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# Nomogram for assistant diagnosing acute suppurative cholangitis: a case-control study

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## Abstract

**Background** Acute suppurative cholangitis (ASC) lacks sensitive and specific preoperative diagnostic criteria. Some researchers suggest treating ASC as severe cholangitis. This study aimed to explore the relationship between the Tokyo Guidelines 2018 (TG18) grading system for acute cholangitis (AC) and the diagnosis of acute suppurative cholangitis (ASC), searching for independent risk factors of ASC and develop a nomogram to discriminate ASC from acute nonsuppurative cholangitis (ANSC) accurately.

**Methods** After applying the inclusion and exclusion criteria, 401 patients with acute cholangitis (AC) were retrospectively analyzed at Nanjing First Hospital between January 2015 and June 2023. SPSS version 27.0 and R studio software were used to analyze data obtained from medical records. The results were validated in a prospective cohort of 82 AC patients diagnosed at Nanjing First Hospital between July 2023 and February 2024.

**Results** Among the 401 patients, 102 had suppurative bile (the ASC group; AC grade I: 40 [39.2%], AC grade II: 27 [26.5%], AC grade III: 35 [34.3%]), whereas 299 did not have (the ANSC group; AC grade I: 157 [52.5%], AC grade II: 92 [30.8%], AC grade III: 50 [16.7%]). The specificity of ASC for diagnosing moderate-to-severe cholangitis is 79.7%. Multivariate logistic regression analysis identified concurrent cholecystitis, CRP, PCT, TBA, and bile duct diameter as independent risk factors for suppurative bile, and all of these factors were included in the nomogram. The calibration curve exhibited consistency between the nomogram and the actual observation, and the area under the curve was 0.875 (95% confidence interval: 0.835–0.915), sensitivity was 86.6%, and specificity was 75.5%.

**Conclusion** Suppurative bile is a specific indicator for diagnosing moderate-to-severe cholangitis. However, diagnosing ASC with AC grade II and AC grade III has the risk of missed diagnosis as the sensitivity is only 60.8%. To improve the diagnostic rate of ASC, this study identified concurrent cholecystitis, CRP, PCT, TBA, and preoperative bile duct diameter as independent risk factors for ASC, and a nomogram was developed to help physicians recognize patients with ASC.

**Keywords** Acute cholangitis, Acute suppurative cholangitis, TG18, Nomogram

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## Background

Acute suppurative cholangitis (ASC), an inflammatory disorder caused by suppurative infection of the bile ducts, is accompanied by pus in the bile ducts. The accumulation of pus causes an elevation in bile duct pressure and facilitates the entry of pyogenic bacteria into the bloodstream, leading to severe sepsis. Compared to acute nonsuppurative cholangitis (ANSC), ASC demonstrates a poorer response to antibiotic treatment, with a mortality rate nearing 100% unless urgent biliary decompression is promptly carried out. [1–6]. Timely drainage plays a pivotal role in treating ASC over antibiotic therapy [7, 8]. Therefore, accurate differentiation between ASC and ANSC is crucial. However, ASC lacks recognized preoperative diagnostic criteria. The Reynolds' Pentad, previously considered to be the diagnostic criterion for acute obstructive septic cholangitis, exhibits low sensitivity. The Tokyo Guidelines 2018 (TG18) does not provide a precise definition of ASC but rather establishes clinical indicators for evaluating patients with mild, moderate, and severe cholangitis [9, 10]. While it has been proposed that ASC should be managed as moderate-to-severe cholangitis, clinicians have observed that some patients with mild cholangitis have suppurative bile during drainage [11–13]. This suggests that the TG18 classification of acute cholangitis (AC), which relies on clinical symptoms and laboratory indices, may not be effective in diagnosing ASC. There could be other factors closely related to ASC. Thus, our study aimed to identify independent risk factors of ASC and develop a nomogram to predict ASC accurately.

## Methods

### Diagnostic criteria

AC is diagnosed and graded according to the TG18 criteria [10]. ASC is diagnosed based on the Reynolds Pentad and evidence of suppurative bile during drainage. Drainage procedures were performed using percutaneous transhepatic cholangial drainage (PTCD), endoscopic retrograde cholangiopancreatography (ERCP), and surgery. The presence of suppurative bile was evaluated through direct observation by clinicians. Bile cultures were partially conducted to support the diagnosis.

### Patients

We retrospectively collected 650 patients between January 2015 and June 2023 and prospectively collected 98 patients between July 2023 and February 2024, who were diagnosed with AC at the Nanjing First Hospital of Nanjing Medical University, by the Electronic Medical Record System. The inclusion criteria were as follows: (1) ≥18 years old; (2) diagnosed with AC; (3) detailed and complete medical data. The exclusion criteria were as follows: (1) patients who did not receive biliary drainage; (2) combined with hematological system disorders or other abnormalities affecting leukocyte and platelet count; (3) Incomplete dataset. Finally, 401 patients were included in the primary cohort and 82 patients were included in the validation cohort. (Fig. 1).

### Data collection

Variables assessed were obtained from medical records and included the following: demographic data, such as gender and age; past history such as hypertension, diabetes, heart disease, respiratory diseases, nervous system diseases, liver and kidney dysfunctions, fatty liver, gallbladder stones, malignant tumor of the hepatobiliary system, history of gallbladder surgery, history of cholangitis, history of ERCP, and history of PTCD, history of percutaneous transhepatic gallbladder drainage (PTGD); clinical characteristics before drainage, including temperature (the highest value from the onset of the disease until drainage), concurrent cholecystitis (diagnosed on the basis of TG18 and evidence of the gallbladder hyperemia and oedema during surgery [14]), concurrent pancreatitis, disorders of consciousness, shock, respiratory insufficiency (PaO2/FiO2 ratio < 300), and the common bile duct diameter (the maximum diameter of the common bile duct measured by Computed Tomography or Magnetic Resonance Cholangiopancreatography); laboratory data, including white blood cell (WBC) count, neutrophil percentage (N%), platelet count (PLT), C-reactive protein (CRP), procalcitonin (PCT), total bilirubin (TB), direct bilirubin (DB), total bile acids (TBA), alanine aminotransferase (ALT), aspartate transferase (AST), glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), serum albumin (ALB), blood creatinine (Scr), carcinoembryonic antigen (CEA), carbohydrate antigen 19−9 (CA19-9), and prothrombin time-international normalized ratio (PT-INR); bile drainage (through PTCD, ERCP or surgery); deaths during hospitalization; duration of preoperative antibiotic therapy.

### Statistical analysis

Patients in the primary cohort were split into two groups based on the above diagnostic criteria (ASC group, $n=102$; ANSC group, $n=299$), and the TG18 classification for AC was applied to grade their condition. To determine whether there was a significant difference between the two groups in the distribution of mild, moderate, and severe AC, the chi-square test was employed. Risk factors for ASC were determined using binary logistic regression analysis.

