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ORIGINAL RESEARCH

Development and Validation of a Nomogram for Predicting the Severity of the First Episode of Hyperlipidemic Acute Pancreatitis

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Purpose: Early detection of hyperlipidemic acute pancreatitis (HLAP) with exacerbation tendency is crucial for clinical decision-making and improving prognosis. The aim of this study was to establish a reliable model for the early prediction of HLAP severity.

Patients and Methods: A total of 225 patients with first-episode HLAP who were admitted to Fujian Medical University Union Hospital from June 2012 to June 2023 were included. Patients were divided into mild acute pancreatitis (MAP) or moderate-severe acute pancreatitis and severe acute pancreatitis (MSAP+SAP) groups. Independent predictors for progression to MSAP or SAP were identified through univariate analysis and least absolute shrinkage and selection operator regression. A nomogram was established through multivariate logistic regression analysis to predict this progression. The calibration, receiver operating characteristic(ROC), and clinical decision curves were employed to evaluate the model's consistency, differentiation, and clinical applicability. Clinical data of 93 patients with first-episode HLAP who were admitted to the First Affiliated Hospital of Fujian Medical University from October 2015 to October 2022 were collected for external validation.

Results: White blood cell count, lactate dehydrogenase, albumin, serum creatinine, serum calcium, D-Dimer were identified as independent predictors for progression to MSAP or SAP in patients with HLAP and used to establish a predictive nomogram. The internally verified Harrell consistency index (C-index) was 0.908 (95% CI 0.867–0.948) and the externally verified C-index was 0.950 (95% CI 0.910–0.990). The calibration, ROC, and clinical decision curves showed this nomogram's good predictive ability.

Conclusion: We have established a nomogram that can help identify HLAP patients who are likely to develop MSAP or SAP at an early stage, with high discrimination and accuracy.

Keywords: early prediction, nomogram, hyperlipidemic acute pancreatitis, risk factor, prognosis

Introduction

Acute pancreatitis (AP) refers to a common inflammatory disease of the pancreas caused by aberrant activation of pancreatic enzymes characterized by local inflammation of the pancreas and subsequent systemic inflammatory response. It is a prominent digestive emergency that leads to hospitalization.[1,2] The common causes of AP encompass biliary diseases, hyperlipidemia, and alcohol consumption. AP caused by serum triglyceride (TG) levels ≥11.30 mmol/L or between 5.65 and 11.30 mmol/L with lipid turbidity is called hyperlipidemic acute pancreatitis (HLAP). With the improvement of living standards and changes in dietary structure, the incidence of HLAP is increasing daily, and HLAP is becoming more severe and affects people at a younger age, which requires vigilance.[3]

HLAP has a high incidence of complications and poor prognosis.[4] The incidence of local complications, acute renal failure, and exacerbation in patients with HLAP is higher than that in patients with non-HLAP.[3] Therefore, it is imperative to stratify patients with HLAP based on their risk level in order to facilitate clinical decision-making and

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optimize treatment administration. Currently, the revised Atlanta Classification in 2012 is employed for grading the severity of AP,[5] but there exists a delay in its implementation. Additionally, there are several scoring systems for early assessment of AP severity, including the Ranson score, Acute Physiology and Chronic Health Evaluation (APACHE) II score, modified computed tomography severity index (MCTSI), and Bedside Index for Severity in Acute Pancreatitis (BISAP) score.[6–8] However, these scoring systems also exhibit specific drawbacks and limitations.

Considering the aforementioned predictive models' limitations and HLAP's unique pathogenesis and clinical characteristics, there are currently few reports on scoring systems specifically designed for early prediction of HLAP severity. Hence, it is crucial to develop an innovative and straightforward scoring system for the early assessment of HLAP severity. The nomogram is a simple, intuitive, and practical graphical model that provides personalized risk estimation and can assess prognostic outcomes associated with various diseases.[9,10] This study aimed to develop and validate a nomogram that can assess the clinical severity of patients with HLAP at an early stage to provide reference values for guiding clinical treatment.

Materials and Methods

Patients

The clinical data of patients with first-episode HLAP, who were admitted to Fujian Medical University Union Hospital between June 2012 and June 2023, as well as the First Affiliated Hospital of Fujian Medical University between October 2015 and October 2022, were retrospectively analyzed. The inclusion criteria were: (1) patients who met the diagnostic criteria for AP with any two of the following three conditions:[5] (i) acute, persistent upper abdominal pain, (ii) serum amylase or lipase level >3 times the upper normal limit, (iii) typical imaging changes of AP; and (2) having blood TG level ≥11.30 mmol/L before treatment or serum blood TG level of 5.65–11.30 mmol/L with lipid turbidity. The exclusion criteria were: (1) AP caused by other factors (gallstones/microlithiasis, alcohol, neoplasia, ischemia, Oddi sphincter dysfunction, drug-induced, and bacterial or viral infections, etc); (2) patients with incomplete clinical data; (3) patients with chronic pancreatitis and recurrent pancreatitis; (4) more than 72 h from onset to admission; and (5) patients referred from other medical institutions. As a result, a total of 225 patients from Fujian Medical University Union Hospital were enrolled in the study as a training cohort, and 93 patients from the First Affiliated Hospital of Fujian Medical University were included in the study as a validation cohort. In each cohort, the patients were divided either into the mild acute pancreatitis (MAP) group or moderate-severe acute pancreatitis and severe acute pancreatitis (MSAP +SAP) group according to the revised Atlanta Classification in 2012.[5] This classification defines MAP as no organ failure and no local or systemic complications, MSAP as transient organ failure (spontaneous recovery within 48 hours) with local or systemic complications, and SAP as persistent organ failure (more than 48 hours).

Data Collection

Data were obtained from the electronic medical records of patients with HLAP, including demographic characteristics (sex, age, and pregnancy), comorbidities (hypertension, diabetes, and fatty liver), vital signs on admission (temperature, pulse rate, respiratory rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure), hospital stay, and hospitalization expenses (total, inspection, and drug expenses). Laboratory indicators including white blood cell count (WBC), hemoglobin (HB), platelet count (PLT), hematocrit (HCT), red blood cell volume distribution width (RDW), blood amylase (AMY), blood glucose (BG), triglycerides (TG), total bilirubin (TBIL), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), albumin (ALB), blood urea nitrogen (BUN), serum creatinine (Scr), bicarbonate (HCO_3^-), serum calcium (Ca^{2+}), blood potassium (K^+), blood sodium (Na^+), blood phosphorus, and D-Dimer (DDi), were assayed within 24 hours after admission. In addition, the APACHE II, BISAP, and MCTSI scores of patients with HLAP were calculated within 24 hours after admission.

Statistical Analyses

The count data expressed as the number of cases or percentages were analyzed using χ^2 test and Fisher's exact probability method when necessary. The measurement data that follow normal distribution are represented as mean and standard

deviation (mean±SD); Student's *t*-test represents the comparison between groups. The measurement data that do not follow normal distribution are represented as median and interquartile range (median [P25–P75]); the differences of the groups were compared using the Mann–Whitney *U*-test. Univariate analysis and least absolute shrinkage and selection operator (LASSO) regression methods were used to screen the best predictors in the training cohort. The screened predictors were included in the multivariate logistic regression analysis. The odds ratios (OR) and 95% confidence intervals (CI) of these factors were analyzed using multivariate logistic regression to determine the predictors of progression to MSAP or SAP in the patients with HLAP. Differences were considered statistically significant at a P-value <0.05.

The multivariable logistic regression analysis results in the training cohort were presented in a nomogram. For internal validation, 1000 bootstrap resamples were used to calculate the Harrell consistency index (C-index). Then, the performance of the nomogram was tested in the validation cohort for external verification.

The nomogram was constructed based on the multivariate logistic regression analysis, assigning points to each value level of each risk factor and then adding each score to obtain the total score. Ultimately, the predicted probability of the outcome event was calculated by applying a conversion function that establishes a quantitative relationship between the total score and the likelihood of occurrence.

