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ORIGINAL RESEARCH

Prediction for Acute Biliary Pancreatitis After Laparoscopic Cholecystectomy

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Background: Acute biliary pancreatitis (ABP), caused by biliary stones, is a severe inflammatory condition with high mortality rates. ABP recurrence is often linked to gallstones, necessitating effective treatment strategies. Despite recent advancements, the prediction of ABP occurrence following LC continues to present challenges, indicating the need for ongoing research and model refinement.

Purpose: This study aims to develop a predictive model for assessing the risk of post- Laparoscopic cholecystectomy pancreatitis in patients with gallstones.

Methods: A retrospective cohort study was conducted on 968 patients who underwent LC. The patients were divided into the training set and validation set to develop and validate the predictive model. Demographic, clinical, and laboratory data were collected, and univariate and multivariate logistic regression analyses identified risk factors for ABP. A nomogram was constructed, and model performance was assessed using ROC curves, calibration, and decision curve analysis.

Results: The incidence of ABP was 9.07% in the training set and 14.43% in the validation set. Significant predictors of post-LC pancreatitis included baseline APACHE II score, choledocholithiasis, number of intubation attempts, timing of cholecystectomy, and biochemical markers (C-reactive protein, white blood cell, red cell distribution width, D-dimer, neutrophils, triglycerides). The predictive model demonstrated high discriminative ability with a receiver operating characteristic value of 0.949 (training set), of folds 1–5 ranged from 0.855 to 0.962 (5-fold cross-validation), and 0.922, (external validation set). Calibration curves confirmed stable prediction performance, and decision curve analysis indicated high net benefit across a range of threshold probabilities.

Conclusion: The developed model effectively predicts the risk of post-LC pancreatitis in patients with gallstones, offering valuable guidance for clinical decision-making. Early identification of high-risk patients could improve treatment outcomes and reduce recurrence rates.

Keywords: acute biliary pancreatitis, prediction model, cholecystectomy, gallstones

Introduction

The onset of acute pancreatitis is primarily attributed to biliary system stones and alcohol consumption.[1] Among these, acute biliary pancreatitis (ABP) is a severe inflammatory condition of the pancreas induced by biliary stones. Epidemiological data suggest that the mortality rate in ABP patients ranges from 20% to 40%, indicating considerable variability in disease progression.[2] Biliary stones not only serve as a major trigger for acute pancreatitis but also significantly influence treatment outcomes and the prognosis of ABP.[3] Therefore, treatment strategies for ABP should encompass both the removal of the underlying cause and the management of the inflammatory response, aiming to reduce recurrence risk and improve overall survival rates.

For patients experiencing their first episode of acute biliary pancreatitis (ABP), treatment options may include conservative management, surgical intervention, or interventional therapy.[4] Clinical studies have shown that gallstones are a major factor contributing to ABP recurrence; as a result, cholecystectomy is widely regarded as an effective approach to reduce recurrence rates.[5,6] Laparoscopic cholecystectomy (LC), considered the "gold standard" for treating gallstones,

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has become the preferred treatment due to its minimally invasive nature, quicker recovery, and shorter hospital stays.[7] While LC has yielded favorable outcomes in the treatment of gallstones, certain postoperative complications, including acute pancreatitis, may still arise. When biliary system stones induce pancreatitis, it leads to ABP, which not only exacerbates postoperative discomfort but also prolongs hospital stays, diminishes the overall benefits of surgery, and, in severe cases, increases the risk of mortality.[8] Furthermore, given the complexity of treating pancreatitis, its often-prolonged course, and its association with a relatively poor prognosis, early prediction of the risk of pancreatitis following LC in patients with gallstones is crucial.[9] Timely and effective interventions to mitigate this risk represent an important area of research aimed at reducing the incidence of postoperative pancreatitis and improving patient outcomes.

This study aims to develop and validate a predictive model for assessing the risk of post-laparoscopic cholecystectomy (LC) pancreatitis in patients with gallstones, utilizing demographic and clinical characteristics. By identifying key risk factors and providing a reliable risk assessment tool, our findings contribute to the advancement of early prevention strategies and the optimization of clinical management for gallstone-related ABP.

Methods

Study Population

This study was designed as a retrospective cohort study, collecting demographic data and clinical characteristics of patients who underwent laparoscopic cholecystectomy at Henan Province Hospital of Traditional Chinese Medicine from June 2021 to December 2023. This dataset was considered as training set (n=871). We then collected the patient's data from March 2024 to October 2024 at the same hospital, and this dataset was considered as external validation set (n=160).

The inclusion criteria are as follows: (1) Patients diagnosed with gallstones according to the Chinese Consensus on the Diagnosis and Treatment of Chronic Cholecystitis and Gallstones (2018),[10] confirmed by ultrasound, magnetic resonance imaging (MRI), or abdominal CT; (2) No history of jaundice; (3) First-time laparoscopic cholecystectomy treatment. The following patients were excluded: (1) Age <18 years; (2) History of pancreatic diseases, such as acute pancreatitis (AP), chronic pancreatitis, or pancreatic cancer; (3) Presence of obstructive cholecystitis or acute cholecystitis; (4) Severe dysfunction of vital organs, including the heart, liver, or kidneys; (5) Severe coagulation disorders or bleeding disorders; (6) History of malignancies; (7) Presence of infectious diseases or systemic inflammatory response syndrome; (8) Women in special physiological stages, such as pregnancy or lactation; (9) Recent use of antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, or other immunosuppressants; (10) Incomplete clinical data. Finally, 968 patients were included in the study.

Laparoscopic Cholecystectomy

Briefly, the laparoscopic cholecystectomy surgical procedure is as follows: Preoperative routine disinfection and draping are performed. After satisfactory anesthesia, the patient is positioned in a head-up, foot-down position with a left tilt of approximately 20°C. Pneumoperitoneum is established, maintaining an intra-abdominal pressure of 8–12 mmHg. The four-port technique is used to enter the abdomen, and laparoscopy is performed to explore the abdominal cavity, confirm the presence of gallstones, and assess the morphology, size, and surrounding structures of the gallbladder. Normal tissues and organs are carefully separated. The cystic artery and cystic duct are clipped with titanium clips and then severed. Hemostasis is achieved through electrocautery, and the gallbladder is removed using a sterile glove. Postoperatively, patients receive routine fluid replacement, anti-infective therapy, and nutritional support.

