院内感染対策の有効性および費用効果に関する研究

研究成果の刊行に関する一覧表

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Clinical prediction rules for bacteremia and in-hospital death based on clinical data at the time of blood withdrawal for culture: an evaluation of their development and use

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Abstract

Rationale, aims and objectives To develop clinical prediction rules for true bacteremia, blood culture positive for gram-negative rods, and in-hospital death using the data at the time of blood withdrawal for culture. **Methods** Data on all hospitalized adults who underwent blood cultures at a tertiary care hospital in Japan were collected from an integrated medical computing system. Logistic regression was used for developing prediction rules followed by the jackknife cross validation. **Results** Among 739 patients, 144 (19.5%) developed true bacteremia, 66 (8.9) were positive for gram-negative rods, and 203 (27.5%) died during hospitalization. Prediction rule based on the data at the time of blood withdrawal for culture stratified them into five groups with probabilities of true bacteremia 6.5, 9.6, 21.9, 30.1, and 59.6%. For blood culture positive for gram-negative rods, the probabilities were 0.6, 4.7, 8.6, and 31.7%, and for in-hospital death, those were 6.7, 15.5, 26.0, 35.5, and 56.1%. The area of receiver operating characteristic for true bacteremia, blood culture positive for gram-negative rods, and in-hospital death were 0.73, 0.64, and 0.64, respectively, in original cohort and 0.72, 0.64, and 0.64 in validation respectively. **Conclusions** The clinical prediction rules are helpful for improved clinical decision making for bacteremia patients.

Introduction

Bacteremia is a serious condition with a high mortality from 11 to 69% (Watanakunakorn & Weber 1989; Arpi *et al.* 1995; Rangel-Frausto *et al.* 1995; Martin *et al.* 2003), and therefore needs prompt and careful management involving the proper use of the antibiotics. However, it usually takes several days to receive results of blood cultures, and as many as 66% of blood cultures are reported to be contaminated (Bates *et al.* 1997). If doctors can accurately estimate the probability of bacteremia, the type of microorganism, and mortality when conducting blood cultures, they can decide the starting and type of antibiotics more rationally and thus reduce inappropriate antibiotics usage.

Several reports have dealt with the risk factors for bacteremia (Bone 1987; Leibovici *et al.* 1990) and clinical prediction rules were formatted for true bacteremia or sepsis using reported blood culture results at hand and other clinical data (Mellors *et al.* 1987; Bates & Lee 1992; Bates *et al.* 1997). However, there are few reports concerning clinical prediction rules for true bacteremia and mortality at once based not on reported blood culture results but on clinical data at the time of blood culture. We therefore conducted a retrospective cohort study to develop clinical prediction rules for (1) true bacteremia; (2) positivity of gram-negative rods; and (3) in-hospital death based on clinical data at the time of blood culture.

Methods

Patient population

Data collection took place in all wards and intensive care unit at Shimane Prefectural Central Hospital, a tertiary care hospital in Japan. This hospital features an Integrated Intelligent Management System, a medical computing system consisting of electronic medical records, nursing logs, doctor's orders, laboratory and imaging results, prescription data, and hospital claims. Subject patients were all adults at the age of 18 or more who underwent blood cultures between August 1999 and December 2002. We took into account the first blood culture for one patient because the likelihood of true bacteremia was strongly suggested by the previous blood culture results.

This study was approved by the Institutional Review Board of Shimane Prefectural Central Hospital, and the informed consent was waived because it was conducted in historical cohort fashion without any intervention and the individual identification information was not used.

Definition of true bacteremia

We considered blood culture results as 'true bacteremia' (1) if the cultured organism was a gram-negative rod, fungus, or anaerobic; (2) if the same organism was cultured more than twice; (3) if the same organism was cultured from such specimens as urine, sputum, catheter or operative sample; and (4) endocarditis was present clinically or at autopsy. All cases were carefully reviewed independently by two internists (TN and OT) and classified as positive when both of them judged true bacteremia, otherwise considered contamination (false-positive). The kappa score of agreement between the reviewers was 0.78 (95% confidence interval: 0.69–0.86).

Data collection

One investigator (TN) identify the patients who underwent blood culture during the study period from the Integrated Intelligent Management System. Clinical data retrieved were age, gender, days from the admission to blood culture, major co-morbidities (coma, brain death, bowel perforation, multiple trauma, multiple burns, cardiopulmonary arrest within the previous 24 h, bone marrow transplant, severe pancreatitis, acute respiratory distress syndrome, and hepatic failure) according to the previous reports by Bates *et al.* (1992). Also collected were other medical condition (malignant diseases, hematological malignant diseases, acute abdomen, central venous line insertion, and use of antibiotics), vital signs [systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), body temperature (BT)], laboratory test results [white blood cell count (WBC), hemoglobin (Hb), platelet cell count (Plt), C-reactive protein (CRP), aspartic aminotransferase (AST), alanine aminotransferase (ALT), blood sugar, serum albumin, total bilirubin, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine, sodium (Na), potassium (K)], results of blood culture and in-hospital death. These predictor variables were obtained just before the blood culture except for vital signs, which were measured three times a day and all values in the calendar day of blood culture were considered potential predictors. Age brackets were categorized into four groups (<60, 60–69, 70–79, and ≥80 years). Missing data were found in laboratory test results, and the observations without final potential predictors were eliminated from the final analysis. However, patient characteristics and outcomes between patients with and without final predictors, that is, CRP, creatinine, WBC, BUN, LDH, and Hb data were similar ($P = 0.06$–0.9).

