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ORIGINAL ARTICLE

# Derivation of a clinical prediction rule for bloodstream infection mortality of patients visiting the emergency department based on predisposition, infection, response, and organ dysfunction concept



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## KEYWORDS

Bacteremia;  
Bloodstream  
infection;  
Mortality;  
Pitt bacteremia score  
predictive model

**Background/Purpose:** Bloodstream infection (BSI) is a serious infection with a high mortality. We aimed to construct a predictive scoring system to stratify the severity of patients with BSI visiting the emergency department (ED).

**Methods:** We conducted a retrospective cohort study consisting of patients who visited the ED of a tertiary hospital with documented BSI in 2010. The potential predictors of mortality were obtained via chart review. Multivariate logistic regression was utilized to identify predictors of mortality. Penalized maximum likelihood estimation (PMLE) was applied for score development.

**Results:** There were 1063 patients with bacteremia included, with an overall 28-day mortality rate of 13.2% ( $n = 140$ ). In multiple logistic regression with penalization, the independent predictors of death were “predisposition”: malignancy ( $\beta$ -coefficient, 0.65; +2 points); “infection”: *Staphylococcus aureus* (*S. aureus*) bacteremia (0.69; +2 points), pneumonia (1.32; +4 points), and bacteremia with an unknown focus (0.70; +2 points); “response”: body

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temperature  $<36^{\circ}\text{C}$  (1.17; +3 points), band form  $>5\%$  (1.00; +3 points), and red blood cell distribution width (RDW)  $>15\%$  (0.63; +2 points); and “organ dysfunction”: pulse oximeter oxygen saturation  $<90\%$  (0.72; +2 points) and creatinine  $>2$  mg/dL (0.69; +2 points). The area under receiver operating characteristic curve (AUROC) for the model was 0.881 [95% confidence interval (CI), 0.848–0.913], with a better performance than the Pitt bacteremia score (AUROC: 0.750; 95% CI 0.699–0.800,  $p < 0.001$ ). The patients were stratified into four risk groups: (1) low, 0–3 points, mortality rate: 1.5%; (2) moderate, 4–6 points, mortality rate: 10.5%; (3) high, 7–8 points, mortality rate: 28.6%; and (4) very high,  $\geq 9$  points, mortality rate: 65.5%.

**Conclusion:** The new scoring system for bacteremia could facilitate the prediction of the risk of 28-day mortality for patients visiting the ED with BSI.

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## Introduction

Bloodstream infection (BSI) is a serious infection. The estimated 28-day and 1-year mortality rates are about 15–20%<sup>1</sup> and 25%,<sup>2</sup> respectively. Given the heterogeneous nature of BSI, patients with BSI have a wide spectrum of risk for death.<sup>3</sup> The ability to stratify patients based on their disease severity and risk of mortality, is important, especially in order to allocate the limited medical resources. Accordingly, a scoring system to quantify the risk of death is helpful to stratify high-risk patients for intensive care unit (ICU) admission, predict hospital length of stay, and guide treatment decisions.<sup>4</sup>

Several scoring systems have been developed for use in the ICU to predict the risk of death, including the acute physiology and chronic health evaluation (APACHE)<sup>5</sup> and sequential-related organ failure assessment score.<sup>6</sup> However, these two scoring systems were developed for general critically ill patients, not only for bacteremic patients. The Pitt bacteremia score has been developed to assess the severity of bacteremic patients, but it only categorizes patients into “severely ill” or not.<sup>7,8</sup> The Pitt bacteremia score does not provide finer gradations of the mortality risk that exist clinically.

In the 2001 International Sepsis Definition Conference, several researchers advocated staging patients with sepsis, to predict the risk of adverse outcome and the response to therapy. The predisposition, infection, response and organ dysfunction (PIRO) concept was proposed for staging of patients with sepsis.<sup>9</sup> It was inspired by the Tumor-Nodes-Metastasis (TNM) system of cancer staging to predict the outcome of patients and to guide the therapy. The elements of PIRO include predisposition (demographics, comorbidities, and genetics), infection (source of infection and pathogen), response (systemic inflammatory response), and organ dysfunction.<sup>10–13</sup> The PIRO concept has been used to construct models for severity assessment in patients with sepsis, community-acquired pneumonia, and ventilator-associated pneumonia.<sup>14–16</sup> However, it has not been incorporated into risk scoring systems for BSI.

