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A Predictive Model for Disseminated Intravascular Coagulopathy in Sepsis: An Observational Study

Yaojie Fu[1,*], Yujing He[2,*], Caixia Zheng[3], Jianyong Zeng[3], Hongjie Ou[3]

[1]Emergency Department, The First Affiliated Hospital of Xiamen University, Xiamen, Fujian, People's Republic of China; [2]Intense Care Unit, The First Affiliated Hospital of Xiamen University, Xiamen, Fujian, People's Republic of China; [3]Department of Infectious Diseases, The First Affiliated Hospital of Xiamen University, Xiamen, Fujian, People's Republic of China

*These authors contributed equally to this work

Correspondence: Hongjie Ou, Department of Infectious Diseases, The First Affiliated Hospital of Xiamen University, No. 10, Shanggu Road, Xiamen, Fujian, 361001, People's Republic of China, Email ouhongjie@sina.com; Yujing He, Intense Care Unit, The First Affiliated Hospital of Xiamen University, No. 10, Shanggu Road, Xiamen, Fujian, 361001, People's Republic of China, Email heyujing1988@126.com

Introduction: Sepsis remains a significant global health challenge due to its high morbidity and mortality rates. Disseminated Intravascular Coagulopathy (DIC) represents a critical complication of sepsis, contributing to increased mortality and economic burden. Despite various prognostic scoring systems, there is a lack of a specific model for DIC prediction in sepsis patients.

Methods: This observational study included 336 sepsis patients. Clinical and laboratory data were collected, and prognoses were defined according to established criteria.

Results: We enrolled 336 patients, with 304 in the non-DIC group and 32 in the DIC group. Patients with DIC had notably lower platelet (PLT) and higher levels of prothrombin time (PT), lactate (LAC), and procalcitonin (PCT) compared to those without DIC. Univariate and multivariate analyses identified risk factors associated with the DIC, showing that PLT (OR = 0.985, 95% CI 0.978–0.993, $p < 0.001$), PT level (OR = 1.140, 95% CI 1.004–1.295, $p = 0.044$), and LAC (OR = 1.101, 95% CI 0.989–1.226, $p = 0.078$) were related factors. A risk model was established, and its sensitivity and specificity in predicting DIC among sepsis patients were assessed by comparing it to the SOFA score. The area under the ROC curve for the model was 0.850, while the SOFA score was 0.813. With a model score >−2.12, the sensitivity for predicting DIC was 84.4%, and the specificity was 75.0%.

Conclusion: Our study introduces a predictive model for DIC detection in sepsis patients, emphasizing the need for clinicians to focus on patients with high model scores for timely intervention.

Keywords: sepsis, risk model, disseminated intravascular coagulopathy, platelet, mortality

Introduction

Sepsis is a life-threatening syndrome arising from a dysregulated host response to infection and poses a substantial global health challenge due to its elevated morbidity and mortality rates.[1] Despite a declining trend in mortality, sepsis remains a leading cause of death in intensive care units, accounting for a significant portion of global mortality. In a survey conducted by the National Intensive Care Society of the United States in 2014, the worldwide prevalence of sepsis in intensive care units was approximately 29.5%, with a mortality rate of about 25.8%.[2,3] Notably, sepsis-related deaths contribute to nearly 20% of all global fatalities.[2–5]

Disseminated Intravascular Coagulopathy (DIC), a serious complication of sepsis, is an acquired clinical syndrome characterized by widespread activation of coagulation.[6,7] This activation leads to vascular fibrin deposition, organ dysfunction, depletion of coagulation factors and platelets, and life-threatening consequences such as bleeding. Recent studies indicate that septic shock occurs in approximately one-third of sepsis patients admitted to the intensive care unit (ICU), with over half of these patients developing DIC.[8] Accurately differentiating between DIC and non-DIC patients is crucial, as DIC is not a distinct disease but rather a spectrum of conditions resulting from coagulation disorders and coagulopathies. Consequently, establishing clear diagnostic boundaries poses a significant clinical challenge. Moreover,

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the efficacy of anticoagulant therapy has been linked to the severity of coagulopathy, underscoring the importance of patient stratification to ensure the administration of tailored treatments. In essence, the high mortality and economic burden associated with sepsis-related DIC emphasize the critical importance of early prevention, identification, diagnosis, and treatment.

While several critical illness scores, such as the Pitt bacteremia score (PITT score) score and Sequential Organ Failure Assessment (SOFA score) score, have been used to assess the prognosis of sepsis patients, a reliable model specifically for predicting the risk of DIC is still lacking.[9–11] Diagnosing DIC requires more than a single coagulation index. The ISTH and JAAM DIC scores are internationally recognized criteria, with the overt DIC diagnosed as ISTH ≥ 5 or JAAM ≥ 4.[12] The mortality rate for ISTH overt DIC is 46%, compared to 22% for JAAM DIC.[12,13] Both scoring systems help assess prognosis in trauma or sepsis patients. However, ISTH and JAAM DIC scores cannot identify all cases.[14] Relying solely on those criteria may overlook patients with poor outcomes.

