Trend and Predictors of Short-term Mortality of Adult Bacteremia at Emergency Departments: A 14-Year Cohort Study of 14 625 Patients

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Background. Bacteremia is a life-threatening condition with a high mortality rate in critical care and emergency settings. The current study investigated the trend of mortality and developed predictive models of mortality for adults with bacteremia at emergency departments (EDs).

Methods. We conducted a retrospective cohort study of adults with bacteremia at the ED of China Medical University Hospital. Patient data were obtained from the Clinical Research Data Repository, and mortality information was obtained from the National Death Registry. We developed a new model to predict 7-day mortality in the derivation population and compared the model performance of the new model with Pitt Bacteremia Score (PBS) and Bloodstream Infection Mortality Risk Score (BSIMRS) in the validation population.

Results. We identified 14 625 adult patients with first-time bacteremia at the ED, of whom 8.4% died within 7 days. From 2003 to 2016, both the cumulative incidence and 7-day mortality rate of bacteremia decreased significantly. The ED bacteremia mortality (ED-BM) model included PBS parameters, age, infection source, baseline steroid use, and biochemical profiles (estimated glomerular filtration rate, platelet, blood urea nitrogen, potassium, and hemoglobin) for predicting 7-day mortality. The discrimination performance of the ED-BM model (area under curve [AUC], 0.903) was significantly better than that of PBS (AUC, 0.848) or BSIMRS (AUC, 0.885).

Conclusions. Although the cumulative incidence and mortality of ED bacteremia decreased, its mortality burden remains critical. The proposed ED-BM model had significantly better model performance than other scoring systems in predicting short-term mortality for adult patients with bacteremia at EDs.

Keywords. bacteremia; emergency department; epidemiology; mortality; prediction model.

Bloodstream infection (BSI) or bacteremia is a life-threatening condition with a high mortality rate (14%–37%), particularly among patients in critical care units [1]. Similarly, a significantly high mortality rate (5.3%–14.4%) has been observed in emergency department (ED) patients with BSIs or bacteremia [2–5]. Therefore, early identification of the mortality risk of bacteremia is crucial for patients at EDs, a common entry point to hospitals for nearly all patients with acute illnesses.

In the past decade, several studies have investigated the burden of bacteremia among adult ED patients receiving blood culture (BC) [6–9]. In a 1-year study conducted by a medical center in the United States, Chase et al. reported that 12.4% (409/3310) of ED adult patients receiving BC had positive culture results [6]. Similarly, a 1-year study by Kao et al. in Taiwan reported a bacteremia rate of 13.5% (831/6137) [7], and another study in a German university hospital reported the 5-year cumulative incidence of bacteremia to be 14.3% (740/5191) [9]. However, the timelines covered by these studies and other studies reporting the mortality of ED bacteremia [2–5] have often been too short to understand the long-term trend and mortality of ED bacteremia.

Subjective variables such as infection symptoms or terminal illness [2] and objective variables such as biochemical measurements and vitals have been used to predict the mortality risk of ED patients with suspected sepsis or bacteremia [2–4, 10]. The Pitt Bacteremia Score (PBS), consisting of 5 variables (mental status, presence of fever, hypotension, requirement for respiratory support, and cardiac arrest), and BSI mortality risk score

(BSIMRS), consisting of PBS and 3 additional clinical conditions (malignancy, cirrhosis, and BSI source), are the 2 scoring systems that use objective variables to predict mortality risk in patients with bacteremia or nonbacteremia conditions [11–14]. Most studies on ED patients with bacteremia or sepsis have evaluated the 28-day mortality rate, a rather long-term mortality evaluation for such an acute event [2–4, 15]. During the 28-day period, other medical conditions, such as health care–associated infections, may influence the outcomes of these patients [16]. Short-term mortality, such as 7-day mortality, represents the direct effect of bacteremia on the outcomes of ED patients. To address this research lacuna, we conducted a 14-year retrospective cohort study in the ED setting of a tertiary medical center to determine the trend in cumulative incidence and mortality rate of bacteremia, and we proposed a new predictive algorithm for the 7-day mortality rate. The performance of our model and that of the existing scoring systems (PBS and BSIMRS) were compared for predicting short-term mortality among adult ED patients with bacteremia.

METHODS

Source Population

The Big Data Center and the Office of Information Technology of China Medical University Hospital (CMUH) established the CMUH Clinical Research Data Repository (CMUH-CRDR), which contains the medical records of 2 988 912 patients who sought medical care at CMUH between January 1, 2003, and December 31, 2019. Details of the data quality and interoperability have been published elsewhere [17–19]. This study was approved by the Big Data Center and Research Ethical Committee/Institutional Review Board of CMUH (CMUH105-REC3–068), and informed consent has been waived.

Definition of Bacteremia at the ED

The index ED admission was ED admission in which BCs were obtained and subsequently yielded positive results during the study period. We treated consecutive ED visits that were ≤3 days apart as a single ED visit. Clinically significant bacteremia was defined as at least 1 blood specimen that grew noncommensal microorganisms. For BCs that grew commensal microorganisms, at least 2 positive culture results on separate occasions during the index ED admission were required to be counted as clinically significant bacteremia (Supplementary Table 1) [20].

Study Population

From the CMUH-CRDR, we analyzed all bacterial BC reports from 2003 and 2016 except those of (1) cultures obtained during outpatient or inpatient visits, (2) cultures obtained >48 hours after the ED admission, (3) culture results that did not meet the definition of clinically significant bacteremia, and (4) patients aged <18 years (Figure 1). The included patients were then randomly divided into derivation and validation populations at a ratio of 8:2 for the subsequent analysis. The clinical characteristics were similar between the derivation and validation populations (Supplementary Table 2). Detailed information on the selection process is summarized in Figure 1.

### Covariates and Mortality Outcome

Baseline demographic information, comorbidities, vital signs, biochemical profiles, and medication history were verified from the CMUH-CRDR. Comorbidities were defined by the International Classification of Diseases (ICD) diagnosis codes recorded within 1 year before the index ED admission, if not otherwise defined (Supplementary Table 3). Furthermore, medication history of the use of systemic antibiotics, steroids, and nonsteroidal anti-inflammatory drugs (NSAIDs) within 14 days before the index ED admission was extracted. Baseline vital signs and biochemical profiles were the first measurements conducted within 48 hours following the index ED visit date. Infection source was defined by ICD diagnosis during the index ED admission or the following hospitalization (Supplementary Table 4). Empirical antibiotic treatment was defined as "appropriate" if the minimal inhibitory concentration tests revealed that the bacterial isolate was susceptible to the given antimicrobial agent(s) during the index ED visit (Supplementary Figure 1); otherwise, they were regarded as "inappropriate."