We assessed the predictive power of the nomogram using a receiver operating characteristic (ROC) curve analysis. Calibration curves were employed to analyze the difference between the nomogram and the ideal model. Decision curve analysis (DCA) was utilized to appraise the clinical utility of the nomogram. The R software packages "rms", "pROC", and "rmda" were used to generate the nomogram, ROC curves, and calibration curves and perform DCA. R software (version 4.3.2) and SPSS software (version 24.0) were used for statistical analysis.

Results

Patient Characteristics

As shown in Figure 1, 318 patients with first-episode HLAP were included in this study. The training cohort consisted of 225 patients with first-episode HLAP, including 150/225 males (66.7%) and 75/225 females (33.3%). The validation cohort comprised 93 patients with first-episode HLAP, including 57/93 males (61.3%) and 36/93 females (38.7%). There were no significant differences in the demographic characteristics, comorbidities, vital signs at admission, hospital stay, hospitalization expenses, APACHE II score, BISAP score, MCTSI, or laboratory indicators within 24 hours after admission between the training and validation cohorts (P >0.05; Table 1). Table 1 shows that the two cohorts were similar, justifying their use as training and validation cohorts.

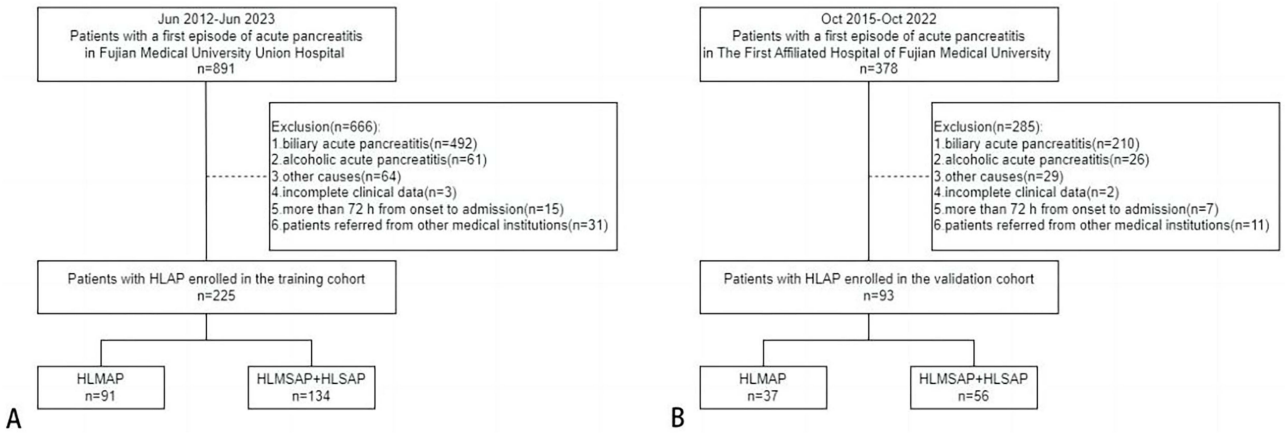

Figure 1 A flow diagram of the patient recruitment procedure (**A**) training cohort; (**B**) validation cohort).
Abbreviations: HLMAP, hyperlipidemic mild acute pancreatitis; HLMSAP, hyperlipidemic moderate-severe acute pancreatitis; HLSAP, hyperlipidemic severe acute pancreatitis.

Table 1 General Data and Laboratory Indicators of Patients in the Training and Validation Cohorts

	Training Cohort (n=225)	Validation Cohort (n=93)	χ^2/Z/T	P value
Age, years	37.52±9.84	38.91±9.90	−1.144	0.253
Sex, male/female	150/75	57/36	0.837	0.360
Pregnancy, n(%)	12(5.3)	1(1.1)	2.054	0.152
Comorbidities				
Hypertension, n(%)	45(20.0)	13(14.0)	1.600	0.206
Diabetes, n(%)	113(50.2)	37(39.8)	2.877	0.090
Fatty liver, n(%)	182(80.9)	73(78.5)	0.237	0.626
Vital signs				
Temperature (°C)	36.8(36.5,37.2)	36.7(36.5,37.2)	−0.042	0.967
Pulse rate (times/minute)	98.0(84.0,113.50)	101.00(87.0,114.0)	−0.817	0.414
Respiratory rate (times/minute)	20.0(19.0,21.0)	20.0(19.0,21.0)	−0.232	0.816
Systolic blood pressure (mmHg)	130.0(120.0,140.0)	130.0(118.0,143.0)	−0.078	0.937
Diastolic blood pressure (mmHg)	80.0(71.0,88.0)	83.0(73.0,90.5)	−1.822	0.068
Mean arterial pressure (mmHg)	97.0(89.0,105.0)	98.0(89.0,108.0)	−1.341	0.180
Score at admission				
APACHE II	5.0(2.0,8.0)	5.0(3.0,6.5)	−0.406	0.685
BISAP	1.0(0,2.0)	1.0(1.0,2.0)	−1.677	0.094
MCTSI	4.0(2.0,6.0)	4.0(3.0,6.0)	−1.303	0.193
MAP/MSAP+SAP	91/134	37/56	0.012	0.913
Hospital stay (days)	12.0(10.0,16.0)	11.0(11.0,14.0)	−1.627	0.104
Total expenses (RMB)	27,183.36 (13,724.39,46,304.45)	28,688.94 (21,459.35,46,121.00)	−1.536	0.125
Inspection expenses (RMB)	5463.00 (3367.50,8351.50)	6342.00 (3807.00,8807.00)	−1.613	0.107
Drug expenses(RMB)	12,325.10 (5818.67,23,826.68)	13,096.33 (8906.29,18,732.28)	−0.562	0.574
Clinical index				
WBC(10^9/L)	11.76(9.43,14.57)	12.41(9.84,16.05)	−1.447	0.148
HB(g/L)	143.11±25.50	147.53±21.15	−1.474	0.141
PLT(10^9/L)	220.00(175.00,279.50)	218.00(186.50,269.50)	−0.246	0.806
HCT(%)	40.48±6.49	41.79±5.18	−1.732	0.084
RDW(%)	13.20(12.80,14.00)	13.30(12.75,13.95)	−0.488	0.626
Blood AMY(U/L)	287.00 (158.00,521.50)	313.00 (151.50,554.00)	−0.520	0.603
BG(mM)	11.32 (7.80,14.92)	10.30 (7.76,14.58)	−0.658	0.510
TG(mM)	16.99(12.13,32.09)	16.28(11.93,22.02)	−1.757	0.079
TBIL(μmol/L)	15.80(11.85,22.90)	13.90(10.45,20.20)	−1.710	0.087
AST(U/L)	29.00 (19.00,39.25)	27.00 (19.50,37.00)	−0.557	0.578
LDH(U/L)	311.00(215.75,436.25)	368.00(244.00,530.50)	−1.925	0.054
ALB(g/L)	35.18±6.03	35.58±5.34	−0.559	0.576
BUN(mM)	4.20(3.20,5.65)	3.90(2.55,6.15)	−1.739	0.082
Scr(μM)	68.00(58.50,78.00)	64.00(47.50,77.50)	−1.772	0.076
HCO_3^-(mM)	20.90(17.35,22.95)	20.00(16.48,23.20)	−0.725	0.468
Ca^{2+}(mM)	2.17(2.02,2.25)	2.15(1.99,2.22)	−1.687	0.092
Na^+(mM)	136.07±5.65	135.05±4.89	1.524	0.129
K^+(mM)	4.05±0.51	4.15±0.59	−1.556	0.121
Blood phosphorus (mM)	0.74±0.32	0.74±0.28	0.075	0.940
DDi (mg/L)	1.89(0.93,3.56)	2.25(0.93,4.28)	−0.746	0.445

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BISAP, Bedside Index for Severity in Acute Pancreatitis; MCTSI, modified computed tomography severity index; WBC, white blood cell count; HB, hemoglobin; PLT, platelet count; HCT, hematocrit; RDW, red blood cell volume distribution width; AMY, amylase; BG, blood glucose; TG, triglycerides; TBIL, total bilirubin; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; ALB, albumin; BUN, blood urea nitrogen; Scr, serum creatinine; HCO_3^-, bicarbonate; Ca^{2+}, serum calcium; K^+, blood potassium; Na^+, blood sodium; DDi, D-Dimer.