Because we would like to make the final prediction rules clear for understanding and easiler for use in clinical practice, continuous variables were dichotomized according to clinical contexts or sample distribution. The cut-off point for the maximum SBP was set at 140 mmHg, for minimum SBP at 90 mmHg, for the maximum DBP at 95 mmHg, and the minimum DBP at 55 mmHg. Maximum/minimum cut-off points were 100/60 beats per min for HR, and 38.5/35.5°C for BT, based on the common practice. The following laboratory test results were dichotomized according to the median of values: WBC with the cut-off point of 10 000 microL^{-1}, Hb with 10.0 g dL^{-1}, Plt with 25 000 microL^{-1}, and CRP with 10.0 mg dL^{-1}. Other laboratory test results were dichotomized by reference values.

Statistical analysis

Univariate correlates for true bacteremia, gram-negative rods, and in-hospital death were determined with chi-square test. These univariate correlates (P-values < 0.10) were then entered into stepwise logistic regression models, which identified the independent predictors for true bacteremia, gram-negative rods, and in-hospital death. Factors with a P-value < 0.05 were retained.

The results of the multivariate analyses were then used to develop clinical prediction models. Beta coefficients of the variables were divided by 0.075 for true bacteremia, 0.5 for gram-negative rods, and 0.11 for in-hospital death, and rounded to the nearest integer (Morimoto *et al.* 2004). The risk scores of an individual patient were determined by assigning points for each factor and totaling these scores. The total risk scores were then stratified into five categories for true bacteremia, four categories for gram-negative rods, and five categories for in-hospital death, according to the level of risk.

The performance of the prediction rule was evaluated by means of receiver operating characteristic (ROC) curve analyses (Metz 1978). The Hosmer-Lemeshow goodness-of-fit statistic was used for calibration (Lemeshow & Hosmer 1982). The jackknife cross validation technique was then applied to the prediction rules to assess their over-fitting (Efron 1982). All statistical analyses were carried out using SAS software (Version 8.02, SAS Institute Inc., Cary, NC).

Results

Patient characteristics

There were 739 blood cultures to analysis during the study period. The patients were 66.0 ± 16.7 (mean ± SD) years old and men accounted for 60.1%. True bacteremia was found in 144 (19.5%) patients and gram-negative rods in 66 (8.9%) (Tables 1 and 2). In-hospital death was recorded for 203 (27.5%) cases including 61 of 144 (42.4%) patients with true bacteremia and 142 of 595 (23.9%) patients without bacteremia, showing a statistically significant difference ($P = 0.001$).

Univariate and multivariate analyses

Univariate correlates for true bacteremia, gram-negative rods, and in-hospital death included age, gender, days from the admission to blood culture, medical condition, vital signs, and laboratory results (Table 3). In-hospital death had a significant correlation with true bacteremia ($P = 0.001$).

Multivariate predictors for true bacteremia comprised age, minimum SBP, maximum BT, minimum BT, days from the admission to blood culture, WBC, CRP, and creatinine. Likewise, multivariate predictors for gram-negative rods included minimum SBP, maximum BT, Plt, CRP, and creatinine, and those for in-hospital death age, major co-morbidity, use of antibiotics, hematological malignant diseases, other malignant diseases, minimum DBP, Hb, LDH, and BUN (Table 4).

Development of the clinical prediction rules

To develop clinical prediction rules, we assigned integer scores proportional to the beta coefficient to the eight identified risk variables for true bacteremia, five for gram-negative rods, and nine for in-hospital death (Table 4). All applicable risk score values were summed to obtain the total risk score for each patient. The rules were then used to categorize the patients into five groups for true bacteremia, four for gram-negative rods, and five for

Table 1 Patient characteristics of blood cultures

	All patients (n = 739) mean ± SD or n (%)
Age, years	66 ± 16.7
Male	444 (60.1)
Days from the admission to blood culture, days	24.2 ± 53.2
Medical conditions	
Major co-morbidity*	153 (20.7)
Malignancy	
Malignancy	132 (17.9)
Hematological malignancy	134 (18.1)
Acute abdomen	69 (9.3)
Medication	
Central venous line insertion	37 (5.0)
On antibiotics	357 (48.3)
Physical examination	
SBP	
Maximum SBP, mmHg	139.5 ± 29.2
Minimum SBP, mmHg	106.5 ± 24.8
DBP	
Maximum DBP, mmHg	78.5 ± 14.7
Minimum DBP, mmHg	58.2 ± 14.8
HR	
Maximum HR, beat min^{-1}	103.9 ± 20.6
Minimum HR, beat min^{-1}	79.5 ± 15.2
BT	
Maximum BT, °C	38.5 ± 1.0
Minimum BT, °C	36.7 ± 0.8
Laboratory results	
WBC, ×100 $microL^{-1}$	104.6 ± 96.8
Hb, g dL^{-1}	10.0 ± 2.5
Plt, ×10 000 $microL^{-1}$	19.2 ± 16.8
CRP, mg dL^{-1}	11.6 ± 9.2
AST, IU L^{-1}	70.6 ± 289.4
ALT, IU L^{-1}	53.7 ± 96.4
Blood Sugar, mg dL^{-1}	153.9 ± 74.2
Albumin, g dL^{-1}	3.0 ± 0.7
Total bilirubin, mg dL^{-1}	1.2 ± 2.0
LDH, IU L^{-1}	456 ± 696.2
BUN, mg dL^{-1}	22.9 ± 18
Creatinine, mg dL^{-1}	1.5 ± 1.6
Na, mEq L^{-1}	136.2 ± 7.4
K, mEq L^{-1}	4.0 ± 0.7
In-hospital death	203 (27.5)
Result of blood culture	
Blood culture positive	243 (32.9)
True positive	144 (19.5)
Gram-negative rods	66 (8.9)
Contamination	99 (13.4)
Blood culture negative	496 (67.1)

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BT, body temperature; WBC, white blood cell count; Hb, hemoglobin; Plt, platelet cell count; CRP, C-reactive protein; AST, aspartic aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; Na, sodium; K, potassium.

