ORIGINAL RESEARCH

Dynamic Nomogram for Predicting Thrombocytopenia in Adults with Acute Pancreatitis

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Objective: Thrombocytopenia increases the risk of hemorrhage in patients with acute pancreatitis (AP), leading to poor clinical outcomes. Currently, there is no reliable tool for the early assessment of thrombocytopenia in these patients. We aimed to develop a nomogram based on available clinical parameters and validate its efficacy in predicting thrombocytopenia.

Methods: This was a retrospective study. All the data were extracted from an electronic database from May 2018 to May 2019. Patients with a diagnosis of AP and staying in the intensive care unit for more than 3 days were retrospectively analyzed. A clinical signature was built based on reproducible features, using the least absolute shrinkage and selection operator method (LASSO), and logistic regression established the model ($P < 0.05$). Nomogram performance was determined by its discrimination, calibration, and clinical usefulness.

Results: A total of 594 eligible patients were enrolled, of whom 399 were allocated to the training sets and the 195 in the test sets. The clinical features, including blood urea nitrogen (BUN), fibrinogen (FIB), and antithrombase III, were significantly associated with the incidence of thrombocytopenia after acute pancreatitis ($p < 0.05$) in training sets. The individualized nomogram showed good discrimination in the training sample (area under the receiver operating characteristic curve [AUC], 0.881) and in the validation sample (AUC, 0.883) with good calibration.

Conclusion: The proposed nomogram has good performance for predicting thrombocytopenia in patients with acute pancreatitis and may facilitate clinical decision-making.

Keywords: acute pancreatitis, thrombocytopenia, systemic inflammatory response syndrome, coagulopathy, nomogram

Introduction

Acute pancreatitis (AP) is an inflammatory disease triggered by acinar cells with various clinical manifestations, and most patients can recover with conservative treatment.[1–4] The activation of inflammatory cells triggers the cascade release of a large number of inflammatory factors, leading to the disorder of pro-inflammatory and anti-inflammatory states, which can induce lethal severe acute pancreatitis (SAP) characterized by systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS).[5–9]

The coagulopathy associated with SIRS is a manifestation of host immune dysfunction stimulated by severe abdominal infection in AP.[10] The body's initial

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response to injury is the local production of inflammatory mediators that lead to the aggregation of inflammatory substances such as white blood cells and platelets and repair of the reticuloendothelial system.[11,12] However, the microthrombects produced by the aggregation of intravascular platelets contribute to the reduction of platelet destruction.[13–15] In AP, recent evidence demonstrated that abnormal platelet count was considered as an indicator of coagulation function and severity of the disease.[16,17]

Thrombocytopenia is defined as an abnormal reduction of platelets in the peripheral blood below 10^{10}/L.[18] Abnormal platelet count is a common complication in patients with AP, and low platelet count often predicts adverse outcomes.[19,20] As far as we know, coagulation treatment of AP is an important clinical issue.[21] The decrease in the number of platelets increases the risk of hemorrhage in AP patients.[16] In addition, the incidence of thrombocytopenia has been strongly associated with ICU mortality in many studies.[22–24] However, there is still no effective clinical model to predict the occurrence of AP-associated thrombocytopenia. Therefore, it is necessary to effectively predict the occurrence of thrombocytopenia or screen out potential risk factors for guiding early clinical intervention to improve prognosis. Machine learning and advances in statistical methodology provide a high-efficiency method for the prediction of thrombocytopenia in patients with AP and can assist clinical investigators and physicians in performing a quick diagnosis especially when there is a high risk of abnormal platelets. Hence, the primary objective of this study was to develop and validate a machine learning model for predicting thrombocytopenia in patients with AP to help clinicians in quick and accurate diagnosis. Further, we hope to design predictive models to monitor coagulation function and guide anticoagulant therapy for AP.

Methods
Data Sources and Patient Selection
A retrospective observational study was conducted among a cohort of patients (n = 594) diagnosed with AP. Conducted from May 2018 to May 2019, these data of patients with AP were obtained from the Center of Severe Acute Pancreatitis (CSAP) of Jinling Hospital, Nanjing, China. The center is a tertiary center for AP located in eastern China. All the data were extracted from an electronic database, which stored prospectively collected clinical data of all AP patients admitted to our center. We obtained

the approval of the Acute Pancreatitis Database Management Committee (2019NZKY-003-03), and all the analyses were performed in accordance with the committee's regulation. Informed consent involving data storage and academic use of data was obtained from each patient during their hospitalization. The study complies with the Declaration of Helsinki. Patients who met the following criteria were included: (1) diagnosis of AP and (2) time in ICU should be more than 3 days. Patients who were younger than 18 years old, already developed thrombocytopenia before admission and were suspected of neoplasms, aplastic anemia, hypersplenism, and splenomegaly will be excluded from the study.