Diagnosis of Acute Biliary Pancreatitis

According to the Chinese Guidelines for the Diagnosis and Treatment of Acute Pancreatitis (2021),[11] a diagnosis of ABP can be made if any two of the following three criteria are met at one month after operation: (1) sudden onset of upper abdominal pain (persistent and severe, often radiating to the back); (2) serum amylase and/or lipase levels ≥ three times the upper limit of normal; (3) typical imaging findings of acute pancreatitis. ABP refers to acute pancreatitis patients in whom biliary stones have been confirmed by examinations such as ultrasound, computed Tomography, magnetic resonance cholangiopancreatography, or endoscopic retrograde cholangiopancreatography.

Data Collection and Definition

The collected data included demographic information and clinical characteristics: age, sex, body mass index (BMI) is equal to weight (kg) divided by the square of height (m), smoking is defined as someone who has smoked continuously or cumulatively for six months or more in their lifetime,[12] alcohol consumption was defined as drinking at least once per week during the past year, duration of disease,[13] diabetes: fasting plasma glucose (FPG) ≥7.0 mmol/L or 2-hour plasma glucose ≥11.1 mmol/L during an oral glucose tolerance test or HbA1c ≥ 6.5% (48 mmol/mol),[14] hypertension: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure≥90 mmHg,[15] hyperlipidemia (total Cholesterol (TC)≥5.2 mmol/L or low-density lipoprotein cholesterol≥3.4 mmol/L or high-density lipoprotein cholesterol < (1.0 mmol/L in men or <50 1.3 mmol/L in women or triglycerides≥1.7 mmol/L),[16] and choledocholithiasis. The following biochemical data were collected: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, TG, TC, total protein, albumin, FBG, blood urea nitrogen, creatinine, C-reactive protein (CRP), white blood cell (WBC), hemoglobin, Hematocrit (HCT), mean corpuscular volume, red cell distribution width (RDW), neutrophil, monocyte, lymphocyte, platelet.

The clinical characteristics: gallbladder size (determined by ultrasound), gallbladder wall thickness (determined by B-mode ultrasound), stone diameter, number of stones (single, >3 stones, determined by ultrasound), stone characteristics (determined by MRCP or MRI), history of pancreatic disease, choledocholithiasis (confirmed by MRCP and endoscopic ultrasound), operation time, intraoperative blood loss, time to pain relief, duration of hospitalization, and number of intubations, somatostatin usage, incisional infection, timing of cholecystectomy (early: within 14 days, delayed: more than 14 days).[2]

Statistical Analysis

In this study, multiple measures were implemented to control potential biases inherent in retrospective research. To ensure data quality, a dual-entry process was conducted independently by two researchers, followed by third-party verification. Outcome assessments were performed in a blinded manner, and strict adherence to predefined inclusion and exclusion criteria was maintained. Regarding data completeness, multiple imputations were applied using the "mice" package to handle missing values, and variables with a missing rate exceeding 10% were excluded from the analysis.

Statistical analyses were conducted using IBM SPSS 23.0 and R 4.4.0. Categorical variables were expressed as frequencies (percentages), and group comparisons were performed using the chi-square (χ^2) test. Continuous variables were presented as mean ± standard deviation (for normally distributed data, analyzed using the independent samples *t*-test) or median [interquartile range] (for non-normally distributed data, analyzed using the Wilcoxon rank-sum test). Univariate and multivariate logistic regression analyses were performed to identify independent risk factors for acute biliary pancreatitis (ABP), with odds ratios (ORs) and 95% confidence intervals (CIs) calculated. Based on the least absolute shrinkage and selection operator (LASSO) and multivariate regression results, a nomogram model was developed to facilitate individualized risk prediction. Internal validation was conducted using a five-fold cross-validation approach, while external validation was performed using datasets from different time periods.

The predictive performance of the model was assessed using a comprehensive evaluation framework. Discriminative ability was quantified by the concordance statistic (C-statistic) based on the area under the receiver operating characteristic (ROC) curve. The SHAP value was used for evaluating the importance of features. Calibration was evaluated using calibration curves to assess the agreement between predicted and observed outcomes. The clinical utility of the model was determined through decision curve analysis (DCA). All statistical tests were two-tailed, with a significance threshold set at $P < 0.05$.

Results

Baseline Characteristics for Training and Validation Set

Based on the inclusion and exclusion criteria, we identified a total of 871 patients in the training set and 97 patients in the validation set who underwent laparoscopic cholecystectomy. The incidences of acute biliary pancreatitis (ABP) were 9.07% and 8.75%, respectively. No significant differences were observed in the ABP incidences between the training set and validation set ($P = 0.897$). The mean age of the training set was 54.27 ± 8.17 years, with 45.01% of patients being female. Among all patients, 19.8% had a history of alcohol consumption, and 36.97% had a history of smoking. The

prevalence of hypertension, diabetes, and hyperlipidemia was 33.52%, 24.57%, and 33.64%, respectively. The mean age of the validation set was 54.98 ± 8.45 years, with 38.75% of patients being female. The proportions of patients with a history of smoking and drinking were slightly higher in the validation set, but no significant differences were found. The rates of hypertension, diabetes, and hyperlipidemia exhibited similar trends in both sets. There were no significant differences in demographic characteristics, clinical features, treatment factors, or laboratory results between the training and validation sets ($P > 0.05$). Detailed results for both groups can be found in Table 1.

