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Development and validation of a nomogram based on Lasso-Logistic regression for predicting splenomegaly secondary to acute pancreatitis

Bohan Huang[1,2†], Feng Cao[1,2†], Yixuan Ding[1,2], Ang Li[1,2], Tao Luo[1,2], Xiaohui Wang[1,2], Chongchong Gao[1,2], Zhe Wang[1,2], Chao Zhang[1,2] and Fei Li[1,2*]

Abstract

Purpose Investigate the clinical characteristics of splenomegaly secondary to acute pancreatitis (SSAP) and construct a nomogram prediction model based on Lasso-Logistic regression.

Methods A retrospective case-control study was conducted to analyze the laboratory parameters and computed tomography (CT) imaging of acute pancreatitis (AP) patients recruited at Xuanwu Hospital from December 2014 to December 2021. Lasso regression was used to identify risk factors, and a novel nomogram was developed. The performance of the nomogram in discrimination, calibration, and clinical usefulness was evaluated through internal validation.

Results The prevalence of SSAP was 9.2% (88/950), with the first detection occurring 65(30, 125) days after AP onset. Compared with the control group, the SSAP group exhibited a higher frequency of persistent respiratory failure, persistent renal failure, infected pancreatic necrosis, and severe AP, along with an increased need for surgery and longer hospital stay ($P<0.05$ for all). There were 185 and 79 patients in the training and internal validation cohorts, respectively. Variables screened by Lasso regression, including platelet count, white blood cell (WBC) count, local complications, and modified CT severity index (mCTSI), were incorporated into the Logistic model. Multivariate analysis showed that WBC count $\leqq 9.71\times10^9$/L, platelet count $\leqq 140\times10^9$/L, mCTSI $\geqq 8$, and the presence of local complications were independently associated with the occurrence of SSAP. The area under the receiver operating characteristic curve was 0.790. The Hosmer-Lemeshow test showed that the model had good fitness ($P=0.954$). Additionally, the nomogram performed well in the internal validation cohorts.

Conclusions SSAP is relatively common, and patients with this condition often have a worse clinical prognosis. Patients with low WBC and platelet counts, high mCTSI, and local complications in the early stages of the illness are at a higher risk for SSAP. A simple nomogram tool can be helpful for early prediction of SSAP.

Keywords Acute pancreatitis, Splenomegaly, Risk factors, Lasso-Logistic regression, Nomogram

†Bohan Huang and Feng Cao are co-first authors and contributed equally to this work.

*Correspondence:
Fei Li
feili36@ccmu.edu.cn
Full list of author information is available at the end of the article

Introduction

Worldwide, acute pancreatitis (AP) is among the most common digestive system emergencies. The incidence of AP is estimated at 110–140 cases per 100,000 population, with over 300,000 annual emergency department visits in the United States [1]. Most patients experience mild AP, typically resolving within a week. However, about 20% of patients progress to moderately severe or severe AP, which carries a mortality rate as high as 20–40% [2]. Current research on the spleen in AP is often mentioned in the context of sinistral portal hypertension. As most of these patients are asymptomatic, spleen changes during AP have historically been easily overlooked in clinical practice [3]. Therefore, understanding the prognosis and risk factors associated with splenomegaly secondary to AP (SSAP) is of clinically significant.

The spleen, a vital immune organ, plays a crucial role in the immunoregulatory processes related to AP [4]. Additionally, there is a close anatomical relationship among the spleen, splenic vessels, and pancreas. Pancreatic inflammation and local complications can affect the spleen and its vessels [5]. Xie et al. reported that 40 out of 239 patients with AP (16.7%) had splenomegaly [6]. Tsushima et al. found that patients with a spleen volume that more than doubled between 4–30 days after onset, compared to the first 3 days, had a more complicated disease course [7]. Furthermore, these patients are also at risk for adverse events such as hypersplenism, abdominal discomfort, gastrointestinal variceal bleeding, and other complications. Early prediction of splenomegaly, using laboratory and radiological indicators identified in the initial stages of the disease could be beneficial. However, such data are rarely reported. In this study, we combine Lasso regression and Logistic regression. The former effectively screens variables, while the latter facilitates modeling and visualization for direct interpretation.

Therefore, this study aims to: (1) explore the clinical characteristics of SSAP; (2) elucidate independent risk factors and develop nomograms for the early prediction of SSAP.

Methods

Study design and participants

This retrospective case-control study was conducted at the Department of General Surgery, Xuanwu Hospital Capital Medical University, a tertiary medical referral center in China. It analyzed patients hospitalized with AP from December 2014 to December 2021. We included patients aged 18 or older experiencing their first episode of AP, as defined by the 2012 Atlanta Classification criteria [8]. Exclusion criteria included lack of early disease data, absence of abdominal contrast-enhanced computed tomography (CECT) within 1 week of onset, failure to obtain serum indicators within 24 h of onset, and certain confounding conditions (pregnancy, chronic liver disease, leukemia, chronic pancreatitis, pancreatic cancer, peritoneal/retroperitoneal tumors, or a history of gastric, splenic, or pancreatic surgery). Of the 950 eligible patients, 88 with splenomegaly identified in computed tomography (CT) scans during hospitalization or follow-up were categorized as the case group. The control group consisted of 176 patients, randomly selected from the remaining 862 patients without splenomegaly, using Excel software (v16.64; MS Corp., Redmond, WA, United States). We randomly divided all patients of the study cohort into the training cohort and internal validation cohort in a 7:3 ratio. The study was approved by the Ethics Committee of Xuanwu Hospital Capital Medical University (NO: 2020-092), and due to its retrospective nature, waived the requirement for written informed consent.