Definition
AP (ICD-10, K85) was diagnosed according to the definition in the 2012 revision of the Atlanta classification.[3] The diagnosis of thrombocytopenia is platelet $<10*10^9$/L. The patient meeting the diagnosis during the whole hospitalization of AP is calculated into the thrombocytopenia group. Suspected infection was defined as having any culture taken and at least two doses of antimicrobials administered.[25] To be classified as suspected infection, cultures had to be taken within 24 hours after the start of antimicrobials or antimicrobials had to be started within 72 hours after culture.

Data Collection
Eighty-nine variables from laboratory examination, vital signs, clinical score, and basic information on the first day after ICU admission, included age, gender, body mass index (BMI), sequential organ failure assessment (SOFA), Glasgow Coma Scale (GCS), acute stage, determinant-based classification type (DBC), infection pancreatic necrosis (IPN), urine output, continuous renal replacement therapy (CRRT), vent, white blood cell (WBC), lymphocyte% (LYM%), monocyte% (MONO%), red blood cell (RBC), blood urea nitrogen (BUN), creatinine, glucose, globulin, Ca^{2+}, platelet (PLT), thrombin time (TT), prothrombin time (PT), the international normalised ratio (INR), activated partial thromboplastin time (APTT), D-dimer, fibrinogen (FIB), antithrombase III, red cell distribution width (RDW), myohemoglobin (MB) and so on. All variables are shown in Supplementary Table 1.

Statistical Analysis
Statistical analyses were performed using SPSS software for Windows Version 25 and R software, version 4.1.1 (R Foundation for Statistical Computing). Continuous

variables in the data were presented as medians and IQRs or means and SDs. Categorical variables are presented as frequency and percentage. Kolmogorov–Smirnov test was used to test the normality. The student *t*-test or Mann–Whitney *U*-test and Chi square or Fisher's exact tests were used to investigate the differences in quantitative and categorical variables, respectively between these groups. The LASSO regression method screened the development group's best predictors. Logistic regression was used to build the model with the screened variables and a nomogram was then constructed. The discriminative ability was measured using the area under the ROC curve (AUC). Calibration of the model was assessed by comparison of the predicted and observed probability of thrombocytopenia, accompanied by the Hosmer-Lemeshow goodness-of-fit test. To estimate the clinical usefulness of the nomogram, decision curve analysis (DCA) was built by calculating the net benefits for a range of threshold probabilities. P value <0.05 was considered statistically significant.

Results

Baseline Patient Characteristics

The flowchart of the study is shown in Figure 1. There were 1039 patients primarily diagnosed with AP in our ICU from May 2018 to May 2019. 445 patients were excluded for the following reasons: age <18 (n=6); incomplete laboratory tests (n=126); ICU days <3 (n=262); with cancer (n=2); with thrombocytopenia at the first day after ICU admission (n=49). 107 cases were diagnosed as thrombocytopenia (18%). The training set consisted of 399 patients (thrombocytopenia group 73 cases, non-thrombocytopenia 326 cases), and the validation set was consisted of 195 patients (thrombocytopenia group 34 cases, non-thrombocytopenia 161 cases). Table 1 shows
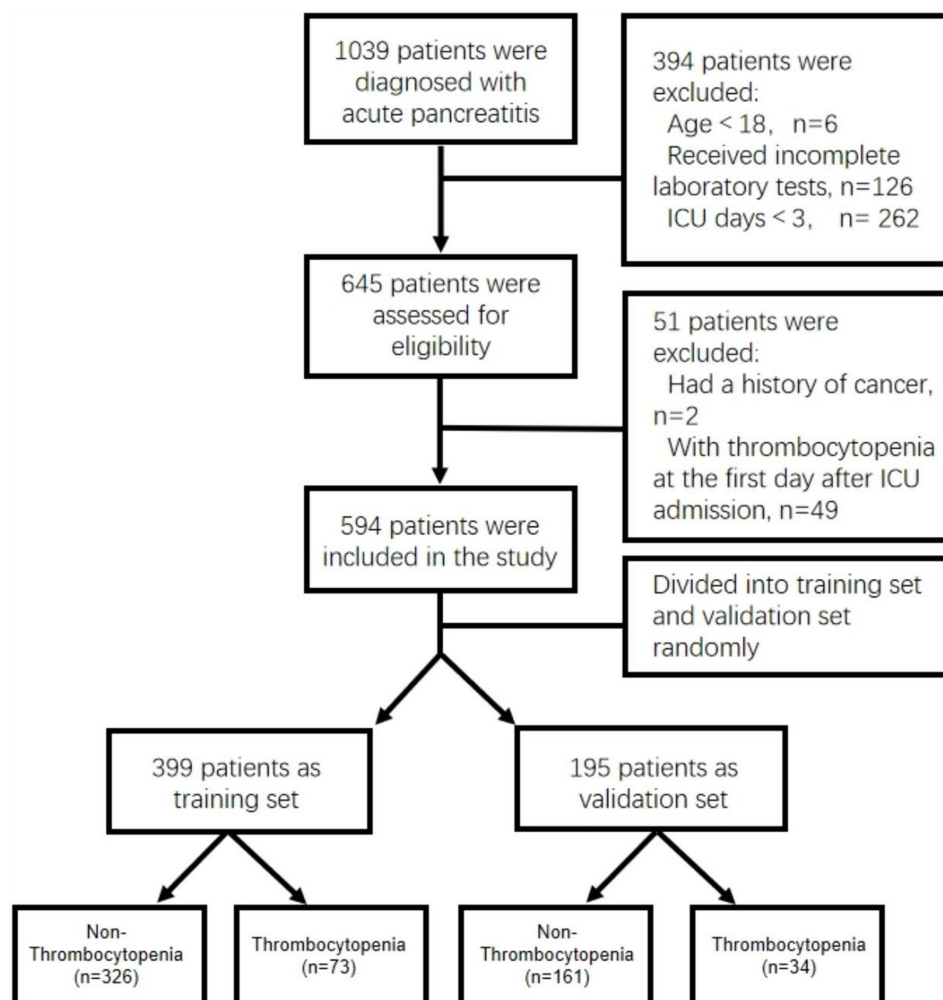

