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A simple scoring algorithm predicting extended-spectrum β-lactamase producers in adults with community-onset monomicrobial Enterobacteriaceae bacteremia

Matters of frequent emergency department users

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Abstract

The incidence of community-onset bacteremia caused by extended-spectrum-β-lactamase (ESBL) producers is increasing. The adverse effects of ESBL production on patient outcome have been recognized and this antimicrobial resistance has significant implications in the delay of appropriate therapy. However, a simple scoring algorithm that can easily, inexpensively, and accurately be applied to clinical settings was lacking. Thus, we established a predictive scoring algorithm for identifying patients at the risk of ESBL-producer infections among patients with community-onset monomicrobial Enterobacteriaceae bacteremia (CoMEB).

In a retrospective cohort, multicenter study, adults with CoMEB in the emergency department (ED) were recruited during January 2008 to December 2013. ESBL producers were determined based on ESBL phenotype. Clinical information was obtained from chart records.

Of the total 1141 adults with CoMEB, 65 (5.7%) caused by ESBL producers were identified. Four independent multivariate predictors of ESBL-producer bacteremia with high odds ratios (ORs)—recent antimicrobial use (OR, 15.29), recent invasive procedures (OR, 12.33), nursing home residents (OR, 27.77), and frequent ED user (OR, 9.98)—were each assigned +1 point to obtain the CoMEB-ESBL score. Using the proposed scoring algorithm, a cut-off value of +2 yielded a high sensitivity (84.6%) and an acceptable specificity (92.5%); the area under the receiver operating characteristic curve was 0.92.

In conclusion, this simple scoring algorithm can be used to identify CoMEB patients with a high ESBL-producer infection risk. Of note, frequent ED user was firstly demonstrated to be a crucial predictor in predicting ESBL-producer infections. ED clinicians should consider adequate empirical therapy with coverage of these pathogens for patients with risk factors.

Abbreviations: AUC = area under the curve, CoMEB = community-onset monomicrobial Enterobacteriaceae bacteremia, ED = emergency department, EKP = *E coli*, *K pneumoniae*, *K oxytoca* and *P mirabilis*, ESBL = extended-spectrum-β-lactamase, OR = odds ratios, ROC = receiver operating characteristic.

Keywords: bacteremia, community, Enterobacteriaceae, extended-spectrum β-lactamase

1. Introduction

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

ESBL producers are generally resistant to all β-lactam antibiotics (except cephamycins), and are also frequently resistant to non-β-lactams, such as fluoroquinolones, trimethoprim–sulfamethoxazole, and aminoglycosides.[4] The antimicrobial resistance has significant implications in empirical therapy because delay in appropriate antimicrobial therapy is associated with worse patient outcomes in patients with Enterobacteriaceae bacteremia.[7–9] Furthermore, some investigations regarding adverse effects of ESBL production on patient outcome have been reported.[9,10] Emergency department (ED) clinicians, who are the foremost professionals responsible for diagnosing and

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managing various community-onset infections, should identify the patients possibly infected by ESBL producers and administer appropriate empirical therapy immediately. However, in addition to recent antimicrobial exposures and prior existence of urinary catheter implant, clinical information regarding other clinical predictors of ESBL producers among ED patients with community-onset Enterobacteriaceae bacteremia remains scant.[9,11,12] Because early identification of ESBL producers in patients with community-onset Enterobacteriaceae bacteremia is crucial, in this study, we developed a simple scoring algorithm that can easily, inexpensively, and accurately be applied to clinical settings for identifying patients at a high risk for ESBL-producer infections.

