Bloodstream infection in moderately severe and severe acute pancreatitis: microbiological features and a prediction model

Dujiang Yang[1#], Huan Xu[2#], Mao Li[3#], Chao Yue[3], Zongguang Zhou[1], Weiming Hu[3], Yong Liu[1*], Huimin Lu[3*]

[1] Department of Gastrointestinal Surgery, West China Hospital, Sichuan University, No. 37, Guoxue Alley, Chengdu, 610041, Sichuan Province, China.
[2] Institute for Disaster Management and Reconstruction, Sichuan University, Chengdu, 610207, Sichuan Province, China.
[3] Department of Pancreatic Surgery, West China Hospital, Sichuan University, No. 37, Guoxue Alley, Chengdu, 610041, Sichuan Province, China.
[#] Dujiang Yang, Huan Xu, and Mao Li have contribute equally to this work.
[*] They are the co-corresponding author.

Abstract

Background

Prediction of BSI would contribute to the management of MSAP and SAP. This study aimed to investigate pathogens distribution of bloodstream infection (BSI) in moderately severe acute pancreatitis (MSAP) and severe acute pancreatitis (SAP) patients and develop a prediction model for BSI development.

Methods

MSAP and SAP patients admit to West China Hospital from January 2012 to December 2018 were collected. Include patients were divided into BSI group and non-bloodstream infection (NBSI) group. Isolated pathogens and antibiotic resistance were recorded. The least absolute shrinkage and selection operator (LASSO) regression was used to select the risk factors for BSI. Logistic regression was used to develop a nomogram. Random forest was used to validate the stable ability of prediction factors. The areas under receiver operating characteristic (AUC) and calibration curves were plotted to evaluate the prediction performance.

Findings:

399 BSI patients and 1155 NBSI patients were enrolled in this study. Of the 408 isolated pathogens, 226 (55.39%) were gram-negative bacteria. Seven predictors (intensive care unit stay, cardiovascular failure, percentage of neutrophil, percentage of lymphocyte, triglyceride, low-density lipoprotein, and albumin) were identified for BSI. The nomogram prediction model has 0.913 and 0.888 AUCs in training and validation sets. The calibration curves show the nomogram has a good consistency.

Interpretation:

Gram-negative bacteria were the major BSI pathogens. A new nomogram with a high predictive value based on selected factors was built. It can be conveniently used to predict BSI development and help clinicians rationally use antibiotics in MSAP and SAP patients.

Funding:

This work was supported by the 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (ZYJC18027); Sichuan Science and Technology Program (2020YFS0263); and Sichuan Science and Technology Program (2021YFS0234).

Keywords:

Bloodstream infection; Acute pancreatitis; Microbiology; Random forest; Nomogram; Prediction model.

Research in Context

Evidence before this study

We searched publications with the following terms on Ovid Medline, Embase, and Web of Science: ("Acute pancreatitis" "Severe acute pancreatitis" OR "Moderately severe acute pancreatitis" OR "Pancreatitis, Acute Necrotizing") AND ("Bloodstream infection" or "Sepsis") AND ("Predict" OR "Prediction"). This search is without limitation of language and data. Finally, 421 studies have been identified. However, no one focuses on the microbiological features and prediction model for bloodstream infection in moderately severe and severe acute pancreatitis.

Added value of this study

As far as we know, this study is the first to investigate the microbiological features and built a prediction model for bloodstream infection. Our results display the species and antibiotic resistance of bloodstream infection pathogens. In addition, we built a simple and useful prediction model which can provide good help for clinicians.

Implication of all the available evidence

The nomogram based on the combination of seven simplified factors can be conveniently used to predicted bloodstream infection in moderately severe and severe acute pancreatitis.

1. Introduction

Acute pancreatitis (AP) is the most common gastrointestinal disease that needs acute admission to hospital.[1] According to the revised Atlanta classification of AP,[2] approximately 20% of AP patients develops moderately severe acute pancreatitis (MSAP) or severe acute pancreatitis (SAP).[3] However, they have a substantial mortality rate of 20–40%.[4,5] Local and systemic injury is the characteristic of MSAP and SAP. The systemic injury usually causes by systemic inflammation which manifests as the systemic inflammatory response syndrome (SIRS). Compensatory anti-inflammatory response syndrome (CARS) as compensator followed SIRS that may contribute to an increased risk of infection.[2] However, routine use of antibiotic prophylaxis is not recommended.[6] Because several studies show that prophylactic antibiotics could not reduce mortality and infectious complications.[7,8] AP patients need to be treated with antibiotics when a clear infection was identified.[9] Thus, early and accurate identification of infection will avoid the abuse of antibiotics and give useful treatment early.

In previous research, necrosis infections have attracted the most attention to infection complications. However, a recent study shows that bloodstream infection (BSI) was the most frequent infectious complication in SAP.[10] In addition, sepsis is the most common systemic inflammation cause of organ failure (OF).[11] Thus, early identified and intervened BSI is vital to the management of MSAP and SAP. Nevertheless, previous studies focus on infection in AP usually have a small sample and the pathogenic spectrum of BSI are varies.[10,12] Therefore, the first aim of this study was to analyze the pathogens spectrum and antimicrobial resistance of BSI. The second aim was to develop and validate a prediction model for bloodstream infection in moderately severe and severe acute pancreatitis patients.

2. Methods

2.1. Study design and patients

Medical records of patients who were diagnosed as MSAP or SAP in West China Hospital from January 2012 to December 2018 were collected. The inclusion criteria were: 1. Diagnosed as AP; 2. Classified as MSAP or SAP. Patients with the following criteria were excluded: 1. Have a pancreatic tumor; 2. Age under 18 years old; 2. Pregnancy; 4. Have an infection in other sites including intra-abdominal infectious diseases, pneumonia, urinary tract infections alone, or other site infection time early than blood infection; 6. Any data missing. The Ethics Committee of West China Hospital approved the study (No. 2021-675) and it was conducted following the declaration of Helsinki. Informed consent of patients was waived.

2.2. Data collection：

Following variables were collected: sex, age, drink, smoking, hypertension, diabetes, respiratory failure, renal failure, cardiovascular failure, intensive care unit (ICU) stay, platelet, white blood cell (WBC), percentage of neutrophil (NEU%), percentage of lymphocyte (LYM%), percentage of eosinophil (EOS%), percentage of basophil (BAS%), total bilirubin (TB), alanine aminotransferase (ALT), albumin (ALB), creatinine (Cr), aspartate aminotransferase (AST), alkaline phosphatase (ALP), creatine kinase (CK), triglyceride (TG), total cholesterol (TG), calcium (Ca), high-density

lipoprotein (HDL), low-density lipoprotein (LDL), sodium (Na), potassium (K). Retest blood variables were shown on average. In BSI group, blood variables were shown as average values before 7 days of the blood infection onset. The data of bloodstream infection onset was defined as the first time positive culture blood sample collection date.

2.3. Definitions

According to the classification of acute pancreatitis 2012[2], acute pancreatitis diagnosis needs two of the following three features: (1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back); (2) serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal; and (3) characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT) and less commonly magnetic resonance imaging (MRI) or transabdominal ultrasonography. The severity of AP was defined according to the 2012 revised Atlanta classification.[2] Patients with persistent organ failure (>48 h) were classified as severe. And patients with transient organ failure (<48h) and/or local or systemic complications without persistent organ failure are classified as moderately severe. The BSI was definition as previously study.[13]

2.4. Statistical analysis

Continuous variables are described as mean (SD) and compared using the Wilcoxon rank-sum test. Categorical variables were expressed as count (%) and compared using the $\chi 2$ -test or Fisher's exact test. Statistical analysis was performed using the R software. (Version 3.6.1) A 2-sided P value <0.05 was considered statistically significant.

2.5 Prediction model development

In present study, 399 and 5778 patients were identified with or without BSI, respectively. Due to the extreme unbalance between the two groups, the undersampling method was performed.[14] 20% of NBSI patients were randomly selected. Finally, 1155 NBSI patients were selected to compare with 399 BSI patients. To reduce the risk of overfitting, the whole data set was randomly divided into the training set and validation set with a ratio of 7:3. Model development was based on the training set and model performance assessment was based on the validation set.

First, the least absolute shrinkage and selection operator (LASSO) regression with the "lambda.1se" criterion was used to select potential prognostic factors for BSI. The logistic regression was used to develop a nomogram. Random forest was used to validate the stable ability of prediction factors. Receiver operating characteristic (ROC) curves and calibration curves were used to evaluate prediction performance. ROC curves were calculated to estimate the discrimination of the prediction model. Calibration curves were plotted to evaluate the consistency between predicted BSI probability and actual BSI proportion. Value of 1 and 0.5 indicates perfect discrimination and no discrimination respectively.

2.6. Role of the funding source.

This study has received funding from This work was supported by the 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University

(ZYJC18027); Sichuan Science and Technology Program (2020YFS0263); and Sichuan Science and Technology Program (2021YFS0234). The funder Mao Li and Weiming Hu had a role in the collection and assembly of the data, development of the methodology, data analysis and interpretation, and manuscript writing.

