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ORIGINAL RESEARCH ARTICLE

The association of ESBL *Escherichia coli* with mortality in patients with *Escherichia coli* bacteremia at the emergency department

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ABSTRACT

Background: *Escherichia coli* is a common bloodstream infection pathogen in the emergency department (ED). Patients with extended-spectrum beta-lactamase (ESBL) *E. coli* have a higher risk of morbidity. However, there is still debate surrounding ESBL *E. coli*-associated mortality in community, intensive care unit, and tertiary care settings. In addition, there have been few studies regarding mortality in ESBL *E. coli* in ED settings, and results have been contradictory.

Methods: This was a retrospective cohort study conducted at the Department of Emergency Medicine, Faculty of Medicine, Khon Kaen University in Thailand aimed at evaluating the possible association between ESBL *E. coli* bacteremia and mortality in the ED. The inclusion criteria were age 18 years or over, clinical presentation suspicious of infection, and positive blood culture for *E. coli*. Predictors for mortality were analyzed by logistic regression analysis.

Results: During the study period, 273 patients presented at the ED with hemoculture positive for *E. coli*. Of those, 27 (9.89%) died. Five factors remained in the final model, of which plasma glucose levels, serum lactate levels, and ESBL *E. coli* were significantly associated with 28-day mortality in the ED with adjusted odds ratios of 0.970, 1.258, and 12.885, respectively. Plasma glucose of less than 113 mg/dL yielded a sensitivity of 80.95% and specificity of 64.29%, while serum lactate over 2.4 mmol/L had a sensitivity of 81.48% and specificity of 45.50%.

Conclusion: ESBL *E. coli*, plasma glucose, and serum lactate levels were associated with 28-day mortality in patients with *E. coli* bacteremia presenting at the ED.

Keywords: Extended-spectrum beta-lactamase-producing *Escherichia coli*, Glucose, Lactate

Introduction

Bloodstream infection (BSI) with Gram-negative bacteria is common in the emergency department (ED), accounting for 39.4% of ED patients with suspected infection (1). A study from China found that *Escherichia coli* was the most common Gram-negative BSI in 3,199 patients and accounted for 34.3% of cases (2). One population-based study found the mortality rate of *E. coli* BSI to be 9.6%. Male patients aged 70 years or older are at higher risk of 30-day mortality with adjusted incidence rate ratios of 1.26 and 10.35 (3). Another study found a mortality rate of 30.6% in patients infected with extended-spectrum beta-lactamase (ESBL) *E. coli* vs 22.2% in those infected with non-ESBL strains or *Klebsiella pneumoniae* (4).

The prevalence of drug-resistant Gram-negative bacteria is increasing, particularly in in-hospital, intensive care unit (ICU), and tertiary care settings (5-8). A study from a multispecialty hospital in India found that rates of multidrug-resistant Gram-negative bacteria increased from 26.16% in 2012 to 33.33% in 2014 (6). Additionally, urinary tract infection patients with resistant Enterobacteriaceae have been shown to be 1.447 times more likely to have severe sepsis or septic shock at presentation than those with nonresistant strains (9). Data regarding the association of ESBL *E. coli* and mortality in community, ICU, and tertiary care settings have been inconclusive. Two studies conducted in community settings, for example, found differences in mortality between

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patients with ESBL and non-ESBL bacteremia (10,11), whereas a study from a tertiary care setting found comparable rates (9.7% vs 9.2%), as did a study in a teaching hospital in China (12,13). However, another study in a teaching hospital in Japan found higher rate of mortality in patients with ESBL strains (14), as did a study in an ICU (37.5% vs 15.6%; p = 0.04) (15). This study thus aimed to evaluate if ESBL *E. coli* bacteremia was associated with mortality in an ED setting.

Methods

This was a retrospective cohort study conducted at the Department of Emergency Medicine, Faculty of Medicine, Khon Kaen University in Thailand as part of an ED infection project. The inclusion criteria were age 18 years or over, clinical presentation suspicious of infection, and positive blood culture for *E. coli*. Patients who received prophylactic antibiotics, presented with cardiac arrest or symptoms related to trauma, were referred from other hospitals, or had missing clinical data were excluded. The study period was between 2016 and 2018.