Table 1 General Characteristics of Training and Validation Set

Variables	Training Set (n = 871)	Validation Set (n = 160)	*P*
Age, year	54.27 ± 8.17	54.98 ± 8.45	0.317
Sex, n (%)			0.143
Female	392 (45.01)	62 (38.75)	
Male	479 (54.99)	98 (61.25)	
BMI, kg/m^2	23.63 ± 3.41	23.55 ± 2.98	0.782
Drinking, n (%)			0.638
No	700 (80.37)	126 (78.75)	
Yes	171 (19.63)	34 (21.25)	
Smoking, n (%)			0.467
No	549 (63.03)	96 (60.00)	
Yes	322 (36.97)	64 (40.00)	
Diabetes, n (%)			0.075
No	657 (75.43)	110 (68.75)	
Yes	214 (24.57)	50 (31.25)	
Hyperlipidemia, n (%)			0.211
No	578 (66.36)	98 (61.25)	
Yes	293 (33.64)	62 (38.75)	
Hypertension, n (%)			0.574
No	579 (66.48)	110 (68.75)	
Yes	292 (33.52)	50 (31.25)	
Duration, year	6.40 ± 0.84	6.43 ± 0.84	0.723
APACHEII	10.03 ± 2.32	10.44 ± 2.59	0.058
Choledocholithiasis, n (%)			0.209
No	432 (49.60)	88 (55.00)	
Yes	439 (50.40)	72 (45.00)	
Gallbladder wall thickness, n (%)			0.944
≤1mm	471 (54.08)	87 (54.38)	
>1mm	400 (45.92)	73 (45.62)	
Gallstone diameter, n (%)			0.702
≤3mm	394 (45.24)	75 (46.88)	
>3mm	477 (54.76)	85 (53.12)	
Gallbladder size, n (%)			0.172
Normal	555 (63.72)	112 (70.00)	
Abnormal	316 (36.28)	48 (30.00)	
Gallstone number, n (%)			0.615
1-3	515 (59.13)	98 (61.25)	
>3	356 (40.87)	62 (38.75)	
Gallstone shape, n (%)			0.789
Sludge-like	562 (64.52)	105 (65.62)	
Granular	309 (35.48)	55 (34.38)	
Operation time, minutes	41.66 ± 6.27	42.00 ± 6.26	0.519
Intraoperative blood loss, mL	167.25 ± 12.42	165.35 ± 11.89	0.074

(*Continued*)

Table 1 (Continued).

Variables	Training Set (n = 871)	Validation Set (n = 160)	*P*
Times of intubations, n	3.09 ± 0.48	3.14 ± 0.51	0.179
Time to pain relief, day	1.83 ± 0.33	1.84 ± 0.32	0.687
Duration of hospitalization, day	6.68 ± 1.78	6.63 ± 1.85	0.714
Balloon dilation usage, n (%)			0.956
No	285 (32.72)	52 (32.50)	
Yes	586 (67.28)	108 (67.50)	
Somatostatin usage, n (%)			0.502
No	428 (49.14)	74 (46.25)	
Yes	443 (50.86)	86 (53.75)	
Incisional infection, n (%)			0.284
No	815 (93.57)	146 (91.25)	
Yes	56 (6.43)	14 (8.75)	
Timing of Cholecystectomy, n (%)			0.751
Early	572 (65.67)	103 (64.38)	
Delayed	299 (34.33)	57 (35.62)	
ALT, IU/L	143.35 (122.36, 165.33)	144.41 (125.33, 166.38)	0.487
AST, IU/L	204.67 (180.33, 229.80)	213.18 (184.21, 235.49)	0.127
Serum amylase, U/L	606.11 (385.17, 801.44)	515.85 (320.96, 821.38)	0.333
D-Dimer, μg/mL	2.40 (2.00, 2.77)	2.41 (1.98, 2.68)	0.167
Alkaline phosphatase, U/L	136.97 ± 38.89	137.12 ± 42.04	0.968
Total bilirubin, IU/L	8.03 ± 3.45	7.95 ± 3.51	0.788
TG, mmol/L	5.64 ± 2.65	5.59 ± 2.70	0.855
TC, mmol/L	5.36 ± 1.11	5.31 ± 1.10	0.583
Total protein, g/L	71.85 ± 12.20	70.31 ± 10.02	0.085
Albumin, g/L	46.05 ± 5.24	45.37 ± 4.79	0.108
FBG, mmol/L	10.08 ± 2.43	10.36 ± 2.44	0.174
Blood urea nitrogen, mmol/L	5.76 ± 1.31	5.58 ± 1.33	0.117
Creatinine, μmol/L	79.13 ± 13.20	79.67 ± 12.56	0.635
CRP, mg/L	117.06 ± 31.70	113.96 ± 34.08	0.286
WBC, 10^9	13.99 ± 2.41	13.91 ± 2.25	0.718
Hemoglobin, g/L	132.48 ± 9.47	133.21 ± 8.88	0.363
HCT, %	0.44 ± 0.04	0.43 ± 0.04	0.563
MCV, %	89.92 ± 2.79	90.27 ± 2.86	0.150
RDW, %	15.82 ± 3.39	15.52 ± 3.43	0.300
Neutrophil, 10^9	8.67 (8.23, 9.11)	8.70 (8.32, 9.13)	0.217
Monocyte, 10^9	0.65 (0.56, 0.76)	0.63 (0.54, 0.73)	0.193
Lymphocyte, 10^9	1.00 (0.88, 1.12)	1.01 (0.85, 1.10)	0.470
Platelet, 10^9	126.67 (119.80, 133.19)	127.53 (122.28, 133.18)	0.112

Baseline Characteristics Between ABP and Non-ABP in Training Set

Our results indicate that there were no significant differences between the ABP and non-ABP groups in terms of age (P = 0.238), sex (P = 0.292), BMI (P = 0.572), smoking status (P = 0.304), drinking (P = 0.103), hypertension (P = 0.897), diabetes (P = 0.872), or disease duration (P = 0.067). However, the prevalence of hyperlipidemia was significantly higher in the ABP group (44.30%) compared to the non-ABP group (32.58%) (P = 0.035). Additionally, the baseline APACHE II score was significantly higher in the ABP group than in the non-ABP group (P < 0.001). Regarding clinical characteristics, the prevalence of choledocholithiasis was significantly higher in the ABP group than in the non-ABP group (P = 0.004). No significant differences were observed in gallbladder wall thickness, diameter, size, number, or shape (P > 0.05). During the operation, there were no significant differences in operation time, intraoperative blood loss, or contrast imaging times between the ABP and non-ABP groups (P > 0.05). However, the number of intubation attempts

was significantly higher in the ABP group than in the non-ABP group ($P < 0.001$). No significant differences were found in time to pain relief, duration of hospitalization, rates of balloon dilation or somatostatin use, or the incidence of incisional infections ($P > 0.05$). The ABP group tended to have a delayed timing of cholecystectomy compared to the non-ABP group ($P < 0.001$). Biochemical parameters revealed that the ABP group had higher levels of triglycerides (TG), C-reactive protein (CRP), white blood cells (WBC), red cell distribution width (RDW), and neutrophils compared to the non-ABP group ($P < 0.05$). There were no significant differences in other biochemical parameters between the two groups ($P > 0.05$). Detailed data for both groups are presented in Table 2.

