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Nomogram for Predicting Sepsis After Percutaneous Transhepatic Cholangioscopic Lithotripsy

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Video abstract

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Purpose: Sepsis is a possible complication of percutaneous transhepatic cholangioscopic lithotripsy (PTCSL) for hepatolithiasis, but risk assessment tools are lacking. This study aimed to identify predictors of sepsis after PTCSL and develop a predictive nomogram.

Patients and Methods: In this nested case–control study, the data from 298 patients who underwent 528 PTCSL sessions between 1 January 2016 and 1 July 2024 were retrospectively reviewed. All sessions demonstrating sepsis complications were included in the sepsis group. For each session in the sepsis group, two treatment date-matched sessions not demonstrating sepsis were randomly selected via a nested case–control design. All the matched sessions were divided into training and validation sets. Least absolute shrinkage and selection operator (LASSO) analysis was conducted to preliminarily select predictors of sepsis complications. Multivariable logistic regression was performed to identify factors for constructing the nomogram.

Results: Sepsis was diagnosed in 46 patients (53 sessions), for an incidence of 10.69% (53 among 496 sessions). Three characteristic variables were included in the model: operation technique (odds ratio [OR]=0.170, 95% confidence interval [CI]: 0.048–0.599, P=0.006), cirrhosis (OR=3.769, 95% CI: 1.474–9.638, P=0.006), and postoperative prophylactic dexamethasone (OR=0.267, 95% CI: 0.101–0.703, P=0.008). The area under the curve (AUC) for the nomogram was 0.756 (95% CI, 0.658–0.853) in the training set and 0.762 (95% CI, 0.618–0.906) in the validation set, demonstrating relatively high discriminability. The calibration curves demonstrated the consistency between the predicted and actual values. Decision curve analysis indicated that the nomogram offers net clinical benefits.

Conclusion: The operation technique, cirrhosis, and postoperative prophylactic dexamethasone may predict the occurrence of sepsis after PTCSL. We developed a nomogram to predict sepsis complications following PTCSL and demonstrated its relatively strong performance.

Keywords: percutaneous transhepatic cholangioscopic lithotripsy, hepatolithiasis, sepsis, *nomogram*

Introduction

The incidence of hepatolithiasis, a benign biliary disorder common in Southeast and East Asia, varies substantially across different parts of the world.[1] Patients are often asymptomatic in the early stages, but in later stages, biliary obstruction often develops, affecting bile discharge.[2] Without timely treatment, this can result in biliary infection, irreversible liver damage, and even cholangiocarcinoma.[3–5] Surgery remains the primary treatment for stone removal and obstruction relief, although it carries certain postoperative risks.[2,6,7]

In recent years, with advances in endoscopic technology, percutaneous transhepatic cholangioscopic lithotripsy (PTCSL) has become increasingly widely used in clinical practice for the treatment of hepatolithiasis. PTCSL allows the direct visualization of the bile ducts, facilitating the detection of stenosis and the fragmentation and extraction of

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stones from various locations within the hepatobiliary system.[8] The procedure is minimally invasive, has a quick recovery period, and has few complications.[9,10] A percutaneous transhepatic puncture is first performed to create an access tract, followed by the insertion of a cholangioscope to extract stones.[11] This process, as well as the continuous use of large volumes of irrigation fluid to maintain a clear view, can increase intraductal pressure and potentially damage the bile duct walls, allowing bacteria and endotoxins to enter the bloodstream and potentially leading to postoperative sepsis.[12–14] Sepsis, a life-threatening condition caused by a dysregulated host response to infection that can progress rapidly without timely intervention, resulting in multiple organ failure or death.[15] Our previous study analysed the data from 284 PTCSL sessions to explore the risk factors for postoperative systemic inflammatory response syndrome (SIRS) following PTCSL.[12] However, sepsis, a more severe complication than SIRS, warrants greater attention from clinicians. According to recent studies, the incidence of sepsis following percutaneous transhepatic cholangiography drainage (PTCD) is 24.6%.[16] However, the clinical features of postoperative sepsis following PTCSL as well as the timing of onset, treatment approaches, and associated predictive factors have not yet been fully elucidated. Furthermore, there is currently no predictive model for assessing the risk of sepsis after PTCSL. Therefore, this study aimed to identify predictors of sepsis after PTCSL and develop a predictive nomogram.

Material and Methods

Patients

This was a single-centre, retrospective, nested case–control study. From 1 January 2016 to 1 July 2024, 298 patients with hepatolithiasis underwent 528 PTCSL sessions at the Second Affiliated Hospital of Chongqing Medical University. The process of patient selection is illustrated in a flow chart (Figure 1). All patients provided written informed consent. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and 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) a confirmed diagnosis of hepatolithiasis according to imaging findings; (b) first episode or recurrent hepatolithiasis after conventional surgery; (c) nonacute suppurative biliary infection or cholangitis with symptomatic improvement after treatment; and (d) one-step or two-step PTCSL for treating hepatolithiasis.

The exclusion criteria were as follows: (a) presence of a malignant tumour; (b) preoperative temperature $\geq 38°C$; (c) sepsis prior to PTCSL; (d) preoperative liver abscesses; (e) the need for conversion to open surgery; (f) preoperative antibiotic treatment for a nonbiliary infection; and (g) preoperative steroid use.

In clinical practice, some patients with hepatolithiasis maybe exhibit signs of biliary infection, and these patients are often treated with antibiotics to control the infection and alleviate symptoms until they are deemed fit for surgery. Therefore, we excluded patients who had received antibiotics for non-biliary infections prior to surgery. This exclusion criterion was established to ensure that patients included in the study had their biliary infection effectively controlled before surgery, while also eliminating potential confounding factors from infections originating outside the biliary system. Since most patients may undergo multiple treatment sessions, we provided descriptive statistics at the "session" level to clarify the association between sepsis and each individual treatment. In this study, sepsis was analysed on a session basis rather than a patient basis, as many variables differed across sessions.