In this study, we aimed to construct a specific risk scoring system, utilizing the predictors readily available in the primary care setting, based on the PIRO concept to predict the severity of patients visiting the emergency department (ED) with BSI.

## Materials and methods

### Study design and patients

We conducted a retrospective cohort study consisted of patients who visited the ED at the Chang Gung Memorial Hospital (CGMH) in Taoyuan, Taiwan, between January 2010 and December 2010. The hospital is a 3700 bed university-affiliated hospital and tertiary referral medical center in northern Taiwan. This study was approved by the Institutional Research Board of CGMH. Patients who visited our ED and received two sets of blood culture were eligible. If the patients experienced more than one episode of bacteremia, only the first episode was included. Patients who were: (1)  $<18$  years old; and (2) referred from other hospitals, were excluded.

### Data collection and case definition

Structured query language (SQL) was used to retrieve clinical information from electronic medical records. We also double-checked the results of the electronic chart review by different program codes, as well as by manual chart review. Potential predictors were obtained, including basic demographic data, underlying disease, blood culture result, infectious focuses, ICU admission, requirement for mechanical ventilation, and mortality date. Body temperature, heart rate, respiratory rate, blood pressure, and Glasgow coma score (GCS) were recorded at triage in the ED. Laboratory data, including complete blood counts, differential counts, serum creatinine, liver function test, serum sodium, serum potassium, C-reactive protein, and arterial blood gas were recorded.

True bacteremia was defined as two separate sets of blood cultures growing the same microorganism, or a single set of positive blood culture with documented infection. When single blood culture yielded coagulase-negative *Staphylococci*, *Corynebacterium* species, *Propionibacterium* species, *Bacillus* species, *Aerococcus* species, or *Micrococcus* species, the blood cultures were considered as contaminants and these cases were not included.

Liver cirrhosis was diagnosed according to the results of abdominal ultrasonography or an abdominal computed

tomography scan. Congestive heart failure was diagnosed by cardiac ultrasonography and clinical symptoms. Malignancy was defined as an active solid tumor or hematological malignancy. The infectious focuses were recorded based on admission and discharge diagnoses, including both primary focuses and secondary focuses. If the admission or discharge diagnoses did not document any infectious focuses, further chart review was done. Mortality was defined as all-cause mortality within 28 days from the emergence of bacteremia.

### Statistical analysis

Statistical analyses were performed with SPSS software version 18.0 (SPSS Inc.; Chicago, IL, USA) and STATA 11.0 (StataCorp, College Station, TX, USA). The candidate predictors were selected according to predisposition, infection, response, and organ dysfunction. Variables of predisposition included age, sex, and underlying disease. Variables of infection included infectious focuses and type of microorganism. Variables of response included body temperature, pulse rate, respiratory rate, white blood cell counts, differential counts, and red blood cell distribution width (RDW). Variables of organ dysfunction included blood pressure, GCS, pulse oximeter oxygen saturation, creatinine level, hemoglobin, and platelet counts. Variables with large amounts of missing values were not considered as candidate predictors. The univariate analysis of continuous variables was compared by Mann-Whitney U test. Continuous variables of clinical interest were converted into categorical variables. The cut-off points for continuous variables were set according to clinical practice, description in other studies, or laboratory references. The univariate relationships between 28-day mortality and the categorical variables were examined by the Chi-square test or Fisher's exact test when appropriate. Univariate logistic regression was used to calculate the odds ratio (OR) and 95% confidence interval (CI). All categorical variables with  $p < 0.25$  were evaluated with multivariate logistic regression with forced enter method. The  $\beta$ -coefficient and  $p$  values were calculated. The Hosmer-Lemeshow Goodness-of-Fit statistics were computed to verify the goodness of the model fit.

### Score development

To avoid overfitting of the model, we used penalized maximum likelihood estimation (PMLE),<sup>17</sup> which yielded shrunk regression coefficients. We rounded each  $\beta$ -coefficient from the penalized model to the nearest integer, to generate a simple scoring system. The new score for each patient was calculated by summation of the points of each variable. The performance of the scoring system was analyzed by receiver-operating characteristic (ROC) curves. Internal validation was done with 200 bootstrap replications. Patients were classified into four risk groups and the observed mortality of each risk group was calculated. The discriminating ability of the new score and the Pitt bacteremia score was compared using the area under ROC (AUROC).