2. Materials and methods

2.1. Study design, setting, and population

This retrospective cohort study was conducted at the EDs of 2 tertiary care hospitals located in Tainan in Southern Taiwan. Combined, the 2 medical centers have 2469 beds (hospital A, 1193 beds; B, 1276 beds) and serve nearly 2 million inhabitants in the Tainan metropolitan area. The ethics committees of 2 study hospitals approved this protocol (ER-100-182), and the requirement for informed consent was waived. This analysis was reported using the format recommended by STROBE.[13]

During the 6-year period between January 2008 and December 2013, an adult with bacterial growth in blood cultures was screened in a computer database in the study hospital A. Among bacteremic isolates, *E coli*, *K pneumoniae*, *K oxytoca*, and *P mirabilis* (EKP) were included. Clinical information was retrieved from the medical records of the ED using a predetermined case record form. Patients with hospital-onset bacteremia, polymicrobial bacteremia, incomplete chart records, or bacteremia before arrival to the ED were excluded. Two authors reviewed the medical records of eligible patients for the above-mentioned clinical information. If any discrepancies were observed, both the authors inspected the medical records simultaneously and a decision was reached through consensus. In cases with multiple bacteremic episodes, only the first episode was included for each patient. Patients infected by ESBL producers were regarded as the ESBL group; otherwise, these were as the non-ESBL group.

2.2. Data collection

Demographic and clinical characteristics were collected by retrospectively reviewing the medical records of all eligible patients in study hospital A. Demographic data, initial syndromes, vital signs and bacteremia severity (a Pitt bacteremia score) at bacteremia onset, comorbidities, comorbidity severity (McCabe classification), bacteremia sources, and recent events (i.e., hospitalizations, prior antimicrobial use, invasive procedures, chemotherapy, and/or surgery performed) during the 4 weeks before arrival to the ED (bacteremia onset) were collected from chart records. Furthermore, the frequency of ED use within 1 year before bacteremia onset was determined through retrospective follow-up at 2 study hospitals during the period between January 2007 and December 2013.

2.3. Microbiological methods

Blood cultures were incubated in a BACTEC 9240 instrument (Becton Dickinson Diagnostic Systems, Sparks, MD) for 5 days at 35°C. EKP were then identified using biochemical tests and confirmed with a Vitek system (Biomerieux, Lyon, France) using a gram-negative identification card. In the clinical microbiology laboratory at the study hospital, ESBL production was detected by the phenotypic confirmatory test with the cephalosporin–clavulanate combination disks recommended by the previous guidelines of the Clinical Laboratory Standard Institute in 2009.[14]

2.4. Definitions

In this study, we considered EKP isolates as Enterobacteriaceae. As previous descriptions,[15,16] a patient having 3 or more ED visits annually was referred as the frequent ED user. The severity of the comorbid illness was stratified according to the McCabe score and categorized as rapid fatal, ultimately fatal, or nonfatal.[17] The bacteremia severity at the time of bacteremia 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.[18] Severe sepsis was defined as the coexistence of sepsis and at least one of the following signs or symptoms of acute organ dysfunction or hypoperfusion: metabolic acidosis, arterial hypoxemia ($PaO_2 < 75$ mm Hg or $PaO_2/FiO_2 < 250$), oliguria (<0.03 L/h for 3 h or 0.7 L/24 h), coagulopathy (increase in prothrombin time or a drop of platelet count by 50% or to $<100 \times 10^7$/L), or encephalopathy (Glasgow coma score $<$ 14).[19] Septic shock was defined as the presence of systemic inflammatory response syndrome and a systolic blood pressure no higher than 90 mm Hg after a crystalloid-fluid challenge of 20 to 30 mL/kg of body weight over a 30-min period or a blood lactate concentration of 4 mmol/L or higher.[20]

Malignancy included both hematological malignancies and solid tumors. A previously described definition of comorbidities was used.[21] The term "community-onset bacteremia" indicates that the place of onset of the bacteremic episode was the community; hence, we included long-term healthcare facility- and community-acquired bacteremia, as previously described.[22] 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.

2.5. Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (Chicago, IL), Version 20.0. Continuous variables were expressed as the means ± standard deviations and compared using Student *t* tests. Categorical variables, expressed as numbers and percentages, were compared using a Chi-squared test or Fisher exact test. All variables with *P* values $<.05$ by univariate analysis were considered for the stepwise, backward logistic regression model. A receiver operating characteristic (ROC) curve was used to assess the sensitivity of a diagnostic test versus its false-positive rate for all possible cut-off levels, which was used to estimate the accuracy of a prediction tool.[23] We did not conduct formal sample size calculations, and all available data were used to maximize the power. As previous studies' suggestion, at least 8 to 10 events per variable are needed for reliable multiple logistic regression analysis.[24] As for missing values, we planned to conduct a complete case analysis if the missing values were below 5%, as

such an analysis might have been feasible in that case. If the missing values were at or above 5%, we planned to perform the appropriate imputation.[25] A P value $<.05$ was considered significant.