Data Collection and Definitions

The primary outcome of the study was the occurrence of sepsis during hospitalization in patients with hepatolithiasis receiving PTCSL treatment. All periprocedural hospitalization data were retrieved from the medical records system of our institution. The demographic data collected for the enrolled patients included age, sex, body mass index (BMI), hypertension, diabetes, cirrhosis, type of hepatolithiasis, number of PTCSL sessions, Child–Pugh classification, and stone location. Preoperative laboratory indicators included albumin, globulin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase (GGT), total bilirubin, direct bilirubin, indirect bilirubin, total bile acids, prealbumin, haemoglobin, leukocyte count, neutrophil percentage, neutrophil count, total lymphocyte count, platelet count, prothrombin activity, prothrombin time-international normalized ratio (PT-INR), prothrombin time, and albumin/globulin (A/G) ratio. Intraoperative indicators included the operation technique, number of operating channels,

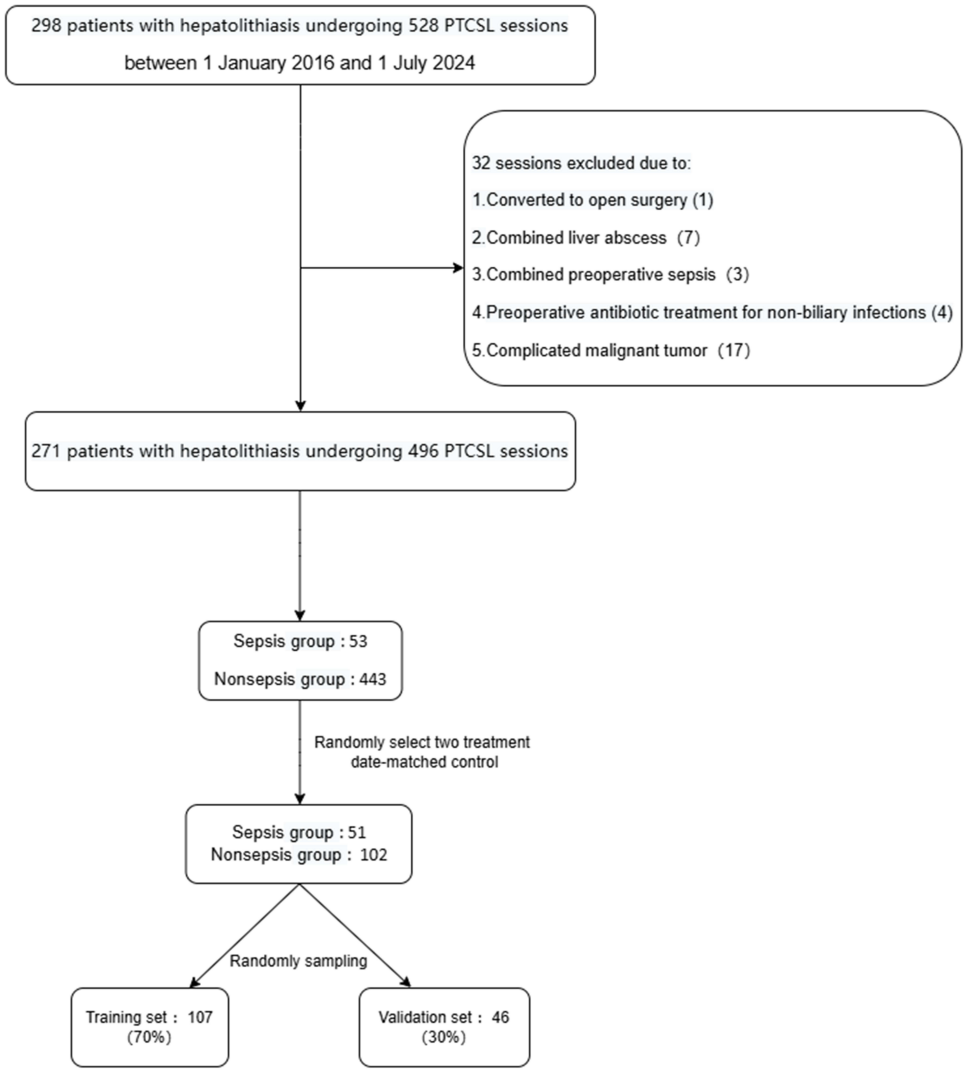

Figure 1 Flowchart of this study.
Abbreviation: PTCSL, percutaneous transhepatic cholangioscopic lithotripsy.

operative time, American Society of Anesthesiologists (ASA) score, residual stones after each session, intraoperative use of norepinephrine solution, puncture method, and intraoperative puncture. Additionally, following a review of the medical records, we collected data on patients' drug use during the perioperative period, including preoperative antibiotic therapy and postoperative prophylactic dexamethasone.

The presence of residual stones after each session was assessed on the basis of the operator's intraoperative cholangioscopy, intraoperative ultrasound, or postoperative cholangiography findings. The diagnosis of cirrhosis was made on the basis of typical imaging features or liver tissue biopsy pathology findings. Preoperative antibiotic use was evaluated according to the patient's symptoms, signs, or test results. In addition, we considered postoperative adjuvant treatments for some patients, including the prophylactic use of dexamethasone, which was determined at the surgeon's discretion. These patients were administered dexamethasone according to a standardized protocol during the perioperative period. This protocol involved administering dexamethasone sodium phosphate injection (Southwest Pharmaceutical Co., Ltd., 5 mg/1 mL per dose) at a dose of 10 mg, which was diluted with 8 mL of normal saline to a total volume of 10 mL, every other day, starting from the day of PTCSL, for a total of 3 doses. We defined a session as a single intervention episode of PTCSL performed for hepatolithiasis. Patients were classified as having an infection if specific treatment (at least 3 days of antibiotic therapy) was initiated for one of the following reasons: 1. systemic signs of

infection (eg, fever, elevated or decreased white blood cell count, increased C-reactive protein level, or elevated procalcitonin level); or 2. Detection of bacteria via blood or bile culture.[17]