The primary outcome of interest was all-cause mortality within 7 days following the index ED visit date. We traced each patient's mortality outcome by linking the CMUH-CRDR to Taiwan's National Death Registry Database. All patients enrolled in the CMUH-CRDR were followed up until December 31, 2019, or death, whichever occurred earlier. We used PBS and BSIMRS as the reference prediction scoring systems (Supplementary Table 5) [12, 21]. We obtained data for each component recorded within 48 hours following the ED admission and calculated PBS and BSIMRS.

Statistical Analysis

Values for continuous and categorical variables are expressed as median (interquartile range) and frequency (%), respectively. Annual cumulative incidence of ED bacteremia was calculated by dividing the number of ED bacteremia episodes per year by the total number of ED visits with BC obtained per year. The yearly proportion of 7-day mortality was calculated by dividing the number of deaths per year by the total number of ED bacteremia episodes per year. The trend during the study period was tested using the Cochran-Armitage trend test, and the age-adjusted trend was analyzed using logistic regression.

To establish a multivariable prediction model for the 7-day mortality rate, we used the derivation population to identify predictors and build the model. We then tested the predictive performance of the model in the validation population. We first chose the input variables for multivariable variable selection based on clinical relevance. We then identified variables
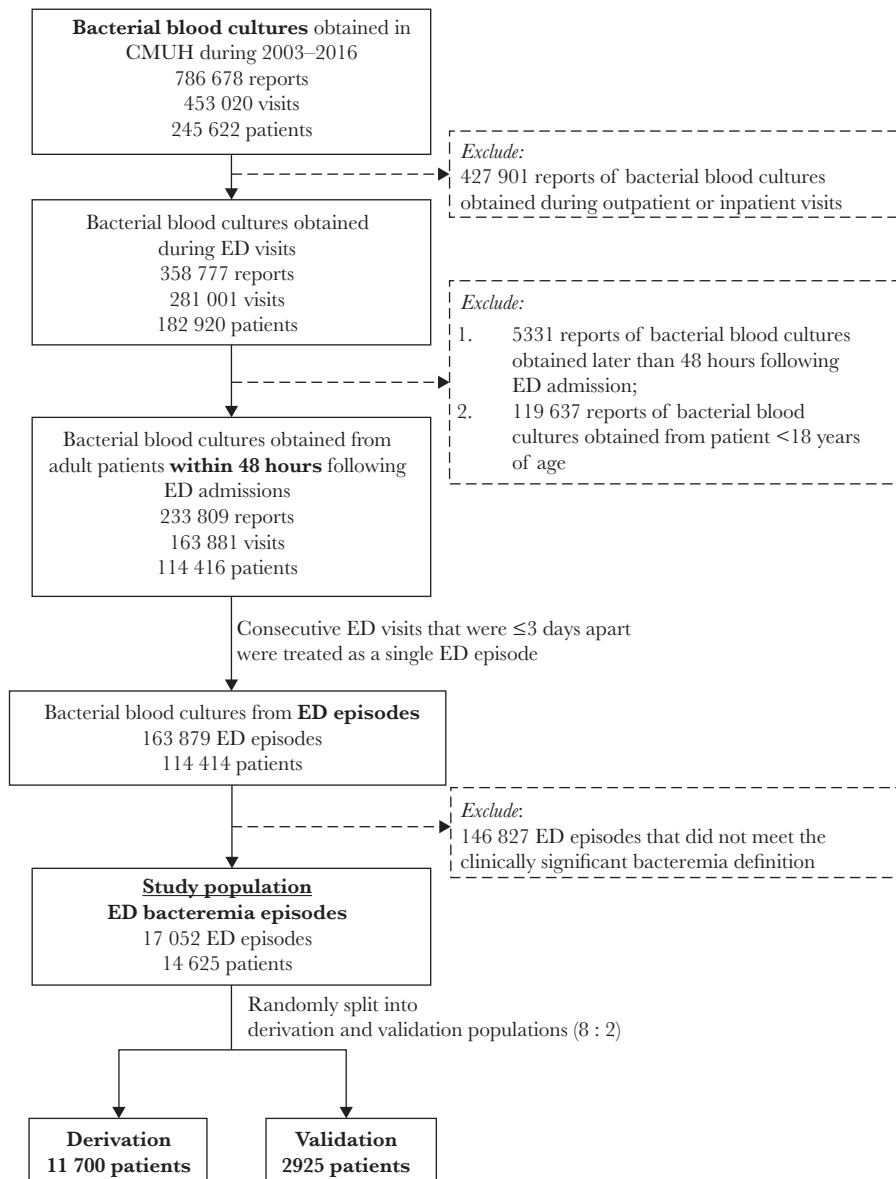
Figure 1. Selection process of the study population of patients admitted to the emergency department (ED) with bacteremia from 2003 to 2016 at China Medical University Hospital (CMUH).

with a *P* value <.25 in the univariable analysis and input them into backward, forward, and stepwise selection methods in multiple logistic regression models to identify variables that were associated with the 7-day mortality rate. From the 17 variables in common, we excluded aspartate aminotransferase due to data unavailability (missing rate >20%) and excluded implants and red blood cell (RBC) because implants information was recorded in infection source variable and because RBC and hemoglobin were similar indicators. We added age and liver cirrhosis back to the model because of clinical relevance and because this variable is included in the BSIMRS model. Finally, the ED bacteremia mortality (ED-BM) model was developed, and it included age, temperature, hypotension, mechanical ventilation, cardiac arrest, mental status, cancer,

liver cirrhosis, infection source, steroid use, estimated glomerular filtration rate (eGFR), platelet, blood urea nitrogen (BUN), red blood cell volume distribution width (RDW), serum potassium, and hemoglobin (Supplementary Figure 2). The variable types and the beta estimates for each variable in the ED-BM model are specified in Supplementary Table 6.

