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Clinical Characteristics and Laboratory Biomarkers in ICU-admitted Septic Patients with and without Bacteremia: A Predictive Analysis

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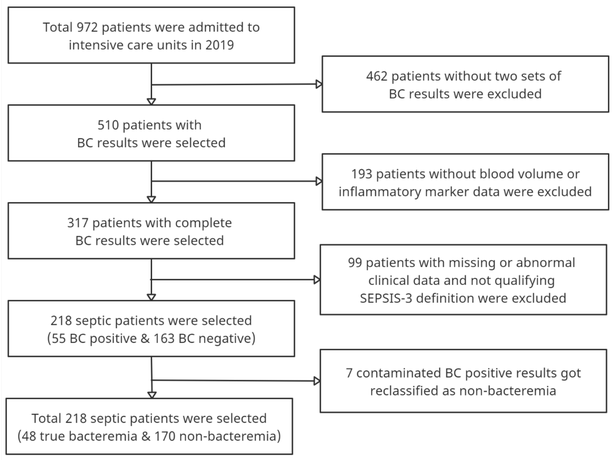
Introduction

- Sepsis is a life-threatening disease that impairs the body's organs and tissues
- Annual mortality rate of sepsis is 15% to 30% globally
- Mortality rate of septic patients particularly rises with the onset of bacteremia
- Early and customized therapy can substantially reduce mortality of bacteremic sepsis patients
- Diagnosis through laboratory biomarkers can significantly save time
- Evaluated diverse biomarkers to optimize the prediction power of the multivariable logistic regression model

Methods

- A retrospective cross-sectional study
- All hospitalized septic patients admitted to intensive care units in 2019 were included
- Of 218 patients, 48 were true bacteremia and 170 were non-bacteremia
- Blood culture testing was the gold standard for determining bacteremic/non-bacteremic patients
- False-positive results of blood culture were reclassified by the evaluation of a medical doctor
- SEPSIS-3 criteria (sequential organ failure assessment score ≥ 2) was the standard for defining septic patients
- Selected worst condition of the patient within 12 hours from the time of blood culture.