Comparison of the Variables Between the Groups

Among the 225 patients in the training cohort, 91 cases (40.4%) were hyperlipidemic mild acute pancreatitis (HLMAP), 134 cases (59.6%) were hyperlipidemic moderate-severe acute pancreatitis and hyperlipidemic severe acute pancreatitis (HLMSAP +HLSAP). There were no statistically significant differences in the demographic characteristics and comorbidities between the HLMAP and HLMSAP+HLSAP groups (P >0.05; Table 2). However, there were statistically significant differences in the vital signs on admission (temperature, pulse rate, respiratory rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure), APACHE II score, BISAP score, MCTSI, hospital stay, and hospitalization expenses between the two groups (P <0.05; Table 2). In the training cohort, the comparison of laboratory indicators between the HLMAP and HLMSAP+HLSAP groups showed that there were no statistically significant differences in HB, PLT, HCT, AMY, TBIL, AST, BUN, K^+, and Na^+ (P >0.05; Table 3). There were statistically significant differences in WBC, RDW, BG, TG, LDH, ALB, Scr, HCO_3^-, Ca^{2+}, blood phosphorus, and DDi between the two patient groups (P <0.05; Table 3).

Logistic Regression Analysis

Vital signs on admission (temperature, pulse rate, respiratory rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure), WBC, RDW, BG, TG, LDH, ALB, Scr, HCO_3^-, Ca^{2+}, blood phosphorus, and DDi were identified as candidate predictors of MASP or SAP in the univariate analysis (P <0.05). LASSO regression was used to screen the variables with non-zero coefficients further among the results of the univariate logistic regression. The best predictors of MASP and SAP were WBC, RDW, BG, LDH, ALB, Scr, HCO_3^-, Ca^{2+}, and DDi (Figure 2). These variables were included in the multivariate logistic regression analysis to construct a regression model. The Hosmer–Lemeshow test yielded a P value of 0.639, indicating that the model was valid. The final results of multivariate analysis

Table 2 Comparison of General Data Between the HLMAP and HLMSAP+HLSAP Groups

	HLMAP Group (n=91)	HLMASP+HLSAP Group (n=134)	χ^2/Z/T	P value
Age, years	38.11±9.78	37.13±9.89	0.735	0.463
Sex, male/female	64/27	86/48	0.923	0.337
Pregnancy, n(%)	2(2.1)	10(7.5)	2.024	0.155
Comorbidities				
Hypertension, n(%)	14(15.4)	31(23.1)	2.034	0.154
Diabetes, n(%)	43(47.3)	70(52.2)	0.539	0.463
Fatty liver, n(%)	73(80.2)	109(81.3)	0.044	0.833
Vital signs				
Temperature (°C)	36.6(36.5,37.0)	36.9(36.5,37.4)	−2.744	***0.006***
Pulse rate (times/minute)	88.42±16.19	107.66±20.26	−7.894	***<0.001***
Respiratory rate (times/minute)	20.0(19.0,20.0)	20.0(20.0,22.0)	−4.998	***<0.001***
Systolic blood pressure (mmHg)	128.24±15.57	133.13±19.52	−1.998	***0.047***
Diastolic blood pressure (mmHg)	75.0(70.0,82.0)	82.5(72.0,90.0)	−3.110	***0.002***
Mean arterial pressure (mmHg)	93.0(87.0,100.0)	99.0(89.0,108.0)	−3.099	***0.002***
Score at admission				
APACHE II	4.0(2.0,6.0)	6.0(3.0,9.0)	−4.836	***<0.001***
BISAP	1.0(0,1.0)	2.0(1.0,2.0)	−9.013	***<0.001***
MCTSI	2.0(2.0,4.0)	4.0(4.0,6.0)	−8.711	***<0.001***
Hospital stay (days)	11.0(8.0,12.0)	14.0(12.0,19.0)	−7.474	***<0.001***
Total expenses (RMB)	12,075.02 (8121.12,21,516.41)	40,363.33 (25,766.59,58,593.22)	−10.369	***<0.001***
Inspection expenses (RMB)	3154.00 (2214.00,4737.00)	6826.25 (4814.75,11,262.50)	−8.767	***<0.001***
Drug expenses (RMB)	5624.43 (2842.27,9744.13)	17,880.41 (11,670.95,31,889.88)	−9.451	***<0.001***

Notes: P value for the comparison between the two groups. The boldfaced and italic P values are statistically different.
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BISAP, Bedside Index for Severity in Acute Pancreatitis; MCTSI, modified computed tomography severity index.

Table 3 Comparison of Laboratory Indicators Between the HLMAP and HLMSAP+HLSAP Groups

Clinical index	HLMAP Group (n=91)	HLMASP+HLSAP Group (n=134)	Z/T	P value
WBC(10^9/L)	10.70(9.12,12.83)	12.33(9.86,15.61)	−3.113	***0.002***
HB(g/L)	145.55±22.85	141.45±27.11	1.184	0.238
PLT(10^9/L)	224.00 (184.00,284.00)	216.50 (168.50,278.50)	−0.742	0.458
HCT(%)	40.72±5.79	40.33±6.95	0.440	0.661
RDW(%)	13.00 (12.50,13.40)	13.50 (13.00,14.40)	−4.779	***<0.001***
Blood AMY (U/L)	262.00 (153.00,477.00)	313.00 (164.75,522.00)	−1.202	0.229
BG(mM)	9.14 (7.11,14.32)	12.50 (8.56,15.17)	−2.505	***0.012***
TG (mM)	15.74 (9.75,32.28)	18.77 (13.23,31.80)	−2.017	***0.044***
TBIL(μmol/L)	15.50 (11.80,21.60)	16.30 (12.08,24.43)	−0.910	0.363
AST(U/L)	27.50 (19.00,35.75)	30.50 (20.75,42.50)	−1.309	0.191
LDH(U/L)	218.00 (175.25,276.25)	407.50 (281.75,548.25)	−7.814	***<0.001***
ALB(g/L)	37.90±5.42	33.33±5.74	5.994	***<0.001***
BUN(mM)	4.20(3.15,5.13)	4.60(3.20,6.03)	−1.623	0.105
Scr(μM)	63.5(53.0,74.0)	70.6(62.8,86.5)	−4.791	***<0.001***
HCO_3^-(mM)	21.50(19.30,23.00)	20.00(16.00,23.00)	−2.228	***0.026***
Ca^{2+}(mM)	2.21(2.15,2.29)	2.13(1.86,2.23)	−5.148	***<0.001***
Na^+(mM)	136.02±4.42	136.11±6.36	−0.120	0.905
K^+(mM)	4.00±0.45	4.08±0.55	−1.122	0.263
Blood phosphorus(mM)	0.81±0.27	0.70±0.34	2.386	***0.018***
DDi (mg/L)	1.11 (0.67,2.07)	2.72 (1.39,3.94)	−6.597	***<0.001***

Notes: P value for the comparison between the two groups. The boldfaced and italic P values are statistically different.
Abbreviations: WBC, white blood cell count; HB, hemoglobin; PLT, platelet count; HCT, hematocrit; RDW, red blood cell volume distribution width; AMY, amylase; BG, blood glucose; TG, triglycerides; TBIL, total bilirubin; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; ALB, albumin; BUN, blood urea nitrogen; Scr, serum creatinine; HCO_3^-, bicarbonate; Ca^{2+}, serum calcium; K^+, blood potassium; Na^+, blood sodium; DDi, D-Dimer.

