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ORIGINAL ARTICLE

A nomogram for predicting stones recurrence in patients with bile duct stones undergoing laparoscopic common bile duct exploration

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Abstract

Background: The recurrence of bile duct stones is a long-term outcome for patients undergoing laparoscopic common bile duct exploration (LCBDE) that is worthy of attention. This study aimed to investigate long-term risk factors for stones recurrence after LCBDE and develop a nomogram for predicting the risk.

Methods: The clinical data on consecutive patients with bile duct stones undergoing LCBDE at Shanghai Tenth People's Hospital between January 2014 and February 2019 with a follow-up period longer than 2 years were reviewed. Independent risk factors of stones recurrence identified by the Cox regression model were used to develop a nomogram in predicting stones recurrence after LCBDE.

Results: Eight hundred and twenty-two patients were eventually included in this study. Of these patients, 42 (5.11%) developed stones recurrence. The cumulative incidences of stones recurrence at 1, 3, and 5 years after LCBDE were 1.34%, 4.36%, and 7.14%, respectively. Independent risk factors of stones recurrence were identified to be age (HR = 1.04, 95% CI = 1.02-1.07), T-tube drainage (HR = 3.28, 95% CI = 1.23-8.72), fatty liver (HR = 2.69, 95% CI = 1.39-5.20), urinary calculus (HR = 4.68, 95% CI = 2.29-9.56), post-cholecystectomy (HR = 5.21, 95% CI = 2.39-11.33), and post-ERCP + EST (HR = 2.87, 95% CI = 1.18-6.96). By these factors, a developed nomogram showed a C-index of 0.770 to predict stones recurrence.

Conclusions: The nomogram, based on identified risk factors, showed good accuracy for predicting stones recurrence, which is valuable to guide these patients' follow-up and prevention.

KEYWORDS
bile duct stones, LCBDE, nomogram, recurrence, risk factors

Wangcheng Xie, Tingsong Yang and Xue Zhou contributed equally to this work.

1 | INTRODUCTION

Choledocholithiasis is a common disease with a 5%-25% underlying prevalence rate, which usually lead to lots of adverse medical events, such as jaundice, acute cholangitis, and biliary pancreatitis.[1,2] At present, the recommended treatment for choledocholithiasis by the European Association for the Study of the Liver (EASL) is endoscopic retrograde cholangiopancreatography with endoscopic sphincterotomy (ERCP+EST), which has been well-considered as the preferred therapeutic method by most medical centers.[3] However, during the process of long-term practice, we have been increasing attention to the disadvantages of ERCP + EST, which could lead to various complications because of duodenal-biliary reflux after destroying Oddi's sphincter, including pancreatitis, high recurrence rate, and cholangiocarcinoma related to chronic cholangitis.[4,5] In recent years, with the development and maturation of the laparoscopic technique, laparoscopic common bile duct exploration (LCBDE) is regarded as an optimal treatment choice for bile duct stones with better short- and long-term postoperative outcomes than ERCP + EST.[6]

As reported previously, recurrent bile duct stones are defined as the detected stones over 6 months after endoscopic stones removal.[7,8] Stone recurrence not only bring these patients financial burden, but also health damage, especially for the elderly and frail patients, who could develop severe adverse events, even life-threatening events.[9] However, at present, there are not effective measure to prevent stone recurrence.[3] In addition, most patients lack awareness of the importance of regular follow-up, the symptoms are often already present when it is diagnosed. Thus, it is necessary to build a model based on a variety of risk factors to predict the possibility of stones recurrence, which could contribute to increased follow-up awareness for the patients with high risk, improve the early diagnosis and treatment, and reduce the severe events.

Several previous studies have shown that the stones recurrence rate after ERCP+EST is 4%-24%, and the investigated risk factors including stone numbers ≥2, cholesterol stone, diameter of common bile duct (CBD) >12 mm, bile duct angulation <145°, and so on.[3,7,10] However, until now, there were lack of studies based on a large-population, long follow-up periods, and comprehensive risk factors affecting recurrence for the patients undergoing LCBDE. Thus, the purpose of this study was to determine the long-term (>2 years) recurrence rate of bile duct stones, identify the risk factors, and develop a nomogram for predicting stones recurrence after LCBDE.

2 | METHODS

2.1 | Patients

The clinical data of a total of 862 consecutive patients with bile duct stones who underwent LCBDE at Shanghai Tenth People's Hospital between January 2014 and February 2019 were reviewed and analyzed. The diagnosis of bile duct stones was established from associated clinical biliary symptoms (abdominal pain, fever, chills, and jaundice), imaging studies (transabdominal ultrasonography, CT, magnetic resonance cholangiopancreatography [MRCP], ERCP, or intraoperatively by cholangiography ultrasonography), or serum liver biochemical tests (high levels of aminotransferase, bilirubin, or alkaline phosphatase). Additionally, the patient would be excluded if any of the following conditions occur: (i) negative exploration of bile duct through LCBDE; (ii) the stone recurring within 6 months after LCBDE; (iii) accompanying malignant tumor (biliary, liver, pancreas); (iv) existing contraindications to surgical intervention.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Research Ethics committee of Shanghai Tenth People's Hospital (SHSY-IEC-4.1/21-125/01).

2.2 | Operation technique

All operations were performed with the experienced chief physician from the hepatobiliary surgery department and assisted by reliable assistants.

The operation process was performed as previous studies, called "four-port and six-step" approach.[11,12] In brief, carbon dioxide gas was applied to create pneumoperitoneum, and a laparoscope was placed to investigate the gallbladder and bile duct. After a longitudinal supraduodenal choledochotomy, a choledochoscope (CHF-V; Olympus Corporation) was inserted into the bile duct to detect stones so that the stones could be removed with a Dormia basket (FG-24X-1; Olympus) under the supervision of a clear vision. While for patients with small enough stones, it might be possible that water flushing or irrigation alone was sufficient. When facing large or impacted stones, the FREDDY (World of Medicine, Berlin, Germany) laser lithotripsy was used to fragment the stones up until they could be flushed away or removed through a Dormia basket. Then, the choledochoscope was utilized to repeatedly examine the upper hepatic duct and the lower common bile duct until the duodenal papilla. Next, after confirming no residual stones, the primary closure—continuous over-and-over locking fashion with absorbable 4-0 PDS II sutures (Ethicon Inc) or T-tube drainage—was selected according to the actual situation. If it was complicated with gallbladder stones, laparoscopic cholecystectomy can be performed simultaneously. Finally, a silicone Jackson-Pratt drain was placed in a subhepatic location for abdominal drainage.

