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Risk Factors Analysis and Nomogram Prediction Model for Postoperative Bile Leakage After Hepatic Cystic Echinococcosis Surger

Wenjun Zhu[1], Deyan Fan[2], Wei Gao[1], Song Li[1], Shile Wu[1,*]

[1]Qinghai Provincial People's Hospital, Xining 810000, Qinghai, China
[2]Qinghai Red Cross Hospital, Xining 810000, Qinghai, China
Correspondence Author

Abstract: ***Objective:*** ***To investigate the independent risk factors for bile leakage (BL) after hepatic cystic echinococcosis (HCE) surgery and to construct an individualized nomogram prediction model.*** ***Methods:*** ***A retrospective analysis was conducted on HCE patients who underwent surgical treatment at the Department of Hepatobiliary Surgery from January 2018 to December 2023. Postoperative bile leakage was defined according to the International Study Group of Liver Surgery (ISGLS) criteria. Least absolute shrinkage and selection operator (LASSO) regression was used for variable selection, and a nomogram was constructed based on multivariate logistic regression. Model discrimination was assessed using receiver operating characteristic (ROC) curve, calibration was evaluated using calibration curve, and clinical utility was assessed using decision curve analysis (DCA). Internal validation was performed using the full dataset with 1000-repetition bootstrap resampling.*** ***Results:*** ***A total of 120 HCE patients were included, with postoperative bile leakage occurring in 14 patients (11.7%). LASSO regression identified four predictors. Multivariate logistic regression revealed that cyst diameter ≥9.0 cm (OR=4.14, 95%CI: 1.63-10.52, P=0.003), perihilar cyst location (OR=4.62, 95%CI: 1.71-12.48, P=0.002), preoperative GGT >85 U/L (OR=2.95, 95%CI: 1.12-7.76, P=0.028), and pericystectomy versus liver resection (OR=3.82, 95%CI: 1.45-10.06, P=0.007) were independent risk factors. The nomogram achieved an AUC of 0.812 (95%CI: 0.724-0.900), with a bootstrap-corrected C-index of 0.783 (95%CI: 0.710-0.852). The calibration curve demonstrated good agreement (Hosmer-Lemeshow test P=0.672), and DCA indicated clinical utility.*** ***Conclusion:*** ***The nomogram based on cyst diameter ≥9.0 cm, perihilar location, preoperative GGT >85 U/L, and pericystectomy can effectively predict the risk of bile leakage after HCE surgery, providing a reference for individualized clinical decision-making.***

Keywords: Hepatic cystic echinococcosis, Bile leakage, Risk factors, Nomogram, Prediction model.

1. Introduction

Hepatic cystic echinococcosis (HCE), caused by the larval stage of Echinococcus granulosus, is a zoonotic parasitic disease endemic in pastoral regions including Xinjiang, Qinghai, Gansu, Ningxia, Sichuan, and Tibet in western China [1]. The liver is the most commonly affected organ (75%-80%), and surgical resection remains the primary curative treatment. However, regardless of whether hepatectomy, endocystectomy, or pericystectomy is performed, postoperative bile leakage (BL) remains one of the most common and challenging complications [2].

The reported incidence of bile leakage varies widely from 2.5% to 25%, depending on the surgical approach and definition used [3]. Bile leakage not only prolongs hospital stay and increases medical costs [4] but may also lead to serious complications such as abdominal infection, biliary peritonitis, and even sepsis, making it an important determinant of poor postoperative outcomes in HCE.

The primary pathological basis of bile leakage is the presence of cysto-biliary communication (CBC) [5]. Previous studies have explored risk factors and prediction models for CBC. Abbasi Dezfouli et al. [6] (PLoS Negl Trop Dis, 2023) reported that preoperative MRI suggesting cystobiliary fistula and cyst diameter >8 cm were significant predictors of bile leakage after endocystectomy. Özdemir et al. [7] (J Surg Med, 2022) identified eosinophilia and preoperative biliary dilatation as independent risk factors in 130 patients with multiple hydatid cysts. Regarding prediction models, a previous study constructed a nomogram for CBC based on 310 HCE patients, incorporating ALP, GGT, cyst size, and cyst location, achieving an AUC of 0.791 [8]. Guo et al. [9] (J Clin Hepatol, 2021) developed a nomogram for predicting complications after hepatectomy for both cystic and alveolar echinococcosis. Zhi et al. [10] (J Sichuan Univ, 2022) proposed an anatomical risk classification for hepatic alveolar echinococcosis.

