

# Risk Factors for Systemic Inflammatory Response Syndrome After Percutaneous Transhepatic Cholangioscopic Lithotripsy

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**Background:** There is a lack of validated predictive models for the occurrence of systemic inflammatory response syndrome (SIRS) after percutaneous transhepatic cholangioscopic lithotripsy (PTCSL) for the treatment of hepatolithiasis. This is the first study to estimate the incidence of SIRS after PTCSL.

**Methods:** A retrospective analysis of 284 PTCSL sessions for the treatment of hepatolithiasis at our institution between January 2019 and January 2023 was performed. The development of SIRS after PTCSL was the primary study endpoint. Independent risk factors for SIRS after PTCSL were identified using univariate and multivariate logistic regression analyses. A nomogram prediction model was constructed using these independent risk factors, and the predictive value was assessed using receiver operating characteristic (ROC) curves.

**Results:** The incidence of SIRS after PTCSL was 20.77%. According to multivariate analysis, the number of PTCSL sessions (odds ratio [OR]=0.399, 95% confidence interval [CI]=0.202–0.786,  $p=0.008$ ), stone location (OR=2.194, 95% CI=1.107–4.347,  $p=0.024$ ), intraoperative use of norepinephrine (OR=0.301, 95% CI=0.131–0.689,  $p=0.004$ ), intraoperative puncture (OR=3.476, 95% CI=1.749–6.906,  $P<0.001$ ), preoperative gamma-glutamyltransferase (OR=1.002, 95% CI=1.001–1.004,  $p=0.009$ ), and preoperative total lymphocyte count (OR=1.820, 95% CI=1.110–2.985,  $p=0.018$ ) were found to be independent risk factors for the development of SIRS after PTCSL. These six independent risk factors were used to construct a nomogram prediction model, which showed satisfactory accuracy with an area under the ROC curve of 0.776 (95% CI: 0.702–0.850).

**Conclusion:** The number of PTCSL sessions, stone location, intraoperative use of norepinephrine, intraoperative puncture, preoperative gamma-glutamyltransferase, and preoperative total lymphocyte count may predict the occurrence of SIRS after PTCSL. This prediction model may help clinicians identify high-risk patients in advance.

**Keywords:** percutaneous transhepatic cholangioscopic lithotripsy, hepatolithiasis, systemic inflammatory response syndrome, risk factors, nomogram

## Introduction

Hepatolithiasis is a common benign disease of the biliary tract in Southeast Asia.<sup>1,2</sup> It is the leading cause of death from nonneoplastic biliary disease.<sup>1,2</sup> The prolonged presence of stones can lead to biliary sepsis, biliary cirrhosis, and cholangiocarcinoma.<sup>1,2</sup> However, due to the complexity of the anatomy of the bile ducts and the specificity of the location of these stones, there is a high rate of stone retention and recurrence after hepatectomy.<sup>3–5</sup> It has been reported that 10–15% of cases of hepatolithiasis cannot be completely resolved by surgery.<sup>6,7</sup> If a patient has a recurrence of a stone and is in need of further surgery, the procedure is difficult, risky and has a long recovery time.<sup>8</sup> Therefore, a safe and reproducible minimally invasive surgical procedure to is needed to overcome the shortcomings of traditional surgeries.

Percutaneous transhepatic cholangioscopic lithotripsy (PTCSL) is derived from percutaneous nephrolithiasis.<sup>9–11</sup> PTCSL has gradually become one of the most important tools used to treat hepatolithiasis. PTCSL is a less invasive treatment than traditional surgery and can preserve more liver parenchyma to maintain liver function. It is particularly suitable for patients who have a history of biliary surgery or scattered stones and who cannot tolerate traditional surgery.<sup>12</sup>

Despite adequate preoperative preparation, PTCSL, as an invasive technique, is inevitably associated with surgical risks and complications. Although PTCSL has a low rate of postoperative complications, infection-related complications such as fever, systemic inflammatory response syndrome (SIRS), and sepsis may still occur postoperatively.<sup>13–15</sup> Intraoperative PTCSL may damage bile duct cells. As a consequence, large numbers of bacteria and endotoxins are released into the blood circulation. Biliary hypertension caused by prolonged biliary flushing can increase the absorption of pathogens with the perfusate and cause an inflammatory response or even sepsis in severe cases.<sup>16,17</sup> This can affect patient prognosis. SIRS is a step in the sepsis cascade, and studies have shown that SIRS is strongly associated with poor prognosis.<sup>18</sup> Thus it is important to assess the risk factors associated with the occurrence of SIRS after PTCSL.

However, there is a paucity of clinical studies on this topic. This study is the first analysis of the factors that influence the occurrence of SIRS after PTCSL. A nomogram prediction model was developed to predict the risk of SIRS after PTCSL.

## Materials and Methods

### Study Subjects

In this retrospective study, the clinical data of 284 PTCSL sessions were collected at the Second Affiliated Hospital of Chongqing Medical University from January 2019 to January 2023. All patients provided written informed consent. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University (No. 2018–207).

The inclusion criteria were as follows: (a) confirmed diagnosis of hepatolithiasis with or without choledocholithiasis based on imaging; (b) primary stones or recurrent stones after traditional open surgery; (c) non-acute septic biliary infection or cholangitis with symptomatic improvement after treatment; and (d) Child-Pugh grade A or B.

The exclusion criteria were as follows: (a) had a combined malignant tumour; (b) had a serious bleeding tendency or coagulation dysfunction; (c) had combined postoperative pneumonia, hypovolaemia, or uncontrolled pain; (d) had a preoperative combination of liver abscess, infection in other parts of the body, or immune system disease; and (e) had Child-Pugh grade C.