showed that the WBC (odds ratio [OR], 1.159; 95% confidence interval [CI], 1.036–1.297; P = 0.010), LDH (OR, 1.008; 95% CI, 1.003–1.012; P <0.001), Scr (OR, 1.029; 95% CI, 1.002–1.056; P=0.034), and DDi (OR, 1.359; 95% CI, 1.005–1.838; P=0.046) were independent risk factors for the onset of MSAP and SAP. ALB (OR, 0.898; 95% CI, 0.825–0.977;

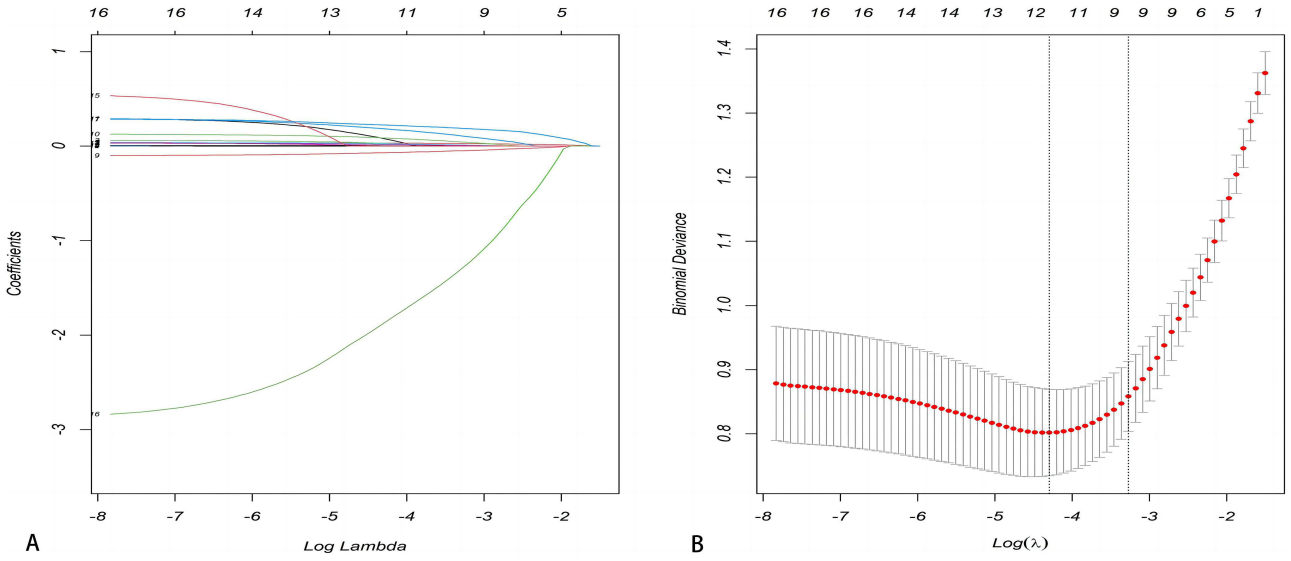

Figure 2 Selection of predictive factors using the least absolute shrinkage and selection operator logistic regression algorithm. (**A**) Least absolute shrinkage and selection operator (LASSO) coefficient profiles of the 17 candidate variables. (**B**) The best value was determined by the two dashed vertical lines drawn according to the minimum mean-square error criterion (left dashed line) and the standard error criterion (right dashed line). In the present study, nine predictors were selected according to the standard error criterion (λ=0.041).

Table 4 Logistic Regression Analysis of Independent Predictors in HLMSAP and HLSAP

	β	Standard Error	Wald	P	OR	95% CI	
						Lower limit	Upper limit
WBC	0.148	0.057	6.634	0.010	1.159	1.036	1.297
LDH	0.008	0.002	12.413	<0.001	1.008	1.003	1.012
ALB	−0.108	0.043	6.294	0.012	0.898	0.825	0.977
Scr	0.028	0.013	4.483	0.034	1.029	1.002	1.056
Ca^{2+}	−2.679	1.252	4.573	0.031	0.067	0.010	0.794
DDi	0.307	0.154	3.966	0.046	1.359	1.005	1.838

Abbreviations: WBC, white blood cell count; LDH, lactate dehydrogenase; ALB, albumin; Scr, serum creatinine; Ca^{2+}, serum calcium; DDi, D-Dimer; β, regression coefficient; OR, odds ratio; CI, confidence interval.

P=0.012) and Ca^{2+} (OR, 0.067; 95% CI, 0.010–0.794; P=0.031) were independent protective factors for MSAP and SAP attack (Table 4).

Nomogram Construction

According to multivariate regression results, the WBC, LDH, ALB, Scr, Ca^{2+}, and DDi were used to construct a MSAP +SAP prediction model; R software was used to visualize the model and obtain a nomogram. A total score reaching approximately 35 points indicates that HLAP could progress to MSAP or SAP. A total score close to 55 points indicates that the risk of progression to MSAP or SAP is as high as 90% (Figure 3).

Discrimination Verification of Nomogram

The C-index value was used to evaluate the degree of discrimination, and R software was employed to sample 1000 times through the bootstrap method to obtain a new sample dataset. The C-index value was 0.908 (95% CI, 0.867–0.948) in the training cohort and 0.950 (95% CI, 0.910–0.990) in the validation cohort. The verification results of the two

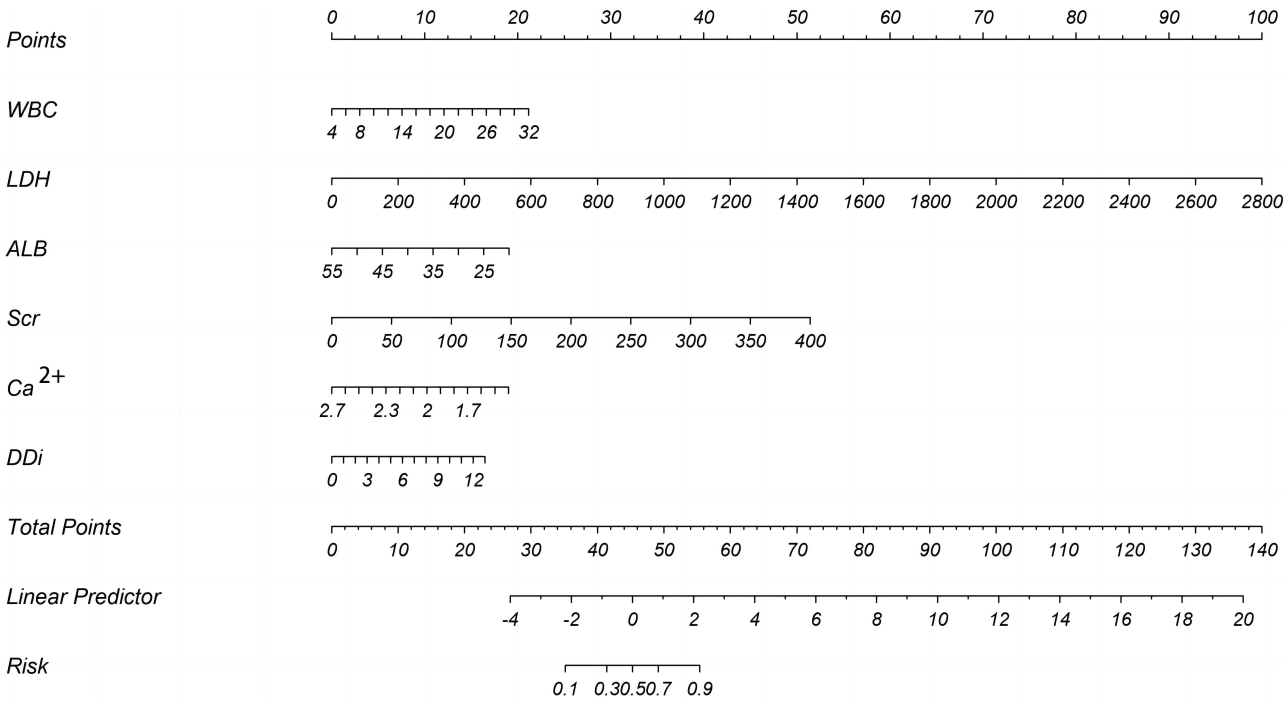

Figure 3 A nomogram for the severity of the first episode of HLAP.
Abbreviations: WBC, white blood cell count; LDH, lactate dehydrogenase; ALB, albumin; Scr, serum creatinine; Ca^{2+}, serum calcium; DDi, D-Dimer.

cohorts were similar, with both values exceeding 0.9, indicating that the nomogram derived from this study could effectively discriminate between MAP and MSAP or SAP.