## Results

Among 11,899 patient visits eligible, there were 2306 patient visits which generated positive blood culture results. After excluding patient visits with contaminated blood culture ( $n = 841$ ), duplicated patient visits ( $n = 67$ ), patients  $<18$  years old ( $n = 11$ ), patients lost to follow-up ( $n = 9$ ), and patients transferred from other hospitals ( $n = 315$ ), 1063 patients with true bacteremia were included in the analysis (Fig. 1). The overall 28-day all-cause mortality rate was 13.2% ( $n = 140$ ). Almost half of the patients were  $>65$  years of age ( $n = 531$ , 50%) and male ( $n = 518$ , 48.7%). Diabetes mellitus was the most common comorbidity ( $n = 369$ , 34.7%), followed by malignancy ( $n = 253$ , 23.8%), cerebrovascular accident ( $n = 159$ , 15.0%), liver cirrhosis ( $n = 133$ , 12.5%), end-stage renal disease ( $n = 83$ , 7.8%), and congestive heart failure ( $n = 82$ , 7.7%; Table 1). Microorganisms recovered from blood culture are reported in Table 2. The most common pathogens of bacteremia were *Escherichia coli* (33.1%), followed by *Klebsiella* sp. (11.9%), and *Staphylococcus aureus* (10.3%). The mean time between the blood culture collection and the final report was  $3.04 \pm 1.78$  days (mean  $\pm$  standard deviation).

In univariate analysis, liver cirrhosis (OR, 2.54; 95% CI, 1.63–3.95) and malignancy (OR, 3.27; 95% CI, 2.26–4.73)

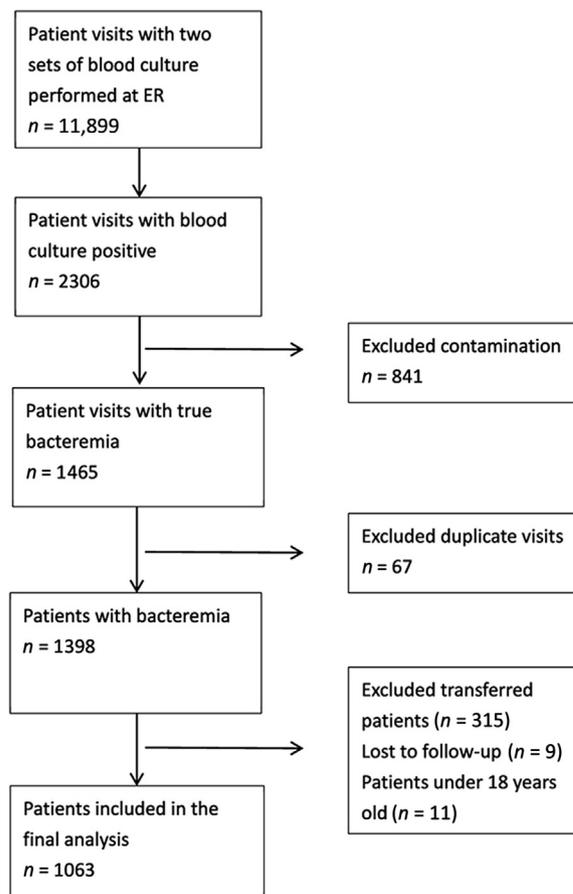


Figure 1. Flow chart of patients included in the study. ER = emergency room.

**Table 1** Variables of predisposition and the result of univariate logistic regression analysis<sup>a</sup>

	All (n = 1063) No.	%	Mortality (n = 140) No.	%	OR	95% CI	p
Age	64	(53–77)	66	(55–78)	1.01	1.00–1.02	0.265
>65 y	531	50.0	74	52.9	1.14	0.80–1.63	0.461
Male	518	48.7	90	64.3	2.08	1.44–3.01	<0.001
Comorbidity							
Diabetes mellitus	369	34.7	39	27.9	0.69	0.47–1.03	0.069
CHF	82	7.7	16	11.4	1.68	0.94–2.99	0.080
ESRD	83	7.8	10	7.1	0.90	0.45–1.78	0.753
Liver cirrhosis	133	12.5	33	23.6	2.54	1.63–3.95	<0.001
CVA	159	15.0	23	16.3	1.14	0.70–1.84	0.601
Malignancy	253	23.8	64	45.7	3.27	2.26–4.73	<0.001

<sup>a</sup> Data are expressed as case numbers and percentages, and as median and interquartile range for age.