Fig 1. Patient enrollment flowchart



Abbreviations: BC, blood culture; SOFA, sequential organ failure

Results

Table 1. Baseline characteristics of patients

	Total patients (N=218)	True bacteremia (N=48)	Non-bacteremia (N=170)	P
Patient Characteristics				
Age (years)	68 [56–77]	65 [55–76]	68 [57–78]	0.529
Male sex, n (%)	140 [64.2%]	33 [68.8%]	107 [62.9%]	0.568
Body temperature (°C)	36.6 [36.3–37.1]	37.0 [36.2–37.4]	36.6 [36.3–37.0]	0.066
28-day mortality (%)	67 [30.7%]	21 [43.8%]	46 [27.1%]	0.042
Prior antibiotics (%)	78 [35.8%]	14 [29.2%]	64 [37.6%]	0.362
Laboratory Findings				
Blood culture bottle volume (ml)	5.9 [4.8–7.6]	5.8 [5.1–7.6]	5.9 [4.6–7.6]	0.455
PaO_2/FiO_2 (mmHg)	210 [135–334]	229 [134–353]	208 [135–317]	0.670
Mean arterial pressure (mmHg)	68 [60–79]	62 [57–71]	70 [62–79]	0.001
Serum sodium (mmol/L)	136.4 [133.2–139.8]	133.8 [129.0–137.3]	137.0 [134.2–140.3]	0.001
GCS score (3-15)	6 [3–13]	4 [3–9]	7 [3–14]	0.016
Neutrophil-lymphocyte ratio	10.0 [4.7–17.8]	18.2 [8.3–36.6]	8.7 [4.3–14.8]	<0.001
Creatinine (mg/L)	1.04 [0.68–1.89]	1.94 [1.02–3.06]	0.96 [0.67–1.57]	<0.001
Lactic acid (mmol/L)	2.2 [1.1–5.6]	3.2 [1.9–9.4]	1.9 [1.1–3.9]	0.001
Bilirubin (mg/dL)	0.86 [0.56–1.42]	1.40 [0.85–2.10]	0.77 [0.50–1.18]	<0.001
Aspartic aminotransferase (U/L)	48.0 [31.5–110.0]	85.0 [39.5–206.0]	44.0 [28.5–87.0]	0.001
Platelets (10^3/ml)	183 [103–265]	111 [69–171]	203 [127–276]	<0.001
Blood urea nitrogen (mg/dL)	22.9 [16.5–37.4]	35.0 [23.4–56.0]	19.9 [14.8–33.3]	<0.001
White blood cell (cells/mm^3)	12.5 [7.8–18.1]	13.4 [6.3–20.8]	12.5 [8.0–18.1]	0.865
Hematocrit (%)	33 [29–38]	34 [29–36]	33 [29–38]	0.453
Erythrocyte sedimentation rate	27 [9–53]	43 [18–59]	26 [7–51]	0.039
C-reactive protein (mg/L)	86.8 [17.0–170.6]	192.1 [90.4–259.5]	67.9 [14.4–139.9]	<0.001
Procalcitonin (ng/ml)	0.37 [0.08–3.68]	14.31 [3.00–45.51]	0.22 [0.04–1.09]	<0.001
Pitt bacteremia score (0-14)	4 [2–6]	6 [3–6]	4 [2–6]	0.165
APACHE II score (0-71)	20 [15–25]	25 [18–30]	19 [15–24]	<0.001
SOFA score (0-24)	10 [7–12]	12 [9–16]	9 [6–11]	<0.001
Medical History				
Diabetes mellintus (%)	71 [32.6%]	17 [35.4%]	54 [31.8%]	0.762
Hypertension (%)	107 [49.1%]	22 [45.8%]	85 [50.0%]	0.729
Heart failure (%)	29 [13.3%]	3 [6.2%]	26 [15.3%]	0.165
Cerebrovascular disease (%)	34 [15.6%]	7 [14.6%]	27 [15.9%]	0.995
Renal disease (%)	27 [12.4%]	5 [10.4%]	22 [12.9%]	0.825
Liver disease (%)	14 [6.4%]	6 [12.5%]	8 [4.7%]	0.107
Chronic obstructive pulmonary disease (%)	16 [7.3%]	2 [4.2%]	14 [8.2%]	0.521
Known neoplasm (%)	24 [11.0%]	8 [16.7%]	16 [9.4%]	0.247
Suspected Source of Infection				
Catheter-related bloodstream infection (%)	4 [1.8%]	1 [2.1%]	3 [1.8%]	>0.999
Intra-abdominal infection (%)	17 [7.8%]	9 [18.8%]	8 [4.7%]	0.004
Respiratory tract infection (%)	155 [71.1%]	21 [43.8%]	134 [78.8%]	0.003
Skin and soft tissue infection (%)	8 [3.7%]	2 [4.2%]	6 [3.5%]	>0.999
Urinary tract infection (%)	33 [15.1%]	17 [35.4%]	16 [9.4%]	<0.001
Others (%)	9 [4.1%]	6 [12.5%]	3 [1.8%]	0.004
Fever of unknown origin (%)	6 [2.8%]	1 [2.1%]	5 [2.9%]	>0.999

Continuous variables are expressed in median [interquartile range] and categorical variables are expressed in counts [proportions (%)]. Mann-Whitney U test performed for continuous variables and chi-squared contingency test or Fisher's exact test, where appropriately, were performed for categorical variables to calculate *P*.