Image analysis

All patients underwent CT imaging within 1 week of AP onset to identify radiological features for early prediction. All images were reassessed and reviewed by two senior radiologists with over 10 years of experience, who were blinded to the clinical data and outcome parameters. All CT examinations were performed using either a 128-layer CT scanner (Somatom Definition AS, Siemens Medical Systems, Erlangen, Germany) or a 256-layer CT scanner (Revolution CT, GE Healthcare, Milwaukee, WI, United States). A dose of 1.3 mL/kg of iopromide (Ultravist 370; Bayer Schering Pharma, Berlin, Germany) was injected intravenously at a rate of 3 ml/s using a high-pressure injector. Subsequently, arterial and portal venous phase scans were performed when the attenuation of the aorta at the thoracolumbar junction reached 180 HU and after a fixed delay of 60 s. The scanning range extended from the diaphragmatic dome to the pubic symphysis. The scan parameters were as follows: detector collimation of 64×0.625 mm, beam pitch of 0.984, kVp of 120, automated dose modulation with a maximum allowable tube current set at 200 mAs, and section thickness/reconstruction interval of 5 mm/5 mm.

Data collection and definition

Demographic, clinicopathological, and CECT data were collected. Demographic data included age, gender, body mass index (BMI), and histories of smoking, drinking, cardiovascular diseases, respiratory diseases, urinary diseases, and diabetes. Clinicopathological data included: (1) etiology; (2) serum indicators within 24 h of onset, such as white blood cell (WBC) count, neutrophil count, hematocrit, platelet count, lymphocyte count, calcium, triglyceride, creatinine, C-reactive protein, procalcitonin,

international normalized ratio, activated partial thromboplastin time (APTT), prothrombin time, thrombin time, fibrinogen, and D-dimer; (3) clinical outcomes, including severity of AP, organ failure, infected pancreatic necrosis (IPN), need for surgery, length of hospital stay, and death. IPN included confirmed or suspected infected pancreatic or peripancreatic necrosis. Confirmed infected necrosis was defined by positive cultures from pancreatic or peripancreatic necrotic tissue obtained via fine-needle aspiration, the first drainage procedure, or surgery, or by the presence of gas in fluid collections on CT. Suspected infected necrosis was defined as persistent sepsis or progressive clinical deterioration despite maximal support in the Intensive Care Unit (ICU), without documented infected necrosis.

The "spleen index" (product of length, depth, and width) and the total volume of consecutive scan slices were both used to diagnose splenomegaly [9–11]. However, their implementation in current clinical routines was somewhat challenging [6, 10, 12]. Research on the relationship between spleen length, width, thickness, and volume showed a good correlation between spleen length, width, and volume [12, 13]. A spleen length threshold of 9.76 cm was found to be a simpler method for diagnosing splenomegaly [13]. In our study, splenomegaly was defined as a spleen length greater than 9.76 cm. Total spleen length was calculated by multiplying the number of observed spleen slices by the thickness of each slice. For example, if the spleen was observed in 20 consecutive 5 mm thick transverse images, its length was recorded as 10 cm. Other imaging features, including pancreatic parenchyma and local complications, were also recorded to explore their predictive value. On CECT scans, areas of the pancreatic parenchyma that did not enhance were considered indicative of pancreatic parenchymal necrosis [8]. Peripancreatic necrosis was characterized by normal pancreatic enhancement on CECT scans, with necrosis in the surrounding tissues [8]. Local complications included Acute Peripancreatic Fluid Collection (APFC) and Acute Necrotic Collection (ANC). APFC is a peripancreatic fluid associated with edematous pancreatitis [8]. ANC is defined as a collection containing variable amounts of fluid and necrotic tissue associated with necrotizing pancreatitis [8]. The CT Severity Index (CTSI) was based on previous studies conducted by Balthazar et al. [14, 15]. The modified CTSI (mCTSI) was drawn on the research of Mortele et al. [16].

Statistical analysis

Continuous variables were presented as mean ± standard deviation or median (interquartile range, IQR), with differences between groups compared using Student's *t* test or Mann-Whitney *U* test. Categorical variables were presented as absolute numbers (proportions) and analyzed for differences using Chi-square test or Fisher's exact test. The optimal cutoff value was identified using receiver operating characteristic curves. Lasso regression was used for identifying potential risk factors. A predictive model was established using Logistic regression based on parameters selected by Lasso regression. A nomogram was constructed from the final multivariate regression analysis results. The prediction model was then validated internally. The model's discriminative ability was evaluated using receiver operating characteristic (ROC) curves. The calibration between predicted and actual risks was assessed using the Hosmer–Lemeshow test and calibration curves. Decision curve analysis (DCA) was employed to quantify the net benefit at different threshold probabilities, assessing the clinical effectiveness of the model. A two-tailed P-value < 0.05 was considered statistically significant. Data analysis was conducted using SPSS software (version 26.0; SPSS Inc., Chicago, IL, United States) or R software (version 4.2.2, R Development Core Team).

Results

Clinical profile, baseline characteristics, and imaging features

Among the 950 patients who met the inclusion and exclusion criteria, 88 cases of splenomegaly were observed (9.2%). The first detection of splenomegaly occurred 65 (30, 125) days after AP onset. Patients with SSAP experienced more frequent IPN, persistent respiratory failure, persistent renal failure, and severe AP (SAP); a higher need for surgery; and longer hospital stay ($P < 0.05$ for all). The proportion of male patients in the SSAP group was significantly higher than in the control group. Biliary pancreatitis was significantly less common in the SSAP group than in the control group. There were no significant differences between the groups in terms of age, BMI, coexisting conditions, smoking and drinking. Comparing serum laboratory indicators within 24 h of onset, the SSAP group had significantly higher triglyceride and APTT, and significantly lower WBC count, neutrophil count, platelet count and hematocrit ($P < 0.05$ for all). Detailed clinical outcomes, baseline characteristics, and serum indicators are presented in Table 1. Patients in the SSAP group were more likely to have pancreatic parenchymal necrosis, local complications, and higher mCTSI ($P < 0.05$ for all). Table 2 provides additional details on the imaging features of pancreatic parenchyma and local complications.