*Major co-morbidity includes coma, brain death, bowel perforation, multiple trauma, multiple burns, cardiopulmonary arrest with in the previous 24 h, bone marrow transplant, severe pancreatitis, acute respiratory distress syndrome, and hepatic failure.

Table 2 Final organism identifications

Organism	*Total (n = 243)* n (%)	*True bacteremia* (n = 144)* n (%)	*Contamination (n = 99)* n (%)
Coagulase (–) Staphylococcus	71 (29.2)	6 (4.2)	65 (65.7)
Coagulase (–) Staphylococcus	71 (29.2)	6† (4.2)	65 (65.7)
Gram-positive rods	12 (4.9)	1 (0.7)	11 (11.1)
Bacillus sp.	11 (4.5)	1‡ (0.7)	10 (10.1)
Corynebacterium sp.	1 (0.4)	0 (0.0)	1 (1.0)
Gram-positive cocci	20 (8.2)	14 (9.7)	6 (6.1)
α-hemolytic Streptococcus	3 (1.2)	2§ (1.4)	1 (1.0)
γ-hemolytic Streptococcus	1 (0.4)	1¶ (0.7)	0 (0.0)
Enterococcus faecalis	5 (2.1)	3** (2.1)	2 (2.0)
Enterococcus faecium	2 (0.8)	2†† (1.4)	0 (0.0)
Streptococcus agalactiae	2 (0.8)	1‡‡ (0.7)	1 (1.0)
Streptococcus constellatus	1 (0.4)	1§§ (0.7)	0 (0.0)
Streptococcus pneumoniae	3 (1.2)	2¶¶ (1.4)	1 (1.0)
Streptococcus pyogenes	3 (1.2)	2*** (1.4)	1 (1.0)
Coagulase-positive Staphylococci	50 (20.6)	33 (22.9)	17 (17.2)
Staphylococcus aureus (MSSA)	21 (8.6)	10††† (6.9)	11 (11.1)
Staphylococcus aureus (MRSA)	29 (11.9)	23‡‡‡ (16.0)	6 (6.1)
Gram-negative rods	66 (27.2)	66 (45.8)	0 (0.0)
Acinetobcter calcoaceticus	3 (1.2)	3 (2.1)	0 (0.0)
Aeromonas hydrophila	1 (0.4)	1 (0.7)	0 (0.0)
Burkholderia cepacia	5 (2.1)	5 (3.5)	0 (0.0)
Citrobacter freundii	1 (0.4)	1 (0.7)	0 (0.0)
Citrobacter koseri	1 (0.4)	1 (0.7)	0 (0.0)
Enterobacter aerogenes	3 (1.2)	3 (2.1)	0 (0.0)
Enterobacter cloacae	3 (1.2)	3 (2.1)	0 (0.0)
Escherichia coli	20 (8.2)	20 (13.9)	0 (0.0)
Haemophilus influenzae	1 (0.4)	1 (0.7)	0 (0.0)
Klebsiella oxytoca	1 (0.4)	1 (0.7)	0 (0.0)
Klebsiella pneumoniae	11 (4.5)	11 (7.6)	0 (0.0)
Morganella morganii	2 (0.8)	2 (1.4)	0 (0.0)
Proteus mirabilis	2 (0.8)	2 (1.4)	0 (0.0)
Proteus vulgaris	1 (0.4)	1 (0.7)	0 (0.0)
Pseudomonas aeruginosa	9 (3.7)	9 (6.3)	0 (0.0)
Serratia marcescens	1 (0.4)	1 (0.7)	0 (0.0)
Other gram negative rods	1 (0.4)	1 (0.7)	0 (0.0)
Fungi	17 (7.0)	17 (11.8)	0 (0.0)
Candida albicans	8 (3.3)	8 (5.6)	0 (0.0)
Candida glabrata	7 (2.9)	7 (4.9)	0 (0.0)
Candida sp.	2 (0.8)	2 (1.4)	0 (0.0)
Anaerobic	4 (1.6)	4 (2.8)	0 (0.0)
Bacteroides fragilis	1 (0.4)	1 (0.7)	0 (0.0)
Clostridium perfrigens	2 (0.8)	2 (1.4)	0 (0.0)
Clostridium sp.	1 (0.4)	1 (0.7)	0 (0.0)
Others	3 (1.2)	3§§§ (2.1)	0 (0.0)