This study aims to evaluate the risk factors, both clinical and laboratory, upon admission for predicting the occurrence of DIC in sepsis patients. The integration of these factors into a predictive model holds the potential for early DIC prediction in sepsis patients.

Methods

Study Population

This study complies with the Declaration of Helsinki and was approved by the Ethics Committee of The First Affiliated Hospital of Xiamen University (No. 2022-037). This observational retrospective study included 336 hospitalized patients diagnosed with sepsis according to Sepsis-3.0 criteria between August 2017 and September 2022.[15] Written consent was obtained from all patients upon admission. All participants were fully informed of the study's purpose and provided their consent prior to their participation. Inclusion criteria were for adult patients with a confirmed diagnosis of sepsis and complete clinical data necessary for analysis. Patients were excluded if 1) they had other known causes of DIC, 2) significant comorbid conditions that could impact coagulation, 3) were HIV antibody positive, 4) or were on anticoagulant therapy at the time of admission. Additionally, patients with incomplete or missing key clinical data were excluded from the study. Flow chart was shown in Supplementary Figure 1.

Prognosis Definition

In the study, the following prognostic definitions were used: 1) **DIC**: The diagnosis of DIC adheres to the overt-DIC criteria established by the International Society on Thrombosis and Haemostasis (ISTH).[16] 2) **ARDS**: ARDS was defined according to the American-European Consensus Conference (AECC) definition established in 1994, which includes the following criteria: a PaO2/FiO2 ratio ≤ 300 mm Hg (regardless of positive end-expiratory pressure level), the presence of bilateral infiltrates on a frontal chest radiograph, and a pulmonary artery wedge pressure ≤ 18 mm Hg when measured, or the absence of clinical evidence indicating left atrial hypertension.[17]

Biomarker Measurement Methods and Data Collection

Blood samples were collected and measured within 30 minutes using the Sysmex SE-9000 analyzer for blood routine examination and the Olympus AU5400 analyzer for biochemical examination. Data were extracted from the electronic medical records system, including demographic characteristics, the laboratory results on admission and treatment outcome. The outcome was defined as DIC and mortality.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation and compared with *t*-test. Categorical variables were expressed as frequency and percentage and compared with the chi-squared test. In all enrolled patients, univariate and multivariate logistic regression analyses were performed to determine independent risk factors, with results presented as odds ratio (OR) and 95% confidence interval (CI). A risk model was established based on the independent factors above, and model scores were compared between survivors and non-survivors for each cohort. All analyses were performed

using R or SPSS software version 13.0 (SPSS Inc., Chicago, IL, USA). A two tailed P-value < 0.05 was defined as statistically significant.

Results

Baseline Characteristics of Sepsis Patients with DIC

A total of 336 patients were enrolled in the study, with 304 in the non-DIC group and 32 in the DIC group. Demographic and laboratory characteristics on admission were compared between the two groups and shown in Table 1. Patients in the DIC group were significantly lower platelets (PLT) ($p < 0.001$). Moreover, prothrombin time (PT) levels ($p < 0.001$), lactate (LAC) levels (p=0.018), and procalcitonin (PCT) levels ($p = 0.018$) were higher in patient with DIC.

Univariate and Multivariate Analyses for DIC in Patients Enrolled

We conducted univariate and multivariate analyses to identify the risk factors associated with DIC in patients enrolled. Multivariate analysis showed that PLT (OR = 0.985, 95% CI 0.978–0.993, $p < 0.001$), PT level (OR = 1.140, 95% CI 1.004–1.295, $p = 0.044$) and LAC (OR = 1.101, 95% CI 0.989–1.226, $p = 0.078$) were independent predictors of DIC (Figure 1).

To further evaluate the results, we conducted lasso multivariable regression. The results were shown in Figure 2. A risk model was established using the above predictors and their regression coefficients, and the formula was shown as follows: Model score = −1.94407−0.01723*PLT+0.07092*PT+0.12144*LAC.

The Predictive Value of the Model for Diagnosing DIC in Sepsis Patients

We assessed the sensitivity and specificity of the model in predicting DIC among sepsis patients by comparing SOFA score. As shown in Figure 3A, the area under the curve for predicting DIC using the model score was 0.850. Correspondingly, the area

Table 1 Demographics and Clinical Characteristics of Patient with or without DIC

Characteristic	Non-DIC Group	DIC Group	P value
Sample size	304	32	–
Gender, male (%)	191 (62.8)	18 (56.3)	0.465
Age, year	62.16±16.98	58.00±16.96	0.189
BMI	22.96±4.04	22.71±4.01	0.742
WBC	14.05±8.73	13.39±9.37	0.685
PLT	182.94±115.18	67.75±63.44	<0.001
CRP	97.45±63.09	109.66±87.97	0.410
PCT	20.65±32.09	35.07±37.77	0.018
FIB	4.46±1.97	3.69±2.12	0.043
PT	15.41±3.49	18.05±3.89	<0.001
ALT	85.49±197.00	132.16±177.47	0.206
ALB	29.60±6.10	30.25±6.97	0.573
BUN	11.77±8.24	15.11±8.91	0.031
CRE	131.26±163.20	143.47±80.56	0.677
PaO2/FiO2	270.88±111.21	230.59±114.66	0.053
LAC	2.35±2.57	4.98±5.94	0.018
SBP	119.93±22.59	111.88±22.08	0.055
DBP	66.38±13.69	63.84±14.77	0.324
SOFA	7.22±3.70	12.09±4.00	<0.001

Abbreviations: ALB, albumin; BMI, Body-mass index; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell; PT, Prothrombin time; FIB, Fibrinogen; ALT, Alanine transaminase; BUN, Blood Urea Nitrogen; CRE, creatinine; LAC, Lactate; SBP, systolic blood pressure; DBP, Diastolic Blood Pressure.