Table 1 Baseline characteristics of all patients

	All ($n=264$)	Cohort			Cohort		
		Case group ($n=88$)	Control group ($n=176$)	*P*-value	Training ($n=185$)	Validation ($n=79$)	*P*-value
Clinical outcomes							
Severity of AP				**0.013**			0.612
MAP[a] and MSAP[a]	196 (74.2%)	57 (64.8%)	139 (79.0%)		139 (75.1%)	57 (72.2%)	
SAP[a]	68 (25.8%)	31 (35.2%)	37 (21.0%)		46 (24.9%)	22 (27.8%)	
Persistent respiratory failure[b]	47 (17.8%)	24 (27.3%)	23 (13.1%)	**0.005**	32 (17.3%)	15 (19.0%)	0.742
Persistent rental failure[b]	40 (15.2%)	19 (21.6%)	21 (11.9%)	**0.039**	28 (15.1%)	12 (15.2%)	0.991
Persistent circulatory failure[b]	33 (12.5%)	14 (15.9%)	19 (10.8%)	0.237	24 (13.0%)	9 (11.4%)	0.722
IPN	108 (40.9%)	56 (63.6%)	52 (29.5%)	**<0.001**	76 (41.1%)	32 (40.5%)	0.931
Need for surgery	89 (33.7%)	48 (54.5%)	41 (23.3%)	**<0.001**	62 (33.5%)	27 (34.2%)	0.917
Length of hospital stay, days	25.0 (12.0, 54.0)	39.5 (20.3, 69.5)	20.0 (11.0, 48.0)	**<0.001**	25.0 (12.5, 51.0)	24.0 (12.0, 55.0)	0.727
Death	20 (7.6%)	6 (6.8%)	14 (8.0%)	0.742	16 (8.6%)	4 (5.1%)	0.313
Baseline characteristics							
Sex				**0.007**			0.809
Male	181 (68.6%)	70 (79.5%)	111 (63.1%)		126 (68.1%)	55 (69.6%)	
Female	83 (31.4%)	18 (20.5%)	65 (36.9%)		59 (31.9%)	24 (30.4%)	
Age, yr	49.3 ± 13.9	48.8 ± 11.9	49.6 ± 14.8	0.652	49.0 ± 13.9	50.0 ± 13.8	0.581
BMI, kg/m^2	24.5 ± 4.3	23.8 ± 4.1	24.8 ± 4.3	0.078	23.9 (21.5, 27.1)	23.4 (21.9, 27.8)	0.844
Etiology				**0.001**			0.085
Biliary	136 (51.5%)	31 (35.2%)	105 (59.7%)		103 (55.7%)	105 (59.7%)	
Hyperlipidemia	54 (20.5%)	26 (29.5%)	28 (15.9%)		35 (18.9%)	19 (24.1%)	
Alcoholic	30 (11.4%)	15 (17.0%)	15 (8.5%)		22 (11.9%)	8 (10.1%)	
Others	44 (16.7%)	16 (18.2%)	28 (15.9%)		25 (13.5%)	19 (24.1%)	
Coexisting condition							
Cardiovascular disease[c]	89 (33.7%)	24 (27.3%)	65 (36.9%)	0.118	59 (31.9%)	30 (38.0%)	0.338
Chronic obstructive pulmonary disease	5 (1.9%)	0 (0.0%)	5 (2.8%)	0.173	3 (1.6%)	2 (2.5%)	0.637
Chronic renal insufficiency	6 (2.3%)	2 (2.3%)	4 (2.3%)	> 0.999	4 (2.2%)	2 (2.5%)	> 0.999
Diabetes	56 (21.2%)	21 (23.9%)	35 (19.9%)	0.456	35 (18.9%)	21 (26.6%)	0.163
Smoking status	79 (29.9%)	29 (33.0%)	50 (28.4%)	0.447	56 (30.3%)	23 (29.1%)	0.851
Drinking status	102 (38.6%)	34 (38.6%)	68 (38.6%)	> 0.999	69 (37.3%)	33 (41.8%)	0.494
Serum indicators within 24 h of onset							
WBC, $\times 10^9$/L	8.9 (5.5, 12.1)	7.2 (4.5, 11.1)	9.6 (6.5, 13.1)	**0.001**	9.0 (5.6, 12.1)	8.8 (5.5, 12.1)	0.901
N, $\times 10^9$/L	7.0 (3.9, 10.2)	5.7 (3.1, 9.0)	7.8 (4.9, 11.4)	**0.001**	7.0 (4.2, 10.0)	7.3 (3.7, 10.9)	0.752
HCT, %	34.7 ± 7.2	32.9 ± 7.6	35.5 ± 6.8	**0.005**	34.8 ± 6.9	34.3 ± 7.7	0.599
PLT, $\times 10^9$/L	212.5 (150.3, 283.5)	193.0 (118.5, 269.3)	219.0 (161.8, 301.8)	**0.022**	219.0 (152.5, 287.5)	195.0 (144.0, 282.0)	0.525
L, $\times 10^9$/L	1.1 (0.8, 1.6)	1.2 (0.7, 1.6)	1.1 (0.8, 1.6)	0.506	1.1 (0.8, 1.6)	1.2 (0.7, 1.5)	0.423
Ca, mmol/L	2.1 (2.0, 2.2)	2.1 (2.0, 2.2)	2.1 (2.0, 2.2)	0.214	2.1 (2.0, 2.2)	2.1 (1.9, 2.3)	0.782
TG, mmol/L	1.2 (0.8, 2.1)	1.6 (1.1, 2.4)	1.0 (0.7, 1.8)	**<0.001**	1.4 (0.8, 2.1)	1.1 (0.7, 2.2)	0.118
Cr, μmol/L	59.0 (48.0, 77.0)	63.0 (47.0, 77.8)	58.0 (48.0, 76.8)	0.569	58.0 (47.0, 77.0)	61.0 (48.0, 78.0)	0.395
CRP, mg/L	120.6 (91.0, 135.6)	118.7 (98.2, 135.9)	121.1 (87.2, 135.5)	0.969	118.8 (84.1, 133.9)	124.8 (103.0, 142.9)	0.207
PCT, ng/mL	1.5 (0.2, 5.3)	1.3 (0.3, 4.8)	1.6 (0.2, 5.5)	0.676	2.0 (0.2, 5.4)	0.8 (0.2, 5.3)	0.368

Table 1 (continued)