Calibration Verification of the Nomogram

The HL goodness-of-fit test (χ^2=7.015, P=0.535) demonstrated a favorable fit for this model; a calibration curve was used to evaluate the calibration of the nomogram model. As shown in Figure 4, "apparent" represents the original curve, "ideal" represents the ideal standard curve, and "bias-corrected" represents the calibration curve. The Brier score of the training cohort was 0.128, and that of the validation cohort was 0.109, indicating that the nomogram used in this study could predict MSAP or SAP (Figure 4).

The ROC Curve Analysis of Nomogram and Scoring System

The area under the curve (AUC) value was calculated through the R software pROC package to compare the accuracy of the nomogram, MCTSI, APACHE II score, and BISAP score predicting MSAP or SAP. In the training cohort, the AUC of the nomogram, MCTSI, APACHE II, and BISAP were 0.908 (95% CI, 0.867–0.948), 0.821 (95% CI, 0.770–0.873), 0.689 (95% CI, 0.622–0.756), and 0.833 (95% CI, 0.786–0.880), respectively (Figure 5A). In the validation cohort, the

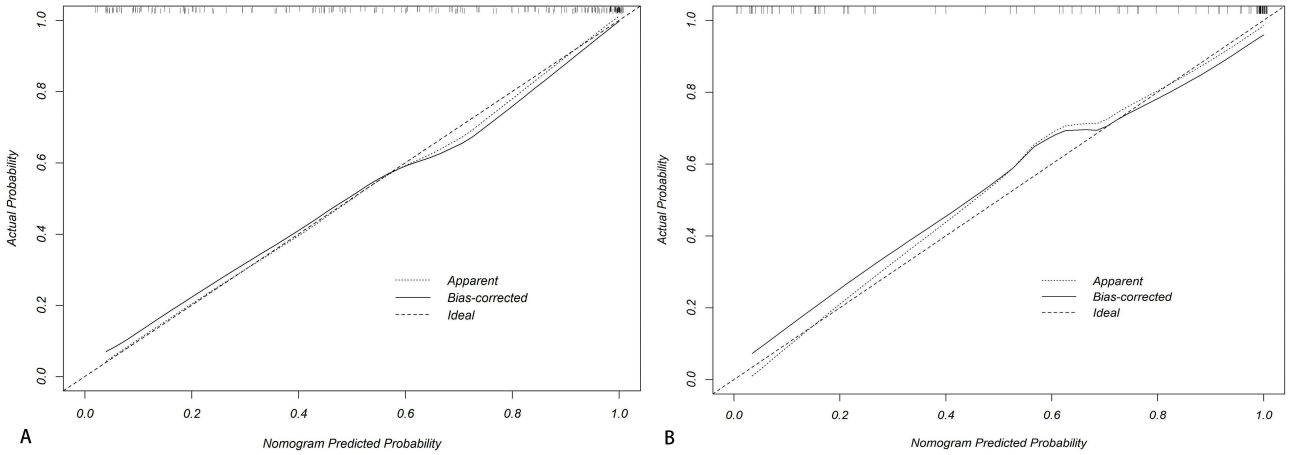

Figure 4 Calibration curve for predicting the first episode of HLAP (**A**) training cohort; (**B**) validation cohort.

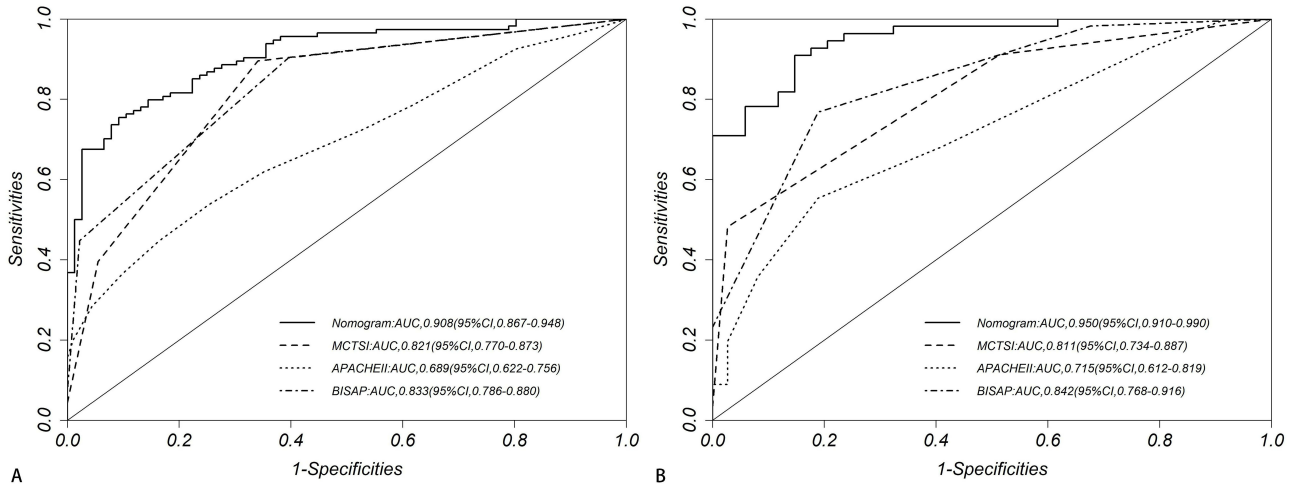

Figure 5 Receiver operating characteristic curve for predicting the first episode of HLAP (**A**) training cohort; (**B**) validation cohort.
Abbreviations: MCTSI, modified computed tomography severity index; APACHE II, Acute Physiology and Chronic Health Evaluation II; BISAP, Bedside Index for Severity in Acute Pancreatitis.

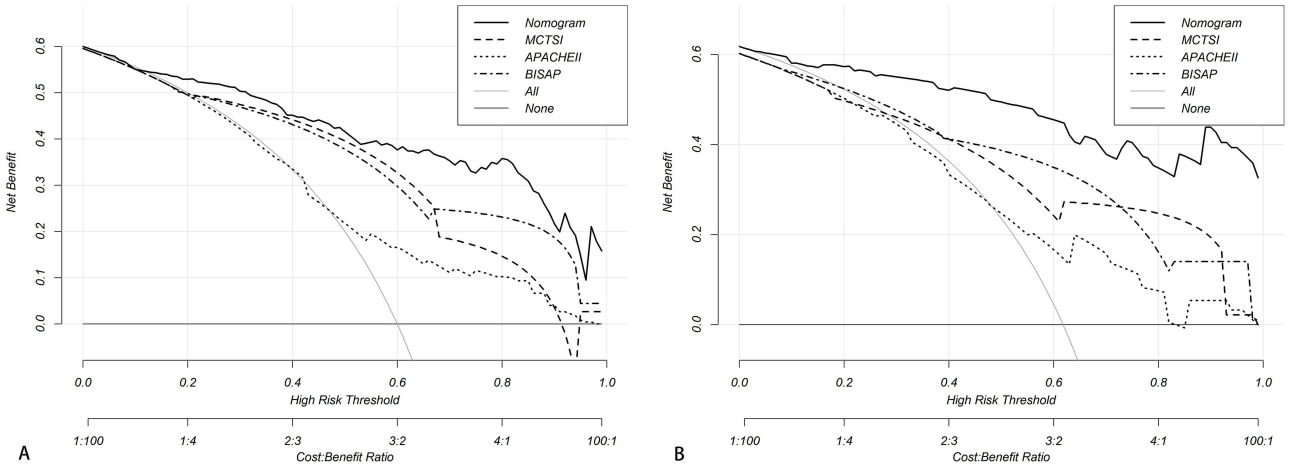

Figure 6 Decision curve of nomogram and the scoring system for predicting the first episode of HLAP (**A**) training cohort; (**B**) validation cohort).
Abbreviations: MCTSI, modified computed tomography severity index; APACHE II, Acute Physiology and Chronic Health Evaluation II; BISAP, Bedside Index for Severity in Acute Pancreatitis.