3. Results

3.1. Patient population

In total, 1141 adult patients with community-onset monomicrobial Enterobacteriaceae bacteremia (CoMEB) were included according to the inclusion and exclusion criteria (Fig. 1). Their mean age was 68.6 years, and 652 (57.1%) were female. Comorbidities included hypertension (564 patients, 49.4%), diabetes mellitus (445, 39.0%), malignancy (307, 26.9%), neurological disorder (241, 21.1%), chronic kidney disease (160, 14.0%), liver cirrhosis (157, 13.8%), coronary artery disease (189, 10.3%), urological disease (77, 6.7%), congestive heart failure (74, 6.5%), chronic obstructive pulmonary disease (49, 4.3%), and autoimmune disease (23, 2.0%). Because 20 patients had multiple foci of infection, the total 1162 portals of entry were found. The most common source of bacteremia was the urinary tract infections (598 patients, 51.5%), followed by biliary tract infections (138, 11.9%), intra-abdominal infections (133, 11.4%), pneumonia (104, 9.0%), primary bacteremia (69, 5.9%), liver abscess (63, 5.4%), skin and soft-tissue infections (25, 2.2%), bone and joint infections (11, 0.9%), vascular line infections (10, 0.9%), central nervous system infections (3, 0.3%), tubo-ovarian abscess (3, 0.3%), endocarditis (2, 0.2%), mycotic aneurysm (2, 0.2%), and acute periodontitis (1, 0.1%).

Of the total 1141 adults, mean (interquartile range) ED stay was 18.3 (5.4–24.1) h. Most (952, 83.4%) patients were admitted to general wards and 115 (10.1%) to intensive care units. Only 74 (6.5%) were discharged through the ED and followed as outpatients. The proportion of critically ill patients (i.e., a Pitt bacteremia score ≥ 4) at bacteremia onset was 17.0% (194 patients). And the proportion of initial syndrome of severe sepsis or septic shock at ED arrival was 42.5% (485 patients) or 17.7% (202), respectively.

3.2. Causative microorganism

Of the total 1141 causative microorganisms identified, the leading was *E coli* (826 isolates, 72.4%), followed by *K pneumoniae* (274, 24.0%), *P mirabilis* (31, 2.7%), and *K oxytoca* (10, 0.9%). Of note, ESBL producers accounted for 5.7% (65 isolates) of the total EKP isolates. Of the 65 ESBL producers, the most common was *E coli* (48 isolates, 73.8%), followed by *K pneumoniae* (14, 21.5%) and *P mirabilis* (3, 4.6%).