Two-sided tests were used to conduct all statistical analyses, with P values < 0.05 considered statistically significant. Risk factors with P values < 0.05 in the univariate analysis were incorporated into the multivariate analysis.

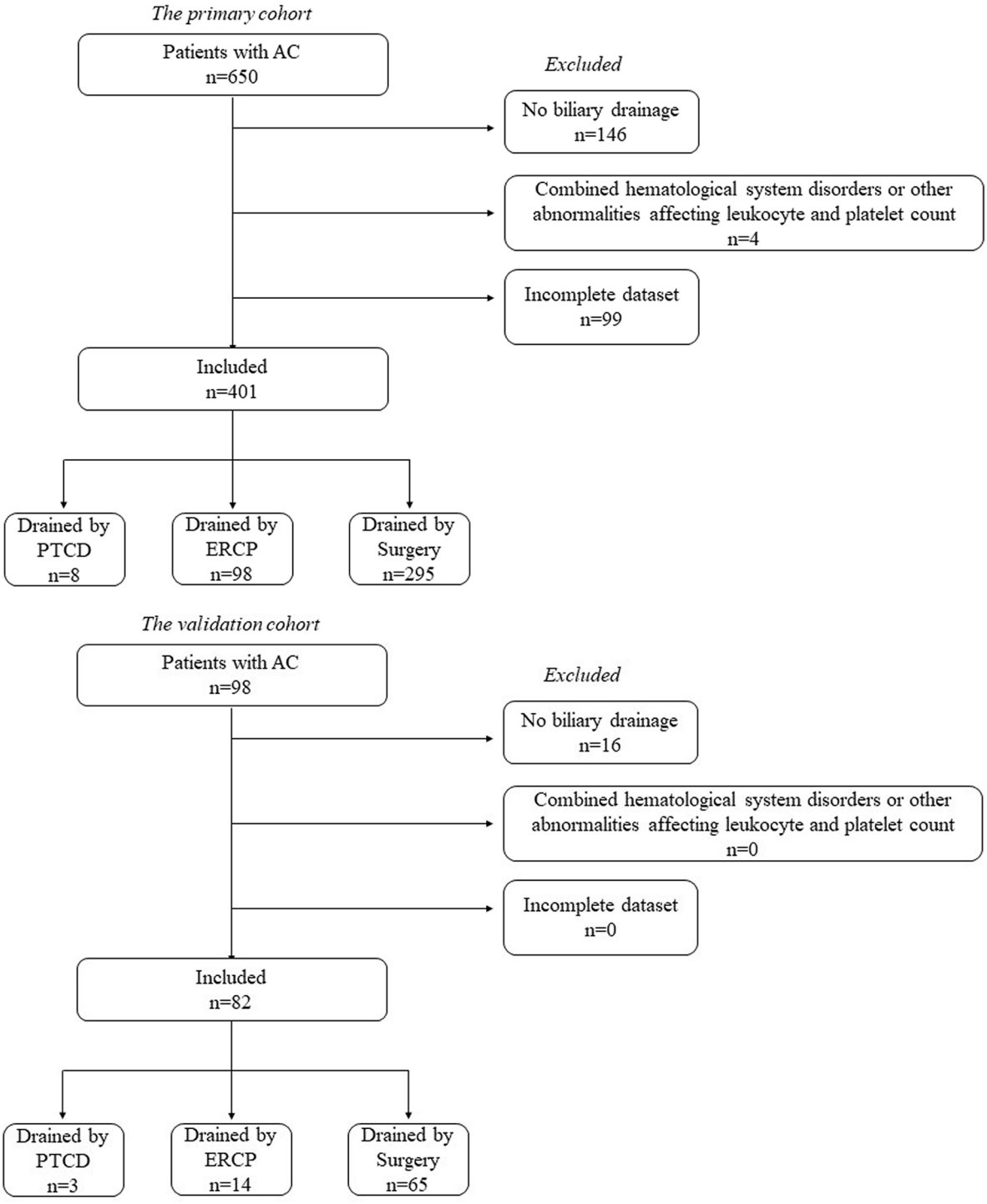


**Fig. 1** Patient flow diagram

Factors with $P<0.05$ in multivariate analysis were finally considered as independent risk factors of ASC.

A nomogram was developed based on the results of the multivariate logistic regression model to facilitate the prediction of ASC. Receiver operating characteristic (ROC) curve analysis and calibration plots with bootstrap samples were used to evaluate the performance of the nomogram. Additionally, the predictive capability of the nomogram in diagnosing ASC was compared with that of TG18 (using moderate-to-severe cholangitis as a predictor).

All the statistical analyses were conducted with SPSS version 27.0. The nomogram is performed using the RMS package from R studio.

## Result

### Patient characteristics

Patient demographics and clinical characteristics of the primary and validation cohorts are detailed in Table 1. In the primary cohort, the ASC rate was 25.4%, and in the validation cohort, it was 18.3%. The distribution of ASC in the primary cohort for each drainage procedure was as follows: PTCD: 5 cases (62.5%), EPCP: 25 cases (25.5%), and surgery: 72 cases (24.4%). In the validation cohort, the distribution was: PTCD: 2 cases (66.6%), EPCP: 2 cases (14.3%), and surgery: 11 cases (16.9%) (data not shown in Table 1). Table 2 shows the clinical characteristics of the primary cohort, which were divided into two groups: 102 individuals with suppurative bile (AC grade I: 40 [39.2%], AC grade II: 27 [26.5%], AC grade III: 35 [34.3%]) and 299 individuals without suppurative bile (AC grade I: 157 [52.5%], AC grade II: 92 [30.8%], AC grade III: 50 [16.7%]). The chi-square test revealed a substantial difference in the grading of AC severity between the ASC group and the ANSC group. Mild cholangitis was substantially less common in the ASC group than in the ASC group (39.2% vs. 52.5%, $P<0.01$), whereas severe cholangitis was substantially more common in the ASC group than in the ANSC group (34.3% vs. 16.7%, $P<0.01$). Also, based on the data in Table 3, the specificity of ASC for diagnosing moderate-to-severe cholangitis is 79.7%. These findings suggest that ASC more frequently progresses to the severity level of AC grade III than ANSC.

### Sensitivity and specificity of TG18 for diagnosing ASC

By using moderate-to-severe cholangitis as an indicator of TG18 to predict ASC, and suppurative bile observed during drainage as the gold standard for ASC diagnosis, we calculated the sensitivity and specificity of TG18 for diagnosing ASC (Sensitivity 60.8%, specificity 52.5%;Table 3).

### Nomogram for assistant diagnosing ASC

In univariate analysis, the relationship between several clinical variables and ASC was examined. The presence of cardiac disease, respiratory disease, concurrent cholecystitis, WBC count, N%, CRP, PCT, TB, DB, TBA, PT-INR, shock, respiratory insufficiency and common bile duct diameter were significantly associated with ASC (Table 4). Multivariate logistic regression analyses were conducted on these factors using a stepwise method, and concurrent cholecystitis, CRP, PCT, TBA, and common bile duct diameter were identified as independent risk factors for ASC (Table 4). A nomogram was developed based on these factors to assist in diagnosing ASC (Fig. 2).