*Positive blood cultures were considered as true bacteremia if the organisms were Gram negative rods, Fungi, or Anaerobic, or if the same organism were cultured more than two times. Two internist's independently reviewed other positive results and classify as positive when both reviewers judge as true positive based on findings; including same organism was detected at the site of infection organ, such as urine, sputa, catheter, operative specimen, and autopsy or patients had endocarditis; †more than 2 times: 6; ‡more than 2 times: 1; §infectious endocarditis and operative specimen: 1, same organism was detected at the site of infection organ: 1; ¶same organism was detected at the site of infection organ: 1; **more than 2 times: 2, same organism was detected at the site of infection organ: 1; ††more than 2 times: 1, same organism was detected at the site of infection organ: 1; ‡‡catheter infection: 1; §§infectious endocarditis: 1; ¶¶same organism was detected at the site of infection organ: 2; ***autopsy: 1, same organism was detected at the site of infection organ: 1; †††more than 2 times: 5, catheter infection: 2, operative specimen: 1, same organism was detected at the site of infection organ: 2; ‡‡‡more than 2 times: 8, Autopsy: 1, Catheter infection: 3, Infectious Endocarditis: 1, same organism was detected at the site of infection organ: 10; §§§more than 2 times: 2, Autopsy.

Table 3 Univariate correlates of true bacteremia, gram-negative rods, and in-hospital death

Variable	*True bacteremia*			*Gram-negative rods*			*In-hospital death*		
	Yes (n = 144) n (%)	*No (n = 595) n (%)*	P-*Value*	*Yes (n = 66) n (%)*	*No (n = 673) n (%)*	P-*Value*	*Yes (n = 203) n (%)*	*No (n = 536) n (%)*	P-*Value*
Age, years									
<60	25 (17.4)	184 (30.9)	0.005	12 (18.2)	197 (29.3)	0.1	32 (15.8)	177 (33.0)	<0.0001
≥60 and <70	31 (21.5)	124 (20.8)		15 (22.7)	140 (20.8)		36 (17.7)	119 (22.2)	
≥70 and <80	60 (41.7)	176 (29.6)		28 (42.4)	208 (30.9)		84 (41.4)	152 (28.4)	
≥80	28 (19.4)	111 (18.7)		11 (16.7)	128 (19.0)		51 (25.1)	88 (16.4)	
Male	93 (64.5)	351 (59.0)	0.2	42 (63.6)	402 (59.7)	0.5	124 (61.1)	320 (59.7)	0.7
Days from the admission to blood culture ≥14 days	67 (46.5)	219 (36.8)	0.03	25 (37.9)	261 (38.8)	0.9	92 (45.3)	194 (36.2)	0.02
Medical conditions									
Major co-morbidity*	38 (26.4)	115 (19.3)	0.06	16 (24.2)	137 (20.4)	0.5	61 (30.1)	92 (17.2)	0.001
Malignancy									
Malignancy	28 (19.4)	104 (17.5)	0.6	16 (24.2)	116 (17.2)	0.2	49 (24.1)	83 (15.5)	0.006
Hematological malignancy	17 (11.8)	117 (19.7)	0.03	12 (18.2)	122 (18.1)	1.0	45 (22.1)	89 (16.6)	0.08
Acute abdomen	16 (11.1)	53 (8.9)	0.4	9 (13.6)	60 (8.9)	0.2	19 (9.4)	50 (9.3)	1.0
Medication									
Central venous line insertion	12 (8.3)	25 (4.2)	0.04	2 (3.0)	35 (5.2)	1.0	14 (6.9)	23 (4.3)	0.1
On antibiotics	74 (51.4)	283 (47.6)	0.4	30 (45.5)	327 (48.6)	0.6	116 (57.1)	241 (45.0)	0.003