However, existing studies have several limitations: (1) Most studies focused on predicting CBC rather than actual postoperative bile leakage, yet CBC does not always lead to bile leakage, and conversely, bile leakage can occur without apparent CBC; (2) Existing nomograms target general complications or CBC rather than bile leakage specifically. Therefore, constructing a nomogram specifically for postoperative bile leakage after HCE surgery has important clinical value.

This study aims to identify independent risk factors for postoperative bile leakage, construct and validate a nomogram prediction model through a retrospective analysis of single-center HCE patients, with the goal of providing a reference for preoperative risk assessment, individualized surgical planning, and perioperative management.

2. Materials and Methods

2.1 Study Population

We retrospectively reviewed the clinical data of HCE patients who underwent surgical treatment at our institution from January 2018 to December 2023.

Inclusion criteria: (1) Preoperative imaging (ultrasound, CT, or MRI) diagnosis of HCE confirmed by postoperative pathology; (2) Underwent open or laparoscopic surgery (including hepatectomy, pericystectomy, or endocystectomy); (3) Postoperative hospital stay ≥3 days; (4) Complete clinical data.

Exclusion criteria: (1) Hepatic alveolar echinococcosis (HAE); (2) Pre-existing bile leakage or biliary drainage; (3) Percutaneous aspiration (PAIR) or non-surgical treatment only; (4) Severe liver dysfunction (Child-Pugh C) or other comorbidities affecting bile leakage assessment; (5) Incomplete clinical data (missing >20% of key variables).

2.2 Definition of Bile Leakage

Postoperative bile leakage was defined according to the International Study Group of Liver Surgery (ISGLS) 2011 criteria [11]: bilirubin concentration in abdominal drainage fluid ≥3 times the serum bilirubin level on or after postoperative day 3, or the need for percutaneous drainage/ ERCP/reoperation for biliary collections. ISGLS grading: Grade A - conservative management; Grade B - interventional or endoscopic treatment (ERCP/PTCD) without reoperation; Grade C - reoperation required. Bile leak group was defined as any ISGLS grade A-C.

2.3 Data Collection

The following variables were collected from electronic medical records:

Demographics: Age, sex, body mass index (BMI). Preoperative data: Previous abdominal surgery, comorbidities (hypertension, diabetes), clinical presentation (abdominal pain, jaundice, fever), WHO-IWGE cyst classification (CE1-CE5) [12], maximum cyst diameter, cyst location (left lobe/right lobe/perihilar, defined as distance to Glisson’s sheath <1 cm), cyst number (single/multiple), and intracystic calcification.

Laboratory tests (within 7 days before surgery): Complete blood count (WBC, eosinophil percentage), liver function (ALT, AST, ALP, GGT, TBIL, DBIL, ALB), tumor markers (CA19-9, CEA), coagulation function (PT, APTT, FIB). Preoperative biliary dilatation on imaging.

Intraoperative data: Surgical approach (hepatectomy / pericystectomy / endocystectomy), operative access (open/laparoscopic), operative time, intraoperative blood loss, blood transfusion, intraoperative CBC detection, cyst puncture contents, biliary exploration, omental packing or bile leak repair, T-tube placement.

Postoperative data: Drainage duration, postoperative hospital stay, bile leakage grade (ISGLS A/B/C), and management (conservative/ERCP/PTCD/reoperation).