### Validation of the nomogram

The ROC curve of the primary cohort was made to evaluate the performance of our nomogram (The area under the curve (AUC) was 0.875; 95% confidence interval (CI) 0.835–0.915; Sensitivity 75.5%, specificity 86.6%, Cutoff 0.320). When the validation cohort was subjected to the nomogram, the AUC was 0.838 (95% CI, 0.725–0.951). The ROC curve of the validation cohort had a sensitivity of 86.7% and a specificity of 71.6% with the cutoff value set to 0.320. There was no significant difference in AUC between the primary cohort and the validation cohort (Fig. 3). Furthermore, the calibration curve showed consistency between the nomogram predictions and the actual observations in the primary cohort and the validation cohort (Fig. 4).

## Discussion

The main contribution of our study is finding independent risk factors associated with ASC and providing a diagnostic reference for ASC. ASC is a life-threatening disease, once the diagnosis is established, urgent surgical decompression should be performed [4–6]. Regrettably, ASC lacks sensitive and specific diagnostic criteria, and TG18 classifies AC as mild, moderate, or severe, without mentioning which grade ASC should be in [9, 10]. Some experts proposed that ASC should be treated as moderate-severe cholangitis, yet instances of suppurative bile have been observed in patients diagnosed with mild cholangitis according to TG18. [11–13]. Therefore, TG18 exhibits limitations in diagnosing ASC. Factors included in the AC grading criteria set by TG18 failed to accurately distinguish ASC from ANSC. Due to this defect, we searched for independent risk factors for ASC and produced a nomogram for assistant diagnosing ASC. The factors outlined in the AC grading criteria established by TG18 were found to be inadequate in effectively distinguishing between ASC and ANSC. Consequently, we conduct this research for independent risk factors specific to ASC and developed a nomogram to aid in its diagnosis. Given the absence of prior research on ASC diagnosis, our study lacks comparative data with other studies. To evaluate the predictive ability of our nomogram, TG18 moderate to severe cholangitis was compared with it as a predictor of ASC. Our study proved that the nomogram we developed exhibits higher sensitivity and specificity in assisting in the diagnosis of ASC than TG18 (86.6% vs. 60.8%; 75.5% vs. 52.5%). The risk factors we identified: concurrent cholecystitis, CRP, PCT, TBA, and bile duct diameter showed significant associations with ASC.

Concurrent acute cholecystitis (ACL) and AC are special clinical conditions. Although the TG18 has proposed management approaches for acute cholecystitis and AC, it has not yet proposed specific guidelines for

**Table 1** Patient demographics and clinical characteristics of the primary and validation cohorts

| Patient's Characteristics | | Total *N* = 483 | Primary cohort *N* = 401 | Validation cohort *N* = 82 | *P*-value |
|---|---|---|---|---|---|
| Gender (male) | | 299(61.9%) | 256(63.8%) | 43 (52.4%) | 0.053 |
| Age(year) | | 69(60,79) | 69(59,79) | 71.5(60,77) | 0.789 |
| Hypertensive | | 224(46.4%) | 179(44.6%) | 45(54.9%) | 0.090 |
| Diabetes | | 83(17.2%) | 68(17%) | 15(18.3%) | 0.770 |
| Heart disease | | 71(14.7%) | 65(16.2%) | 6(7.3%) | 0.038 |
| Respiratory diseases | | 20(4.1%) | 18(4.5%) | 2(2.4%) | 0.394 |
| Nervous System Diseases | | 60(12.4%) | 57(14.2%) | 3(3.7%) | 0.008 |
| Liver dysfunction | | 3(0.6%) | 3(0.7%) | 0(0.0%) | 0.572* |
| Kidney dysfunction | | 17(3.5%) | 13(3.2%) | 4(4.9%) | 0.686† |
| Fatty Liver | | 23(4.8%) | 22(5.5%) | 1(1.2%) | 0.171† |
| Gallbladder Stones | | 403(83.4%) | 326(81.3%) | 77(93.9%) | 0.005 |
| Malignant tumor of the hepatobiliary system | | 20(4.2%) | 14(3.5%) | 6(7.3%) | 0.206† |
| History of gallbladder surgery | | 142(29.4%) | 124(30.9%) | 18(22.0%) | 0.104 |
| History of cholangitis | | 84(17.4%) | 77(19.2%) | 7(8.5%) | 0.020 |
| History of ERCP | | 30(6.2%) | 27(6.7%) | 3(3.7%) | 0.293 |
| History of PTCD | | 5(1.0%) | 4(1.0%) | 1(1.2%) | 0.607* |
| History of PTGD | | 2(0.4%) | 2(0.5%) | 0(0.0%) | 0.689* |
| Temperature (℃) | | 36.8(36.5,38.2) | 36.9(36.6,38.3) | 36.5(36.4,36.8) | < 0.001 |
| Concurrent cholecystitis | | 295(61.1%) | 237(59.1%) | 58(70.7%) | 0.049 |
| Concurrent pancreatitis | | 33(6.8%) | 29(7.2%) | 4(4.9%) | 0.441 |
| Disorders of consciousness | | 10(2.1%) | 9(2.2%) | 1(1.2%) | 0.866† |
| Shock | | 18(3.7%) | 15(3.7%) | 3(3.7%) | 1.000 |
| Respiratory insufficiency | | 12(2.5%) | 10(2.5%) | 2(2.4%) | 1.000 |
| Common bile duct diameter (mm) | | 10.31(8.38,13.10) | 10.40(8.55,12.67) | 9.98(7.62,14.02) | 0.288 |
| AC grade | I | 240(49.7%) | 197(49.1%) [a] | 43(52.4%) [a] | 0.694 |
| | II | 144(29.8%) | 119(29.7%) [a] | 25(30.5%) [a] | |
| | III | 99(20.5%) | 85(21.2%) [a] | 14(17.1%) [a] | |
| Bile drainage | PTCD | 11(2.3%) | 8(2.0%) [a] | 3(3.7%) [a] | 0.257 |
| | ERCP | 112(23.2%) | 98(24.4%) [a] | 14(17.1%) [a] | |
| | Surgery | 360(74.5%) | 295(73.6%) [a] | 65(79.3%) [a] | |
| Suppurative bile | | 117(24.2%) | 102(25.4%) | 15(18.3%) | 0.169 |
| WBC($10^9$/l) | | 9.51(6.26,13.18) | 10.28(6.72,13.94) | 6.89(5.86,9.65) | < 0.001 |
| N% | | 82.60(74.60,89.00) | 83.20(76.10,89.12) | 77.60(67.4,86.8) | 0.002 |
| PLT($10^9$/l) | | 168.00(123.00,211.00) | 165.00(122.00,2100) | 178.50(130.50,218.00) | 0.247 |
| CRP(mg/l) | | 54.55(24.50,88.68) | 55.10(30.00,81.00) | 27.02 (9.46,92.96) | 0.002 |
| PCT(ng/ml) | | 0.27(0.11,0.79) | 0.26(0.11,0.74) | 0.30(0.11,1.30) | 0.089 |
| TB(umol/l) | | 61.30(27.20,99.50) | 61.70(29.65,100.75) | 49.00(67.40,86.80) | 0.124 |
| DB(umol/l) | | 38.20(14.50,70.60) | 39.90(16.60,71.10) | 32.95(6.42,68.72) | 0.048 |
| TBA(umol/l) | | 77.40(12.50,194.70) | 85.34(14.80,195.50) | 31.25(6.15,188.90) | 0.109 |
| ALT(U/L) | | 146.00(64.90,280.75) | 151.00(69.00,286.00) | 105.50(45.20,232.50) | 0.042 |
| AST(U/L) | | 97.00(45.00,193.00) | 104.00(47.50,209.50) | 74.50(39.75,169.00) | 0.097 |
| GGT(U/L) | | 364.00(181.00,521.64) | 370.00(190.00,521.99) | 337.50(150.75,511.00) | 0.178 |
| ALP(U/L) | | 202.00(131.00,305.92) | 207.00(138.00,311.50) | 174.00(117.25,268.63) | 0.033 |
| ALB(g/l) | | 34.66(31.6,37.6) | 34.5(31.5,37.3) | 36.03 ± 5.98 | 0.008 |
| Scr(umol/l) | | 70.0(56.80,88.40) | 70.0(57.0,86.0) | 71.05(54.76,91.78) | 0.795 |
| CEA(ng/ml) | | 2.51(1.75,3.97) | 2.71(1.87,3.97) | 2.05(1.55,2.60) | < 0.001 |
| CA19-9(U/L) | | 43.14(19.59,160.10) | 43.37(20.83,158.95) | 39.71(15.80,167.68) | 0.528 |
| PT-INR | | 1.08(1.01,1.17) | 1.08(1.05,1.16) | 1.11(1.04,1.18) | 0.111 |
| Deaths during hospitalization | | 8(1.7%) | 7(1.7%) | 1(1.2%) | 1.000† |
| Duration of preoperative antibiotic therapy(day) | | 2(2,3) | 2(2,3) | 2(2,4) | 0.675 |

