Risk Prediction for Early Biliary Infection after Percutaneous Transhepatic Biliary Stent Placement in Malignant Biliary Obstruction

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ABSTRACT

Purpose: To establish a nomogram for predicting the occurrence of early biliary infection (EBI) after percutaneous transhepatic biliary stent (PTBS) placement in malignant biliary obstruction (MBO).

Materials and Methods: In this multicenter study, patients treated with PTBS for MBO were allocated to a training cohort or a validation cohort. The independent risk factors for EBI selected by multivariate analyses in the training cohort were used to develop a predictive nomogram. An artificial neural network was applied to assess the importance of these factors in predicting EBI. The predictive accuracy of this nomogram was determined by concordance index (c-index) and a calibration plot, both internally and externally.

Results: A total of 243 patients (training cohort: n = 182; validation cohort: n = 61) were included in this study. The independent risk factors were length of obstruction (odds ratio [OR], 1.061; 95% confidence interval [CI], 1.013–1.111; $P = .012$), diabetes (OR, 5.070; 95% CI, 1.917–13.412; $P = .001$), location of obstruction (OR, 2.283; 95% CI, 1.012–5.149; $P = .047$), and previous surgical or endoscopic intervention (OR, 3.968; 95% CI, 1.709–9.217; $P = .001$), which were selected into the nomogram. The c-index values showed good predictive performance in the training and validation cohorts (0.792 and 0.802, respectively). The optimum cutoff value of risk was 0.25.

Conclusions: The nomogram can facilitate the early and accurate prediction of EBI in patients with MBO who underwent PTBS. Patients with high risk (> 0.25) should be administered more effective prophylactic antibiotics and undergo closer monitoring.

ABBREVIATIONS

ANN = artificial neural network, c-index = concordance index, CI = confidence interval, EBI = early biliary infection, ERCP = endoscopic retrograde cholangiopancreatography, ^{125}I = iodine-125, MBO = malignant biliary obstruction, OR = odds ratio, PTBD = percutaneous transhepatic biliary drainage, PTBS = percutaneous transhepatic biliary stent, RPEBI = Risk Prediction for Early Biliary Infection

Malignant biliary obstruction (MBO) is caused by known malignant neoplastic obstruction of the biliary tract (cholangiocarcinoma, gallbladder carcinoma, or ampullary carcinoma), pancreatic cancer, or metastases. Percutaneous transhepatic biliary stent (PTBS) placement is a common palliative treatment for unresectable MBO. With the widespread use of biliary stents, early biliary infection (EBI) is one of the most common and intractable complications of

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Appendix A, Appendix B, Figure E1, and Tables E1 and E2 can be found by accessing the online version of this article on *www.jvir.org* and clicking on the Supplemental Material tab.

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biliary intervention (1–6). EBI refers to early infectious complications occurring within 30 days after biliary intervention, including cholangitis, cholecystitis, liver abscess, and other infections related to the biliary system (7). According to the reported literature (7,8) and guidelines (9,10), EBI after PTBS is defined as biliary infection within 30 days after PTBS by leukocytosis, fever (>38°C), exacerbation of jaundice or epigastric pain, and exclusion of the presence of other infections, plus positive bile culture or imaging findings of biliary inflammation. Biliary infection is a serious and life-threatening infectious disease, and according to the 2013 Tokyo Guideline, the fatality rate of acute cholangitis has been reported to range from 2.7% to 10% (3).

The risk factors for biliary infection after percutaneous transhepatic biliary drainage (PTBD), endoscopic biliary stent placement, or biliary surgery are reported in previous studies (7,8,11–18). Studies done in settings other than PTBS have shown some risk factors associated with biliary infection; these previous results were the basis for this study, in which PTBS will be investigated.

Although PTBS has been widely used for patients with MBO, there is no tool to predict the common complication of biliary infection for early management. Researchers have made efforts to find possible risk factors for biliary infection, but this calls for additional studies to evaluate risk factors for EBI after PTBS and possibly establish a model for risk prediction.

Thus, the aim of this study was to assess pre-procedural independent risk factors and to establish a "Risk Prediction for Early Biliary Infection" (RPEBI) nomogram for patients with MBO who underwent PTBS.

MATERIALS AND METHODS

Patients

This multicenter retrospective study was approved by the institutional review boards at all 3 participating centers. The need for informed consent was waived due to the study's retrospective nature. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institutions' human research committees.