AUC of the nomogram, MCTSI, APACHE II, and BISAP were 0.950 (95% CI, 0.910–0.990), 0.811 (95% CI, 0.734–0.887), 0.715 (95% CI, 0.612–0.819), and 0.842 (95% CI, 0.768–0.916), respectively (Figure 5B). These results indicated that the developed nomogram could accurately predict the HLAP severity and it had a robust performance.

Decision Curve Analysis of Nomogram and Scoring System

The "rmda" package in the R software was utilized for generating the decision curve. The four distinct DCA curves correspond to the four distinct clinical diagnostic models. The DCA curve shows that the developed nomogram has a greater net benefit than the other system scores in predicting the severity of disease in patients with HLAP; this demonstrates its utility in clinical decision-making (Figure 6).

Discussion

AP is a common inflammatory disease of the pancreas. Hypertriglyceridemia (HTG) has emerged as a prominent etiological factor of AP in young individuals.[11] HLAP is characterized by a unique pathogenesis, rapid progression, and a propensity to worsen in severity,[3] which poses a significant challenge for clinicians in terms of its clinical management. Early diagnosis and assessment of HLAP severity have assumed paramount importance. Clinical scoring systems such as Ranson, BISAP, APACHE II, and MCTSI scores, have been used to predict the severity of the disease in patients with AP.[8] The Ranson score is calculated based on data from admission and within 48 h after admission and cannot be evaluated within 24 h, resulting in a relatively poor timeliness.[12] The BISAP score incorporates five easily-obtainable predictive factors; but its sensitivity and positive predictive values were 70% and 40%, respectively.[13] APACHE II is designed to predict the severity and mortality of patients with AP admitted to the ICU with a large set of mandatory variables. Although the AUC of APACHE II in prediction of SAP is 0.820, it is not specific.[14] Imaging data obtained by computed tomography (CT) is one of the criteria for AP diagnosis. However, CT may underestimate or incorrectly classify AP severity if obtained less than 72 h after the symptoms' onset.[15] A specific scoring system for HLAP in clinical practice is currently not available. Therefore, there is an urgent need to explore evaluation methods with good sensitivity and specificity that are easily implemented in clinical practice.

We selected six independent predictors through multivariate analysis to construct a nomogram. WBC, LDH, ALB, Scr, Ca^{2+}, and DDi were independent predictors for the tendency of HLAP to become severe. HTG is the main characteristic feature of HLAP; however, a meta-analysis including 11,965 patients from 16 eligible studies revealed no significant difference in the severity of AP based on the extent of HTG.[16]

The WBC count of the patients with HLMSAP and HLSAP was significantly higher than that of the patients with HLMAP. The elevation in WBC count may be attributed to AP-related inflammation or pancreatic infection. Mayer et al

concluded that the WBC count provides a good distinction between MAP and SAP. They also confirmed that this difference was evident on the day of admission in the patients with AP.[17] Compared with AP due to other etiological factors, HLAP is more likely to develop into severe systemic inflammatory response syndrome and has a poor prognosis.[18]

LDH, as a glycolytic enzyme, is widely distributed in the cytoplasm of tissues, mainly in the myocardium, skeletal muscles, kidneys, and liver.[19] Patients with MASP and SAP are more likely to have cardiac, pulmonary, or renal dysfunction; thus, they have elevated LDH levels. The organ specificity of LDH is poor, but it can indicate the extent of the pancreatitis-caused damage to other organs.[20] At present, LDH has been used by the Ranson, Glasgow, and Japanese Severity Scores to predict the severity of early AP.[8] The level of LDH can serve as a simple and valuable parameter for predicting AP associated with organ failure and pancreatic necrosis.[21,22]

ALB is a natural plasma protein that is exclusively synthesized by the liver but can be catabolized in most organs. During the development of AP, trypsin and elastase damage vascular endothelial cells, resulting in increased vascular permeability and subsequent penetration of ALB into the tissue space.[23] In addition, the decrease in the ALB levels in patients with MSAP and SAP may be attributed to the liver's decreased capacity to biosynthesize ALB due to reduced food intake and stimulation of inflammatory factors.[23] During the development of HLAP, pancreatic lipase hydrolyzes high levels of TG in the pancreas and surrounding areas, resulting in a substantial release of free fatty acids that surpasses the binding capacity of ALB. As the ALB levels decrease, further damage to the pancreatic acinar cells and small blood vessels occurs. Thus, serum ALB may act as a serum biomarker for assessing the severity of AP.[24,25] The incidences of organ failure and pancreatic necrosis in patients with AP complicated by hypoalbuminemia were significantly higher than those in patients without hypoalbuminemia.[26,27] Thus, ALB levels were negatively correlated with the severity of AP.[28]

Scr is a critical indicator of kidney function. During AP development, vascular permeability increases with the release of inflammatory mediators, resulting in a significant accumulation of body fluid in the interstitial space. This leads to decrease in renal perfusion and circulating blood volume, ultimately causing an elevation of Scr level and other metabolites.[29] During the development of AP, a plethora of inflammatory factors are released, such as TNF-α, which directly acts on the glomeruli and capillaries, leading to ischemia and tubular necrosis. Cytokines, such as IL-1β, IL-8, and IL-6, exert their effects on endothelial cells, leading to renal ischemia and thrombosis by releasing oxygen-free radicals.[30] Due to the unique pathogenesis pattern of HLAP, the hypercoagulable state induced by HTG gives rise to microcirculation disorders and thrombosis, which in turn leads to renal ischemia and hypoxic damage.[31] Elevated Scr, an indicator of acute kidney, is associated with pancreatic necrosis, organ failure, and mortality in patients with AP.[32,33] A large multicenter study conducted in China indicated that the incidence of acute renal failure in patients with HLAP is higher than that in patients with non-HLAP.[3] Early changes in Scr levels, especially in the first 24 hours after admission, can serve as a predictive indicator for the severity of AP,[34] which is consistent with our research findings.

Studies have demonstrated that serum Ca^{2+} levels can determine the exocrine functions of the pancreas and pathological progression of AP.[35,36] AP is usually accompanied by a decrease in serum Ca^{2+} levels. Ca^{2+} has been proven to be an independent predictor of the development of AP complicated by organ failure.[37] Ca^{2+} is negatively correlated with the severity of AP,[38,39] which is line with our findings. The hypocalcemia induce by AP may be attributed to the autodigestion of mesenteric fat by pancreatic enzymes, which in turn leads to the release of free fatty acids that subsequently form calcium salts. Furthermore, catecholamines are involved in mediating the translocation of serum Ca^{2+} into tissues.[40] Additionally, HLAP's special pathogenesis involves the hydrolysis of high concentrations of TG in the pancreas and its surroundings by pancreatic lipase, which locally produces large amounts of free fatty acids and forms calcium salts through complexing with Ca^{2+}.[41]

DDi is a marker of coagulation and fibrinolysis. Elevated levels of DDi suggest a possible hypercoagulable state in the blood. During AP, the HTG-induced hypercoagulable state of blood leads to microcirculation disorders and thrombosis, further leading to ischemia and hypoxia-induced damage.[31] Our previous studies showed that HLAP patients with acute renal failure have significantly higher DDi levels than those without acute renal failure.[42] Previous studies have shown that patients with AP and elevated DDi levels are more likely to develop pancreatic necrosis and organ failure than those with normal DDi levels, indicating a positive correlation between DDi levels and the severity of AP.[43] Changes in the coagulation system are closely associated with AP complications.[44] Therefore, WBC count, LDH, ALB,

Scr, Ca^{2+}, and DDi are all important indicators that can effectively predict the trend of HLAP towards moderate-severe or severe exacerbation.