Eligible patients were selected from the hospital database. We reviewed participants' clinical data at the time of presentation as well as mortality data over the following 28 days. Clinical data included baseline characteristics, laboratory results, and treatment. Baseline characteristics reviewed were age, sex, comorbid diseases, Charlson Comorbidity Index, physical signs, and quick Sepsis Related Organ Failure Assessment (qSOFA) score. Laboratory results included complete blood count, chemistry, arterial blood gas, serum lactate levels, and blood culture results (for ESBL *E. coli* positivity). The primary outcome was 28-day mortality.

Statistical analyses

Eligible patients were categorized into two groups by mortality. Descriptive statistics were used to calculate differences between the two groups. Predictors for mortality were analyzed using logistic regression analysis. Univariate logistic analysis was used to calculate the unadjusted odds ratio with 95% confidence interval and p value for each factor. Factors with a p value less than 0.05 by univariate logistic regression analysis or those that were clinically significant were subsequently subjected to stepwise, multivariate logistic regression analysis. The final model was tested for goodness of fit using the Hosmer-Lemeshow method. Results were reported as unadjusted/adjusted odds ratios with their 95% confidence intervals. A numerical predictor for mortality as an appropriate diagnostic cutoff point was computed with its sensitivity and specificity. All statistical analyses were performed using STATA version 10.1 (College Station, Texas, USA).

Results

During the study period, 273 patients presented at the ED with hemoculture positive for *E. coli*. Of those, 27 (9.89%) died. In terms of baseline characteristics and physical signs, there were 12 factors that differed significantly between those who survived and those who died (Tab. I). For example, nonsurvivors had a significantly higher Charlson Comorbidity Index (5 vs 4), respiratory rate (28 vs 24 breaths/min), and qSOFA score (2 vs 1), but oxygen saturation at presentation was lower (96% vs 97%; p 0.040). qSOFA scores were significantly higher in those who died than those who survived (2 vs 1; p < 0.001).

With regard to laboratory tests and treatment, seven factors differed significantly between groups (Tab. II). For example, the nonsurvival group had significantly lower levels of serum bicarbonate (17 vs 21 mEq/L) and plasma glucose (94 vs 131 mg/dL), higher serum lactate levels (4.5 vs 2.6 mmol/L), and a greater percentage of patients with ESBL

TABLE I - Baseline characteristics of patients with *Escherichia coli* bacteremia presenting at the emergency department categorized by mortality at 28 days

Factors	Survivors n = 246	Nonsurvivors n = 27	p-Value
Age, years	66 (18-100)	73 (19-93)	0.161
Male sex	125 (50.81)	10 (37.04)	0.224
Comorbid diseases			
Liver disease	50 (20.33)	10 (37.04)	0.053
Diabetes	57 (23.85)	2 (7.41)	0.053
CKD (moderate-severe)	24 (9.76)	4 (14.81)	0.499
Solid organ tumor	74 (30.08)	15 (55.56)	0.010
Palliative care	4 (1.63)	4 (14.81)	0.004
Leukemia	2 (0.81)	1 (3.70)	0.269
Lymphoma	2 (0.81)	2 (7.41)	0.050
Hypertension	90 (36.59)	7 (25.93)	0.299
HIV infection	2 (0.81)	0	0.999
Cholangiocarcinoma	34 (13.82)	8 (29.63)	0.045
Charlson Comorbidity Index	4 (0-12)	5 (1-12)	<0.001
Temperature, °C	38.6 (35.9-41.5)	38.2 (35.6-41.0)	0.184
Pulse rate, beats/min	96 (58-190)	96 (52-148)	0.898
Respiratory rate, breaths/min	24 (18-50)	28 (18-40)	0.008
SBP, mm Hg	126 (64-218)	112 (80-167)	0.003
DBP, mm Hg	70 (33-112)	67 (37-95)	0.071
MAP, mm Hg	91 (48-138)	80 (56-119)	0.009
Oxygen saturation, %	97 (60-100)	96 (65-100)	0.040
GCS	15 (4-15)	15 (7-15)	<0.001
Sepsis score			
qSOFA	1 (0-3)	2 (1-3)	<0.001

Data are presented as median (range) or number (percentage).
CKD = chronic kidney disease; DBP = diastolic blood pressure; GCS = Glasgow coma scale; MAP = mean arterial pressure; qSOFA = quick Sepsis Related Organ Failure Assessment; SBP = systolic blood pressure.
Data presented as number (percentage) unless indicated otherwise.