Physical examination									
SBP									
Maximum SBP ≥ 140 mmHg	76 (52.8)	236 (39.7)	0.004	34 (51.5)	278 (41.3)	0.1	100 (49.2)	212 (39.6)	0.02
Minimum SBP ≤ 90 mmHg	54 (37.5)	107 (18.0)	<0.0001	30 (45.5)	131 (19.5)	<0.0001	56 (27.6)	105 (19.6)	0.02
DBP									
Maximum DBP ≥ 95 mmHg	18 (12.5)	67 (11.3)	0.7	8 (12.1)	77 (11.4)	0.9	27 (13.3)	58 (10.8)	0.3
Minimum DBP ≤ 55 mmHg	73 (50.7)	176 (29.6)	<0.0001	40 (60.6)	209 (31.1)	<0.0001	89 (43.8)	160 (29.9)	0.0003
HR									
Maximum HR ≥ 100 min^{-1}	93 (64.6)	264 (44.4)	0.001	43 (65.2)	314 (46.7)	0.004	128 (63.1)	229 (42.7)	<0.0001
Minimum HR ≤ 60 min^{-1}	9 (6.3)	59 (9.9)	0.2	5 (7.6)	63 (9.4)	0.6	14 (6.9)	54 (10.1)	0.2
BT									
Maximum BT ≥ 38.5 °C	89 (61.8)	278 (46.7)	0.001	49 (74.2)	318 (47.3)	0.001	96 (47.3)	271 (50.6)	0.4
Minimum BT ≤ 35.5 °C	12 (8.3)	22 (3.7)	0.02	6 (9.1)	28 (4.2)	0.07	16 (7.9)	18 (3.4)	0.009
Laboratory results									
WBC ≥ 10 000 $microL^{-1}$	77 (53.5)	247 (41.5)	0.009	33 (50.0)	291 (43.2)	0.3	101 (49.8)	223 (41.6)	0.05
Hb ≤ 10.0 g dL^{-1}	90 (62.5)	295 (49.6)	0.005	40 (60.6)	345 (51.3)	0.1	133 (65.5)	252 (47.0)	<0.0001
Plt ≤ 25 000 $microL^{-1}$	16 (11.1)	42 (7.1)	0.1	12 (18.2)	46 (6.8)	0.001	20 (9.9)	38 (7.1)	0.2
CRP ≥ 10.0 mg dL^{-1}	82 (56.9)	238 (40.0)	0.001	40 (60.6)	280 (41.6)	0.003	97 (47.8)	223 (41.6)	0.1
AST ≥ 40 IU L^{-1}	61 (42.4)	165 (27.7)	0.001	21 (31.8)	205 (30.5)	0.8	76 (37.4)	150 (28.0)	0.01
ALT ≥ 35 IU L^{-1}	60 (41.7)	175 (29.4)	0.005	24 (36.4)	211 (31.4)	0.4	69 (14.0)	166 (31.0)	0.4
Blood Sugar ≥126 mg dL^{-1}	81 (56.3)	237 (39.8)	0.001	35 (53.0)	283 (42.1)	0.09	87 (42.9)	231 (43.1)	1.0
Albumin ≤3.5 g dL^{-1}	104 (72.2)	292 (49.1)	<0.0001	49 (74.2)	347 (51.6)	0.0004	122 (60.1)	274 (51.1)	0.03
Total bilirubin ≥1.0 mg dL^{-1}	53 (36.8)	145 (24.4)	0.002	29 (43.9)	169 (25.1)	0.001	60 (29.6)	138 (25.8)	0.3
LDH ≥ 400 IU L^{-1}	34 (23.6)	138 (23.2)	0.9	18 (27.3)	154 (22.9)	0.4	64 (31.5)	108 (20.2)	0.001
BUN ≥ 20.0 mg dL^{-1}	76 (52.8)	179 (30.1)	0.001	34 (51.59)	221 (32.8)	0.002	103 (50.7)	152 (28.4)	0.001
Creatinine ≥1.3 mg dL^{-1}	57 (39.6)	119 (20.0)	0.001	28 (42.4)	148 (22.0)	0.001	69 (34.0)	107 (20.0)	0.001
Na ≥ 145.0 mEq L^{-1}	12 (8.3)	25 (4.2)	0.04	3 (4.6)	34 (5.1)	1.0	18 (8.9)	19 (3.5)	0.003
K ≥ 5.0 mEq L^{-1}	11 (7.6)	33 (5.6)	0.3	3 (4.6)	31 (4.6)	1.0	18 (8.9)	26 (4.9)	0.04

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BT, body temperature; WBC, white blood cell count; Hb, hemoglobin; Plt, platelet cell count; CRP, C-reactive protein; AST, aspartic aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; Na, sodium; K, potassium.
*Major co-morbidity includes coma, brain death, bowel perforation, multiple trauma, multiple burns, cardiopulmonary arrest with in the previous 24 h, bone marrow transplant, severe pancreatitis, acute respiratory distress syndrome, and hepatic failure.

Table 4 Independent Predictors Identified by Multivariate Analysis

Variable	*Beta*	*Odds ratio*	*95% Confidence interval*	*Points**
True bacteremia				
Intercept	−3.82			
Minimum SBP ≤ 90 mmHg	1.19	3.3	2.0–5.4	16
CRP ≥ 10.0 mg dL^{-1}	0.78	2.2	1.3–3.6	10
Creatinine ≥1.3 mg dL^{-1}	0.75	2.1	1.3–3.4	10
Days from the admission to blood culture ≥14 days	0.82	2.3	1.4–3.7	11
Age ≥ 70 and < 80 years	0.67	2.0	1.2–3.2	9
Maximum BT ≥ 38.5°C	0.93	2.5	1.5–4.2	12
Minimum BT ≤ 35.5°C	0.92	2.5	1.1–5.9	12
WBC ≥ 10 000 $microL^{-1}$	0.45	1.6	1.0–2.5	6
Gram-negative rods				
Intercept	−5.01			
Minimum SBP ≤ 90 mmHg	1.43	4.2	2.2–7.9	3
CRP ≥ 10.0 mg dL^{-1}	1.28	3.6	1.8–7.2	3
Plt ≤ 25 000 $microL^{-1}$	1.53	4.6	1.6–13.1	3
Creatinine ≥1.3 mg dL^{-1}	0.97	2.6	1.4–5.1	2
Maximum BT ≥ 38.5°C	1.44	4.2	2.0–9.0	3
In-hospital death				
Intercept	−4.11			
BUN ≥ 20.0 mg dL^{-1}	1.02	2.8	1.7–4.5	9
LDH ≥ 400 IU L^{-1}	1.01	2.7	1.7–4.4	9
Major co-morbidity†	1.07	2.9	1.7–4.9	10
Hb ≤ 10.0 g dL^{-1}	0.60	1.8	1.1–2.9	6
Age ≥ 60 years	0.89	2.4	1.4–4.4	8
On antibiotics	0.58	1.8	1.1–2.9	5
Hematological malignancy	0.98	2.7	1.5–4.8	9
Malignancy	1.03	2.8	1.5–5.1	9
Minimum DBP ≤ 55 mmHg	0.65	1.9	1.2–3.1	6

The risk score for an individual patient was determined each true bacteremia, gram-negative rods, and in-hospital death by assigning points for each factor present and summing. The resulting risk score was then used in Table 4 to estimate the each probability of true bacteremia, gram-negative rods, and in-hospital death.

