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ORIGINAL ARTICLE

Predictive model for bacteremia in adult patients with blood cultures performed at the emergency department: A preliminary report

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KEYWORDS
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Background: Useful predictive models for identifying patients at high risk of bacteremia at the emergency department (ED) are lacking. This study attempted to provide useful predictive models for identifying patients at high risk of bacteremia at the ED.
Methods: A prospective cohort study was conducted at the ED of a tertiary care hospital from October 1 to November 30, 2004. Patients aged 15 years or older, who had at least two sets of blood culture, were recruited. Data were analyzed on selected covariates, including demographic characteristics, predisposing conditions, clinical presentations, laboratory tests, and presumptive diagnosis, at the ED. An iterative procedure was used to build up a logistic model, which was then simplified into a coefficient-based scoring system.

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Results: A total of 558 patients with 84 episodes of true bacteremia were enrolled. Predictors of bacteremia and their assigned scores were as follows: fever greater than or equal to 38.3°C [odds ratio (OR), 2.64], 1 point; tachycardia greater than or equal to 120/min (OR, 2.521), 1 point; lymphopenia less than $0.5 \times 10^3/\mu L$ (OR, 3.356), 2 points; aspartate transaminase greater than 40 IU/L (OR, 2.355), 1 point; C-reactive protein greater than 10 mg/dL (OR, 2.226), 1 point; procalcitonin greater than 0.5 ng/mL (OR, 3.147), 2 points; and presumptive diagnosis of respiratory tract infection (OR, 0.236), −2 points. The area under the receiver operating characteristic curves of the original logistic model and the simplified scoring model using the aforementioned seven predictors and their assigned scores were 0.854 (95% confidence interval, 0.806−0.902) and 0.845 (95% confidence interval, 0.798−0.894), respectively.
Conclusion: This simplified scoring system could rapidly identify high-risk patients of bacteremia at the ED.
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Introduction

Bacteremia is one of the most serious infectious diseases encountered in the emergency department (ED). The overall trend of bacteremia is increasing incidence, changing pathogens, and continued high mortality rates.[1] Inappropriate or lack of empirical antimicrobial therapy is associated with poorer outcomes in bacteremic patients.[2,3] Blood culture remains the gold standard for diagnosis of bacteremia.[4] However, it takes hours to days for bacteria to grow to detectable numbers in blood culture. The timely identification of patients with bacteremia is, thus, a great challenge for the emergency physician.

Although many predictive models for bacteremia have been developed,[5−17] the studies that led to their development had three main types of restrictions. First, most previous studies that developed predictive models enrolled hospitalized patients but not ED patients.[5,7−11,13−15] Second, most developmental studies did not include comprehensive set of categories of potential risk factors. Third, none of these developmental studies evaluated the role of procalcitonin (PCT) as a clinical predictor. This study attempted to overcome these previous design limitations of models for the prediction of bacteremia by using a sample of patients from the ED.

Methods

Study design and settings

This prospective cohort study was conducted from October 1 to November 30, 2004, in the ED of National Taiwan University Hospital, a 2,400-bed university-affiliated teaching hospital that provides both primary and tertiary care in northern Taiwan. The hospital has more than 100,000 ED visits annually. This study was approved by the institutional review board of the hospital, and informed consent was required for patient enrollment.

Patient enrollment

All adult patients aged 15 years or older, who had at least two sets of blood cultures from separate sites during the study period, were recruited. The decision to order blood culture was made by the attending emergency physician. Those who were referred from another hospital and had received empirical intravenous antimicrobial therapy before blood cultures and those with active thyroid cancer were excluded. With the exception of blood sampling for PCT measurement, there were no protocol-driven decisions regarding disposition from the ED or specimen collection other than those made by attending physicians.

Participant interview and follow-up

All enrollees were systematically evaluated by a well-trained study nurse using a structured record form on the same day as the sample for blood culture was obtained or on the next day if the blood sample for culture was obtained when the nurse was off work or unavailable. Eligible patients were interviewed and their medical records were reviewed if they were hospitalized. Family members or caregivers were visited if the patient could not independently complete the interview. Hospitalized patients were regularly followed up until discharge. Patients released from the ED were followed up at outpatient clinics or by telephone contact at the end of the first month.

