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Original Article

Factors influencing recurrence and model development for recurrence of minimally invasive percutaneous transhepatic lithotripsy: a single-center retrospective study

Yong-Rong Liang, Jia-Peng Zhou, Yong-Xiang Luo, Qi-Bin Su, Kun-Wei Ye, Fu-Yan Lu, Pei-Sheng Wu

Department of Hepatobiliary and Pancreatic Surgery, The First People's Hospital of Qinzhou, Qinzhou 535000, Guangxi, China

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Abstract: Objective: To identify factors influencing recurrence after percutaneous transhepatic choledochoscopic lithotripsy (PTCSL) and to develop a predictive model. Methods: We retrospectively analyzed clinical data from 354 patients with intrahepatic and extrahepatic bile duct stones treated with PTCSL at Qinzhou First People's Hospital between February 2018 and January 2020. Patients were followed for three years and categorized into non-recurrence and recurrence groups based on postoperative outcome. Univariate analysis identified possible predictors of stone recurrence. Data were split using the gradient boosting machine (GBM) algorithm, assigning 70% as the training set and 30% as the test set. The predictive performance of the GBM model was assessed using the receiver operating characteristic (ROC) curve and calibration curve, and compared with a logistic regression model. Results: Six factors were identified as significant predictors of recurrence: age, diabetes, total bilirubin, biliary stricture, number of stones, and stone diameter. The GBM model, developed based on these factors, showed high predictive accuracy. The area under the ROC curve (AUC) was 0.763 (95% CI: 0.695-0.830) for the training set and 0.709 (95% CI: 0.596-0.822) for the test set. Optimal cutoff values were 0.286 and 0.264, with sensitivities of 62.30% and 66.70%, and specificities of 77.20% and 68.50%, respectively. Calibration curves indicated good agreement between predicted probabilities and observed recurrence rates in both sets. DeLong's test revealed no significant differences between the GBM and logistic regression models in predictive performance (training set: D = 0.003, P = 0.997 > 0.05; test set: D = 0.075, P = 0.940 > 0.05). Conclusion: Biliary stricture, stone diameter, diabetes, stone number, age, and total bilirubin significantly influence stone recurrence after PTCSL. The GBM model, based on these factors, demonstrates robust accuracy and discrimination. Both GBM and logistic regression models effectively predicted stone recurrence post-PTCSL.

Keywords: Hepatolithiasis, percutaneous transhepatic cholangioscopic lithotripsy, stone recurrence, influencing factors, gradient boosting machine

Introduction

Hepatolithiasis is a prevalent and challenging benign biliary condition in China. The exact mechanisms underlying its pathogenesis remain unclear [1]. Common complications include bile duct infection, biliary cirrhosis, and portal hypertension, all of which may lead to biliary cancer [2, 3]. Percutaneous transhepatic choledochoscopic lithotripsy (PTCSL) is a favored minimally invasive treatment among biliary surgeons and hepatolithiasis patients due to its precision in diagnosis and treatment. Despite its advantages, stone recurrence post-surgery remains a significant issue, with the literature indicating recurrence rates between 6.44% and 24% depending on the duration of follow-up [4, 5]. Therefore, identifying factors influencing recurrence and developing an effective predictive model are crucial. In the past, logistic regression models were primarily utilized to predict PTCSL recurrence. However, these models often struggle with data imbalance and may not accurately reflect the true data distribution. The gradient boosting machine (GBM) is a widely used tool in machine

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learning for both classification and regression tasks. It employs the concept of "ensemble learning", which integrates multiple "weak learners" to create a "strong learner". GBM is particularly effective in medical data analysis due to its rapid model training time and high predictive accuracy and has been successfully applied in various clinical settings [6, 7]. Perez et al. [8] assessed GBM's performance against linear models in predicting complex phenotypes in outcrossing mice, finding that GBM, although more sensitive to data size and connectivity between the reference set and validation set, significantly enhances predictive accuracy. Zhao et al. [9] utilized GBM to predict ovarian metastasis in endometrial cancer patients, demonstrating that a GBM-based model can efficiently predict ovarian metastasis from identified predictors.