3. Results

3.1 Patients clinical characteristics

In this study, 8213 MSAP and SAP patients were first identified from West China Hospital during seven years. 2036 patients were excluded for variables reasons. The flow chart was shown in Figure 1. During the 6177 patients, 399 of them (6.5%) were diagnosed with a bloodstream infection and 5778 patients without a bloodstream infection. Undersampling was used to randomly select 20% of NBSI patients. Finally, 1155 NBSI patients (74.3%) and 399 (25.7%) BSI patients were included in this study. Table 1 shows the characteristics and clinical features of the BSI and NBSI patients.

The age of NBSI was significantly lower than in the BSI group (P<0.001). Sex （P=0.767）, drinking (P=0.834), smoking (P=0.088), hypertension (P=0.163), and diabetes (P=0.05) have no difference between the two groups. Organ failure like respiratory failure (P<0.001), renal failure (P<0.001), and cardiovascular failure (P<0.001) in the NBSI group are all less than the BSI group. The rate of ICU stay in the BSI group (59.4%) is significantly higher than the NBSI group (10.3%) (P<0.001). The blood index like ALT, ALP, and Na have no difference between the two groups. Others blood variables are significantly different between the two groups.

3.2 Pathogens of BSI patients

In total, 408 pathogens from 399 blood samples were isolated. Details of microbiology distribution were displayed in Table 2. Of these, 226 (55.39%) were gram-negative bacteria, 116 (28.43%) were gram-positive bacteria, while the other 66 (16.18%) were fungi. Klebsiella pneumonia, Escherichia coli, and Acinetobacter baumannii were the top three gram-negative bacteria. Enterococcus faecium, Staphylococcus epidermidis, and Staphylococcus hominis accounted for the main gram-positive bacteria. Candida albicans, Candida tropicalis, and Candida glabrata are the majority fungi. Figure 2 shows the antibiotic resistance of gram-negative. Klebsiella pneumoniae and Escherichia coli both have the highest incidence of resistance to Ceftriaxone. For Acinetobacter baumannii and Enterobacter cloacae, Aztreonam and Cefotetan is the first resistance antibiotic, respectively. Figure 3 shows the antibiotic resistance of gram-positive bacteria. Ciprofloxacin is the top one resistance drug of Enterococcus faecium and Staphylococcus epidermidis. Oxacillin and Penicillin G have the highest incidence in Staphylococcus hominis and Staphylococcus aureus antibiotic resistance.

3.3 Identification and validation predictive factors for bloodstream infection.

3.3.1 Variable selection using the LASSO regression model

The data were randomly divided into the training set and validation t set with a ratio of 7:3. The characteristics of patients in the training and validation sets were displayed in Table Supplement 1. The LASSO regression model was used to select variables. Among the 31 features, seven variables with non-zero coefficients were selected as the risk factors to develop prediction models based on minimum criteria,

including ICU stay, cardiovascular failure, percentage of neutrophil, percentage of lymphocyte, albumin, triglyceride, and low-density lipoprotein (Figure Supplement 1).

3.3.2 Logistic regression development and validation prediction model.

The weight of variables in this model was calculated by the regression coefficient of the multivariate logistic regression model (Table 4).[15] A nomogram was developed on the seven variables (Figure 4). This nomogram in the training set had an AUC of 0.913, a sensitivity of 0.850, and a specificity of 0.860; the model in the validation set had an AUC of 0.888, a sensitivity of 0.765, and a specificity of 0.870 (Figure 5 AB). The nomogram calibration curves showed strong agreement between prediction and actual observation in both training and validation sets (Figure 5CD).

3.3.3 Random forest development and validation prediction model

The relationship between out-of-bag error and the number of trees were shown in figure Supplement 2A. In total, 100 trees are selected to establish a random forest model. Two methods rank the importance of variables (Figure Supplement 2B). ICU stay and cardiovascular failure were the most and least important variables in both Accuracy and Gini methods. Random forest in training had an AUC of 1.000, a sensitivity of 1.000, and a specificity of 1.000 (Figure Supplement 2C). And it in the validation set had an AUC of 0.886, a sensitivity of 0.882, and a specificity of 0.798 (Figure Supplement 2D). Calibration curves of random forest in training and validation sets were shown in Figure Supplement 2EF.

4. Discussion

MSAP and SAP patients have high morbidity. The infection in the bloodstream would accelerate the deterioration of the disease. In clinical, the results of blood culture have to wait several days. If the BSI could be confirmed early, patients could receive treatment early and avoid the abuse of antibiotics. In present study, we collected MSAP and SAP information in a large medical center in China. Analyze the pathogens spectrum of BSI and developed a novel prediction model for BSI in MSAP and SAP patients.

Infection complications in MSAP and SAP patients were the main cause of aggravation in the late phase of the disease and may lead to death due to uncontrollable infections.[10] BSI takes first place in infection complications.[10] The results of this study indicate that the incidence of BSI was 6.5% (399/6177) in MSAP and SAP patients. In this study, gram-negative bacteria were the main pathogens in bloodstream infection which is consistent with the previous study.[10] Among them, Klebsiella pneumonia was found to be the most common pathogen. MSAP and SAP patients sometimes need mechanical ventilation and urinary catheters. However, these conventional treatment measures were provided to be the risk factors of Klebsiella pneumonia.[16] And also, the study shows mechanical ventilation and nasogastric tube use were the risk factors of another gram-negative bacteria Acinetobacter baumannii.[17] Expect bacteria, fungi also the main pathogens of bloodstream infection. In present study, 16.18% of BSI pathogens are fungi. Among them, Candida albicans, an opportunistic infection pathogen, is the most common fungal. Immune system damage was thought to be the risk factor for opportunistic fungal infection.[18] In the

human body, gastrointestinal tract is the largest microecological reservoir. It is not only filled with bacteria but also the main reservoir for Candida albicans.[19] The intestinal bacterial translocation theory may explain the bacteria of normal gut flora were found in the bloodstream. In SAP patients, gut barrier would be damaged and leading to dysfunction.[20] That gives the chance to pathogens through the damaged barrier into the bloodstream. That may further lead to systemic endotoxemia.[21] For acute pancreatitis patients, the system inflammation may lead to the lung[22], kindy[23], and intestinal[24] injury. When the condition deteriorated, the occurrence of respiratory failure leads patients to receive mechanical ventilation or admit to ICU. ICU environment and various invasive operations all increasing the chance of bloodstream infection. That's why the pathogens isolated from ICU stay patients were usually related to the ICU exposure.[25,26]

AP as an inflammatory disease, inflammatory mediators has a critical role in its pathogenesis. Neutrophils, one of the main responders to acute inflammation, defense against bacteria, fungi, and so on pathogens in the host.[27] Previous studies have shown that neutrophils have a key role in AP development. They were recruited to the pancreas and lung during AP.[27] In addition, NET and oxygen free radicals produced by neutrophils were causing the organ injury.[28] That may be the reason for lung injury can be observed at an early stage.[29] The neutrophil-derived elastase could increase the permeability of intestinal mucosa, destroy the tissue, and lead to microecological imbalance. The clinical research found that neutrophils can predict AP severity and respiratory failure.[30] In recent, the neutrophil-lymphocyte ratio (NLR) has been considered as a predictive factor for AP.[31,32] When compared with other predictors, NLR performed best for predicting AP complications.[33] In present study, the NEU% and LYM% are both included in the prediction model. This further displays the importance of these cells in inflammation.

In the nomogram model, triglycerides have the biggest weight in seven consist variables. Study shows AP patients with severely high triglyceride is not rare in Asia.[34] And it was the second leading causing of AP.[35,36] Recently study suggested that increase serum triglyceride is associated with organ failure in AP.[37] In addition, LDL was thought to be a risk factor for SAP.[38,39] That relationship may owe to lipid metabolism have a directly linked to pancreatic exocrine function.[40] And also, serum lipid levels may correlate with nutritional status.[41,42] In infection patients, hypermetabolic state and undernutrition may lead to low plasma lipid concentrations.[43] Many immune responses and infection metabolic pathways participate in these alterations.[43]

The body condition of MSAP and SAP patients has a rapid progression. Thus, timely observation and intervention are necessary and beneficial to patients. For seven selected factors, most of them could be modifiable to a better value by clinical measurements. That could reduce the chance of bloodstream infection.

In a word, we collected MSAP and SAP information in a large medical center in China. Our results show that gram-negative bacteria is the most common pathogen of BSI in MSAP and SAP patients. ICU stay, cardiovascular failure, percentage of neutrophil, percentage of lymphocyte, albumin, triglyceride, and low-density lipoprotein were selected as the risk factors for BSI. A nomogram prediction model

with a high predictive value was built. It can be conveniently used to predict BSI development and help clinicians rationally use antibiotics in MSAP and SAP patients.