Data collection

The following five categories of covariates were prospectively collected before the blood culture results became available: demographic data, predisposing conditions, clinical presentations, laboratory data, and assumptive diagnoses made by emergency physicians. Assumptive diagnoses were classified into the following six entities according to the "Centers for Disease Control and Prevention (CDC) definitions for nosocomial infections"[18]: respiratory tract infections (RTIs), urinary tract infections, intra-abdominal infections, skin and soft tissue infections, bloodstream infections, and fever of unknown origin. Predictors (assigned scores) of bacteremia were fever greater than or equal to 38.3°C (1); tachycardia greater than or equal to 120/min (1); lymphopenia less than $0.5 \times 10^3/\mu L$ (2); aspartate transaminase greater than 40 IU/L (1); C-reactive protein (CRP) greater than 10 mg/dL (1); PCT greater than 0.5 ng/mL (2); and presumptive diagnosis of RTI (−2).

PCT assay

The PCT levels were measured by a quantitative automated system using immunoluminomeric assay (Brahms Diagnostica, Berlin, Germany). The detection limit of this test was 0.06 ng/mL. For ease of statistical analysis, a PCT level of 0.05 ng/mL was assigned if the report was "low."

Outcomes

The primary outcome of this study was a clinically significant positive blood culture, as independently assessed by three investigators. The definitions of true bacteremia were adopted from the CDC and MacGregor and Beaty guidelines as one or more of the following[18,19]: (1) two sets of positive blood culture obtained at separate sites; (2) one set positive for a gram-negative bacterial pathogen; or (3) one set positive for a gram-positive pathogen in a patient with an intravascular device and compatible clinical characteristics. Patients who did not fit the aforementioned criteria were considered to be false bacteremic and were classified into the nonbacteremic group for analysis.

Statistical analysis

Univariate analysis was performed using Student *t* test for continuous variables and χ^2 analysis or Fisher's exact test (if the expected number in any cell was less than 5) for categorical variables. Significant continuous variables were then converted into categorical data based on the cutoff points used in clinical practice for univariate logistic regression analysis.

In contrast to the previously reported models for predicting the risk of bacteremia, our predictive model adopted the following four-step iterative procedure to consider the possible negative confounding factors that remained significant in the presence of other significant factors. (1) Identify significant variables using univariate logistic regression analysis. (2) Formulate a multivariate logistic regression model with the inclusion of all significant factors in the univariate analysis. (3) Test factors that are not significant in the multivariate logistic regression model one by one using a parsimonious model in the second step. This step is called "re-certified model for negative confounding factors." (4) Test all insignificant factors in the first step as earlier one by one using the final parsimonious model in the third step to ensure these factors would not become negative confounding factors.

To check the sensitivity against the false-positive rate, evaluation of discrimination was performed using the receiver operating characteristic (ROC) curve. The C-statistics of various regression models in the model selection steps were reported. The confidence intervals (CIs) of the area under the ROC curves (AUCs) were computed using Hanley—McNeil's formula.[20] Internal validation for the comparison between the observed and the expected values was done using the Hosmer—Lemeshow goodness-of-fit test. Cross-validation was done with 1,000 bootstrap replications of the model using half data for model training and half data for validation.

To make the prediction rule sensible and feasible, we simplified the model by using a coefficient-based scoring method. To generate a simple integer-based scoring system, the relative values of β coefficients for significant predictors were adjusted and rounded up to the nearest integer.[21] To evaluate the discrimination of the scoring model, AUCs of the original logistic model and the scoring model were compared using Hanley—McNeil's method.[22]

Results

A total of 558 patients were recruited (Fig. 1), of whom 316 (56.6%) were men. The mean age (±standard deviation) was 60.8 ± 19.2 years. There were a total of 84 episodes (15.1%) of true bacteremia and 14 episodes (2.5%) of false bacteremia in this study population. The microbes isolated from blood cultures are listed in Table 1. The most frequently isolated pathogen in blood cultures was *Escherichia coli* (28 episodes, 48.3%), followed by *Klebsiella pneumoniae* (17 episodes, 29.3%).