However, the application of GBM in predicting stone recurrence post-PTCSL remains underexplored. This study retrospectively analyzes the clinical data of patients with intrahepatic and extrahepatic bile duct stones treated with PTCSL. The aim is to develop a predictive model for stone recurrence post-PTCSL, thereby assisting clinicians in identifying high-risk patients and standardizing treatment to improve long-term outcome.

Data and methods

Research subjects

We retrospectively collected clinical data from 354 patients with intrahepatic and extrahepatic bile duct stones who underwent PTCSL at Qinzhou First People's Hospital between February 2018 and January 2020. The inclusion criteria were as follows: (1) Diagnosis of hepatolithiasis in accordance with established criteria [10], with all patients confirmed by abdominal ultrasound, CT, or magnetic resonance cholangiopancreatography (MRCP) imaging, and successful lithotomy achieved through PTCSL. (2) Postoperative imaging evaluations including CT, MRCP, choledochoscopy, or cholangiography to confirm the absence of residual stones. (3) Availability of complete clinical and follow-up data. The exclusion criteria included: (1) Patients with congenital choledochal cysts, duodenal papillary tumors, lower common bile duct stenosis, or hepatobiliary malignancies. (2) Patients with significant organ dysfunction (heart, lung, kidney, etc.). (3) Patients with a history of gastroduodenal surgery. (4) Patients previously treated with PTCSL. This study received approval from the Ethics Committee of Qinzhou First People's Hospital.

Methods

Data collection: We collected comprehensive data through electronic medical record system of Qinzhou First People's Hospital for all selected patients. The data included demographic and clinical characteristics such as gender, age, body mass index, presence of hypertension, diabetes, hyperlipidemia, smoking status, and histories of cholecystectomy, appendectomy, and biliary tract surgery, along with any occurrence of biliary tract infections. Preoperative assessments encompassed imaging examinations - namely abdominal ultrasound, CT, and MRCP. Laboratory biochemical indicators were also evaluated, including lymphocyte count, total bilirubin (TB), albumin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Surgical details, such as biliary stricture, number of stones, and stone diameter, were documented to complete the preoperative evaluation.

Surgical methods: All patients underwent PTCSL for common bile duct stones. The choice of left or right bile duct puncture was based on the patient's specific condition. Under general anesthesia and ultrasound guidance, the target bile duct was punctured and a guide wire was placed. Using this guide wire, a series of expanders (14-18 F) progressively enlarged the channel, after which an 18 F sheath was inserted along the wire into the intrahepatic bile duct. Following the removal of the guide wire and expander, the sheath was retained to maintain a direct channel from the intrahepatic bile duct to the exterior. Rigid choledochoscopy through this sheath facilitated the lithotripsy of both intrahepatic and extrahepatic bile duct stones. For areas inaccessible by rigid choledochoscopy, electronic choledochoscopy with a stone removal basket could maneuver stones to reachable locations for extraction. Larger stones were addressed using electrohydraulic, pneumatic, or holmium laser lithotripsy, while smaller stones or localized stenoses were managed with a basket or flushing water vortex techniques. Postoperative biliary drainage tubes were maintained for over two weeks. Subsequent imaging with ultrasound or CT determined the necessity of additional lithotomy. If no further treatment was required, the percutaneous transhepatic biliary drainage tube was removed the following day.

Follow-up

All patients were followed up for three years. Initially, follow-ups were conducted every three months during the first year post-stone removal and subsequently by telephone every six to twelve months. If patients exhibited typical symptoms of biliary diseases - such as high fever, abdominal pain, and jaundice - further imaging was warranted. Depending on the facilities available, CT or MRI scans were preferred for diagnosing suspected common bile duct stones. Diagnostic criteria for recurrence were as follows: patients exhibiting symptoms of acute biliary diseases at least six months post-follow-up, with recurrence confirmed through abdominal color Doppler ultrasound, CT, or MRCP indicating the formation of hepatolithiasis. Alternatively, if clinical symptoms were subtle but small stones were suspected, further examination confirmed the recurrence of common bile duct stones [11].