	All ($n=264$)	Cohort			Cohort		
		Case group ($n=88$)	Control group ($n=176$)	*P*-value	Training ($n=185$)	Validation ($n=79$)	*P*-value
INR	1.1 (1.0, 1.2)	1.1 (1.1, 1.2)	1.1 (1.0, 1.2)	0.213	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	0.403
APTT, seconds	40.3 (36.2, 44.4)	41.5 (37.9, 46.1)	39.7 (35.3, 43.3)	**0.002**	40.5 (36.9, 45.0)	39.1 (35.2, 43.8)	0.161
PT, seconds	14.5 (13.6, 15.5)	14.5 (13.8, 15.5)	14.4 (13.6, 15.5)	0.328	14.4 (13.6, 15.5)	14.5 (13.6, 15.4)	0.587
TT, seconds	15.5 (14.7, 16.4)	15.5 (14.7, 16.4)	15.6 (14.8, 16.5)	0.877	15.5 (14.7, 16.3)	15.7 (14.8, 16.8)	0.644
FIB, g/L	4.3 (3.6, 5.8)	4.3 (3.5, 6.0)	4.4 (3.7, 5.7)	0.643	4.2 (3.5, 5.6)	4.7 (3.6, 6.1)	0.209
D-dimer, μg/mL	2.7 (1.3, 4.5)	2.2 (0.8, 4.3)	2.8 (1.5, 4.6)	0.050	2.7 (1.4, 4.4)	2.5 (1.2, 4.7)	0.881

Date are median (interquartile ranges), mean ± standard deviation or absolute numbers (proportions)

BMI Body mass index, *WBC* White blood cell, *N* Neutrophil, *HCT* Hematocrit, *PLT* Platelet, *L* lymphocyte, *Ca* Calcium, *TG* Triglyceride, *Cr* Creatinine, *CRP* C-reactive protein, *PCT* Procalcitonin, *INR* International normalized ratio, *APTT* Activated partial thromboplastin time, *PT* Prothrombin time, *TT* Thrombin time, *FIB* Fibrinogen, *MAP* Mild acute pancreatitis, *MSAP* Moderately severe acute pancreatitis, *SAP* Severe acute pancreatitis, *IPN* Infected pancreatic necrosis, *AP* Acute pancreatitis

P < 0.05 was bolded

[a] According to revised Atlanta classification

[b] According to revised Marshall score

[c] Cardiovascular disease includes hypertension, coronary atherosclerotic heart disease and cardiac arrhythmia requiring pharmacological management

Prediction of risk factors based on Lasso-Logistic regression

All variables were included in the LASSO regression analysis. The LASSO regression algorithm was used to screen for risk factors, and the optimal λ value was selected through 10-fold cross-validation (Fig. 1A and B).

The two dashed lines in Fig. 1B represented lambda.min and lambda.1se. Lambda.min denoted the value of λ when the model error was at its minimum. Lambda.1se represented the model error within a standard error range of λ. The variables screened by lambda.1se included WBC count, platelet count, local complications, and mCTSI. A Logistic regression model was then established based on the parameters selected by Lasso regression. Multivariate analysis showed that WBC count ≦ 9.71×10^9/L (adjusted odds ratio (adjOR), 2.31; 95% confidence interval (CI) 1.08–4.94; $P=0.030$), platelet count ≦ 140×10^9/L (adjOR, 2.65; 95% CI, 1.12–6.28; $P=0.027$), presence of local complications (adjOR, 4.18; 95% CI, 1.28–13.63; $P=0.018$), and mCTSI ≧ 8 (adjOR, 2.74; 95% CI, 1.17–6.44; $P=0.021$) were independently associated with the development of SSAP (Table 3).

Development and validation of a nomogram

Based on multivariate analysis, a new nomogram was constructed by assigning weighted points to each independent risk factor (Fig. 2).

The higher the total score of all risk factors, the higher the risk of developing SSAP. In the training cohort, the area under the ROC curve (AUC) was 0.796 (Fig. 3A). When the predictive probability exceeded 50%, indicating positive for SSAP, the model exhibited a sensitivity of 62.9% and a specificity of 82.1%. The calibration curve showed good fit between the predicted values of the model and the actual observations (Fig. 4A), and the Hosmer-Lemeshow test also demonstrated good fit ($P=0.954$). Furthermore, the DCA demonstrated that the predictive model achieved higher net benefits compared to the extreme curves within the threshold probability range of 0.1 to 0.7. (Fig. 5A). In the internal validation cohort, 79 patients were used to test the nomogram. The AUC was 0.773 (Fig. 3B), indicating good accuracy of the nomogram. The model demonstrated a sensitivity of 50% and a specificity of 83%. Meanwhile, the calibration curve of the validation cohort was also close to the ideal diagonal line (Fig. 4B). Moreover, the DCA in the internal validation cohort also showed the predictive model has high clinical application value within the threshold probability range of 0.1 to 0.5. (Fig. 5B).

Discussion

During AP, complications related to the spleen may occur, including intrasplenic pseudocysts, abscess, infarction, splenic rupture, splenic artery pseudoaneurysm, and splenic vein thrombosis [17]. SSAP is not a rare phenomenon in clinical practice and is often mentioned as one of the characteristics of sinistral portal hypertension [18]. However, the real clinical significance remains underexplored. Therefore, we conducted a retrospective case-control study to investigate this issue.