The bacteremic group was more likely to be older (≥60 years) than the nonbacteremic group (69.05% *vs.* 55.7%, $p = 0.022$) (Table 2). There were more diabetic patients in the bacteremic group (32.14% *vs.* 21.10%, $p = 0.027$). Fever greater than or equal to 38.3°C [odds ratio (OR), 2.41; 95% CI, 1.50—3.86] and chills (OR, 2.67; 95% CI, 1.64—4.35) were both significant symptomatic predictors of bacteremia. The physical signs of hypotension (OR, 3.46; 95% CI, 1.40—8.52) and tachycardia (OR, 2.23; 95% CI, 2.01—5.21) were significant predictors.

Laboratory predictors included leukopenia (white blood cell count $< 4 \times 10^3/\mu L$); lymphocytopenia (lymphocyte count $< 0.5 \times 103/\mu L$); bandemia (band form of neutrophils > 10%); thrombocytopenia (platelets $< 15 \times 10^3/\mu L$); azotemia (blood urea nitrogen > 30 mg/dL); aspartate transaminase (AST > 40 IU/L); CRP value greater than 10 mg/dL; and PCT value greater than 0.5 ng/mL. Among the initial diagnostic categories, bloodstream infection (OR, 10.5; 95% CI, 3.78—26.76) and RTI (OR, 0.23; 95% CI, 0.11—0.47) were associated with bacteremia.

Significant predictors in the multivariate analysis included the following (Table 3): (1) fever greater than or equal to 38.3°C [adjusted OR (aOR), 2.64; 95% CI, 1.262—5.522]; (2) tachycardia (aOR, 2.521; 95% CI, 1.227—5.182); (3) lymphocytopenia (aOR, 3.356; 95% CI, 1.559—7.225); (4) AST greater than 40 IU/L (aOR, 2.355; 95% CI, 1.185—4.682); (5) CRP value

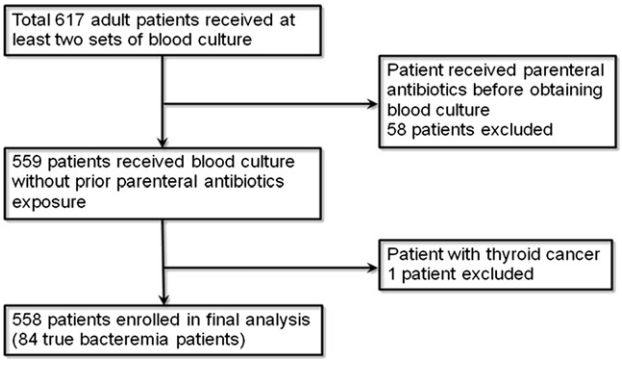

Figure 1. Flowchart of patient enrollment.

Table 1 Microbes isolated from blood cultures

Microbes	Number of isolates
True bacteremia	
Gram positive	22
Bacillus cereus	1
Streptococcus pneumoniae	1
Group A *Streptococcus*	5
Group B *Streptococcus*	3
Streptococcus constellatus	1
Staphylococcus aureus	8
Clostridium spp.	2
Lactobacillus spp.	1
Gram negative	67
Escherichia coli	28
Klebsiella pneumoniae	17
Proteus mirabilis	1
Serratia marcescens	1
Enterobacter aerogenes	1
Salmonella spp.	7
Pseudomonas aeruginosa	5
Acinetobacter baumannii	4
Fusobacterium spp.	1
Bacteroides spp.	2
False bacteremia	13
Coagulase-negative staphylococci	5
Propionibacterium acnes	4
Bacillus spp.	3
Micrococcus spp.	1

greater than 10 mg/dL (aOR, 2.226; 95% CI, 1.070—4.631); (6) PCT value greater than 0.5 ng/mL (aOR, 3.147; 95% CI, 1.498—6.610); and (7) assumptive diagnosis of RTIs (aOR, 0.236; 95% CI, 0.084—0.661). All of these predictors were used in the final logistic model.