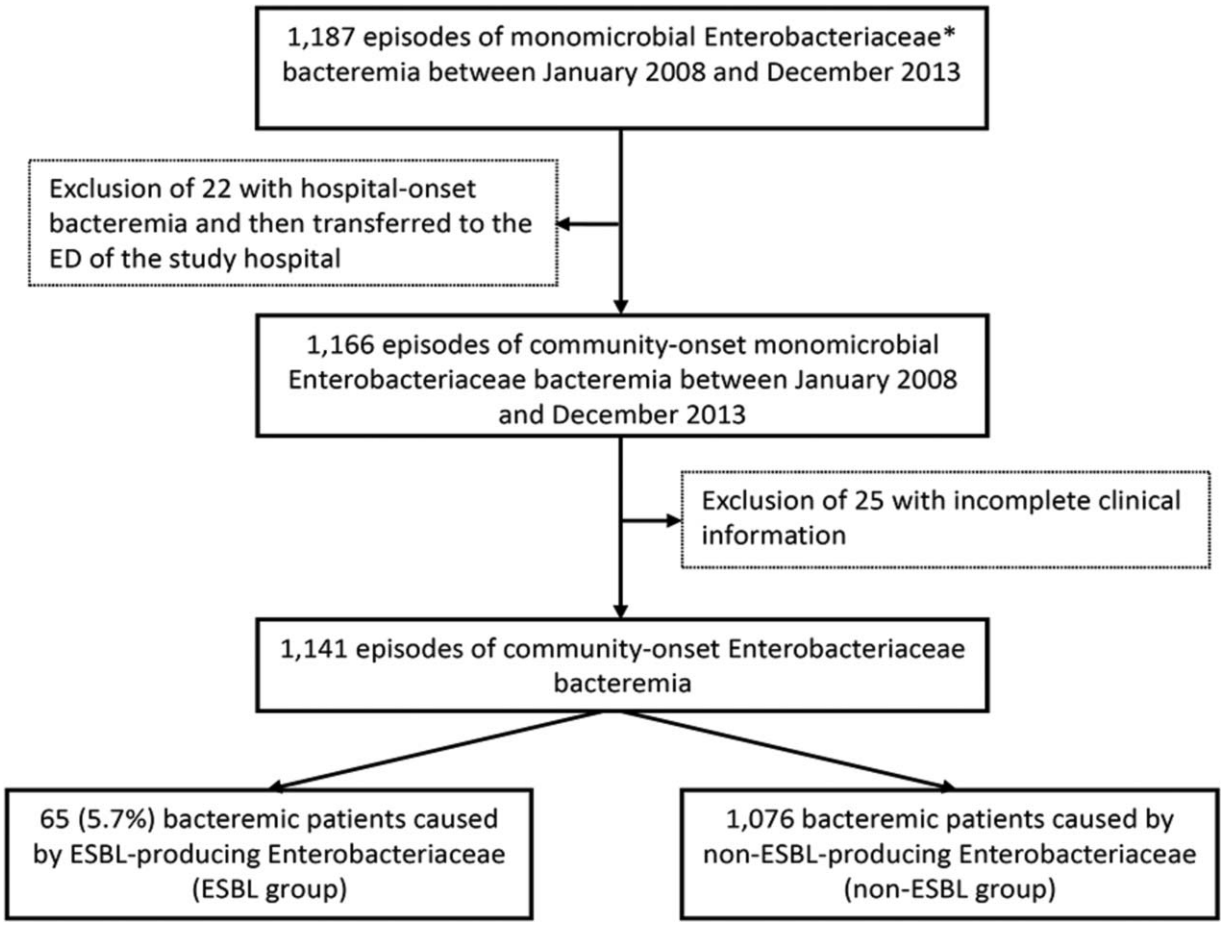

Figure 1. Patient selection flowchart. *Include *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis*. ED = emergency department, ESBL = extended-spectrum β-lactamase.

3.3. Predictors of ESBL producers

The associations between bacteremia caused by ESBL producers and clinical characteristics, recent events before the ED visit, bacteremia severity, major comorbidities, comorbidity severity (McCabe classification), causative microorganisms, and frequencies of ED users were examined using univariate analyses (Table 1). The following predictors were significantly associated with bacteremia caused by ESBL producers: old age; female sex; nursing home residents; recent hospitalization; recent invasive procedures; recent antimicrobial use; frequent ED user within 1 year before bacteremia onset; critical illness (a Pitt bacteremia score of ≥4) at bacteremia onset; bacteremia because of urinary tract infections or liver abscess; and comorbid diabetes mellitus, urological disorders, or neurological diseases. In further multivariate regression analysis, only the following risk factors were significant: nursing home residents, recent hospitalization, recent invasive procedures, recent antimicrobial use, and frequent ED use within 1 year before bacteremia onset, and comorbid diabetes mellitus or urological diseases. Notably, nursing home residents, recent antimicrobial use, recent invasive procedures, and frequent ED use were the major predictors.