However, this study has some limitations. First, the results of this study are only based on a single medical center. Thus, the results of this study should be validated from other medical centers or large prospective studies. Second, there are kinds of bloodstream infectious pathogens. However, subgroup analysis didn't perform in this study. Third, a potential bias may take place in this retrospective study.

Funding sources

This work was supported by the 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (ZYJC18027); Sichuan Science and Technology Program (2020YFS0263); and Sichuan Science and Technology Program (2021YFS0234).

Data sharing

Data are available from the corresponding author upon reasonable request.

Author contributions

Conception and design: Yong Liu and Huimin Lu;

Collection and assembly of the data: Chao Yue, Zongguang Zhou, and Weiming Hu;

Development of the methodology: Dujiang Yang, Huan Xu, and Mao Li;

Data analysis and interpretation: Dujiang Yang, Huan Xu, and Mao Li, Chao Yue, Zongguang Zhou, and Weiming Hu;

Manuscript writing: Dujiang Yang, Huan Xu, and Mao Li;

Manuscript revise: Yong Liu and Huimin Lu;

Final approval of the manuscript: All authors.

Declaration of Competing Interest

The authors declare no potential conflicts of interest.

Acknowledgements

No

REFERENCE:

1. Boxhoorn L, Voermans RP, Bouwense SA, et al. Acute pancreatitis. *Lancet* 2020; **396**(10252): 726-34.
2. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; **62**(1): 102-11.
3. van Dijk SM, Hallensleben NDL, van Santvoort HC, et al. Acute pancreatitis: recent advances through randomised trials. *Gut* 2017; **66**(11): 2024-32.
4. van Santvoort HC, Bakker OJ, Bollen TL, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology* 2011; **141**(4): 1254-63.
5. Schepers NJ, Bakker OJ, Besselink MG, et al. Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis. *Gut* 2019; **68**(6): 1044-51.
6. Shah AP, Mourad MM, Bramhall SR. Acute pancreatitis: current perspectives on diagnosis and management. *J Inflamm Res* 2018; **11**: 77-85.
7. Lim CL, Lee W, Liew YX, Tang SS, Chlebicki MP, Kwa AL. Role of antibiotic prophylaxis in necrotizing pancreatitis: a meta-analysis. *J Gastrointest Surg* 2015; **19**(3): 480-91.
8. Mandal AK, Chaudhary S, Shrestha B, et al. Efficacy of Prophylactic use of Ciprofloxacin and Metronidazole in Mild and Moderately Severe Acute Pancreatitis. *JNMA; journal of the Nepal Medical Association* 2017; **56**(206): 207-10.
9. Mourad MM, Evans R, Kalidindi V, Navaratnam R, Dvorkin L, Bramhall SR. Prophylactic antibiotics in acute pancreatitis: endless debate. *Ann R Coll Surg Engl* 2017; **99**(2): 107-12.
10. Tian H, Chen L, Wu X, et al. Infectious Complications in Severe Acute Pancreatitis: Pathogens, Drug Resistance, and Status of Nosocomial Infection in a University-Affiliated Teaching Hospital. *Dig Dis Sci* 2020; **65**(7): 2079-88.
11. Garg PK, Singh VP. Organ Failure Due to Systemic Injury in Acute Pancreatitis. *Gastroenterology* 2019; **156**(7): 2008-23.
12. Noor MT, Radhakrishna Y, Kochhar R, et al. Bacteriology of infection in severe acute pancreatitis. *Jop* 2011; **12**(1): 19-25.
13. Huerta LE, Rice TW. Pathologic Difference between Sepsis and Bloodstream Infections. *J Appl Lab Med* 2019; **3**(4): 654-63.
14. Liu XY, Wu J, Zhou ZH. Exploratory undersampling for class-imbalance learning. *IEEE transactions on systems, man, and cybernetics Part B, Cybernetics : a publication of the IEEE Systems, Man, and Cybernetics Society* 2009; **39**(2): 539-50.
15. Royston P, Moons KG, Altman DG, Vergouwe Y. Prognosis and prognostic research: Developing a prognostic model. *Bmj* 2009; **338**: b604.
16. Song F, Zhang K, Huang J, et al. Clinical Characteristics, Risk Factors, and Outcomes of Patients with Polymicrobial Klebsiella pneumoniae Bloodstream Infections. *BioMed research international* 2021; **2021**: 6619911-.
17. Zhou HY, Yuan Z, Du YP. Prior use of four invasive procedures increases the risk of Acinetobacter baumannii nosocomial bacteremia among patients in intensive care units: a systematic review and meta-analysis. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases* 2014; **22**: 25-30.
18. Zhao XW, Yan L, Xu D, et al. Enterogenous infection of Candida albicans in immunocompromised rats under severe acute pancreatitis. *World J Emerg Med* 2016; **7**(4): 294-9.
19. Nucci M, Anaissie E. Revisiting the source of candidemia: skin or gut? *Clinical infectious diseases :*

an official publication of the Infectious Diseases Society of America 2001; **33**(12): 1959-67.

20. Tian R, Tan JT, Wang RL, Xie H, Qian YB, Yu KL. The role of intestinal mucosa oxidative stress in gut barrier dysfunction of severe acute pancreatitis. *European review for medical and pharmacological sciences* 2013; **17**(3): 349-55.

21. Liu J, Huang L, Luo M, Xia X. Bacterial translocation in acute pancreatitis. *Critical reviews in microbiology* 2019; **45**(5-6): 539-47.

22. Zhou J, Huang Z, Lin N, et al. Abdominal paracentesis drainage protects rats against severe acute pancreatitis-associated lung injury by reducing the mobilization of intestinal XDH/XOD. *Free radical biology & medicine* 2016; **99**: 374-84.

23. Wajda J, Dumnicka P, Maraj M, Ceranowicz P, Kuźniewski M, Kuśnierz-Cabala B. Potential Prognostic Markers of Acute Kidney Injury in the Early Phase of Acute Pancreatitis. *International journal of molecular sciences* 2019; **20**(15).

24. Zhou X, Wang W, Wang C, et al. DPP4 Inhibitor Attenuates Severe Acute Pancreatitis-Associated Intestinal Inflammation via Nrf2 Signaling. *Oxidative medicine and cellular longevity* 2019; **2019**: 6181754.

25. Li Y, Shen H, Zhu C, Yu Y. Carbapenem-Resistant Klebsiella pneumoniae Infections among ICU Admission Patients in Central China: Prevalence and Prediction Model. *Biomed Res Int* 2019; **2019**: 9767313.

26. Zheng B, Dai Y, Liu Y, et al. Molecular Epidemiology and Risk Factors of Carbapenem-Resistant Klebsiella pneumoniae Infections in Eastern China. *Frontiers in microbiology* 2017; **8**: 1061.

27. Wan J, Ren Y, Yang X, Li X, Xia L, Lu N. The Role of Neutrophils and Neutrophil Extracellular Traps in Acute Pancreatitis. *Front Cell Dev Biol* 2020; **8**: 565758.

28. Feddersen CO, Willemer S, Karges W, Püchner A, Adler G, Wichert PV. Lung injury in acute experimental pancreatitis in rats. II. Functional studies. *International journal of pancreatology : official journal of the International Association of Pancreatology* 1991; **8**(4): 323-31.

29. Zhou MT, Chen CS, Chen BC, Zhang QY, Andersson R. Acute lung injury and ARDS in acute pancreatitis: mechanisms and potential intervention. *World J Gastroenterol* 2010; **16**(17): 2094-9.

30. Novovic S, Andersen AM, Nord M, et al. Activity of neutrophil elastase reflects the progression of acute pancreatitis. *Scandinavian journal of clinical and laboratory investigation* 2013; **73**(6): 485-93.

31. Liu G, Tao J, Zhu Z, Wang W. The early prognostic value of inflammatory markers in patients with acute pancreatitis. *Clin Res Hepatol Gastroenterol* 2019; **43**(3): 330-7.

32. Abaylı B, Gençdal G, Değirmencioğlu Ş. Correlation between neutrophil/lymphocyte ratio and Ranson score in acute pancreatitis. *Journal of clinical laboratory analysis* 2018; **32**(6): e22437.

33. Junare PR, Debnath P, Nair S, et al. Complete hemogram: simple and cost-effective in staging and predicting outcome in acute pancreatitis. *Wien Klin Wochenschr* 2021; **133**(13-14): 661-8.

34. Jo SI, Chang JH, Kim TH, Kim CW, Kim JK, Han SW. Subsets associated with developing acute pancreatitis in patients with severe hypertriglyceridemia and the severity of pancreatitis. *Pancreatology* 2019; **19**(6): 795-800.

35. Yin G, Cang X, Yu G, et al. Different Clinical Presentations of Hyperlipidemic Acute Pancreatitis: A Retrospective Study. *Pancreas* 2015; **44**(7): 1105-10.

36. Jin M, Bai X, Chen X, et al. A 16-year trend of etiology in acute pancreatitis: The increasing proportion of hypertriglyceridemia-associated acute pancreatitis and its adverse effect on prognosis. *J Clin Lipidol* 2019; **13**(6): 947-53.e1.