CHF = congestive heart failure; CI = confidence interval; CVA = cerebrovascular accident; ESRD = end-stage renal disease; OR = odds ratio.

were significantly associated with a higher 28-day mortality among the variables categorized as “predisposition” (Table 1). Variables of “infection” associated with a higher mortality were pneumonia (OR, 6.38; 95% CI, 4.09–9.94) and an unknown infectious focus (OR, 3.64; 95% CI, 2.48–5.33),

whereas urinary tract infection (OR, 0.15; 95% CI, 0.074–0.29) and intra-abdominal infection (OR, 0.39; 95% CI, 0.22–0.69) were associated with a lower mortality rate. *S. aureus* (OR, 2.01; 95% CI, 1.23–3.29), *Pseudomonas aeruginosa* (OR, 2.65; 95% CI, 1.08–6.46), anaerobes (OR,

**Table 2** Result of univariate logistic regression of infectious focuses and microorganism associated with mortality

	All (n = 1063) No.	%	Mortality (n = 140) No.	%	OR	95% CI	p
Infectious focuses							
Urinary tract	302	28.4	9	6.4	0.15	0.07–0.29	<0.001
Intra-abdomen	220	20.7	14	10.0	0.39	0.22–0.69	0.001
Pneumonia	103	9.7	43	30.7	6.38	4.09–9.94	<0.001
Skin and soft tissue	74	7.0	7	5.0	0.67	0.30–1.50	0.331
Cardiovascular system	41	3.9	3	2.1	0.51	0.16–1.67	0.267
Bone and joint	30	2.8	1	0.7	0.22	0.03–1.64	0.140
Catheter	28	2.6	1	0.7	0.24	0.03–1.77	0.161
Gastrointestinal tract	26	2.4	3	2.1	0.86	0.25–2.89	0.803
Multiple sites	14	1.3	3	2.1	1.82	0.50–6.59	0.365
Unknown	199	18.7	56	40.0	3.64	2.48–5.33	<0.001
Gram-positive							
<i>Staphylococcus aureus</i>	110	10.3	24	17.0	2.01	1.23–3.29	0.005
CONS	33	3.1	1	0.7	0.20	0.03–1.48	0.115
<i>Enterococci</i>	19	1.8	3	2.1	0.73	0.36–4.32	0.734
<i>Streptococcus pneumonia</i>	14	1.3	2	1.4	1.10	0.24–4.97	0.901
Other streptococci	111	10.3	11	7.9	0.70	0.37–1.34	0.285
Gram-negative							
<i>Escherichia coli</i>	352	33.1	16	11.4	0.23	0.13–0.39	<0.001
<i>Klebsiella</i> sp.	126	11.9	16	11.4	0.95	0.55–1.67	0.868
<i>Salmonella</i> sp.	21	2.0	3	2.1	1.10	0.32–3.79	0.879
<i>Pseudomonas aeruginosa</i>	25	2.4	7	5.0	2.65	1.08–6.46	0.032
<i>Acinetobacter</i> sp.	15	1.4	4	2.9	2.44	0.77–7.77	0.132
Other gram-negative	74	7.0	14	10.0	1.60	0.87–2.94	0.133
Anaerobes	39	3.7	10	7.1	2.37	1.13–4.98	0.023
Fungus	11	1.0	4	2.9	3.85	1.11–13.32	0.033
Polymicrobial	109	10.3	25	17.9	2.17	1.33–3.53	0.002

CI = confidence interval; CONS = coagulase-negative staphylococci; OR = odds ratio.

2.37; 95% CI, 1.13–4.98), and polymicrobial bacteremia (OR, 2.17; 95% CI, 1.33–3.53) were associated with a higher 28-day mortality, whereas *E. coli* bacteremia (OR, 0.23; 95% CI, 0.13–0.39) was associated with a lower 28-day mortality (Table 2). There were 110 episodes of *S. aureus* bacteremia (10.3%) in our study. Among them, 72 episodes (65.5%) were methicillin-sensitive and 38 episodes (34.5%) were methicillin-resistant. The mortality rate of methicillin-sensitive *S. aureus* (MSSA) bacteremia and methicillin-resistant *S. aureus* (MRSA) bacteremia was 18.1% and 28.9%, respectively ( $p = 0.188$ ).