TABLE II - Laboratory results and treatment of patients with *Escherichia coli* bacteremia presenting at the emergency department categorized by mortality at 28 days

Factors	Survivors n = 246	Nonsurvivors n = 27	p-Value
Hb, g/dL	11.0 (4.6-16.0)	9.6 (4.8-13.8)	0.002
WBC, $\times 10^3/mm^3$	33.8 (13.0-51.7)	26.6 (14.9-41.9)	0.010
Platelet, $\times 10^6$	179 (4-584)	138 (13-451)	0.098
BUN, mg/dL	17.9 (3.7-144.8)	27.3 (6.7-153.2)	0.009
Creatinine, mg/dL	1.1 (0.4-10.4)	1.5 (0.5-11.1)	0.118
Bicarbonate, mEq/L	21 (7-30)	17 (7-27)	<0.001
Total bilirubin, mg/dL	1.4 (0.2-33.8)	2.1 (0.3-33.8)	0.251
Glucose, mg/dL	131 (53-548)	94 (35-172)	<0.001
PaO_2, mmHg	76 (23-512)	89 (33-253)	0.702
pH	7.44 (7.16-7.58)	7.40 (7.11-7.56)	0.194
Lactate level, mmol/L	2.6 (0.5-18.3)	4.5 (1.3-17.9)	0.003
ESBL *E. coli*	5 (2.03)	4 (14.81)	0.007
Treatment			
Mechanical ventilator	21 (8.54)	5 (18.52)	0.155
ICU admission	83 (3.74)	17 (62.96)	0.005
Vasopressor*	62 (25.20)	21 (77.78)	<0.001
LOS	11 (2-56)	8 (1-54)	0.013

Data are presented as median (range) or number (percentage).
BUN = blood urea nitrogen; ESBL ***E. coli*** = extended-spectrum beta-lactamase-producing *Escherichia coli*; Hb = hemoglobin; ICU = intensive care unit; LOS = length of stay; PaO_2 = partial pressure of oxygen; pH = power of hydrogen; WBC = white blood cell.
*indicates that the patient received norepinephrine, adrenaline, or dopamine.

TABLE III - Factors associated with a 28-day mortality in patients with *Escherichia coli* bacteremia presenting at the emergency department

Factors	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Oxygen saturation	0.933 (0.883, 0.985)	0.934 (0.860, 1.015)
Hemoglobin	0.732 (0.605, 0.885)	0.856 (0.662, 1.106)
Plasma glucose	0.971 (0.955, 0.987)	0.970 (0.954, 0.987)
Serum lactate level	1.185 (1.067, 1.317)	1.258 (1.090, 1.451)
ESBL *E. coli**	8.382 (2.103, 33.407)	12.885 (1.082, 153.338)
Age	1.008 (0.981, 1.036)	Not retained
Sex	0.569 (0.251, 1.293)	Not retained
Liver disease	2.306 (0.995, 5.344)	Not retained
Diabetes	0.255 (0.058, 1.111)	Not retained
Cholangiocarcinoma	2.625 (1.065, 6.469)	Not retained
Solid organ tumor	2.905 (1.297, 6.508)	Not retained
qSOFA	3.761 (1.974, 7.164)	Not retained
DBP	0.974 (0.947, 1.001)	Not retained
GCS	0.770 (0.630, 0.941)	Not retained
Hemoglobin	0.732 (0.605, 0.885)	Not retained
WBC	1.014 (0.995, 1.032)	Not retained
Serum bicarbonate	0.836 (0.762, 0.918)	Not retained

Factors in the model included age, sex, liver disease, diabetes, cholangiocarcinoma, solid organ tumor, qSOFA, DBP, GCS, WBC, and serum bicarbonate.
DBP = diastolic blood pressure; ESBL = extended-spectrum beta-lactamase; GCS = Glasgow coma scale; qSOFA = quick Sepsis Related Organ Failure Assessment; WBC = white blood cell.

E. coli (14.81% vs 2.03%) than the survival group. In addition, patients in the nonsurvival group underwent significantly more aggressive treatment (such as vasopressor treatment) and had a higher rate of ICU admission. However, duration of hospital stay in the nonsurvival group was shorter (8 vs 11 days; p 0.013).

Five factors remained in the final model for predicting death (Tab. III). Plasma glucose, serum lactate levels, and ESBL *E. coli* were significantly associated with mortality, with adjusted odds ratios of 0.970, 1.258, and 12.885, respectively. The final model had a Hosmer-Lemeshow Chi square of 6.73 (p = 0.565). Plasma glucose of 113 mg/dL or lower yielded a sensitivity of 80.95% and specificity of 64.29%, while serum lactate level of over 2.4 mmol/L had a sensitivity of 81.48% and specificity of 45.50%.