37. Nawaz H, Koutroumpakis E, Easler J, et al. Elevated serum triglycerides are independently

associated with persistent organ failure in acute pancreatitis. *The American journal of gastroenterology* 2015; **110**(10): 1497-503.

38. Hong W, Zimmer V, Stock S, Zippi M, Omoshoro-Jones JA, Zhou M. Relationship between low-density lipoprotein cholesterol and severe acute pancreatitis ("the lipid paradox"). *Ther Clin Risk Manag* 2018; **14**: 981-9.

39. Khan J, Nordback I, Sand J. Serum lipid levels are associated with the severity of acute pancreatitis. *Digestion* 2013; **87**(4): 223-8.

40. Wu Q, Zhong X, Fu M, et al. High-density lipoprotein cholesterol to low-density lipoprotein cholesterol ratio in early assessment of disease severity and outcome in patients with acute pancreatitis admitted to the ICU. *BMC Gastroenterol* 2020; **20**(1): 164.

41. You S, Zhong C, Xu J, et al. LDL-C/HDL-C ratio and risk of all-cause mortality in patients with intracerebral hemorrhage. *Neurol Res* 2016; **38**(10): 903-8.

42. Sharif S, van der Graaf Y, Nathoe HM, de Valk HW, Visseren FL, Westerink J. HDL Cholesterol as a Residual Risk Factor for Vascular Events and All-Cause Mortality in Patients With Type 2 Diabetes. *Diabetes care* 2016; **39**(8): 1424-30.

43. Trinder M, Boyd JH, Brunham LR. Molecular regulation of plasma lipid levels during systemic inflammation and sepsis. *Curr Opin Lipidol* 2019; **30**(2): 108-16.

Figure legends

Figure 1. Flow chart of this study.

Figure 2. Antimicrobial resistance of the four main gram-negative bacteria.

A: Klebsiella pneumoniae;

B: Escherichia coli;

C: Acinetobacter baumannii;

D: Enterobacter cloacae.

Figure 3. Antimicrobial resistance of the four main gram-positive bacteria.

A: Enterococcus faecium;

B: Staphylococcus epidermidis;

C: Staphylococcus hominis;

D: Staphylococcus aureus.

Figure 4. Nomogram to predict bloodstream infection.

CF: cardiovascular failure; NEU%: percentage of neutrophil; LYM%: percentage of lymphocyte; ALB: albumin; TG: triglyceride; LDL: low-density lipoprotein.

Figure 5. Performance of the logistic regression algorithm in bloodstream prediction.

A: Receiver-operating characteristic curve in the training set;

B: Receiver-operating characteristic curve in the validation set;

C: Calibration curves in the training set;

D: Calibration curves in the validation set.

Supplement Figure legends

Figure Supplement 1. Selection of risk factors of bloodstream infection using the LASSO logistic regression algorithm.

Figure Supplement 2. Development and assessment of the random forest algorithm in bloodstream infection prediction.

A: Relationship between out-of-bag error and number of trees.

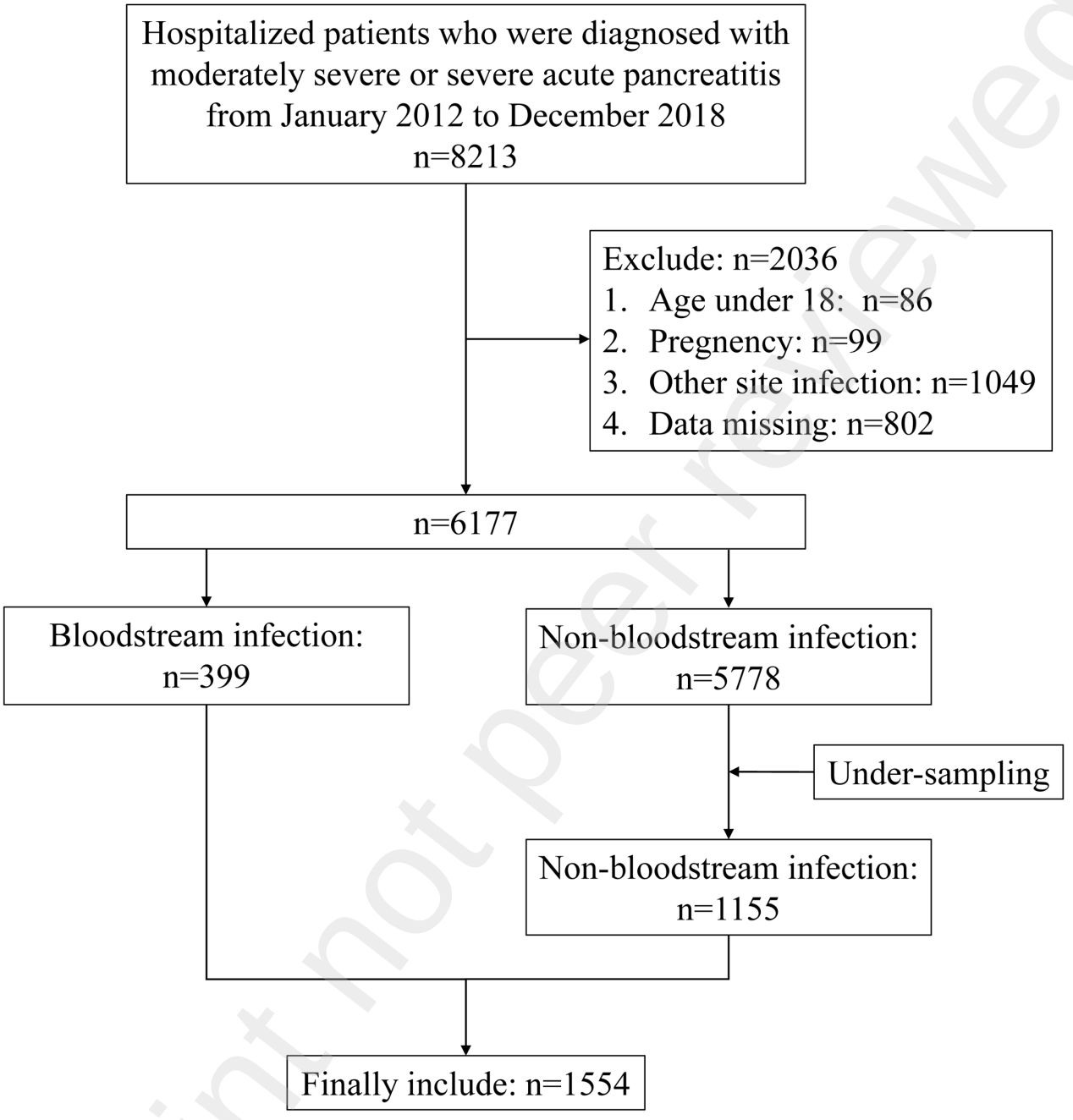
B: Feature importance;

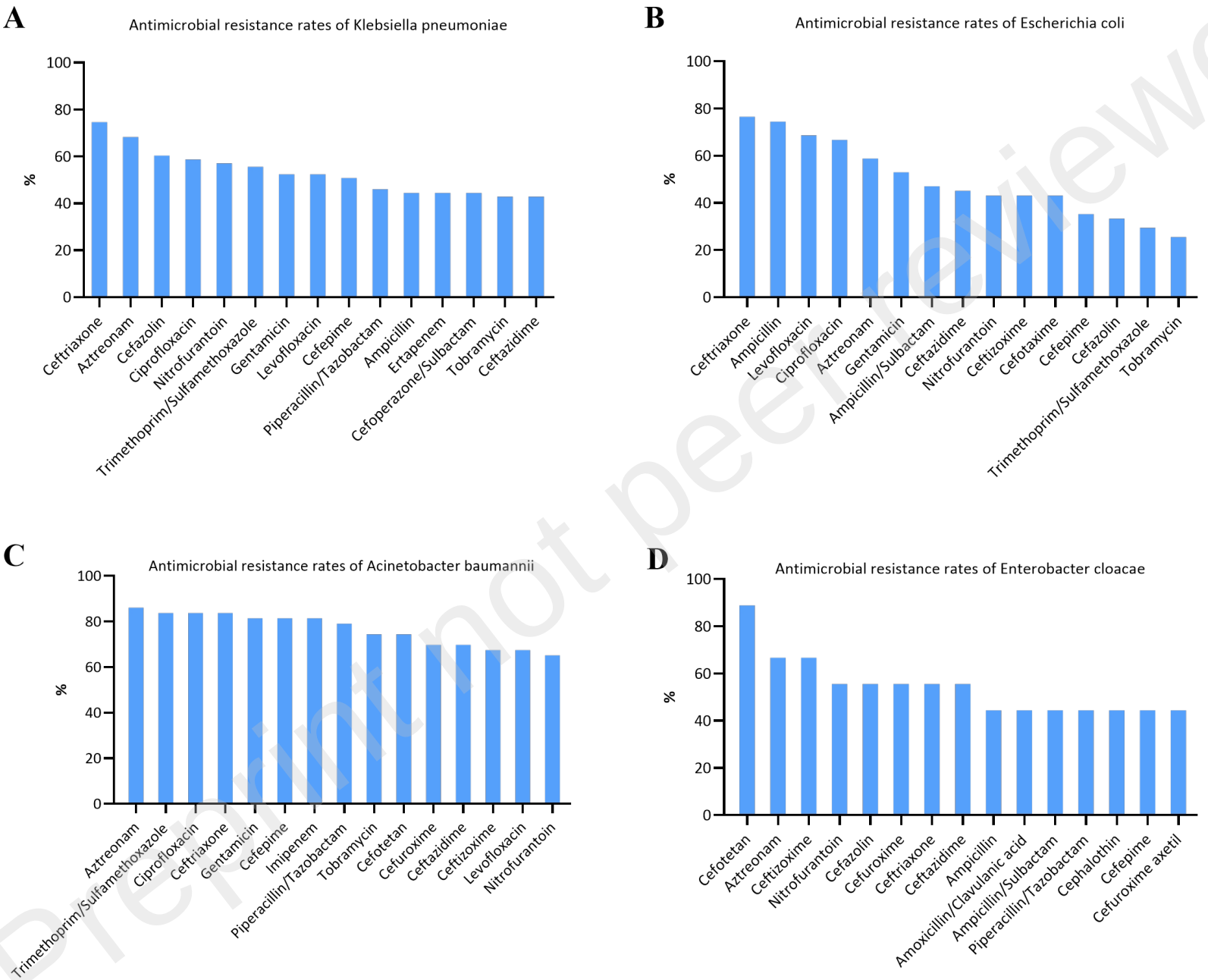
C: Receiver-operating characteristic curves in the training set;