The Hosmer—Lemeshow test revealed a goodness of fit of 6.832 ($p = 0.5549$), which suggests that the model had good calibration. The mean of area under the 1,000 bootstrapped ROC curves reduced to 0.664 (95% CI, 0.593—0.734). The lower limit of 95% CI was still greater than 50%, indicating that this model still had a good discriminative power.

The clinical prediction rule was then simplified by using integral scores based on the regression coefficients obtained from the logistic regression model (Table 3). The coefficients were rescaled by dividing by 0.708, the coefficient of the "CRP value greater than 10 mg/dL," which was the lowest value among the predictors, and the result rounded to the nearest integer.

The AUCs (and their 95% CIs) of CRP, PCT, the logistic model using the aforementioned seven predictors, and the scoring model derived from the logistic model for predicting bacteremia were 0.639 (0.562—0.716), 0.737 (0.667—0.808), 0.854 (0.806—0.902), and 0.845 (0.796—0.894), respectively (Fig. 2). The closeness of fit of the ROC curves between the original logistic model and the coefficient-based scoring model suggests a good predictive validity; the narrowing of the 95% CIs indicated the precision of these models. There was no significant difference between the AUCs of the logistic model and the scoring model (difference of AUCs = 0.009; 95% CI, −0.010 to 0.029; $p = 0.361$). ROC analyses showed that both models were superior to the CRP model and the PCT model in predicting bacteremia in patients. The performance of the scoring system in patients with unexplained fever was evaluated using a subgroup analysis of patients with an assumptive diagnosis of fever with occult foci. The AUC of the scoring system was 0.792 (95% CI, 0.687—0.874) (Fig. 3).

We next tried to select the optimal cutoff point for applicability of the scoring model to clinical practice. Using the Youden index method, we obtained the optimal cutoff point of "greater than 3 points" with a sensitivity of 66.2% (95% CI, 53.7—77.2) and a specificity of 85.9% (95% CI, 81.9—89.3), respectively. However, because a false-negative prediction of bacteremia could lead to more serious consequences than a false-positive prediction, a cutoff point with higher sensitivity could be more useful considering such a risk. This led to the selection of a scoring "greater than 1 point" as the cutoff point because of the increased sensitivity of 89.7% (95% CI, 79.9—95.7) with consequent decreased specificity of 56.9% (95% CI, 51.7—62.0).

Discussion

Bacteremia is associated with high short- and long-term mortality rates.[1,2,23] Delay in appropriate empirical antimicrobial therapy leads to poor outcomes.[3,24] In this study, we developed a simplified scoring model to predict bacteremia using only clinically available data. This model may help emergency physicians in detecting patients at high risk of bacteremia in daily clinical practice. It is also the first study to develop a predictive model for bacteremia at the ED.

Fever ($\geq$38.3°C), an important risk factor for bacteremia, was also significant in our model (aOR, 2.970). Similar results were also reported in hospitalized patients by Bates et al and Jaimes et al.[10] Tachycardia with a heart rate greater than 120 beats/min was the other vital sign that was significantly associated with bacteremia in our cohort. Fever and tachycardia are known markers of inflammation, infection, and even sepsis[25]; hence, it is quite reasonable to find that they are significant risk factors associated with bacteremia. Previous studies also found that chills or shaking rigors was an even more frequently identified risk factor for bacteremia than nonbacteremia.[5,8,16] In the present study, although chills was significantly associated with bacteremia in the univariate analysis with an OR of 2.67 (95% CI, 1.64—4.35; $p < 0.0001$), it lost its significance in the multivariate analysis.