2.3 | Data collection

The data included demographic information, clinical symptoms, CBD and stone characters, surgical treatment process, preoperative laboratory parameters, comorbidities, past surgical and disease history. Moreover, clarification was needed for some variables. According to the shape of stones, in contrast to muddy stones, stones that were large enough to have a shape and angular were defined as shaped stones. The location of bile duct stones was classified as CBD stones

and other stones, with the latter meaning that stones occurred solely in the intrahepatic bile duct, common hepatic duct, cystic duct, or in multiple locations. The diagnosis of fatty liver was based on preoperative image examination.[13] The severity of the complications was evaluated with Dindo-Clavien classification.[14,15]

Patients were followed up every 3-6 months after conducting the first follow-up examinations in the second week. The primary follow-up data was the recurrence of bile duct stones; the secondary data considered biliary symptoms, liver function test, and complications. Recurrent bile duct stones were defined as those detected over 6 months after LCBDE and diagnosis depended on imaging.[7,8] The patients who did not adhere to follow-up were contacted by telephone to ensure the follow-up time was not <2 years. Likewise, those patients would be included in the recurrence group if they were confirmed to have recurrence through imaging studies or surgery (ERCP + EST or LCBDE).

2.4 | Statistical analysis

Quantitative data that follows a normal distribution were expressed as mean ± standard deviation (mean ± SD) and was compared through the Student's *t*-test. Otherwise, it would be described as medians with interquartile range and be compared using the Mann-Whitney *U* test. Qualitative data were reported as frequencies with percentages and evaluated using the chi-square test or Fisher's exact test. The Kaplan-Meier curve was used for describing the cumulative recurrence incidences. After getting rid of several variables with low incidence, Cox proportional-hazards regression was applied to analyze significant risk factors associated with the recurrence of bile duct stones after LCBDE. Variables with a *P*-value <.05 in univariate analysis and demographic variables would be included in the multivariate model to explore the significant factors ($P < .05$) associated with recurrence.

Based on the multivariate model, a nomogram was constructed to predict recurrence probabilities of bile duct stones at 1, 3, and 5 years for patients treated with LCBDE. The area under the ROC curve (AUC) was used to assess the discriminative ability of the nomogram. Meanwhile, the calibration curve was applied to contrast the association between the observed and the predicted non-recurrence probabilities.

All statistical analyses were conducted by IBM SPSS Statistics version 26.0 and R V.4.0.4. The *P*-value below .05 was considered to indicate statistical significance, and tests for all the data comparisons were two-sided.

3 | RESULTS

3.1 | Patients' characteristics

A total of 862 patients with bile duct stones received LCBDE, 36 of whom were not found with bile duct stones during the operation. During the follow-up period, four patients recurred within

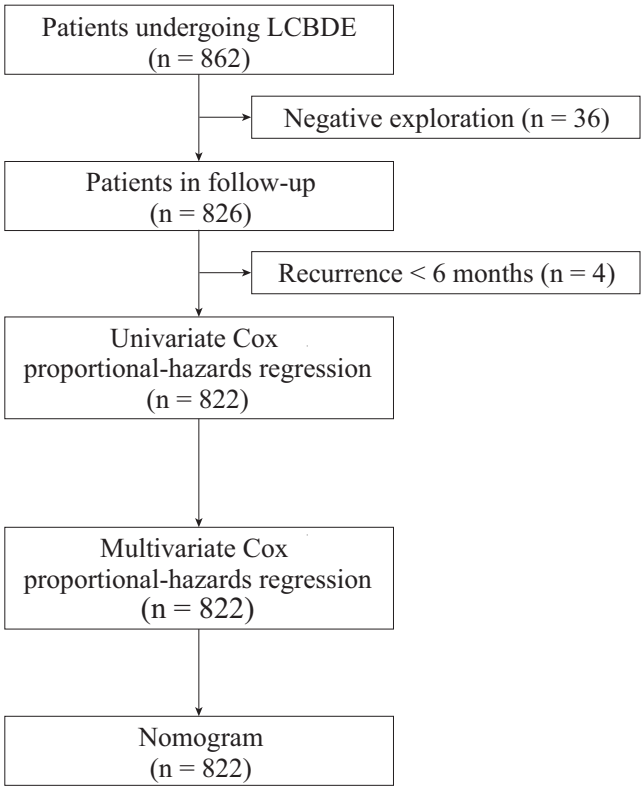

FIGURE 1 Flow diagram of selection of patients. LCBDE, Laparoscopic common bile duct exploration

6 months and were excluded based on the definition of recurrence. Therefore, 822 patients were eventually included in the retrospective study (Figure 1). All patients were followed up for a median of 38.10 months. At the time of analysis, recurrence of bile duct stones was detected in 42 patients (5.11%) with a median follow-up time of 24.42 months (range 6.27-70.43 months). According to the Kaplan-Meier curve, the cumulative recurrence incidences among all patients at 1, 3, and 5 years were 1.34% (95%CI, 0.55%-2.13%), 4.36% (95%CI, 2.83%-5.89%), and 7.14% (95%CI, 4.66%-9.61%), respectively (Figure 2A).

It was apparent that patients with recurrence are older than those without recurrence, whose median age was 67.00 years. Meanwhile, the patients of the recurrence group suffered more clinical symptoms than the non-recurrence group, such as jaundice and cholecystitis. In addition, a more significant proportion of patients in the recurrence group had undergone cholecystectomy and ERCP + EST before LCBDE. For the characteristics of the bile duct stones, almost all the patients of the recurrence group suffered from the shaped stones, and patients with the size of the stones over 15 mm had 12.66% more than the non-recurrence group. Meanwhile, there was no significant difference in other features of stones between the two groups, like the number and location. More patients take longer operation time and postoperative hospital time in the recurrence group regarding the surgical treatment process, and similarly, a greater proportion of patients chose the T-tube drainage to close the CBD. There was