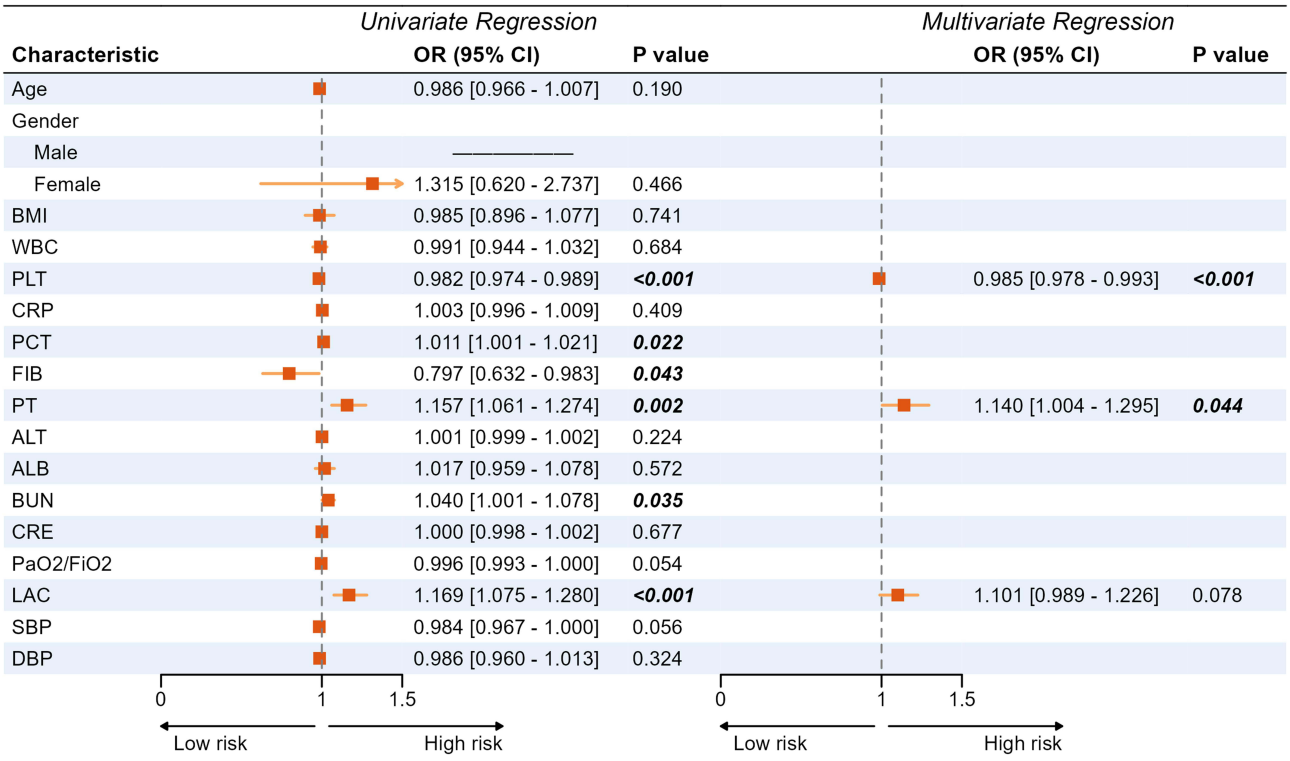

Figure 1 Univariate and multivariate analyses to identify the risk factors associated with DIC in patients enrolled. Univariate analysis reveals that PLT, PCT, FIB, PT, BUN and LAC were factors associated with DIC while multivariate analysis showed that PLT (OR=0.985, 95% CI 0.978–0.993, p<0.001), PT level (OR=1.140, 95% CI 1.004–1.295, p=0.044) and LAC (OR=1.101, 95% CI 0.989–1.226, p=0.078) were independent factors.

under the ROC curve for the SOFA score in predicting DIC is 0.813. With a model score > -2.12, the sensitivity for predicting DIC in sepsis patients was 84.4%, with a specificity of 75.0%.

We also analyzed the PR curve of both the model and the SOFA score for predicting DIC. The area under the PR curve for the SOFA score is 0.388. When using the equation to predict DIC, the area under the PR curve is 0.477, which is higher than that of the SOFA score (Figure 3B). To confirm the clinical validity of this equation, we also performed a calibration curve and a DCA curve, as shown in Figure 3C and D.