### Observation Indicators

The following baseline information was collected: age, gender, body mass index (BMI), hypertension, diabetes, cirrhosis, preoperative history of acute cholangitis, the number of PTCSL sessions, type of previous surgery, type of hepatolithiasis, and stone location. The preoperative laboratory indicators were as follows: albumin, globulin, alanine transferase, aspartate transferase, alkaline phosphatase, gamma-glutamyl transferase (GGT), total bilirubin, direct bilirubin, indirect bilirubin, total bile acids, prealbumin, haemoglobin, leukocytes, neutrophil percentage, neutrophil count, total lymphocyte count (TLC), and platelets. The NLR, PLR, SII, and PNI were calculated from preoperative peripheral blood samples. The intraoperative indicators were as follows: the number of puncture channels, puncture method (ultrasound or X-ray), perfusion volume, operative time, intraoperative bleeding, American Society of Anaesthesiologists (ASA) score, intraoperative use of norepinephrine solution, intraoperative puncture, and postoperative stone residue.

### Standard Definition

The diagnostic criteria for SIRS are as follows: SIRS can be diagnosed if two or more of the following indicators are met: (a) shortness of breath, respiratory rate >20 breaths/min, or PaCO<sub>2</sub><32 mmHg; (b) temperature >38 °C or <36 °C; (c) heart rate >90 /min; and (d) leukocyte count >12×10<sup>9</sup>/L or <4×10<sup>9</sup>/L or immature granulocytes >10%.

## Surgical Techniques

Preoperatively, patients with acute cholangitis require antibiotic therapy. In the absence of bile culture results,  $\beta$ -lactam antibiotics were used; in the presence of positive bile culture results, appropriate antibiotics based on susceptibility testing were used until the patient's infection symptoms had recovered. A single dose of the same antibiotic was given 30 minutes before surgery. A single dose of  $\beta$ -lactam antibiotic prophylaxis 30 minutes before surgery was given to patients without preoperative acute cholangitis. Intraoperative biliary irrigation was performed with a saline solution in 3-litre bags connected to a choledochoscope by an infusion set suspended at a height of 2.0 m, with the irrigation speed set to the maximum. After induction of general anaesthesia, the surgical procedure followed the standardised PTCSL protocol: for patients treated with one-step PTCSL, the stone location was clarified based on preoperative imaging, and the puncture pathway was planned.<sup>19</sup> The target bile duct was punctured with a coarse 18G needle (9,013,606, Zhengzhou Dior Medical Technology Company, China) under ultrasound guidance (DC-7T, Shenzhen Mindray Bio-Medical Electronics Company, China). Then the sinusoid was dilated from 8-Fr to 18-Fr by a fascial tearing device (9,013,606, Zhengzhou Dior Medical Technology Company, China) after placement of a guide wire (10S13508, Hunan Epte Medical Equipment Company, China). Finally, a 16-Fr or 18-Fr protective sheath (G06444, Cook Medical Holdings LLC, America) was placed into the intrahepatic bile ducts to create a channel. A combination of a rigid choledochoscope (8968.405, Richard Wolf Company, Germany) and an electronic choledochoscope (EyeMax CDS11001, Nanjing Micro-Tech Company, China) was used to search for intrahepatic bile duct stones. For stones smaller than the diameter of the sheath, a basket (VDK-BAS-18-70-15-N4-D, Jiangsu Vedkang Medical Technology Company, China) was used to remove the stones. For larger stones, holmium laser lithotripsy (DHL-1-D, Wuxi Dahua Laser Device Company, China) was used to remove the stones. Postoperative support drains (9,013,606, Zhengzhou Dior Medical Technology Company, China) were removed at regular intervals. Patients treated with two-step PTCSL underwent puncture and drainage of the target bile ducts under ultrasound or X-ray guidance before surgery. Approximately two weeks after the puncture, the procedure was performed in the same way as the one-step procedure. All surgical treatments and postoperative care were performed under the guidance of the same surgeon Yao Cheng, who has over 10 years of experience performing surgery, to ensure the quality and safety of the procedures.

## Statistical Analysis

The obtained data were analysed using SPSS 26.0 statistical software. Continuous variables with a normal distribution are described by the mean  $\pm$  standard deviation (SD); nonnormally distributed continuous variables are described by the median (interquartile range); and categorical variables are described by the frequency (percentage). The chi-square test was used to compare categorical variables. Student's *t*-test was used to compare continuous variables with a normal distribution between the two groups. The Mann–Whitney *U*-test was used for nonnormally distributed variables. Those with significance in the univariate logistic analyses were analysed by multivariate logistic stepwise regression using the Forward: LR method. R software was used to construct a nomogram for predicting the occurrence of SIRS after PTCSL. Receiver operating characteristic (ROC) curves were plotted to calculate the area under the curve (AUC) to evaluate the predictive ability of the model. Additionally, calibration and decision curves were plotted for assessment of the model discrimination, calibration, and net clinical benefit of the model.  $P < 0.05$  was regarded as statistically significant.

## Results

A total of 284 PTCSL sessions were included in this study, and the incidence of SIRS after PTCSL was 20.77%. Treatment with  $\beta$ -lactam antibiotics is usually needed for approximately one week in patients who develop postoperative SIRS, and these patients usually have recovery of their infectious marker levels and clinical symptoms. There were no patients who experienced adverse outcomes such as MODS, biliary sepsis, or death.

The number of PTCSL sessions, stone location, hypertension, operation time, perfusion volume, intraoperative use of norepinephrine solution, intraoperative puncture, preoperative GGT, preoperative total bile acid, preoperative platelets, and preoperative PNI were significantly different between the two groups ( $p < 0.05$ ). There was no significant difference ( $p > 0.05$ ) in the other clinical indices between the two groups (Table 1).