Nomograms can be readily employed to evaluate the odds of a given clinical outcome in an individual patient. Thus, they are increasingly and frequently used as prognostic tools in clinical decision-making.[9,45] We endeavored to develop a nomogram capable of promptly evaluating the progression of patients with HLAP towards moderate-severe or severe exacerbation at an early stage. This nomogram consists of six variables that can be readily measured within 24 h after admission and can predict the risk of progression to MSAP or SAP in patients with HLAP for early intervention and treatment, improving the prognosis of patients with HLAP. The ROC curve of this model was further plotted and revealed an AUC value of 0.908, indicating excellent prediction accuracy and recognition performance. The AUC of this prediction model had obvious advantages compared with that of APACHE II, BISAP, and MCTSI. The calibration curve of this model revealed a strong concordance between the predicted and standard curves. The DCA curve was constructed to evaluate the net benefit of this prediction model, demonstrating its favorable applicability in clinical practice. The nomogram was validated in another provincial tertiary grade A hospital, showing good predictive value and clinical applicability. The overall findings of our study demonstrate that our nomogram exhibits superior predictive reliability, accuracy and optimal net benefit when compared to other clinical scoring systems, such as APACHE II, BISAP, and MCTSI. This study's nomogram can be further developed into a web calculator or APP in the future. After the user inputs the value of the predictor variable, the risk probability can be calculated based on the prediction model, thereby streamlining the assessment process.

There are some limitations in this study. First, this study is a retrospective design, and selection bias is inevitable Therefore, prospective studies are needed, and sample sizes are further expanded to enhance the level of evidence. Second, this nomogram was established based on the clinical data of patients with a first episode of HLAP, and further research is required to determine its applicability to recurrent HLAP. Finally, the lack of validation of this study across diverse populations may limit the extrapolation and generalization of this nomogram to other populations worldwide.

Conclusions

The WBC count, LDH, ALB, Scr, Ca^{2+}, and DDi are crucial indicators that can predict the trend of HLAP towards moderate-severe or severe exacerbation. Moreover, the established nomogram prediction model exhibited excellent differentiation, calibration, and clinical applicability, which holds significant implications for early evaluation, timely treatment, personalized management, and prognosis improvement of HLAP.

Data Sharing Statement

The datasets generated/analyzed during the present study are available from the corresponding authors on reasonable request.

Ethics Approval and Informed Consent

This study conforms to the Declaration of Helsinki, as revised in 2013, and other relevant regulations. The ethical approval was granted by the Ethics Committee of Fujian Medical University (Ethical approval number: 2023KY220). The need for patient consent to review their medical records was waived by the Ethics Committee of Fujian Medical University. The waiver was granted based on the following reasons: (1) The retrospective nature of the study; (2) The lack of intervention administration to the participants; (3) The minimal risk posed to patients; (4) The absence of adverse impact on patient rights and health, and (5) The unequivocal assurance that patient data confidentiality would be rigorously safeguarded throughout the research process. To ensure the confidentiality of patient data, all personal identifiers have been anonymized and eliminated from the dataset.

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 conflict of interest in this work.

References

1. Li X, Ke L, Dong J, et al. Significantly different clinical features between hypertriglyceridemia and biliary acute pancreatitis: a retrospective study of 730 patients from a tertiary center. *BMC Gastroenterol*. 2018;18(1):89. doi:10.1186/s12876-018-0821-z
2. Iannuzzi JP, King JA, Leong JH, et al. Global incidence of acute pancreatitis is increasing over time: a systematic review and meta-analysis. *Gastroenterology*. 2022;162(1):122–134. doi:10.1053/j.gastro.2021.09.043
3. Yin G, Cang X, Yu G, et al. Different clinical presentations of hyperlipidemic acute pancreatitis: a retrospective study. *Pancreas*. 2015;44 (7):1105–1110. doi:10.1097/MPA.0000000000000403
4. Nawaz H, Koutroumpakis E, Easler J, et al. G.I. Elevated serum triglycerides are independently associated with persistent organ failure in acute pancreatitis. *Am J Gastroenterol*. 2015;110(10):1497–1503. doi:10.1038/ajg.2015.261
5. 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):102–111. doi:10.1136/gutjnl-2012-302779
6. Biberci Keskin E, Taşlıdere B, Koçhan K, Gülen B, İnce AT, Şentürk H. Comparison of scoring systems used in acute pancreatitis for predicting major adverse events. *Gastroenterol Hepatol*. 2020;43(4):193–199. doi:10.1016/j.gastrohep.2019.10.008
7. Harshit Kumar A, Singh Griwan M. A comparison of APACHE II, BISAP, Ranson's score and modified CTSI in predicting the severity of acute pancreatitis based on the 2012 revised Atlanta Classification. *Gastroenterol Rep*. 2018;6(2):127–131. doi:10.1093/gastro/gox029
8. Mounzer R, Langmead CJ, Wu BU, et al. Comparison of existing clinical scoring systems to predict persistent organ failure in patients with acute pancreatitis. *Gastroenterology*. 2012;142(7):1476–1482; quiz e15-e16. doi:10.1053/j.gastro.2012.03.005
9. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. *Lancet Oncol*. 2015;16(4):e173–e180. doi:10.1016/S1470-2045(14)71116-7
10. Callegaro D, Miceli R, Bonvalot S, et al. Development and external validation of two nomograms to predict overall survival and occurrence of distant metastases in adults after surgical resection of localised soft-tissue sarcomas of the extremities: a retrospective analysis. *Lancet Oncol*. 2016;17(5):671–680. doi:10.1016/S1470-2045(16)00010-3
11. Petrov MS, Yadav D. Global epidemiology and holistic prevention of pancreatitis. *Nat Rev Gastroenterol Hepatol*. 2019;16(3):175–184. doi:10.1038/s41575-018-0087-5
12. Yin X, Zhong X, Li J, Le M, Shan S, Zhu C. The value of RANSON score combined with BMI in predicting the mortality in severe acute pancreatitis: a retrospective study. *Int J Gen Med*. 2022;15:5015–5025. doi:10.2147/IJGM.S356626
13. Valverde-López F, Matas-Cobos AM, Alegría-Motte C, Jiménez-Rosales R, Úbeda-Muñoz M, Redondo-Cerezo E. BISAP, RANSON, lactate and others biomarkers in prediction of severe acute pancreatitis in a European cohort. *J Gastroenterol Hepatol*. 2017;32(9):1649–1656. doi:10.1111/jgh.13763
14. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13(10):818–829. doi:10.1097/00003246-198510000-00009
15. Sahu B, Abbey P, Anand R, Kumar A, Tomer S, Malik E. Severity assessment of acute pancreatitis using CT severity index and modified CT severity index: correlation with clinical outcomes and severity grading as per the revised Atlanta Classification. *Indian J Radiol Imaging*. 2017;27 (2):152–160. doi:10.4103/ijri.IJRI_300_16
16. Kiss L, Fűr G, Mátrai P, et al. The effect of serum triglyceride concentration on the outcome of acute pancreatitis: systematic review and meta-analysis. *Sci Rep*. 2018;8(1):14096. doi:10.1038/s41598-018-32337-x
17. Mayer AD, McMahon MJ, Bowen M, Cooper EH. C reactive protein: an aid to assessment and monitoring of acute pancreatitis. *J Clin Pathol*. 1984;37(2):207–211. doi:10.1136/jcp.37.2.207
18. Tsuang W, Navaneethan U, Ruiz L, Palascak JB, Gelrud A. Hypertriglyceridemic pancreatitis: presentation and management. *Am J Gastroenterol*. 2009;104(4):984–991. doi:10.1038/ajg.2009.27
19. Yin X, Xu J, Zhang Q, Yang L, Duan Y. Quantification analysis of lactate dehydrogenase and C-reactive protein in evaluation of the severity and prognosis of the acute pancreatitis. *Cell Mol Biol*. 2020;66(1):122–125. doi:10.14715/cmb/2019.66.1.20
20. Singh VK, Wu BU, Bollen TL, et al. Early systemic inflammatory response syndrome is associated with severe acute pancreatitis. *Clin Gastroenterol Hepatol*. 2009;7(11):1247–1251. doi:10.1016/j.cgh.2009.08.012
21. Tian F, Li H, Wang L, et al. The diagnostic value of serum C-reactive protein, procalcitonin, interleukin-6 and lactate dehydrogenase in patients with severe acute pancreatitis. *Clin Chim Acta*. 2020;510:665–670. doi:10.1016/j.cca.2020.08.029
22. Komolafe O, Pereira SP, Davidson BR, Gurusamy KS. Serum C-reactive protein, procalcitonin, and lactate dehydrogenase for the diagnosis of pancreatic necrosis. *Cochrane Database Syst Rev*. 2017;4(4):CD012645. doi:10.1002/14651858.CD012645
23. Li S, Zhang Y, Li M, Xie C, Serum Albumin WH. a good indicator of persistent organ failure in acute pancreatitis. *BMC Gastroenterol*. 2017;17 (1):59. doi:10.1186/s12876-017-0615-8