Differences in Model Scores Among Patients with Varying Prognoses

We conducted further analysis to evaluate model scores among patients with different prognoses. We used the model to predict ARDS and survival in patients with sepsis. Both the ROC and PR curves (Figure 4A and B) indicated that the model had no clinical significance for predicting ARDS. However, the model effectively predicted survival in sepsis patients, with an area below the ROC curve of 0.633 ($p < 0.001$). Despite this, the sensitivity and specificity need improvement for clinical application. Additionally, we performed a calibration curve and a DCA curve analysis (Figure 4C and D) to further verify the results.

Correlation Between Model Scores and Clinical Variables

We explored the association between model scores and clinical parameters. The results were shown in Figure 5A. We also performed dose–response analysis on three important clinical variables in the model -PLT, PT, and LAC- to evaluate their relationship with DIC, as shown in Figure 5B–D.

Relationship of Model Scores to Other Clinical Variables

We further analyzed differences in clinical indicators between high-risk and low-risk groups by cut-off value −2.12 (Table 2). Patients in the high-risk group exhibited unsurprised lower PLT ($p < 0.001$) and longer PT time ($P < 0.001$).

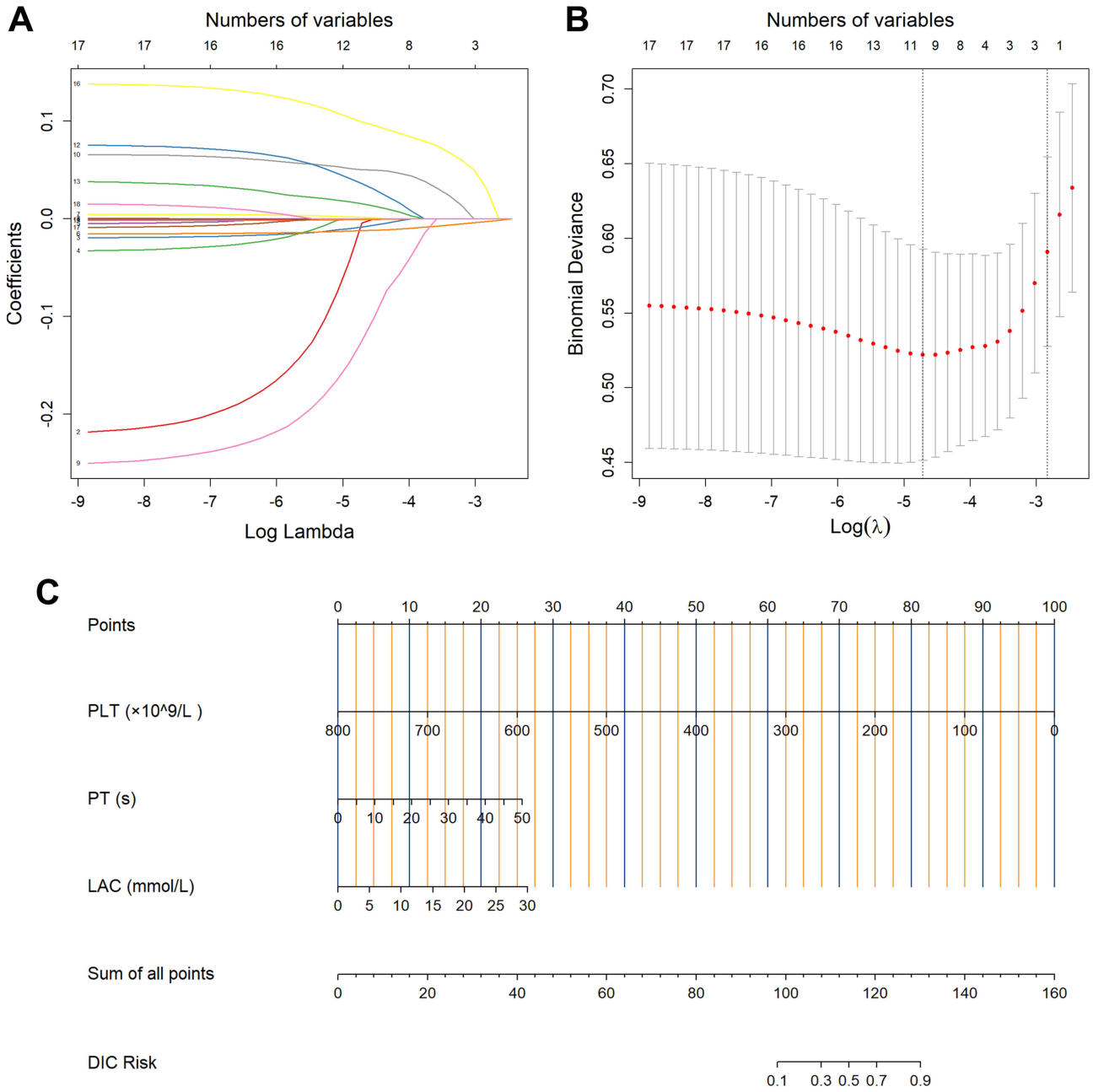

Figure 2 Lasso multivariate regression of DIC in sepsis patient and nomograph of model. (**A**) Lasso regression paths showing the relationship between Log Lambda and coefficient shrinkage. (**B**) Relationship between binomial deviance and Log Lambda. (**C**) Nomograph for predicting DIC risk, incorporating PLT, PT, and LAC levels.