The cutoffs for eGFR, platelet, BUN, RDW, serum potassium, and hemoglobin were determined based on clinical practice and statistical evidence of sensitivity, specificity, and Youden's index (Supplementary Table 7). We also performed multicollinearity diagnostics of variables included in the ED-BM model by variance inflation factor (VIF) and tolerance. All variables included in the ED-BM model had VIF <10 and tolerance >0.1, showing no evidence of multicollinearity (Supplementary Table 8).

We compared the discrimination and calibration performance of the ED-BM model with those of PBS and BSIMRS in the validation population using the area under curve (AUC) and calibration plots [22]. Furthermore, we estimated the net reclassification index to determine the improvement in prediction of 7-day mortality risk of ED bacteremia when using our ED-BM model compared with PBS and BSIMRS. All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA), and R, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). A 2-sided statistical significance level of α was set at .05.

RESULTS

Trends and Characteristics of Adult Patients With Bacteremia

During 2003 and 2016, a declining trend of cumulative incidence of ED bacteremia was observed, with a peak of 13.48%


A Bacteremia at ED
— Overall — Female — Male

$P_{trend} < .001$
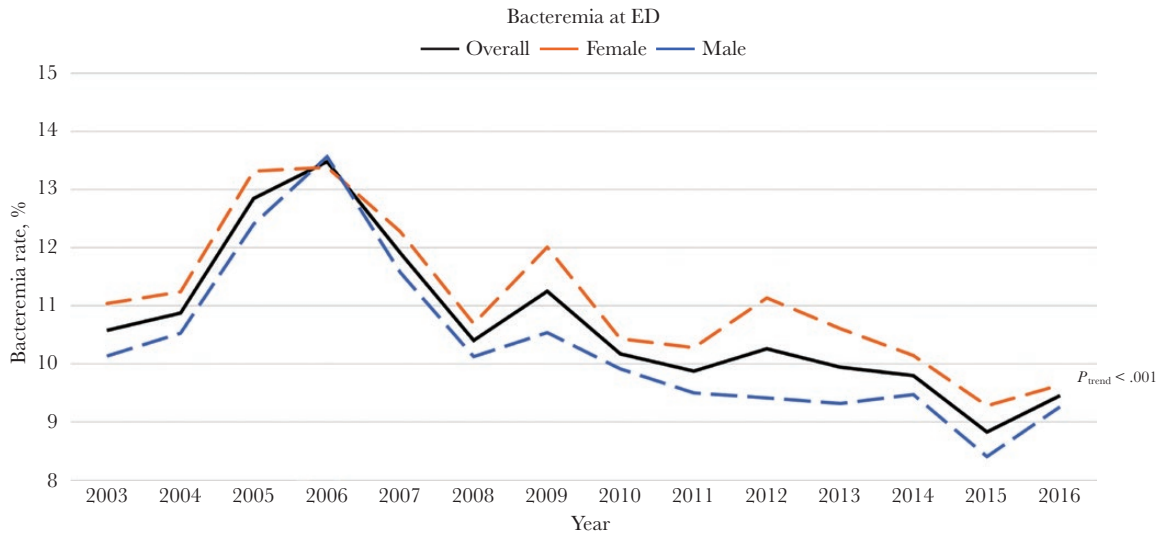
	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
No. of adult ED visit[a]	5617	5231	7891	7776	9481	10 760	12 254	12 708	13 348	14 593	14 593	15 283	17 316	17 028
No. of bacteremia episodes	594	569	1014	1048	1130	1120	1379	1293	1319	1497	1451	1498	1530	1610
Cumulative incidence of bacteremia, %	10.58	10.88	12.85	13.48	11.92	10.41	11.25	10.17	9.88	10.26	9.94	9.80	8.84	9.46

[a]Visits of blood cultures obtained per year

B Trend of 7-day mortality

$P_{trend} = .009$
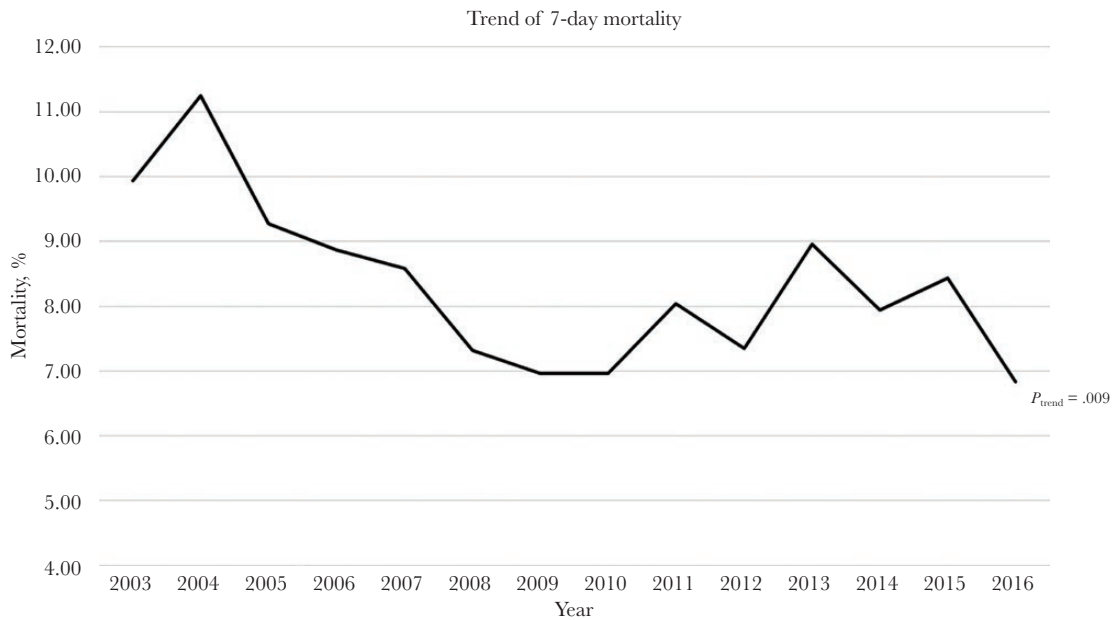
	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
No. of bacteremia episode	594	569	1014	1048	1130	1120	1379	1293	1319	1497	1451	1498	1530	1610
No. of deaths	59	64	94	93	97	82	96	90	106	110	130	119	129	110
Mortality (%)	9.93	11.25	9.27	8.87	8.58	7.32	6.96	6.96	8.04	7.35	8.96	7.94	8.43	6.83