Figure 1 Flowchart of the study.

Table 1 Characteristics of Acute Pancreatitis Patients in Training Set and Validation Set

	Training Set (n=399)	Validation Set (n=195)	p value
Thrombocytopenia	73(18.3%)	34(17.4%)	0.887
Age (year)	44.8(34.8 ~ 53.5)	42.6(35.0 ~ 53.6)	0.564
Gender	270(67.7%)	126(64.6%)	0.517
BMI	24.6(22.0 ~ 27.5)	24.7(22.0 ~ 27.3)	0.656
SOFA	3(1 ~ 5)	2(0 ~ 5)	0.013
GCS	15 (15 ~ 15)	15 (15 ~ 15)	0.697
Acute stage	137(34.3%)	65(15%)	0.881
Etiology			0.601
Biliary	173(16.8%)	78(16.8%)	
Hyperlipidemic	175(16.8%)	87(16.8%)	
Others	51(16.8%)	30(16.8%)	
DBC			0.849
Mild	67(16.8%)	35(17.9%)	
Moderate	162(40.6%)	83(42.6%)	
Severe	118(29.6%)	56(28.7%)	
Critical	52(13.0%)	21(10.8%)	
IPN	87(21.8%)	46(23.6%)	0.700
Suspected Infection	187(46.6%)	92(47.1%)	0.999
Urine output (ml/24h)	1620 (1250 ~ 2340)	1620(1390 ~ 2220)	0.626
CRRT	31(7.8%)	7(3.6%)	0.076
Vent	67(16.8%)	26(13.3%)	0.333
WBC ($\times 10^9$/L)	10 (7 ~ 13.8)	10.4 (7.1 ~ 14.4)	0.705
Ly ($\times 10^9$/L)	10.1(6.8 ~ 15.8)	10.2(7 ~ 14.9)	0.912
MONO ($\times 10^9$/L)	6.3(4.6 ~ 8.4)	6.2(4.5 ~ 8.5)	0.938
RBC ($\times 10^{12}$/L)	3.3(2.8 ~ 3.8)	3.4(2.9 ~ 3.9)	0.193
BUN (mmol/L)	4.7(3.2 ~ 7.9)	4.7(3.3 ~ 7.2)	0.657
Creatinine (μmol/L)	56.5(42.1 ~ 79)	52.3(40.3 ~ 72.3)	0.125
Glucose (mmol/L)	7.2(5 ~ 10)	7.4(5.4 ~ 10.2)	0.377
Globulin (g/L)	26.6(23 ~ 29.8)	26.9(22 ~ 31.2)	0.749
Ca^{2+} (mmol/L)	2.1 (2.0 ~ 2.2)	2.1(2.0 ~ 2.2)	0.950
PLT ($\times 10^9$/L)	206(160 ~ 293)	219(171 ~ 302)	0.107
TT (s)	16.6(15.3 ~ 18.8)	16.5(15.1 ~ 18.2)	0.410
PT (s)	13.8(13 ~ 15)	13.8(12.8 ~ 15.4)	0.583
INR	1.2(1.1 ~ 1.3)	1.2(1.1 ~ 1.3)	0.396
APTT (s)	31.1(27.5 ~ 36.1)	30.5(27.3 ~ 35.2)	0.397

(*Continued*)

Table 1 (Continued).