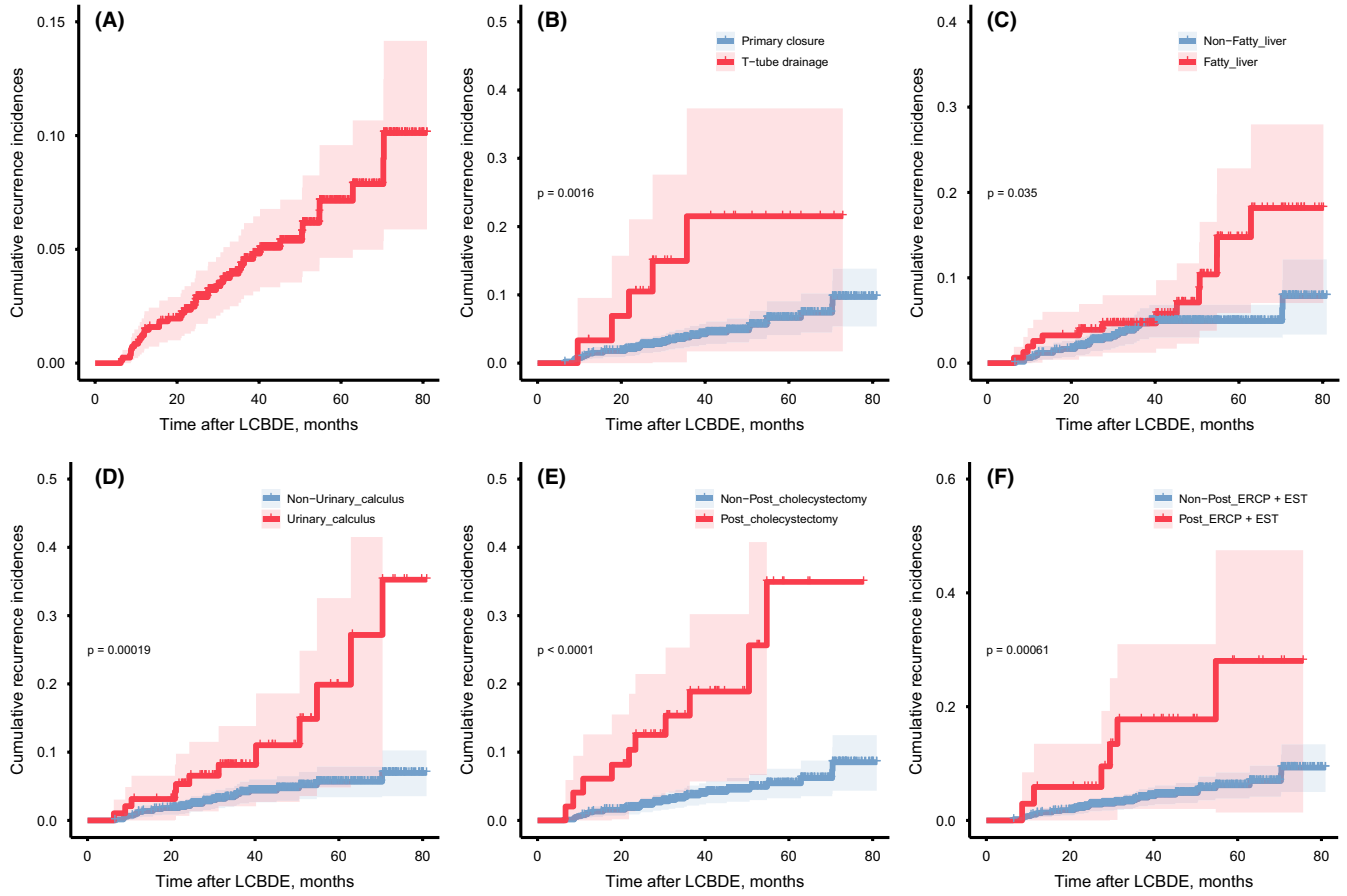

FIGURE 2 Kaplan-Meier curves for the cumulative recurrence incidences of bile duct stones after successful LCBDE in patients with independent risk factors. A, All patients; B, T-tube drainage; C, Fatty liver; D, Urinary calculus; E, Post-cholecystectomy; F, post-ERCP + EST. ERCP, Endoscopic retrograde cholangiopancreatography; EST, Endoscopic sphincterotomy; LCBDE, Laparoscopic common bile duct exploration

no evidence of a difference between the two groups for all the variables concerning preoperative laboratory parameters. In the end, it was apparent that the proportion of patients who had a history of or were suffering from coronary heart disease, fatty liver, urinary calculus, and psychosis was significantly higher in the recurrence group than in the non-recurrence group (Table 1).

3.2 | Risk factors for recurrence

Ten variables were showed statistically significant in the univariate Cox proportional-hazards regression, for which the 95%CI of the crude HR did not include one (Table 2). Next, demographic variables (sex, age, and BMI) and the aforementioned variables were included in the multivariate model through stepwise regression. The final results indicated that the following six variables would significantly increase the risk of recurrence of bile duct stones after LECBD: age (HR = 1.04, 95% CI = 1.02-1.07, P = .003), T-tube drainage (HR = 3.28, 95% CI = 1.23-8.72, P = .017), fatty liver (HR = 2.69, 95% CI = 1.39-5.20, P = .003), urinary calculus (HR = 4.68, 95% CI = 2.29-9.56, P < .001), post-cholecystectomy (HR = 5.21, 95% CI = 2.39-11.33, P < .001), post-ERCP + EST (HR = 2.87, 95% CI = 1.18-6.96, P = .020; Table 2, Figure 2B-F and 3).

3.3 | Nomogram construction

Based on the six risk factors predicted by the multivariate Cox proportional-hazards regression model, we developed a nomogram to predict recurrence probabilities of bile duct stones after LCBDE at 1, 3, and 5 years (12, 36, and 60 months; Figure 4). Furthermore, by assigning a corresponding score on the points scale to each level of the factor, a total score could be obtained by summing the scores for each factor, which would help us estimate the specific incidences of recurrence of stones at different times after treatment.