GBM model construction and verification

We employed the R package 'gbm' to construct the GBM model. The model's performance was evaluated using five-fold cross-validation (cv.folds = 5). Model parameters were set as follows: shrinkage = 0.005, n.trees = 5000, interaction.depth = 1, n.minobsinnode = 5, and bag.fraction = 0.5. Model construction and validation were facilitated using the R packages 'gbm', 'PROC', 'rms', and 'caret'.

Statistical analysis

SPSS 24.0 software was utilized for statistical analysis. Measured data were reported as mean ± standard deviation, and counted data as proportions (%). T-tests and chi-squared (χ^2) tests were applied for statistical evaluations. Initial analysis involved single-factor exploration to identify predictors of stone recurrence post-PTCSL. Subsequently, using R software version 4.1.2, GBM and Logistic regression models were developed to predict recurrence risk. The dataset was randomly split into a training set (70%) and a test set (30%), with the former used to build the models and the latter to evaluate their performance. The models' discriminative abilities were assessed using the receiver operating characteristic (ROC) curve, while model fit was determined by the calibration curve. Comparative analysis of the predictive efficiencies of GBM and Logistic regression models was conducted. A p-value < 0.05 was deemed significant.

Results

Comparison of clinical characteristics and univariate analysis

In a study of 354 patients who underwent PTCSL for intrahepatic and extrahepatic bile duct stones, 88 patients (24.86%) experienced recurrence, while 266 (75.14%) did not. Significant differences were observed between the recurrent and non-recurrent groups in terms of age, presence of diabetes, TB levels, biliary stricture, number of stones, and stone diameter (P < 0.05). No significant differences were found for the other variables studied (P > 0.05), as detailed in **Table 1**.

GBM model construction

The GBM model incorporated variables that were statistically significant in the univariate analysis: age, diabetes, TB levels, biliary stricture, number of stones, and stone diameter. The model was developed using the 'gbm' function with the shrinkage parameter set at 0.005 and an initial number of iterations (n.trees) of 5000. The optimal number of iterations, determined through 5-fold cross-validation, was 998, at which the model exhibited the smallest generalization error (**Figure 1**). The relative importance of the variables, ranked from highest to lowest, included biliary stricture, stone diameter, diabetes, number of stones age, and TB levels, as shown in **Figure 2**.

GBM model validation

The ROC and calibration curves for both the training and test sets were analyzed. The GBM model demonstrated high predictive accuracy in both sets, with AUC values of 0.763 (95% CI: 0.695-0.830) for the training set and 0.709 (95% CI: 0.596-0.822) for the test set. The optimal cut-off values were determined to be 0.286

Table 1. Comparison of clinical features by univariate analysis

Clinical feature	Recurrence group (n = 88)	Non-recurrence group (n = 266)	t/χ^2	*P*
Gender [n (%)]			0.567	0.451
Males	34 (38.64)	91 (34.21)		
Female	54 (61.36)	175 (65.79)		
Age [n (%)]			5.804	0.016
≥ 60	57 (64.77)	133 (50.00)		
< 60	31 (35.23)	133 (50.00)		
Body mass index (kg/m^2, $\bar{x}\pm s$)	23.13±2.32	23.36±2.48	-0.734	0.463
Hypertension [n (%)]			1.936	0.164
Yes	24 (27.27)	94 (35.34)		
No	64 (72.73)	172 (64.66)		
Diabetes [n (%)]			13.352	< 0.001
Yes	45 (51.14)	79 (29.70)		
No	43 (48.86)	187 (70.30)		
Hyperlipidemia [n (%)]			2.631	0.105
Yes	18 (20.45)	78 (29.32)		
No	70 (79.55)	188 (70.67)		
Smoking [n (%)]			0.251	0.617
Yes	31 (35.23)	86 (32.33)		
No	57 (64.77)	180 (67.67)		
History of cholecystectomy [n (%)]			0.476	0.490
Yes	5 (5.68)	21 (7.89)		
No	83 (94.32)	245 (92.10)		
History of appendectomy [n (%)]			0.056	0.812
Yes	12 (13.64)	39 (14.66)		
No	76 (86.36)	227 (85.34)		
History of biliary tract surgery [n (%)]			0.798	0.372
Yes	5 (5.68)	23 (8.64)		
No	83 (94.32)	243 (91.35)		
Biliary tract infection [n (%)]			0.503	0.478
Yes	21 (23.86)	54 (20.30)		
No	67 (76.14)	212 (79.70)		
Number of lymphocytes [n (%)]			1.894	0.169
< 1.5 × 10^9/L	56 (63.64)	190 (71.43)		
≥ 1.5 × 10^9/L	32 (36.36)	76 (28.57)		
ALT [n (%)]			3.789	0.052
≤ 50 U/L	52 (59.09)	187 (70.30)		
> 50 U/L	36 (40.91)	79 (29.70)		
AST [n (%)]			0.024	0.877
≤ 40 U/L	60 (68.18)	179 (67.29)		
> 40 U/L	28 (31.82)	87 (32.71)		
Total bilirubin [n (%)]			8.865	< 0.001
≤ 20.5 umol/L	27 (30.68)	130 (48.87)		
> 20.5 umol/L	61 (69.32)	136 (51.13)		
Albumin [n (%)]			0.979	0.322
< 40 g/L	59 (67.05)	193 (72.56)		
≥ 40 g/L	29 (32.95)	73 (27.44)		