	Training Set (n=399)	Validation Set (n=195)	p value
D-dimer (µg/L)	4.6(2.2 ~ 8.6)	4.0(2.3 ~ 7.3)	0.434
FIB (g/L)	4.3(3.2 ~ 5.4)	4.4(3.4 ~ 5.5)	0.325
Antithrombase III (%)	66.5(55 ~ 79)	67.4(55.6 ~ 78.4)	0.815
RDW (%)	14.1(13.2 ~ 15.2)	14.1(13.1 ~ 15.1)	0.314
MB (ng/mL)	36.9(21 ~ 95.7)	36.2(20 ~ 83.8)	0.523

the main baseline characteristics of patients in the training set and validation set. The thrombocytopenia incidence was comparable between two data sets (18.3% vs 17.4%; P=0.887). The SOFA of patients was higher in the training set. There were no significant differences in age, gender, BMI, or other comorbidities between these two data sets.

Patients in the thrombocytopenia group were older than those in the non-thrombocytopenia group (P<0.001). Significant differences were observed in the clinic scores and laboratory indicators between these two groups. In summary, patients in the thrombocytopenia group had more severe organ function damage, a hypercoagulable state, and increased renal injury compared with those in the non-thrombocytopenia group (Table 2).

Nomogram Development

The association of the variables with thrombocytopenia is presented in Supplementary Table 1. There were 5 parameters selected by the LASSO-penalized logistic regression model, including BUN, FIB, MB, antithrombase III and BNPP (Figure 2A and B). Multivariate logistic analysis showed three independent risk-predictive factors for thrombocytopenia: BUN, FIB, antithrombase III (Table 3). A nomogram was established to determine the influence of the three variables on thrombocytopenia (Figure 3). Antithrombase III showed the most extended scale and the most significant effect on thrombocytopenia.

The nomogram and dynamic nomogram applications are described as follows: The scores corresponding to each variable can be obtained, and the sum of these scores is recorded as the total score. The prediction risk corresponding to the total score is the risk of thrombocytopenia in AP (Figure 3). To obtain the dynamic nomogram, visit https://hongbindeng.shinyapps.io/nomogram/. It is a practical and accurate online tool (Supplementary Figure 1).

Evaluation and Validation of the Dynamic Nomogram
Discrimination and Calibration

The c-statistic of the nomogram was 0.881 in the training set data (Figure 4A), and 0.883 in the validation set (Figure 4B). The P value for the Hosmer–Lemeshow test was both more than 0.05 in the training set and validation set (P = 0.339, P = 0.464; respectively). The calibration curves are shown in Figure 4C, and D. The Brier scores in the development and validation groups were 0.096 and 0.098, respectively. Both the Hosmer–Lemeshow tests and the calibration curves showed that the model's predicted probability was highly consistent with the actual probability, and the model had good calibrations in both the training and validation sets.

Decision Curve Analysis

Decision curve analysis results of the risk nomogram in the training set and validation set were shown to determine an optimal decision point of the nomogram (Figure 4E and F). For predicted risk thresholds between 0% and 63%, the nomogram model showed a positive net benefit in two data sets.

Discussion

The changes of coagulation function during AP greatly affect the clinical manifestations and prognosis of patients. However, the question of whether platelets are directly involved in the pathophysiology of AP remains uncertain.[26–28] It is clear that in the early stages of AP, the leucocyte – endothelial cell response in the pancreatic microcirculation causes vascular damage that recruits platelet activation.[15,29] Upon activation, platelets can generate reactive oxygen species and nitric oxide as well as release pro-inflammatory mediators. Furthermore, the accumulation

Table 2 Characteristics of Acute Pancreatitis Patients in Thrombocytopenia Set and Non-Thrombocytopenia Set