**Table I** Procedure Characteristics of Percutaneous Transhepatic Cholangioscopic Lithotripsy (PTCSL)

		All (n=284)	Without SIRS (n=225)	With SIRS (n=59)	P-value
Age <sup>†</sup> , Years		54 (47–62)	54 (47–63)	53 (45–61)	0.261
Genders, N (%)	Male	106 (37.32%)	81 (28.52%)	25 (8.8%)	0.368
	Female	178 (62.68%)	144 (50.7%)	34 (11.97%)	
BMI <sup>†</sup>		20.96 (19.03–22.89)	21.09 (19.05–22.89)	20.81 (18.73–23.03)	0.341
Hypertension, N (%)	No	265 (93.31%)	214 (75.35%)	51 (17.96%)	0.018
	Yes	19 (6.69%)	11 (3.87%)	8 (2.82%)	
Diabetes, N (%)	No	269 (94.72%)	213 (75%)	56 (19.72%)	0.939
	Yes	15 (5.28%)	12 (4.23%)	3 (1.06%)	
Cirrhosis, N (%)	No	215 (75.7%)	168 (59.15%)	47 (16.55%)	0.426
	Yes	69 (24.3%)	57 (20.07%)	12 (4.23%)	
Type of previous surgery, N (%)	No	64 (22.54%)	50 (17.61%)	14 (4.93%)	0.649
	Biliary-enteric anastomosis	54 (19.01%)	43 (15.14%)	11 (3.87%)	
	Hepatectomy	60 (21.13%)	44 (15.49%)	16 (5.63%)	
	Choledocholithotomy	53 (18.66%)	43 (15.14%)	10 (3.52%)	
	Biliary-enteric anastomosis +Hepatectomy	53 (18.66%)	45 (15.85%)	8 (2.82%)	
Type of hepatolithiasis, N (%)	Primary stones	64 (22.54%)	50 (17.61%)	14 (4.93%)	0.805
	Recurrent stones	220 (77.46%)	175 (61.62%)	45 (15.85%)	
Number of PTCSL sessions, N (%)	First	129 (45.42%)	90 (31.69%)	39 (13.73%)	<0.001
	Non-first	155 (54.58%)	135 (47.54%)	20 (7.04%)	
Stone location, N (%)	Non-bilateral bile duct	128 (45.07%)	111 (39.08%)	17 (5.99%)	0.005
	Bilateral bile ducts	156 (54.93%)	114 (40.14%)	42 (14.79%)	
Puncture method, N (%)	B-ultrasound	268 (94.37%)	212 (74.65%)	56 (19.72%)	0.837
	DSA	16 (5.63%)	13 (4.58%)	3 (1.06%)	
Postoperative stone retention, N (%)	No	133 (46.83%)	109 (38.38%)	24 (8.45%)	0.287
	Yes	151 (53.17%)	116 (40.85%)	35 (12.32%)	
Number of operating channels, N (%)	1	107 (37.68%)	87 (30.63%)	20 (7.04%)	0.602
	2	154 (54.23%)	118 (41.55%)	36 (12.68%)	
	3	22 (7.75%)	19 (6.69%)	3 (1.06%)	
	4	1 (0.35%)	1 (0.35%)	0 (0%)	
Operating time <sup>†</sup> , Minute		139.5 (90.5–185)	130 (90–185)	155 (135–185)	0.005
Intraoperative bleeding <sup>†</sup> , Milliliter		20 (20–50)	20 (20–50)	30 (20–50)	0.202
ASA class, N (%)	1	1 (0.35%)	0 (0%)	1 (0.35%)	0.084
	2	206 (72.54%)	167 (58.8%)	39 (13.73%)	
	3	77 (27.11%)	58 (20.42%)	19 (6.69%)	
Perfusion volume <sup>†</sup> , Litre		15 (9–18)	12 (9–18)	15 (12–18)	0.002
Intraoperative use of norepinephrine solution, N (%)	No	203 (71.48%)	154 (54.23%)	47 (17.25%)	0.027
	Yes	81 (28.52%)	71 (25.00%)	10 (3.52%)	
Intraoperative puncture, N (%)	No	207 (72.89%)	178 (62.68%)	29 (10.21%)	<0.001
	Yes	77 (27.11%)	47 (16.55%)	30 (10.56%)	
Preoperative acute cholangitis, N (%)	No	235 (82.75%)	186 (65.49%)	49 (17.25%)	0.945
	Yes	49 (17.25%)	39 (13.73%)	10 (3.52%)	
Albumin <sup>†</sup> , (g/L)		38.6 (35.8–41.8)	38.6 (35.7–41.8)	38.6 (36.2–41.8)	0.650
Globulin, Mean ± SD, (g/L)		30.73±6.03	30.74±6.15	30.68±5.58	0.949
Alanine transferase <sup>†</sup> , (U/L)		48 (28–78.75)	48 (28–79)	46 (19–74)	0.574
Aspartate transferase <sup>†</sup> , (U/L)		44 (27–68)	44 (27–66)	42 (28–78)	0.829
Alkaline phosphatase <sup>†</sup> , (U/L)		190 (127.5–302.75)	185 (125–287.5)	226 (134–379)	0.062
GGT <sup>†</sup> , (U/L)		205 (123.5–329.5)	195 (119–307.5)	248 (149–526)	0.016
Total bilirubin <sup>†</sup> , (μmol/L)		15.15 (10.3–25.075)	15.4 (10.35–25.4)	14.8 (9.7–22.3)	0.468
Direct bilirubin <sup>†</sup> , (μmol/L)		8.55 (5.325–16.075)	8.6 (5.4–17.15)	8.2 (4.9–14.1)	0.461
Indirect bilirubin <sup>†</sup> , (μmol/L)		5.8 (3.8–8.275)	5.9 (3.8–8.35)	5.4 (4.1–8.2)	0.852
Total bile acids <sup>†</sup> , (μmol/L)		5.2 (2.6–11.8)	5.1 (2.4–10.2)	7.3 (4.1–15.6)	0.010
Prealbumin, Mean ± SD, (mg/L)		164.89±56.52	167.07±57.42	156.59±52.59	0.206

(Continued)