Biliary stricture [n (%)]			4.339	0.037
Yes	25 (28.41)	48 (18.05)		
No	63 (71.59)	218 (81.95)		
Number of stones [n (%)]			10.272	0.001
≤ 1	35 (39.77)	158 (59.40)		
> 1	53 (60.23)	108 (40.60)		
Stone diameter [n (%)]			11.465	0.001
≤ 10 mm	56 (63.64)	216 (81.20)		
> 10 mm	32 (36.36)	50 (18.80)		

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

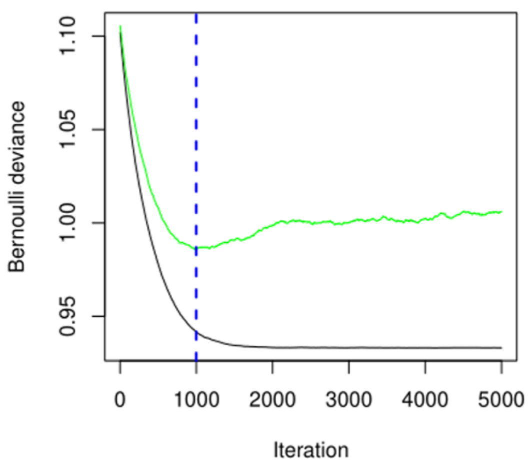

Figure 1. Minimum generalization error of GBM model. GBM, gradient boosting machine.

and 0.264, with sensitivities of 62.30% and 66.70%, and specificities of 77.20% and 68.50%, respectively, as shown in **Figure 3**. The calibration curves indicated a strong correspondence between the predicted probabilities of stone recurrence by the GBM model and the actual postoperative recurrence rates in both the training and test sets, as depicted in **Figure 4**.

Comparison between GBM and logistic regression models

The predictive efficacy of the GBM and Logistic regression models for stone recurrence post-PTCSL was compared. The accuracy, specificity, sensitivity, and AUC for both the training and test sets of these models are detailed in **Table 2**. The DeLong test revealed no significant difference between the AUCs of the training set of the GBM model and the logistic regression model (D = 0.003, P = 0.997 > 0.05); similarly, for the test sets, the difference was not significant (D = 0.075, P = 0.940 > 0.05). Overall, the performance of both models was comparable.

Discussion

In this study, 354 patients with intrahepatic and extrahepatic bile duct stones who underwent PTCSL were followed for three years. We observed a postoperative stone recurrence rate of 24.86%, consistent with clinical literature findings [5]. Univariate analysis revealed statistically significant differences between the recurrence and non-recurrence groups in age, diabetes, TB levels, biliary stricture, number of stones, and stone diameter. According to Lee et al. [12], age is a critical risk factor for stone recurrence post-choledocholithotomy. Increased age is associated with decreased bile duct wall elasticity and bile duct motility. Chronic inflammation and long-term stone presence contribute to bile duct wall roughness and damage, enhancing cholestasis and bile concentration, which promote stone formation. Moreover, studies have identified diabetes as an independent risk factor for postoperative stone recurrence, influencing cholesterol metabolism and promoting cholesterol stone formation [13, 14]. Although research on the relationship between preoperative TB levels and postoperative stone recurrence is limited, high TB levels can impair liver and multiorgan recovery, potentially affecting recurrence rates [15]. The 2019 edition of the expert consensus on choledochoscopy identifies biliary stricture as a critical factor in postoperative stone recurrence. Establishing a sinus tract preoperatively is challenging in cases of biliary stricture, complicating the selection of needle insertion angle and puncture site. Narrowed sites impede stone removal and lithotripsy, increasing the likelihood of residual stones [16]. Furthermore,