But also, we observed that the high-risk group showed with higher PCT ($p < 0.001$), CRP ($P = 0.003$), elevated LAC level ($p < 0.001$), higher ALT levels ($P=0.009$), and elevated BUN levels ($p = 0.018$).

Discussion

In this study, we identified the risk factors for DIC in patients with sepsis. Furthermore, we developed a risk model based on these predictors and confirmed its ability to independently predict the occurrence of DIC.

DIC is characterized by systemic intravascular activation of coagulation due to various causes.[18] DIC can stem from multiple etiologies while exhibiting similar pathophysiological changes in coagulation system imbalance.[18] Therefore, it warrants further investigation of whether uniform diagnostic criteria should be applied irrespective of the underlying

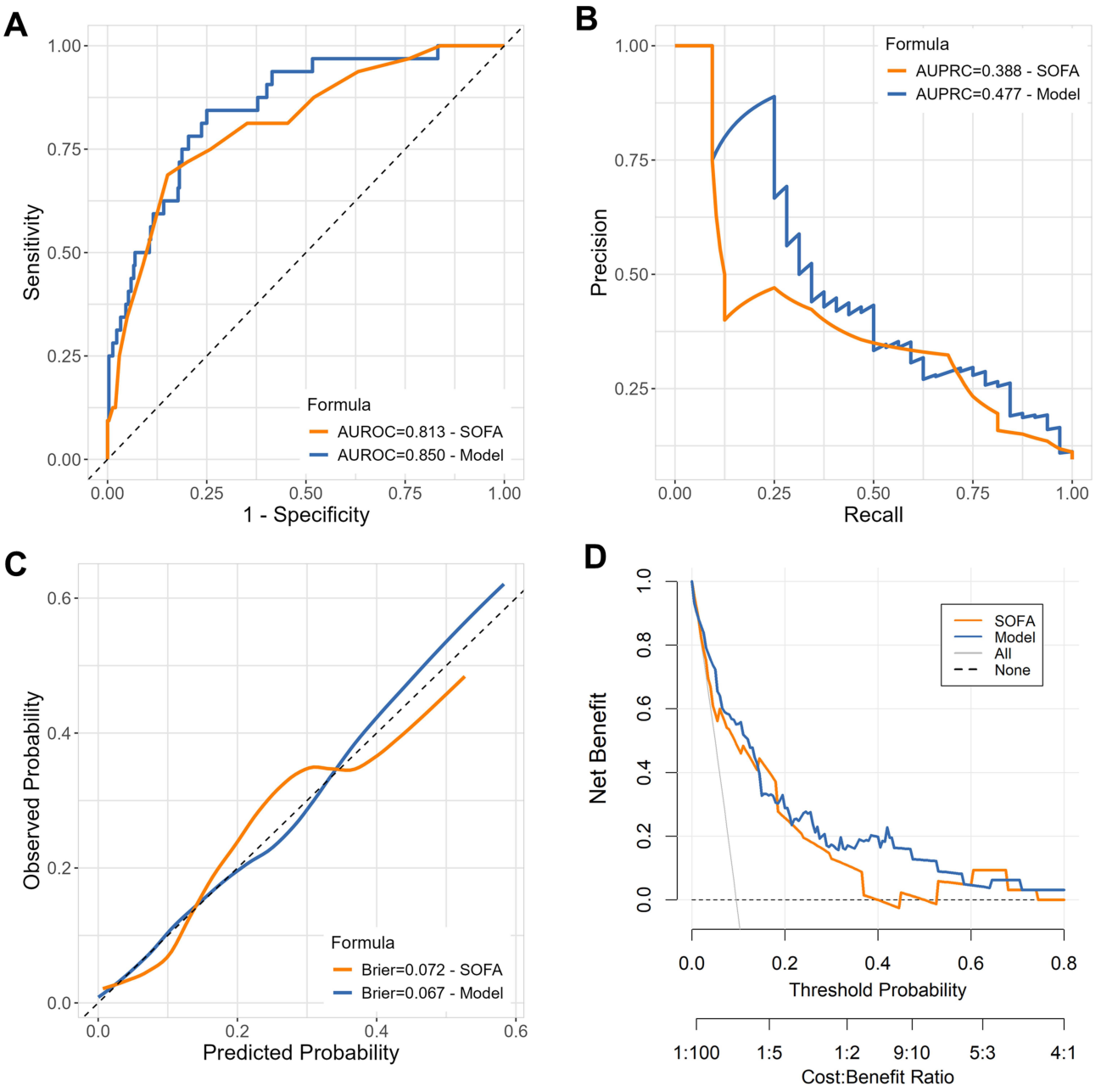

Figure 3 Performance of the equation in predicting sepsis prognosis. (**A**) The area under the ROC curve for the SOFA score in predicting DIC is 0.813. The area under the curve of model score was 0.850 to predict DIC. When a model score >−2.12, the sensitivity and specificity of predicting DIC was 84.4% and 75.0%. (**B**) PR curve of both the model and the SOFA score for predicting DIC. (**C**) Calibration curve of model score and SOFA score to predict DIC. (**D**) DCA curve of model score and SOFA score to predict DIC.