3.4. Performance of the prediction rule

The score of each risk factor was determined on the basis of the odds ratios (ORs) of the independent predictors (Table 2). Next, 2 scoring algorithms, named models 1 and 2, were developed on the basis of the CoMEB-ESBL scores. In model 1, +1 point was allotted for each of the 7 variables positively associated with bacteremia caused by ESBL producers, nursing home residents, recent hospitalization, recent invasive procedures, recent antimicrobial use, frequent ED use, and comorbid urological diseases or diabetes mellitus). To emphasize the importance of the 4 considerable predictors with high ORs, in model 2, 0 point was assigned to the following 3 predictors: recent hospitalization, urological diseases, and diabetes mellitus.

ROC curve of model 1 (Fig. 2) demonstrated a strong ability to predict the bacteremia caused by ESBL producers, with an area under the ROC curve (AUC) of 0.89 (95% confidence interval, 0.86–0.93; $P < .001$). However, the prediction capability of model 2 was superior to that of model 1, with an AUC of 0.92. The sensitivity, specificity, predictive values, and likelihood ratio of model 2 for bacteremia caused by ESBL producers in adult patients with CoMEB were shown in Table 3. Various cut-off points (range, 1–3) were used; when higher cut-off values were

Table 1

Clinical characteristics, comorbidities, and bacteremia resource in 1141 patients with community-onset monomicrobial Enterobacteriaceae bacteremia, categorized by ESBL producers and non-ESBL producers.

Variables	Patient number		*P*
	ESBL producer (n = 65)	Non-ESBL producer (n = 1076)	
Old age, ≥65 y	51 (78.5)	672 (62.5)	.009
Gender: female	27 (41.5)	625 (58.1)	.009
Nursing home residents	26 (40.0)	34 (3.2)	<.001
Events within 4 wk before bacteremia onset			
Prior hospitalization	26 (40.0)	212 (19.7)	<.001
Invasive procedure*	9 (13.8)	20 (1.9)	<.001
Antibiotic therapy	45 (70.8)	187 (17.4)	<.001
Immunosuppressive agents	5 (7.7)	33 (3.1)	.06
Chemotherapy	3 (4.6)	68 (6.3)	.79
Surgery	0 (0)	50 (4.6)	.11
Frequent ED users† within 1 y before bacteremia onset	50 (76.9)	294 (27.3)	<.001
Comorbid fatal disease (McCabe classification)	16 (24.6)	227 (21.1)	.50
Severity-of-illness marker at the ED			
Pitt bacteremic score ≥4 points	19 (29.2)	175 (16.3)	.007
Initial syndrome			
Severe sepsis	29 (44.6)	456 (42.4)	.72
Septic shock	17 (26.2)	185 (17.2)	.07
Major sources of bacteremia			
Urinary tract	42 (64.6)	556 (51.7)	.04
Biliary tract	10 (15.4)	128 (11.9)	.40
Pneumonia	8 (12.3)	96 (8.9)	.36
Intra-abdomen	3 (4.6)	130 (12.1)	.07
Primary bacteremia	2 (3.1)	67 (6.2)	.43
Liver abscess	0 (0)	63 (5.9)	.045
Major comorbidities			
Diabetes mellitus	35 (53.8)	410 (38.1)	.01
Hypertension	30 (46.2)	534 (49.6)	.59
Neurological disorder	27 (41.5)	213 (19.9)	<.001
Malignancy	21 (32.3)	286 (26.6)	.31
Coronary artery diseases	11 (16.9)	107 (9.9)	.07
Urological diseases	10 (15.4)	67 (6.2)	.009

ED = emergency department, ESBL = extended-spectrum β-lactamase.

* Included 11 patients received endoscopic retrograde cholangiopancreatography, 9 colonoscopy, 8 urodynamic examinations, and 1 sigmoidoscopy.

† Indicated 3 or more ED visits annually.

Table 2

Independent risk factors of ESBL producers in patients with CoMEB, using a backward stepwise logistic regression model.