* Fisher Precision Inspection

† Calibrated chi-square test

a, a at the 0.05 level, the two columns are not significantly different from each other

**Table 2** Patient characteristics of the primary cohort

| Variables | | Suppurative bile | | | |
|---|---|---|---|---|---|
| | | **Total** ***N*** **= 401** | **ASC** ***N*** **= 102** | **ANSC** ***N*** **= 299** | ***P*-value** |
| Gender (male) | | 256(63.8%) | 66(64.7%) | 190(63.5%) | 0.466 |
| Age(year) | | 69(59,79) | 71.5(61,80) | 68(58,79) | 0.319 |
| Hypertensive | | 179(44.6%) | 50(49%) | 129(43.1%) | 0.303 |
| Diabetes | | 68(17%) | 22(21.6%) | 46(15.4%) | 0.151 |
| Heart disease | | 65(16.2%) | 23(22.5%) | 42(14%) | 0.044 |
| Respiratory diseases | | 18(4.5%) | 12(11.9%) | 6(2.0%) | < 0.001 |
| Nervous System Diseases | | 57(14.2%) | 20(19.6%) | 37(12.4%) | 0.071 |
| Liver dysfunction | | 3(0.7%) | 2(2.0%) | 1(0.3%) | 0.160* |
| Kidney dysfunction | | 13(3.2%) | 5(4.9%) | 8(2.7%) | 0.440† |
| Fatty Liver | | 22(5.5%) | 6(5.9%) | 16(5.4%) | 0.839 |
| Gallbladder Stones | | 326(81.3%) | 86(84.3%) | 240(80.3%) | 0.366 |
| Malignant tumor of the hepatobiliary system | | 14(3.5%) | 3(21.4%) | 11(78.6%) | 1.000† |
| History of gallbladder surgery | | 124(30.9%) | 26(25.5%) | 98(32.8%) | 0.169 |
| History of cholangitis | | 77(19.2%) | 20(19.6%) | 57(19.1%) | 0.904 |
| History of ERCP | | 27(6.7%) | 7(6.9%) | 20(6.7%) | 0.952 |
| History of PTCD | | 4(1.0%) | 1(1.0%) | 3(1%) | 1.00† |
| History of PTGD | | 2(0.5%) | 1(1.0%) | 1(0.3%) | 0.445* |
| Temperature (℃) | | 36.9(36.6,38.3) | 37.1(36.6,38.5) | 36.9(36.5,38.3) | 0.158 |
| Concurrent cholecystitis | | 237(59.1%) | 75(73.5%) | 162(54.2%) | < 0.001 |
| Concurrent pancreatitis | | 29(7.2%) | 10(9.8%) | 19(6.4%) | 0.245 |
| Disorders of consciousness | | 9(2.2%) | 5(4.9%) | 4(1.3%) | 0.087† |
| Shock | | 15(3.7%) | 10(9.8%) | 5(1.7%) | < 0.001† |
| Respiratory insufficiency | | 10(2.5%) | 9(8.8%) | 1(0.3%) | < 0.001† |
| Common bile duct diameter (mm) | | 10.40(8.55,12.67) | 13.62(11.44,16.30) | 9.66(8.13,11.30) | < 0.001 |
| AC grade | I | 197(49.1%) | 40(39.2%) [a] | 157(52.5%) [b] | < 0.001 |
| | II | 119(29.7%) | 27(26.5%) [a] | 92(30.8%) [a] | |
| | III | 85(21.2%) | 35(34.3%) [a] | 50(16.7%) [b] | |
| WBC($10^9$/l) | | 10.28(6.72,13.94) | 10.73(7.45,15.95) | 9.60(6.26,13.07) | 0.009 |
| N% | | 83.20(76.10,89.12) | 90.85(87.87,94.10) | 81.50(75.48,88.53) | < 0.001 |
| PLT($10^9$/l) | | 165.00(122.00,2100) | 160.00(116.75,210.00) | 166.00(124.00,210.00) | 0.774 |
| CRP(mg/l) | | 55.10(30.00,81.00) | 70.50 (52.20,106.25) | 45.66 (25.00,73.81) | < 0.001 |
| PCT(ng/ml) | | 0.26(0.11,0.74) | 0.68(0.30,0.99) | 0.19(0.09,0.46) | < 0.001 |
| TB(umol/l) | | 61.70(29.65,100.75) | 84.15(38.30,125.28) | 52.20(27.30,93.18) | < 0.001 |
| DB(umol/l) | | 39.90(16.60,71.10) | 56.55(22.97,85.85) | 32.70(14.50,63.50) | < 0.001 |
| TBA(umol/l) | | 85.34(14.80,195.50) | 144.50(22.98,247.08) | 60.30(10.40,185.00) | < 0.001 |
| ALT(U/L) | | 151.00(69.00,286.00) | 146.50(63.00,241.25) | 154.00(72.00,304.00) | 0.243 |
| AST(U/L) | | 104.00(47.50,209.50) | 106.50(47.25,218.50) | 98.00(47.00,198.00) | 0.769 |
| GGT(U/L) | | 370.00(190.00,521.99) | 370.50(175.00,476.00 | 370.00(214.00,532.22) | 0.254 |
| ALP(U/L) | | 207.00(138.00,311.50) | 228.50(135.84,325.00) | 205.00(139.00,305.00) | 0.489 |
| ALB(g/l) | | 34.5(31.5,37.3) | 33.95(31.55,36.61) | 34.66(31.40,37.60) | 0.136 |
| Scr(umol/l) | | 70.0(57.0,86.0) | 73.25(62.75,89.40) | 69.00(56.60,84.00) | 0.032 |
| CEA(ng/ml) | | 2.71(1.87,3.97) | 2.85(1.97,3.98) | 2.69(1.80,3.97) | 0.648 |
| CA19-9(U/L) | | 43.37(20.83,158.95) | 68.03(22.22,214.03) | 39.76(19.81,147.40) | 0.055 |
| PT-INR | | 1.08(1.05,1.16) | 1.11(1.03,1.23) | 1.07(1.00,1.14) | 0.013 |
| Deaths during hospitalization | | 7(1.7%) | 5(4.9%) | 2(0.7%) | 0.017† |
| Duration of preoperative antibiotic therapy(day) | | 2(2,3) | 2(2,3) | 2(2,3) | 0.090 |