SBP, systolic blood pressure; CRP, C-reactive protein; BT, body temperature; WBC, white blood cell count; Plt, platelet cell count; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; Hb, hemoglobin; DBP, diastolic blood pressure.

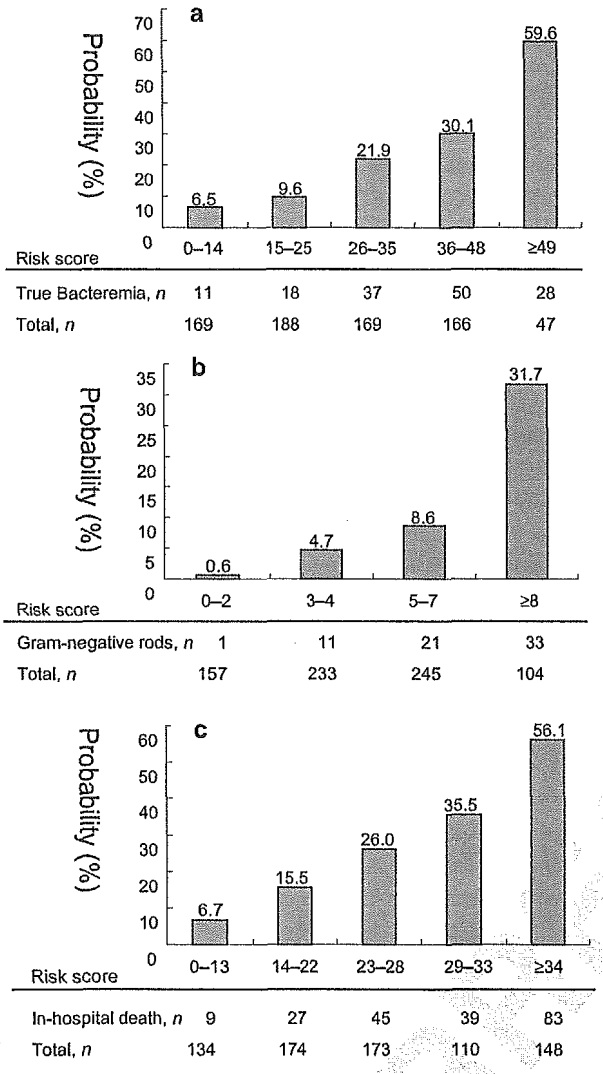
*Calculated by diving the β coefficient by 0.075 (True bacteremia), 0.5 (Gram-negative rods), and 0.11 (In-hospital death) and rounding to the nearest integer.

†major co-morbidity includes coma, brain death, bowel perforation, multiple trauma, multiple burns, cardiopulmonary arrest with in the previous 24 h, bone marrow transplant, severe pancreatitis, acute respiratory distress syndrome and hepatic failure.

in-hospital death with varying likelihood of each outcome (Fig. 1).

The subject patients were divided into the following 5 groups according to the risk probability of bacteremia: (1) patients with 7% risk (very-low-risk group, score: 0–14); (2) those with 10% risk (low-risk group, risk score: 15–25); (3) those with 22% risk (average-risk group, risk score: 26–35); (4) those with 30% risk (intermediate-risk group, risk score: 36–48); and (5) those with 60% risk (high-risk group, score ≥ 49) (Fig. 1).

Similarly, risks of blood culture positive for gram-negative rods were predicted from 1% (very-low-risk group, risk score: 0–2) to 32% (high-risk group, risk score ≥ 8) and those of in-hospital death were estimated from 7% (very-low-risk group, risk score: 0–13) to 56% (high-risk group, risk score ≥ 34) (Fig. 1).



11 **Figure 1 Performance of the prediction rules. a, true bacteremia; b, gram-negative rods; c, in-hospital death.**

Calibration

The rules we came up with here performed well with ROC curve analyses in predicting true bacteremia, blood culture positive for gram-negative rods, and in-hospital death. The respective areas under the curve were 0.73 ± 0.02 (mean ± SE), 0.64 ± 0.02, and 0.64 ± 0.02 respectively (Fig. 2). Calibrations of the three models were tested on the entire cohort and proved satisfactory (Fig. 3). Hosmer-Lemeshow goodness-of-fit test *P*-values were 0.6, 1.0, and 0.07 for true bacteremia, blood culture positive for gram-negative rods, and in-hospital death respectively.