	Thrombocytopenia (n=107)	Non-Thrombocytopenia (n=487)	p value
Age (year)	50.6(38.0 ~ 60.8)	43.9(34.0 ~ 51.4)	<0.001
Gender	69(64.4%)	327(67.1%)	0.678
BMI	24.2(22.3 ~ 26.9)	24.7(22.0 ~ 27.6)	0.535
SOFA	6(3 ~ 8)	2(0 ~ 4)	<0.001
GCS	15 (15 ~ 15)	15 (15 ~ 15)	<0.001
Acute stage	16(14.9%)	186(38.1%)	<0.001
Etiology			0.012
Biliary	58(54.2%)	193(39.6%)	
Hyperlipidemic	34(31.7%)	228(46.8%)	
Others	15(14.0%)	66(13.5%)	
DBC			<0.001
Mild	7(6.5%)	95(19.5%)	
Moderate	27(25.2%)	218(44.7%)	
Severe	44(41.1%)	130(26.6%)	
Critical	29(27.1%)	44(9.0%)	
IPN	36(33.6%)	97(19.9%)	0.003
Suspected Infection	57(53.2%)	222(45.5%)	0.182
Urine output (ml/24h)	1540 (907.5 ~ 1820)	1620(1450 ~ 2350)	<0.001
CRRT	14(13.0%)	24(4.9%)	0.004
Vent	43(40.1%)	50(10.2%)	<0.001
WBC (×10^9/L)	10.4 (7.3 ~ 14.8)	10.1 (7.0 ~ 13.8)	0.358
Ly (×10^9/L)	0.9(0.5 ~ 1.4)	1.0(0.7 ~ 1.6)	0.088
MONO (×10^9/L)	4.8(3.5 ~ 7.0)	6.5(4.8 ~ 8.7)	<0.001
RBC (×10^{12}/L)	2.8(2.5 ~ 3.2)	3.5(2.9 ~ 4.0)	<0.001
BUN (mmol/L)	9.7(4.9 ~17.0)	4.3(3.1 ~3.2)	<0.001
Creatinine (μmol/L)	82.7(51.9 ~ 201.3)	52.6(40.9 ~ 68.9)	<0.001
Glucose (mmol/L)	8.7(6.5 ~ 13.3)	6.8(5.1 ~ 9.5)	<0.001
Globulin (g/L)	27.5(23.1 ~ 32.1)	26.6(22.6 ~ 30.1)	0.206
Ca^{2+} (mmol/L)	2.1 (1.9 ~ 2.2)	2.1(2.0 ~ 2.2)	0.035
PLT (×10^9/L)	187(141 ~ 287)	213(169 ~ 300)	0.006
TT (s)	17.1(15.9 ~ 19.7)	16.4(15.1 ~ 18.1)	0.001
PT (s)	15.3(13.8 ~ 17.0)	13.7(12.8 ~ 14.6)	<0.001
INR	1.3(1.2 ~ 1.5)	1.2(1.1 ~ 1.3)	<0.001
APTT (s)	34.2(29.1 ~ 40.6)	30.3(27.1 ~ 34.8)	<0.001
D-dimer (μg/L)	6.5(3.6 ~ 9.2)	4.2(2.1 ~ 7.6)	<0.001

(*Continued*)

Table 2 (Continued).

	Thrombocytopenia (n=107)	Non-Thrombocytopenia (n=487)	p value
FIB (g/L)	3.4(2.7 ~ 4.4)	4.5(3.4 ~ 5.7)	<0.001
Antithrombase III (%)	51.5(40.8 ~ 63.8)	69.9(59.2 ~ 81.3)	<0.001
RDW (%)	15.1(14.2 ~ 16.3)	13.8(13.0 ~ 14.9)	<0.001
MB (ng/mL)	116.8(34.8 ~ 531.2)	33.0(20.0 ~ 66.7)	<0.001

of platelets in the microvasculature during the reperfusion period enhances the recruitment of activated leukocytes, thereby exacerbating the intensity of the inflammatory response.[30,31] Therefore, from this point of view platelets can exacerbate the injury of AP while consuming themselves in a vicious cycle and even inducing thrombocytopenia.

In our study, we developed and validated a machine learning-based model that incorporates the clinical changes of patients and the platelet signature and distribution, individualized prediction of thrombocytopenia in patients with AP. The nomogram demonstrated favorable discrimination in both the training set (AUC, 0.881) and the validation set cohort (AUC, 0.883) and good calibration, which confirms that the training-validation model achieved excellent predictive efficacy. Decision curve analysis (DCA) indicated the clinical usefulness of the mixed

model. Moreover, our prediction model is straightforward and can be used directly with online tools to avoid the computational errors associated with standard nomogram. From this point of view, clinicians can actively carry out early fluid resuscitation and close monitoring according to the early predictive value of patients with AP, and even timely transfer patients to pancreatic hospitals or large medical institutions with better conditions.