**Table 1** (Continued).

	All (n=284)	Without SIRS (n=225)	With SIRS (n=59)	P-value
Haemoglobin, Mean ± SD, (g/L)	115.87±18.23	115.21±18.43	118.36±17.37	0.239
Leucocyte <sup>†</sup> , (×10 <sup>9</sup> /L)	5.3 (4.23–6.5375)	5.2 (4.205–6.45)	5.68 (4.53–7.18)	0.130
Percentage of neutrophils <sup>†</sup> ,%	63 (55.9–70.925)	63.2 (55.45–71.25)	62.4 (56.8–67.1)	0.761
Neutrophil count <sup>†</sup> , (×10 <sup>9</sup> /L)	3.23 (2.5125–4.32)	3.17 (2.5–4.255)	3.29 (2.82–5.02)	0.141
Total lymphocyte count <sup>†</sup> , (×10 <sup>9</sup> /L)	1.32 (0.9525–1.71)	1.3 (0.94–1.655)	1.42 (1.02–1.92)	0.093
Platelets <sup>†</sup> , (×10 <sup>9</sup> /L)	173 (127–225.75)	169 (126.5–215.5)	194 (133–279)	0.044
NLR <sup>†</sup>	2.46 (1.73–3.565)	2.46 (1.705–3.71)	2.43 (1.8–2.91)	0.791
PLR <sup>†</sup>	133.145 (102.21–171.8125)	132.65 (104–169.23)	133.64 (95.4–181.31)	0.672
SII <sup>†</sup>	429.765 (276.795–665.7625)	416.22 (275.215–656.355)	475.96 (304.40–738.32)	0.314
PNI <sup>†</sup>	45.625 (41.5625–49.675)	45.45 (41.575–49.05)	47.35 (41.35–51.55)	0.042

**Notes:** <sup>†</sup>Data are medians, and data in parentheses are interquartile ranges.

**Abbreviations:** PTCSL, percutaneous transhepatic cholangioscopic lithotripsy; SIRS, systemic inflammatory response syndrome; SD, standard deviation; BMI, body mass index; ASA, American Society of Anaesthesiologists score; GGT, gamma-glutamyl transferase; NLR, neutrophil-to-lymphocyte count ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune inflammation index; PNI, prognostic nutritional index.

After univariate logistic analysis, the results showed the following: number of PTCSL sessions (odds ratio [OR]=0.342, 95% confidence interval [CI]=0.187–0.624,  $p<0.001$ ), stone location (OR=2.406, 95% CI=1.293–4.477,  $p=0.006$ ), hypertension (OR=3.052, 95% CI=1.168–7.975,  $p=0.023$ ), operation time (OR=1.006, 95% CI=1.001–1.010,  $p=0.010$ ), perfusion volume (OR=1.067, 95% CI=1.021–1.116,  $p=0.004$ ), intraoperative use of norepinephrine solution (OR=0.443, 95% CI=0.212–0.924,  $p=0.030$ ), intraoperative puncture (OR=3.918, 95% CI=2.143–7.161,  $p<0.001$ ), preoperative alkaline phosphatase (OR=1.002, 95% CI=1.001–1.004,  $p=0.003$ ), preoperative GGT (OR=1.002, 95% CI=1.001–1.004,  $p<0.001$ ), preoperative leucocyte (OR=1.122, 95% CI=1.012–1.244,  $p=0.029$ ), preoperative total lymphocyte count (OR=1.840, 95% CI=1.198–2.826,  $p=0.005$ ), preoperative platelet count (OR=1.004, 95% CI=1.001–1.007,  $p=0.007$ ), and preoperative PNI (OR=1.049, 95% CI=1.004–1.096,  $p=0.033$ ) were the potential risk factors for the development of post-operative SIRS after PTCSL ( $P < 0.05$ ) (Table 2). The results of the multivariate logistic stepwise regression analysis revealed that the number of

**Table 2** Univariate and Multivariate Logistic Regression Analyses for Predictors of SIRS After PTCSL

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Age	0.985	0.960–1.010	0.244			
Genders	0.765	0.427–1.371	0.368			
BMI	0.966	0.871–1.072	0.518			
Hypertension	3.052	1.168–7.975	0.023			
Diabetes	0.951	0.259–3.485	0.939			
Cirrhosis	0.753	0.373–1.518	0.427			
Type of previous surgery	0.916	0.748–1.122	0.398			
Type of hepatolithiasis	0.918	0.467–1.808	0.805			
Number of PTCSL sessions	0.342	0.187–0.624	<0.001	0.399	0.202–0.786	0.008
Stone location	2.406	1.293–4.477	0.006	2.194	1.107–4.347	0.024
Puncture method	0.874	0.241–3.172	0.837			
Postoperative stone retention	1.37	0.766–2.451	0.288			
Number of operating channels	1.014	0.638–1.610	0.954			
Operating time	1.006	1.001–1.010	0.01			
Intraoperative bleeding	1.002	0.994–1.011	0.598			
ASA	1.255	0.675–2.335	0.473			
Perfusion volume	1.067	1.021–1.116	0.004			
Intraoperative use of norepinephrine solution	0.443	0.212–0.924	0.03	0.301	0.131–0.689	0.004

(Continued)

Table 2 (Continued).

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Intraoperative puncture	3.918	2.143–7.161	<0.001	3.476	1.749–6.906	<0.001
Preoperative acute cholangitis	0.973	0.454–2.087	0.945			
Albumin	1.017	0.963–1.075	0.539			
Globulin	0.998	0.952–1.047	0.949			
Alanine transferase	1.001	0.997–1.006	0.533			
Aspartate transferase	1.004	0.996–1.011	0.368			
Alkaline phosphatase	1.002	1.001–1.004	0.003			
GGT	1.002	1.001–1.004	<0.001	1.002	1.001–1.004	0.009
Total bilirubin	1.004	0.995–1.013	0.379			
Direct bilirubin	1.004	0.994–1.015	0.404			
Indirect bilirubin	1.019	0.959–1.083	0.542			
Total bile acids	1.012	0.999–1.025	0.063			
Prealbumin	0.997	0.992–1.002	0.206			
Haemoglobin	1.01	0.994–1.026	0.239			
Leucocyte	1.122	1.012–1.244	0.029			
Percentage of neutrophils	0.994	0.967–1.021	0.644			
Neutrophil count	1.086	0.955–1.235	0.209			
Total lymphocyte count	1.84	1.198–2.826	0.005	1.82	1.110–2.985	0.018
Platelets	1.004	1.001–1.007	0.007			
NLR	0.937	0.830–1.058	0.291			
PLR	1	0.995–1.004	0.892			
SII	1	1.000–1.001	0.747			
PNI	1.049	1.004–1.096	0.033			

**Abbreviations:** PTCSL, percutaneous transhepatic cholangioscopic lithotripsy; SIRS, systemic inflammatory response syndrome; BMI, body mass index; ASA, American Society of Anaesthesiologists; GGT, gamma-glutamyl transferase; NLR, neutrophil to lymphocyte count ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune inflammation index; PNI, prognostic nutritional index; CI, confidence interval; OR, odds ratio.