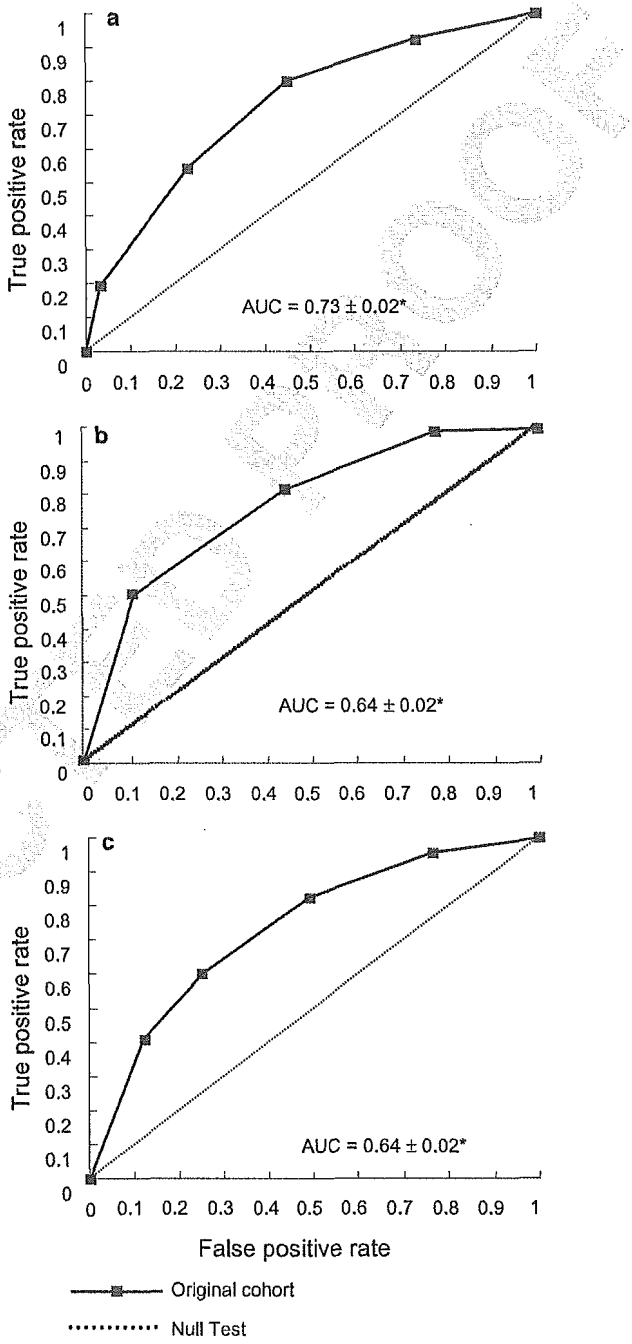
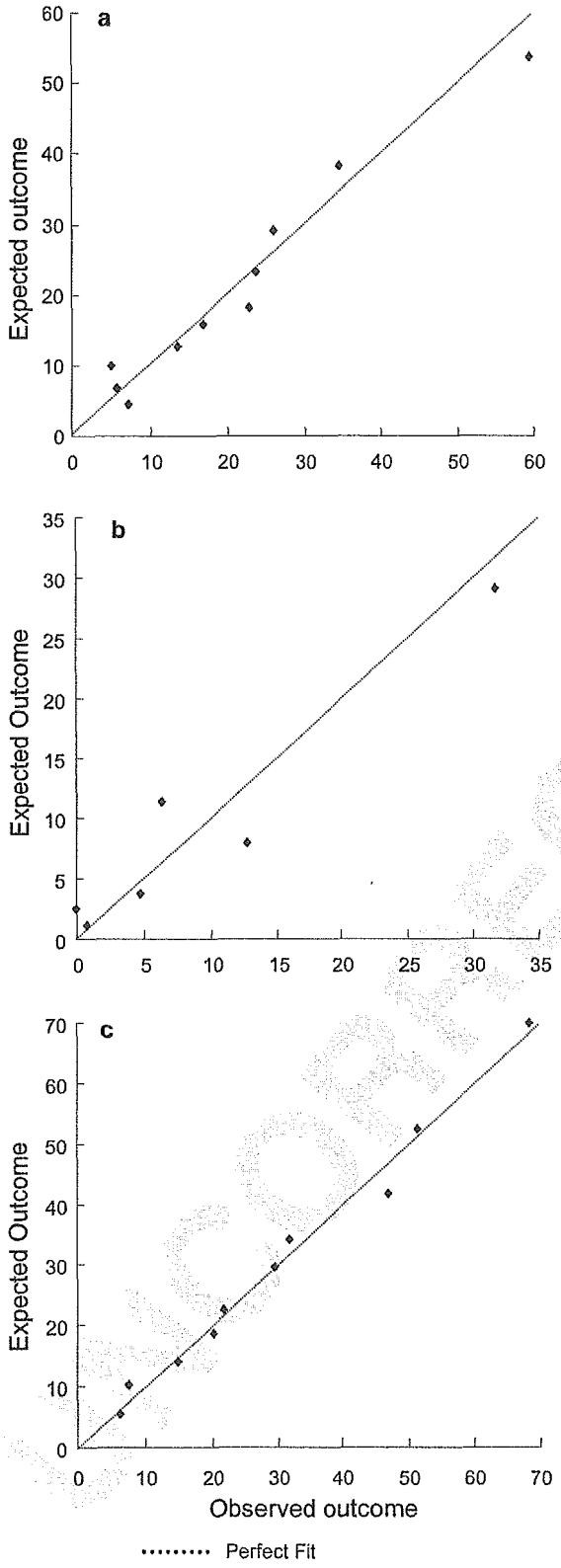


Figure 2 Receiver operating characteristic curves for true bacteremia (a), gram-negative rods (b), and in-hospital death (c). The area under the curves are 0.73 ± 0.02 (a), 0.64 ± 0.02 (b), and 0.64 ± 0.02 (c) and for the original cohort. The straight, diagonal broken lines represent the tests without discriminative ability. AUC, area under the receiver operating characteristic curve ± standard error. 12



Validation

We conducted jackknife cross validation for the three prediction rules. The areas under the ROC curves for each validation of true bacteremia, blood culture positive for gram-negative rods, and in-hospital death were 0.72 ± 0.02, 0.64 ± 0.02, and 0.64 ± 0.02 respectively. These were not significantly different from those of the original cohort.