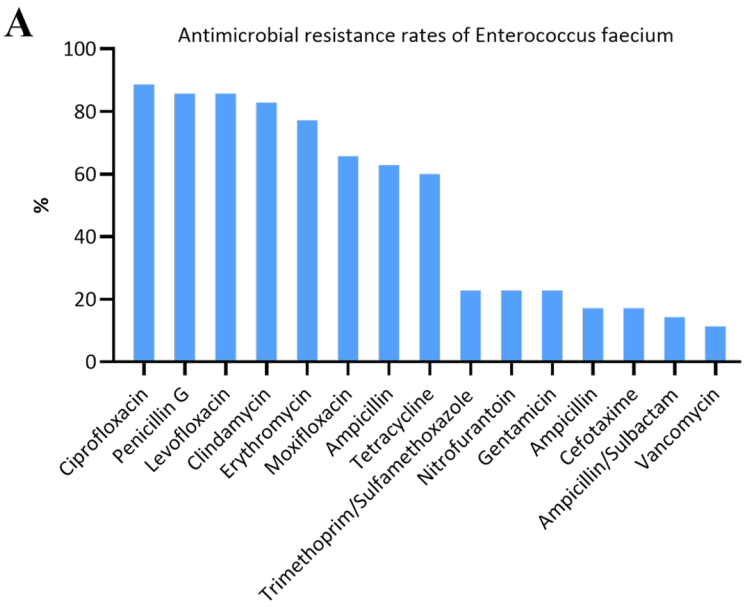
D: Receiver-operating characteristic curves in the validation set;

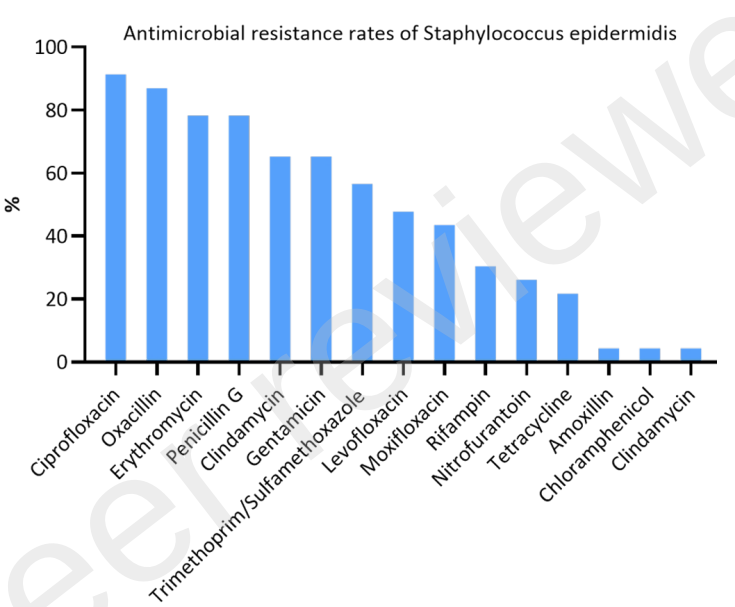
E: Calibration curves in the training set;

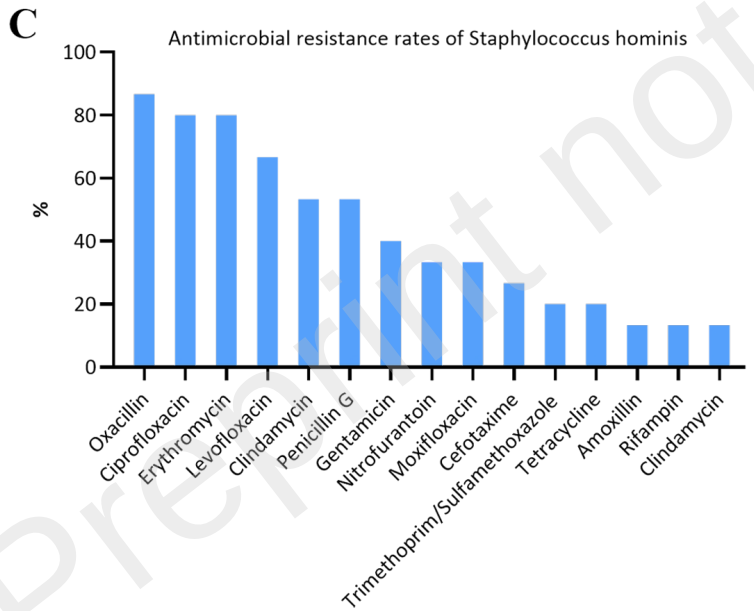
F: Calibration curves in the validation set.