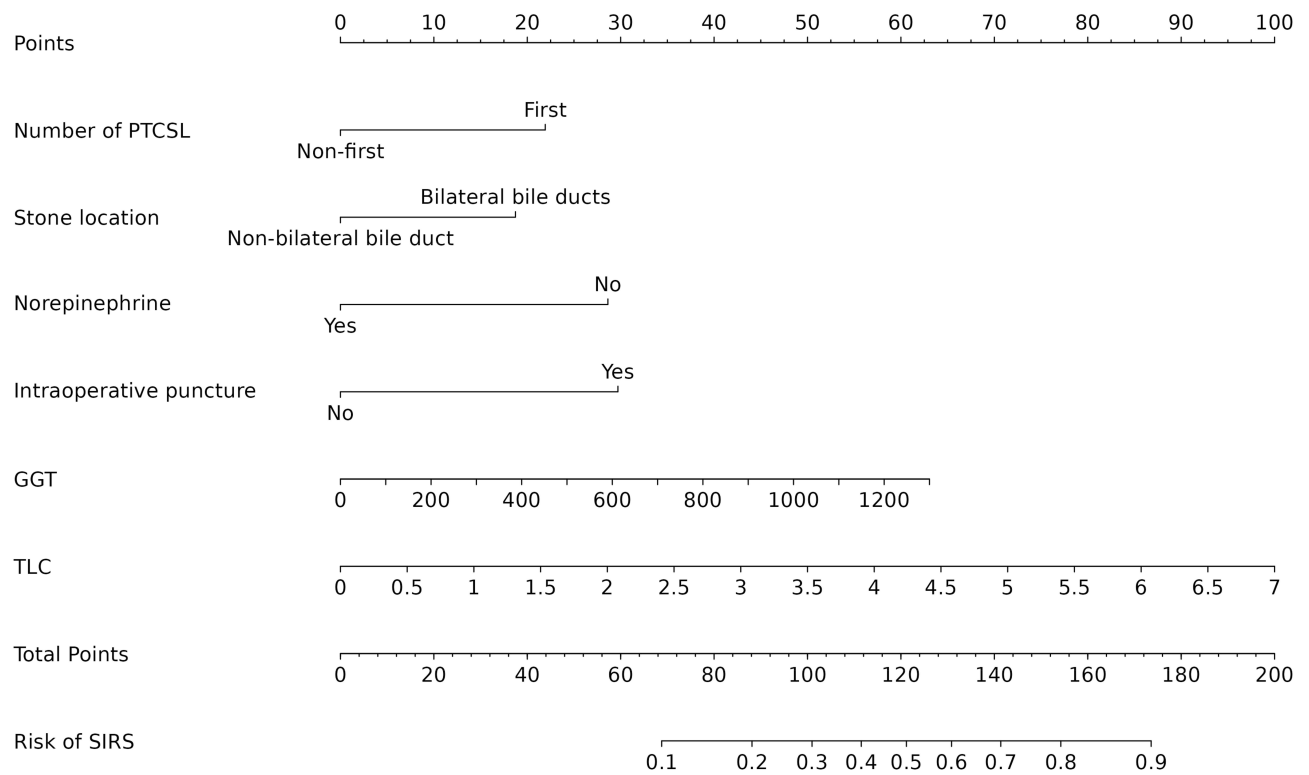
PTCSL sessions (OR=0.399, 95% CI=0.202–0.786,  $p=0.008$ ), stone location (OR=2.194, 95% CI=1.107–4.347,  $p=0.024$ ), intraoperative use of norepinephrine (OR=0.301, 95% CI=0.131–0.689,  $p=0.004$ ), intraoperative puncture (OR=3.476, 95% CI=1.749–6.906,  $p<0.001$ ), preoperative gamma-glutamyl transferase (OR=1.002, 95% CI=1.001–1.004,  $p=0.009$ ), and preoperative total lymphocyte count (OR=1.820, 95% CI=1.110–2.985,  $p=0.018$ ) were the independent risk factors for the occurrence of SIRS postoperatively (Table 2).

The nomogram prediction model was constructed from the results of the multivariate logistic stepwise regression (Figure 1). The area under the ROC curve of the model was 0.776 (95% CI: 0.702–0.850) (Figure 2). The bootstrap method was used for the internal validation of the dataset and for the construction of calibration curves. The calibration curves showed that the actual predicted probability curves fit well with the ideal predicted probability curves (Figure 3). This indicates that the model has good accuracy and consistency. The decision curve showed that if the threshold probability was 0.1–0.8, the net benefit of the model was greater than that of either the intervention scenario for all patients or the no-intervention scenario (Figure 4). The clinical impact curve showed a narrowing of the gap when the risk threshold was 0.4, which is a good fit (Figure 5).