* Fisher Precision Inspection

† Calibrated chi-square test

a, b at the 0.05 level, the two columns are significantly different from each other

a, a at the 0.05 level, the two columns are not significantly different from each other

**Table 3** The sensitivity and specificity of TG18

| | | Gold standard | | Total |
|---|---|---|---|---|
| | | Suppurative bile | Non-suppurative bile | |
| TG18 | moderate-to-severe cholangitis | 62* | 142 | 204 |
| | mild cholangitis | 40 | 157† | 197 |
| Total | | 102 | 299 | 401 |

* Sensitivity of TG18:60.8%

† Specificity of TG18:52.5%

managing AC combined with ACL [15]. This study identified concurrent ACL as an independent risk factor for suppurative bile in patients with AC. We propose two possibilities: First, suppurative inflammation of the bile ducts may increase biliary pressure, leading to a retrograde spread of inflammation to the gallbladder and resulting in cholecystitis. Second, suppurative inflammation within the gallbladder could extend into the bile ducts, potentially be associated with dislodging of gallstones. According to previous studies, the prevalence of common bile duct stones in patients with symptomatic gallbladder stones is estimated to be between 4.6% and 20.9%, a condition known as gallstone cholangitis [16].

PCT and CRP are widely considered to be associated with bacterial infections. Several studies have established a substantial relationship between PCT and CRP levels with severe AC [17–22]. In one study, high levels of CRP were identified as a risk factor for ASC, while another study observed a substantial increase in PCT levels in patients with suppurative bile discharge [19, 22]. These results are consistent with the findings of our study.

Bile acids are crucial signaling molecules in the interaction between the liver, bile, and intestinal tract. In patients with AC, obstruction of the bile duct and cholestasis lead to the accumulation of primary bile acids, which do not reach the small intestine and form secondary bile acids. Primary bile acids exhibit substantial cytotoxicity and can cause irreversible cellular damage. Increased levels of bile acids are highly significant and serve as early predictors of critical illness in patients with septic shock [23]. It was hypothesized that TBA levels would be higher in suppurative cholangitis because high bile acid levels are associated with severe infections.

The preoperative diameter of the bile duct is associated with the extent and duration of obstruction. In cases of complete bile duct obstruction, a long duration of obstruction, and high bile duct pressure, the bile duct will expand. Previous research has also demonstrated that patients with common bile duct stones complicated with acute suppurative cholangitis exhibit a substantially larger common bile duct width and a significantly higher bile duct pressure than other patients [24]. Inflammation and damage to the common bile duct and its branches, as well as an increase in biliary infection and suppuration, can be caused by dilation of the bile duct and an increase in pressure. Thus, preoperative bile duct diameter