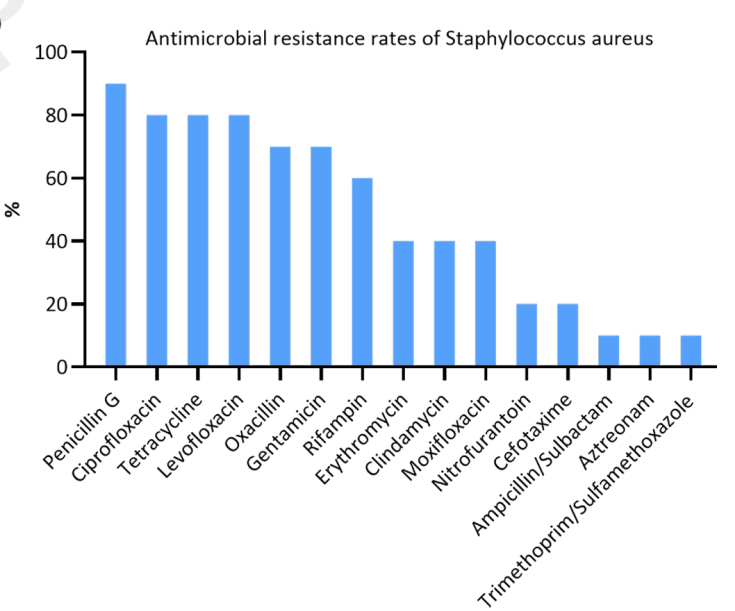


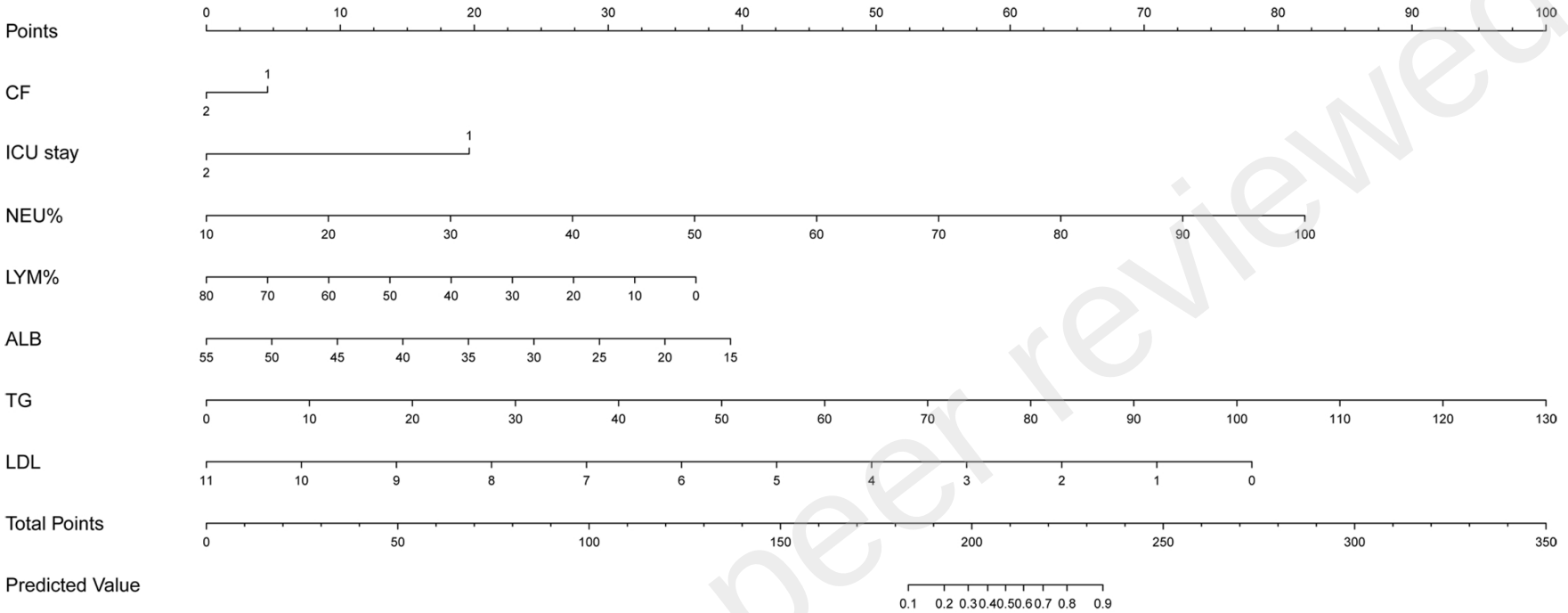


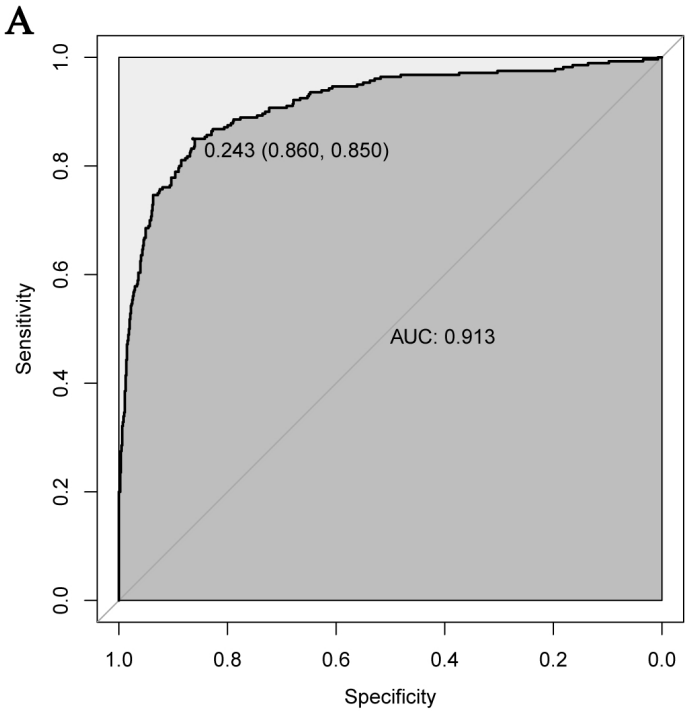


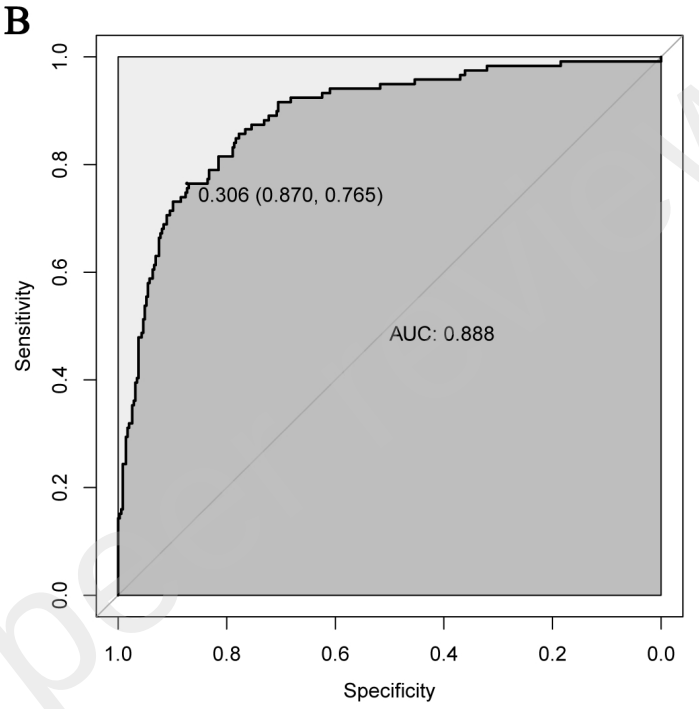


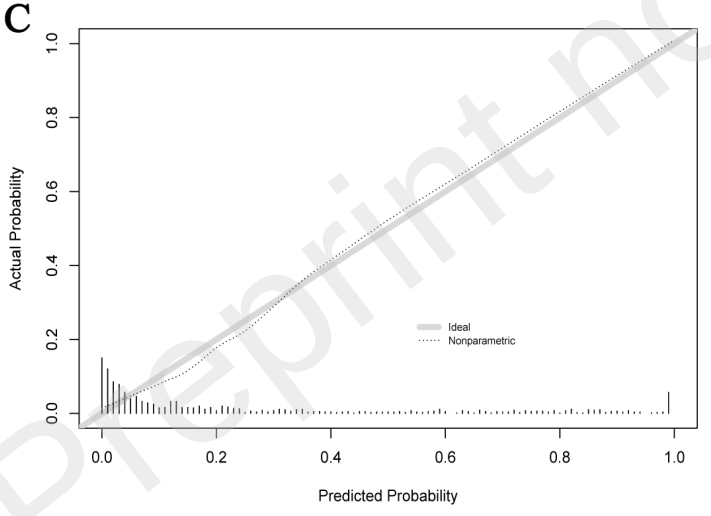


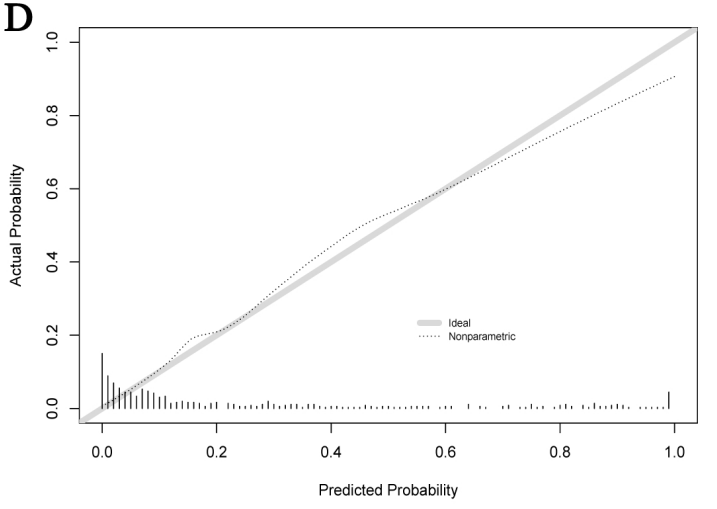


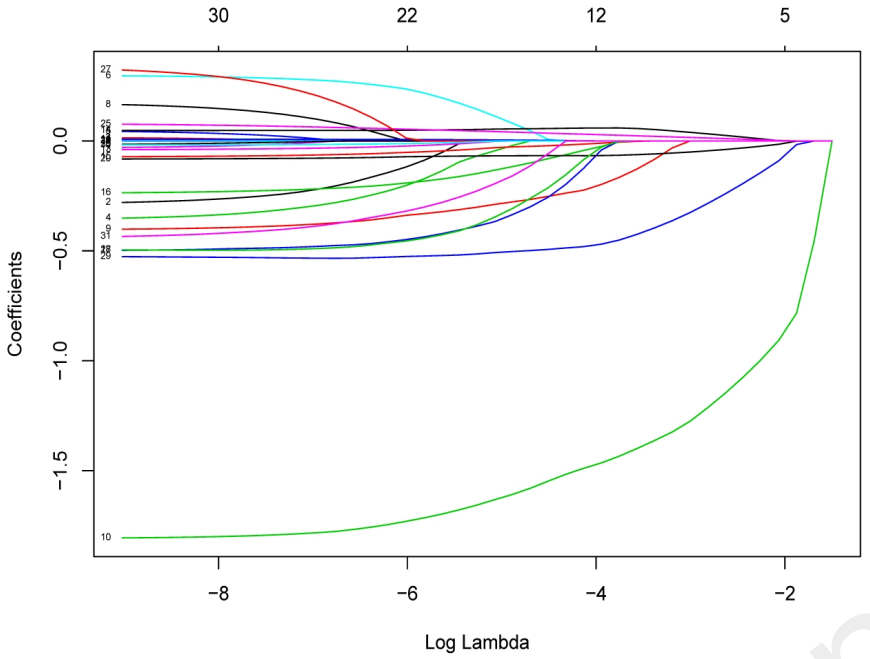




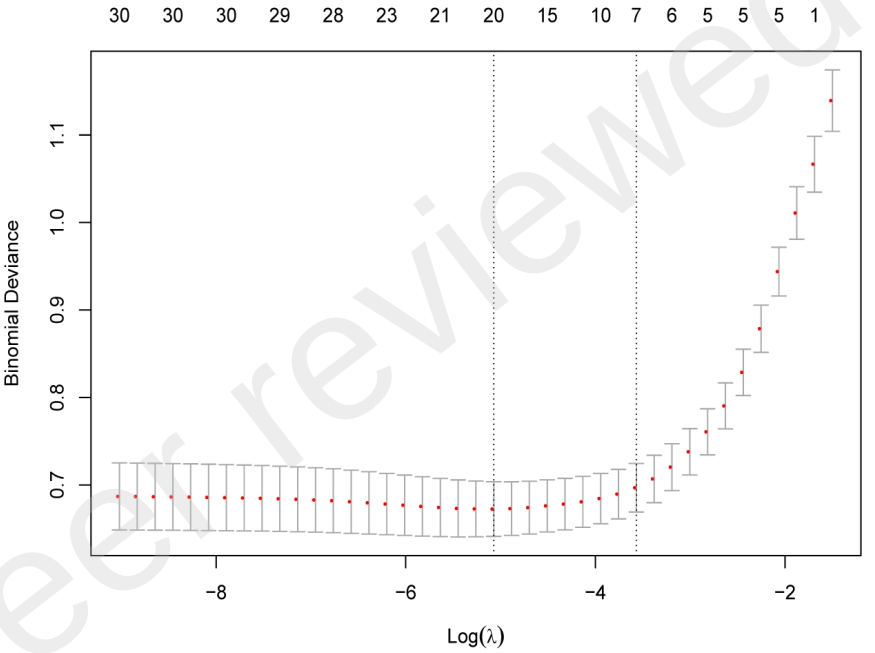