Figure 2. Trends of the (A) cumulative incidence of bacteremia and (B) 7-day mortality rate of bacteremia in the emergency department (ED) from 2003 to 2016 at China Medical University Hospital (CMUH).

in 2006 and a nadir of 8.84% in 2015. A similar trend was observed for both males and females ($P_{trend} < .0001$) (Figure 2A). The trend of the 7-day mortality rate peaked in 2004 (11.25%) and then significantly decreased in 2016 (6.83%; $P_{trend} = .009$; age-adjusted $P_{trend} = .002$) (Figure 2B). Overall, 14 625 adult patients with first-time bacteremia at CMUH ED were included in the present study, and 80% of them (11 700 patients) were randomly selected as the derivation population for model establishment; the remaining patients (2925 patients) were included as the validation population for model performance evaluation. In the derivation population, the median age was 65.5 years and 48.6% were men. Renal insufficiency (55.6%), hypertension (24.1%), cancer (18.7%), and diabetes mellitus (17.2%) were the most common comorbidities (Table 1). Genitourinary system (36.0%) was the most common source of bacteremia, followed by the respiratory (18.0%) and digestive (16.2%) systems (Supplementary Figure 3). Gram-negative bacteria (73.4%) were the predominant pathogens. The most common bacteremia pathogens were *Escherichia coli* (38.3%), *Klebsiella pneumoniae* (12.5%), *Staphylococcus aureus* (11.7%), polymicrobial (7.48%), and *Pseudomonas aeruginosa* (2.34%) (Supplementary Table 9). The clinical and microbiological characteristics of the validation population did not differ significantly from those of the derivation population (Supplementary Tables 2 and 9).

Prediction Model for 7-Day Mortality (Derivation Population)

The pooled 7-day mortality of ED bacteremia was 8.53% in the derivation population. Table 1 summarizes the differences between patients who survived ≥7 days (survivors) and those who died within 7 days (nonsurvivors) after ED admission. Compared with the survivors, nonsurvivors were more likely to be older and men; to have chronic lung disease, liver cirrhosis, renal insufficiency, and cancer; and to have a history of steroid use, NSAID use, or recent hospitalization. Furthermore, the quick Sepsis-Related Organ Failure Assessment (qSOFA) score, PBS, and BSIMRS were more frequently higher among nonsurvivors than among survivors. Similarly, the levels of high-sensitive C-reactive protein (hs-CRP), BUN, serum creatinine, RDW, serum potassium, and liver enzymes were more likely to be higher in the nonsurvivors than in the survivors. Contrarily, the values of white blood cell count, neutrophil-to-lymphocyte ratio, platelet count, and hemoglobin were significantly lower among the survivors than among the nonsurvivors. The nonsurvivors were marginally more likely to receive inappropriate antibiotic treatment than the survivors (39.5% vs 36.7%; $P = .08$) (Table 1).

We then established the ED-BM model for predicting 7-day mortality of ED bacteremia. This model contained the following variables: variables derived from PBS and BSIMRS (Supplementary Table 5), steroid use, eGFR, platelet, BUN, RDW, potassium, and hemoglobin (Table 2). The variable with the most significant effect size was cardiac arrest (odds ratio [OR], 7.29), followed by comatose (Glasgow Coma Scale of 3; OR, 3.62), hypotension (OR, 2.74), infection source of nongenitourinary or central venous catheter (OR, 2.62), cancer (OR, 2.58), BUN >30 mg/dL (OR, 2.29), platelet <100 × 10³/μL (OR, 2.14), steroid use (OR, 1.62), mechanical ventilation (OR, 1.58), age ≥85 (OR, 1.55), eGFR <45 mL/min/1.73 m² (OR, 1.53), and RDW >14.5% (OR, 1.47).

Discrimination and Calibration Performance of the ED-BM Model

The ED-BM model had good discrimination and calibration performance in both the derivation and validation populations, with AUCs of 0.909 (95% CI, 0.900–0.919) and 0.903 (95% CI, 0.882–0.924), respectively (Figure 3; Supplementary Table 10). In predicting the 7-day mortality rate of ED bacteremia, the discrimination performance of the ED-BM model was significantly better than that of PBS (AUC, 0.848; 95% CI, 0.817–0.879; $P < .0001$) and BSIMRS (AUC, 0.885; 95% CI, 0.860–0.910; $P = .01$) in the validation population. This improved discrimination performance of our model was retained in predicting the 28-day mortality rate of ED bacteremia and was better than that of PBS and BSIMRS (Supplementary Table 10). Furthermore, the ED-BM model had satisfactory additive reclassification performance because it could correctly reclassify 9.49% and 1.53% of patients compared with PBS and BSIMRS, respectively (Supplementary Table 11).

Sensitivity Analysis

We conducted a few sensitivity analyses to test the robustness of our ED-BM model. First, because PBS and BSIMRS were initially developed to predict the 14-day mortality and 28-day mortality related to gram-negative bacteremia, we examined our model performance in predicting the 14-day and 28-day mortality in all ED adults with bacteremia and in those with GN bacteremia. In the validation set, our ED-BM model had an AUC of 0.891 (95% CI, 0.782–0.909) for 14-day mortality and 0.879 (95% CI, 0.862–0.896) for 28-day mortality in all bacteremia. The AUC was 0.909 (95% CI, 0.889–0.928) for the 14-day mortality and 0.899 (95% CI, 0.881–0.916) for the 28-day mortality related to GN bacteremia (Supplementary Table 10). Our ED-BM model remained significantly superior to PBS and BSIMRS in predicting 14-day mortality and 28-day mortality in all bacteremia and in GN bacteremia (Supplementary Table 10). Second, we created an additional model with fewer variables (ED-BM$_{minus}$) by excluding mechanical ventilation and cardiac arrest because they present only in critically ill patients (Supplementary Table 12). In the derivation population, the Akaike information criterion increased to 3493.66 with a minor drop in AUC (ED-BM vs ED-BM$_{minus}$, 0.909 vs 0.893; $P < .0001$). In the validation population, the AUC of the ED-BM model was also better than that of the ED-BM$_{minus}$ model (0.903 vs 0.884; $P < .0001$). Third, we tested our model performance by patients' severity as indicating by intensive care