A total of 142 patients in the training cohort were part of a prior phase III randomized controlled trial (19) and were included between October 2013 and March 2016. Other patients not included in the prior study decided to choose irradiation stent or conventional stent for themselves. Therefore, patient selection was not randomized in this study.

From January 2012 to December 2016, 242 consecutive patients successfully received PTBS for MBO in 3 centers; 60 patients were excluded, and 182 patients were included in a training cohort. From January 2017 to August 2017, 75 consecutive patients received PTBS for MBO in 2 centers; 14 patients were excluded, and 61 patients were included in the validation cohort. Patients included in this study met the following criteria: (a) 18 years or older; (b) clinical or histopathologic diagnosis was MBO; and (c) stent placement was performed the first time, and prior biliary drainage (pre-PTBD) was allowed. Patients were excluded from this study for the following reasons: (a) EBI occurred before PTBS; (b) organ failure was present before PTBS; (c) any surgery was performed within 1 month before PTBS; (d) death within 30 days after PTBS due to a cause other than EBI; (e) infections in other systems, such as lung infection, urinary tract infection. and gastrointestinal infection, were present in before EBI; and (f) clinical data were missing before or 30 days after PTBS.

Data Collection

The study data were collected as follows: (a) demographics, such as age, gender, body mass index, and pre-procedural Eastern Cooperative Oncology Group scores; (b) laboratory test results; and (c) parameters related to MBO, such as location of obstruction (low or high level). High-level obstruction is located at or above the common hepatic duct, which means hilar or intrahepatic obstruction. Low-level obstruction is distal obstruction located below the insertion of the cystic duct, which involves the common bile duct (20). Data collection is discribed in detail in **Appendix A** (available online on the article's Supplemental Material page at *www.jvir.org*).

PTBS Procedure

Before stent placement, the site and length of the obstruction were measured by PTBS operators based on magnetic resonance cholangiopancreatography and/or contrast-enhanced computed tomography with multiplanar reconstruction. A standard PTBS procedure was performed under fluoroscopic and ultrasonic guidance by experienced interventional radiologists (M.H., J.-S.J., and J.-H.G. with > 20 years of experience). An external drainage catheter was placed after stent insertion and removed 2 weeks later if the stent retained patency.

As described in the previous study (19), the irradiation stent was a metal biliary stent loaded with iodine-125 (^{125}I) seeds (CIAE-6711; Chinese Atomic Energy Science Institution, Beijing, China), which was designed in 2 separate parts: an outer self-expandable ^{125}I radioactive seed-loaded stent (Nanjing Micro-Invasive Medical Inc, Nanjing, China) and an inner bare self-expanding biliary nitinol alloy stent (Nanjing Micro-Invasive Medical Inc). The conventional biliary stent was the same bare self-expandable biliary nitinol alloy stent used as the inner part of the ^{125}I seed-loaded biliary stent (Nanjing Micro-Invasive Medical Inc). The prior report compared the efficacies of the 2 kinds of stents and showed no difference in the incidence of biliary infection between them. Therefore, the type of stent may not affect the results.

The length of the stent depended on the individual lesion, and balloon dilatation was selectively used. Routine bile culture was performed during the first biliary puncture. Prophylactic antibiotics administration occurred within 1