24. Li S, Liu Z, Wu H. The product value of serum albumin and prothrombin time activity could be a useful biomarker for severity prediction in AP: an ordinal retrospective study. *Pancreatology*. 2019;19(2):230–236. doi:10.1016/j.pan.2019.02.001
25. Xu X, Ai F, Huang M. Deceased serum bilirubin and albumin levels in the assessment of severity and mortality in patients with acute pancreatitis. *Int J Med Sci*. 2020;17(17):2685–2695. doi:10.7150/ijms.49606
26. Kaplan M, Ates I, Akpinar MY, et al. Predictive value of C-reactive protein/albumin ratio in acute pancreatitis. *Hepatobiliary Pancreat Dis Int*. 2017;16(4):424–430. doi:10.1016/S1499-3872(17)60007-9
27. Karabuga B, Gemcioglu E, Konca Karabuga E, Baser S, Ersoy O. Comparison of the predictive values of CRP, CRP/albumin, RDW, neutrophil/lymphocyte, and platelet/lymphocyte levels in determining the severity of acute pancreatitis in patients with acute pancreatitis according to the BISAP score. *Bratisl Lek Listy*. 2022;123(2):129–135. doi:10.4149/BLL_2022_020
28. Yue W, Liu Y, Ding W, et al. The predictive value of the prealbumin-to-fibrinogen ratio in patients with acute pancreatitis. *Int J Clin Pract*. 2015;69(10):1121–1128. doi:10.1111/ijcp.12682
29. Komara NL, Paragomi P, Greer PJ, et al. Severe acute pancreatitis: capillary permeability model linking systemic inflammation to multiorgan failure. *Am J Physiol Gastrointest Liver Physiol*. 2020;319(5):G573–G583. doi:10.1152/ajpgi.00285.2020
30. Zhang XP, Wang L, Zhou YF. The pathogenic mechanism of severe acute pancreatitis complicated with renal injury: a review of current knowledge. *Dig Dis Sci*. 2008;53(2):297–306. doi:10.1007/s10620-007-9866-5
31. Naqvi R. Acute kidney injury in association with acute pancreatitis. *Pak J Med Sci*. 2018;34(3):606–609. doi:10.12669/pjms.343.14953
32. Papachristou GI, Muddana V, Yadav D, Whitcomb DC. Increased serum creatinine is associated with pancreatic necrosis in acute pancreatitis. *Am J Gastroenterol*. 2010;105(6):1451–1452. doi:10.1038/ajg.2010.92
33. Wan J, Shu W, He W, et al. Serum creatinine Level and APACHE-II Score within 24 h of admission are effective for predicting persistent organ failure in acute pancreatitis. *Gastroenterol Res Pract*. 2019;2019:8201096. doi:10.1155/2019/8201096
34. Lipinski M, Rydzewski A, Rydzewska G. Early changes in serum creatinine level and estimated glomerular filtration rate predict pancreatic necrosis and mortality in acute pancreatitis: creatinine and eGFR in acute pancreatitis. *Pancreatology*. 2013;13(3):207–211. doi:10.1016/j.pan.2013.02.002
35. Petersen OH, Gerasimenko JV, Gerasimenko OV, Gryshchenko O, Peng S. The roles of calcium and ATP in the physiology and pathology of the exocrine pancreas. *Physiol Rev*. 2021;101(4):1691–1744. doi:10.1152/physrev.00003.2021
36. Frick TW. The role of calcium in acute pancreatitis. *Surgery*. 2012;152(3):S157–S163. doi:10.1016/j.surg.2012.05.013
37. Peng T, Peng X, Huang M, et al. Serum calcium as an indicator of persistent organ failure in acute pancreatitis. *Am J Emerg Med*. 2017;35(7):978–982. doi:10.1016/j.ajem.2017.02.006
38. Gupta V, Narang SS, Gill CS, Selhi PK, Gupta M. Red cell distribution width and ratio of red cell distribution width-to-total serum calcium as predictors of outcome of acute pancreatitis. *Int J Appl Basic Med Res*. 2023;13(1):5–9. doi:10.4103/ijabmr.ijabmr_286_22
39. Han T, Cheng T, Liao Y, et al. The ratio of red blood cell distribution width to serum calcium predicts severity of patients with acute pancreatitis. *Am J Emerg Med*. 2022;53:190–195. doi:10.1016/j.ajem.2022.01.024
40. Shahbaz AU, Zhao T, Zhao W, et al. Calcium and zinc dyshomeostasis during isoproterenol-induced acute stressor state. *Am J Physiol Heart Circ Physiol*. 2011;300(2):H636–H644. doi:10.1152/ajpheart.00900.2010
41. Scherer J, Singh VP, Pitchumoni CS, Yadav D. Issues in hypertriglyceridemic pancreatitis: an update. *J Clin Gastroenterol*. 2014;48(3):195–203. doi:10.1097/01.mcg.0000436438.60145.5a
42. Lin Y, Yu S, Wu X, et al. Clinical analysis of the therapeutic effect of plasma exchange on hypertriglyceridemic acute pancreatitis: a retrospective study. *Transfusion*. 2022;62(1):72–81. doi:10.1111/trf.16724
43. Zhang GQ, Wang G, Li L, et al. Plasma D-dimer level is an early predictor of severity of acute pancreatitis based on 2012 Atlanta classification. *Med Sci Monit*. 2019;25:9019–9027. doi:10.12659/MSM.918311
44. Zheng J, Han M, Chen J, Deng MM, Luo G. Predictive value of D-dimer and fibrinogen degradation product for splanchnic vein thrombosis in patients with severe acute pancreatitis: a single-center retrospective study. *Scand J Gastroenterol*. 2023;58(10):1166–1172. doi:10.1080/00365521.2023.2215367
45. Rose PG, Java J, Whitney CW, et al. Nomograms predicting progression-free survival, overall survival, and pelvic recurrence in locally advanced cervical cancer developed from an analysis of identifiable prognostic factors in patients from NRG oncology/gynecologic oncology group randomized trials of chemoradiotherapy. *J Clin Oncol*. 2015;33(19):2136–2142. doi:10.1200/JCO.2014.57.7122