Abbreviations: GCS, Glasgow coma scale; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment

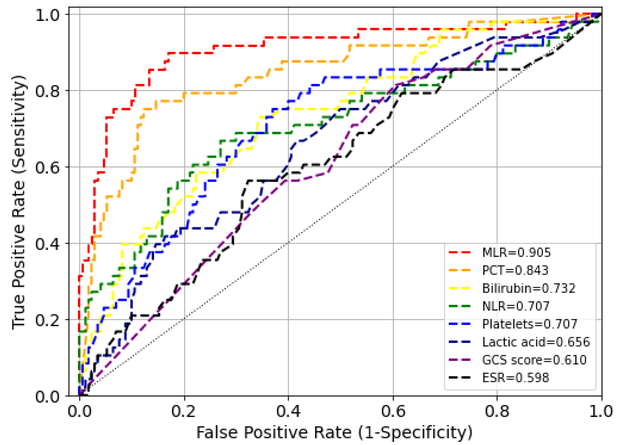
Table 2. Univariate and multivariable logistic regression analysis to predict bacteremia

	Cut-off	AUC	Sensitivity	Specificity	DOR	P
MLR model*		0.907 [0.843–0.956]	87.9% [74.5–96.6]	86.6% [78.8–96.0]	41.81	<0.001
PCT (ng/ml)	3.18	0.845 [0.771–0.907]	77.3% [64.4–88.9]	87.2% [79.1–92.5]	21.29	<0.001
CRP (mg/L)	164.3	0.757 [0.670–0.833]	63.8% [48.8–84.2]	84.2% [59.5–90.9]	8.45	<0.001
SOFA score (0-24)	13	0.734 [0.650–0.814]	60.8% [38.5–92.2]	80.4% [41.3–93.2]	5.88	<0.001
Bilirubin (mg/dL)	0.97	0.733 [0.647–0.809]	70.9% [42.1–91.1]	69.1% [45.3–93.2]	5.07	<0.001
BUN (mg/dL)	19.2	0.712 [0.624–0.791]	82.7% [47.3–96.0]	57.4% [41.5–89.9]	7.29	<0.001
NLR	14.26	0.709 [0.612–0.798]	65.9% [46.7–80.4]	76.6% [66.1–88.4]	5.39	<0.001
Platelets (10^3/ml)	168	0.707 [0.616–0.793]	77.8% [56.2–91.3]	63.5% [50.3–80.1]	5.1	<0.001
Creatinine (mg/L)	1.86	0.702 [0.619–0.780]	61.0% [46.2–88.5]	81.8% [50.9–88.3]	6.25	0.005
APACHE II score (0-71)	24	0.673 [0.573–0.766]	56.2% [34.0–79.5]	78.6% [51.7–93.1]	3.77	<0.001
Na (mmol/L)	133.4	0.662 [0.568–0.750]	54.8% [32.6–87.0]	79.2% [42.4–93.3]	3.86	0.004
Lactic acid (mmol/L)	6.1	0.657 [0.564–0.741]	64.6% [34.6–91.8]	64.3% [33.7–90.0]	3.62	0.008
AST (U/L)	62	0.655 [0.562–0.742]	65.0% [41.7–89.8]	67.2% [36.0–84.8]	3.34	0.015
MAP (mmHg)	67.3	0.653 [0.562–0.742]	68.4% [42.4–87.3]	63.1% [41.1–83.0]	3.22	0.003
GCS score (3-15)	10	0.611 [0.526–0.694]	79.6% [50.0–93.8]	43.8% [25.4–70.6]	2.82	0.017
ESR (mm/hr)	41	0.597 [0.503–0.690]	59.6% [29.4–89.2]	67.4% [31.8–90.3]	2.69	0.029

Cut-off is calculated through using the Youden's index and 95% confidence interval through bootstrapping the logistic regression model 10,000 times.

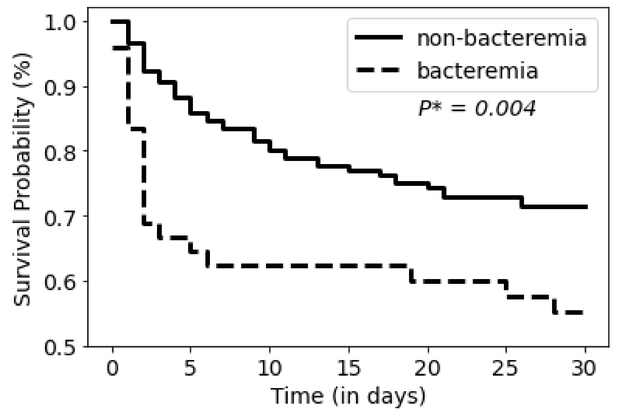
*MLR model is constructed by combining PCT, Bilirubin, NLR, Platelets, Lactic acid, GCS score, and ESR

Fig 2. Plot of ROC curves of univariate and multivariable prediction model for bacteremia



Abbreviations: MLR, multivariable logistic regression; PCT, procalcitonin; NLR, neutrophil-lymphocyte ratio; GCS, Glasgow coma scale; ESR, erythrocyte sedimentation rate.