Pfitzenmeyer et al.[13] found that lymphocytopenia, defined as a lymphocyte count less than or equal to $10^3/\mu L$, was a risk factor for both community- and hospital-acquired bacteremia. Other changes in the blood cell counts reported to be associated with bacteremia include leukocytosis, bandemia, and thrombocytopenia. In this study, however, although these factors were significant in univariate analysis except for leukocytosis, only lymphocytopenia remained significant in the multivariate analysis. Elevated serum AST, another significant laboratory predictor in our

Table 2 Clinical characteristics of 558 patients and results of univariate logistic regression analyses[a]

Variable	Bacteremic patients ($n = 84$)	Nonbacteremic patients ($n = 474$)	OR	95% CI	p
Demographic characteristics					
Age (yr)	62.5 ± 22.3	60.5 ± 20.6	1.01	0.99–1.02	0.377
Older (age > 60 yr)	58 (69.05)	264 (55.70)	1.77	1.08–2.92	0.022
Gender (male)	51 (60.7)	265 (55.9)	1.22	0.76–1.96	0.413
Underlying diseases					
Diabetes mellitus	27 (32.14)	100 (21.10)	1.77	1.07–2.95	0.027
Liver cirrhosis	6 (7.14)	35 (7.38)	0.97	0.39–2.37	0.938
End-stage renal disease	2 (2.38)	14 (2.95)	0.80	0.18–3.56	0.773
Hematologic malignancy	5 (5.95)	13 (2.74)	2.24	0.78–6.47	0.135
Solid organ cancer	16 (19.05)	81 (17.09)	1.14	0.63–2.07	0.662
Signs (%)					
Fever ≥ 38.3°C	73 (86.90)	326 (68.78)	2.41	1.50–3.86	0.0003
Hypotension (systolic blood pressure < 90 mmHg)	8 (9.52)	14 (2.95)	3.46	1.40–8.52	0.007
Tachycardia (heart rate > 120/min)	42 (50)	112 (23.63)	2.23	2.01–5.21	<0.0001
Symptoms					
Chills	35 (41.67)	100 (21.10)	2.67	1.64–4.35	<0.0001
Altered mental status	11 (13.10)	35 (7.38)	1.89	0.92–3.89	0.084
Laboratory data					
Leukopenia (<$4 \times 10^3/\mu L$)	14 (16.67)	32 (6.75)	2.76	1.40–5.44	0.003
Bandemia (>10%)	14 (16.67)	24 (5.06)	3.75	1.85–7.59	0.0002
Lymphocytopenia (<$0.5 \times 10^3/\mu L$)	39 (46.43)	60 (12.74)	5.94	3.58–9.86	<0.0001
Thrombocytopenia (<$15 \times 10^3/\mu L$)	41 (48.81)	117 (24.68)	2.91	1.81–4.68	<0.0001
AST > 40 IU/L	41 (53.95)	127 (32.07)	2.48	1.51–4.08	0.0003
BUN > 30 mg/dL	28 (33.33)	97 (21.00)	1.88	1.13–3.12	0.014
Hyponatremia (Na < 130 mEq/L)	18 (21.43)	59 (12.58)	1.90	1.05–3,41	0.033
CRP > 10 mg/dL	32 (42.67)	100 (22.83)	2.52	1.51–4.19	0.0004
PCT > 0.5 ng/mL	59 (70.24)	135 (28.48)	5.93	3.56–9.85	<0.0001
Initial diagnostic category					
Bloodstream infection	11 (13.10)	7 (1.48)	10.5	3.78–26.76	<0.0001
Intra-abdominal infection	18 (21.43)	83 (17.51)	1.29	0.73–2.28	0.391
Respiratory tract infection	9 (10.71)	163 (34.39)	0.23	0.11–0.47	<0.0001
Skin and soft tissue infection	8 (9.52)	60 (12.66)	0.73	0.33–1.58	0.420
Urinary tract infection	19 (22.62)	77 (16.24)	1.51	0.86–2.66	0.156
Fever of unknown origin	19(22.62)	83 (17.51)	1.38	0.78–2.42	0.265

[a] Data are presented as mean ± standard deviation or n (%).
AST = aspartate transaminase; BUN = blood urea nitrogen; CI = confidence intervals; CRP = C-reactive protein; OR = odds ratio; PCT = procalcitonin; SD = standard deviation.

study, has not been previously reported as a significant risk factor for bacteremia. Elevated AST in bacteremic patients might be because of the effect of sepsis and subsequent end-organ damage.