In this study, almost all clinical data of the patients in our AP center were included and the machine learning model was used for step-by-step double-validation. Finally, laboratory blood indicators BUN, FIB, and antithrombase III were screened for the first time and confirmed to be able to predict the occurrence of thrombocytopenia after AP efficiently and accurately. To our knowledge, blood urea nitrogen (BUN) is a well-established marker of mortality in AP, which may explain its potential
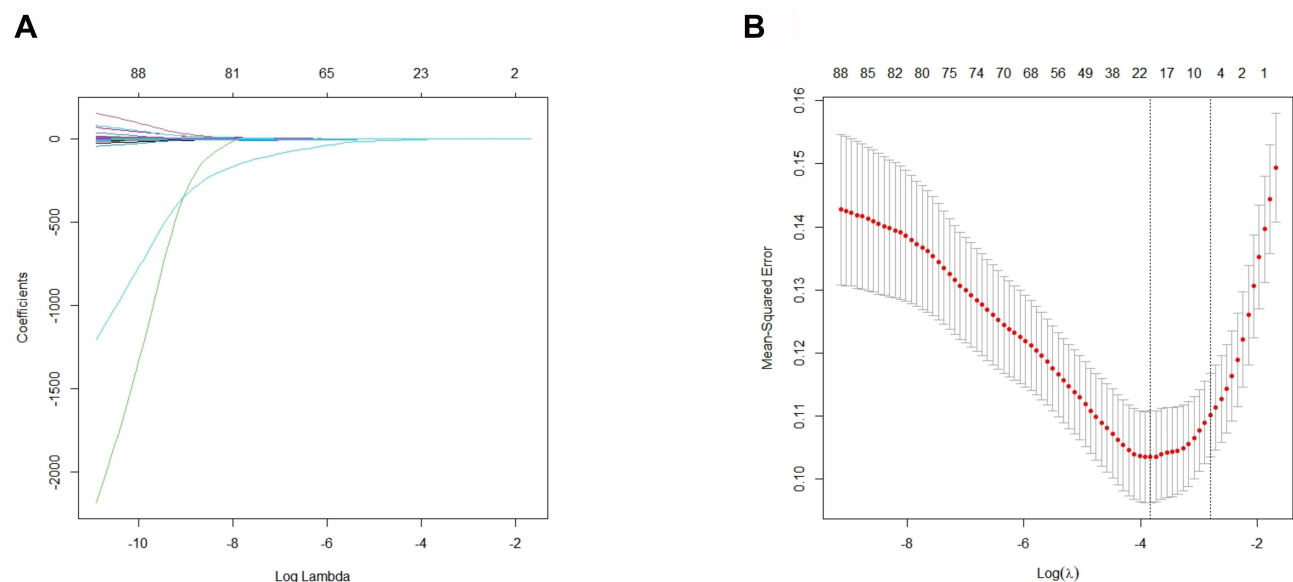

Figure 2 Identification of significant predictors for the thrombocytopenia in patients with acute pancreatitis. (**A**) LASSO coefficient profiles of the candidate predictors. (**B**) Selection of the optimal penalization coefficient in the LASSO regression.

Table 3 The Result of Multivariate Analysis

Variables	Training Set		Validation Set		Total	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
BUN (mmol/L)	1.160 (1.098~1.225)	<0.001	1.195 (1.077~1.325)	0.001	1.165 (1.111~1.221)	<0.001
FIB (g/L)	0.694 (0.539~0.893)	0.005	0.609 (0.433~0.856)	0.004	0.668 (0.546~0.817)	<0.001
MB (ng/mL)	1.000 (1.000~1.001)	0.128	1.000 (1.000~1.001)	0.083	1.000 (1.000~1.001)	0.022
Antithrombase III (%)	0.946 (0.924~0.967)	<0.001	0.948 (0.918~0.978)	0.001	0.947 (0.930~0.964)	<0.001
BNPP (pmol/L)	1.002 (1.000~1.005)	0.034	0.999 (0.996~1.002)	0.472	1.001 (0.999~1.003)	0.242