Among variables of “response”, body temperature <36°C (OR, 5.82; 95% CI, 3.44–9.85), respiratory rate >20 breaths/minute (OR, 2.03; 95% CI, 1.42–2.91), RDW >15% (OR, 4.34; 95% CI, 2.98–6.32), white blood cell counts <4000/μL (OR, 4.55; 95% CI, 2.87–7.21) and band form of neutrophil >5% (OR, 4.86; 95% CI, 3.32–7.11) were associated with a higher mortality rate. Variables of “organ dysfunction” associated with increased mortality were systolic blood pressure <90 mmHg (OR, 5.49; 95% CI, 3.54–8.51), GCS <8 (OR, 4.56; 95% CI, 2.77–7.51), pulse

oximeter oxygen saturation <90% (OR, 5.87; 95% CI, 3.81–9.06), hemoglobin <8 g/dL (OR, 3.75; 95% CI, 2.31–6.09), platelet count <10×10<sup>3</sup>/μL (OR, 3.36; 95% CI, 2.31–4.88), and creatinine >2 mg/dL (OR, 3.84; 95% CI, 2.65–5.56; Table 3).

Twenty-eight predictors with  $p < 0.25$  in the univariate analysis were included in the multivariate analysis. Ten predictors with  $p < 0.05$  were included in the full unpenalized multivariate logistic regression model (Table 4). After penalizing the full model, liver cirrhosis lost its statistical significance as a predictor of mortality. The penalized model, included nine independent predictors of death, was finalized as following: “predisposition”: malignancy ( $\beta$ -coefficient, 0.65; 95% CI, 0.18–1.12); “infection”: *S. aureus* bacteremia (0.69; 95% CI, 0.05–1.32), pneumonia (1.32; 95% CI, 0.68–1.96), and bacteremia with an unknown focus (0.70; 95% CI, 0.16–1.24); “response”: body temperature <36°C (1.17; 95% CI, 0.48–1.87), band form >5% (1.00; 95% CI, 0.52–1.48), and RDW >15% (0.63; 95% CI, 0.19–1.07); “organ dysfunction”: pulse oximeter oxygen saturation <90% (0.72; 95% CI, 0.15–1.30), and creatinine >2 mg/dL (0.69; 95% CI,

**Table 3** Variables of response and organ dysfunction of 1063 patients and result of univariate logistic regression<sup>a</sup>

	Mortality (n = 140) No.	%	OR	95% CI	p
<b>Response</b>					
Body temperature <sup>b</sup>	36.9	(36.2–37.9)	0.54	0.46–0.62	<0.001
BT <36°C	28	20.0%	5.82	3.44–9.85	<0.001
Respiratory rate <sup>b</sup>	22	(19–25)	1.03	1.00–1.08	0.081
RR >20/min	73	52.1%	2.03	1.42–2.91	<0.001
RDW (%) <sup>b,c</sup>	15.7	(14.4–18.1)	1.26	1.19–1.33	<0.001
RDW >15% <sup>c</sup>	92	65.7%	4.34	2.98–6.32	<0.001
WBC (10 <sup>3</sup> /μL) <sup>b</sup>	9.8	(3.7–17.2)	0.99	0.96–1.01	0.308
WBC <4000 μL	35	25%	4.55	2.87–7.21	<0.001
Band form (%) <sup>b</sup>	3.4	(0.0–13.2)	1.12	1.09–1.15	<0.001
Band >5%	63	45.0%	4.86	3.32–7.11	<0.001
<b>Organ dysfunction</b>					
Systolic blood pressure (mmHg) <sup>b,d</sup>	109	(82–140)	0.98	0.97–0.98	<0.001
SBP <90 mmHg <sup>d</sup>	42	30.4%	5.49	3.54–8.51	<0.001
GCS <sup>b</sup>	15	(9–15)	0.85	0.81–0.90	<0.001
GCS <8	29	20.7%	4.56	2.77–7.51	<0.001
Pulse oximetry (%) <sup>b,e</sup>	92	(82–97)	0.95	0.93–0.96	<0.001
SpO <sub>2</sub> <90% <sup>e</sup>	45	36.6%	5.87	3.81–9.06	<0.001
Hemoglobin (g/dL) <sup>b,f</sup>	10.1	(8.4–11.6)	0.76	0.71–0.82	<0.001
Hemoglobin <8 g/dL <sup>f</sup>	29	20.7%	3.75	2.31–6.09	<0.001
Platelet (10 <sup>3</sup> /μL) <sup>b,c</sup>	10.5	(4.6–19.2)	0.99	0.99–1.00	<0.001
Platelet <10 × 10 <sup>3</sup> /μL <sup>c</sup>	61	43.6%	3.36	2.31–4.88	<0.001
Creatinine (mg/dL) <sup>b,g</sup>	2.05	(1.19–3.64)	1.17	1.09–1.25	0.001
Creatinine >2 mg/dL <sup>g</sup>	70	50.7%	3.84	2.65–5.56	<0.001

<sup>a</sup> Data are expressed as case numbers and percentages, unless indicated specifically.