The validation of the nomogram also showed the desired results. The Concordance-index (C-index) of nomogram was 0.770 (95% CI = 0.697-0.843). And AUC demonstrated a good discriminative ability of recurrence, with the AUC of 0.822 (95% CI = 0.729-0.916), 0.766 (95% CI = 0.679-0.853), 0.856 (95% CI = 0.772-0.939) at 1, 3, 5 years, respectively (Figure 5). Besides, the calibration plots of the nomogram illustrated a good

TABLE 1 Baseline clinical characteristics of patients undergoing LCBDE

	Total (n = 822)	Non-recurrence (n = 780)	Recurrence (n = 42)	*P* value
Follow-up time (mo)	38.10 (27.73, 53.63)	38.90 (28.31, 54.32)	24.42 (11.79, 36.76)	<.001
Sex, female, n (%)	447 (54.40)	425 (54.49)	22 (52.38)	.790
Age (y)	63.00 (55.00, 72.00)	63.00 (55.00, 71.00)	67.00 (60.00, 79.25)	.013
BMI	23.40 (21.25, 25.40)	23.40 (21.30, 25.50)	23.30 (20.78, 24.30)	.181
≥24, n (%)	352 (42.82)	337 (43.21)	15 (35.71)	.339
Symptoms				
Abdominal pain, n (%)	739 (89.90)	704 (90.26)	35 (83.33)	.235
Jaundice, n (%)	221 (26.89)	204 (26.15)	17 (40.48)	.041
Cholecystitis, n (%)	613 (74.57)	590 (75.64)	23 (54.76)	.002
Cholangitis, n (%)	270 (32.85)	252 (32.31)	18 (42.86)	.156
CBD diameter (mm)	11.00 (10.00, 12.00)	11.00 (10.00, 12.00)	12.00 (10.00, 12.00)	.155
≥10, n (%)	713 (86.74)	675 (86.54)	38 (90.48)	.464
Stone				
Shape				
Muddy stone, n (%)	111 (13.50)	110 (14.19)	1 (2.38)	.030
Shaped stone, n (%)	706 (85.89)	665 (85.81)	41 (97.62)	
Size ≥15 mm, n (%)	77 (9.37)	68 (8.77)	9 (21.43)	.014
Number ≥3, n (%)	276 (33.58)	256 (32.99)	20 (47.62)	.051
Location				
CBD, n (%)	790 (96.11)	751 (96.28)	39 (92.86)	.479
Other, n (%)	32 (3.89)	29 (3.72)	3 (7.14)	
Impaction, n (%)	67 (8.15)	64 (8.21)	3 (7.14)	1.000
Mirrizzi syndrome, n (%)	7 (0.85)	7 (0.90)	0 (0.00)	1.000
Surgical treatment process				
ASA score, n (%)				
1	105 (12.77)	101 (12.95)	4 (9.53)	.902
2	663 (80.66)	628 (80.51)	35 (83.33)	
3	53 (6.45)	50 (6.41)	3 (7.14)	
4	0 (0.00)	0 (0.00)	0 (0.00)	
5	1 (0.12)	1 (0.13)	0 (0.00)	
Abdominal adhesion, n (%)	690 (83.94)	654 (83.85)	36 (85.71)	.748
Laser lithotripsy, n (%)	30 (3.65)	27 (3.46)	3 (7.14)	.414
Operation time (min)	111.00 (88.00, 147.00)	111.00 (87.00, 145.00)	132.00 (92.00, 163.75)	.073
>120, n (%)	339 (41.24)	315 (40.86)	24 (57.14)	.037
Blood loss (mL)	20.00 (20.00, 50.00)	20.00 (20.00, 50.00)	20.00 (20.00, 50.00)	.315
>50, n (%)	46 (5.60)	42 (5.38)	4 (9.52)	.428
Perforation, n (%)	1 (0.12)	1 (0.13)	0 (0.00)	1.000
Method of CBD closure, n (%)				
Primary closure	792 (96.35)	755 (96.79)	37 (88.10)	.012
T-tube drainage	30 (3.65)	25 (3.21)	5 (11.90)	
Conversion to open surgery, n (%)	14 (1.70)	12 (1.54)	2 (4.76)	.157
Postoperative bile leakage, n (%)	28 (3.41)	28 (3.59)	0 (0.00)	.416
Postoperative hospital time (d)	6.00 (5.00, 8.00)	6.00 (5.00, 8.00)	7.00 (6.00, 8.00)	.033
≥7, n (%)	353 (42.94)	329 (42.18)	24 (57.14)	.056
Postoperative drainage time (d)	5.00 (4.00, 6.00)	5.00 (4.00, 6.00)	5.00 (4.00, 6.25)	.457
≥5, n (%)	489 (59.49)	461 (59.56)	28 (66.67)	.360

(Continues)

TABLE 1 (Continued)