Multifactorial analysis identified early onset of lower WBC count, lower platelet count, higher mCTSI, and local complications as independent risk factors for SSAP. A WBC count < 4×10^9/L is one of the criteria for diagnosing systemic inflammatory response syndrome (SIRS) [19]. Early and persistent SIRS upon admission

Table 2 Imaging features on CECT within 1 weeks of AP onset

	All ($n=264$)	Cohort			Cohort		
		Case group ($n=88$)	Control group ($n=176$)	*P*-value	Training ($n=185$)	Validation ($n=79$)	*P*-value
Pancreatic parenchyma							
Type of pancreatic necrosis				**0.001**			0.858
Non-necrosis	91 (34.5%)	11 (12.5%)	80 (45.5%)		63 (34.1%)	28 (35.4%)	
EXPN only	8 (3.0%)	3 (3.4%)	5 (2.8%)		6 (3.2%)	2 (2.5%)	
PPN only	41 (15.5%)	16 (18.2%)	25 (14.2%)		31 (16.8%)	10 (12.7%)	
EXPN and PPN	124 (47.0%)	58 (65.9%)	66 (37.5%)		85 (45.9%)	39 (49.4%)	
Proportion of PPN, %				**< 0.001**			0.943
0	99 (37.5%)	14 (15.9%)	85 (48.3%)		69 (37.3%)	30 (38.0%)	
< 30	76 (28.8%)	28 (31.8%)	48 (27.3%)		55 (29.7%)	21 (26.6%)	
30–50	52 (19.7%)	24 (27.3%)	28 (15.9%)		35 (18.9%)	17 (21.5%)	
> 50	37 (14.0%)	22 (25.0%)	15 (8.5%)		26 (14.1%)	11 (13.9%)	
Location of PPN							
Head	79 (29.9%)	39 (44.3%)	40 (22.7%)	**< 0.001**	55 (29.7%)	24 (30.4%)	0.916
Neck	62 (23.5%)	30 (34.1%)	32 (18.2%)	**0.004**	44 (23.8%)	18 (22.8%)	0.861
Body-tail	115 (43.6%)	56 (63.6%)	59 (33.5%)	**< 0.001**	84 (45.4%)	31 (39.2%)	0.355
Local complications	177 (67.0%)	63 (71.6%)	70 (39.8%)	**< 0.001**	125 (67.6%)	52 (65.8%)	0.782
Location of local complications							
Perisplenic and left subphrenic space	103 (39.0%)	51 (58.0%)	52 (29.5%)	**< 0.001**	71 (38.4%)	32 (40.5%)	0.745
Left anterior, posterior, or surrounding renal space	133 (50.4%)	63 (71.6%)	70 (39.8%)	**< 0.001**	95 (51.4%)	38 (48.1%)	0.629
Left paracolic sulci	91 (34.5%)	42 (47.7%)	49 (27.8%)	**0.001**	66 (35.7%)	25 (31.6%)	0.528
Left iliac fossa	45 (17.0%)	14 (15.9%)	31 (17.6%)	0.728	34 (18.4%)	11 (13.9%)	0.378
Perihepatic and right subphrenic space	60 (22.7%)	32 (36.4%)	28 (15.9%)	**< 0.001**	43 (23.2%)	17 (21.5%)	0.760
Right anterior, posterior, or surrounding renal space	94 (35.6%)	46 (52.3%)	48 (27.3%)	**< 0.001**	70 (37.8%)	24 (30.4%)	0.247
Right paracolic sulci	65 (24.6%)	30 (34.1%)	35 (19.9%)	**0.012**	49 (26.5%)	16 (20.3%)	0.282
Right iliac fossa	28 (10.6%)	10 (11.4%)	18 (10.2%)	0.777	20 (10.8%)	8 (10.1%)	0.869
Anterior or posterior rectal space	29 (11.0%)	14 (15.9%)	15 (8.5%)	0.070	20 (10.8%)	9 (11.4%)	0.890
Transverse mesocolic or mesenteric root	21 (8.0%)	10 (11.4%)	11 (6.3%)	0.148	16 (8.6%)	5 (6.3%)	0.524
Lesser omentum	97 (36.7%)	43 (48.9%)	54 (30.7%)	**0.004**	68 (36.8%)	29 (36.7%)	0.994
CTSI	5.0 (2.0, 8.0)	7.0 (5.0, 9.0)	4.0 (2.0, 6.0)	**< 0.001**	5.0 (2.0, 8.0)	5.0 (2.0, 8.0)	0.893
mCTSI	6.0 (4.0, 10.0)	8.0 (6.5, 10.0)	4.0 (2.0, 8.0)	**< 0.001**	6.0 (4.0, 10.0)	6.0 (2.0, 8.0)	0.706

Date are median (interquartile ranges), mean ± standard deviation or absolute numbers (proportions)

P < 0.05 was bolded

CECT Contrast-enhanced computed tomography, *AP* Acute pancreatitis, *EXPN* Extrapancreatic necrosis, *PPN* Pancreatic parenchymal necrosis, *APFC* Acute peripancreatic fluid collection, *ANC* Acute necrotic collection, *CTSI* Computed tomography severity index, *mCTSI* Modified computed tomography severity index

is associated with higher Marshall scores and increased mortality [20]. In a study on sepsis, Belok et al. found a J-shaped curve relationship between WBC count and mortality [21]. After adjusting for baseline data, a decrease in WBC count, compared to an increase, was significantly associated with increased mortality. Furthermore, Knaus et al. found that a decrease in WBC count was more common in deceased sepsis patients compared to survivors in sepsis [22]. These findings all suggest that a decrease in WBC count is closely related to the inflammatory response. It should be noted that the early stages of AP are primarily associated with sterile inflammation, which differs in some aspects from sepsis-induced inflammation. However, clinical features, biochemical characteristics, cytokines, and inflammatory mediator profiles are very similar in