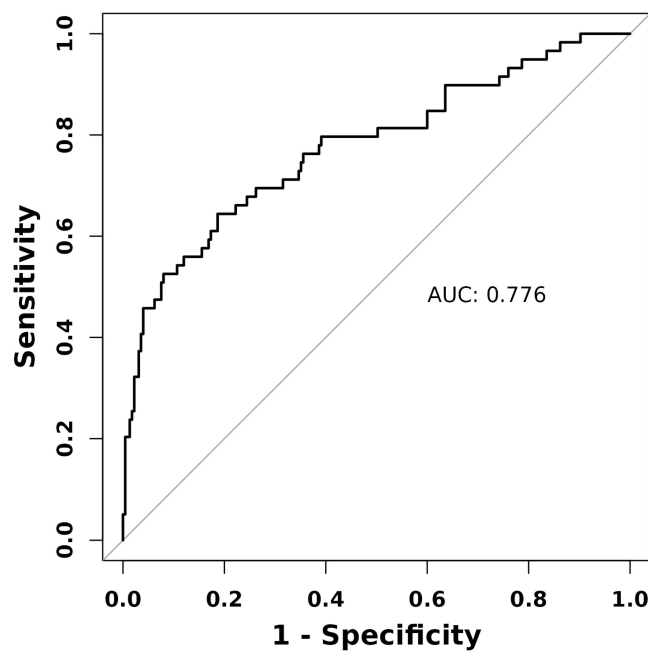
## Discussion

PTCSL has the same research value as percutaneous nephrolithotripsy (PCNL). However, there are no reports in the literature on the occurrence of SIRS after PTCSL up to now. Thus, this study is the first to investigate the occurrence of SIRS after PTCSL.

Hwang and Robert B used percutaneous nephrolithotomy successively to treat hepatolithiasis, their technique was based on the technique of PCNL, and the traditional technique of percutaneous hepatic cholangioscopy was continuously improved by Yanmin Liu et al<sup>9,10,20,21</sup> PTCSL gradually became mature. PTCSL and PCNL therefore have many



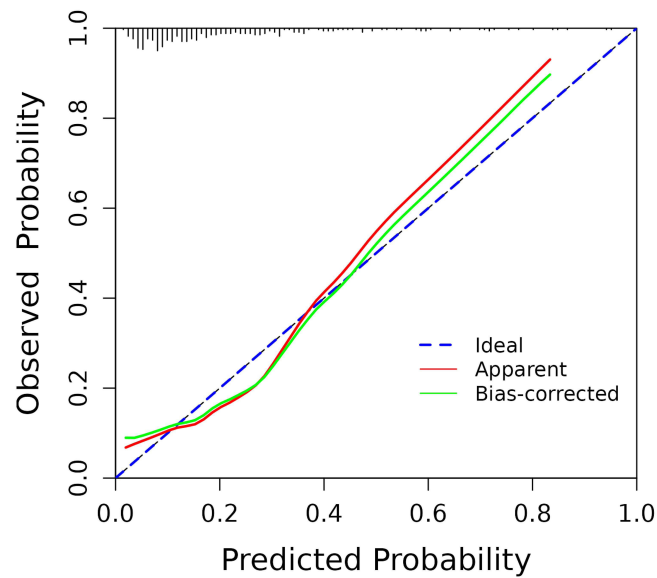
**Figure 1** A nomogram for predicting the incidence of SIRS after PTCSL.



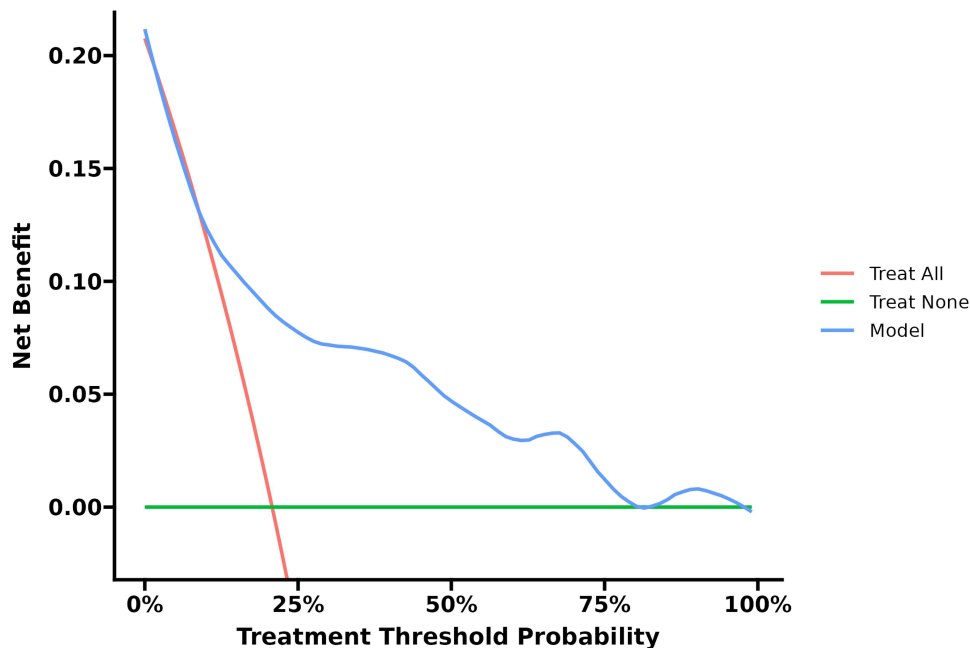
**Figure 2** ROC curves for predicting SIRS after PTCSL.

similarities in operation. PTCSL is an invasive procedure that requires the creation of a skin-to-intrahepatic bile duct channel rather than a natural channel. It is not possible to avoid the risks and complications of surgery. The complications of PTCSL are similar to those of PCNL because when the pressure in the bile duct exceeds 30 mmH<sub>2</sub>O during lithotripsy,