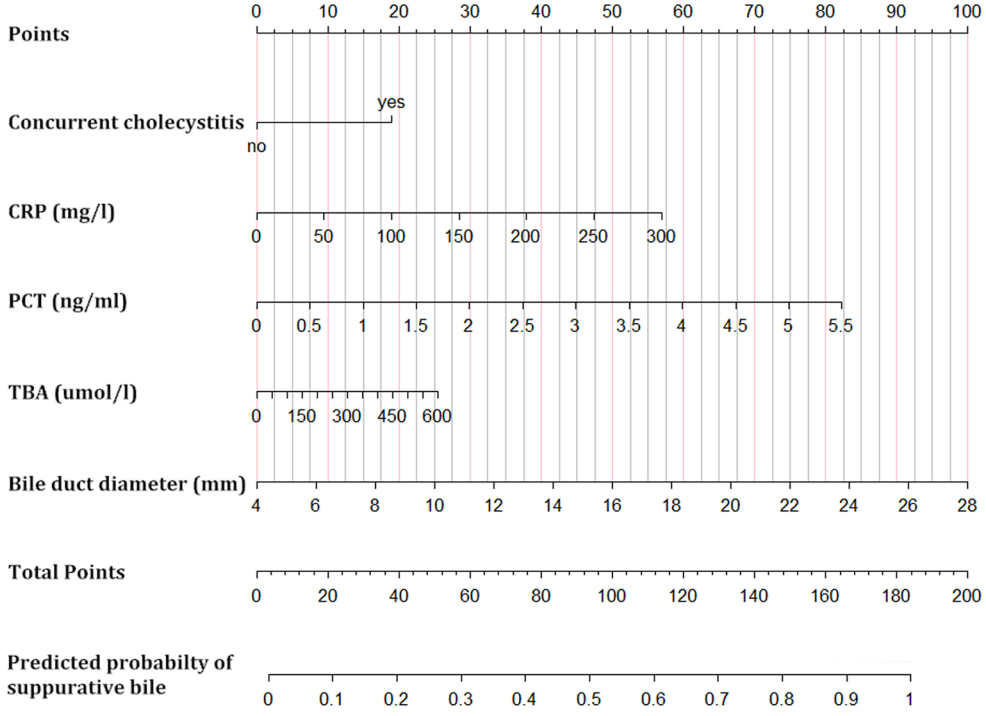


**Fig. 2** Nomogram for predicting suppurative bile caused by AC

**Table 4** Factors associated with suppurative bile caused by AC

| Factor | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR(95%CI) | *P* value | OR(95%CI) | *P* value |
| Sex(male) | 1.052(0.658,1.682) | 0.833 | | |
| Age(year) | 1.009(0.992,1.025) | 0.301 | | |
| Hypertensive | 1.267(0.807,1.989) | 0.303 | | |
| Diabetes | 1.512(0.858,2.666) | 0.153 | | |
| Heart disease | 1.781(1.010,3.142) | 0.046 | 1.299(0.592,2.851) | 0.514 |
| Respiratory diseases | 6.584(2.402,18.047) | < 0.001 | 2.934(0.803,10.716) | 0.103 |
| Nervous System Diseases | 1.727(0.950,3.140) | 0.073 | | |
| Liver dysfunction | 5.960(0.535,66.433) | 0.147 | | |
| Kidney dysfunction | 1.875(0.599,5.867) | 0.280 | | |
| Fatty Liver | 1.105(0.421,2.906) | 0.839 | | |
| History of Gallbladder Stones | 1.321(0.722,2.419) | 0.367 | | |
| History of gallbladder surgery | 0.702(0.423,1.164) | 0.170 | | |
| Concurrent malignant tumor of the hepatobiliary system | 0.818(0.224,2.994) | 0.762 | | |
| History of cholangitis | 1.036(0.587,1.827) | 0.904 | | |
| History of ERCP | 1.028(0.421,2.507) | 0.952 | | |
| History of PTCD | 0.977(0.100,9.498) | 0.984 | | |
| History of PTGD | 2.950(0.183,47.606) | 0.446 | | |
| Concurrent cholecystitis | 2.349(1.432,3.855) | < 0.001 | 3.715(1.906,7.239) | < 0.001 |
| Concurrent pancreatitis | 1.602(0.719,3.569) | 0.249 | | |
| WBC($10^9$/l) | 1.057(1.015,1.101) | 0.007 | 0.981(0.920,1.046) | 0.559 |
| N% | 1.046(1.018,1.074) | < 0.001 | 1.024(0.990,1.060) | 0.171 |
| PLT($10^9$/l) | 1.000(0.997,1.003) | 0.849 | | |
| CRP(mg/l) | 1.017(1.011,1.023) | < 0.001 | 1.012(1.004,1.020) | 0.003 |
| PCT(ng/ml) | 4.644(2.809,7.675) | < 0.001 | 3.156(1.675,5.948) | < 0.001 |
| T(℃) | 1.147(0.950,1.385) | 0.153 | | |
| TB(umol/l) | 1.003(1.000,1.005) | 0.027 | 1.002(0.985,1.020) | 0.787 |
| DB(umol/l) | 1.005(1.001,1.009) | 0.008 | 0.999(0.972,1.026) | 0.926 |
| TBA(umol/l) | 1.003(1.001,1.005) | < 0.001 | 1.003(1.000,1.005) | 0.043 |
| ALT(U/L) | 1.000(0.998,1.001) | 0.440 | | |
| AST(U/L) | 1.000(0.999,1.001) | 0.722 | | |
| GGT(U/L) | 1.000(0.999,1.001) | 0.869 | | |
| ALP(U/L) | 1.001(1.000,1.002) | 0.135 | | |
| ALB(g/l) | 1.006(0.992,1.021) | 0.389 | | |
| Scr(umol/l) | 1.003(0.999,1.006) | 0.162 | | |
| CEA(ng/ml) | 0.994(0.963,1.025) | 0.686 | | |
| CA19-9(U/L) | 1.000(1.000,1.001) | 0.172 | | |
| PT-INR | 5.217(1.439,18.918) | 0.012 | 0.977(0.155,6.166) | 0.980 |
| Disorders of consciousness | 3.802(1.001,14.441) | 0.05 | | |
| shock | 6.391(2.130,19.177) | < 0.001 | 2.334(0.461,11.821) | 0.306 |
| Respiratory insufficiency | 28.839(3.606,230.621) | 0.002 | 3.995(0.380,42.010) | 0.249 |
| Bile duct diameter(mm) | 1.361(1.262,1.468) | < 0.001 | 1.312(1.204,1.429) | < 0.001 |
| Duration of preoperative antibiotic therapy | 0.902(0.801,1.016) | 0.090 | | |

examination can offer crucial references and guidance for surgical treatment.

This study has a certain degree of originality because previous studies on suppurative cholangitis are very rare. Our study demonstrates that ASC is a specific indicator for diagnosing moderate-to-severe cholangitis, with an accuracy of 79.7%. We suggest the Tokyo Guidelines consider suppurative bile as a potential criterion for the postoperative grading of AC. Despite the current recommendation for early drainage in cases of AC, patients with suppurative bile who have not yet developed severe cholangitis face the risk of delayed diagnosis and increased mortality during hospitalization. Predicting suppurative bile and early intervention can prevent potential complications.

This study has several limitations. First, as a single-center retrospective study, it may be subject to selection bias due to the exclusion of 146 patients who did not

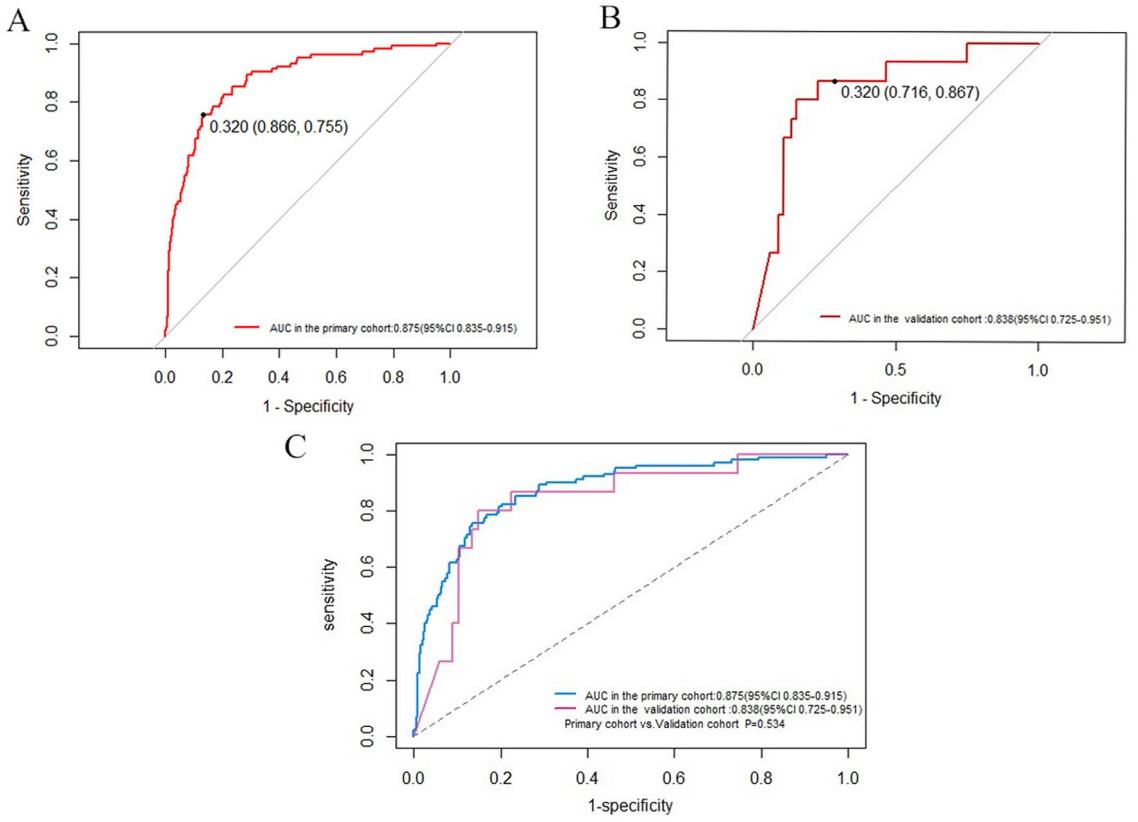


**Fig. 3** The ROC curve of the nomogram. The ROC curve for the primary cohort (**A**) and the validation cohort (**B**). Both ROC curves were plotted on the same figure which showed no significant difference in AUC ($p=0.534$, **C**)