Many biomarkers were evaluated to detect early bacterial infection or sepsis, including CRP and PCT. CRP has long been recognized as an indicator of inflammation.[26] CRP levels increase not only in response to bacterial infection but also to many types of inflammation.[27] The reported diagnostic accuracy of CRP for bacteremia has varied across studies. Tokuda et al.[16] identified CRP as a risk factor for bacteremia. A meta-analysis found that the discriminative value of PCT was superior to CRP for both bacterial infections and nonbacterial illnesses.[26] In another meta-analysis, the summary ROC of PCT to predict bacterial infection was 0.84 (95% CI, 0.75–0.90).[28] In the present study, the discriminative power for detecting bacteremia of PCT was also superior to that of CRP. CRP was elevated after 24 hours and reached peak after 48 hours. Different parameters, such as heparin-binding protein (azurocidin) and interleukin 6, were introduced after PCT. Interleukin-6 peak is found after 12 hours, in contrast to PCT after 24 hours and roughly heparin-binding protein after 6–10 hours.[29–31]

Although assumptive diagnosis of RTI was a significant predictor of bacteremia in our model, it was a rather heterogeneous variable that included both upper and lower RTIs. Tokudo et al.[16] developed a predictor of bacteremia called "physician's diagnosis of low-risk sites," which included most of the upper and lower RTIs. These infections are mostly viral in etiology. Even a lower RTI, such as

Table 3 Multivariate logistic regression model

Parameter	β Coefficient	aOR	95% LCL	95% UCL	p	Scores
Intercept	−3.905				<0.0001	
Fever ≥ 38.3°C	1.0885	2.970	1.559	5.655	0.0009	1
Tachycardia	1.0302	2.802	1.478	5.313	0.0016	1
Lymphocytopenia	1.3457	3.841	1.979	7.456	<0.0001	2
AST > 40 IU/L	1.0240	2.784	1.492	5.197	0.0013	1
CRP > 10 mg/dL	0.7080	2.030	1.022	4.031	0.0431	1
PCT > 0.5 ng/mL	1.2560	3.511	1.806	6.826	0.0002	2
Respiratory tract infection	−1.5297	0.217	0.083	0.566	0.0018	−2

C-statistics = 0.855. Hosmer–Lemeshow goodness-of-fit test: $\chi^2 = 6.832$ (df = 8), $p = 0.5549$.
aOR = adjusted odds ratio; AST = aspartate transaminase; CI = confidence interval; CRP = C-reactive protein; LCL = lower confidence limits; OR = odds ratio; PCT = procalcitonin; UCL = upper confidence limits.

pneumonia, is associated with a low risk of bacteremia.[32] The limited utility of blood culture for community-acquired pneumonia was evident by the low yield rate, high false-positive rate, and by the fact that it infrequently led to changes in antibiotic therapy.[33] The 2007 Infectious Diseases Society of America/American Thoracic Society consensus guidelines for community-acquired pneumonia recommend blood cultures only in selected patients.[34]

Two previous studies were designed to predict bacteremia in patients with unexplained fever.[13,17] In the present study, the performance of the scoring system in patients with unexplained fever was evaluated using a subgroup analysis of patients with an assumptive diagnosis of fever of unknown origins. The AUC of the scoring system was 0.792 (95% CI, 0.687–0.874) in this model, a value similar to that found by Pfitzenmeyer et al.[13] (AUC = 0.772 ± 0.058).