predictive value in AP-associated thrombocytopenia.[32,33] In addition, antithrombase III reduction is associated with severity of AP, low levels could be caused by consumption due to coagulopathy or increased elimination due to renal complications.[34] Both are indicative for AP severity and can cause thrombocytopenia.[35] Fibrinogen (FIB) is an acute-phase protein with commonly high plasma levels due to the inflammatory state of AP.[36] When FIB is low, it is again a sign of consumption (eg in DIC) secondary to AP causing thrombocytopenia.[37] As for the effects of disseminated intravascular coagulation (DIC), although some patients met the criteria based on ISTH Diagnostic Scoring System for DIC, none of the patients included in the analysis was diagnosed with DIC during their ICU stay (Supplementary Table 2). This may mean that the DIC score is not appropriate for AP, and a special DIC score for AP should be developed. In other words, although DIC constitutes a potential cause of thrombocytopenia, it is not present in our patients. This suggests that we should pay attention to DIC problems in the diagnosis and treatment of AP in the future to avoid missed diagnosis and misdiagnosis. Finally, it is generally known that AP can lead
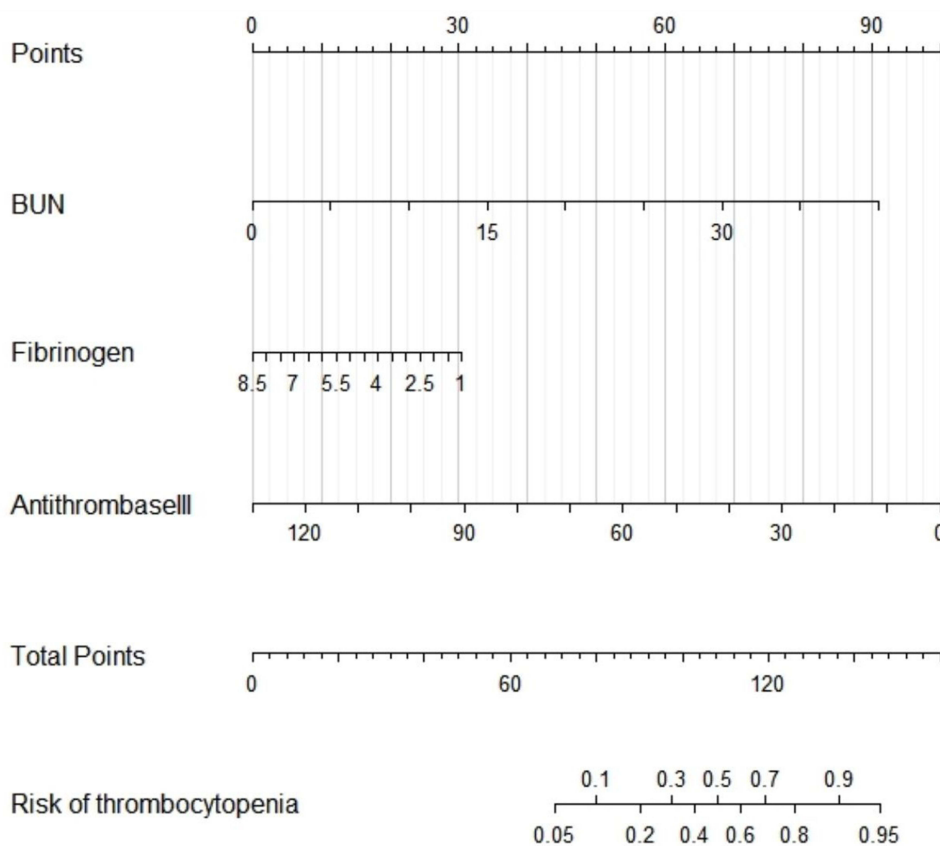

Figure 3 Construction and validation of the predictive nomogram for the thrombocytopenia in patients with acute pancreatitis.
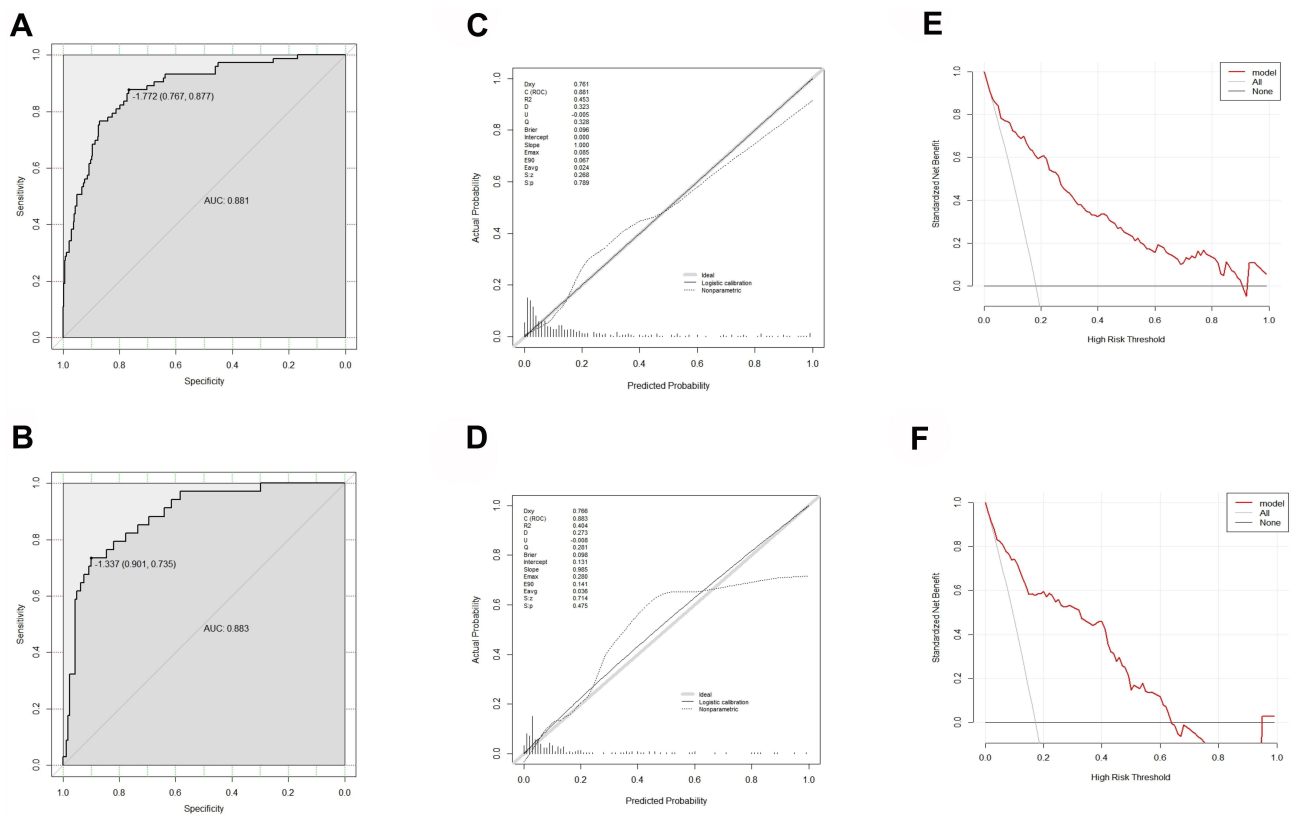
Figure 4 (**A**) Receiver operating characteristic (ROC) curves of the nomogram in the training cohort. (**B**) ROC curves of the nomogram in the validation cohort. (**C**) Calibration curve of the nomogram in the training cohort. (**D**) Calibration curve of the nomogram in the validation cohort. (**E**) Decision curve analysis in the training cohort. (**F**) Decision curve analysis in the validation cohort.