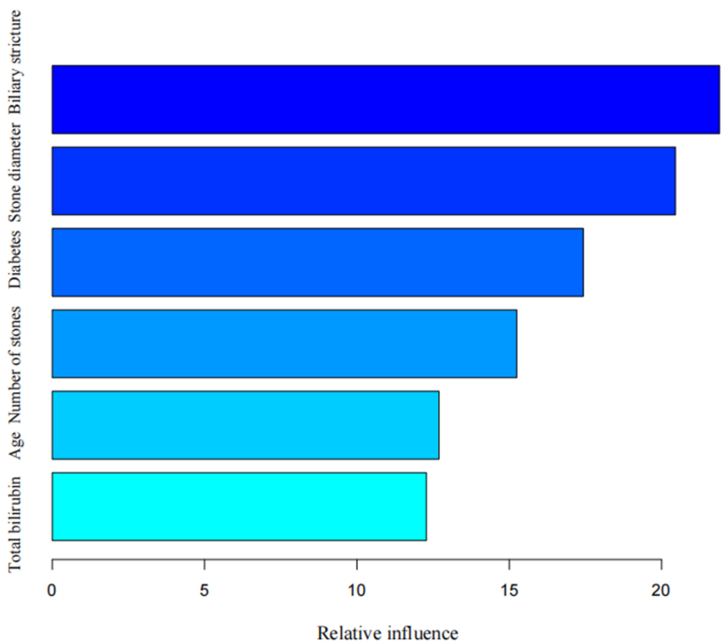

Figure 2. The influence of variables in the GBM model. GBM, gradient boosting machine.

repeated puncture and mechanical dilation of the bile duct stenosis can exacerbate bile duct injury, promoting stone formation and associated complications [17]. Thus, intraoperative identification of biliary stricture can be promptly addressed through stenosis ring incision, balloon dilation, and sheath dilation.

Previous studies [18, 19] have established that both stone diameter and number are significant predictors of postoperative stone recurrence. Larger or more numerous stones increase the duration of stone removal, which in turn prolongs bile duct wall stimulation, elevating the risk of chronic inflammation and fibrosis that can precipitate stone recurrence [20]. Additionally, the propensity for bile cholesterol to crystallize and form stones post-surgery is enhanced by intrinsic factors [13, 14].

The GBM model inherits the clear and comprehensible attributes of decision trees, providing excellent interpretability through its tree-based structural approach. This method ranks the relative importance of variables, from most to least significant, as biliary stricture, stone diameter, diabetes, number of stones, age, and TB level, offering valuable insight for clinical application and supporting individual-level predictive reasoning. The GBM model enhances the predictive efficiency of machine learning models through its sequential iterative training of decision trees, known as boosting. Ji et al. [21] utilized statistically significant factors from univariate analysis to construct a GBM model that accurately predicts the risk of stone recurrence post-PTCSL. Zou et al. [22] applied an advanced GBM model to assess the risk of central lymph node metastasis in patients with papillary thyroid carcinoma, highlighting the model's capacity to intuitively demonstrate the impacts of various factors. Golden et al. [23] developed GBM and Random Forest (RF) models to predict the prevalence of Listeria in fecal and soil samples from breeding sites, with the soil GBM model exhibiting superior performance, achieving AUCs of 0.873 and 0.700, respectively, outperforming the RF model. In this study, the GBM model's efficacy was validated using ROC and calibration curves, with results indicating high predictive accuracy in both the training and test sets. The AUCs for the GBM model were 0.763 (95% CI: 0.695-0.830) and 0.709 (95% CI: 0.596-0.822) for the training and test sets, respectively. The optimal cut-off values were 0.286 and 0.264, respectively. Sensitivity was measured at 62.30% and 66.70%, and specificity at 77.20% and 68.50%, for each set respectively. The calibration curve results indicated that the predicted probabilities from the GBM model closely matched the actual postoperative stone recurrence rates in both the training and test sets.