Sepsis was diagnosed on the basis of the following criteria, recently redefined by the Sepsis-3 Working Group: (a) confirmed or suspected infection and (b) a postoperative sequential (sepsis-related) organ failure assessment (SOFA) score 2 or more points greater than the preoperative (baseline) score.[18,19]

PTCSL Procedures

For patients with preoperatively diagnosed hepatolithiasis and biliary infection, antibiotics were administered until the lead surgeon confirmed that the patient was fit to proceed with PTCSL treatment. For patients with positive bile cultures, antibiotics were selected based on the susceptibility of the identified bacteria, prioritizing antibiotics to which the bacteria were susceptible for targeted treatment. In the absence of bile culture results, empirical broad-spectrum intravenous antibiotics were administered. The same antibiotics were given 30 minutes before the PTCSL procedure. Regarding resistance patterns, we strictly followed the hospital's antibiotic management guidelines and incorporated regional antibiotic resistance monitoring data to ensure the rational and scientific use of antibiotics. Patients without preoperative biliary infection received a single dose of broad-spectrum antibiotic prophylaxis 30 minutes prior to PTCSL. During the procedure, the biliary system was irrigated with saline solution via choledochoscope connected to 3-litre bags via an infusion set suspended 2.0 metres above. The irrigation speed was set to maximum. The PTCSL procedure was performed according to the standardized protocol after the induction of general anaesthesia.[12] The surgical procedure includes both one-step and two-step PTCSL. For patients who underwent one-step PTCSL, the optimal puncture point and pathway were determined on the basis of preoperative imaging, and the procedure was performed according to established protocols. The target bile duct was punctured with an 18G needle (9013606, Zhengzhou Dior Medical Technology Company, China) under intraoperative ultrasonography guidance (DC-7T, Shenzhen Mindray Bio-Medical Electronics Company, China). The sinus was immediately expanded with biliary expanders from 8 Fr to 18 Fr (9013606, Zhengzhou Dior Medical Technology Company, China) via a stepwise procedure after a zebra guidewire (10S13508, Hunan Epte Medical Equipment Company, China) had been placed in the bile duct. 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 fistulous 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 identify intrahepatic bile duct stones. For stones smaller than the diameter of the sheath, a basket or clamp (VDK-BAS-18-70-15-N4-D, Jiangsu Vedkang Medical Technology Company, China) was used for removal; larger stones were crushed with lithotripsy performed with a holmium laser (DHL-1-D, Wuxi Dahua Laser Device Company, China). All operational manipulations were performed within the protective sheath. Biliary drainage catheters (9013606, Zhengzhou Dior Medical Technology Company, China) were routinely placed through the fistulous channel in all patients postoperatively and maintained for a minimum of 1 month. A video of the one-step PTCSL procedure is available online (Supplementary Video 1). In contrast, two-step PTCSL is performed in two stages: the first stage involves PTCD for bile duct drainage under ultrasound or X-ray guidance; the second stage, typically after an interval of more than two weeks, is performed under general anesthesia. The drainage tube is removed, and a dilator is used to establish a passage from the surface to the intrahepatic bile duct stones, after which stone fragmentation and removal are performed. To guarantee that the procedures were performed safely and accurately, all PTCSL treatments and postoperative care were overseen by Dr. Yao Cheng, who has over a decade of experience and has performed at least 60 PTCSL sessions each year. For patients with complex hepatolithiasis, treatment was divided into two or more sessions.

Model Development

The incidence of sepsis following PTCSL is relatively low. To investigate this rare complication, a nested case-control study design was utilized. This design aims to minimize unquantifiable biases related to differences in surgeon experience, management, and other potential confounding factors across different time periods. All sessions with sepsis complications were included in the sepsis group (53 sessions in 46 patients). For each session in the sepsis group, two nonsepsis sessions were randomly selected from those performed within 14 days before or after the procedure.[20–22] As a result, the sepsis group comprised 51 sessions in 44 patients, whereas the nonsepsis group comprised 102 sessions in 86 patients.

The matched sessions were randomly divided into training and validation sets at a 7:3 ratio. The training set was used for model development, whereas the validation set was used for model validation. The performance of the models was assessed with the area under the receiver operating characteristic curve (AUC). Model calibration was assessed with calibration curves, and decision curve analysis (DCA) was performed to evaluate the nomogram's clinical benefits.

Statistical Analysis

Statistical analysis was performed using R (version 4.3.0) and SPSS (version 26.0.0) software. Normally distributed variables are presented as the mean ± standard deviation (SD) and were compared using Student's *t*-test. Nonnormally distributed variables are presented as medians (interquartile ranges) and were compared using the Mann–Whitney *U*-test. Categorical variables are presented as frequencies (percentages) and were compared with the chi-square test. Variables included in the training set were subjected to least absolute shrinkage and selection operator (LASSO) regression analysis to identify potential features associated with the occurrence of sepsis. Then, multivariable logistic regression analysis was used to identify the variables independently associated with sepsis following PTCSL. A p value of < 0.05 was considered to indicate statistical significance.

Results

From 1 January 2016 to 1 July 2024, our hospital treated a total of 298 patients with hepatolithiasis who underwent 528 PTCSL sessions. Among them, 1 patient (1 session) required conversion to open surgery during the procedure, 3 patients (3 sessions) were diagnosed with sepsis prior to surgery, 7 patients (7 sessions) were diagnosed with liver abscesses prior to surgery, 4 patients (4 sessions) received preoperative antibiotic treatment for nonbiliary infections, and 12 patients (17 sessions) had malignant tumours. As a result, 271 patients (496 sessions) met the inclusion criteria. A total of 46 patients (53 sessions) diagnosed with sepsis were categorized into the sepsis group, among whom 1 patient (1 session) developed septic shock after surgery. To ensure an adequate sample size, 44 patients (51 sessions) in the sepsis group and 86 patients (102 sessions) in the non-sepsis group were successfully matched at a 1:2 ratio using the date of surgery as the matching criterion. Consequently, the final study comprised 153 sessions, the data of which were then randomly assigned to the training and validation sets.