Table 2 Comparisons of Clinical Characteristics Between ABP and Non-ABP in Training Set

Variables	Non-ABP (n = 792)	ABP (n = 79)	*P*
Age, year	54.17 ± 8.24	55.30 ± 7.39	0.238
Sex, n (%)			0.292
Female	352 (44.44)	40 (50.63)	
Male	440 (55.56)	39 (49.37)	
BMI, kg/m^2	23.61 ± 3.39	23.84 ± 3.64	0.572
Drinking, n (%)			0.103
No	642 (81.06)	58 (73.42)	
Yes	150 (18.94)	21 (26.58)	
Smoking, n (%)			0.304
No	495 (62.50)	54 (68.35)	
Yes	297 (37.50)	25 (31.65)	
Diabetes, n (%)			0.872
No	598 (75.51)	59 (74.68)	
Yes	194 (24.49)	20 (25.32)	
Hyperlipidemia, n (%)			**0.035**
No	534 (67.42)	44 (55.70)	
Yes	258 (32.58)	35 (44.30)	
Hypertension, n (%)			0.897
No	527 (66.54)	52 (65.82)	
Yes	265 (33.46)	27 (34.18)	
No	207 (26.14)	13 (16.46)	
Yes	585 (73.86)	66 (83.54)	
Duration, year	6.39 ± 0.83	6.57 ± 0.83	0.067
APACHEII	9.94 ± 2.31	10.90 ± 2.28	**<0.001**
Choledocholithiasis, n (%)			**0.004**
No	405 (51.14)	27 (34.18)	
Yes	387 (48.86)	52 (65.82)	
Gallbladder wall thickness, n (%)			0.211
≤1mm	423 (53.41)	48 (60.76)	
>1mm	369 (46.59)	31 (39.24)	
Gallstone diameter, n (%)			0.950
≤3mm	358 (45.20)	36 (45.57)	
>3mm	434 (54.80)	43 (54.43)	
Gallbladder size, n (%)			0.120
Normal	511 (64.52)	44 (55.70)	
Abnormal	281 (35.48)	35 (44.30)	
Gallstone number, n (%)			0.258
1-3	473 (59.72)	42 (53.16)	
>3	319 (40.28)	37 (46.84)	

(*Continued*)

Table 2 (Continued).

Variables	Non-ABP (n = 792)	ABP (n = 79)	*P*
Gallstone shape, n (%)			0.455
Sludge-like	508 (64.14)	54 (68.35)	
Granular	284 (35.86)	25 (31.65)	
Operation time, minutes	41.57 ± 6.10	42.52 ± 7.75	0.291
Intraoperative blood loss, mL	167.10 ± 9.97	168.74 ± 26.63	0.587
Contrast imaging times, n	2.19 ± 0.33	2.25 ± 0.37	0.134
Times of intubations, n	3.06 ± 0.46	3.35 ± 0.62	**<0.001**
Time to pain relief, day	1.82 ± 0.32	1.87 ± 0.44	0.363
Duration of hospitalization,	6.69 ± 1.80	6.64 ± 1.58	0.844
Balloon dilation usage, n (%)			0.141
No	265 (33.46)	20 (25.32)	
Yes	527 (66.54)	59 (74.68)	
Somatostatin usage, n (%)			0.847
No	390 (49.24)	38 (48.10)	
Yes	402 (50.76)	41 (51.90)	
Incisional infection, n (%)			0.658
No	742 (93.69)	73 (92.41)	
Yes	50 (6.31)	6 (7.59)	
Timing of Cholecystectomy, n (%)			**<0.001**
Early	537 (67.80)	35 (44.30)	
Delayed	255 (32.20)	44 (55.70)	
ALT, IU/L	143.78 (122.78, 165.54)	139.69 (119.95, 162.66)	0.523
AST, IU/L	204.00 (180.05, 229.61)	207.89 (186.45, 232.94)	0.245
Serum amylase, U/L	603.58 (385.19, 793.34)	631.00 (381.76, 877.35)	0.355
D-Dimer, μg/mL	2.39 (2.00, 2.75)	2.50 (1.94, 2.99)	0.112
Alkaline phosphatase, U/L	136.26 ± 37.59	144.16 ± 49.81	0.174
Total bilirubin, IU/L	8.01 ± 3.51	8.24 ± 2.82	0.500
TG, mmol/L	5.54 ± 2.62	6.62 ± 2.80	**<0.001**
TC, mmol/L	5.35 ± 1.03	5.55 ± 1.75	0.312
Total protein, g/L	71.81 ± 10.22	72.24 ± 24.52	0.879
Albumin, g/L	46.11 ± 5.33	45.42 ± 4.17	0.175
FBG, mmol/L	10.10 ± 2.44	9.86 ± 2.36	0.411
Blood urea nitrogen, mmol/L	5.75 ± 1.29	5.86 ± 1.54	0.529
Creatinine, μmol/L	79.10 ± 13.21	79.47 ± 13.26	0.813
CRP, mg/L	113.38 ± 30.13	154.01 ± 21.97	**<0.001**
WBC, 10^9	13.79 ± 2.36	15.95 ± 2.00	**<0.001**
Hemoglobin g/L	132.57 ± 9.59	131.51 ± 8.13	0.341
HCT, %	0.44 ± 0.04	0.44 ± 0.04	0.645
MCV, %	89.89 ± 2.79	90.22 ± 2.85	0.314
RDW, %	15.63 ± 3.29	17.77 ± 3.79	**<0.001**
Neutrophil,	8.66 (8.21, 9.08)	8.82 (8.41, 9.32)	**<0.001**
Monocyte,	0.65 (0.56, 0.75)	0.67 (0.56, 0.79)	0.166
Lymphocyte, 10^9	1.00 (0.88, 1.12)	1.03 (0.85, 1.17)	0.505
Platelet, 10^9	126.39 (119.21, 133.86)	127.54 (124.88, 130.52)	0.166

Note: The bold data means significantly different between two groups.