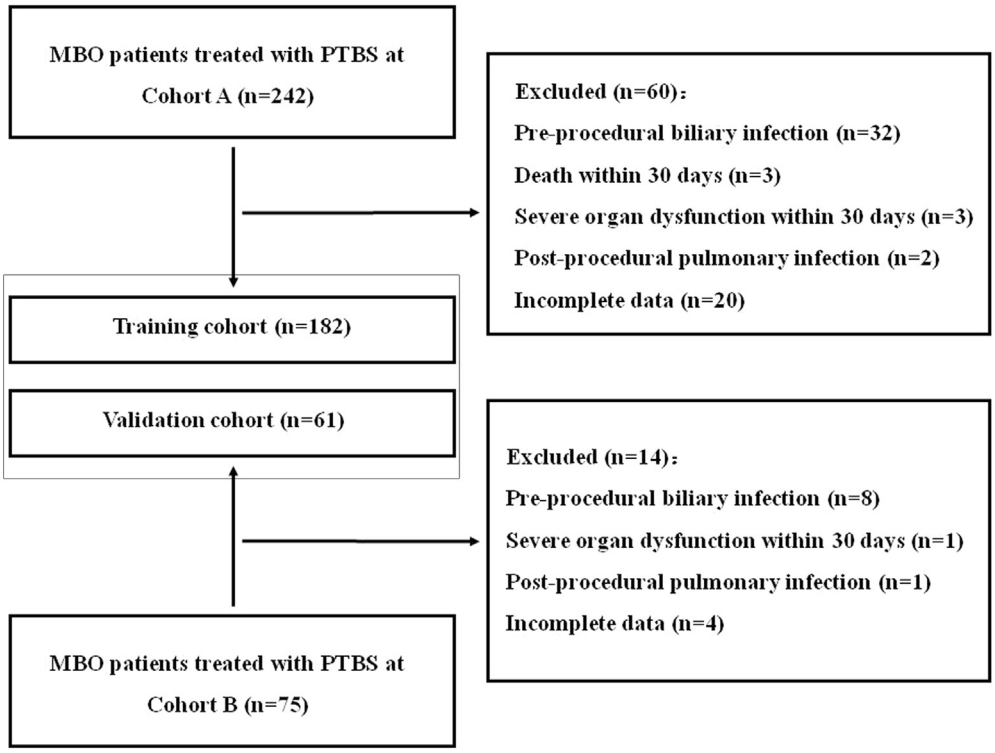

Figure 1. Flowchart showing patient selection.

hour, followed immediately by PTBS (**Appendix B** [available online on the article's Supplemental Material page at *www.jvir.org*]). Patients were followed up for 30 days after the PTBS procedure in this study.

Statistical Analysis

For the training sample size, at least 10 events per-predictor variable were required to produce reasonably stable estimates (21–23). Four features were selected for the final model in this study, and the minimum training data size was 178, with 40 events and 138 non-events. For the validation sample size, a power calculation to estimate the sample size was performed in PASS 15 (NCSS, LLC, Kaysville, Utah), and the minimum sample size was 50, with 10 events and 40 non-events (24,25). In this study, the numbers in the training and validation cohorts were 182 (41 events; 141 non-events) and 61 (11 events; 50 non-events), respectively, which were sufficient.

Statistical analysis was performed using SPSS version 22.0 software (IBM Corporation, Somers, New York). Continuous variables are described as medians and interquartile ranges, and categorical variables are described as numbers and percentages. The data were examined by Student's *t*-test or the Mann-Whitney *U* test for continuous variables and by Pearson's chi-squared test or Fisher's exact test for categorical variables. All of the variables that showed statistical significance in the univariate analysis were used in multivariate logistic regression analysis to identify predictors in the training cohort. The enter method was performed to find the odds ratios (ORs) with 95% confidence intervals (CIs) and the relationships of each variable in the multivariate analysis. A P value $< .05$ was considered statistically significant.

The RPEBI nomogram was formulated in the training cohort based on the results of the multivariate analysis and by the regression modeling strategies in the R package (version 3.4.3; R Package for Statistical Computing; www.r-project.org). After establishing the RPEBI nomogram, the concordance index (c-index) and a calibration plot were applied to validate the accuracy and discriminative capacity of this nomogram internally (in the training cohort) and externally (in the validation cohort) in the R package. The c-index was calculated as the area under the receiver operating characteristic curve, which was used to assess prediction performance in the risk model. The calibration plot, also known as the standard curve, was used for showing agreement between prediction and observation. The optimum cutoff value for clinical use was determined by maximizing the Youden index (sensitivity + specificity−1). An artificial neural network (ANN) model established with SPSS 22.0 compared the importance and the standardized importance among the independent risk factors.

RESULTS

Patient Characteristics and Clinical Outcomes

A total of 182 patients were included in the training cohort; 61 patients were included in the validation cohort (**Fig 1**).