The GBM algorithm employs an ensemble of decision trees, integrating multiple independent classification and regression trees into a robust classifier to deliver precise and stable predictions [8]. Its internal structure is modular, making it accessible for clinicians to apply and interpret the GBM algorithm effectively. Additionally, the GBM algorithm inherently handles missing data, with built-in functions that classify based on existing data [24, 25].

Traditionally, postoperative stone recurrence prediction has largely relied on the Logistic regression model, which is underpinned by lin-

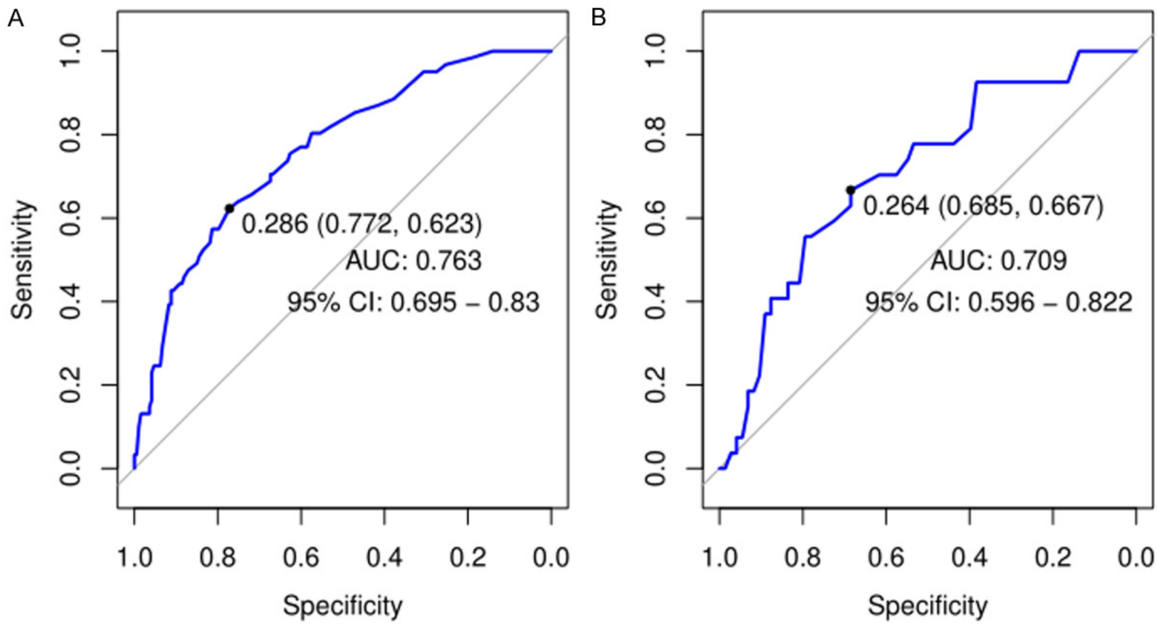

Figure 3. ROC curve analysis of GBM model predicting stone recurrence after PTCSL surgery; A. Training set; B. Test set. GBM, gradient boosting machine; ROC, receiver operating characteristic; PTCSL, percutaneous transhepatic choledochoscopic lithotripsy.