Developing of Model Predicting ABP in the Training Set

Univariate logistic regression analysis revealed that hyperlipidemia, baseline APACHE II score, choledocholithiasis, number of intubation attempts, timing of cholecystectomy, levels of D-Dimer, triglycerides (TG), C-reactive protein (CRP), white blood cells (WBC), neutrophils, and red cell distribution width (RDW) were significantly associated with

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the occurrence of acute biliary pancreatitis (ABP) (P < 0.001). To refine the model, a LASSO regression was performed prior to the multivariate logistic regression (Figure 1A and B). In the final multivariate logistic regression model, ten variables were identified as significant predictors of ABP: baseline APACHE II (OR: 1.30, 95% CI: 1.10–1.52, P < 0.001), choledocholithiasis (OR: 2.49, 95% CI: 1.25–4.95, P = 0.010), number of intubation attempts (OR: 3.17, 95% CI: 1.70–59.1, P < 0.001), timing of cholecystectomy (OR: 3.17, 95% CI: 1.63–6.15, P < 0.001), D-Dimer (OR: 1.99, 95% CI: 1.02–3.85, P = 0.042), TG (OR: 1.21, 95% CI: 1.06–1.37, P = 0.003), CRP (OR: 1.06, 95% CI: 1.04–1.08, P < 0.001), WBC (OR: 1.62, 95% CI: 1.37–1.93, P < 0.001), neutrophils (OR: 1.91, 95% CI: 1.01–3.61, P = 0.047), and RDW (OR: 1.24, 95% CI: 1.12–1.37, P < 0.001). Further details are presented in Table 3. We also performed the ROC analysis using these variables. The results were presented in the Supplementary material 1. The results suggested that the AUCs were 0.617 for APACHE II, 0.585 for choledocholithiasis, 0.620 for times of intubations, 0.617 for timing of cholecystector, 0.613 for TG, 0.750 for WBC, 0.845 for CRP, 0.619 for neutrophil, 0.654 for RDW and 0.554 for D-dimer.

Validation and Assessment of Model Predicting ABP

The predictive ability of the established model was assessed using the training set. The model's ROC curve in the training set was 0.949 (95% CI: 0.930–0.969, Figure 1C), indicating a relatively high predictive capability. We then performed internal validation using 5-fold cross-validation, which demonstrated high and stable predictability across the five random samples. The ROC values for folds 1–5 ranged from 0.855 to 0.962 (Figure 1D). In the external validation set, the ROC value was 0.924 (95% CI: 0.874–0.973, Figure 1E). SHAP analysis revealed that CRP had the highest feature importance, followed by WBC, RDW, timing of cholecystectomy, and baseline APACHE II. D-Dimer ranked last in importance (Figure 1F). Based on these variables, we developed an individualized risk scoring system (Figure 2A).

Calibration analyses were performed for both the training and validation sets. The training set showed stable prediction performance for ABP (Figure 2B). Although the validation set exhibited some fluctuations, it remained stable with a predicted probability greater than 0.35 (Figure 2C). Decision curve analysis (DCA) further demonstrated that the model provided high net benefit across a range of threshold probabilities in both the training and validation sets (Figure 2D and E). The optimized DCA yielded similar results (Figure 2F and G). A threshold effect analysis revealed a significant dose-response relationship between the risk score and ABP occurrence. Specifically, for risk scores <0.032, the association was marginally significant (P = 0.035), while for risk scores ≥0.032, the association was highly significant (P < 0.001) (Figure 3).

Discussion

Laparoscopic cholecystectomy (LC) is considered the "gold standard" for treating gallstones, as it effectively alleviates the patient's condition. However, LC necessitates gallbladder removal, involves a certain degree of surgical trauma, and still carries a relatively high risk of postoperative complications. Among these, acute biliary pancreatitis (ABP) is one of the most common and severe, often manifesting with multiple symptoms that can compromise surgical outcomes and prolong hospital stays. Currently, no effective drugs are available for the treatment or prevention of pancreatitis. Previous studies have reported that the incidence of post-LC pancreatitis in gallstone patients ranges from approximately 2% to 9%.[17,18] In this study, the incidence of postoperative pancreatitis was 9.07%, consistent with previous findings. ABP can present with symptoms such as fever, nausea, vomiting, and abdominal pain; in severe cases, it may lead to respiratory distress, shock, or even sudden death. Although systematic treatment can alleviate primary symptoms, pancreatitis still impacts overall therapeutic outcomes, underscoring the importance of early prevention.

To address this, we developed a logistic regression-based predictive model using diverse clinical and laboratory parameters, with thorough validation to ensure reliability. Univariate analysis identified significant risk factors for ABP, including hyperlipidemia, APACHE II score, choledocholithiasis, intubation, cholecystectomy timing, and inflammatory markers (D-dimer, TG, CRP, WBC, neutrophils, RDW). LASSO regression was applied to prevent overfitting, yielding ten key predictors for the final multivariate model. These combined clinical and biochemical variables demonstrated strong predictive performance, with an AUC of 0.949 in the training set and 0.924 in external validation. Five-fold cross-validation (AUC: 0.855–0.962) confirmed model stability. SHAP analysis highlighted CRP, WBC, RDW, cholecystectomy timing, and APACHE II score as top contributors, underscoring the importance of inflammation and disease