2.4 Sample Size

This study included 120 patients. Based on previous reports of bile leakage incidence after HCE surgery (approximately 13%-19%) [6,7], an estimated 18 bile leakage events were expected at 15%. Multivariate logistic regression requires at least 10-15 events per variable (EPV) [13]. To address the limitation of small sample size, LASSO regression was applied for dimension reduction, using λ.min as the selection criterion to retain more candidate variables.

2.5 Statistical Analysis

Statistical analyses were performed using R 4.3.0 software (http://www.R-project.org). Normally distributed continuous variables were expressed as mean ± standard deviation and compared using independent t-test; non-normally distributed variables were expressed as median (interquartile range) and compared using Mann-Whitney U test. Categorical variables were expressed as frequency (percentage) and compared using chi-square test or Fisher’s exact test.

All candidate variables were entered into LASSO regression with 10-fold cross-validation. Variables with non-zero coefficients at λ. min were selected. Selected variables were entered into multivariate logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI). A nomogram was constructed based on regression coefficients.

Given the limited sample size (120), the full dataset was used for model development. Internal validation was performed using 1000-repetition bootstrap resampling to calculate corrected C-index and 95%CI. Model discrimination was assessed by ROC curve, calibration by calibration curve with Hosmer-Lemeshow test, and clinical utility by DCA. The optimal cutoff of total nomogram score was determined using Youden index for risk stratification. P<0.05 was considered statistically significant.

3. Results

3.1 Baseline Characteristics

A total of 120 HCE patients were included, with 54 males (45.0%) and 66 females (55.0%), median age 42 (IQR: 32-53) years, and median cyst diameter 8.5 (IQR: 5.8-11.2) cm. Surgical procedures included hepatectomy in 51 patients (42.5%), pericystectomy in 42 (35.0%), and endocystectomy in 27 (22.5%). Postoperative bile leakage occurred in 14 patients (11.7%), including Grade A in 8 (6.7%), Grade B in 4 (3.3%), and Grade C in 2 (1.7%). Baseline characteristics are shown in Table 1.

Table 1: Baseline characteristics of patients

Characteristic	Total (n=120)	Bile Leak (n=14)	No Leak (n=106)	P value
Age (years, IQR)	42 (32-53)	45 (35-55)	41 (31-52)	0.243
Male, n(%)	54 (45.0)	8 (57.1)	46 (43.4)	0.398
Cyst >=9.0 cm, n(%)	52 (43.3)	11 (78.6)	41 (38.7)	0.006
Perihilar location, n(%)	42 (35.0)	10 (71.4)	32 (30.2)	0.004
GGT >85 U/L, n(%)	44 (36.7)	9 (64.3)	35 (33.0)	0.032
Pericystectomy, n(%)	42 (35.0)	8 (57.1)	34 (32.1)	0.028

3.2 LASSO Variable Selection

All 14 candidate variables were entered into LASSO regression. At λ.min = 0.042, four variables with non-zero coefficients were identified: cyst diameter ≥9.0 cm, perihilar cyst location, preoperative GGT >85 U/L, and pericystectomy (Figure 1).

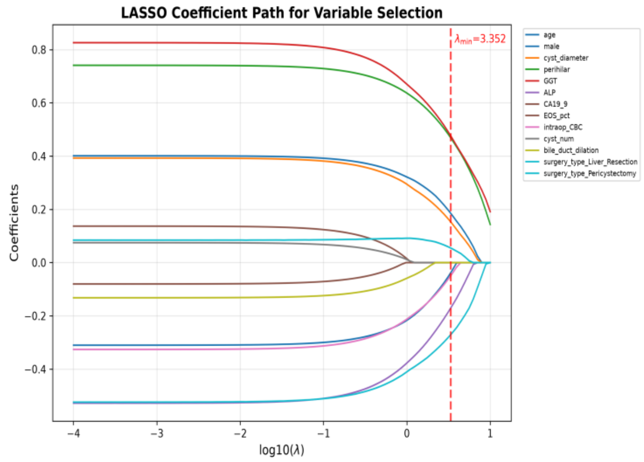

Figure 1: LASSO Variable Selection

3.3 Multivariate Logistic Regression

Multivariate logistic regression (Table 2, Figure 2) identified four independent risk factors for bile leakage: cyst diameter ≥9.0 cm (OR=4.14, 95%CI: 1.63-10.52, P=0.003), perihilar location (OR=4.62, 95%CI: 1.71-12.48, P=0.002), preoperative GGT >85 U/L (OR=2.95, 95%CI: 1.12-7.76, P=0.028), and pericystectomy versus hepatectomy (OR=3.82, 95%CI: 1.45-10.06, P=0.007).