The incidence of sepsis complications was 10.69% (53 of 496 sessions) when defined per procedure and 16.97% (46 of 271 patients) when defined per patient. The median interval between PTCSL and the onset of sepsis complications was 1 day (interquartile range [IQR], 1–2 days), and the maximum interval was 7 days postoperatively. A short course of intravenous antibiotics was generally effective in treating all patients who developed postoperative sepsis. Unfortunately, three patients who developed postoperative sepsis died from liver failure (Supplementary Table 1). All three had a history of cirrhosis and exhibited signs of liver dysfunction prior to surgery.

Baseline Characteristics

A total of 153 PTCSL sessions meeting the criteria were included. Of the total sessions, primary hepatolithiasis was present in 69 sessions (45.10%), while secondary hepatolithiasis accounted for 84 sessions (54.90%). Among these, the data of 107 sessions were allocated to the training set, and those of 46 sessions were allocated to the validation set. Among the sessions, 51 resulted in postoperative sepsis: 33 in the training set and 18 in the validation set (Table 1). There were significant differences in operation technique, stone location, cirrhosis, and postoperative prophylactic dexamethasone in the training set.

Variable Selection and Nomogram Construction

First, in the training set, preliminary screening was conducted via LASSO regression to identify potential predictors, ensuring the avoidance of model overfitting (Figure 2). Three candidate predictors were identified: operation technique, cirrhosis, and postoperative prophylactic dexamethasone. These three variables were then subjected to multivariable logistic regression analyses, which revealed (Table 2) that the two-step technique (odds ratio [OR]=0.170, 95% confidence interval [CI]: 0.048–0.599, P=0.006) and postoperative prophylactic dexamethasone (OR=0.267, 95% CI: 0.101–0.703, P=0.008) were protective factors against the development of postoperative sepsis, whereas the presence of cirrhosis (OR=3.769, 95% CI: 1.474–9.638, P=0.006) was a risk factor for sepsis following PTCSL.

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Table 1 Baseline Characteristics of Patients With and Without Sepsis in the Training and Validation Sets

		Training Set (n=107)			Validation Set (n=46)		
		Without Sepsis (n=74)	With Sepsis (n=33)	P-Value	Without Sepsis (n=28)	With Sepsis (n=18)	P-Value
Sex, N (%)	Male	25(33.78%)	14(42.42%)	0.391	14(50%)	14(77.78%)	0.060
	Female	49(66.22%)	19(57.58%)		14(50%)	4(22.22%)	
Age†, Years		55(49–64)	54(45.5–58)	0.237	55(48.25–62.5)	50(45–59.25)	0.316
BMI, Mean ± SD		21.489±2.832	20.813±2.997	0.266	22.275±3.536	20.713±3.031	0.130
Hypertension, N (%)	No	67(90.54%)	32(96.97%)	0.243	27(96.43%)	15(83.33%)	0.124
	Yes	7(9.46%)	1(3.03%)		1(3.57%)	3(16.67%)	
Diabetes, N (%)	No	68(91.89%)	33(100%)	0.092	22(78.57%)	17(94.44%)	0.144
	Yes	6(8.11%)	0(0%)		6(21.43%)	1(5.56%)	
Cirrhosis, N (%)	No	53(71.62%)	14(42.42%)	0.004	19(67.86%)	6(33.33%)	0.022
	Yes	21(28.38%)	19(57.58%)		9(32.14%)	12(66.67%)	
Child–Pugh, N (%)	Child A	63(85.14%)	32(96.97%)	0.073	26(92.86%)	16(88.89%)	0.641
	Child B	11(14.86%)	1(3.03%)		2(7.14%)	2(11.11%)	
Type of hepatolithiasis, N (%)	Primary stones	32(43.24%)	16(48.48%)	0.615	13(46.43%)	8(44.44%)	0.895
	Secondary hepatolithiasis	42(56.76%)	17(51.52%)		15(53.57%)	10(55.56%)	
Number of PTCSL sessions, N (%)	First	41(55.41%)	21(63.64%)	0.426	16(57.14%)	11(61.11%)	0.790
	Non-first	33(44.59%)	12(36.36%)		12(42.86%)	7(38.89%)	
Stone location, N (%)	Non-bilateral bile duct	41(55.41%)	11(33.33%)	0.035	15(53.57%)	6(33.33%)	0.179
	Bilateral bile ducts	33(44.59%)	22(66.67%)		13(46.43%)	12(66.67%)	
Puncture method, N (%)	B-ultrasound	69(93.24%)	31(93.94%)	0.893	27(96.43%)	16(88.89%)	0.312
	DSA	5(6.76%)	2(6.06%)		1(3.57%)	2(11.11%)	
Postoperative stone retention, N (%)	No	36(48.65%)	13(39.39%)	0.375	14(50%)	2(11.11%)	0.007
	Yes	38(51.35%)	20(60.61%)		14(50%)	16(88.89%)	
Number of operating channels, N (%)	Single-channel	31(41.89%)	12(36.36%)	0.590	17(60.71%)	5(27.78%)	0.029
	Multi-channel	43(58.11%)	21(63.64%)		11(39.29%)	13(72.22%)	
Operating time†, Minute		137.5(90–181.25)	130(105.5–165)	0.816	137.5(90.75–180)	168.5(148.75–211.25)	0.024
ASA class, N (%)	≤2	53(71.62%)	24(72.73%)	0.906	20(71.43%)	17(94.44%)	0.055
	≥3	21(28.38%)	9(27.27%)		8(28.57%)	1(5.56%)	
Intraoperative use of norepinephrine solution, N (%)	No	53(71.62%)	26(78.79%)	0.436	23(82.14%)	8(44.44%)	0.008
	Yes	21(28.38%)	7(21.21%)		5(17.86%)	10(55.56%)	
Intraoperative puncture, N (%)	No	56(75.68%)	20(60.61%)	0.113	21(75%)	7(38.89%)	0.014
	Yes	18(24.32%)	13(39.39%)		7(25%)	11(61.11%)	
Operation technique, N (%)	One-step	7(9.46%)	8(24.24%)	0.042	3(10.71%)	5(27.78%)	0.136
	Two-step	67(90.54%)	25(75.76%)		25(89.29%)	13(72.22%)	
Preoperative antibiotic therapy, N (%)	No	49(66.22%)	19(57.58%)	0.391	18(64.29%)	13(72.22%)	0.575
	Yes	25(33.78%)	14(42.42%)		10(35.71%)	5(27.78%)	
Postoperative prophylactic dexamethasone, N (%)	No	17(22.97%)	16(48.48%)	0.008	3(10.71%)	9(50%)	0.003
	Yes	57(77.03%)	17(51.52%)		25(89.29%)	9(50%)	