There were several notable limitations of this study. First, data used for the formulation of predictive model are only based on a single site; the generalizability of our thus predictive model needs to be further explored. As the sample population was enrollees from a tertiary hospital ED, the target population in this study might not be representative of other community hospital EDs. Second, because the decision to order blood culture was made by physicians as opposed to being determined by a specific study protocol, the enrollees represented a selected thought to be at high risk by physicians. It is thus unclear whether the results can be applied to all febrile patients at the ED. Third, the classification of assumptive diagnoses into only six categories may not adequately represent the potential heterogeneity and importance of some underlying conditions, such as biliary tract infection. Fourth, the use of CDC surveillance definition to support true bacteremia when there was one gram-positive microbe in blood cultures in a catheterized patient is not always appropriate. Some of the patients who had an intravascular device implanted and compatible clinical characteristics had single positive blood cultures (catheter drawn or even

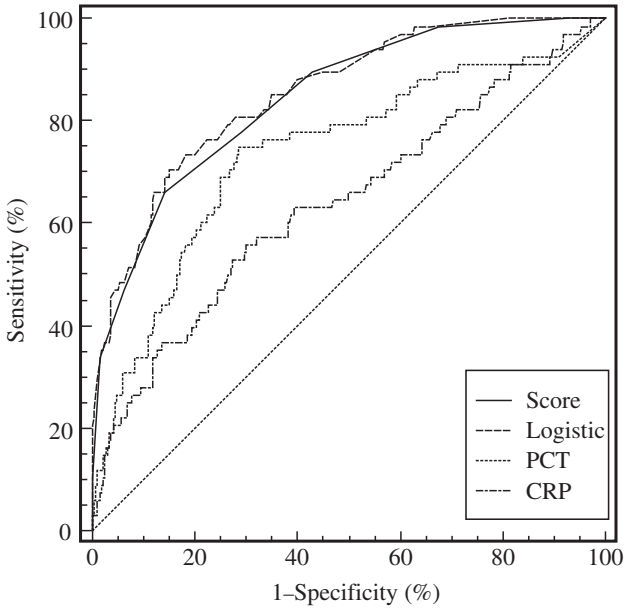

Figure 2. The receiver operating characteristic curves for C-reactive protein (CRP), procalcitonin (PCT), logistic model (logistic), and scoring model (score) for patients with bacteremia.

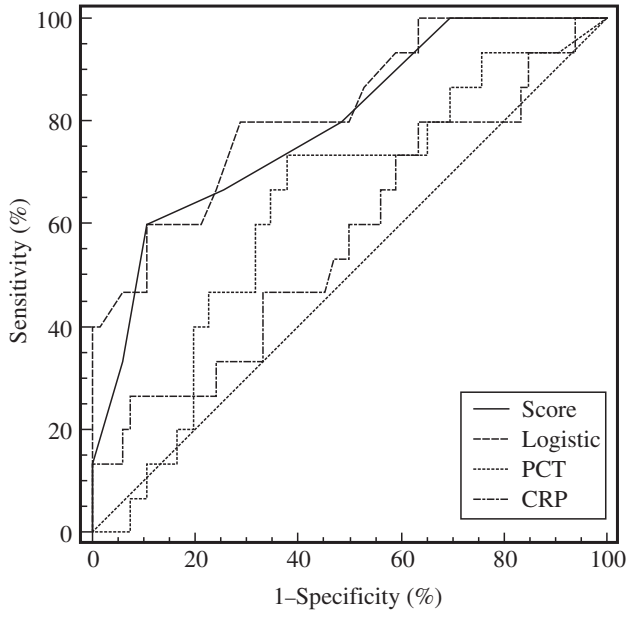

Figure 3. The receiver operating characteristic curves for C-reactive protein (CRP), procalcitonin (PCT), logistic model (logistic), and scoring model (score) for patients with unexplained fever.

percutaneously drawn) for a gram-positive pathogen, which might still be a false bacteremia. Fifth, some data on laboratory tests were not available because the study did not use protocol-driven decisions regarding specimen collection, which were instead made entirely by attending physicians. Finally, on selection of a scoring "greater than 1 point" as the cutoff point, the specificity of this predictive model was slightly greater than 50% (56.9%). These limitations have significantly restricted the accuracy of discrimination in the testing of this model for internal validation.

In conclusion, we developed a predictive model for bacteremia at the ED based on a scoring system of associated risk factors. Application of this model may help physicians in an overcrowded ED to rapidly identify patients at high risk of bacteremia to release the stress of overcrowding. Further prospective validation of this model in other centers would be the ultimate goal.

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