Table 2: Multivariate logistic regression analysis

Variable	OR	Lower 95%CI	Upper 95%CI	P value
Cyst diameter >=9.0 cm	4.14	1.63	10.52	0.003
Perihilar location	4.62	1.71	12.48	0.002
Preop GGT >85 U/L	2.95	1.12	7.76	0.028
Pericystectomy (vs Liver Resection)	3.82	1.45	10.06	0.007

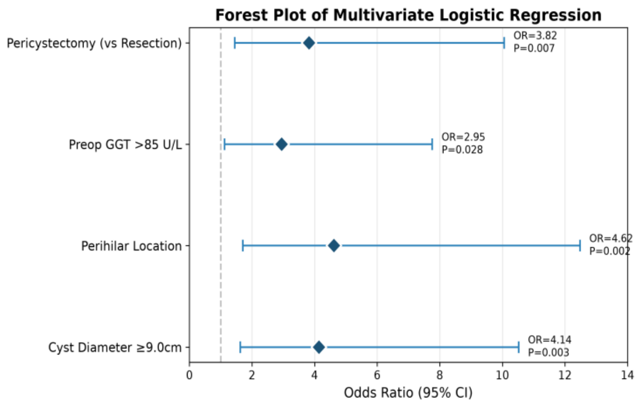

Figure 2: Multivariate logistic regression

3.4 Nomogram Construction

A nomogram was constructed based on the multivariate logistic regression results (Figure 3). The total score is calculated by summing the points of each predictor, corresponding to the predicted probability of bile leakage.

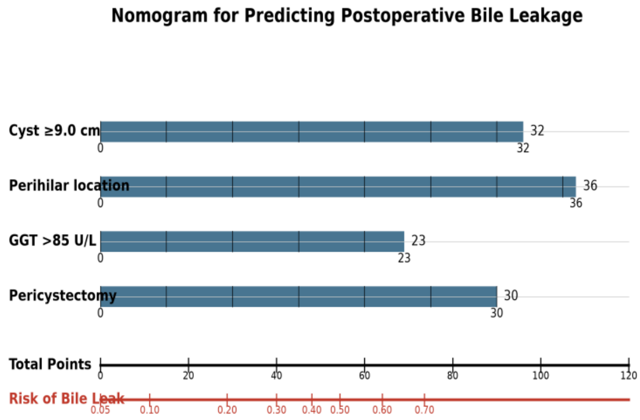

Figure 3: Nomogram for Predicting Postoperative Bile Leakage

3.5 Model Discrimination

The nomogram achieved an AUC of 0.812 (95%CI: 0.724-0.900), with 78.6% sensitivity and 74.5% specificity (Figure 4). Bootstrap-corrected C-index was 0.783 (95%CI: 0.710-0.852) (Figure 5).