Table 1. Demographic and Clinical Characteristics of 11 700 Patients With First-Time Bacteremia Identified at the Emergency Department in the Derivation Population

Characteristics	Available No.	Patients With Bacteremia[a]	7-Day Mortality		
			Survivors	Nonsurvivors	
		n = 11 700	n = 10 702 (91.5%)	n = 998 (8.53%)	P Value
Age, median (Q1, Q3), y		65.5 (52.6, 77.0)	65.1 (52.4, 76.8)	68.0 (54.6, 79.1)	<.0001
Male	11 700	5681 (48.6)	5066 (47.3)	615 (61.6)	<.0001
Comorbidity[b]					
Hypertension	11 700	2819 (24.1)	2569 (24.0)	250 (25.1)	.46
Congestive heart failure	11 700	798 (6.82)	723 (6.76)	75 (7.52)	.36
Coronary artery disease	11 700	979 (8.37)	906 (8.47)	73 (7.31)	.21
Chronic lung disease	11 700	921 (7.87)	811 (7.58)	110 (11.0)	.0001
Diabetes mellitus	11 700	2015 (17.2)	1838 (17.2)	177 (17.7)	.65
Liver cirrhosis	11 700	723 (6.18)	619 (5.78)	104 (10.4)	<.0001
Renal insufficiency (eGFR <60 mL/min/1.73 m^2)	11 693	6506 (55.6)	5658 (52.9)	848 (85.0)	<.0001
Rheumatic disease	11 700	158 (1.35)	141 (1.32)	17 (1.70)	.31
Transplantation	11 700	74 (0.63)	72 (0.67)	2 (0.20)	.07
Cancer	11 700	2187 (18.7)	1834 (17.1)	353 (35.4)	<.0001
AIDS/HIV	11 700	45 (0.38)	40 (0.37)	5 (0.50)	.53
Medication use within 14 d before index ED admission					
Recent systemic antibiotic use	11 700	1005 (8.59)	909 (8.49)	96 (9.62)	.22
Recent steroid use	11 700	1200 (10.3)	974 (9.10)	226 (22.7)	<.0001
Recent NSAID	11 700	823 (7.03)	732 (6.84)	91 (9.12)	.007
Medical history before index ED admission					
Dialysis within 30 d prior	11 700	289 (2.47)	267 (2.49)	22 (2.20)	.57
Hospitalization within 90 d prior	11 700	2700 (23.1)	2354 (22.0)	346 (34.7)	<.0001
Implants in placed within 90 d prior	11 700	481 (4.11)	448 (4.19)	33 (3.31)	.18
Central venous catheter in placed within 14 d prior	11 700	27 (0.23)	22 (0.21)	5 (0.5)	.06
Physiological measurement within 48 h after the index ED admission (first)					
Systolic blood pressure, mmHg	11 146	127 (108, 149)	128 (110, 150)	108 (88, 131)	<.0001
Heart rate, /min	11 179	108 (92, 122)	107 (92, 121)	112 (92, 132)	<.0001
Respiratory rate, /min	9150	20 (20, 22)	20 (20, 22)	22 (20, 26)	<.0001
Ear temperature, °C	11 343	38.2 (37.1, 39.1)	38.2 (37.2, 39.1)	36.9 (36, 38.1)	<.0001
qSOFA, median (Q1, Q3)	8926	1 (0, 1)	0 (0, 1)	1.5 (1, 2)	<.0001
0		4266 (47.8)	4186 (50.7)	80 (11.8)	
1		3137 (35.1)	2879 (34.9)	258 (38.2)	
2		1267 (14.2)	1018 (12.3)	249 (36.8)	
3		256 (2.87)	167 (2.02)	89 (13.2)	
Components of Pitt Bacteremia Score[c]					
Ear temperature	11 343				.70
36.1°C–38.9°C		7247 (61.9)	6692 (64.0)	555 (62.6)	
35.1°C–36.0°C or 39.0°C–39.9°C		2985 (25.5)	2743 (26.2)	242 (27.3)	
≤35°C or ≥ 40°C		1111 (9.50)	1021 (9.76)	90 (10.2)	
Hypotension	11 700	3429 (29.3)	2663 (24.9)	766 (76.8)	<.0001
Mechanical ventilation	11 700	1865 (15.9)	1308 (12.2)	557 (55.8)	<.0001
Cardiac arrest	11 700	569 (4.86)	233 (2.18)	336 (33.7)	<.0001
Mental status	11 688				<.0001
Alert (GCS 15)		9137 (78.1)	8693 (81.3)	444 (44.6)	
Disoriented (GCS 9–14)		1554 (13.3)	1302 (12.2)	252 (25.3)	
Stuporous (GCS 4–8)		657 (5.62)	520 (4.86)	137 (13.8)	
Comatose (GCS 3)		340 (2.91)	178 (1.66)	162 (16.3)	
Pitt Bacteremia Score	11 343	1 (0, 2)	1 (0, 2)	5 (2, 8)	<.0001
Bloodstream Infection Mortality Risk Score	11 343	4 (2, 7)	4 (2, 6)	9 (7, 9)	<.0001
Biochemical profiles within 48 h after the index ED admission (first)					
hs-CRP, mg/dL	11 522	11.0 (3.35, 21.1)	10.3 (3.02, 20.2)	18.3 (8.51, 28.0)	<.0001
White blood cell count, ×10^3/μL	11 687	11.9 (7.89, 16.7)	11.9 (8.10, 16.5)	10.6 (3.97, 18.5)	<.0001
Neutrophil-to-lymphocyte ratio	11 611	13.2 (7.37, 22.8)	13.3 (7.56, 22.7)	11.9 (4.83, 24.1)	<.0001
Neutrophil band	410	7.0 (3.0, 16.0)	6.0 (2.5, 15.0)	8.0 (3.0, 18.0)	.14