Albumin, Mean ± SD, (g/L)		38.676±4.527	40.027±4.122	0.146	40.686±4.316	39.094±4.428	0.233
Globulin, Mean ± SD, (g/L)		31.623±6.483	31.806±5.952	0.890	32.157±6.426	31.911±5.058	0.891
Alanine aminotransferase†, (U/L)		56.5(29.75–92.25)	54(23–87.5)	0.330	54(39–76.75)	63(31.5–110)	0.597
Aspartate aminotransferase†, (U/L)		48(31–82.25)	41(24.5–74)	0.242	42(35.5–68.25)	54(27.75–79.25)	0.884
Alkaline phosphatase†, (U/L)		177(120.75–326.75)	236(136.5–330)	0.632	245(134.75–344.25)	189(142.5–336)	0.620
GGT†, (U/L)		195.5(102.25–348)	244(172.5–401.5)	0.185	274.5(143–469.5)	274.5(189–350.75)	0.804
Total bilirubin†, (μmol/L)		15.9(9.2–25.725)	15.8(12.55–21.5)	0.542	15.45(11.325–24.9)	18.9(14.175–37.05)	0.196
Direct bilirubin†, (μmol/L)		8.25(3.775–17.975)	10.6(5.2–16.55)	0.576	8.7(5–13.525)	12.3(7.725–28.75)	0.081
Indirect bilirubin†, (μmol/L)		5.9(4.025–8.925)	5.2(3.85–8.5)	0.599	7.1(4.325–10.225)	6.65(3.525–10.375)	0.636
Total bile acids†, (μmol/L)		5.5(2.275–13.225)	7(2.7–13.8)	0.585	7.3(3.85–17.7)	6.4(3.375–14.825)	0.597
Prealbumin, Mean ± SD, (mg/L)		181.149±63.761	190.091±67.397	0.512	167.607±48.496	191.111±53.359	0.130
Haemoglobin, Mean ± SD, (g/L)		117.419±14.947	116.393±17.299	0.756	122.893±16.554	122.000±22.016	0.876
Leukocytes†, (×109/L)		5.53(4.2–7.0575)	4.9(3.78–5.74)	0.100	4.635(4.44–7.1925)	5.56(4.6875–5.93)	0.464
Neutrophil percentage, Mean ± SD,%		63.626±9.857	62.882±11.953	0.737	63.836±13.064	63.917±12.488	0.983
Neutrophil count†, ($\times 10^9$/L)		3.49(2.5425–4.6175)	3.23(2.06–3.97)	0.139	3.1(2.5575–4.155)	3.365(2.615–4.245)	0.804
Total lymphocyte count†, ($\times 10^9$/L)		1.37(0.9775–1.74)	1.26(0.85–1.74)	0.498	1.2(0.9575–1.515)	1.42(0.8475–1.84)	0.875
Platelet count†, ($\times 10^9$/L)		190(127.75–243.25)	163(140–180.5)	0.151	160.5(124.75–213.5)	179.5(128–224.25)	0.551
Prothrombin activity, Mean ± SD,%		98.622±16.983	99.636±13.897	0.764	99.929±13.627	98.611±13.382	0.749
PT-INR†		1.01(0.95–1.0925)	0.99(0.96–1.04)	0.653	1.005(0.945–1.09)	1.005(0.955–1.065)	0.892
Prothrombin time†, second		13.3(12.7–14.025)	13.1(12.65–13.6)	0.472	13.4(12.6–14.075)	13.3(12.775–14.075)	0.848
A/G ratio†		1.28(1.0175–1.4525)	1.27(1.14–1.48)	0.533	1.235(1.06–1.5025)	1.225(1.0675–1.45)	0.644

Notes: † Data are presented as the medians with the interquartile ranges in parentheses.

Abbreviations: PTCSL, percutaneous transhepatic cholangioscopic lithotripsy; BMI, body mass index; ASA, American Society of Anesthesiologists; GGT, gamma-glutamyltransferase; PT-INR, prothrombin time-international normalized ratio; A/G, albumin/globulin; DSA, digital subtraction angiography; SD, standard deviation.