<sup>b</sup> Data are presented as median and interquartile range.

<sup>c</sup> Missing data for three patients.

<sup>d</sup> Missing data for four patients.

<sup>e</sup> Missing data for 57 patients.

<sup>f</sup> Missing data for 2 patients.

<sup>g</sup> Missing data for 12 patients.

BT = body temperature; CI = confidence interval; GCS = Glasgow Coma Score; OR = odds ratio; RDW = red blood cell distribution width; RR = respiratory rate; SpO<sub>2</sub> = pulse oximeter oxygen saturation; WBC = white blood cell count.

**Table 4** Multivariate analysis of full model and penalized maximum likelihood estimation

	$\beta$ coefficients of full model	$p$	$\beta$ coefficients of PMLE	$p$	Score
Predisposition					
Liver cirrhosis	0.67	0.045			
Malignancy	0.89	0.003	0.65	0.007	+2
Infections					
Pneumonia	1.72	<0.001	1.32	<0.001	+4
Unknown focus	0.94	0.019	0.70	0.011	+2
<i>S. aureus</i> bacteremia	0.95	0.020	0.69	0.034	+2
Response					
Body temperature <36°C	1.47	<0.001	1.17	0.001	+3
Band form >5%	1.33	<0.001	1.00	<0.001	+3
RDW >15% <sup>a</sup>	0.77	0.006	0.63	0.005	+2
Organ dysfunction					
SpO <sub>2</sub> <90% <sup>b</sup>	0.78	0.028	0.72	0.014	+2
Creatinine >2 mg/dL <sup>c</sup>	0.87	0.002	0.69	0.002	+2

<sup>a</sup> Missing data for three patients.

<sup>b</sup> Missing data for 57 patients.

<sup>c</sup> Missing data for 12 patients.

PMLE = penalized maximum likelihood estimation; RDW = red blood cell distribution width.

0.24–1.14; Table 4). The Hosmer-Lemeshow test revealed a fair goodness of fit of 5.745 ( $p = 0.676$ ) for the model.

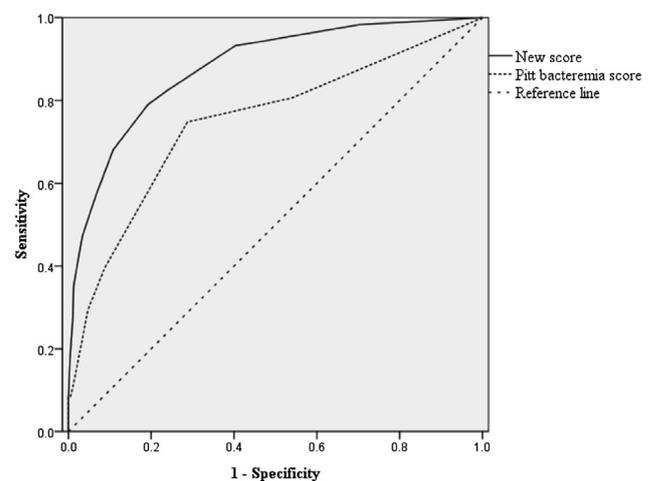
To simplify the model, each coefficient was divided by 0.35 and rounded to the nearest integer. For the new model, +2 points were assigned for malignancy, +4 for pneumonia, +2 for an unknown infectious focus, +2 for *S. aureus* bacteremia, +3 for body temperature <36°C, +3 for band form >5%, +2 for RDW >15%, +2 for pulse oximeter oxygen saturation <90%, and +2 for creatinine >2 mg/dL. The new score was calculated based on the summation of the points of the above nine variables. Seventy-one patients who had missing values of pulse oximetry data, RDW, or creatinine levels were not included in the final analysis. The AUROC for the new score of 992 patients with complete predictor data was 0.881 (95% CI, 0.848–0.913), with a better performance than Pitt bacteremia score (AUROC: 0.750; 95% CI, 0.699–0.800,  $p < 0.001$ ; Fig. 2). Internal validation of this model was done with 200 bootstrap replications. The mean AUROC of the 200 bootstrap replications was 0.881 (95% CI, 0.879–0.883).