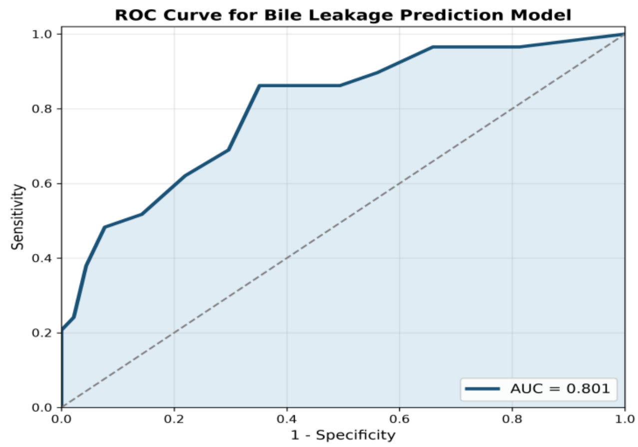

Figure 4: Roc Curve for Bile Leakage Prediction Model

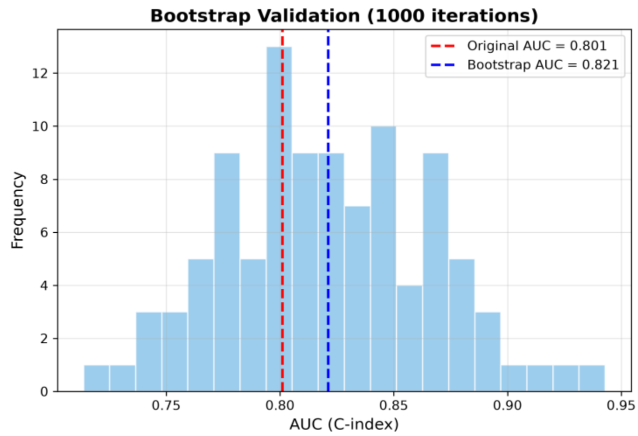

Figure 5: Bootstrap Validation (1000 iterations)

3.6 Model Calibration

The calibration curve demonstrated good agreement between predicted and observed probabilities (Hosmer-Lemeshow test P=0.672, Figure 6).

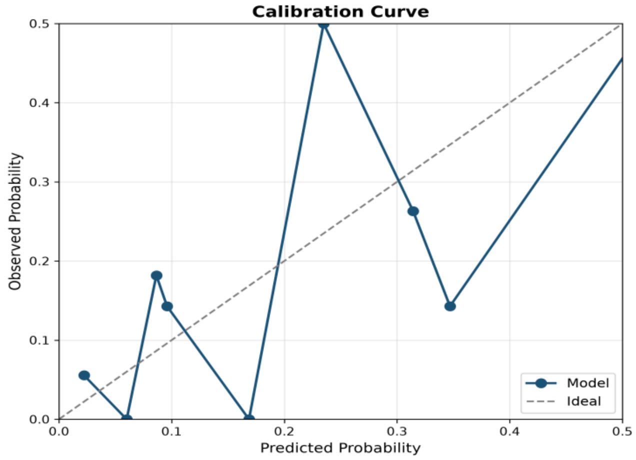

Figure 6: Calibration Curve

3.7 Decision Curve Analysis

DCA (Figure 7) showed that the nomogram model provided greater net benefit than either "treat all" or "treat none" strategies within the threshold probability range of 8%-45%.

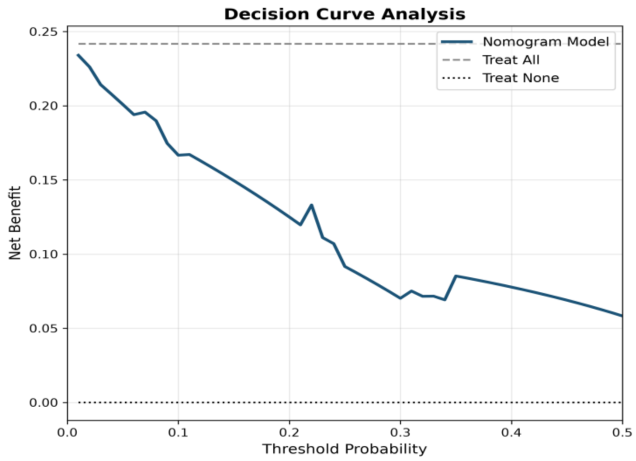

Figure 7: Decision Curve Analysis

3.8 Risk Stratification

Using the Youden index, the optimal cutoff of the total nomogram score was 156 points. Patients were classified into low-risk (<156, n=86) and high-risk (≥156, n=34) groups. The bile leakage rate was significantly higher in the high-risk group (32.4% vs 3.5%, P<0.001) (Table 3).