Variables	Odds ratio (95% CI)	*P*	CoMEB-ESBL score	
			I	II*
Nursing home residents	27.77 (12.57–61.35)	<.001	1	1
Events within 4 wk before bacteremia onset				
Antimicrobial therapy	15.29 (7.68–61.35)	<.001	1	1
Invasive procedure	12.33 (5.59–27.20)	<.001	1	1
Prior hospitalization	3.75 (1.56–9.00)	.003	1	0
Frequent ED visits† within 1 y before bacteremia onset	9.98 (4.94–20.15)	<.001	1	1
Comorbidities				
Urological diseases	3.38 (1.12–10.18)	.03	1	0
Diabetes mellitus	2.08 (1.05–4.11)	.04	1	0

CoMEB = community-onset monomicrobial Enterobacteriaceae bacteremia, ED = emergency department, ESBL = extended-spectrum β-lactamase.

* Only 4 predictors having high odds ratios were enrolled.

† Indicated 3 or more ED visits annually.

used, sensitivity decreased and specificity increased. The maximum sensitivity (95.4%) was observed at the lowest cut-off point (total score = 1), and the maximum specificity (99.6%) was observed at the highest cut-off point (total score = 3).

4. Discussion

For adult patients with CoMEB, 7 clinical predictors had a strong association with ESBL-producer bacteremia. However, on the basis of their high ORs, only 4 factors pertaining to patient characteristics—nursing home residents, frequent ED use, recent antimicrobial use, and recent invasive procedures—were selected to develop a simple scoring algorithm (indicated as model 2). Compared with model 1 (the scoring algorithm containing the 7 risk factors), the ROC curve suggested by model 2 (the rapid and easy scoring system) was found to be more accurate in the early identification of patients at a high risk of bacteremia caused by ESBL producers. Based on model 2, we obtained substantial sensitivity and satisfactory specificity.

Several patient characteristics associated with bacteremia caused by ESBL producers, including healthcare facility residents, urinary catheter use, previous antimicrobial therapy, old age, and previous hospitalization, have been reported[4,9,26–28]; however, these data were almost limited to hospital-onset or healthcare-facility-associated infections. Similar to a previous hospital-based study on community-onset bacteremia,[9] a strong association between nursing home stay, previous antimicrobial therapy, and ESBL-producer bacteremia was observed here. Furthermore, patients who have undergone invasive procedures frequently develop bacteremic episodes caused by ESBL producers.[27,28] To our knowledge, this is the first study demonstrating an association between frequent ED use and ESBL-producer bacteremia. Several disadvantages of frequent ED use, such as increased use of other healthcare services, serious ill health, and socioeconomic distress, have been reported previously.[15,16] We suspected that because frequent ED use and increased healthcare or hospital service use are strongly related, frequent ED use may be associated with bacteremia caused by ESBL producers as well.

In this study, we included patients with community-onset bacteremia, rather than those with community-acquired bacteremia, for the following 2 reasons. First, because the study hospital is a medical center and tertiary hospital, many patients with bacteremia may have been transferred from other local hospitals and they may have acquired bacteremia at the previous nursing home or healthcare facility. According to a strict and formal definition,[29] patients with community-acquired bacteremia must be admitted to the hospital directly from home without a history of hospitalization within the previous 30 days, should have no history of undergoing an invasive procedure just before or at the time of admission, must not be receiving long-term dialysis, and must not be admitted with intravascular devices. However, 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. Second, as reported previously,[30] more than 80% of patients with bacteremia visiting the ED have community-onset bacteremia; thereby, this easy, rapid, and accurate scoring algorithm proposed in this aimed population would be highly useful. After excluding ED patients transferred from other hospitals, only the eligible ED patients with community-onset bacteremia were considered the study population.

Results of our study should be interpreted in light of both its strengths and limitations. First, to assess appropriate clinical