The overall 28-day mortality of the 992 patients was 12.2%. On the basis of observed mortality of each score, the patients were stratified into four risk groups: (1) low, 0–3 points, mortality rate: 1.5%; (2) moderate, 4–6 points, mortality rate: 10.5%; (3) high, 7–8 points, mortality rate: 28.6%; and (4) very high,  $\geq 9$  points, mortality rate: 65.5% (Fig. 3). Table 5 showed sensitivity, specificity, and predictive values for different cut-off points of the new score of bacteremia.

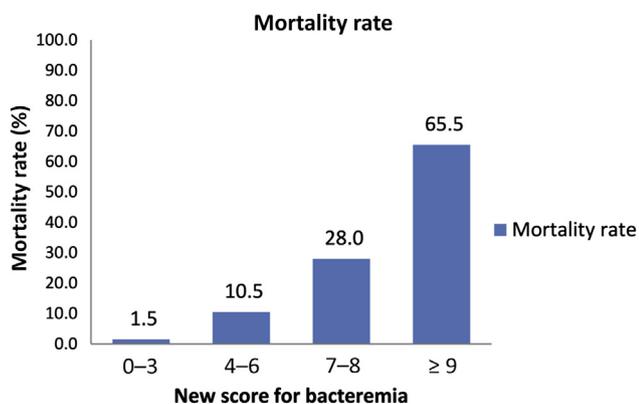
Among the 71 patients who were not included in the final analysis, 57 patients had missing values of pulse oximetry, 12 patients had missing values of creatinine levels, and three patients had missing values of RDW. Patients with missing values of pulse oximetry tended to have a higher mortality rate (29.8%). The mortality rate of patients with missing values of creatinine levels was 16.7%. There was no mortality among patients with missing values of RDW.

## Discussion

In this retrospective cohort study, which consisted of patients with laboratory confirmed BSI, we derived a clinical prediction rule for mortality based on the PIRO concept. It combines several clinically available factors, including “predisposition” with malignancy, “infections” with pneumonia, an unknown infectious focus, and *S. aureus* bacteremia, “response” with body temperature <36°C, band form >5%, and RDW >15%, and “organ dysfunction” with pulse oximeter oxygen saturation <90% and creatinine >2 mg/dL. This prediction rule could facilitate prediction of 28-day mortality for patients with documented BSI and



**Figure 2.** The receiver operating characteristic curves (ROC) comparing new score and Pitt bacteremia score to predict 28-day mortality of patients with bacteremia. The area under ROC (AUROC) for the new score is 0.881, with a better performance than Pitt bacteremia score (AUROC: 0.750,  $p < 0.001$ ).



**Figure 3.** The 28-day mortality rate according to the new score for bacteremia in 992 bacteremic patients. Seventy-one patients with missing data are not included.

could be helpful in stratifying high-risk patients who need ICU admission and close monitoring.

The newly derived score incorporated from the PIRO concept performed better than the Pitt bacteremia score in our study. Compared with the Pitt bacteremia score, our new score could stratify patients into four risk groups. The Pitt bacteremia score, which was developed to assess the severity of bacteremic patients based on mental status, body temperature, presence of shock, requirement for mechanical ventilation, and cardiac arrest, only stratifies patients into two risk groups.<sup>7</sup> Predisposing factors such as comorbidities, and infection factors, such as laboratory data, infectious sites and microorganisms, were not utilized by the Pitt bacteremia score, but these factors were found to be significant predictors of 28-day mortality and could further be used for finer risk stratification in our study. For patients with ICU-acquired sepsis, the Pitt bacteremia score was significantly correlated with the APACHE II score (correlation coefficient = 0.738,  $p < 0.001$ ) with a relatively fair discriminating power to predict mortality (AUROC: 0.799; 95% CI, 0.722–0.876).<sup>18</sup> However, in another study, for patients at low to moderate risk of mortality without admission to the ICU, with gram-negative bacteremia, the Pitt bacteremia score did not provide further risk stratification.<sup>8</sup> Therefore, we suspect that the different study populations would be the reason that the Pitt bacteremia score did not perform well in our study.

**Table 5** Test characteristics of new score for bacteremia in 992 bacteremic patients

New score for bacteremia	Sensitivity	Specificity	Positive predictive value	Negative predictive value
≥2	98.4	29.9	16.3	99.2
≥3	94.2	54.2	22.2	98.5
≥4	93.4	59.6	24.3	98.5
≥5	82.6	76.1	32.5	96.9
≥6	79.3	80.7	36.4	96.6
≥7	68.6	89.1	46.6	95.3

Data are presented as %.