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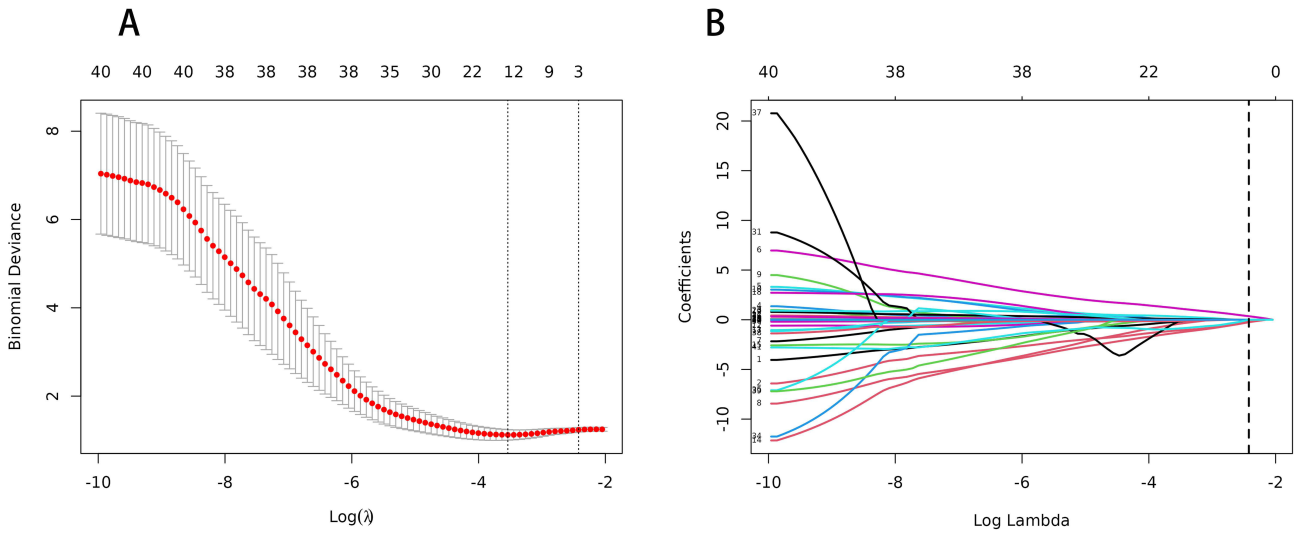

Figure 2 LASSO variable selection diagram. (**A**) Cross-validation curve of the LASSO regression analysis; (**B**) Coefficient path diagram of the risk variables.

To further validate the predictor variables, we also conducted univariable and multivariable logistic regression analyses for the overall group, obtaining similar results (Supplementary Table 2). A nomogram was constructed on the basis of these three variables (Figure 3).

Performance of the Sepsis Prediction Nomogram

The predictive performance of the nomogram is illustrated in Figure 4. The area under the curve was 0.756 (95% CI, 0.658–0.853) in the training set (Figure 4A) and 0.762 (95% CI, 0.618–0.906) in the validation set (Figure 4B). The calibration curve plot indicated good concordance between the predicted probabilities and the observed sepsis rates in both the training and validation sets (Figure 4C and D). Moreover, the results of decision curve analysis indicated that the nomogram could yield favourable net clinical benefits (Figure 4E and F).

Discussion

This study revealed that sepsis occurred in 10.69% (53 out of 496 sessions) following PTCSL. Additionally, analysis of high-risk periods for sepsis after PTCSL revealed that the highest incidence occurred on postoperative day 1, reaching 73.5%, followed by day 3, with an incidence of 13.2%. The independent predictive factors for sepsis after PTCSL identified in our study include the operation technique, cirrhosis, and postoperative prophylactic dexamethasone. Based on these variables, we developed a prediction model. A nomogram is a tool that combines multiple predictive factors, which might assist in making more well-considered decisions in clinical practice. For patients with cirrhosis, a two-step PTCSL approach could be taken into account, and postoperative prophylactic dexamethasone can be given to potentially decrease the risk of sepsis.

Notably, our previous studies explored the risk factors for the occurrence of SIRS after PTCSL.[12] SIRS is a step in the sepsis cascade characterized by a systemic inflammatory response, which may be triggered by sterile inflammation; once an

Table 2 Results of Multivariable Logistic Regression for Creating the Prediction Model

	OR	95% CI	P-Value
Operation technique	0.170	0.048–0.599	0.006
Cirrhosis	3.769	1.474–9.638	0.006
Postoperative prophylactic dexamethasone	0.267	0.101–0.703	0.008

Abbreviations: CI, confidence interval; OR, odds ratio.

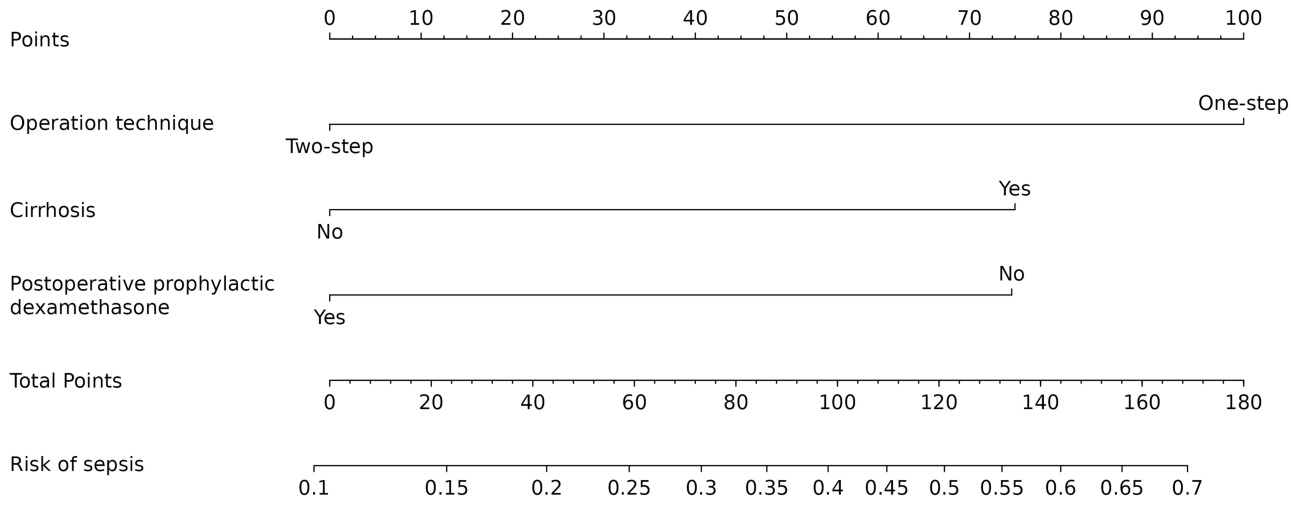

Figure 3 Nomogram prediction model for the incidence of sepsis after percutaneous transhepatic cholangioscopic lithotripsy (PTCSL).

infection occurs, it can potentially lead to the development of sepsis.[18,23] Sepsis represents a more severe condition characterized by a dysregulated host response to infection and therefore has greater clinical value and diagnostic significance than SIRS. Thus, the latest diagnostic criteria for sepsis no longer rely on SIRS standards but instead use the updated SOFA scoring system.[18] The SOFA score has high sensitivity and has become a standard tool for diagnosing sepsis.[24] This new diagnostic approach is closely related to the research results of this study, providing a reliable basis for accurately identifying sepsis cases. We applied a matching method to minimize unquantifiable biases related to differences in surgeon experience, management, and other potential confounding factors across different time periods, ensuring that our findings would be reliable and scientifically rigorous. At the same time, this study included new variables such as postoperative prophylactic dexamethasone and operation technique, the were not considered in our previous research. The differing endpoints and the inclusion of new variables led to divergent findings from our previous work.