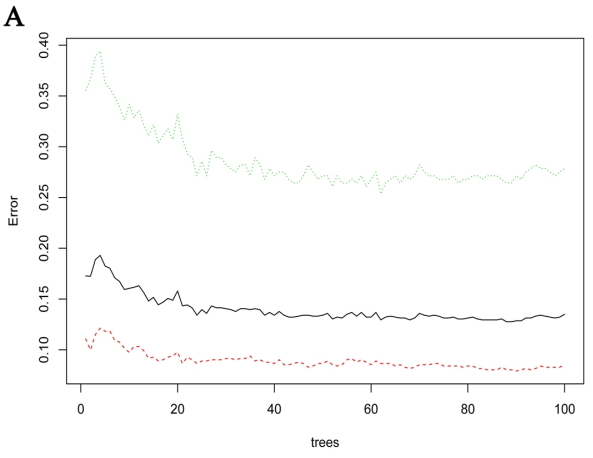


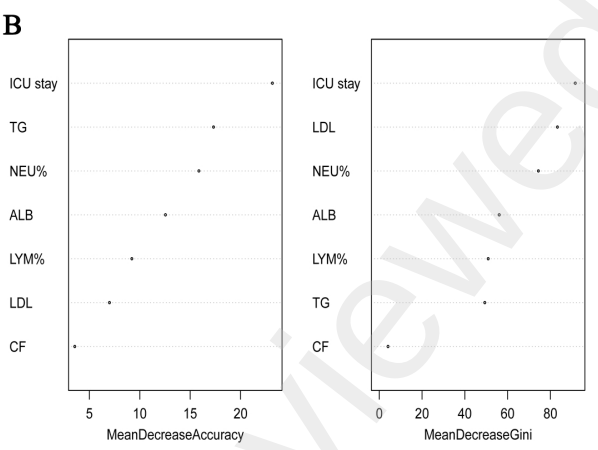


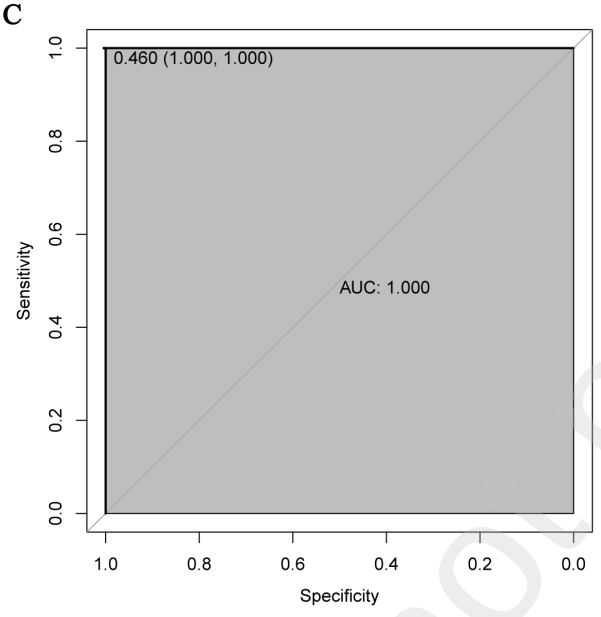
A

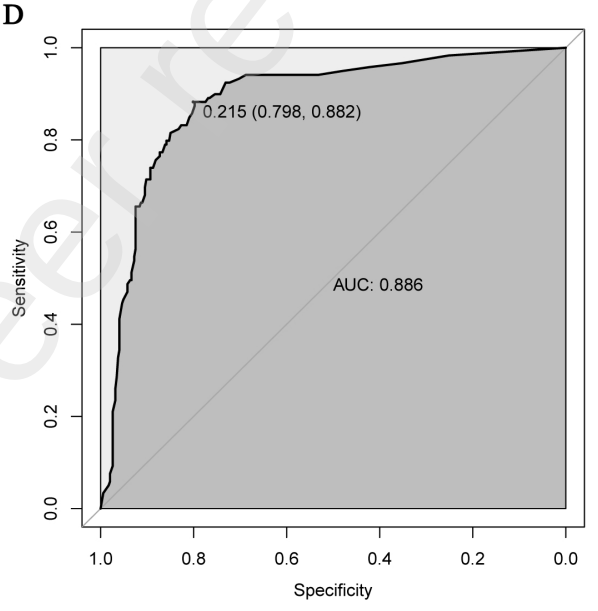


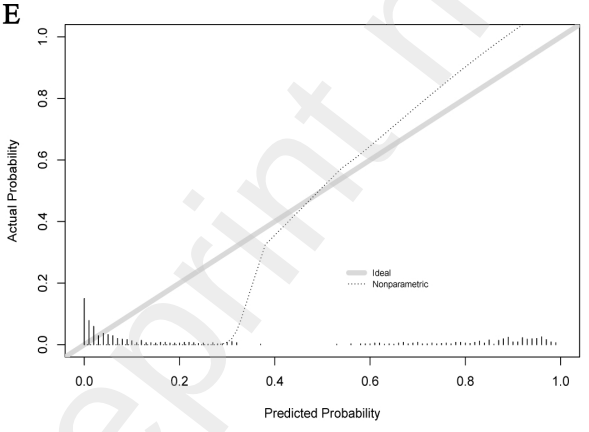
B











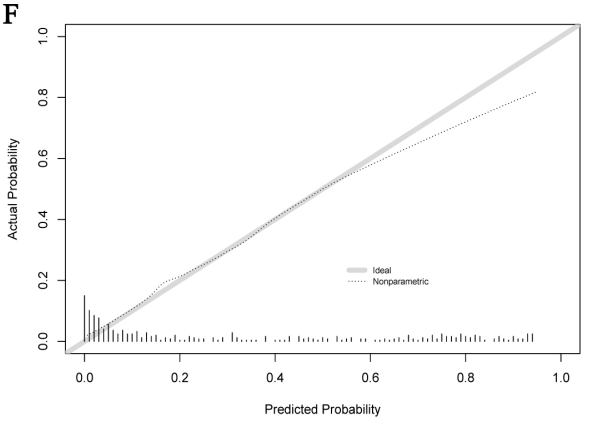


Table 1 Demographics and clinical characteristics of include patients.