Fig 3. Plot of Kaplan-Meier estimates for the survival of bacteremic vs. non-bacteremic patients



*P is calculated through running the log-rank test

Summary

- CRP and PCT showed significance in discriminating bacteremic sepsis (0.757 and 0.845, respectively)
- A combined model of PCT, bilirubin, neutrophil-lymphocyte ratio (NLR), platelets, lactic acid, erythrocyte sedimentation rate, and Glasgow coma scale score had predictive power with an AUC of 0.907 [0.843-0.956]
- A high association between bacteremia and mortality rate was discovered through the survival analysis (*P*=0.004)

Conclusions

- Optimal prediction model for diagnosing bacteremia was constructed using multivariable logistic regression model
- A strong association between bacteremic sepsis and mortality indicates the substantial clinical utility of the model for enabling early-goal directed therapy
- More research is necessary to confirm the applicability or validity of this new prediction model for bacteremic sepsis
- PCT alone has adequate diagnostic value, but prediction power can be maximized by adding bilirubin, NLR, platelets, lactic acid, ESR, and GCS score

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References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801-10.
2. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47:1181-247.
3. Mellhammar L, Kahn F, Whitlow C, Kander T, Christensson B, Linder A. Bacteremic sepsis leads to higher mortality when adjusting for confounders with propensity score matching. Sci Rep 2021;11:6972.
4. Investigators P, Rowan KM, Angus DC, Bailey M, Barnato AE, Bellomo R, et al. Early, Goal-Directed Therapy for Septic Shock - A Patient-Level Meta-Analysis. N Engl J Med 2017;376:2223-34.
5. Gonzalez MD, Chao T, Pettengill MA. Modern Blood Culture: Management Decisions and Method Options. Clin Lab Med 2020;40:379-92.
6. Doern GV, Carroll KC, Diekema DJ, Garey KW, Rupp ME, Weinstein MP, et al. Practical Guidance for Clinical Microbiology Laboratories: A Comprehensive Update on the Problem of Blood Culture Contamination and a Discussion of Methods for Addressing the Problem. Clin Microbiol Rev 2019;33.
7. Hoeboer SH, van der Geest PJ, Nieboer D, Groeneveld AB. The diagnostic accuracy of procalcitonin for bacteraemia: a systematic review and meta-analysis. Clin Microbiol Infect 2015;21:474-81.
8. Mosevoll KA, Skrede S, Markussen DL, Fanebust HR, Flaatten HK, Assmus J, et al. Inflammatory Mediator Profiles Differ in Sepsis Patients With and Without Bacteremia. Front Immunol 2018;9:691.
9. Lambden S, Laterre PF, Levy MM, Francois B. The SOFA score-development, utility and challenges of accurate assessment in clinical trials. Crit Care 2019;23:374.
10. Cheng K, Bassil R, Carandang R, Hall W, Muehlschlegel S. The Estimated Verbal GCS Subscore in Intubated Traumatic Brain Injury Patients: Is it Really Better? J Neurotrauma 2017;34:1603-9.
11. Ranganathan P, Pramesh CS, Aggarwal R. Common pitfalls in statistical analysis: Logistic regression. Perspect Clin Res 2017;8:148-51.
12. Goel MK, Khanna P, Kishore J. Understanding survival analysis: Kaplan-Meier estimate. Int J Ayurveda Res 2010;1:274-8.
13. Thomas-Ruddel DO, Poidinger B, Kott M, Weiss M, Reinhart K, Bloos F, et al. Influence of pathogen and focus of infection on procalcitonin values in sepsis patients with bacteremia or candidemia. Crit Care 2018;22:128.