disease. Specifically, with advancements in understanding DIC pathophysiology, it has been observed that DIC induced by different underlying diseases manifests different characteristics. For instance, Sepsis associated with DIC is marked by excessive suppression of fibrinolysis arising from the overproduction of plasminogen activator inhibitor-1, as believed to be one of the host defense pathogen mechanisms.[19–22] In contrast, such mechanism is absent in DIC associated with hematological malignancies.[23–25] Consequently, the thrombotic phenotype of sepsis-associated DIC often presents with organ dysfunction, while the fibrinolytic phenotype of DIC commonly accompanies hematopoietic malignancies.[23–25]

Hence, developing individual diagnostic criteria based on the pathophysiological characteristics of DIC induced by diverse underlying diseases would be more persuasive.[26] Studies have previously proposed similar concepts, suggesting

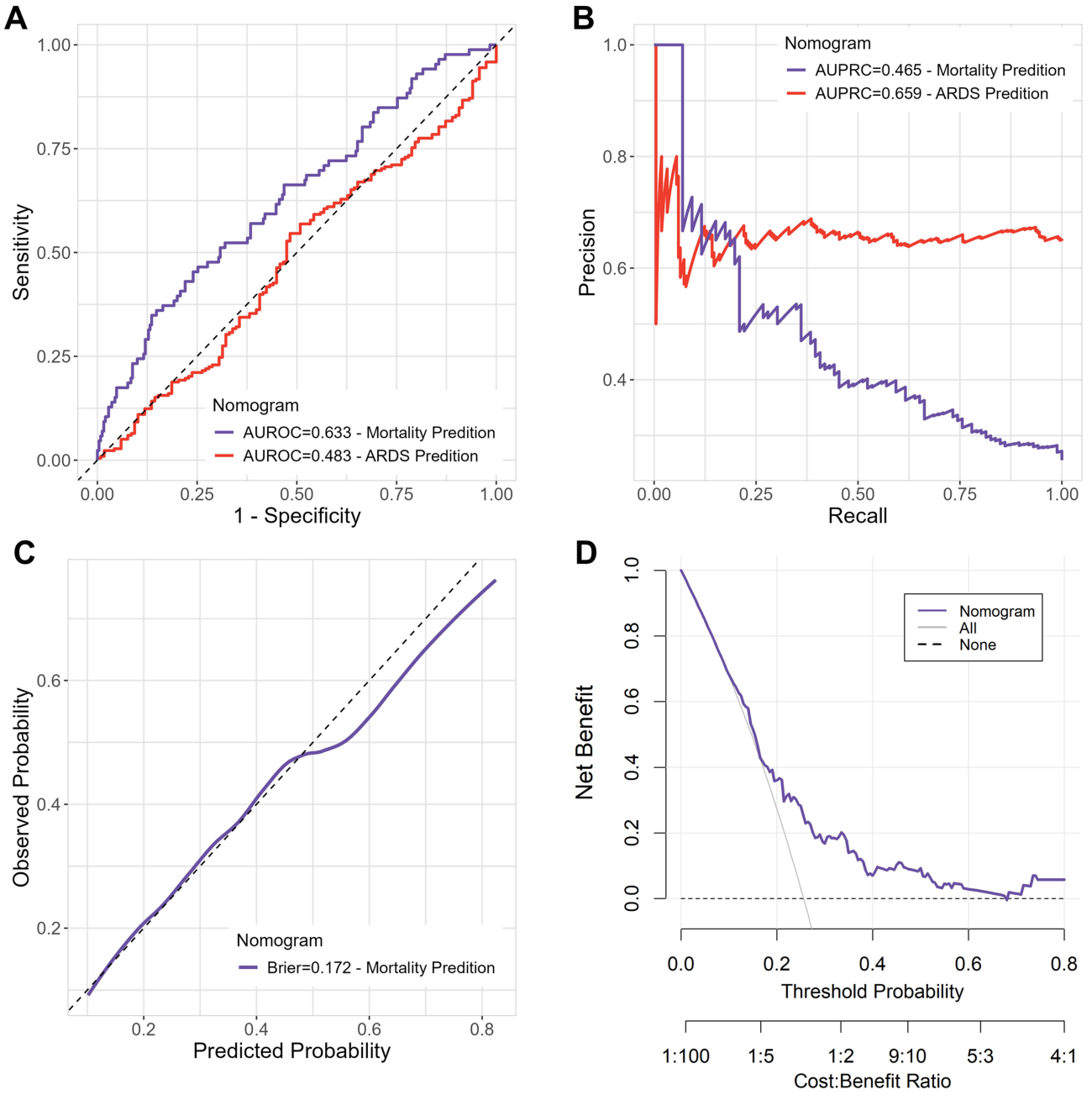

Figure 4 Differences in model scores among patients with varying prognoses. (**A**) Using model to predict ARDS and survival in patients with sepsis, the area under the ROC curve of 0.633 when predicting survival ($p<0.001$). (**B**) PR curve when using model to predict ARDS and survival. (**C**) Calibration curve analysis when using model to predict survival. (**D**) DCA curve analysis when using model to predict survival.