	Total (n = 822)	Non-recurrence (n = 780)	Recurrence (n = 42)	*P* value
Clavien-Dindo classification, n (%)				
1	783 (95.26)	743 (95.38)	40 (95.24)	.675
2	25 (3.04)	24 (3.08)	1 (2.38)	
3	7 (0.85)	6 (0.77)	1 (2.38)	
4	6 (0.73)	6 (0.77)	0 (0.00)	
5	0 (0.00)	0 (0.00)	0 (0.00)	
SSSI, n (%)	1 (0.12)	1 (0.13)	0 (0.00)	1.000
Preoperative laboratory parameters				
ALT (U/L)	93.40 (22.60, 256.08)	95.05 (22.58, 257.78)	72.05 (22.50, 186.43)	.494
>40, n (%)	525 (63.89)	500 (64.60)	25 (59.52)	.504
AST (U/L)	53.70 (22.85, 151.05)	54.20 (22.90, 153.80)	35.75 (22.05, 86.25)	.193
>40, n (%)	464 (56.45)	444 (57.29)	20 (47.62)	.218
AST/ALT > 1, n (%)	287 (34.91)	275 (35.71)	12 (28.57)	.346
GGT (U/L)	268.00 (70.80, 509.55)	275.20 (70.40, 517.55)	199.80 (69.35, 392.40)	.353
>50, n (%)	593 (72.14)	560 (77.78)	33 (80.49)	.684
ALP (U/L)	142.90 (88.23, 233.65)	142.70 (88.00, 234.90)	144.10 (98.70, 206.90)	.947
>135, n (%)	419 (50.97)	396 (53.23)	23 (56.10)	.720
TBIL (μmol/L)	21.70 (12.80, 57.40)	21.90 (12.80, 57.70)	19.05 (14.00, 49.35)	.708
>17.1, n (%)	498 (60.58)	473 (60.72)	25 (59.52)	.877
DBIL (μmol/L)	9.20 (4.30, 36.80)	9.20 (4.30, 37.65)	9.15 (5.50, 30.85)	.980
>6.8, n (%)	471 (57.30)	448 (57.51)	23 (54.76)	.726
DBIL/TBIL > 0.5, n (%)	376 (45.74)	356 (45.70)	20 (47.62)	.808
Bile acid (μmol/L)	7.90 (3.75, 56.05)	7.90 (3.60, 66.90)	16.80 (5.80, 51.60)	.357
>10, n (%)	89 (10.83)	83 (42.13)	6 (54.55)	.619
Creatinine (μmol/L)	67.60 (56.63, 79.00)	67.40 (56.50, 79.00)	71.30 (58.30, 78.85)	.465
>106, n (%)	36 (4.38)	34 (4.43)	2 (4.88)	1.000
Blood amylase (U/L)	60.00 (45.00, 84.75)	59.00 (44.98, 83.25)	74.50 (49.50, 106.75)	.159
>220, n (%)	43 (5.23)	38 (7.76)	5 (16.67)	.168
CRP (mg/L)	5.12 (3.17, 25.43)	4.95 (3.17, 24.30)	8.50 (3.30, 50.35)	.101
>8.2, n (%)	325 (39.54)	305 (41.55)	20 (50.00)	.292
WBC (*10^9/L)	5.99 (4.83, 7.72)	5.97 (4.82, 7.73)	6.26 (4.85, 7.73)	.739
>10, n (%)	103 (12.53)	97 (12.44)	6 (14.29)	.724
Percentage of neutrophils (%)	65.55 (56.80, 76.33)	65.55 (56.73, 76.08)	65.25 (57.55, 80.80)	.601
>75, n (%)	221 (26.89)	208 (26.67)	13 (30.95)	.542
Fasting blood glucose (mmol/L)	5.40 (4.80, 6.40)	5.40 (4.70, 6.40)	5.40 (5.00, 6.30)	.726
>6.1, n (%)	237 (28.83)	226 (30.54)	11 (28.21)	.757
HbA1c (%)	5.70 (5.40, 6.15)	5.70 (5.40, 6.20)	5.60 (5.15, 6.05)	.419
>6, n (%)	65 (7.91)	63 (29.03)	2 (22.22)	.947
Cholesterol (mmol/L)	4.35 (3.71, 5.07)	4.35 (3.75, 5.07)	4.35 (3.56, 5.54)	.974
>5, n (%)	35 (4.26)	31 (19.02)	4 (33.33)	.411
Triglyceride (mmol/L)	1.23 (0.87, 1.63)	1.23 (0.87, 1.56)	1.60 (0.74, 2.03)	.436
>1.7, n (%)	40 (4.87)	34 (20.86)	6 (50.00)	.050
HDL (mmol/L)	1.05 ± 0.42	1.04 ± 0.42	1.23 ± 0.35	.157
<1, n (%)	66 (8.03)	62 (46.62)	4 (40.00)	.940
LDL (mmol/L)	2.55 ± 0.84	2.55 ± 0.84	2.60 ± 0.91	.858
>3.4, n (%)	23 (2.80)	20 (14.93)	3 (30.00)	.419

TABLE 1 (Continued)

	Total (n = 822)	Non-recurrence (n = 780)	Recurrence (n = 42)	*P* value
Comorbidities and past history				
Hypotension, n (%)	414 (50.36)	390 (50.00)	24 (57.14)	.367
Diabetes, n (%)	138 (16.79)	130 (16.67)	8 (19.05)	.688
Coronary heart disease, n (%)	57 (6.93)	50 (6.41)	7 (16.67)	.025
Fatty liver, n (%)	154 (18.73)	140 (17.95)	14 (33.33)	.013
Lipid abnormality, n (%)	108 (13.14)	99 (60.74)	9 (75.00)	.501
Viral hepatitis, n (%)	473 (57.54)	450 (57.69)	23 (54.76)	.708
Cerebral infarction, n (%)	45 (5.47)	41 (5.26)	4 (9.52)	.403
Urinary calculus, n (%)	96 (11.68)	84 (10.77)	12 (28.57)	.001
Chronic gastritis, n (%)	58 (7.06)	55 (7.05)	3 (7.14)	1.000
Pulmonary tuberculosis, n (%)	6 (0.73)	5 (0.64)	1 (2.38)	.271
Psychosis, n (%)	6 (0.73)	4 (0.51)	2 (4.76)	.034
Post-cholecystectomy, n (%)	50 (6.08)	40 (5.13)	10 (23.81)	<.001
Post-ERCP + EST, n (%)	34 (4.26)	28 (3.59)	6 (14.29)	<0.001

Abbreviations: ALP, Antileukoproteinase; ALT, Alanine aminotransferase; ASA score, American Society of Anesthesiologists score; AST, Aspartate aminotransferase; BMI, Body mass index; CBD, Common bile duct; CRP, C-reactive protein; DBIL, Direct bilirubin; ERCP, Endoscopic retrograde cholangiopancreatography; EST, Endoscopic sphincterotomy; GGT, γ-glutamyl transpeptidase; HbA1c, Glycated hemoglobin; HDL, High-density lipo-protein; LCBDE, Laparoscopic common bile duct exploration; LDL, Low-density lipo-protein; SSSI, Skin and skin structure infection; TBIL, Total bilirubin; WBC, White blood cell count.

consistency between the actual observed clinical results and the predicted outcomes (Figure 6).

4 | DISCUSSION

As mentioned previously, ERCP + EST is still the mainstream management method for the patients with biliary stones, although some serious adverse events have been reported, such as pancreatitis, cholecystitis, bleeding, duodenal perforation, and so on.[2,16,17] However, one of the most important disadvantages of ERCP + EST is the permanent damage of Oddi's sphincter, which causes continuous reflux of duodenal contents, and the reflux would transport contents with bacteria into the bile duct, which has been proved to be a crucial potential element in stones recurrence.[18–20]

Accumulating studies have shown that 4%-24% of patients treated with ERCP + EST would suffer recurrent bile duct stones.[3,7] Moreover, several recent retrospective studies have revealed some high-risk factors associated with stones recurrence, such as age >65 years, CBD stone number ≥2, periampullary diverticulum, dilated CBD >12 mm, angulation of the CBD (≤145°), pneumobilia, biliary stricture, papillary stenosis, and so on.[7,10,21–23]