**Figure 3** Calibration curve for the prediction of SIRS after PTCSL by using the nomogram.



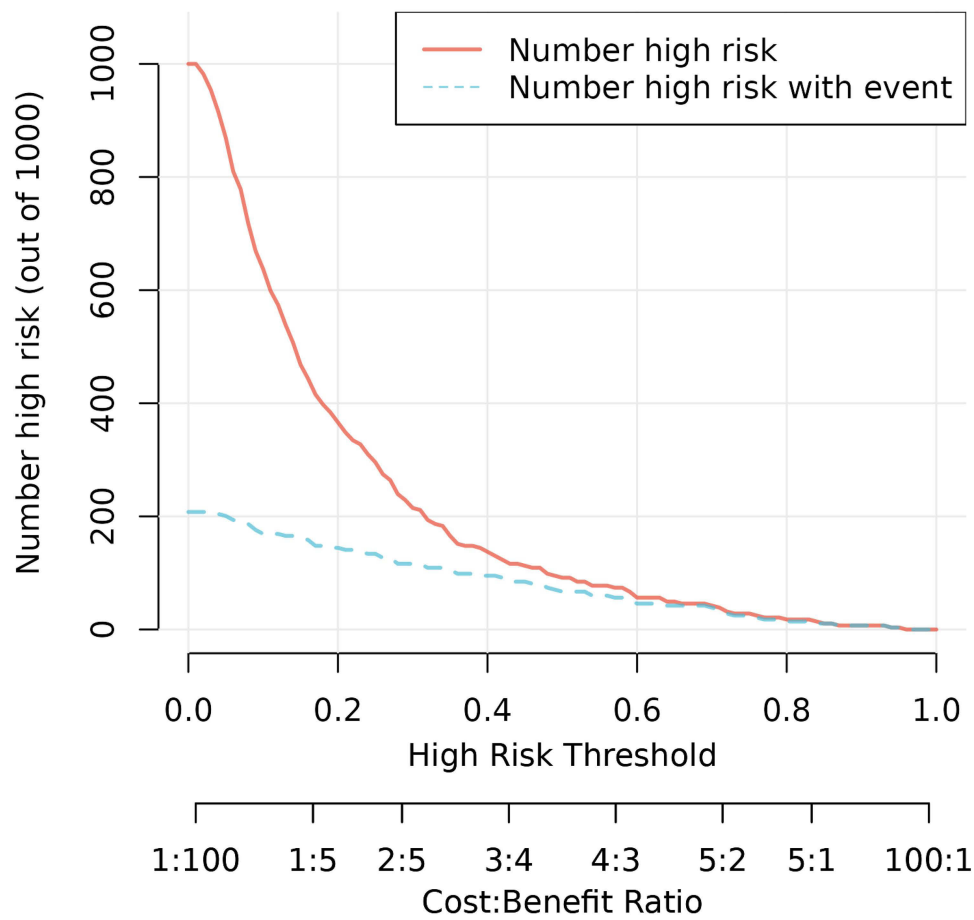
**Figure 4** Prediction of the DCA curve of SIRS after PTCSL by using the nomogram.

the venous sinuses in the bile duct wall are opened and a variety of bacteria and endotoxins inevitably enter the bloodstream with the irrigation fluid.<sup>16</sup>

SIRS is an uncontrolled inflammatory response of the body to a variety of cytokines and inflammatory mediators.<sup>22</sup> Numerous studies have shown that the incidence of SIRS after PCNL is 22.1%-43.0%.<sup>23-25</sup> In our study, the incidence of SIRS after PTCSL was 20.77%. This may be due to intraoperative injury to the peribiliary vessels during puncture or sinusoidal dilatation and to the lining of the bile ducts during lithotripsy. This may result in the release of inflammatory factors into the circulation through the bile ducts, leading to the development of SIRS.

Multivariate logistic stepwise regression analysis revealed that the number of PTCSL sessions, stone location, intraoperative use of norepinephrine solution, intraoperative puncture, preoperative GGT, and preoperative TLC were





**Figure 5** Prediction of the clinical impact curve of SIRS after PTCSL by using the nomogram.

independent risk factors for the development of SIRS after PTCSL. PTCSL is a percutaneous transhepatic puncture of the hepatic bile duct to create a corresponding sinusoidal channel and then, after gradual dilatation of the sinusoidal channel, a sheath is placed through which choledochoscopy can be repeated to remove stones with reproducibility. A PTC tube may be left in place until the patient's condition stabilises, and then a PTCSL may be used to remove the stones again in some patients who are unable to have the stones removed with one surgery due to complicated stone distribution, intraoperative biliary bleeding, or poor general condition and who cannot tolerate prolonged surgery. Most of the patients in our study did not receive PTCSL for the first time. In our study, the incidence of postoperative SIRS was greater in patients treated for the first time with PTCSL. This may be because the prolonged presence of biliary stones in these patients has the potential to cause occult biliary infections or even preexisting bacterial colonisation of the biliary tract, which increases the chances of bacterial entry into the bloodstream during sinus dilatation and biliary flushing. In patients undergoing PTCSL for the first time, intraoperative gradual dilatation of the sinus tract destroys the surrounding granulation tissue, and excessive traction on the sinus tract wall when the choledochoscope enters the angulated bile ducts during lithotripsy tends to cause sinus tract laceration. Patients who undergo another PTCSL usually require time between surgeries, during which time the surrounding fibrous tissue proliferates and wraps around the sinus to make the sinus tract firmer and the procedure more tolerable for the patient. In addition, the removal of stones during the previous operation relieved the partial obstruction of the biliary tract, and the use of an indwelling drain to drain the bile effectively controlled the biliary tract infection, thus reducing the risk of postoperative SIRS. Hepatolithiasis usually occurs in the left or right posterior lobe of the liver and is often associated with choledocholithiasis. Patients with bilateral bile duct stones are more prone to cryptogenic biliary tract infection because of the large stone burden, which is usually associated with narrowing or dilatation of the intrahepatic bile ducts. According to the results of multifactorial