Table 1. Patient Characteristics

Characteristics	Training cohort (n = 182)	Validation cohort (n = 61)	*P* Value
Gender, No. (%)			.842
Male	113 (62.1)	37 (60.7)	
Female	69 (37.9)	24 (39.3)	
Age, Median (IQR), years	64.5 (57.0–75.3)	69.0 (60.0–77.0)	.131
BMI, Median (IQR), kg/m^2	20.63 (19.03–22.23)	20.32 (18.62–22.51)	.781
Biliary infection, No. (%)			.459
Yes	41 (22.5)	11 (18.0)	
No	141 (77.5)	50 (82.0)	
ECOG score, No. (%)			.841
0	6 (3.3)	3 (4.9)	
1	28 (15.4)	11 (18.0)	
2	75 (41.2)	22 (36.1)	
3	73 (40.1)	25 (41.0)	
Child-Pugh classification, No. (%)			.054
A	8 (4.4)	8 (13.1)	
B	150 (82.4)	47 (77.1)	
C	24 (13.2)	6 (9.8)	
Accompanying disease, No. (%)			
Diabetes			.626
Yes	28 (15.4)	11 (18.0)	
No	154 (84.6)	50 (82.0)	
Gallstones			.672
Yes	23 (12.6)	9 (14.8)	
No	159 (87.4)	52 (85.2)	
Pre-procedural PTBD, No. (%)			.227
Yes	134 (73.6)	40 (65.6)	
No	48 (26.4)	21 (34.4)	
Location of obstruction, No. (%)			.680
High	81 (44.5)	29 (47.5)	
Low	101 (55.5)	32 (52.5)	
Tumor etiology, No. (%)			.411
Biliary tract cancer	81 (44.5)	33 (54.1)	
Pancreatic carcinoma	58 (31.9)	17 (27.9)	
Metastases	43 (23.6)	11 (18.0)	
Length of obstruction, Median (IQR), mm	35 (30–40)	35 (30–45)	.289
Prior surgical or endoscopic intervention, No. (%)			.218
Yes	45 (24.7)	20 (32.8)	
No	137 (75.3)	41 (67.2)	
Chemotherapy, No. (%)			.177
Yes	41 (22.5)	19 (31.1)	
No	141 (77.5)	42 (69.9)	
Radiotherapy, No. (%)			.629
Yes	17 (9.3)	7 (11.5)	
No	165 (90.7)	54 (88.5)	
Stent types, No. (%)			.369
Irradiation stent	113(62.1)	23(56.1)	
Conventional stent	69(37.9)	18(43.9)	
WBC, Median (IQR), $\times 10^9$/L	6.61 (5.15-9.13)	6.31 (4.55-8.06)	.164
GLU, Median (IQR), mmol/L	5.72 (5.12–6.27)	5.41(4.88–6.53)	.357
TB, Median (IQR), umol/L	206.35 (123.90–306.63)	174.50 (113.40–248.00)	.134
DB, Median (IQR), umol/L	147.50 (86.60–223.40)	124.40 (73.85–183.45)	.129
ALB, Median (IQR), g/L	34.00 (29.10–37.50)	33.65 (30.03–36.98)	.867

ALB = albumin; BMI = body mass index; DB = direct bilirubin; ECOG = Eastern Cooperative Oncology Group; GLU = blood glucose; IQR = interquartile range; PTBD = percutaneous transhepatic biliary drainage; TB = total bilirubin; WBC = white blood cell.

Table 2. Univariate Analysis of Risk Factors for EBI after PTBS

Variables	OR	95% CI	*P* Value
Gender (female, male)	0.825	0.406–1.677	.595
Age, years	0.980	0.950–1.010	.190
BMI, kg/m^2	1.038	0.913–1.179	.572
ECOG score (0–1, 2-3) *	0.636	0.275–1.469	.289
Child-Pugh classification			
A	1		
B	1.974	0.234–16.624	.531
C	2.882	0.297–27.974	.361
Pre-procedural PTBD (no, yes)	0.398	0.190–0.832	.014
Diabetes (no, yes)	5.680	2.418–13.344	<.001
Gallstones (no, yes)	3.176	1.275–7.914	.013
Prior surgical or endoscopic intervention (no, yes)	5.119	2.409–10.875	<.001
Chemotherapy (no, yes)	1.598	0.727–3.511	.243
Radiotherapy (no, yes)	2.026	0.700–5.862	.193
Length of obstruction, mm	1.053	1.014–1.094	.008
Location of obstruction (low, high)	2.372	1.163–4.836	.018
Tumor etiology			
Biliary tract cancer	1		
Pancreatic carcinoma	0.480	0.186–1.240	.130
Metastases	2.074	0.922–4.664	.078
Stent types (conventional stent, irradiation stent)	0.724	0.357–1.467	.370
WBC, $\times 10^9$/L	1.021	0.925–1.128	.674
GLU, mmol/L	1.337	0.964–1.855	.082
TB, umol/L	1.000	0.998–1.003	.847
DB, umol/L	1.001	0.998–1.005	.524
ALB, g/L	0.975	0.913–1.042	.460

ALB = albumin; BMI = body mass index; CI = confidence interval; DB = direct bilirubin; EBI = early biliary infection; ECOG = Eastern Cooperative Oncology Group; GLU = blood glucose; OR = odds ratio; PTBD = percutaneous transhepatic biliary drainage; PTBS = percutaneous transhepatic biliary stent; TB = total bilirubin; WBC = white blood cell.
*The risk analysis could not be carried out due to the very small number of cases in both groups. Therefore, ECOG score 0–1 were merged in the same category, and ECOG score 2–3 were merged in the other category.