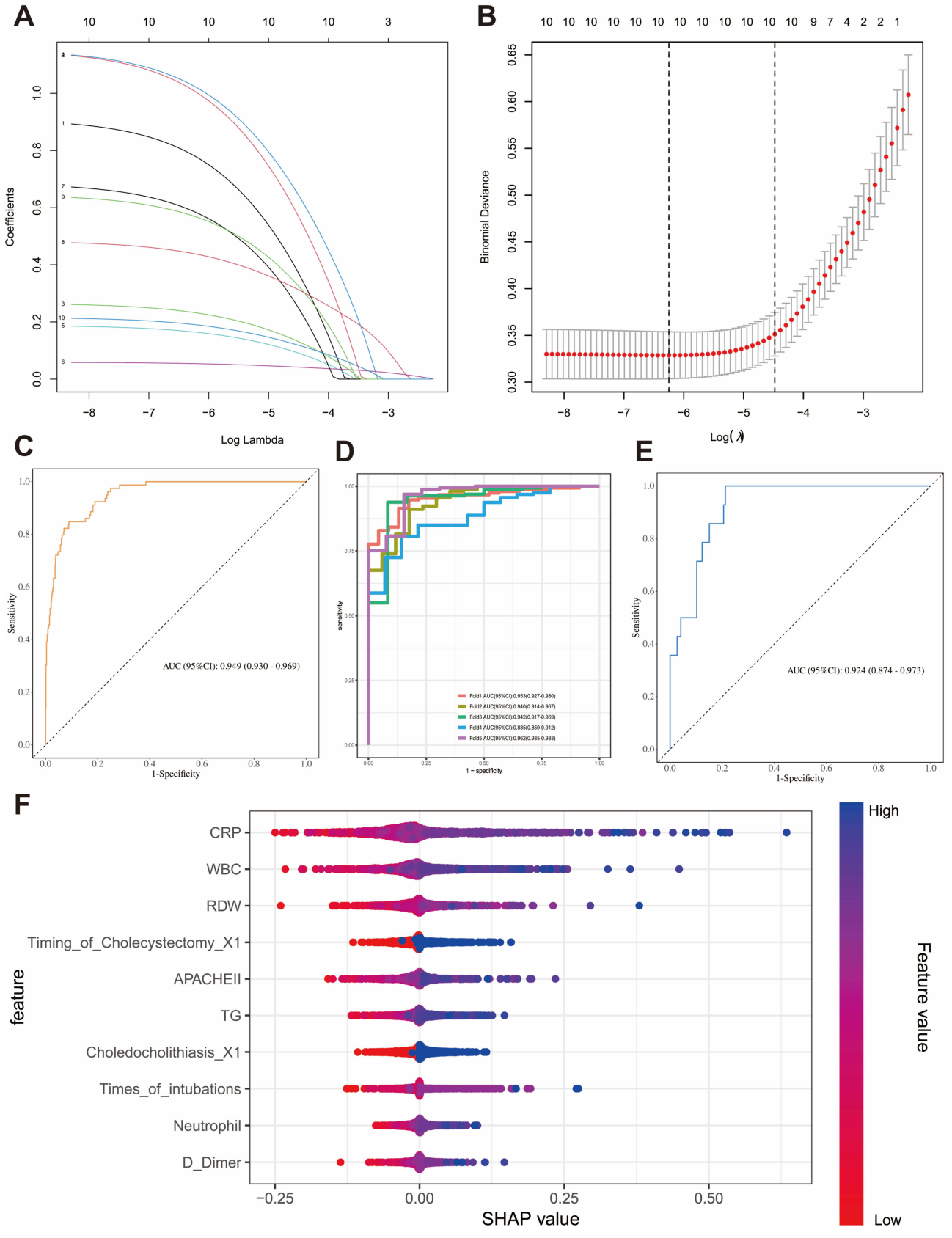

Figure 1 Development and validation of the predict model for ABP after LC. (**A** and **B**) LASSO regression identified the relevant risk factors. (**C**) Receiver operating characteristics curve (ROC) of predict model in training set. (**D**) ROCs of five samples using five-fold cross validation. (**E**) ROC of predicting model in external validation set. (**F**) SHAP analyses identified the importance of features in the model.

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Table 3 Univariate and Multivariate Logistic Regression for ABP in the Training Set

Variables	Univariate		Multivariate	
	OR (95%CI)	P	OR (95%CI)	P
Age	1.02 (0.99–1.05)	0.237		
Sex (Male vs Female)	0.78 (0.49–1.24)	0.293		
BMI	1.02 (0.95–1.09)	0.571		
Drinking (Yes vs No)	1.55 (0.91–2.63)	0.105		
Smoking (Yes vs No)	0.77 (0.47–1.27)	0.305		
Diabetes (Yes vs No)	1.04 (0.61–1.78)	0.872		
Hyperlipidemia (Yes vs No)	1.65 (1.03–2.63)	**0.037**		
Hypertension (Yes vs No)	1.03 (0.63–1.68)	0.897		
Duration	1.30 (0.98–1.72)	0.067		
APACHEII	1.20 (1.08–1.33)	**<0.001**	1.30 (1.12–1.52)	**<0.001**
Choledocholithiasis (Yes vs No)	2.02 (1.24–3.27)	**0.005**	2.49 (1.25–4.95)	**0.010**
Gallbladder wall thickness (>1mm vs ≤1mm)	0.74 (0.46–1.19)	0.213		
Gallstone diameter (3mm vs ≤3mm)	0.99 (0.62–1.57)	0.950		
Gallbladder size (Abnormal vs normal)	1.45 (0.91–2.31)	0.121		
Gallstone number (>3 vs 1–3)	1.31 (0.82–2.08)	0.259		
Gallstone shape (Granular vs Sludge-like)	0.83 (0.50–1.36)	0.456		
Operation time	1.02 (0.99–1.06)	0.197		
Intraoperative blood loss	1.01 (0.99–1.03)	0.261		
Times of intubations	3.17 (2.03–4.95)	**<0.001**	3.17 (1.70–5.91)	**<0.001**
Time to pain relief	1.54 (0.76–3.13)	0.229		
Duration of hospitalization	0.99 (0.87–1.12)	0.843		
Balloon dilation usage (Yes vs No)	1.48 (0.87–2.52)	0.143		
Somatostatin usage (Yes vs No)	1.05 (0.66–1.66)	0.847		
Incisional infection (Yes vs No)	0.82 (0.34–1.98)	0.658		
Timing of cholecystectomy (Delayed vs early)	2.65 (1.66–4.23)	**<0.001**	3.17 (1.63–6.15)	**<0.001**
Contrast imaging times	1.70 (0.85–3.43)	0.134		
ALT	1.00 (0.99–1.01)	0.769		
AST	1.00 (1.00–1.01)	0.393		
Serum amylase	1.00 (1.00–1.00)	0.288		
D-Dimer	1.83 (1.08–3.11)	**0.025**	1.99 (1.02–3.85)	**0.042**
Alkaline phosphatase	1.01 (1.00–1.01)	0.086		
Total bilirubin	1.02 (0.95–1.09)	0.571		
TG	1.17 (1.07–1.28)	**<0.001**	1.21 (1.06–1.37)	**0.003**
TC	1.18 (0.96–1.45)	0.123		
Total protein	1.00 (0.98–1.02)	0.767		
Albumin	0.98 (0.93–1.02)	0.264		
FBG	0.96 (0.87–1.06)	0.410		
Blood urea nitrogen	1.07 (0.90–1.27)	0.467		
Creatinine	1.00 (0.98–1.02)	0.813		
CRP	1.06 (1.05–1.07)	**<0.001**	1.06 (1.04–1.08)	**<0.001**
WBC	1.56 (1.38–1.77)	**<0.001**	1.62 (1.37–1.93)	**<0.001**
Neutrophil	2.61 (1.59–4.27)	**<0.001**	1.91 (1.01–3.61)	**0.047**
Hemoglobin	0.99 (0.96–1.01)	0.341		
HCT	3.77 (0.01–1051.71)	0.644		
MCV	1.04 (0.96–1.13)	0.314		
RDW	1.19 (1.12–1.28)	**<0.001**	1.24 (1.12–1.37)	**<0.001**
Monocyte	6.57 (0.86–50.47)	0.070		
Lymphocyte	1.72 (0.35–8.34)	0.501		
Plt	1.02 (0.99–1.05)	0.183		

