia source, comorbidities, and comorbidity severity. The ESBL group exhibited the following factors relative to the non-ESBL group: a higher proportion of nursing home residents, higher use of inappropriate empirical antibiotic therapy, higher Pitt bacteremia scores ($\geq$4), higher rates of bacteremic urosepsis, higher rates of diabetes mellitus or neurological disease comorbidities, a lower proportion of women, and lower rates of bacteremia caused by liver abscesses. Of note, a higher 14-day and 28-day crude mortality rate was evidenced in patients in the ESBL group.

Risk factor for 28-day mortality among all patients

Univariate analyses were used to compare the groups of deceased patients with those who survived within 28 days from the onset of bacteremia. The variables for comparison were clinical characteristics, demography, major bacteremia source, major comorbidities, comorbidity severity, bacteremia severity at onset, causative microorganisms, and inappropriate empirical antibiotic therapy (Table 2).

Table 1 Comparisons of clinical characteristic, source of bacteremia, bacteremia severity, comorbidity severity, and mortality in adults with community-onset bacteremia caused by ESBL-producing EKP and those by non-ESBL-producing EKP.

Variable at bacteremia onset	Patients no. (%)		*P* value
	ESBL n = 65	Non-ESBL n = 1076	
Gender, female	27 (41.5)	631 (58.6)	0.007
Age, year, mean ± SD	74.8 ± 13.5	68.2 ± 15.3	0.001
Nursing home residents	26 (40.0)	32 (3.0)	<0.001
Inappropriate empirical antibiotic therapy	47 (72.3)	80 (7.4)	<0.001
Severity-of-illness marker at bacteremia onset			
Pitt bacteremia score			
≥ 4 points	19 (29.2)	177 (16.4)	0.008
0 point	16 (24.6)	291 (27.0)	0.67
Initial syndrome			
Severe sepsis	29 (44.6)	463 (43.0)	0.80
Septic shock	17 (26.2)	186 (17.3)	0.07
Causative microorganism			
Escherichia coli	48 (73.8)	778 (72.3)	0.79
Klebsiella species	14 (21.5)	270 (25.1)	0.52
Proteus species	3 (4.6)	28 (2.6)	0.42
Major source of bacteremia			
Urinary tract infection	42 (64.6)	556 (51.7)	0.04
Biliary tract infection	10 (15.4)	127 (11.8)	0.39
Pneumonia	8 (12.3)	97 (9.0)	0.37
Intra-abdominal infection	3 (4.6)	129 (12.0)	0.07
Primary bacteremia	2 (3.1)	68 (6.3)	0.29
Liver abscess	0 (0)	64 (5.9)	0.04
Major comorbidities			
Diabetes mellitus	35 (53.8)	409 (38.0)	0.01
Hypertension	30 (46.2)	534 (49.6)	0.59
Neurological disease	27 (41.5)	211 (19.6)	<0.001
Malignancy	21 (32.3)	286 (26.6)	0.31
Chronic kidney disease	13 (20.0)	150 (13.9)	0.18
Liver cirrhosis	11 (16.9)	143 (13.3)	0.41
Coronary artery disease	11 (16.9)	106 (9.9)	0.07
Comorbidity severity (McCabe classification)			0.55
Ultimately and rapidly fatal	16 (24.6)	231 (21.5)	
Nonfatal	49 (75.4)	845 (78.5)	
Crude mortality rate			
14-day	12 (18.5)	70 (6.5)	0.001
28-day	21 (32.3)	99 (9.2)	<0.001

The following were significantly positively associated with 28-day mortality: nursing-home residents, critical illness (a Pitt bacteremia score ≥ 4) at bacteremia onset, underlying fatal comorbidities (McCabe classification), inappropriate empirical antibiotic therapy, bacteremia due to pneumonia, primary bacteremia, bacteremia caused by *Klebsiella* species, and comorbidities with malignancy, liver cirrhosis, or neurological disease. Additionally, female sex, bacteremia caused by urosepsis, bacteremia caused by *E. coli*, and underlying hypertension were significantly negatively associated with 28-day mortality. In subsequent multivariate regression analysis, the following were independently associated with 28-day mortality: inappropriate empirical antibiotic therapy, critical illness (a Pitt bacteremia score ≥ 4) at bacteremia onset, underlying fatal comorbidities, comorbidities with liver cirrhosis, and bacteremia caused by pneumonia or urosepsis.