In recent years, LCBDE has increasingly been proven to not only have the advantages of faster postoperative recovery, shorter hospital stays, and lower costs, but is also a safer and more effective method for the choledocholithiasis patients with fewer ERCP-related short-term adverse events, such as bleeding, perforation, and pancreatitis, and lower rate of long-term complications, such as biliary stones recurrence.[6] Even so, LCBDE still has a certain rate of stones recurrence. A recent retrospective analysis with 156 choledocholithiasis cases has shown that 14.1% cases were diagnosed with recurrent stones after LCBDE with median 38.18 months follow-up. In addition, multivariate logistic regression showed that age was an independent risk factor, with up to 86.4% of the recurrences in patients aged >65 years.[24] Another retrospective study with 230 choledocholithiasis patients reported a 13.5% recurrence rate of bile duct stones after LCBDE, with risk factors of size >9 mm, CBD diameter ≥10 mm, and prior history of laparoscopic cholecystectomy.[8]

In our study, we performed a retrospective study of a larger population that included 822 patients with bile duct stones treated with LCBDE, and after a median follow-up period of 38.1 months, recurrent stones were observed in only 5.11% of cases. Additionally, we developed a nomogram based on the following six high-risk factors including increasing age, T-tube drainage, fatty liver, urinary calculus, post-cholecystectomy, and post-ERCP + EST. This finding is partially consistent with that of previous studies that identified the risk factors for recurrence of biliary stones after LCBDE. However, some factors in this study are inconsistent with those in ERCP methods reported previously, and we even noticed that the recurrence rate is higher in the post-ERCP group. The reason for this may mainly be attributed to the fact that the ERCP method could bring about refluxing of duodenal fluid, which is caused by permanent injury of Oddi's sphincter.

The elderly is a common population for recurrence of bile duct stones, which can be as high as 30%.[25,26] One of the reasons might be the alteration of bile composition due to the metabolic dysfunction of the body with increasing age. Moreover, elderly patients have higher incidence rates of duodenal peripapillary diverticulum and cholangiectasis, which would lead to sphincter dysfunction and

TABLE 2 COX proportional-hazards regression regarding clinical risk factors associated with bile duct stones recurrence after LCBDE

	Crude HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Sex (female)	0.93 (0.51-1.70)	.800		
Age	1.04 (1.02,1.07)	.002	1.04 (1.02, 1.07)	.003
BMI (≥24)	0.70 (0.37-1.32)	.267		
Symptoms				
Abdominal pain	0.52 (0.23-1.17)	.112		
Jaundice	1.50 (0.80-2.79)	.206		
Cholecystitis	0.54 (0.29-1.00)	.049		
Cholangitis	1.75 (0.95-3.25)	.075		
CBD diameter (≥10 mm)	1.36 (0.49-3.82)	.557		
Stone				
Shape (Shaped)	6.15 (0.85-44.73)	.073		
Size (≥15 mm)	2.67 (1.27-5.58)	.009		
Number (≥3)	1.72 (0.94-3.16)	.079		
Location (Other)	1.92 (0.59-6.20)	.278		
Impaction	0.98 (0.30-3.17)	.970		
Surgical treatment process				
ASA score	1.46 (0.78-2.75)	.239		
Abdominal adhesion	1.39 (0.58-3.30)	.459		
Laser lithotripsy	2.09 (0.64-6.76)	.220		
Operation time (>120 min)	1.60 (0.87-2.96)	.132		
Blood loss (>50 mL)	2.14 (0.76-6.00)	.150		
Method of CBD closure				
Primary closure	Ref			
T-tube drainage	4.03 (1.58-10.25)	.003	3.28 (1.23-8.72)	.017
Conversion to open surgery	2.47 (0.60-10.26)	.212		
Postoperative bile leakage	0.05 (0.00-69.67)	.412		
Postoperative hospital time (≥7 d)	1.70 (0.92-3.13)	.089		
Postoperative drainage time (≥5 d)	1.38 (0.73-2.63)	.322		
Clavien-Dindo classification	1.12 (0.47-2.65)	.800		
Preoperative blood examination				
ALT (>40 U/L)	0.79 (0.43-1.47)	.463		
AST (>40 U/L)	0.67 (0.37-1.23)	.196		
AST/ALT (>1)	0.78 (0.40-1.53)	.468		
GGT (>50 U/L)	1.20 (0.56-2.60)	.642		
ALP (>135 U/L)	1.09 (0.59-2.02)	.780		
TBIL (>17.1 μmol/L)	0.94 (0.51-1.75)	.855		
DBIL (>6.8 μmol/L)	0.91 (0.49-1.67)	.755		
DBIL/TBIL (>0.5)	1.03 (0.56-1.89)	.917		
Bile acid (>10 μmol/L)	1.63 (0.50-5.33)	.421		
Creatinine (>106 μmol/L)	1.15 (0.28-4.77)	.846		
Blood amylase (>220 U/L)	2.22 (0.85-5.81)	.103		
CRP (>8.2 mg/L)	1.40 (0.75-2.60)	.290		
WBC (>10 × 10^9/L)	1.20 (0.51-2.85)	.678		
Percentage of neutrophils (>75%)	1.20 (0.63-2.31)	.580		
Fasting blood glucose (>6.1 mmol/L)	0.94 (0.47-1.90)	.869		
HbA1c (>6%)	0.74 (0.15-3.58)	.709		

TABLE 2 (Continued)

	Crude HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Comorbidities and past history				
Hypotension	1.53 (0.83-2.82)	.174		
Diabetes	1.20 (0.55-2.58)	.651		
Coronary heart disease	2.83 (1.26-6.37)	.012		
Fatty liver	1.97 (1.04-3.75)	.038	2.69 (1.39, 5.20)	.003
Lipid abnormality	2.30 (0.62-8.56)	.213		
Viral hepatitis	0.89 (0.48-1.63)	.698		
Cerebral infarction	2.03 (0.73-5.70)	.178		
Urinary calculus	3.32 (1.70-6.50)	<.001	4.68 (2.29, 9.56)	<.001
Chronic gastritis	0.94 (0.29-3.04)	.916		
Pulmonary tuberculosis	3.70 (0.51-26.96)	.197		
Psychosis	5.64 (1.36-23.43)	.017		
Post-cholecystectomy	5.75 (2.82-11.75)	<.001	5.21 (2.39, 11.33)	<.001
Post-ERCP + EST	4.04 (1.70-9.58)	.002	2.87 (1.18, 6.96)	.020

Abbreviations: ALP, Antileukoproteinase; ALT, Alanine aminotransferase; ASA score, American Society of Anesthesiologists score; AST, Aspartate aminotransferase; BMI, Body mass index; CBD, Common bile duct; CRP, C-reactive protein; DBIL, Direct bilirubin; ERCP, Endoscopic retrograde cholangiopancreatography; EST, Endoscopic sphincterotomy; GGT, γ-glutamyl transpeptidase; HbA1c, Glycated hemoglobin; LCBDE, Laparoscopic common bile duct exploration; TBIL, Total bilirubin; WBC, White blood cell count.