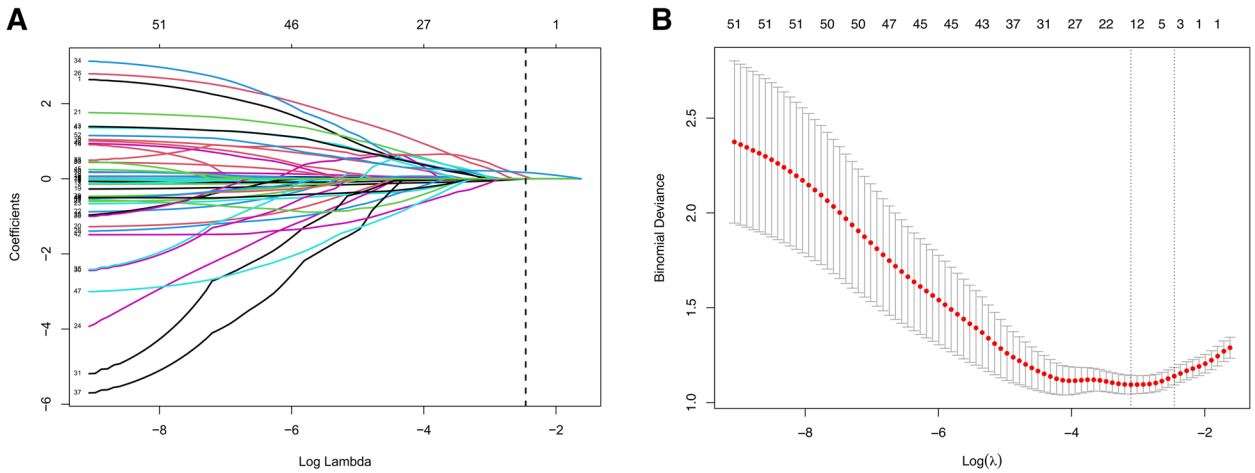

Fig. 1 Screening of variables based on Lasso regression. **A** The characteristics of variability in the coefficients of variables; **B** Determining the optimal value for parameter λ in the Lasso regression model using the cross-validation method

Table 3 Multivariate logistic regression analysis for SSAP

	B	Adjusted OR (95% CI)	*P*-value
WBC (ref: > 9.71 × 10^9 /L)			
≦9.71 × 10^9 /L	0.84	2.31 (1.08, 4.94)	**0.030**
PLT (ref: > 140 × 10^9 /L)			
≦140 × 10^9 /L	0.98	2.65 (1.12, 6.28)	**0.027**
Local complication (ref: Absence)			
Presence	1.43	4.18 (1.28, 13.63)	**0.018**
mCTSI (ref: < 8)			
≧8	1.01	2.74 (1.17, 6.44)	**0.021**

Factors associated with the occurrence of SSAP in Lasso regression were included in the multivariable models, and only results with $P < 0.05$ in the multivariate regression were listed above. Receiver operating characteristics (ROC) curves were constructed to determine the optimal threshold for predicting clinical outcomes

SSAP Splenomegaly secondary to acute pancreatitis, *OR* Odds ratio, *CI* Confidence interval, *N* Neutrophil, *PLT* Platelet, *mCTSI* Modified computed tomography severity index

SAP and sepsis [23, 24]. Therefore, much of research data obtained from sepsis studies is also applicable to SAP. A decrease in WBC count might more accurately represent severe dysregulation of the inflammatory response. Normally, pro-inflammatory mediators are followed by anti-inflammatory mediators to coordinate the inflammatory response. However, the compensatory response to inflammation could also be excessive, leading to a compensatory anti-inflammatory response syndrome and subsequent immunosuppression [24, 25]. As an immune organ, the spleen may enlarge due to its involvement in this complex regulatory process.

WBC is commonly considered a key factor in immunity, while platelet is crucial for hemostasis. However, evidence suggested that platelet also contribute to inflammation, immunity, and infection [26]. The interplay between coagulation and inflammation was bidirectional, operating through a positive feedback mechanism. The inflammatory process activated the coagulation system, reduced the activity of natural anticoagulants, and disrupted the function of the fibrinolytic system, leading to microvascular thrombosis [27]. Conversely, previous studies have observed a decrease in platelet count and an increase in platelet activation in the early stages of AP [27]. The activated platelet exacerbated the inflammation in AP by interacting with WBC [27–30]. The depletion of platelet count in this complex inflammatory process may have led to consumptive coagulopathy [27, 31]. Vaquero et al. observed that patients with reduced platelet count within 48 h of onset experienced more severe disease on CT and more frequent ICU admissions [32]. Osada et al. found that only patients with SAP showed a reduction in platelet count on the first day of admission [33]. Fujimura et al. found that among patients with different platelet trajectories, those with persistent thrombocytopenia had the poorest prognosis [34]. Chiba et al. reported that renal and cardiovascular dysfunction, as well as mortality, were lower in patients with increased or normal platelet count compared to those with thrombocytopenia [35].

Early characteristics of AP included the occurrence of SIRS and organ dysfunction [8]. Patients exhibiting early immune dysregulation during the course of the disease may have a worse prognosis. This was consistent with the observation that SSAP was associated with a higher incidence of organ dysfunction and increased disease severity.

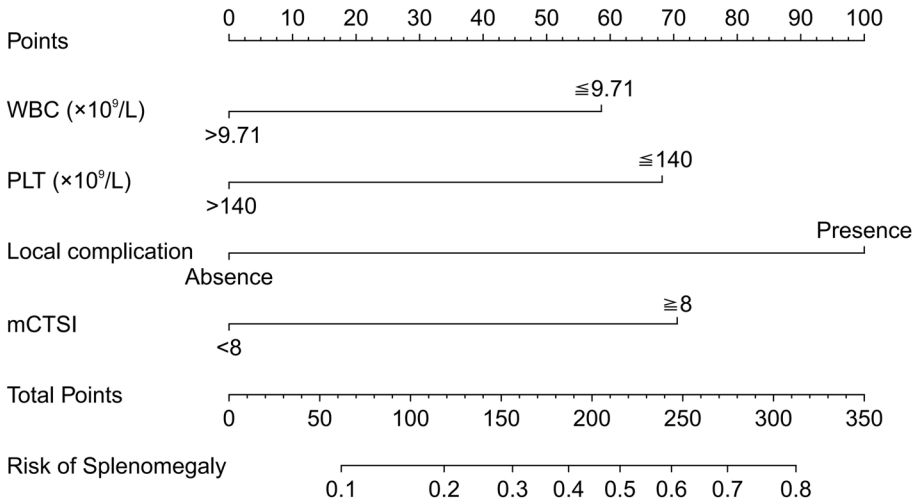

Fig. 2 Nomogram for predicting splenomegaly secondary to acute pancreatitis. WBC, white blood cell; PLT, platelet; CTSI, modified computed tomography severity index