to thrombotic thrombocytopenic purpura (TTP), yet this cause was also not present in our patient.

Large amounts of platelets are activated and consumed in the early stages of AP, and the mean platelet volume (MPV) is considered to be a marker of platelet depletion and the resulting compensatory bone marrow response over the course of the disease. In other words, elevated mean platelet volume is a marker of organ failure and platelet depletion in patients with AP. Furthermore, thrombocytopenia caused by persistent platelet depletion is considered to be an adverse complication of SAP, which is consistent with recent reports that platelet levels predict the severity of AP.[16,17] In our study, our nomogram performed well in both the training set and the validation set, and it also showed good calibration in both the training and validation samples.

In order to go beyond pure mathematics and evaluate the model from the perspective provided by performance measures such as AUC, DCA is used to evaluate the expected net benefit of the model under all possible risk thresholds, thereby assessing the impact of various risk thresholds.[38,39] DCA showed that if the threshold probability was between

0% and 63%, using the nomogram in the current study to predict thrombocytopenia in patients with AP adds more benefit than either of these two data sets. Therefore, our research mainly includes technological innovations and advantages in the following aspects: firstly, this is the first predictive model developed for patients with thrombocytopenia in AP; secondly, the results are displayed in dynamic nomogram, and the data can be input directly, which avoids the calculation difficulty of continuous variables and improves the validity of the model; thirdly, DCA was introduced in our study to make risk stratification more intuitive and reasonable.

However, there are some limitations to our analysis. The major limitation of the present study might be that it was a single-centre retrospective in nature, and selection bias cannot be ignored. Secondly, since we collected platelet counts from hospitalized patients in the acute phase, a small number of patients were diagnosed with thrombocytopenia for some transient reason, thus potentially causing bias. Thirdly, the number of patients included in the analysis in this study is still limited, so further validation with a large

sample is necessary. Finally, there are some clinical questions of thrombocytopenia in patients with AP not to be resolved, such as classification of severity and exploration of the clinical relationship. In the next step, we will continue to carry out multidisciplinary cooperation, and select more precise features to develop a deep learning model, and also should focus on multicenter validation with a larger sample size to obtain high-level evidence for the clinical application of deep learning model. In this way, clinicians and patients can benefit to a greater extent.

In conclusion, the nomogram model, which is consisted of three independent risk factors for thrombocytopenia, may empower clinicians with earlier and more accurate information regarding the risk of thrombocytopenia and help in clinical decision-making.

Data Sharing Statement

The datasets used or analysed during the current study are available from the corresponding author (Weiqin Li) on reasonable request.

Consent for Publication

All authors have agreed to publish this article.

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 report no conflicts of interest in this work.

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