Discussion

We developed clinical prediction rules for true bacteremia, blood culture positive for gram-negative rods, and in-hospital death using the data at the time of blood withdrawal for culture. The true bacteremia prediction rule resulted in the categorization of the patients into five groups with risk probabilities ranging from 7 to 60%. Likewise, for the gram-negative rod prediction rule there were four groups with risk probabilities ranging from 1 to 32%, and for the in-hospital death prediction rule five groups with risk probabilities ranging from 7 to 56%.

Our prediction rules were based on the data of vital signs, medical conditions, and laboratory findings. Without medical computing systems, all predictors were usually available for patients undergoing blood cultures, and there were reports that showed the usefulness of some of these clinical data in predicting bacteremia (Bone 1987; Mellors *et al.* 1987; Bates *et al.* 1990; Leibovici *et al.* 1990; Jaimes *et al.* 2004). However, the purpose of these previous prediction rules was 'interpretation' of blood culture results to make clinical judgement whether the results were true or owing to contamination (Mellors *et al.* 1987; Bates *et al.* 1990, 1992, 1997; Leibovici *et al.* 1990), or predicting only for bacteremia (Jaimes *et al.* 2004). On the other hand, the purpose of our clinical prediction rules was 'prediction' for true

Figure 3 Observed vs. expected incidence of true bacteremia (a), gram-negative rods (b), and in-hospital death (c). Scatterplots allowing for visual assessment of the linearity of the increase in event rates across risk groups (a–c). The straight, diagonal broken lines represent perfect calibration and deviations from this line represent over-prediction or under-prediction of actual risk.

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bacteremia, blood culture positive for gram-negative rods, and in-hospital death using the data at the time of blood withdrawal for culture. In terms of in-hospital death, we used all death irrespective of causes and timing of death because death owing to bacteremia was difficult to clearly distinguish from that owing to other causes in clinical situations.

To predict in-hospital death, several prediction rules were suggested. Acute Physiology and Chronic Health Evaluation II, Simplified Acute Physiology Score, and Mortality Probability Models II predicted for in-hospital death using age, vital signs, Glasgow coma scale, pulmonary artery pressure, urinary output, laboratory tests (blood gas, sodium, potassium, creatinine, urea, bilirubin, bicarbonate, prothrombin time, hematocrit, WBC), type of admission, and comorbidity such as infection, vasoactive drugs, cardiopulmonary resuscitation, mechanical ventilation, and nonelective surgery (Knaus *et al.* 1985; Le Gall *et al.* 1993; Lemeshow *et al.* 1993). On the other hand, our prediction rules could simultaneously estimate the likelihood of bacteremia as well as in-hospital death based on the similar predictors.

Our clinical prediction rules are thus expected to be used for clinical decision regarding the use of antibiotics and other management before the results of blood culture become available. For examples, if the likelihood of true bacteremia is very low, antibiotics can be withheld until the results become available. On the other hand, positivity of gram-negative rods is highly likely, antibiotics covering gram-negative rods can be started immediately after blood withdrawal for culture. By using the estimated mortality at the time of blood culture, a doctor can inform the patient and his family about the prognosis more rationally. Prediction rules such as these are also useful in educating doctors, residents, and medical students to make proper clinical decisions in an explicit way.

Although the process of assigning risk points, as shown in Table 4 and Fig. 1, may appear a bit cumbersome for busy doctors to use manually, current information technology will undoubtedly resolve such concerns (Bates & Gawande 2003). All the risk factors used for clinical prediction, such as patient characteristics, physical examination results, and laboratory results are easily incorporated with computerized systems. In fact, many hospitals already employ computerized doctor ordering entry, which can incorporate clinical decision rules based on clinical data in real time (Kaushal *et al.* 2003; Wrobel 2003). There was a report that by using a computerized decision support system, doctors changed 28% of their treatment decisions (Wang *et al.* 2000). Mullett *et al.* (2004) also reported that a computerized antimicrobial decision support programme based on past patient demographic data, and culture results had improved the rate of effectiveness of empiric antimicrobial therapy for bacteremia patients by 20%. Our study extended their findings to clinical prediction rules for true bacteremia, blood culture positive for gram-negative rods, and in-hospital death.

There are several limitations to our study. First, only one set of blood culture was done in half of the patients in our study. To minimize possible misclassification bias, we conducted scrupulous reviews of the cases by two doctor reviewers. Although the reviewers judged the results of blood culture independently and agreement between reviewers was used for definition of true bacteremia, the high proportion of S. aureus (17.2%) in the contamination could be due to the lack of two sets of blood culture for this organism. However, the contamination rate in our study (41%) was similar to that (47%) in a previous report (19), indicating that current data were acceptable. Second, the proportion of missing data were as high as 25% (LDH). However, it is common to have missing data in clinical setting, and the relationship between missing status and patient characteristics or outcomes were not statistically significant. Third, as shown in Fig. 3, the performance of the prediction rule for gram-negative rods was not as good as that for other two prediction rules. This is mainly due to small sample size, leaving some concern about reliability. Finally, we used here jackknife cross validation technique. Previous studies were prospective in design and utilized other patient cohort for validation (Bates *et al.* 1990, 1992, 1997). Prospective validation will be necessary for our prediction rules in the future.

In conclusion, we developed clinical prediction rules for true bacteremia, blood culture positive for gram-negative rods, and in-hospital death using the clinical data from medical computing system at the time of blood withdrawal for culture. These clinical prediction rules may well be useful in making rational clinical decisions before blood culture results