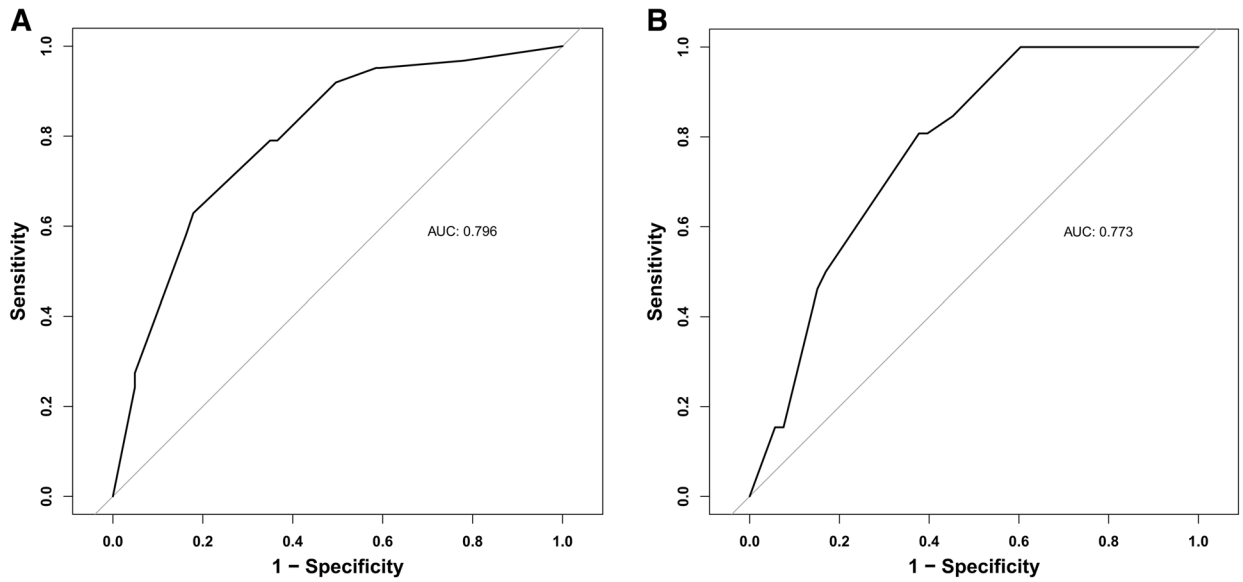

Fig. 3 Receiver operating curves. **A** Training cohort. **B** Internal validation cohort. AUC, area under the ROC (receiver operating characteristic) curve

The mCTSI was determined by pancreatic inflammation, pancreatic necrosis, and extrapancreatic complications [16]. Exudates from AP could dissect across tissue planes, leading to local complications [17]. Such complications occurred near the spleen and could potentially impact the spleen through direct stimulation [36]. When local complications became infected, the local stimulatory effect was possibly further enhanced. Previous studies have found that splenomegaly could be seen in bloodborne infection [7], and local complications following secondary infection could also enter the bloodstream, causing sepsis and leading to splenomegaly. In the later stage of AP, local complications, especially infections, were important factors affecting the condition, and patients who did not respond to antibiotic treatment usually required invasive intervention. This was consistent with the observation that SSAP was associated with a higher proportion of infections and surgeries. Moreover, due to the close anatomical relationship, local complications such as inflammatory exudates, necrotic tissue, and abscess could directly stimulate the splenic vein

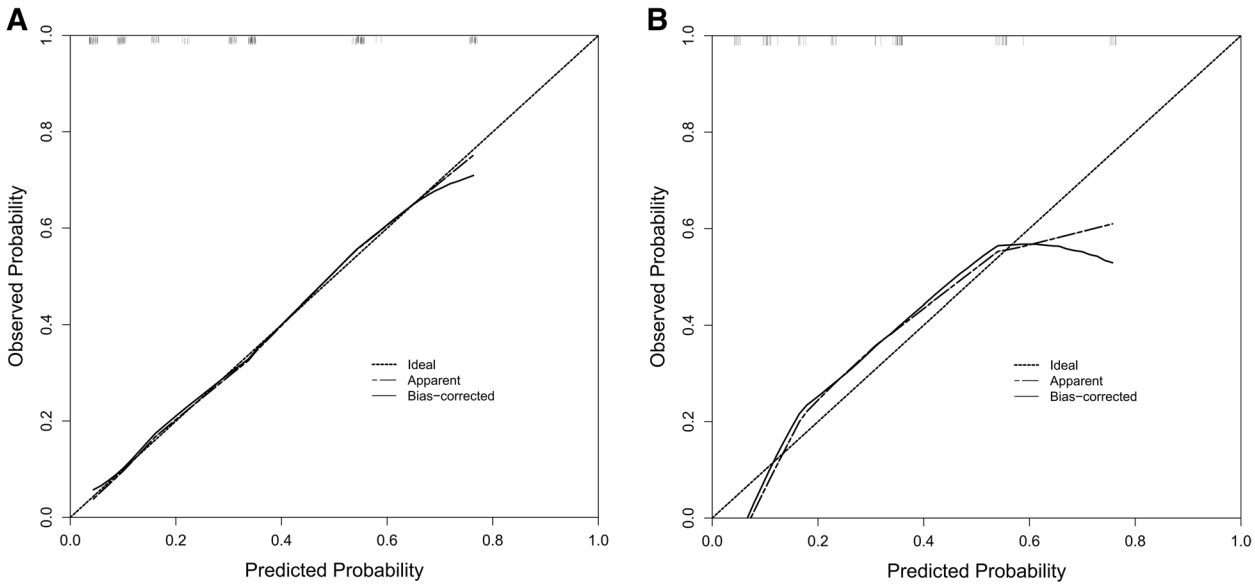

Fig. 4 Calibration curves for predicting the probability of splenomegaly secondary to acute pancreatitis. **A** Training cohort. **B** Internal validation cohort