Patients excluded in this study are indicated with numbers and reasons (**Fig 1**). The baseline demographics of the patients in both the training and validation cohorts are described in detail (**Table 1**). The different types of EBI are displayed with numbers and percentages (**Table E1** [available online on the article's Supplemental Material page at *www.jvir.org*]).

Factors Related to EBI

The univariate analysis revealed that pre-procedural PTBD, diabetes, gallstones, previous surgical or endoscopic intervention, length of obstruction, and location of obstruction were the potential risk factors related to EBI (all $P < .05$; **Table 2**). Consequently, multivariate logistic regression analysis determined that the independent risk factors for EBI after PTBS in patients with MBO were length of obstruction (OR, 1.061; 95% CI, 1.013–1.111; $P = .012$), diabetes (OR, 5.070; 95% CI, 1.917–13.412; $P = .001$), location of obstruction (OR, 2.283; 95% CI, 1.012–5.149; $P = .047$), and previous surgical or endoscopic intervention (OR, 3.968; 95% CI, 1.709–9.217; $P = .001$) (**Table 3**).

Table 3. Multivariate Analysis of Risk Factors for EBI after PTBS

Variables	OR (95% CI)	B Value	*P* Value
Length of obstruction, mm	1.061 (1.013–1.111)	0.059	.012
Diabetes			
No	1		
Yes	5.070 (1.917–13.412)	1.623	.001
Location of obstruction			
Low	1		
High	2.283 (1.012–5.149)	0.825	.047
Prior surgical or endoscopic intervention			
No	1		
Yes	3.968 (1.709–9.217)	1.378	.001

CI = confidence interval; EBI = early biliary infection; OR = odds ratio; PTBS = percutaneous transhepatic biliary stent.

Development and Validation of the Nomogram

Based on these 4 factors, the RPEBI nomogram was established to evaluate the risk for EBI earlier in patients with MBO who underwent PTBS (**Fig 2**). According to internal validation, the c-index of the RPEBI nomogram in the training cohort was 0.792 (**Fig 3a**), and the calibration plot showed no significant difference between prediction by nomogram and actual observation ($P = .975$; **Fig 4a**). According to external validation, the c-index of the RPEBI nomogram in the validation cohort was 0.802 (**Fig 3b**), and the calibration plot also showed no significant difference between prediction and observation ($P = .206$; **Fig 4b**).

Establishment of an ANN Model

The importance and standardized importance of each variables were shown as follows: length of obstruction (0.439; 100%), diabetes (0.269; 61.2%), previous surgical and endoscopic intervention (0.168; 38.3%), and location of obstruction (0.123; 28.0%) (**Fig 5**). According to the ANN model, length of obstruction was the most important factor of these 4 independent risk factors.

Clinical Use

According to the maximized Youden index, the optimum cutoff value of risk was 0.25, and the cutoff total score was