undergo biliary drainage and the additional 99 patients with severely incomplete data. We analyzed the 146 undrained cases and compared their clinical characteristics with those of the primary cohort, finding a higher incidence of mild cholangitis in the undrained cases, along with significant differences in WBC, CRP, PCT, and bile duct diameters ($P<0.05$; Table 5). Second, the diagnosis of suppurative bile was primarily based on direct

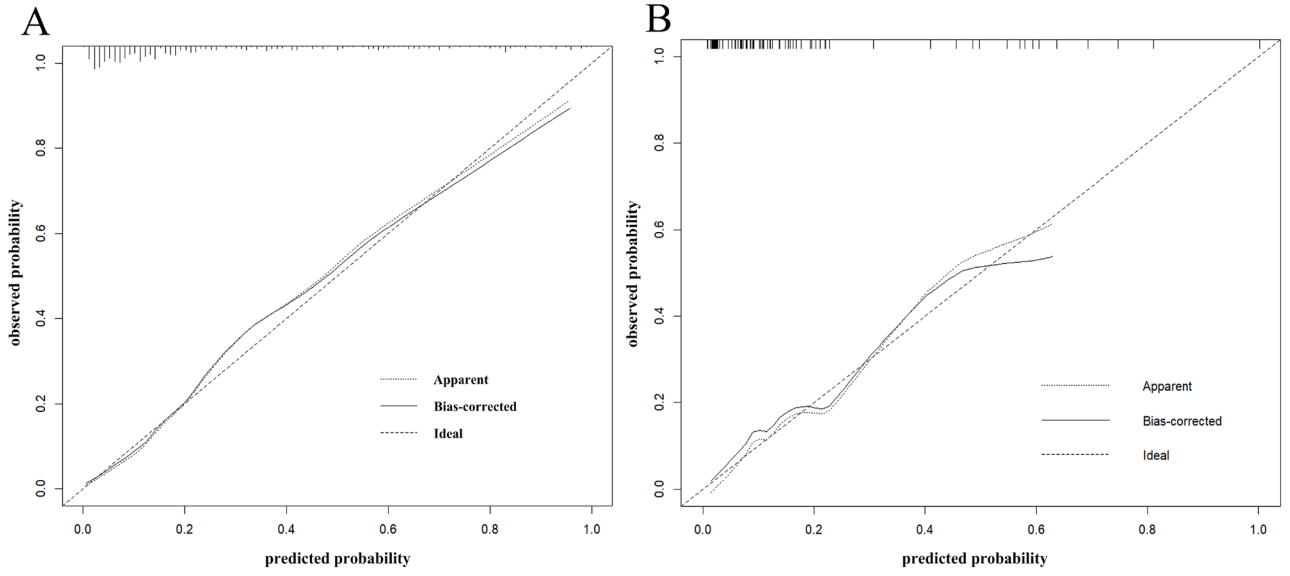


**Fig. 4** Calibration of the nomogram for ASC showed consistency between the nomogram prediction and the actual observation. The calibration curve for the primary cohort (**A**) and the validation cohort (**B**)