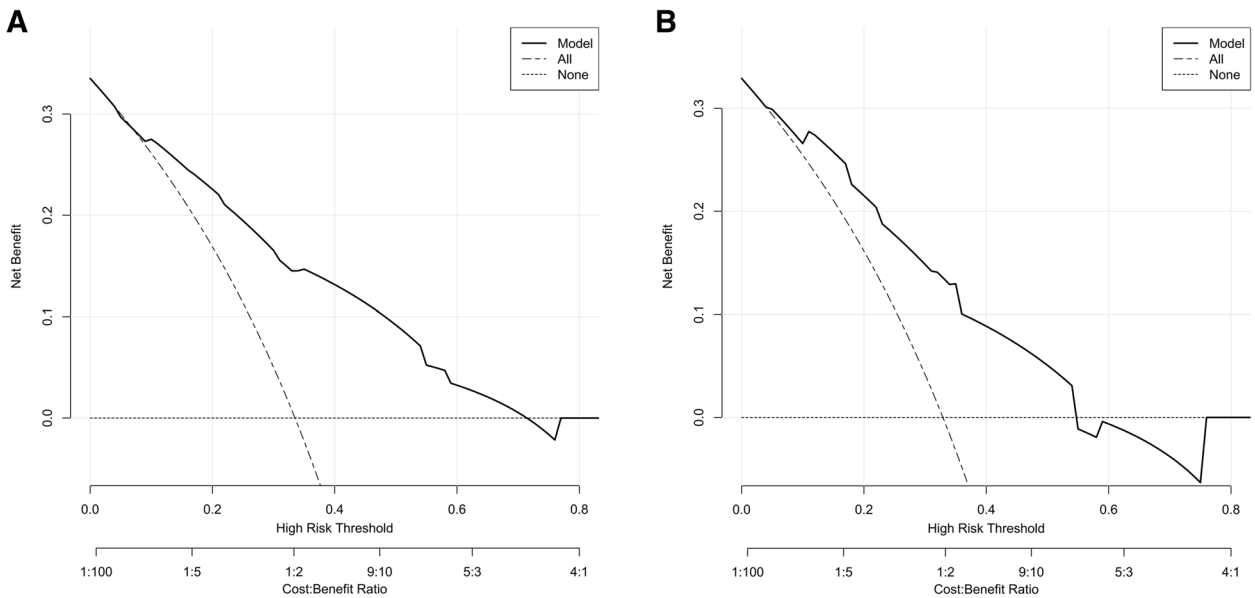

Fig. 5 Decision curve analysis in the prediction of splenomegaly secondary to acute pancreatitis. **A** Training cohort. **B** Internal validation cohort

causing vascular damage, and the swollen pancreas could directly compress the splenic vein, leading to splenic vein thrombosis, narrowing, and occlusion [3]. When the splenic vein or portal vein was affected, the blood return of the spleen was impeded, becoming a potential risk for splenomegaly. Although the formation of splanchnic vein thrombosis was not always evident in the early stage of the disease [36], pancreatic damage and local complications created a milieu for the involvement of splanchnic veins, potentially leading to splenomegaly.

This study found that 9.2% of patients with AP developed splenomegaly, a rate lower than the 16.7% reported by Xie et al. [6]. Splenomegaly was first detected 65 (30, 126) days after the onset of AP. This variability suggests multiple potential causes for splenomegaly in

these patients, including immune dysregulation, infectious complications, and involvement of visceral veins. Although Xie et al. did not establish a correlation between SSAP and disease severity [6], our larger-scale study found that secondary splenomegaly was associated with organ dysfunction and increased disease severity. This association underscores the complexity of the disease course in patients with SSAP, emphasizing the need for vigilant monitoring and timely follow-up to detect changes in the spleen.

Our study, for the first time, elucidates the relationship between AP and splenomegaly, identifies risk factors and establishes a reliable predictive model. Compared to univariate analysis, Lasso regression addresses multicollinearity among variables. Establishing a nomogram based on the Lasso-Logistic regression model allows medical workers to intuitively assess an individual's risk of developing splenomegaly, which is crucial for guiding follow-up strategies. However, this study has certain limitations: (1) It was a single-center retrospective study, subject to selection bias and a small sample size. The efficacy of the predictive model requires validation with a larger sample size. (2) Additionally, this study lacked long-term follow-up. Consequently, it remains undetermined what proportion of patients with SSAP experienced abdominal discomfort, hypersplenism, etc. This will be further refined in subsequent work. (3) The size of the spleen is influenced by factors like gender and age. Relying solely on imaging to define splenomegaly may lead to misclassification in some patients.

Conclusion

In summary, SSAP is relatively common. Patients with SSAP tend to have more severe conditions and poorer clinical prognoses. We have developed a nomogram for the early prediction of SSAP, which demonstrates good discrimination, calibration, and clinical utility. Larger prospective studies are necessary to further validate our findings.

Abbreviations

SSAP	Splenomegaly secondary to acute pancreatitis
CT	Computed tomography
AP	Acute pancreatitis
mCTSI	Modified computed tomography severity index
CECT	Contrast-enhanced computed tomography
BMI	Body mass index
WBC	White blood cell
APTT	Activated partial thromboplastin time
IPN	Infected pancreatic necrosis
ICU	Intensive Care Unit
APFC	Acute Peripancreatic Fluid Collection
ANC	Acute Necrotic Collection
ROC	Receiver operating characteristic
AUC	Area under the ROC curve
DCA	Decision curve analysis
SAP	Severe acute pancreatitis
SIRS	Systemic Inflammatory Response Syndrome

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Authors' contributions

FC and BH concepted and designed the study and wrote the manuscript; YD and BH collected data; AL made critical revisions; ZW and CZ reviewed all CT images. FL revised the manuscript. TL, XW and CG made substantial contributions to conception, design and coordination of the study. All authors read and approved the final manuscript.

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Availability of data and materials

Data to replicate findings are in the Figures and Tables of the paper. Due to patient privacy protection, any additional materials of the study are only available upon individual request directed to the corresponding author.

Declarations

Ethics approval and consent to participation

The studies involving human participants were reviewed and approved by Ethics Committee of Xuanwu Hospital Capital Medical University (Approval Number: 2020-092). Written informed consent was waived due to the retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of General Surgery, Xuanwu Hospital Capital Medical University, No.45, Changchun Street Xicheng District, Beijing 100053, China. [2]Clinical Center for Acute Pancreatitis, Capital Medical University, Beijing 100053, China.

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