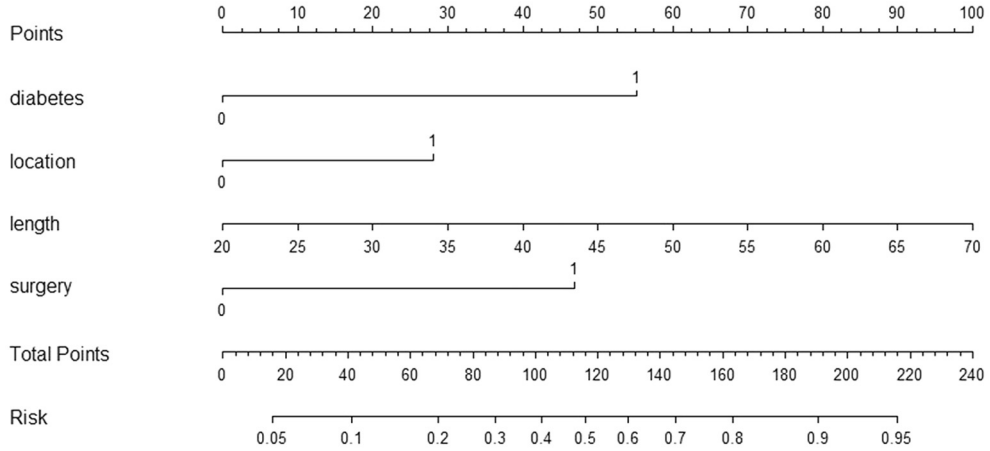

Figure 2. The RPEBI nomogram for EBI in patients with MBO who underwent PTBS. To use the nomogram, the user locates an individual patient's value on each variable axis and draws a line upward to determine the number of points received for each variable value. The sum of these numbers is located on the axis of total points, and a line is drawn downward to the risk axes to determine the likelihood of EBI. In this nomogram, a patient with diabetes is shown as 1 and without is 0; location of obstruction with high level is 1 and with low level is 0; length of obstruction is shown as value in millimeters (mm); and a patient with surgery, meaning previous surgical or endoscopic intervention, is shown as 1 and without as 0.

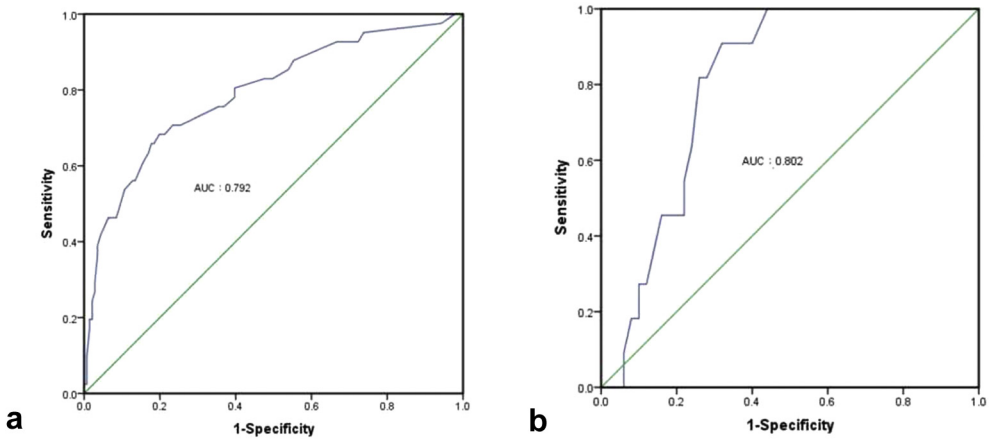

Figure 3. Receiver operating characteristics curve analysis for the RPEBI nomogram in the training and validation cohorts. The area under the curve (c-index) in the training cohort is 0.792 (**a**); the area under the curve (c-index) in the validation cohort is 0.802 (**b**).

78 points. A patient had a high possibility for EBI with a predicted risk > 0.25, and a low risk was ≤ 0.25. In the training cohort, the high-risk group had significantly more EBI patients than the low-risk group ($P < .001$) (**Fig E1** [available online on the article's Supplemental Material page at *www.jvir.org*]). The sensitivity, specificity, positive predictive value, and negative predictive value using this cutoff for predicting EBI in the training cohort were 68.3%, 80.1%, 50.0%, and 89.7%, and those of the validation cohort were 81.8%, 72.0%, 39.1%, and 94.7%, respectively (**Table E2** [available online on the article's Supplemental Material page at *www.jvir.org*]).

DISCUSSION

It is challenging to reduce the incidence of biliary infection after PTBS, but it is possible to predict the risk of biliary infection. Due to the lack of a tool to predict biliary infection earlier and objectively before interventions, the RPEBI nomogram was established in this study and performed well in predicting the risk of EBI based on independent preprocedural risk factors. The following scenario was introduced to use this RPEBI nomogram. A patient with MBO who underwent PTBS has diabetes (55 points), digestive surgery history (48 points), low-level obstruction (0 points), and an obstruction length of 60 mm (80 points). The total points are 183 (> 78 points), and the risk is 0.87 (> 0.25) on the nomogram. He is in the high-risk group for EBI, and broad-spectrum antibiotics, covered both Gram-negative and anaerobic organisms, should be taken before PTBS. Additionally, closer monitoring should be conducted, including body temperature, inflammatory biochemical indexes, imaging examination, and bile culture.