Continuing from the above, in the field of clinical treatment of hepatolithiasis, there are currently two main intervention methods: endoscopic and surgical interventions.[2,25] However, compared with endoscopic treatments, surgical interventions may result in more significant trauma and a greater risk of complications.[26,27] With advancements in minimally invasive endoscopic techniques, endoscopic stone removal has become an effective approach for treating hepatolithiasis. Endoscopic retrograde cholangiopancreatography (ERCP) combined with mother-baby cholangioscopy initially required two operators but has since evolved into a single-operator technique.[28] However, the complexity and time-consuming nature of the procedure, along with the need for additional endoscopic equipment and the high degree of wear and tear on the cholangioscope, results in high costs.[29] Hwang and Robert B successfully treated hepatolithiasis with PTCSL, a technique adapted from percutaneous nephrolithotomy (PCNL), leading to many similarities in the operating procedures between the two.[30,31] PTCSL is an invasive procedure involving percutaneous transhepatic puncture of the bile duct to create a sinusoidal channel; thus, the associated risks and complications inherent to this invasiveness cannot be avoided.[32] Theoretically, the PTCSL can be used to remove stones from any location, and the sinus tract can be retained as needed to allow repeated sessions for stone removal until the stones are completely cleared. This approach effectively relieves biliary obstruction, reduces biliary pressure, and facilitates drainage.[10] The sinusoidal is gradually dilated, and a sheath is placed to allow repeated choledochoscopy for stone removal, allowing the procedure to be repeated as needed. Under normal conditions, liver cells are tightly connected, maintaining cell polarity through the functional bile canalicular structure, thereby forming a blood–bile barrier essential for liver cell function.[33,34] However, during PTCSL, puncturing or dilation procedures, along with lithotripsy, can damage blood vessels around the bile duct or its inner wall. Moreover, repeated stone removal can cause congestion and oedema of the bile duct wall. If bacteria are not promptly cleared, they are more likely to enter the bloodstream and cause infection. Additionally, an excessively elevated bile duct pressure can disrupt hepatocyte structure, weaken the blood–bile barrier, and make it easier for bacteria

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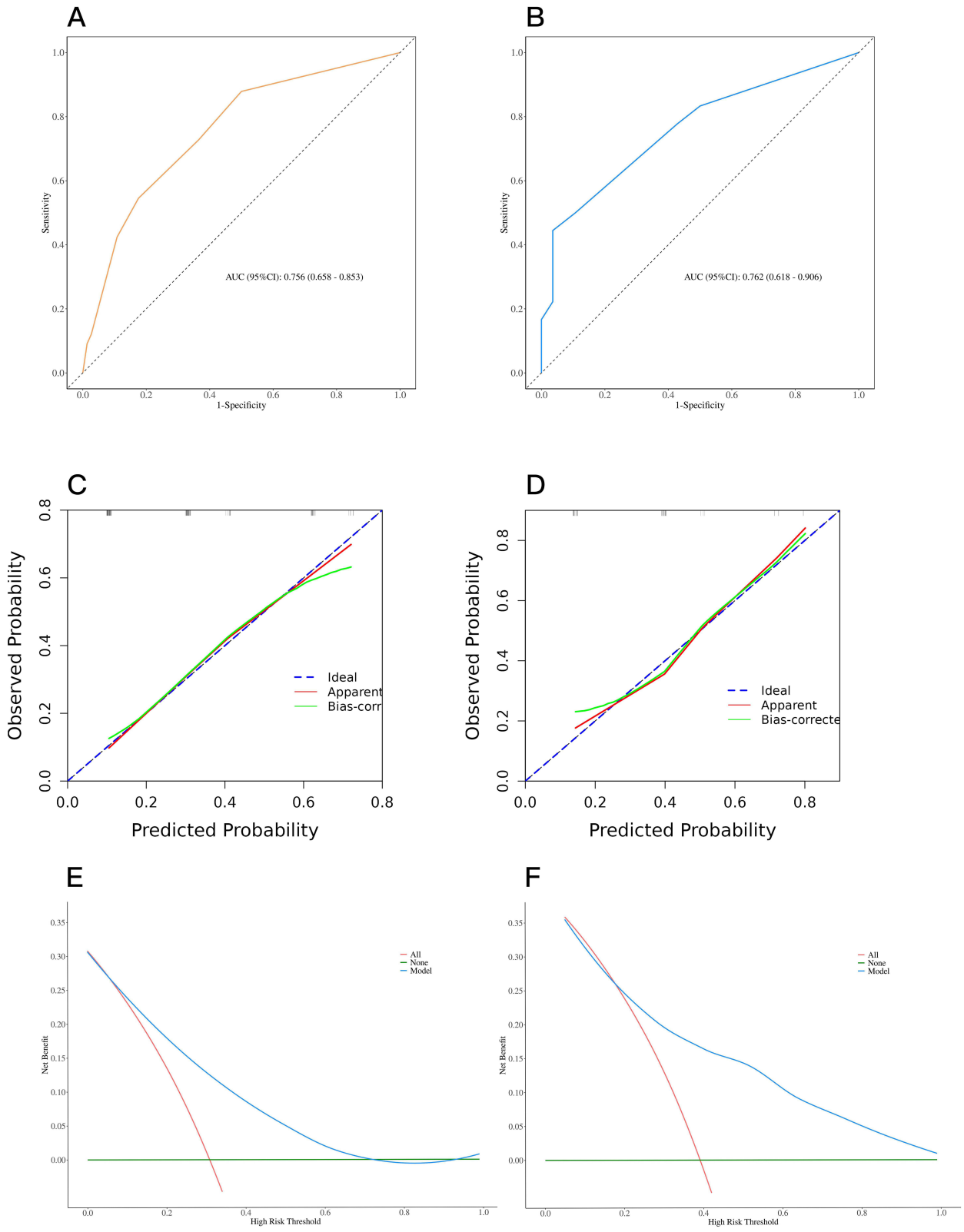