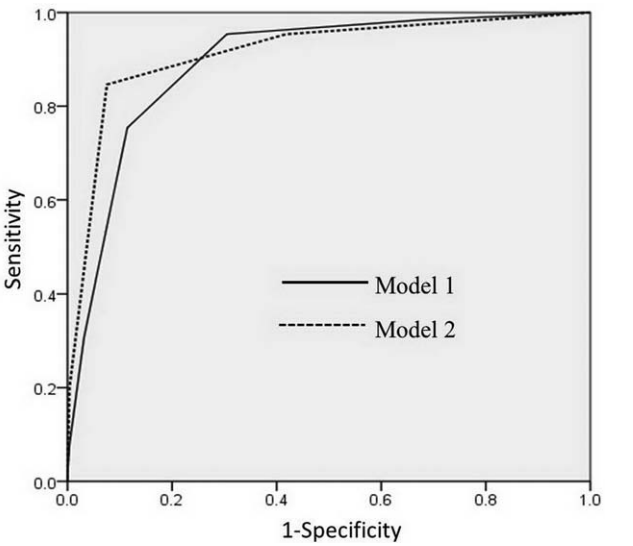

Figure 2. Receiver operating characteristic (ROC) curves of 3 models of CoMEB-ESBL scoring to predict bacteremia caused by ESBL producers in patients with CoMEB. The area under the ROC curve is 0.89 (95% confidence interval [CI], 0.86–0.93; $P < .001$) in model 1 and 0.92 (95% CI, 0.88–0.96; $P < .001$) in model 2. CoMEB = community-onset monomicrobial Enterobacteriaceae bacteremia, ESBL = extended-spectrum β-lactamase.

Table 3

The sensitivity, specificity, predictive value, and likelihood ratio of the prediction rule (CoMEB-ESBL score, model 2) for ESBL-producer bacteremia, with various cut-off points for adults with community-onset monomicrobial Enterobacteriaceae bacteremia.

Cut-off point	Patient no. with ESBL-producing isolates (patient numbers with indicated risk scores)	Sensitivity, %	Specificity, %	Predictive values		Likelihood ratio	
				Positive	Negative	Positive	Negative
1	62 (512)	95.4	58.2	12.1	99.5	2.3	0.2
2	55 (136)	84.6	92.5	40.4	99.0	11.3	0.2
3	13 (17)	20.0	99.6	76.5	95.4	50.0	0.8

CoMEB = community-onset monomicrobial Enterobacteriaceae bacteremia, ESBL = extended-spectrum β-lactamase.

predictors of ESBL producers, patients with incomplete clinical information on the chart records were excluded. Nevertheless, only 2.1% (25) of the eligible (1166) patients with CoMEB were excluded; hence, this issue may not have considerably influenced the study results. Second, on the basis of the previous reports regarding the risk factors for ESBL producers in patients with hospital- or healthcare-facility-onset bacteremia, several predictors were collected from medical records using a predetermined case record form. Despite these efforts, residual confounding from poorly measured or unmeasured covariates cannot be totally excluded. We lacked data on history of urinary catheter placement and thus these factors by including voiding dysfunction such as urodynamic examination and urological comorbidity, were adjusted here. Third, the importance of frequent ED use in predicting ESBL was emphasized here, and thus diminishing underestimation of the frequency of ED visits was crucial. Notably, of 5 hospitals with ED facilities in the Tainan metropolitan area, only the study hospitals were medical centers; thus, it was reasonable that we calculated ED frequency only for these 2 centers. Fourth, this study design was retrospective; hence, errors may have occurred because of missing information linked to clinical predictors. To diminish patient number lacking complete clinical information and reduce the errors of capturing information, 2 authors reviewed the medical records of eligible patients in study design. Fifth, ESBL producers were often reported in EKP, but a growing number of other ESBL-producing Enterobacteriaceae (such as *Enterobacter cloacae*) have been observed worldwide. However, in the community, EKP accounts for the majority of ESBL producers, so our finding may not be generalizable to other microorganisms. Finally, because of the highly varied incidence of ESBL producers in different areas, it remains unclear where the 4 predictors are adequately useful worldwide and if the cut-off value of +2 is appropriate for a region with a high incidence. Therefore, a well-designed, multinational study is warranted to externally validate the clinical significance of this scoring system.

5. Conclusions

To assess ESBL-producer infections among adult patients with CoMEB, we proposed a simple clinical scoring algorithm comprising only 4 predictors, with substantial sensitivity and satisfactory specificity. Of these 4 independent multivariate predictors, for the first time, frequent ED user was demonstrated to be a crucial predictor. For ED clinicians, an antimicrobial coverage may also be empirically considered for those with a CoMEB-ESBL score of ≥2. However, the cost-effectiveness of this algorithm should be studied prospectively to assess its clinical utility.

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