Baseline characteristics, severity, and clinical outcomes after PSM

Of the 1076 patients in the non-ESBL group, 120 patients were matched with the 60 patients in the ESBL group with the closest propensity scores on the basis of six independent predictors of crude mortality (Table 2). No significant difference was observed between the two groups in demographic characteristics, causative microorganisms, major comorbidities, and major bacteremia sources (Table 3). Of importance, no significant difference was observed between the groups in the proportion of inappropriate empirical antibiotic therapy, bacteremia severity at onset, and comorbidity severity. Notably, the ESBL group exhibited a poorer prognosis than did the non-ESBL group, with a higher 28-day crude and sepsis-related mortality rate. Additional analyses of the survival curves revealed a

Table 2 Association of 28-day crude mortality with clinical demography, severity, comorbidity, source of bacteremia, and empirical appropriate antibiotic therapy in adults with community-onset EKP bacteremia.

Variable	Patients no. (%)		Univariate	Multivariate analysis	
	Non-survivors n = 120	Survivor n = 1021	*P* value	Adjusted odds ratio (95%CI)	*P* value
Old age, ≧65years	78 (65.0)	647 (63.4)	0.73	—	—
Gender, female	44 (36.7)	614 (60.1)	<0.001	NS	NS
Nursing-home residents	19 (15.8)	39 (3.8)	<0.001	NS	NS
Pitt bacteremia score at bacteremia onset					
≥4	76 (63.3)	120 (11.8)	<0.001	11.50 (6.98—18.97)	<0.001
0	12 (10.0)	295 (28.9)	<0.001	NS	NS
Ultimately and rapidly fatal comorbidity (McCabe classification)	63 (52.5)	184 (18.0)	<0.001	3.85 (2.30—6.42)	<0.001
Major source of bacteremia					
Pneumonia	43 (35.8)	62 (6.1)	<0.001	4.01 (2.30—7.35)	<0.001
Urinary tract infection	25 (20.8)	573 (56.1)	<0.001	0.45 (0.25—0.82)	0.009
Intra-abdomen infection	20 (16.7)	112 (11.0)	0.07	—	—
Primary bacteremia	13 (10.8)	57 (5.6)	0.02	NS	NS
Causatic microorganisms					
Escherichia coli	63 (52.5)	763 (74.7)	<0.001	NS	NS
Klebsiella species	52 (43.3)	232 (22.7)	<0.001	NS	NS
Inappropriate empirical antibiotic therapy	28 (23.3)	99 (9.7)	<0.001	2.17 (1.19—3.93)	0.01
Major comorbidities					
Malignancy	55 (45.8)	252 (24.7)	<0.001	NS	NS
Liver cirrhosis	39 (32.5)	115 (11.3)	<0.001	2.55 (1.39—4.66)	0.002
Hypertension	38 (31.7)	526 (51.5)	<0.001	0.59 (0.35—0.10)	0.05
Diabetes mellitus	37 (30.8)	407 (39.9)	0.06	—	—
Neurological disorder	34 (28.3)	204 (20.0)	0.03	NS	NS

NS indicated no significance (after processing the stepwise and backward multivariate regression).

significant difference in 28-day mortality between the ESBL and non-ESBL patients both before (Fig. 1A) and after (Fig. 1B) PSM.

Discussion

In conformity with previous studies examining the adverse impact of hospital-[7] and community-onset[8,9] bacteremia caused by ESBL-producing Enterobacteriaceae, the ESBL and non-ESBL patients exhibited a significantly different presentation at bacteremia onset in this long-term cohort study. Crucially, a high proportion of inappropriate empirical antibiotic therapy and severe bacteremia episodes were observed in the ESBL patients. Using PSM analyses, bacteremia due to ESBL producers remained a significant adverse influence on clinical outcome after the independent risk factors of crude mortality, such as baseline characteristics, inappropriate empirical antibiotic therapy, and bacteremia severity, were controlled for.