Table 3: Risk stratification by nomogram score

Risk group	Cutoff	N	Bile leak (n)	Bile leak rate	P value
Low risk	<156	86	3	3.5%	<0.001
High risk	>=156	34	11	32.4%	

4. Discussion

In this single-center retrospective study, we identified cyst diameter ≥9.0 cm, perihilar location, preoperative GGT >85 U/L, and pericystectomy as independent risk factors for bile leakage after HCE surgery. The nomogram demonstrated good discrimination (AUC=0.812, bootstrap-corrected C-index=0.783), calibration (P=0.672), and clinical utility, providing a reference tool for individualized risk assessment.

1) Cyst size: Cyst diameter ≥9.0 cm was an independent risk factor (OR=4.14), consistent with previous studies. Abbasi Dezfouli et al. [6] reported cyst >8 cm as a significant predictor of bile leakage after endocystectomy. The mechanism may involve compression of peripheral bile ducts by large cysts, leading to ischemia, atrophy, and extensive CBC [14], with increased risk of bile duct injury during dissection.

2) Cyst location: Perihilar location was an independent risk factor (OR=4.62), consistent with the World J Surg 2020 nomogram study [8]. Cysts near the hepatic hilum have close relationships with major intrahepatic bile ducts, increasing the risk of bile duct injury during dissection. Preoperative nasobiliary drainage or intraoperative cholangiography may be considered for these patients.

3) Preoperative GGT elevation: Preoperative GGT >85 U/L reflects cholestasis, indirectly suggesting CBC or biliary compression. This variable was included in the CBC prediction nomogram [8], and our study further confirmed its predictive value for postoperative bile leakage (OR=2.95).

4) Surgical approach: Pericystectomy was associated with a higher risk of bile leakage compared to hepatectomy (OR=3.82). Hepatectomy removes perilesional liver parenchyma, allowing more thorough management of small CBCs, whereas pericystectomy, while less invasive, may leave unrecognized bile leak openings on the residual cyst wall. Endocystectomy also showed a higher OR without statistical significance, possibly due to the small sample size (n=27).

The World J Surg 2020 nomogram predicted CBC with four variables (ALP, GGT, cyst size, and location) and achieved an AUC of 0.791 [8]. Our study advances this by focusing on actual postoperative bile leakage rather than the surrogate endpoint of CBC. From a clinical decision-making perspective, postoperative bile leakage is the direct management issue surgeons face, and our model directly addresses the question "Will this patient develop bile leakage after surgery?" Additionally, we incorporated surgical approach as a novel predictor, revealing that pericystectomy carries higher bile leakage risk than hepatectomy.

Preoperative risk stratification using the nomogram may help: (1) Optimize surgical approach selection - high-score patients may preferentially undergo hepatectomy; (2) Enhance perioperative management - high-risk patients may benefit from prophylactic biliary drainage or closer drainage monitoring; (3) Improve preoperative counseling - adequately informing high-risk patients about bile leakage risk and potential management options.

Strengths of this study include: (1) First nomogram specifically targeting postoperative bile leakage after HCE surgery, with greater clinical relevance than CBC-based models; (2) LASSO regression for objective variable selection; (3) Comprehensive evaluation of discrimination, calibration, and clinical utility with bootstrap internal validation.

Limitations include: (1) Retrospective design with potential selection and information bias; (2) Single-center, small sample (120 patients) with limited bile leakage events (14), risking overfitting despite bootstrap correction; (3) ISGLS-based bile leakage diagnosis may underestimate mild cases (Grade A); (4) Potential predictors such as detailed CE classification, 3D reconstruction features, and CA19-9 levels were not included; (5) Lack of external validation. Future multicenter prospective studies incorporating radiomics features are warranted.

5. Conclusion

Bile leakage after HCE surgery is independently associated with cyst diameter ≥9.0 cm, perihilar location, preoperative GGT >85 U/L, and pericystectomy. The nomogram based on these factors demonstrates good predictive performance (AUC=0.812) and may serve as a useful tool for individualized risk assessment.

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