analyses, the location of the stones influences the safety of the procedure. Patients with widely distributed stones have a severe biliary inflammatory response and poor-quality intrahepatic bile ducts, which undoubtedly increases the risk of intraoperative injury and postoperative infection. Second, widely distributed stones are more difficult and time-consuming to remove, and most of these patients need to be treated with holmium laser lithotripsy, in which pathogens and endotoxins on the surface of the stone are released into the irrigation fluid after the stone is broken up and these pathogens and endotoxins are then absorbed into the bloodstream. Therefore, for hepatolithiasis, we should pay attention to the location of the stone before surgery and consider the location of the stone along with the findings on imaging to develop an optimal surgical program and minimise intraoperative damage to the bile ducts during the procedure.<sup>26</sup> The results of this study showed that intraoperative use of a norepinephrine solution may act as a protective factor and reduce the incidence of postoperative SIRS. The reason may be that during lithotripsy, a small amount of biliary exudate or diffuse mucosal bleeding occurs due to biliary inflammation or stone friction, and the norepinephrine solution acts uniformly on the intrahepatic bile ducts, causing constriction of the blood vessels to reduce the absorption of harmful substances. In clinical work, some patients with two-step PTCSL had to be repunctured because the biliary drainage tube had fallen out, which was not addressed in time, and the original sinus tract could not be found. In our study, when intraoperative puncture was performed at the same time as stone extraction, puncture damage to tissues and blood vessels resulted in an increased risk of infection. Therefore, in patients who cannot tolerate surgery, the first step is to try to drain the bile by puncture, reduce the pressure on the bile duct and control the inflammation of the bile duct with antibiotics, and then, once the condition has stabilised, to try lithotripsy as a second step. We found that the occurrence of SIRS after PTCSL may be influenced by both preoperative GGT and preoperative TLC. GGT is widely distributed in the biliary system, is mostly excreted through the bile ducts, and is an important serum marker for the assessment of biliary obstruction. In our study, patients with higher preoperative GGT levels had a greater risk of postoperative SIRS after PTCSL, which may be related to prolonged preoperative biliary obstruction and poor bacterial growth in the bile. Animal studies have shown that the GGT concentration can predict the occurrence of SIRS-related death.<sup>27</sup> Lymphocytes play an important role in the regulation of the immune response and are involved in the pathophysiological processes of inflammation.<sup>28</sup> This finding implies that the lymphocyte count has great potential for predicting postoperative SIRS. Multifactorial analysis revealed that preoperative TLC served as an independent risk factor, suggesting that lymphocytes may play an important role in the development of postoperative SIRS. Therefore, preoperative GGT and TLC can be used as important reference indicators for the clinical prediction of postoperative SIRS. Patients with hepatolithiasis often experience impaired bile drainage due to stone obstruction, frequently leading to latent biliary infections and cholangitis. Effective biliary drainage and antibiotic therapy are paramount in managing hepatolithiasis complicated by cholangitis.<sup>29</sup> In cases where preoperative leucocyte levels indicate a high likelihood of infection, extended preoperative antibiotic therapy becomes essential to mitigate the infection and ameliorate patient symptoms, thereby ensuring surgical safety. However, it's crucial to emphasize that while antibiotics play a pivotal role in infection control, they are not a substitute for surgical intervention aimed at alleviating biliary obstruction. For patients who exhibit inadequate response to initial antibiotic therapy, prompt surgical intervention should be considered once the patient's systemic condition permits, with the objective of relieving biliary pressure.<sup>29,30</sup> PTCSL present a dual advantage by facilitating both stone removal to alleviate obstruction and bile drainage through the establishment of a sinusoidal passage.

Based on the results of the above studies, a nomogram prediction model with good predictive efficacy was constructed. We believe that the utilization of this prediction model enables the early identification of high-risk patients during the preoperative phase, thereby enhancing future clinical decision-making support.

The recent Sepsis-3 Task Force recommended the use of the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score and the quick SOFA (qSOFA) score to screen patients at high risk of developing septic shock.<sup>31,32</sup> However, we deliberately used the concept of SIRS because SOFA scoring is too cumbersome, qSOFA lacks the necessary sensitivity, and sepsis is uncommon in the postoperative period.<sup>33,34</sup> The SIRS criteria are still widely used in clinical practice because they are easy to measure, reproducible and sensitive compared to the first two scores.<sup>35,36</sup> We used the SIRS criteria to identify patients at risk of developing sepsis. SIRS can be associated with noninfectious causes and is not specific for infection; therefore, we excluded other potential causes of fever and tachycardia that would have occurred postoperatively.

This study has several limitations. First, surgical time and perfusion volume were statistically significant only in the univariate analyses and were not independent prognostic factors. This may be because the time from the establishment of the puncture or sinus dilation to the end of the procedure could not be accurately recorded from the chart review. The specific perfusion volume could not be recorded at the time of data collection and could only be assessed by the number of 3-litre saline bags used intraoperatively. Second, we were unable to directly evaluate the intrabiliary pressure. Third, we did not include certain specific inflammatory markers, such as C-reactive protein or procalcitonin, in the study due to incomplete data. Finally, based on this study, we believe that these indicators can predict the occurrence of postoperative SIRS after PTCSL, but their impact on the specific mechanisms of postoperative SIRS occurrence needs to be further investigated in the future. Future multicentre studies with larger sample sizes are needed to elucidate the clinical significance of this model.

## Conclusion

This study shows for the first time that the number of PTCSL sessions, stone location, intraoperative use of norepinephrine, intraoperative puncture, preoperative GGT, and preoperative TLC are independent risk factors for the development of SIRS after PTCSL. A nomogram prediction model was established to predict the occurrence of SIRS after PTCSL. The results of the study showed that the nomogram may help clinicians identify high-risk patients.

## Data Sharing Statement

All data generated or analyzed during this study are included in this article. For further information, please contact the corresponding author, Shengwei Li.

## Ethics Approval and Informed Consent

Written informed consent was obtained from all participants. Individuals cannot be identified based on the data presented. We declare to ensure the confidentiality of patient data. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Review Board of The Second Hospital of Chongqing Medical University (No.2018-207).

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception and design, data acquisition, or data analysis and interpretation, participated in the drafting of the article or critically revising it for important intellectual content, agreed to submit to the current journal, gave final approval for the version to be published, and agreed to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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