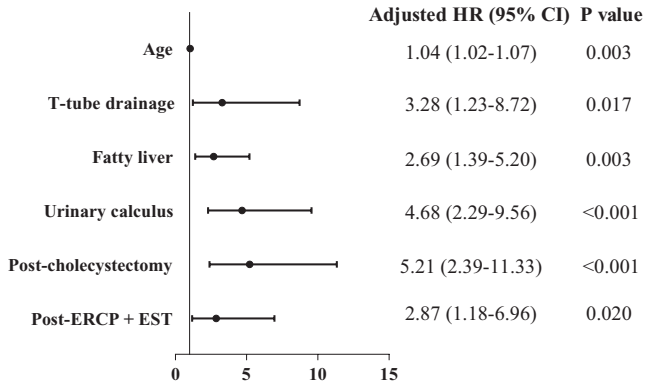

FIGURE 3 Forest map for the risk factors of bile duct stones recurrence after LCBDE included in multivariate Cox proportional-hazards regression. ERCP, Endoscopic retrograde cholangiopancreatography; EST, Endoscopic sphincterotomy; HR, Hazard ratio; LCBDE, Laparoscopic common bile duct exploration

poor bile flow, thus contributing to the recurrence of stones.[27] Of these, cholangiectasis is mainly associated with chronic intra-biliary pressure elevation, the contractile dysfunction of smooth muscle, which results in the difficulty of bile excretion. Although the present study showed no correlation between the CBD diameter and the recurrence of bile duct stones after LCBDE, several previous studies have confirmed it.[8,28,29] In addition, the presence of parapapillary diverticulum tends to accumulate bacteria and metabolic material, such as shedding mucosal cells, which then leads to infection and chronic inflammation and stimulates the Oddi's sphincter, which results in the blockage of the duodenal papilla and the inability to drain bile smoothly.[30–32]

Several previous studies have confirmed that metabolic abnormalities represented by hyperlipidemia, choledocholithiasis, obesity, non-alcoholic fatty liver disease, diabetes, and insulin resistance are important risk factors that promote the development of choledocholithiasis.[33–35] Here, we demonstrated that fatty liver was an independent risk factor in the recurrence of bile duct stones after LCBDE, which is consistent with the previous studies.[36] Lipids have a direct role in the formation of stones and insulin resistance, which increase the capacity of biliary cholesterol saturation.[36,37] Moreover, several studies have already pointed to a significant correlation between cholelithiasis and nephrolithiasis, and this study further supports the conclusion.[38,39]

CBD stones are classified as primary and secondary stones based on etiology and pathogenesis. A primary stone in the CBD indicates that it was formed within the bile duct, whereas the secondary indicates a stone that has migrated from the gallbladder where it was formed. In this study, we found that post-cholecystectomy was a significant risk factor for stones recurrence. This finding can be explained by two aspects, one is the presence of cystic duct stone that may migrate into the CBD duct after the surgical procedure. The other is that after gallbladder removal, most patients experienced increasing bile duct pressure and dilating bile duct, which is a high-risk factor for stone recurrence.

The recurrence rate of bile duct stones is lower in patients with LCBDE than those with ERCP + EST. Moreover, it is also lower in patients with non ERCP + EST who underwent LCBDE than those with post-ERCP + EST. However, the patient's intrinsic factors that promote stone formation are not altered, and there is a potential for the patients with LCBDE to reoccur stones. For

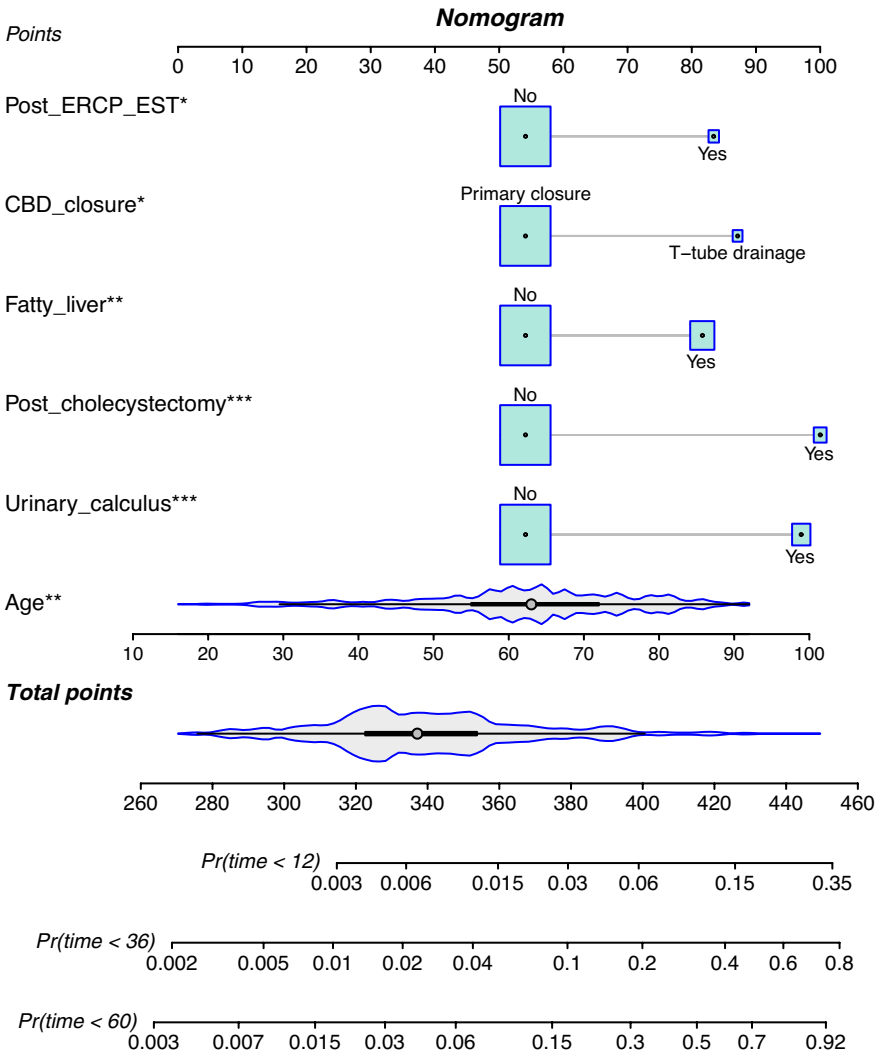

FIGURE 4 Nomogram for predicting recurrence among patients with bile duct stones underdoing LCBDE. CBD, Common bile duct; ERCP, Endoscopic retrograde cholangiopancreatography; EST, Endoscopic sphincterotomy; LCBDE, Laparoscopic common bile duct exploration