The 4 risk factors contributing to the RPEBI nomogram were diabetes, prior endoscopic and surgical intervention, location of obstruction, and length of obstruction. First, a previous study reported that diabetes indicates a higher risk of infection and great difficulty in controlling infection (26).

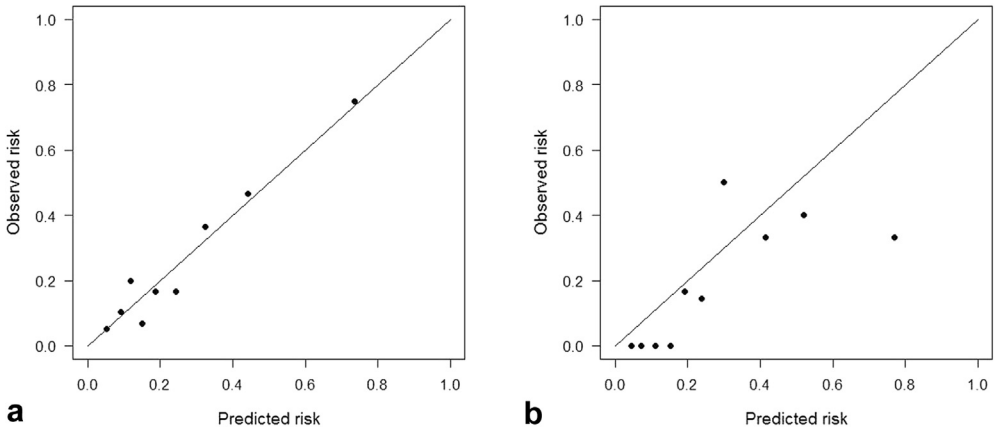

Figure 4. Calibration plot for the RPEBI nomogram in the training and validation cohorts. The calibration plot shows good agreement between prediction and observation in both the training cohort (**a**, $P = .975$) and the validation cohort (**b**, $P = .206$).

Pessaux et al (27) developed a model to predict postoperative infection complications after hepatectomy, and diabetes was an important risk factor (OR [95% CI]: 2.4 [1.3–4.5]). Some studies also showed the association between diabetes and biliary infection after biliary interventions (13,18). Related research has reported possible mechanisms (28,29). Second, it is already known that the risk of EBI may be increased due to endoscopic retrograde cholangiopancreatography (ERCP) and hepatobiliary surgeries (15,30,31), which result from the bacterial entry into obstructed biliary system and the damage to physiological barrier between bile duct and intestine. In the training cohort, the proportion of infection was significantly higher in patients with previous surgical or endoscopic intervention than in patients without previous intervention (46.7% vs 14.6%; $P < .001$). Previous futile ERCP indicates a need of fast referral for percutaneous intervention to relieve obstruction. Third, Chen et al (18) reported that hilar biliary obstruction had a higher risk of cholangitis after ERCP than distal biliary obstruction (OR [95% CI]: 2.586 [2.066–2.743]; $P = .000$), possibly due to the multiple branches of obstruction and the complex interventional procedure (32).

Interestingly, the length of obstruction was associated with EBI in this study (OR [95% CI], 1.061 [1.013–1.111]; $P = .012$). This result was rarely mentioned in previous studies, and the mechanism has been unclear. Zhang et al (33) reported that length of biliary stricture ($\geq$ 1.5 cm) was an independent risk factor for deep abdominal infection (OR [95% CI], 5.20 [2.23–12.16]; $P = .000$), because longer length of biliary stricture may increase the difficulty of ERCP and prolong operative time, which can cause procedure-related cholangitis or bacterial translocation. To evaluate the importance of length of obstruction to this nomogram, an ANN model was developed, which indicated that length of obstruction was the most important variable of the 4 independent risk factors in **Figure 5**. Therefore, the mechanism should be proposed, explored, and verified.

However, some variables were not selected to the RPEBI nomogram. First, irradiation stents had been applied in MBO patients, and previous studies showed a similar risk of