**Table 5** Patient demographics and clinical characteristics of the primary cohort and undrained patients

| Patient's Characteristics | | Total<br>*N* = 547 | Primary cohort<br>*N* = 401 | Undrained patients<br>*N* = 146 | *P*-value |
|---|---|---|---|---|---|
| Gender (male) | | 340(62.2%) | 256(63.8%) | 84 (57.5%) | 0.073 |
| Age(year) | | 69(58,79) | 69(59,79) | 66(58,76) | 0.791 |
| Hypertensive | | 256(46.8%) | 179(44.6%) | 77(52.7%) | 0.153 |
| Diabetes | | 90(16.5%) | 68(17%) | 22(15.1%) | 0.651 |
| Heart disease | | 80(14.6%) | 65(16.2%) | 15(10.27%) | 0.066 |
| Respiratory diseases | | 23(42.0%) | 18(4.5%) | 5(3.4%) | 0.515 |
| Nervous System Diseases | | 70(12.8%) | 57(14.2%) | 13(8.9%) | 0.124 |
| Liver dysfunction | | 3(0.5%) | 3(0.7%) | 0(0.0%) | 0.572* |
| Kidney dysfunction | | 16(2.9%) | 13(3.2%) | 3(2.1%) | 0.811† |
| Fatty Liver | | 25(4.6%) | 22(5.5%) | 3(2.1%) | 0.281† |
| Gallbladder Stones | | 446(81.54%) | 326(81.3%) | 120(82.2%) | 0.774 |
| Malignant tumor of the hepatobiliary system | | 24(4.4%) | 14(3.5%) | 10(6.8%) | 0.310† |
| History of gallbladder surgery | | 158(28.9%) | 124(30.9%) | 34(23.3%) | 0.151 |
| History of cholangitis | | 98(17.9%) | 77(19.2%) | 21(14.4%) | 0.098 |
| History of ERCP | | 33(6.0%) | 27(6.7%) | 6(4.1%) | 0.302 |
| History of PTCD | | 5(0.9%) | 4(1.0%) | 1(0.07%) | 0.535* |
| History of PTGD | | 2(0.4%) | 2(0.5%) | 0(0.0%) | 0.689* |
| Temperature (℃) | | 36.9(36.5,38.0) | 36.9(36.6,38.3) | 36.8(36.5,37.8) | 0.051 |
| Concurrent cholecystitis | | 315(57.5%) | 237(59.1%) | 78(53.4%) | 0.089 |
| Concurrent pancreatitis | | 36(6.6%) | 29(7.2%) | 7(4.8%) | 0.442 |
| Disorders of consciousness | | 9(1.6%) | 9(2.2%) | 0(0.0%) | 0.877† |
| Shock | | 16(2.9%) | 15(3.7%) | 1(0.6%) | 0.024* |
| Respiratory insufficiency | | 12(2.2%) | 10(2.5%) | 2(1.4%) | 1.000 |
| Common bile duct diameter (mm) | | 9.81(7.93,11.13) | 10.40(8.55,12.67) | 8.13(5.57,10.08) | < 0.001 |
| AC grade | I | 281(51.4%) | 197(49.1%) [a] | 89(60.9%) [b] | < 0.001 |
| | II | 176(32.1%) | 119(29.7%) [a] | 53(36.3%) [a] | |
| | III | 90(16.5%) | 85(21.2%) [a] | 5(3.4%) [b] | |
| WBC($10^9$/l) | | 9.82(6.32,13.21) | 10.28(6.72,13.94) | 9.11(5.75,12.12) | < 0.001 |
| N% | | 82.61(74.60,89.03) | 83.20(76.10,89.12) | 80.75(73.47,88.21) | 0.057 |
| PLT($10^9$/l) | | 168.31(124.12,211.43) | 165.00(122.00,210.00) | 179.50(143.54,215.36) | 0.458 |
| CRP(mg/l) | | 52.74(24.10,78.67) | 55.10(30.00,81.00) | 35.15 (7.41,66.18) | 0.021 |
| PCT(ng/ml) | | 0.16(0.05,0.61) | 0.26(0.11,0.74) | 0.05(0.01,0.15) | 0.027 |
| TB(umol/l) | | 59.11(31.26,92.14) | 61.70(29.65,100.75) | 49.50(64.35,81.23) | 0.133 |
| DB(umol/l) | | 38.05(14.15,68.61) | 39.90(16.60,71.10) | 33.43(10.41,65.63) | 0.210 |
| TBA(umol/l) | | 77.87(11.45,188.71) | 85.34(14.80,195.50) | 55.16(6.37,167.91) | 0.071 |
| ALT(U/L) | | 145.04(64.92,278.55) | 151.00(69.00,286.00) | 130.78(51.20,244.50) | 0.155 |
| AST(U/L) | | 97.35(44.60,189.74) | 104.00(47.50,209.50) | 73.15(34.47,153.53) | 0.099 |
| GGT(U/L) | | 362.00(172.06,511.14) | 370.00(190.00,521.99) | 321.54(120.15,431.37) | 0.132 |
| ALP(U/L) | | 193.84(124.53,287.93) | 207.00(138.00,311.50) | 134.00(86.31,207.13) | 0.021 |
| ALB(g/l) | | 34.97(31.6,38.3) | 34.5(31.5,37.3) | 36.8(32.7,40.5) | 0.433 |
| Scr(umol/l) | | 70.0(56.80,87.81) | 70.0(57.0,86.0) | 71.45(53.86,92.88) | 0.766 |
| CEA(ng/ml) | | 2.43(1.73,3.88) | 2.71(1.87,3.97) | 2.21(1.55,3.60) | 0.045 |
| CA19-9(U/L) | | 42.53(19.04,153.44) | 43.37(20.83,158.95) | 39.64(17.40,144.18) | 0.531 |
| PT-INR | | 1.08(1.04,1.16) | 1.08(1.05,1.16) | 1.10(1.04,1.16) | 0.774 |
| Deaths during hospitalization | | 8(1.5%) | 7(1.7%) | 1(0.7%) | 0.431† |

* Fisher Precision Inspection

† Calibrated chi-square test

a, a at the 0.05 level, the two columns are not significantly different from each other

a, b at the 0.05 level, the two columns are significantly different from each other

**Table 6** The true positive rate of bile culture

| | | Direct observation | | Total |
|---|---|---|---|---|
| | | Suppurative bile | Non-suppurative bile | |
| Bile culture | positive | 22* | 7 | 29 |
| | negative | 7 | 9 | 16 |
| Total | | 29 | 16 | 45 |

*The true positive rate of bile culture: 75.9%

observation, and bile cultures were not conducted in every case, which led to potential measurement bias. In the primary cohort of this study, bile cultures were performed in only 45 cases, of which 29 cases were positive (22 ASC, 7 ANSC; Table 6). The positivity rate for bile cultures was 64.4%, consistent with findings from other studies [25]. The true positive rate of bile cultures in identifying ASC was 75.9%, indicating that the diagnosis of ASC based on clinicians' direct observation is relatively reliable. In addition, our study only included basic clinical data for analysis, and other factors potentially associated with ASC were perhaps missed, such as ASC-specific imaging findings [6]. Finally, further research is required to examine the association between ASC and the factors incorporated in the predictive model, including concurrent cholecystitis and TBA levels.

## Conclusion

Suppurative bile is a specific indicator for diagnosing moderate-to-severe cholangitis, and plays a vital role in guiding the postoperative grading and treatment of patients with acute cholangitis. However, diagnosing ASC with AC grade II and AC grade III has the risk of missed diagnosis as the sensitivity is only 60.8%. To improve the diagnostic rate of ASC, this study identified concurrent cholecystitis, CRP, PCT, TBA, and preoperative bile duct diameter as independent risk factors for ASC, and a nomogram was developed to help physicians recognize patients with ASC.

#### Abbreviations

| | |
|---|---|
| ASC | Acute Suppurative Cholangitis |
| ANSC | Acute Nonsuppurative Cholangitis |
| TG18 | Tokyo Guidelines 2018 |
| AC | Acute Cholangitis |
| ERCP | Endoscopic Retrograde Cholangiopancreatography |
| PTCD | Percuteneous Transhepatic Cholangio Drainage |
| PTGD | Percutaneous Transhepatic Gallbladder Drainage |
| WBC | White Blood Cell |
| N% | Neutrophil Percentage |
| PLT | Platelet Count |
| CRP | C-Reactive Protein |
| PCT | Procalcitonin |
| TB | Total Bilirubin |
| DB | Direct Bilirubin |
| TBA | Total Bile Acids |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Transferase |
| GGT | Glutamyl Transpeptidase |
| ALP | Alkaline Phosphatase |
| ALB | Serum Albumin |
| Scr | Blood Creatinine |
| CEA | Carcinoembryonic Antigen |
| CA19-9 | Carbohydrate Antigen 19−9 |
| PT-INR | Prothrombin Time-International Normalized Ratio |
| ROC | Receiver Operating Characteristic |
| AUC | The Area Under the Curve |
| CI | Confidence Interval |

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#### Author contributions

YQH and ZJL designed this research. YQH, YZ, and GTL collected and analyzed data. YQH, HW, and ZJL wrote the main manuscript text. YQH, HW, ZJL, PT, and KF revised the manuscript. All authors had full access to the data, contributed to the study, approved the final version for publication, and took responsibility for its accuracy and integrity.

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#### Data availability

No datasets were generated or analysed during the current study.

## Declarations

#### Ethics approval and consent to participate

The study was conducted with adherence to the declaration of Helsinki. The study protocol was approved by the Ethics Committee of Nanjing First Hospital (Ref No.:KY20220805-08). The requirement for written informed patient consent was waived by the Ethics Committee of Nanjing First Hospital due to the retrospective nature of the research.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare no competing interests.

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## Publisher's note