*S. aureus* bacteremia was a significant predictor of mortality in our study. In another study, Shorr et al<sup>19</sup> also found that *S. aureus* was associated with a higher mortality rate in patients with bacteremia. In that study, both MRSA and MSSA bacteremia produced a higher mortality. Furthermore, a previous meta-analysis indicated that MRSA bacteremia is associated with a significantly higher mortality rate than is MSSA bacteremia, with a relative risk of 1.42.<sup>20</sup> However, in order to simplify our prediction rule, we did not further differentiate MRSA or MSSA in our study.

In our model, increased RDW (>15%) was associated with a higher 28-day mortality. RDW is reported as part of the results of a complete blood cell count and is readily obtained in a routine work-up of patients with suspected bacteremia. Several studies found that higher RDW was associated with an increased risk of death in patients with acute myocardial infarction,<sup>21</sup> chronic heart failure,<sup>22</sup> and critical illness.<sup>23</sup> In addition, Ku et al<sup>24</sup> also found that increased RDW can be an independent predictor of mortality in patients with Gram-negative bacteremia. The mechanism of association between RDW and death is still unclear. Some researchers suggested that the increased RDW level could be caused by sepsis-induced cytokine production and inflammation, which may play a role in the suppression of red blood cell maturation and iron metabolism.<sup>25</sup>

In our study, bacteremic patients with an unknown infectious site had a higher mortality rate in multivariate analysis. Bacteremia, with an unknown source of infection as an independent predictor of mortality, was also found in other studies.<sup>1</sup> However, there may be a survival bias, because early mortality or critical conditions may preclude intensive diagnostic studies for identification of the precise infectious focuses. Nevertheless, delayed identification and intervention of the infectious focus may be a factor contributing to mortality. Rapid confirmation of the infectious source and emergent source control can improve the outcome of septic patients.<sup>26</sup>

Besides the use of multivariate analysis to develop the model, we also used PMLE to prevent overoptimism.<sup>17</sup> PMLE is a shrinkage method to adjust the regression coefficients of the model. Compared with the bootstrap shrinkage technique, in which the coefficient of each predictor is adjusted equally, the coefficients are differently shrunk in PMLE. The stronger predictors with low  $p$  values, such as pneumonia, body temperature <36°C, and band form >5%, were shrunk less than other predictors. Although PMLE can be used to prevent model overfitting, further external validation of our prediction rule is still needed.

There are several limitations in this study. First, missing data is inevitable in retrospective studies. There was a large number of missing data in laboratory test results, such as bilirubin, arterial blood gas analysis, and C-reactive protein. These items were not included into the multivariate analysis. Furthermore, 57 patients who had missing values of pulse oximetry showed a higher mortality rate compared with other patients. We suspected that the data was not missing at random and the reason may be that critical patients have difficulty in pulse oximeter monitoring, due to low perfusion or vasoconstriction. Although we excluded patients with those missing values of pulse oximetry, our sensitivity analysis with multiple imputed

data did not show any significant change in the final multivariate model (data not shown). Second, our target population is patients with laboratory confirmed bacteremia, which might not be easily identified in their early courses, as the blood culture tests took 3 days on average to have the final results in our study. This limits the on-site point-of-care utilization of our prediction rule. However, in the future, identification of pathogens in positive blood culture can be reduced to 2 hours, with novel molecular techniques.<sup>27</sup> Furthermore, this limitation can be compensated by another prediction rule proposed by Su et al,<sup>28</sup> which identified patients with bacteremia in ED with a relatively good performance (AUROC, 0.845; 95% CI, 0.796–0.894). The combination of diagnostic aids mentioned above could facilitate clinicians to rapidly identify highly probable patients with bacteremia. Third, an unknown infectious focus was identified as one of the important predictors of mortality in our study. The duration of the survey for the infectious focus relied on the clinician's discretion in retrospective cohort studies. Therefore, this predictor may be difficult to apply in the clinical settings, because it depends on individual judgment. Fourth, we did not evaluate the adequacy of initial empirical antibiotic therapy in this study. Inappropriate empirical antibiotic therapy was also associated with increased mortality in patients with BSI and may also be an independent predictor of mortality.<sup>3</sup>

In conclusion, our new score could facilitate predictions of the risk of the 28-day mortality for patients with BSI visiting the ED. The score stratifies patients into four risk groups and had a better performance than the Pitt bacteremia score. Further prospective external validation is merited.

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