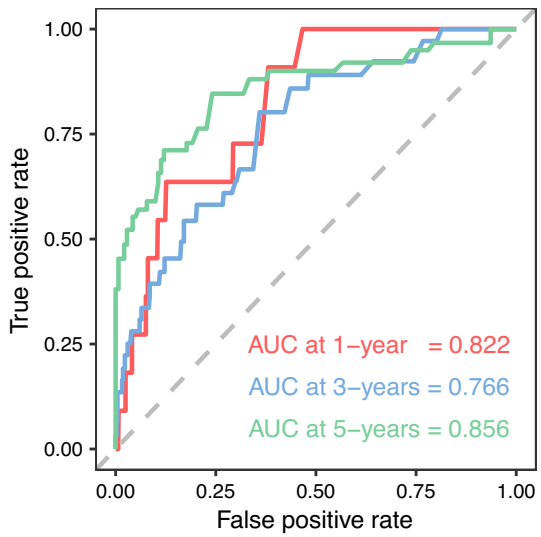

FIGURE 5 The ROC curves of the nomogram for predicting bile duct stones recurrence after LCBDE at 1, 3, and 5 years. LCBDE, Laparoscopic common bile duct exploration; ROC, Receiver operating characteristic

example, lithotripsy and T-tube drainage could cause bile duct mucosal damage, local adhesion, and scar healing.[32] On the other hand, T-tube can lead to bile duct distortion and obstructed bile drainage. Besides, the retrograde bacterial infection might occur with continuous T-tube drainage, leading to bacterial colonization in the bile ducts, which is an influencing factor in the recurrence of bile duct stones.[40] Fortunately, with the improvement of the surgical technique, most surgeons performed the primary closure of bile duct rather than T-tube drainage, which has also been proven to be safer and effective.[41]

Up to now, it is lack of standardized follow-up recommendations for the patients with bile duct stones after LCBED which leads to most patients not following up and therefore not being diagnosed in time. Thus, we constructed a nomogram with the significance of predicting the cumulative recurrence rate of stones in a high-risk population, which has a potential value to guide doctors and remind high-risk patients to follow-up reasonably.

There were some limitations in our study. Firstly, the research was a retrospective study, which has its inherent bias in data collection. Secondly, it was a single-center study with a relatively

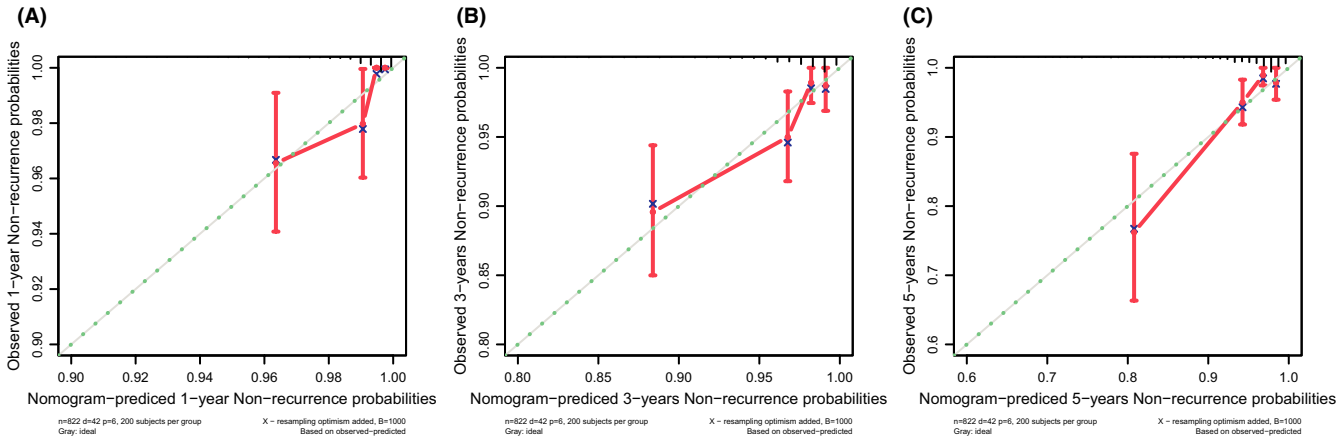

FIGURE 6 The calibration curves of the nomogram for predicting bile duct stones recurrence after LCBDE at 1, 3, and 5 years. A, The calibration curves at 1 year; B, The calibration curves at 3 years; C, The calibration curves at 5 years. LCBDE, Laparoscopic common bile duct exploration

insufficient sample of patients, which slightly diminished the statistical efficacy of identifying independent risk factors considering the number of variables included in the analysis. Thirdly, some of the proven risk factors were not included in this study, such as bile duct diverticulum and common bile duct angulation. Finally, we did not perform further validation of the final model using the validation set. Thus, a multicenter prospective study is essential in the future to further elucidate the risk factors for recurrence of bile duct stones after LCBDE.

5 | CONCLUSIONS

In summary, this study demonstrated that the overall stones recurrence rate for patients with bile duct stones undergoing LCBDE is 5.11%. Moreover, six independent risk factors for stone recurrence, including age, T-tube drainage, fatty liver, urinary calculus, post-cholecystectomy, and post-ERCP + EST, were identified. Additionally, based on these factors, the nomogram developed good accuracy for predicting stones recurrence, which is of potential value to guide doctors and remind high-risk patients to follow-up reasonably.

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DISCLOSURE

Ethical Approval: The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. Committee of Shanghai Tenth People's Hospital, Approval No. SHSY-IEC-4.1/21-125/01.

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