Table 1. Continued

Characteristics	Available No.	Patients With Bacteremia[a]	7-Day Mortality		P Value
			Survivors	Nonsurvivors	
		n = 11 700	n = 10 702 (91.5%)	n = 998 (8.53%)	
Platelet, ×10³/μL	11597	171 (115, 234)	174 (121, 236)	113 (47.7, 211)	<.0001
Red blood cell, ×10⁶/μL	9732	4.02 (3.40, 4.52)	4.06 (3.47, 4.55)	3.44 (2.85, 4.00)	<.0001
Blood urine nitrogen, mg/dL	10 947	20 (13, 37)	19 (13, 33)	45 (27, 72)	<.0001
Serum creatine, mg/dL	11 651	1.20 (0.88, 2.00)	1.16 (0.85, 1.84)	2.10 (1.37, 3.55)	<.0001
eGFR, mL/min/1.73 m²	11 651	54.1 (28.9, 82.4)	56.9 (31.5, 84.0)	28.1 (14.8, 47.0)	<.0001
Serum sodium, mmol/L	11 593	134 (131, 137)	134 (131, 137)	133 (128, 138)	.0008
Serum potassium, mmol/L	11 623	3.7 (3.4, 4.2)	3.7 (3.3, 4.1)	4.2 (3.6, 5.0)	<.0001
AST, IU/L	8703	40 (27, 79)	38 (26, 72)	66 (38, 158)	<.0001
ALT, IU/L	9367	30 (18, 57)	29 (18, 56)	38 (22, 73)	<.0001
RDW, %	9680	14.1 (13.2, 15.7)	14.0 (13.1, 15.5)	15.8 (14.3, 18.1)	<.0001
Glucose, mg/dL	11 603	145 (117, 212)	145 (118, 210)	143 (103, 228)	.0002
Lactate, mg/dL	4433	26.2 (16.1, 45.9)	23.8 (14.9, 39.5)	54.5 (28.5, 99.8)	<.0001
Hemoglobin, g/dL	11 641	11.9 (10.1, 13.4)	12.1 (10.2, 13.5)	10.4 (8.6, 12.2)	<.0001
Infection source[d]	11 700				<.0001
Genitourinary		4214 (36.0)	4100 (38.3)	114 (11.4)	
Respiratory		2108 (18.0)	1727 (16.1)	381 (38.2)	
Digestive		1891 (16.2)	1796 (16.8)	95 (9.52)	
Skin and soft tissue		838 (7.16)	782 (7.31)	56 (5.61)	
Nervous system		149 (1.27)	137 (1.28)	12 (1.20)	
Musculoskeletal		112 (0.96)	109 (1.02)	3 (0.30)	
Circulatory		126 (1.08)	116 (1.08)	10 (1.00)	
Primary bacteremia		2222 (19.0)	1896 (17.7)	326 (32.7)	
Implant		34 (0.29)	33 (0.31)	1 (0.10)	
Unclassified		6 (0.05)	6 (0.06)	0 (0)	
Pathogens causing bacteremia	11 700				<.0001
Gram-negative		8589 (73.4)	7903 (73.9)	686 (68.7)	
Gram-positive		2849 (24.4)	2587 (24.2)	262 (26.3)	
Both		262 (2.24)	212 (1.98)	50 (5.01)	
Resistant pathogens causing bacteremia					
Methicillin-resistant *Staphylococcus aureus*	1470	574 (39.1)	493 (37.9)	81 (47.9)	.01
Vancomycin-resistant *Enterococcus*	354	34 (9.60)	30 (9.49)	4 (10.5)	.84
Carbapenem-resistant *Enterobacteriaceae*	7245	81 (1.12)	76 (1.13)	5 (0.96)	.71
Ceftriaxone-resistant *Enterobacteriaceae*	7245	809 (11.2)	737 (11.0)	72 (13.8)	.05
Antibiotic treatment during episode[e]	11 700				
Inappropriate use		4318 (36.9)	3924 (36.67)	394 (39.48)	.08
Time to antibiotic use, h	9946	1.70 (1.12, 2.60)	1.75 (1.17, 2.65)	1.28 (0.80, 1.93)	<.0001

Abbreviations: AST, aspartate aminotransferase; ALT, alanine transaminase; ED, emergency department; eGFR, estimated glomerular filtration rate; GCS, Glasgow Coma Scale; hs-CRP, high-sensitive C-reactive protein; ICD, International Classification of Diseases; NSAID; nonsteroid anti-inflammatory drug; qSOFA, quick Sepsis-Related Organ Failure Assessment; RDW, red blood cell volume distribution width.

[a]Values for the continuous variables are expressed as median (interquartile range), and values for the categorical variables are expressed as frequency (%).

[b]Comorbidities were defined as having ICD diagnosis within 1 year before the index ED admission, if not otherwise defined. Rheumatic diseases, transplantation, and cancer were defined as having the catastrophic illness diagnosis any time before the index ED admission (Supplementary Table 3).

[c]We obtained data for each component recorded within 48 hours after the ED admission and calculated the Pitt Bacteremia Score.

[d]Infection source was defined as the ICD diagnosis during the index ED episode or the following hospital admission (Supplementary Table 4).

[e]Inappropriate antibiotic was defined as when the susceptibility results did not prove that bacteria were susceptible to the given antibiotic (Supplementary Figure 1).

unit (ICU) admission status and qSOFA level (Supplementary Table 13). Overall, the model discrimination performance in the validation set remained the highest for the ED-BM model and the lowest for the PBS model or ED-BM$_{minus}$. The model performance decreased in patients with more severe conditions (ie, ICU admission, qSOFA ≥2). However, almost all AUCs of ED-BM or ED-BM$_{minus}$ were around 0.80, indicating good discrimination performance. To conclude, the above-mentioned

evidence indicates that the original ED-BM model is robust and that overfitting is not of concern.