14. Mansur A, Klee Y, Popov AF, Erlenwein J, Ghadimi M, Beissbarth T, et al. Primary bacteraemia is associated with a higher mortality risk compared with pulmonary and intra-abdominal infections in patients with sepsis: a prospective observational cohort study. BMJ Open 2015;5:e006616.
15. Nishikawa H, Shirano M, Kasamatsu Y, Morimura A, Iida K, Kishi T, et al. Comparison between procalcitonin and C-reactive protein in predicting bacteremias and confounding factors: a case-control study. Clin Chem Lab Med 2017;55:1043-52.
16. Komori A, Abe T, Kushimoto S, Ogura H, Shiraishi A, Saitoh D, et al. Characteristics and outcomes of bacteremia among ICU-admitted patients with severe sepsis. Sci Rep 2020;10:2983.
17. Ljungstrom L, Pernestig AK, Jacobsson G, Andersson R, Usener B, Tilevik D. Diagnostic accuracy of procalcitonin, neutrophil-lymphocyte count ratio, C-reactive protein, and lactate in patients with suspected bacterial sepsis. PLoS One 2017;12:e0181704.
18. Kern WV and Rieg S. Burden of bacterial bloodstream infection-a brief update on epidemiology and significance of multidrug-resistant pathogens. Clin Microbiol Infect 2020;26:151-7.
19. Jekarl DW, Lee S, Kim M, Kim Y, Woo SH, Lee WJ. Procalcitonin as a prognostic marker for sepsis based on SEPSIS-3. J Clin Lab Anal 2019;33:e22996.
20. Tan M, Lu Y, Jiang H, Zhang L. The diagnostic accuracy of procalcitonin and C-reactive protein for sepsis: A systematic review and meta-analysis. J Cell Biochem 2019;120:5852-9.
21. Su CP, Chen TH, Chen SY, Ghiang WC, Wu GH, Sun HY, et al. Predictive model for bacteremia in adult patients with blood cultures performed at the emergency department: a preliminary report. J Microbiol Immunol Infect 2011;44:449-55.
22. Jeong S, Park Y, Cho Y, Kim HS. Diagnostic utilities of procalcitonin and C-reactive protein for the prediction of bacteremia determined by blood culture. Clin Chim Acta 2012;413:1731-6.
23. Memar MY and Baghi HB. Presepsin: A promising biomarker for the detection of bacterial infections. Biomed Pharmacother 2019;111:649-56.
24. Ryoo SM, Han KS, Ahn S, Shin TG, Hwang SY, Chung SP, et al. The usefulness of C-reactive protein and procalcitonin to predict prognosis in septic shock patients: A multicenter prospective registry-based observational study. Sci Rep 2019;9:6579.
25. Yan J, Li S, Li S. The role of the liver in sepsis. Int Rev Immunol 2014;33:498-510.
26. Huang Z, Fu Z, Huang W, Huang K. Prognostic value of neutrophil-to-lymphocyte ratio in sepsis: A meta-analysis. Am J Emerg Med 2020;38:641-7.
27. de Jager CP, van Wijk PT, Mathoera RB, de Jongh-Leuvenink J, van der Poll T, Wever PC. Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit. Crit Care 2010;14:R192.
28. Vandijck DM, Blot SI, De Waele JJ, Hoste EA, Vandewoude KH, Decruyenaere JM. Thrombocytopenia and outcome in critically ill patients with bloodstream infection. Heart Lung 2010;39:21-6.
29. Lin CT, Lu JJ, Chen YC, Kok VC, Horng JT. Diagnostic value of serum procalcitonin, lactate, and high-sensitivity C-reactive protein for predicting bacteremia in adult patients in the emergency department. PeerJ 2017;5:e4094
30. Yang Q, Jiang XZ, Zhu YF, Lv FF. Clinical risk factors and predictive tool of bacteremia in patients with cirrhosis. J Int Med Res 2020;48:300060520919220.

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