Figure 4 Performance evaluation of the nomogram for predicting sepsis after percutaneous transhepatic cholangioscopic lithotripsy (PTCSL); (**A**) Receiver operating characteristic curve in the training set. (**B**) Receiver operating characteristic curve in the validation set. (**C**) Calibration curves in the training set. (**D**) Calibration curves in the validation set; (**E**) Decision curve analysis in the training set. (**F**) Decision curve analysis in the validation set.

Abbreviations: AUC, area under the receiver operating characteristic curve; ROC, receiver operating characteristic.

and endotoxins to enter the bloodstream, potentially leading to sepsis.[12,13,35] Importantly, sepsis is a severe complication following PTCSL, but patient outcomes can be improved with early diagnosis and appropriate interventions.[36,37]

Previous studies have suggested that the risk of postoperative sepsis is greater in patients with cirrhosis than in those without cirrhosis.[38] In our study, we reached the same conclusion: patients with cirrhosis were more likely to develop sepsis after PTCSL. The reason maybe behind this lies in the pathophysiological changes of cirrhosis. Cirrhosis causes the formation of pseudolobules, which shatters the structural integrity of hepatic lobules. This disruption creates an abnormal bile - blood pathway between capillary bile ducts and hepatic blood sinusoids.[39,40] As a result, there is an increased probability of bacterial and toxin release into the circulation. The pathophysiology underlying the development of infection in cirrhotic patients involves altered haemodynamics, bacterial translocation, and immune dysfunction.[41]

After successful puncture, sinus tract dilation can be performed via either a one-step or two-step method. In this study, we recognized the potential influence of operation technique on the occurrence of postoperative complications and therefore incorporated it as a variable into our analysis. Our study revealed that patients who underwent the one-step PTCSL procedure were more likely to develop sepsis postoperatively. The one-step approach involves immediate dilation after puncture, which shortens the hospital stay time and allows for simultaneous choledochoscopy and stone extraction.[42] However, since the sinus tract is not fully formed, this method can lead to significant bleeding and infection. On the other hand, the two-step method involves placing a drainage tube after puncture and delaying dilation until the tract has matured.[32,43] Although this method takes longer, it significantly reduces intraoperative bleeding and post-operative infection rates via the dilation of a relatively mature tract.[13] A fresh tract is more prone to bleeding during repeated stone fragmentation and extraction, and increased biliary pressure facilitates bacterial entry into the blood-stream. Conversely, a well-established sinus tract wall provides better outcomes during repeated choledochoscope procedures. Consequently, to ensure patient safety, lithotripsy should be delayed. Initially, PTCD can relieve obstructions, ensure smooth drainage, and reduce inflammation-induced oedema in the bile ducts. This approach effectively lowers biliary pressure and reduces the risk of sepsis.

In this retrospective study, we collected data on perioperative medication usage and observed that some patients received prophylactic dexamethasone treatment postoperatively. Aware of the potential influence of the lead surgeon's clinical experience on the results, we employed a time-matching method to control for such differences during the same period. This was crucial to ensure the fairness and reliability of our study. Our analysis revealed that postoperative prophylactic dexamethasone could serve as a protective measure, effectively reducing the risk of postoperative sepsis. These preliminary findings provide a basis for further exploration of dexamethasone in preventing postoperative infectious complications, as it is a commonly used corticosteroid with anti-inflammatory, anti-endotoxin, and stress response-enhancing properties.[44,45] Postoperative administration of a small dose of dexamethasone can alleviate oedema in bile duct epithelial cells, inhibit the release of proinflammatory mediators, and reduce the degree of inflammation in the bile ducts, assisting in controlling postoperative inflammation.[46] Additionally, it can protect the patency of small bile ducts and improve bile drainage.[47] To reduce the incidence of postoperative infectious complications, perioperative drug intervention, in addition to changing treatment strategies, is essential. Currently, there are no reports on the prophylactic use of dexamethasone after PTCSL. However, in some randomized controlled trials, the use of prophylactic dexametha-sone has been shown to have positive effects on postoperative outcomes, such as improving liver function and reducing the incidence of postoperative complications.[48–50] This is achieved by inhibiting systemic inflammation and oxidative stress through the reduction of inflammatory cytokines.[50,51]

There are several limitations to this study. The first is related to the retrospective nature of the study. The decision to use prophylactic dexamethasone postoperatively was based on the surgeon's judgement, which could introduce potential bias. Furthermore, as a single-center study, the choice of operation techniques may be influenced by the experience level of the surgical team, the technical platform, and surgical habits, and future multicenter studies could help further validate these results. Additionally, due to the retrospective nature of this study and constraints limitations, some important factors were not systematically collected or analyzed. Furthermore, this study did not delve further into bile and blood cultures, and only some of the results are presented, as these procedures require time for bacterial growth and sensitivity testing, and the results are not promptly available postoperatively. Since postoperative infections often progress rapidly, clinical management typically relies on empirical antibiotic therapy, leading to gaps in clinical data and limiting our ability to explore this issue in depth.

Conclusion

This study demonstrates for the first time that operation technique, cirrhosis, and postoperative prophylactic dexamethasone use are independent predictive factors for sepsis after PTCSL. A nomogram prediction model was established to predict the occurrence of sepsis after PTCSL. Future multicenter prospective studies are needed to further validate our findings and explore the role of these predictive factors.

Data Sharing Statement

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

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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