DISCUSSION

The current study demonstrated the decreasing trends of the cumulative incidence of ED bacteremia (from 13.48% to 8.84%) and ED bacteremia–associated 7-day mortality (from 11.25% to

Table 2. Multivariable Logistic Regression Models of 7-Day All-Cause Mortality in the Derivation Population (n = 8808)

Variables	PBS[a] OR (95% CI)	BSIMRS[b] OR (95% CI)	ED-BM[c] OR (95% CI)
Age			
<65 y			Reference
65–84 y			0.95 (0.78–1.17)
≥85 y			1.55 (1.13–2.14)
Ear temperature			
36.1°C–38.9°C	Reference	Reference	Reference
35.1°C–36.0°C or 39.0°C–39.9°C	0.91 (0.74–1.11)	0.95 (0.77–1.17)	0.92 (0.74–1.14)
≤35.0°C or ≥ 40.0°C	0.82 (0.61–1.11)	0.94 (0.68–1.28)	1.02 (0.73–1.42)
Hypotension	4.00 (3.23–4.95)	3.76 (3.03–4.68)	2.74 (2.18–3.44)
Mechanical ventilation	1.92 (1.57–2.36)	1.90 (1.54–2.36)	1.58 (1.26–1.98)
Cardiac arrest	6.43 (5.04–8.20)	6.53 (5.07–8.40)	7.29 (5.57–9.56)
Mental status			
Alert (GCS 15)	Reference	Reference	Reference
Disoriented (GCS 9–14)	2.46 (1.98–3.04)	2.45 (1.97–3.06)	1.81 (1.43–2.29)
Stuporous (GCS 4–8)	2.35 (1.76–3.14)	2.48 (1.83–3.34)	1.90 (1.37–2.62)
Comatose (GCS 3)	4.75 (3.37–6.70)	4.98 (3.50–7.07)	3.62 (2.50–5.24)
Cancer		3.24 (2.66–3.94)	2.58 (2.07–3.23)
Liver cirrhosis		1.55 (1.15–2.09)	1.11 (0.81–1.53)
Infection source			
Genitourinary		Reference	Reference
Nongenitourinary or CVC		2.61 (2.03–3.36)	2.62 (2.01–3.41)
Steroid use			1.62 (1.26–2.10)
eGFR <45 mL/min/1.73 m^2			1.53 (1.19–1.97)
Platelet <100 ×10^3/μL			2.14 (1.75–2.61)
BUN >30 mg/dL			2.29 (1.78–2.94)
RDW >14.5%			1.47 (1.19–1.81)
Serum potassium <4.0 mmol/L			0.70 (0.58–0.86)
Hemoglobin <11.5 g/dL			1.17 (0.95–1.44)
Model performance			
AIC	3579.948	3533.314	3228.458
AUC (95% CI)	0.850 (0.835–0.865)	0.883 (0.871–0.895)	0.909 (0.900–0.919)
$P_{\text{difference in AUC}}$	<.0001	<.0001	Reference

Abbreviations: AIC, Akaike information criterion; AUC, area under curve; BSIMRS, Bloodstream Infection Mortality Risk Score; BUN, blood urea nitrogen; CVC, central venous catheter; ED-BM, emergency department bacteremia mortality model; eGFR, estimated glomerular filtration rate; GCS, Glasgow Coma Scale; OR, odds ratio; PBS, Pitt Bacteremia Score; RDW, red cell distribution width.

[a]PBS model included temperature, hypotension, mechanical ventilation, cardiac arrest, and mental status.

[b]BSIMRS model included components of PBS, cancer, liver cirrhosis, and infection source.

[c]ED-BM model included components of PBS and BSIRMS, age, cancer, liver cirrhosis, infection source, eGFR, platelet, BUN, RDW, serum potassium, and hemoglobin.

6.83%) from 2003 to 2016 in a tertiary medical center in central Taiwan. In addition, the novel ED-BM model proposed in this study demonstrated better discrimination, calibration, and reclassification performance than PBS and BSIMRS in predicting 7- and 28-day mortality rates among adult ED patients with bacteremia.

Depending on patient populations or bacterial species studied, the positive rate (ie, diagnostic yields) of ED BCs have varied widely (range, 9.8%–31.7%) [7, 23–26]. Similar to prior studies [5, 7], the following findings were observed in the present study: Only 1 of 10 patients receiving BCs had clinically significant bacteremia; gram-negative microorganisms (particularly *E. coli*) were the most common isolates; and urinary tract infection was the most common infection source (Table 1). The consistently low positive rate of BC indicates a clinical practice gap in identifying the patients who require BC exam in the ED [1]. In our study, the trend of bacteremia declined slightly from 2003 to 2016, which was similar to the observation in a Denmark study of community-acquired bacteremia from 2000 to 2008 (3.7% decrease per year) [27]. The decreasing trend may be partially due to the increased ED patient volume and the liberal performance of BCs. In our study, the number of ED visits with BC obtained increased by 3.03-fold, and the number of bacteremia events increased by only 2.7-fold (Figure 1).

In the literature, the 28-day mortality rate of ED bacteremia has been commonly reported to range from 5.3% to 14.4% [2–5]. An earlier study found that the 7-day mortality rate could more accurately reflect the clinical impact of bacteremia itself
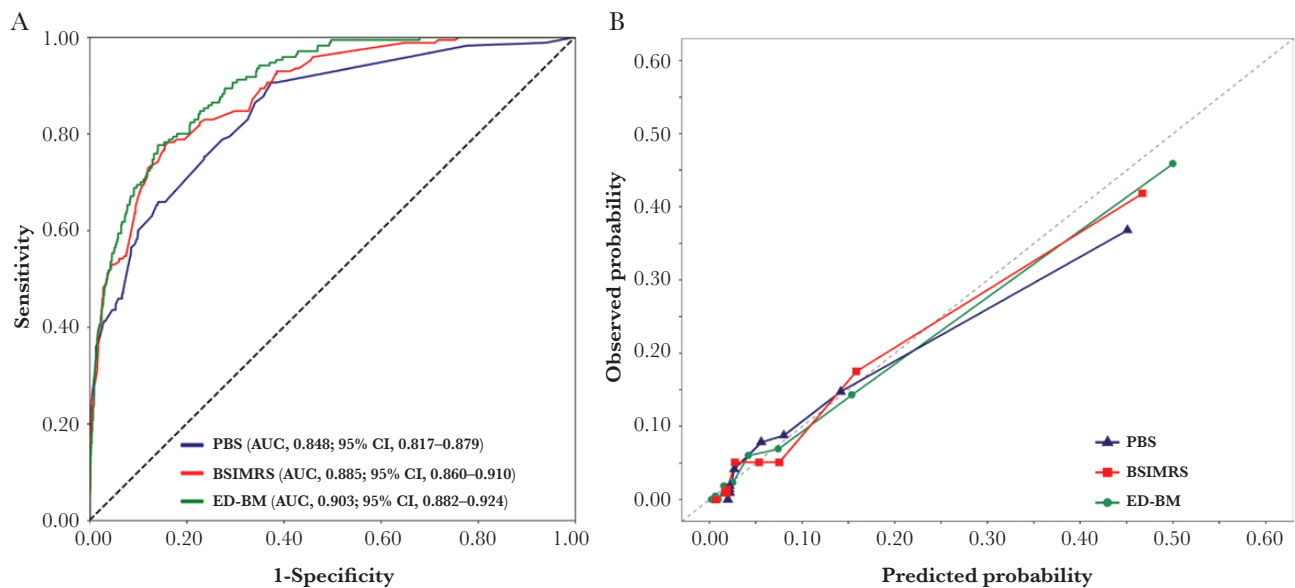
Figure 3. Discrimination and calibration performance of the Pitt Bacteremia Score (PBS), Bloodstream Infection Mortality Risk Score (BSIMRS), and emergency department bacteremia mortality (ED-BM) model in the validation population (n = 2172): (A) receiver operating characteristic curves and (B) calibration curves.