Variables	BSI (N=399)	NBSI (N=1155)	P
Age	50.69 (15.03)	47.37 (13.55)	<0.001
Sex (Female)	148 (37.1)	440 (38.1)	0.767
Drinking	170 (42.6)	501 (43.4)	0.834
Smoking	159 (39.8)	519 (44.9)	0.088
Hypertension	87 (21.8)	213 (18.4)	0.163
Diabetes	68 (17.0)	252 (21.8)	0.05
Respiratory failure	313 (78.4)	392 (66.1)	<0.001
Renal failure	119 (29.8)	103 (8.9)	<0.001
Circulation failure	146 (36.6)	103 (8.9)	<0.001
ICU stay	237 (59.4)	119 (10.3)	<0.001
PLT	194.34 (114.60)	218.42 (97.69)	<0.001
WBC	13.20 (5.29)	10.94 (4.45)	<0.001
NEU%	83.92 (8.24)	76.12 (9.20)	<0.001
LYM%	8.96 (5.26)	15.11 (7.92)	<0.001
EOS%	0.83 (1.07)	1.69 (1.64)	<0.001
BAS%	0.22 (0.18)	0.35 (0.24)	<0.001
TB	36.09 (45.34)	22.92 (29.66)	<0.001
ALT	57.84 (114.35)	51.67 (88.63)	0.268
ALB	30.36 (4.55)	35.30 (4.73)	<0.001
Cr	127.75 (140.07)	81.05 (80.89)	<0.001
AST	97.95 (239.19)	54.25 (138.57)	<0.001
ALP	136.74 (153.04)	116.51 (95.68)	0.002
CK	390.80 (1024.68)	167.76 (837.66)	<0.001
TG	20.38 (39.01)	3.02 (2.60)	<0.001
TC	3.20 (2.10)	4.31 (1.80)	<0.001
Ca	1.93 (0.24)	2.08 (0.18)	<0.001
HDL	0.45 (0.30)	0.68 (0.29)	<0.001
LDL	1.05 (0.75)	2.01 (0.94)	<0.001
Na	139.29 (6.17)	138.41 (3.44)	<0.001
K	4.00 (0.44)	3.95 (0.37)	0.056

BSI: Bloodstream infection; NBSI: Non-bloodstream infection; ICU: Intensive care unit; PLT: Platelet; WBC: White blood cell; NEU%: Percentage of Neutrophil; LYM%: Percentage of Lymphocyte; EOS%: Percentage of eosinophil; BAS%: Percentage of Basophil; TB: Total bilirubin; ALT: Alanine aminotransferase; ALB: Albumin; Cr: Creatinine; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; CK: Creatine kinase; TG: Triglyceride; TC: Total cholesterol; Ca: Calcium; HDL: High density lipoprotein; LDL: Low density lipoprotein; Na: Sodium; K: Potassium.

Table 2 Microbiology distribution of the 408 pathogens from 399 patients with bloodstream infection.

Pathogens	Strains	Constituent ratio (%)
Gram-negative bacteria	226	55.39
Klebsiella pneumoniae	63	15.44
Escherichia coli	51	12.50
Acinetobacter baumannii	43	10.54
Enterobacter cloacae	9	2.21
Pseudomonas aeruginosa	9	2.21
Others	51	12.50
Gram-positive bacteria	116	28.43
Enterococcus faecium	35	8.58
Staphylococcus epidermidis	23	5.64
Staphylococcus hominis	15	3.68
Staphylococcus aureus	10	2.45
Staphylococcus haemolyticus	6	1.47
Others	27	6.62
Fungi	66	16.18
Candida albicans	25	6.13
Candida tropicalis	14	3.43
Candida glabrata	7	1.72
Candida parapsilosis	6	1.47
Yeast-like fungi	5	1.23
Others	9	2.21

Table 3 Risk factors for BSI in MSAP and SAP.

Variable	β	95% OR	P value
Circulation failure	-0.395	0.673 (0.44,1.031)	0.069
ICU stay	-1.698	0.183 (0.127,0.265)	<0.001
NEU%	0.079	1.082 (1.037,1.129)	<0.001
LYM%	-0.040	0.961 (0.908,1.018)	0.178
ALB	-0.085	0.919 (0.882,0.958)	<0.001
TG	0.067	1.069 (1.038,1.1)	<0.001
LDL	-0.614	0.541 (0.419,0.699)	<0.001

ICU: Intensive care unit; NEU%: Percentage of Neutrophil; LYM%: Percentage of Lymphocyte; ALB: Albumin; TG: Triglyceride; LDL: Low density lipoprotein.

Table 4 Receiver-operating characteristic curves at the optimal cut-off point according to different models

Models	AUC	Sensitivity	Specificity
Training set			
Logistic regression	0.913	0.850	0.860
Random forest	1.000	1.000	1.000
Validation set			
Logistic regression	0.888	0.765	0.870
Random forest	0.886	0.798	0.882

AUC: Area under receiver operating characteristic curve.

Table Supplement 1 Demographic and clinical characteristics of patients in training group.

	Training set			Validation set		
Variables	**BSI (N=280)**	**NBSI (N=809)**	**P**	**BSI (N=119)**	**NBSI (N=346)**	**P**
Age	49.99 (14.81)	47.31 (13.18)	0.005	52.34 (15.46)	47.52 (14.40)	0.002
Sex (Female)	100 (35.7)	310 (38.3)	0.482	48 (40.3)	130 (37.6)	0.67
Drinking	129 (46.1)	349 (43.1)	0.434	41 (34.5)	152 (43.9)	0.089
Smoking	116 (41.4)	364 (45.0)	0.334	43 (36.1)	155 (44.8)	0.123
Hypertension	60(21.4)	154 (19.0)	0.435	27(22.7)	59(17.1)	0.219
Diabetes	47 (16.8)	178(22.0)	0.076	21 (17.6)	74 (21.4)	0.459
Respiratory failure	224 (80.0)	266 (32.9)	<0.001	89 (74.8)	126 (36.4)	<0.001
Renal failure	84 (30.0)	69 (8.5)	<0.001	35 (29.4)	34 (9.8)	<0.001
Circulation failure	102 (36.4)	69 (8.5)	<0.001	44 (37.0)	34 (9.8)	<0.001
ICU stay	174 (62.1)	79 (9.8)	<0.001	63 (52.9)	40 (11.6)	<0.001
PLT	186.76 (102.21)	219.49 (100.09)	<0.001	212.17 (138.35)	215.93 (91.93)	0.738
WBC	12.90 (5.25)	10.87 (4.36)	<0.001	13.89 (5.33)	11.11 (4.66)	<0.001
NEU%	84.05 (7.79)	76.01 (9.06)	<0.001	83.59 (9.23)	76.38 (9.52)	<0.001
LYM%	9.11 (5.37)	15.12 (7.74)	<0.001	8.61 (5.01)	15.08 (8.34)	<0.001
EOS%	0.87 (1.15)	1.73 (1.56)	<0.001	0.74 (0.86)	1.61 (1.81)	<0.001
BAS%	0.22 (0.18)	0.36 (0.25)	<0.001	0.22 (0.16)	0.32 (0.21)	<0.001
TB	34.48 (39.73)	22.68 (26.90)	<0.001	39.86 (56.41)	23.50 (35.32)	<0.001
ALT	58.71 (122.57)	51.89 (96.96)	0.345	55.79 (92.58)	51.16 (65.27)	0.552
ALB	30.37 (4.58)	35.40 (4.69)	<0.001	30.34 (4.48)	35.08 (4.83)	<0.001
Cr	130.03 (149.98)	81.76 (85.04)	<0.001	122.39 (113.80)	79.39 (70.32)	<0.001
AST	96.46 (250.64)	53.35 (145.26)	0.001	101.44 (210.77)	56.37 (121.68)	0.005
ALP	137.78 (171.44)	116.14 (94.08)	0.009	134.28 (97.47)	117.39 (99.44)	0.109
CK	347.81 (623.30)	152.58 (619.78)	<0.001	491.97 (1614.96)	203.27 (1202.32)	0.04

TG	21.52 (39.98)	3.03 (2.60)	<0.001	17.70 (36.65)	2.99 (2.60)	<0.001
TC	3.20 (2.27)	4.33 (1.84)	<0.001	3.20 (1.64)	4.26 (1.72)	<0.001
Ca	1.92 (0.23)	2.09 (0.18)	<0.001	1.94 (0.27)	2.08 (0.18)	<0.001
HDL	0.46 (0.31)	0.68 (0.29)	<0.001	0.44 (0.29)	0.68 (0.29)	<0.001
LDL	1.05 (0.77)	2.02 (0.93)	<0.001	1.07 (0.71)	2.00 (0.96)	<0.001
Na	139.25 (5.76)	138.29 (3.37)	0.001	139.37 (7.05)	138.67 (3.57)	0.162
K	3.98 (0.44)	3.96 (0.36)	0.549	4.03 (0.42)	3.93 (0.38)	0.011

BSI: Bloodstream infection; NBSI: Non-bloodstream infection; ICU: Intensive care unit; PLT: Platelet; WBC: White blood cell; NEU%: Percentage of Neutrophil; LYM%: Percentage of Lymphocyte; EOS%: Percentage of eosinophil; BAS%: Percentage of Basophil; TB: Total bilirubin; ALT: Alanine aminotransferase; ALB: Albumin; Cr: Creatinine; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; CK: Creatine kinase; TG: Triglyceride; TC: Total cholesterol; Ca: Calcium; HDL: High density lipoprotein; LDL: Low density lipoprotein; Na: Sodium; K: Potassium.