Of six independent risk factors for mortality, the leading was a high Pitt bacteremia score at onset in our population. The value of this score for determining illness severity at the onset of bacteremia by ESBL-producing microorganisms such as *E. coli*[22] and *K. pneumoniae*[17,22] has been well documented; bacteremia severity at bacteremic onset was also a crucial predictor of mortality in these published studies. Similarly, as a previous ED-based cohort that enrolled the general population of all community-onset bacteremia determined, a high Pitt bacteremia score at bacteremia onset always leads to poor prognosis.[2]

Traditionally, PSM analyses are especially useful for retrospective clinical trials that overcome the different distribution of baseline covariates between treatment groups because they provide a natural weighting scheme that yields unbiased estimates of the treatment impact.[23] Similar to previous report using propensity-scoring to match the patient groups,[24] this analysis controlled for the baseline factors linked to crude mortality for the ESBL-producer and non-ESBL-producer groups. Moreover, inappropriate empirical antibiotic therapy was determined to be the second most powerful factor linked to poor patient outcome in the present study. This is consistent with the results of previous investigations of patients with community-onset bacteremia; irrespective of patients having numerous infections and various causative microorganisms, research has consistently indicated that delayed appropriate antibiotic therapy leads to poor prognosis.[25] Crucially, corroborating prior reports,[9,26] a vastly different proportion of patients in the ESBL group received inappropriate empirical antibiotic therapy relative to the non-ESBL groups here. PSM analyses were a suitable means of overcoming the different impact of the inappropriate therapy on two groups. Despite this crucial difference leading to limited patient numbers for the two groups when processing the PSM, more patients with critical illnesses (51/180, 28.3% *vs.* 196/1161, 16.9%; $P < 0.001$) and fatal comorbidities (51/180, 28.3% *vs.* 247/

Table 3 Clinical baseline characteristics and outcome of 60 adults with community-onset bacteremia caused by ESBL-producing EKP and 120 matched patients with community-onset, non-ESBL-producing EKP bacteremia.

Variable	Patient number		*P* value
	ESBL group n = 60	Non-ESBL group n = 120	
Age, mean ± standard deviation (year)	74.7 ± 13.5	70.5 ± 14.2	0.06
Gender, female	34 (56.7)	51 (42.5)	0.07
Nursing home residents	24 (40.0)	8 (6.7)	<0.001
Causatic microorganisms			
Escherichia coli	44 (73.3)	92 (76.7)	0.62
Klebsiella pneumoniae	14 (23.3)	23 (19.2)	0.51
Proteus mirabilis	2 (3.3)	5 (4.2)	0.79
Major source of bacteremia			
Urinary tract infection	38 (63.3)	61 (50.8)	0.11
Biliary tract infection	10 (16.7)	17 (14.2)	0.66
Pneumonia	7 (11.7)	14 (11.7)	1.00
Intra-abdomen infection	3 (5.0)	15 (12.5)	0.11
Primary bacteremia	2 (3.3)	6 (5.0)	0.61
Major comorbidities			
Diabetes mellitus	33 (55.0)	55 (45.8)	0.25
Hypertension	28 (46.7)	59 (49.2)	0.75
Neurological disorder	25 (41.7)	33 (27.5)	0.06
Malignancy	20 (33.3)	42 (35.0)	0.82
Chronic kidney diseases	11 (18.3)	20 (16.7)	0.78
Liver cirrhosis	11 (18.3)	19 (15.8)	0.67
Inappropriate empirical antibiotic therapy	42 (70.0)	73 (60.8)	0.23
Ultimately and rapidly fatal comorbidity (McCabe classification)	14 (23.3)	37 (30.8)	0.29
Severity-of-illness marker at bacteremia onset			
Pitt bacteremic score			
≥4 points	18 (30.0)	33 (27.5)	0.73
0 point	15 (25.0)	31 (25.8)	0.90
Initial syndrome			
Severe sepsis	26 (43.3)	63 (52.5)	0.25
Septic shock	16 (26.7)	31 (25.8)	0.90
Length of stay, mean ± standard deviation (day)			
Total hospitalization	16.0 ± 9.7	14.5 ± 18.0	0.55
Intensive care units	3.3 ± 8.1	1.4 ± 4.1	0.09
Mortality rate			
14-day			
Crude	11 (18.3)	19 (15.8)	0.67
Sepsis-related	11 (18.3)	19 (15.8)	0.67
28-day			
Crude	22 (36.7)	26 (21.7)	0.03
Sepsis-related	20 (33.3)	23 (19.2)	0.04

1161, 21.3%; $P = 0.03$) were observed in the study population after PSM than were in the original population before matching.