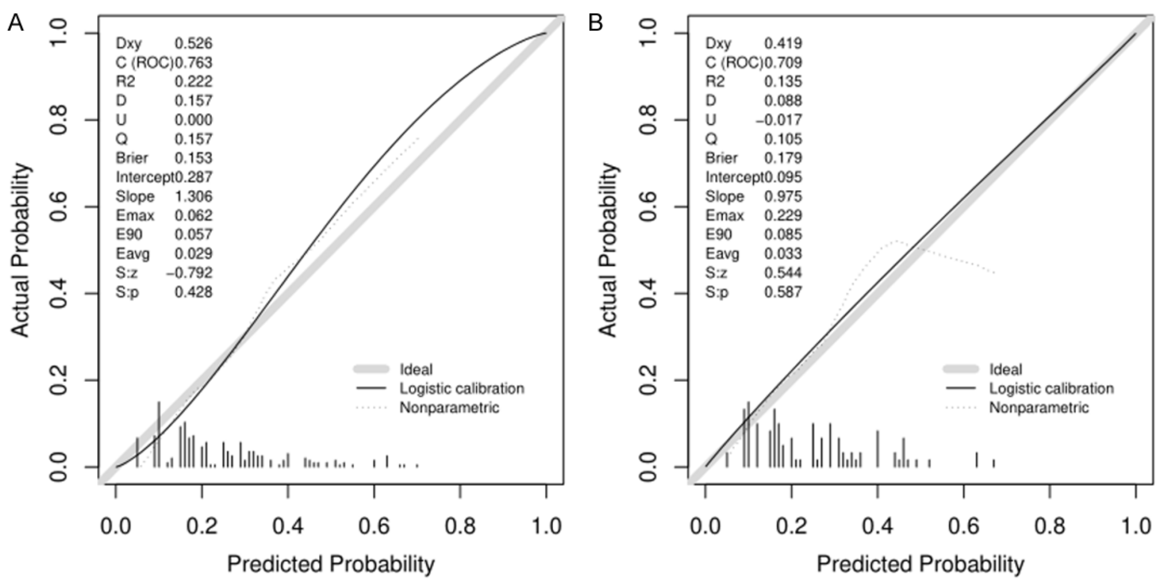

Figure 4. Calibration curve of GBM model predicting stone recurrence after PTCSL surgery; A. Training set; B. Test set. GBM, gradient boosting machine; PTCSL, percutaneous transhepatic choledochoscopic lithotripsy.

ear regression theory and often struggles to fit the true distribution of data due to its linear assumptions through a sigmoid function. In contrast, machine learning techniques like GBM use a non-linear approach, assuming a non-linear hyperplane for classification. This allows GBM to better capture complex interrelations among features and mitigate the effects of unbalanced sample distribution, enhancing model accuracy. However, in this study, the comparative performance analysis between the GBM and Logistic regression models indicated that both models delivered comparable prediction results. While the GBM algorithm

Table 2. Comparison between GBM and logistic regression models

Index	GBM algorithm model		Logistic regression model	
	Training set	Test set	Training set	Test set
Accuracy	0.768	0.710	0.791	0.730
Specificity	0.772	0.685	0.772	0.795
Sensitivity	0.623	0.667	0.623	0.556
AUC	0.763	0.709	0.763	0.715

GBM, gradient boosting machine; AUC, area under the curve.

involves serially generating multiple weak learners, it is relatively robust against overfitting due to its iterative nature and parameter settings. However, for clinical applicability and interpretability, the Logistic regression model requires minimal clinical data to achieve comparable predictive accuracy. Thus, employing both models in a complementary manner could enhance overall predictive performance.

This study has several limitations: it is retrospective, potentially subject to selection bias, and the sample size is restricted. Additionally, the study exclusively utilized the GBM algorithm for predictions, which may limit the accuracy and generalizability of the findings. Future research should involve larger datasets to gather more comprehensive clinical information and employ various machine learning algorithms for enhanced predictive analysis.

In conclusion, factors such as biliary stricture, stone diameter, diabetes, number of stones, age, and TB levels significantly influence stone recurrence post-PTCSL. The GBM model, based on these factors, demonstrates robust accuracy and discriminative ability. Both Logistic regression and GBM models perform effectively in predicting stone recurrence after PTCSL. The GBM model introduces innovative approaches for classification and prediction in this context, providing valuable insight for clinical decision-making.

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Disclosure of conflict of interest

None.

Address correspondence to: Pei-Sheng Wu, Department of Hepatobiliary and Pancreatic Surgery, The First People's Hospital of Qinzhou, No. 8 Mingyang Street, Qinnan District, Qinzhou 535000, Guangxi, China. Tel: +86-0777-2833419; E-mail: peishengwu2023@163.com

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