rather than underling diseases of patients [28]. In addition to comorbidities, other in-hospital factors, such as nosocomial infections, can have an unfavorable effect on a patient's outcome. The 7-day mortality rate of our study was 8.53%, which was comparable with the results reported by Al-Hasan and Rannikko [11, 28]. Furthermore, we observed a declining trend of short-term mortality, which has rarely been mentioned in previous studies [7, 23–26], among adult ED patients with bacteremia. A nationwide study that evaluated the sepsis trend between 2009 and 2014 found a significantly decreasing trend of in-hospital mortality using either the claims-based (6.6% decrease per year) or electronic health record–based criterion (3.3% decrease per year) [29]. The timing of decline in the mortality of ED bacteremia coincided with the first release of the Surviving Sepsis Campaign guidelines [30]. The implementation of these guidelines at the ED may partially explain the reduction in short-term mortality of bacteremia. Additionally, a significant decrease in antibiotic inappropriateness from 52.7% in 2003 to 26.5% in 2016 was observed in our study, which could be another ecological explanation for the decreasing 7-day mortality rate due to precise empirical antibiotic selection (Supplementary Figure 4). Furthermore, in studies of organism-specific bacteremia (carbapenem-resistant *Acinetobacter baumannii* or *S. aureus*), a decreasing mortality rate was observed, and appropriateness of antibiotic use was found to be associated with decreased mortality [31–33]. Further studies are required to investigate guideline adherence or antibiotic treatment behaviors and their association with mortality reduction in patients with bacteremia at EDs.

Numerous scoring systems have been used to assess the disease severity and death risk of non-ED patients with bacteremia [12, 34–39]. However, these models typically require information that is not readily available in ED settings. Thus, these scoring systems may not be practical for ED physicians to predict the mortality risk of patients with bacteremia. Several scoring systems to predict the mortality of ED bacteremia or sepsis have been proposed [2–5, 10, 40]. Each of these scoring systems, however, has its own limitations. For example, some prediction models used poorly defined predictors, such as the status of terminal illness and absence of chill, which may lead to nonstandardized assessment [2, 4]. Yeh [3] used *S. aureus* bacteremia and bacteremia with an unknown focus as predictors to stratify the mortality rate of ED patients with BSIs; however, as in real-world practice, clinicians usually need to make disposition decisions before BC results. In other studies, certain clinical conditions of the patient population (eg, cardiac arrest) have posed a substantial mortality risk [10, 40]. Using variables that tightly link to an extremely high risk of death makes these equations unsuitable for most ED patients with bacteremia.

Compared with the aforementioned models [2–4, 10, 40], the ED-BM model has the following strengths: The included variables are objective and readily available during ED admission, the process of variable selection is robust, and the evaluation method of model performance is comprehensive and is validated in the validation population. In addition to the variables proposed by PBS and BSIMRS, we found that impaired renal function, low platelet count, recent steroid use, and wide RDW have a significant effect on the mortality of ED bacteremia, which has been confirmed in studies of mortality for bacteremia or sepsis [2–4, 41]. For instance, a study reported that baseline steroid use is associated with an increased risk of infection and sepsis [42]. Moreover, steroid use per se can compromise the host's immune response to infections and thus influence the clinical prognosis [43].

Compared with PBS and BSIMRS [12, 14], our model had a better discrimination performance in predicting 7-, 14-, and 28-day mortality among adult ED patients with bacteremia and among adult ED patients with gram-negative bacteremia (Supplementary Table 10). Our model could correctly reclassify high-risk patients (Figure 3; Supplementary Table 11). Although the ED-BM predicts lower mortality than the true mortality, the calibration curve of our model aligns closer to the diagonal line of an ideal prediction model than PBS and BSIMRS. Although model overfitting is a potential concern for the ED-BM model with 16 variables, this concern seems to be negligible considering its good performance in the validation population. In the modern Health Information System (HIS), the ED-BM model could be embedded in the ED setting and assist in risk stratification for adult patients with bacteremia. We expect that the ED-BM can be used to predict patient outcomes when physicians highly suspect a bacteremia etiology or when the initial reports of gram stain culture results are available (within 24–48 hours after blood culture collection). However, further efforts should be allocated in the external validation and implementation of different digital health care systems worldwide.

This study has several limitations. First, the retrospective design could not take into account the trend of changing practice patterns. Further research is required to address potential practice changes, such as the pattern of antimicrobial prescription or the proportion of responsiveness of ED physicians to guidelines. Second, the derivation data set was from a single institution, which may limit its generalizability to other patient populations such as regional or community hospitals. External databases with the data from emergency services, such as the Medical Information Mart for Intensive Care (MIMIC)–IV database [44], should be used to validate our mortality prediction model for ED bacteremia.

In conclusion, this study showed a decreasing trend of short-term mortality of ED bacteremia at a tertiary center in central Taiwan. Moreover, we derived and validated a new prediction tool, the ED-BM model, with better discrimination and calibration performance than PBS and BSIMRS in predicting 7-day mortality among adult ED patients with bacteremia. Further studies are required to validate the ED-BM model and evaluate its effectiveness in the real-world settings of other health care systems.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

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