Note: The bold data means significantly different between two groups.

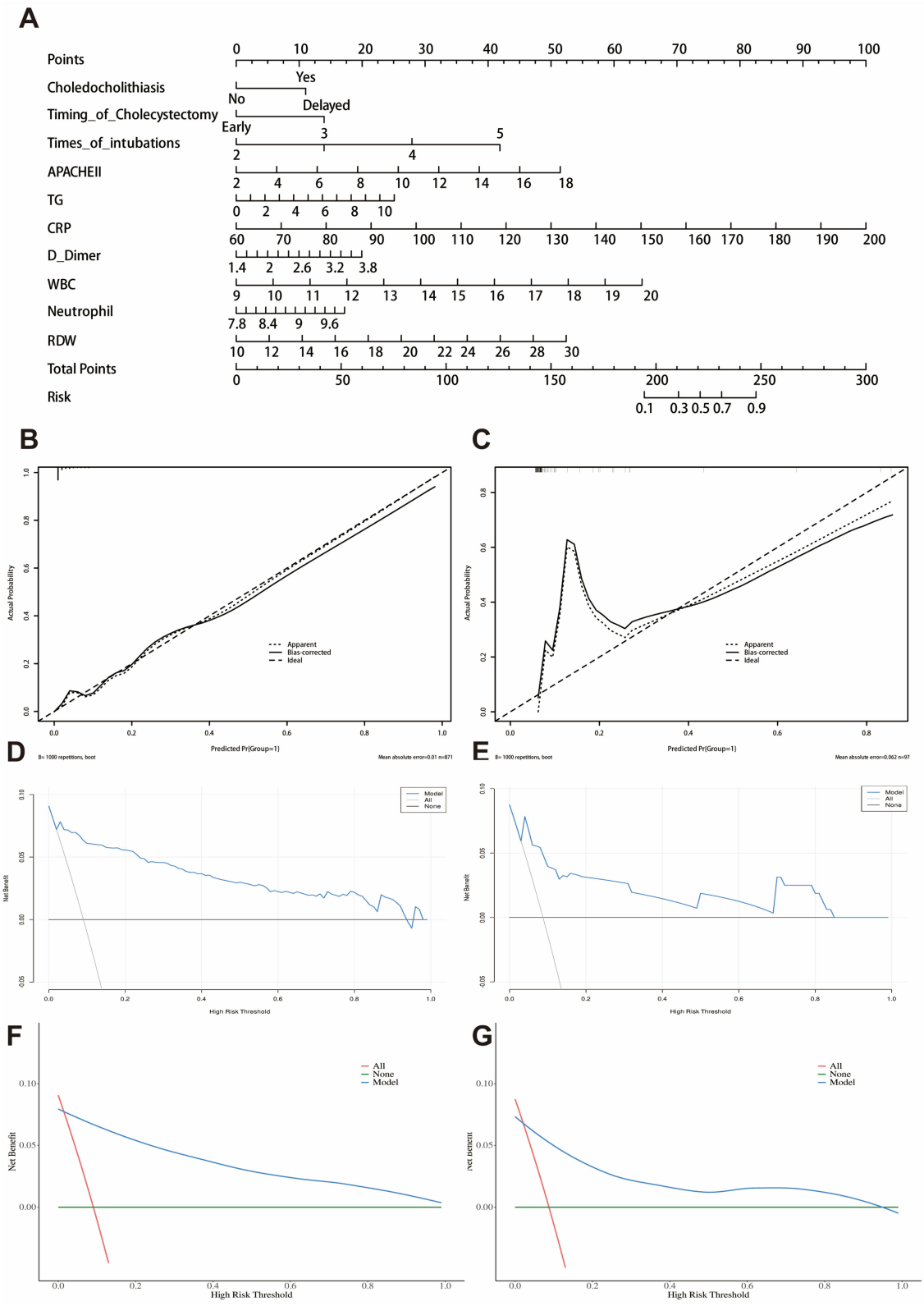

Figure 2 Assessment of predicting model for ABP. (**A**) Nomogram using identified risk factors for ABP after LC. (**B** and **C**) Calibration plots of predicting model in training and validation sets. (**D** and **E**) Unoptimized decision curves of training and validation sets. (**F** and **G**) Optimized decision curves of training and validation sets.