The virulence of ESBL-producing *E. coli* of the CTX-M type has been documented. Several small investigations have indicated that the virulence factors of *E. coli* producing CTX-M-type ESBL were similar to, or fewer than, those of three control groups: CTX-M non-producers, ESBL producers of the TEM and SHV types, and non-ESBL producers.[27–29] However, the SHV type was frequently detected in Taiwan in bacteremia-causing *K. pneumoniae* and *E. coli* with ESBL production.[30] Therefore, further study to compare the virulence of EKP-producing SHV-type ESBL and non-ESBL producers is necessary.

This study has several design limitations. First, to adequately assess the clinical impact of ESBL producers, several exclusion criteria were implemented, which may have led to selection bias. However, only 25 (2.1%) of the bacteremic patients were excluded from our population, which should have only exerted a minimal effect on the results. Second, the clinical information was collected retrospectively by reviewing medical records. Despite retrieving patient outcome by telephone for those with uncertain short-term outcomes to diminish the confounding of primary outcomes, this retrospective approach for other parameters has inherent limits because of possible confounding data and selection bias. Third, the therapeutic role of carbapenems in patients with ESBL-producing EKP

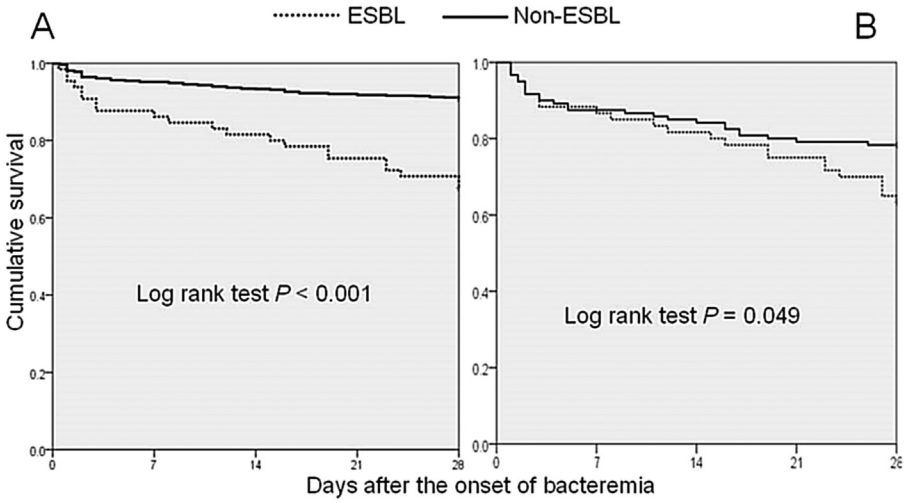

Figure 1. Kaplan—Meier survival curves comparing 28-day mortality among bacteremic patients caused by ESBL-producing EKP and those by non-ESBL-producing EKP. (A) All the 1141 patients. (B) 180 matched patients.

bacteremia is well established.[4] Nevertheless, the susceptibility testing was interpreted on the basis of contemporary CLSI criteria here; thus, the therapeutic role of *in vitro* active non-carbapenem antimicrobials was not discussed. For example, the antimicrobial therapy was regarded as appropriate if patients received cefepime therapy of the standard dosage for bacteremia caused by the susceptible EKP adjusted by disk diffusion method. Fourth, because the patient demography was collected retrospectively in the present study, clinical information was insufficient to distinguish the true community-acquired bacteremia forms other bacteremia types. Furthermore, for ED clinicians, it is difficult to rapidly recognize the category of the patients from the community visiting the ED, particularly in the overcrowded ED. Therefore, we included patients with community-onset bacteremia, rather than those with community-acquired bacteremia. Finally, ESBL producers were often reported in EKP, but a growing number of other ESBL-producing Enterobacteriaceae (such as *Enterobacter cloacae*) have been observed worldwide.[31] Despite EKP accounting for most community-onset ESBL producers,[5] our finding may not be generalizable to other microorganisms.

Conclusively, focusing on adults with community-onset EKP bacteremia, the adverse impact of ESBL producers on clinical outcome was determined by using a PSM analysis to control the baseline covariates affecting the crude mortality. Considerable effort should be made to optimize the detection of bacteremia caused by ESBL-producing microorganisms. Careful attention must be paid to barrier precautions to prevent their community spread.

Competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jmii.2017.05.006.