that sepsis-related DIC diagnosis maybe should rely on a system involving PLT count and PT levels.[27–30] Interestingly, among septic patients enrolled in this study, multivariate analysis also confirmed that PLT and PT levels are the only independent factors associated with DIC in sepsis. Based on the results, we further construct a novel sepsis-related DIC diagnostic model. Subsequent data analysis has proved the efficacy of the model in early prediction of DIC among sepsis patients, demonstrating its direct applicability in clinical settings. Notably, our findings also unveil the model's capability to predict survival. While acknowledging that further improvements in sensitivity and specificity are necessary for its full clinical integration, our results underscore its promising potential in enhancing sepsis patient care and outcomes.

The diagnostic approach to DIC has evolved over several stages. In 1980s, the JMHLW introduced the first DIC diagnostic-scoring system, which included clinical symptoms, PT, PLT, FDP, and FIB.[31] A score of more than seven indicated

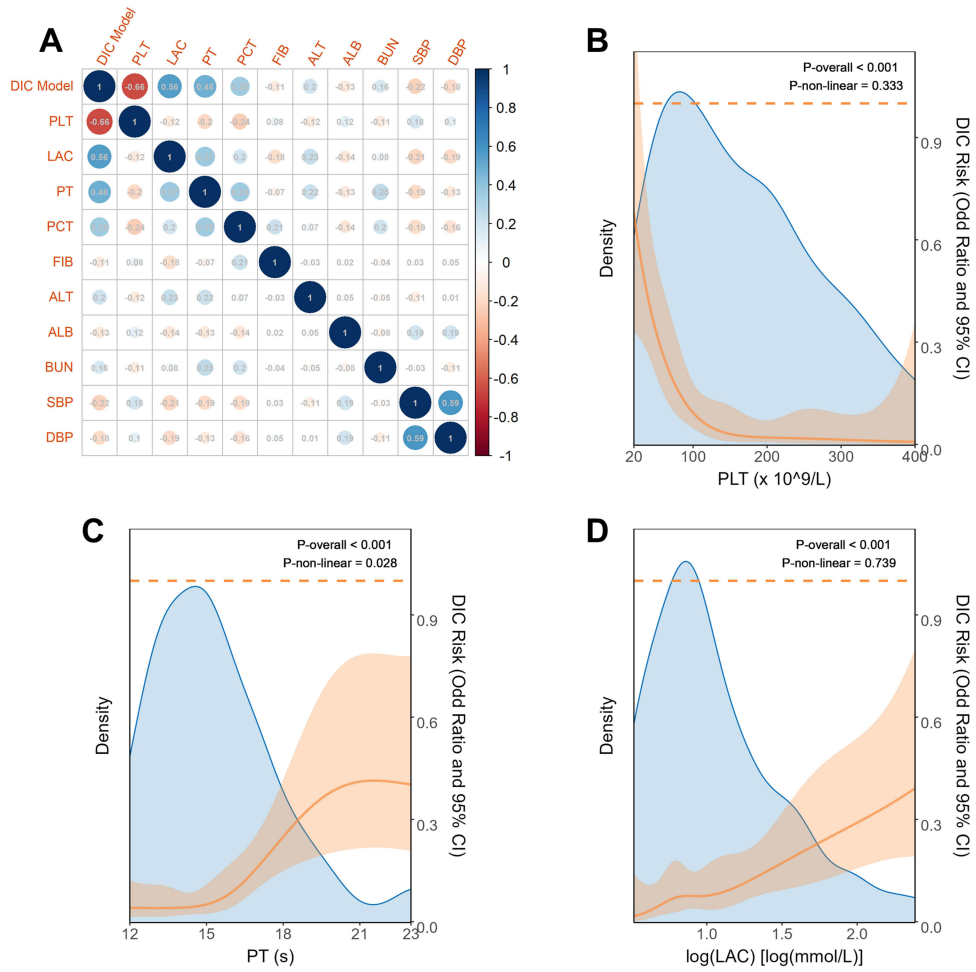

Figure 5 Correlation between model scores and clinical variables. (**A**) Association between model scores and clinical parameters. (**B**) Dose relationship between PLT levels and DIC in sepsis patients. (**C**) Dose relationship between PT levels and DIC in sepsis patients. (**D**) Dose relationship between LAC levels and DIC in sepsis patients.