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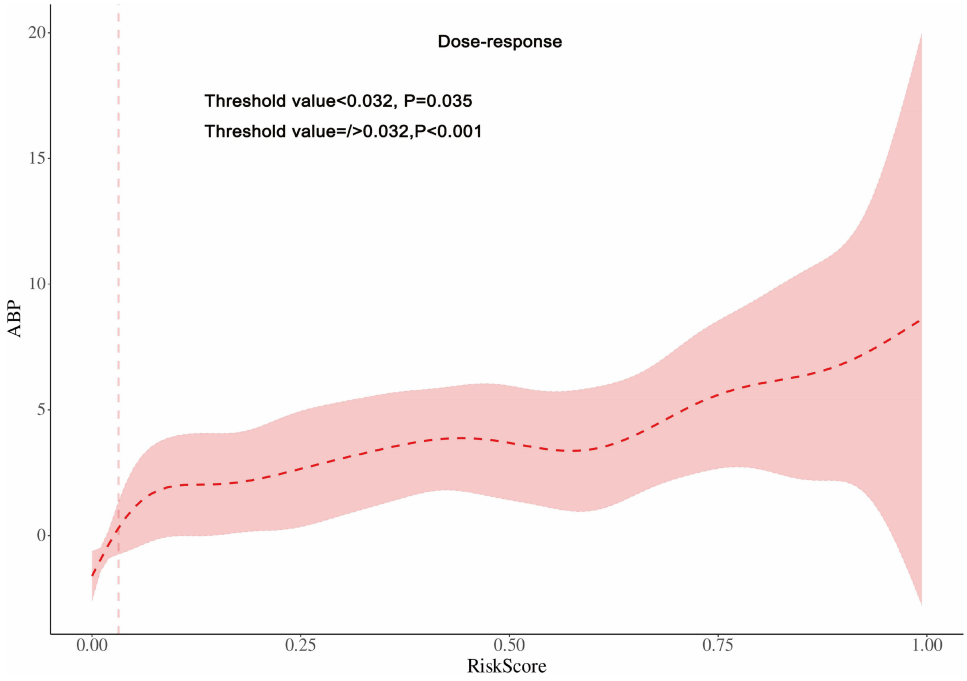

Figure 3 Dose-response between risk score and ABP in training set.

severity. Threshold effect and decision curve analyses further supported the model's clinical utility. Despite minor calibration fluctuations, overall performance was consistent, affirming its robustness.

Among the identified risk factors, the APACHE II score was significantly associated with ABP occurrence. Although the APACHE II score primarily reflects systemic physiological changes rather than localized disease status, it is widely regarded as an effective early diagnostic and prognostic tool for pancreatitis.[19,20] Our statistical analysis showed that the APACHE II score was significantly higher in the ABP group than in the non-ABP group. Moreover, ROC analysis suggested that the APACHE II score could help differentiate ABP from non-ABP cases, highlighting the need for comprehensive assessments in LC patients to improve ABP prediction. Choledocholithiasis also emerged as a critical risk factor for ABP after LC. When gallstones are present in the common bile duct, they can cause obstruction, impair bile drainage, and lead to bile reflux into the pancreatic duct. This process can activate pancreatic enzymes such as trypsin, chymotrypsin, and elastase, triggering pancreatitis.[21] Additionally, the increased bile duct pressure resulting from obstruction further exacerbates bile reflux into the pancreatic duct, worsening pancreatic injury.[22] The number of intubations during surgery was another key factor influencing ABP risk. Overfilling of the pancreatic duct with contrast agents can lead to reflux into the interstitial space and venous circulation, causing pancreatic duct visualization. This phenomenon is often associated with acinar clouding in the pancreas, which can induce chemical damage and increase ABP risk.[23] To minimize this risk, LC procedures should avoid unnecessary pancreatic duct imaging, limit multiple intubations, and employ soft guidewires to reduce pancreatic juice reflux. The timing of cholecystectomy is also related to the occurrence of post-operative ABP. Studies show that if gallstones are left untreated, the recurrence rate of ABP is 32–61%.[24] Early LC in patients has a lower incidence and recurrence rate. Regardless of laboratory test results and pain status, laparoscopic cholecystectomy can be safely performed within the first 48 hours for patients with gallstone-induced pancreatitis.[25] It was suggested that performing laparoscopic cholecystectomy within the first 48 hours on approximately half of the patients with acute pancreatitis due to biliary causes, and the results showed significant reductions in both the occurrence of ABP and hospital stay.[26]

This study also confirms that multiple biochemical markers are closely related to the pathological process of ABP. In ABP patients, TG levels are significantly elevated. The free fatty acids released by lipoprotein hydrolysis by lipase form micelle structures that directly damage pancreatic cells, leading to local ischemia and acidosis, which in turn activate

proenzymes, triggering pancreatic autodigestion. The damage to acinar cells also triggers an inflammatory cascade, and unsaturated fatty acids further promote the release of inflammatory mediators.[27] The study also found that D-dimer levels are significantly elevated in ABP patients, reflecting hypercoagulability and a tendency toward thrombosis. D-dimer promotes inflammatory cell infiltration and cytokine release, forming a coagulation-inflammation vicious cycle, which exacerbates pancreatic microcirculation disorder.[28] Additionally, CRP, WBC, neutrophils, and RDW are all associated with ABP. CRP, as an acute-phase protein, rises rapidly within 2–12 hours after inflammation onset, playing a dual role in regulating the inflammatory response and protecting the body. WBC elevation is primarily driven by neutrophils, and their overactivation may worsen tissue damage. RDW elevation is associated with the suppression of erythrocyte maturation by pro-inflammatory factors and erythrocyte membrane damage caused by reactive oxygen species.[29–31] These markers provide important basis for the diagnosis and assessment of ABP.

Our study has several limitations that should be acknowledged. First, it is a single-center, retrospective study, which may introduce information bias and limit the ability to infer causal relationships. Second, the sample size of the validation cohort is relatively small; future studies with larger sample sizes and prospective cohort data are needed. Third, the study population consisted exclusively of patients who underwent LC, which may limit the generalizability of the predictive model to other populations. Furthermore, future research should extend the follow-up period to evaluate the long-term predictive performance of the model.

In conclusion, the predictive model developed in this study effectively estimates the risk of post-LC pancreatitis in patients with gallstones. Calibration curves and decision curve analyses demonstrated the model's robust predictive performance and considerable net clinical benefit. In addition, this study highlights the multifactorial nature of acute biliary pancreatitis (ABP) following LC and emphasizes the value of a predictive model that integrates both clinical and biochemical parameters. By identifying key risk factors and providing a reliable risk assessment tool, our findings contribute to the advancement of early prevention strategies and the optimization of clinical management for gallstone-related ABP. Nonetheless, further studies with larger sample sizes and prospective designs are warranted to validate the model and enhance its generalizability.

Data Sharing Statement

All original data can be available from the corresponding author upon request.

Ethical Approval and Consent to Participate

This study adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the Ethics Committee of Henan Province Hospital of Traditional Chinese Medicine (HNSZYYWZ-20241105030). The informed consent is waived by the ethics committee because this is a retrospective design study. Patient confidentiality and data privacy were strictly safeguarded throughout the study.

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Disclosure

The authors have no conflicts of interest.

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