Discussion

The prevalence of ESBL *E. coli* bacteremia at the ED in this study was 3.29%, which is lower than previously reported in community settings (6.7%-9.5%) (10,11,16). In addition to the difference in setting, these results may indicate differing rates among countries, as higher rates have been found in developed countries (South Korea and Spain). A previous report found that frequent visits to the ED increased the risk of ESBL bacteremia by a factor of 9.98, including in those patients who had undergone previous antibiotic treatment. In Thailand, the rate of previous antibiotic use may be lower than in some other countries. Despite the inconsistency in the ESBL *E. coli* mortality rate in other settings, this study found that patients with ESBL *E. coli* had a 13 times higher risk of mortality than those with non-ESBL strains. Other factors associated with mortality in patients with *E. coli* infection may be personal characteristics and inappropriate antibiotic use. A report from Korea found that presenting with septic shock or malignancy increased mortality risk by 26.6 and 11.9 times, respectively, while another study found that mortality rates were comparable in patients with ESBL and non-ESBL *E. coli* if antibiotics were administered appropriately (p = 0.23) (11,15).

Hypoglycemia has been shown to be related with higher mortality in sepsis patients and critically ill patients (17-19). Although the causal relationship between hypoglycemia and mortality is not well understood, several mechanisms have been proposed including the inhibition of the physiological responses of hormones such as insulin and epinephrine,

increased inflammatory response, and cellular damage from glucose administration (19). Previous studies have also found low plasma glucose to be associated with mortality in patients with sepsis (11,20). This study found that glucose of 113 mg/dL or lower yielded a sensitivity of 80.95% compared to a previous study, in which plasma glucose of 40-69 mg/dL resulted in an adjusted odds ratio of 3.43 (95% confidence interval of 1.51, 7.82) for mortality (19,20). These results may imply that patients with *E. coli* bacteremia and hypoglycemia may have as high of a risk of mortality as other patients with sepsis. The different plasma glucose cutoff points in the two studies may be due to differences in study population. This study enrolled only patients with *E. coli* bacteremia at the ED, while the previous study included patients with sepsis, which may have been caused by various pathogens. The plasma glucose cutoff point in this study may be more specific to patients with *E. coli* bacteremia at the ED.

As previously reported, serum lactate is an indicator for mortality in patients with infection at the ED (21-23). A previous study found that serum lactate greater than 4 mmol/L was associated with higher mortality than at 2 mmol/L (40.7% vs 2.7%) (24). In this study, we found that serum lactate over 2.4 mmol/L yielded sufficient sensitivity to predict fatality in patients with *E. coli* bacteremia at the ED. Another study found a serum lactate cutoff point of 5.80 mmol/L in patients with necrotizing fasciitis (25). This indicates that *E. coli* bacteremia may be severe and that the serum lactate cutoff point may vary depending on the causative agents.

Although oxygen saturation and hemoglobin were significantly associated with mortality by univariate logistic regression analysis (Tab. III), they were no longer significant in the final model. These results may indicate that neither factor was a strong predictor compared with the other three. Additionally, there might have been some related confounding factors. Other factors included in the model that had p values of less than 0.05 by univariate analysis were not retained in the final model for the same reasons. Some comorbid diseases, such as diabetes, were found to be significant predictors for mortality in a previous observational study (26). However, comorbid diseases were not significant in this study, as previously mentioned. Additionally, the model used in this study differed from that in the previous study. In this study, we included clinical factors such as ESBL *E. coli* in the model, while the previous study did not include ESBL *E. coli* and included treatment-related factors such as peak inspiratory pressure and positive end-expiratory pressure.

There were some limitations to this study. First, the ED at which it was conducted was a single site at a university hospital. Further prospective studies in other settings may be required to confirm the results. In addition, this was an exploratory study without validation. The final predictive model included more factors than event outcomes. There were five factors in the model with only 27 nonsurvivors, resulting in a ratio of more than 1:10. Moreover, the total number of patients in the final model was 130. These limitations could have caused the model to be unbalanced or biased. However, the final model had a high goodness of fit. Another limitation was that some factors were not studied such as previous antibiotic use, previous history of resistant pathogens, or special conditions (27-35). Finally, mortality was defined as 28-day mortality.

ESBL *E. coli*, plasma glucose, and serum lactate levels were associated with 28-day mortality in patients with *E. coli* bacteremia presenting at the ED.

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Disclosures

Conflict of interest: The authors declare that they have no conflicts of interest.
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