DIC, making diagnosis straightforward and feasible. However, a limitation of this system was the absence of a clear definition of DIC. In 2001, the ISTH introduced the widely used DIC diagnostic criteria.[18] This scoring system relies on PT, PLT, FIB, and D-dimer levels. A score of more than five diagnoses overt DIC, while a score of <5 points indicate non-overt DIC, requiring ongoing daily assessment. Unlike the JMHLW criteria, the ISTH criteria exclude clinical symptoms and signs, emphasizing the importance of the underlying disease. The ISTH criteria also introduced the concepts of overt and non-overt DIC and highlighted the need for dynamic monitoring of coagulation disorders.[32] The ISTH criteria are more specific but less sensitive than the JMHLW criteria.[32] In 2005, the JAAM proposed new DIC diagnostic criteria, focusing on the interaction between inflammation and coagulation in DIC.[33] However, due to DIC can result from infections, tumors, trauma, poisoning, liver disease, and other diseases, a single standard may not effectively cover all DIC arises from vary causes, leading to potential limitations. Especially, increasing evidence suggests that different causes of DIC have distinct pathophysiological mechanisms, and diagnostic criteria may be needed to reflect these differences.[34–36]

Although the sensitivity and specificity of these three DIC diagnostic criteria vary in predicting patient prognosis, all these criteria emphasize two crucial indicators: PLT and PT. In our study, we also identified PLT and PT as independent factors for diagnosing DIC. Additionally, we found that LAC is a key factor associated with DIC. Hence, in our study, we incorporated LAC into our model. In our study, instead of using a traditional scoring method, we adopted a continuous scoring approach with our equation. We found that our model effectively diagnoses sepsis-related DIC. However, whether our equation is applicable to DIC caused by other etiologies requires further investigation.

Table 2 Characteristics of Patient in High- and Low-Risk DIC

Characteristic	Low-Risk Group	High-Risk Group	P value
Sample size	233	103	–
Gender, male (%)	149 (63.9)	60 (58.3)	0.321
Age, year	61.76±17.81	61.77±15.09	0.997
BMI	23.05±4.03	22.67±4.02	0.425
WBC	14.40±8.19	13.06±9.97	0.196
PLT	222.74±103.12	57.13±31.68	<0.001
CRP	90.28±58.55	119.49±76.38	0.003
PCT	16.14±29.18	35.98±36.93	<0.001
FIB	4.48±1.92	4.19±2.14	0.232
PT	14.79±2.57	17.61±4.73	<0.001
ALT	70.96±91.17	132.11±199.39	0.009
ALB	30.15±6.29	28.56±5.79	0.030
BUN	11.37±8.39	13.71±8.08	0.018
CRE	129.23±161.20	139.63±148.13	0.577
PaO2/FiO2	269.65±108.49	261.05±119.95	0.519
LAC	2.02±2.07	3.90±4.49	<0.001
SBP	122.23±22.17	112.24±22.25	<0.001
DBP	67.47±13.55	63.12±13.97	0.008
SOFA	6.35±3.32	10.69±3.76	<0.001

Abbreviations: ALB, albumin; BMI, Body-mass index; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell; PT, Prothrombin time; FIB, Fibrinogen; ALT, Alanine transaminase; BUN, Blood Urea Nitrogen; CRE, creatinine; LAC, Lactate; SBP, systolic blood pressure; DBP, Diastolic Blood Pressure.

Platelets have been closely linked to inflammation.[37,38] For instance, in sepsis, lung injury mechanisms involve leukocyte and platelet recruitment and platelet activation in sepsis patients enhances the release of membranous vesicles and platelet microparticles, exacerbating inflammatory responses and leading to acute lung injury.[39–41] Additionally, DIC is more prevalent in sepsis patients, with a high mortality rate. While platelets typically function to stop bleeding and stabilize blood clots, activated platelets can promote neutrophil recruitment, form NETs, and induce thrombocytopenia, contributing to DIC induction during sepsis.[40–43] Anticoagulation therapies, including antiplatelet drugs, have been studied for treating sepsis-induced coagulopathy, with clinical trials demonstrating reduced severity and mortality rates in patients taking long-term antiplatelet drugs like aspirin and clopidogrel.[44,45]

Further studies should be conducted to compare the model with five established DIC assessment models. While our new model shows potential for predicting patient survival, we recognize that its sensitivity and specificity need improvement. Moreover, we did not find evidence that our model can predict ARDS. For early ARDS diagnosis, a more specialized prediction model may be necessary.

Using these easily obtainable predictors, we developed a model for early identification of DIC high-risk patients. However, our study has limitations due to its retrospective design and limited sample size. Future prospective, multi-center studies are needed to further validate the performance of the risk model.

Conclusion

Our study developed a prediction model for DIC in sepsis patients, which is essential for early risk assessment and guiding treatment decisions. By identifying patients with high model scores, clinicians can prioritize timely interventions. Given the significant clinical implications of predicting DIC and Sepsis-Induced Coagulopathy, further research is needed to compare our model with other established DIC diagnostic models. This comparison will help validate the effectiveness of our model and enhance patient outcomes.

Data Sharing Statement

The data used in the current study are available from the corresponding author upon reasonable request.

Ethical Approval and Consent to Participate

This retrospective study complies with the Declaration of Helsinki and was approved by the Ethics Committee of The First Affiliated Hospital of Xiamen University, and patient written consent was obtained. All participants were fully informed of the study's purpose and provided their consent prior to their participation.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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