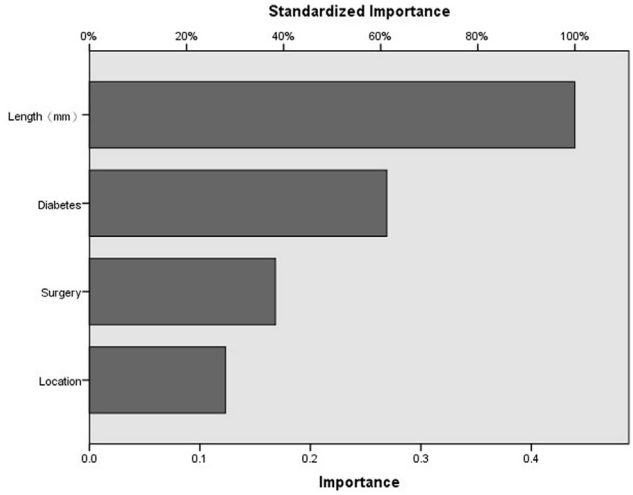

Figure 5. Importance of each variable in the ANN model. The importance of each variable along the bottom x-axis varied between 0.123 and 0.439. The standardized importance of each variable along the top x-axis was shown as a percentage between 28.0% and 100%.

biliary infection between irradiation stents and conventional stents (19,34,35). This study also clarified that irradiation stents would not increase the risk of EBI compared to conventional stents ($P = .370$). Second, it was demonstrated hyperbilirubinemia can stimulate the cytotoxic response and reduce the defense capacity of cells (36), and the reduction of bilirubin level after biliary drainage could decrease the risk of EBI (37–40). In this study, patients with preprocedural PTBD may have less risk for EBI by univariate analysis ($P = .014$), but it was excluded in the nomogram by multivariate analysis. Third, the presence of gallstones affects the function of gallbladder constriction and causes bacteria to thrive in bile, which may lead to EBI (41). Suk et al (8) reported that the presence of gallstones is an important risk factor for EBI after endoscopic biliary stent placement. However, it is known that endoscopic retrograde stent placement is a therapy limited to high-level biliary obstruction. Untreated gallstones often exist in the

superior part of the bile duct. Because Suk et al's study did not show the position of the biliary obstruction, the possibility that high-level biliary obstruction led to an increased incidence of EBI cannot be ruled out. This study showed that gallstones were associated with EBI in the univariate analysis ($P = .013$), but it was not an independent risk factor. Fourth, malignancy is the leading cause of severe cholangitis (5,42), possibly due to immune damage from cell toxicity reactions stimulated by high bilirubin levels and further reduction of defense capacity (28,43). The difference of EBI in different tumor etiology is unclear, and this study did not show significant difference of EBI in terms of tumor etiology.

As shown in **Table E1** (available online on the article's Supplemental Material page at *www.jvir.org*) the general definition of EBI adopted in this study would increase the proportion of the infection group (training cohort: 10.4%; validation cohort: 11.5%), which included the unclassified infection. In EBI patients, unclassified infections are implicated if the patient has negative bile culture and undefined imaging findings of biliary inflammation but with adequate evidence of clinical symptoms and laboratory data. Providing prophylactic administration can improve the detection efficiency of the predictive model and reduce the occurrence of infection, especially for patients with unclassified infection. In the RPEBI nomogram, the cutoff value of risk was 0.25, which provided sufficient predictive efficacy in the training cohort (sensitivity: 68.3%; specificity: 80.1%) and the validation cohort (sensitivity: 81.8%; specificity: 72.0%).

This study also had several limitations. First, it was a retrospective study with a small population. Compared to the entire MBO population, there may be patient selection bias. Second, patient selection was nonrandomized, which may be a potential confounder. Third, this study did not explore the intraprocedural risk factors associated with EBI. Fourth, it did not include a comparison with patients who underwent endoscopic biliary stent placement. Additional trials with large samples are needed to externally validate the findings and expand the population to which the findings can be generalized.

In conclusion, the RPEBI nomogram proposed in this study was established successfully to objectively and accurately predict the risk of EBI at an earlier point before PTBS. Length of obstruction may be a very important risk factor for predicting EBI. Patients with high risk (> 0.25) should be recommended for more effective prophylactic antibiotics administration and closer monitoring.

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APPENDIX A. DATA COLLECTION

The study data were collected as follows: (a) demographics, including age, gender, body mass index, and concomitant disease (eg, diabetes and gallstones); pre-procedural Child-Pugh classification; pre-procedural PTBD or not; pre-procedural Eastern Cooperative Oncology Group score; history of chemotherapy; history of radiotherapy; previous hepatobiliary or upper gastrointestinal surgery (eg, choledochojejunostomy, cholecystectomy, hepatectomy, gastrectomy, and pancreaticoduodenectomy); ERCP; or post-procedural biliary infection; (b) laboratory test results, such as white blood cell, total bilirubin, direct bilirubin, albumin, and blood glucose; and (c) parameters related to MBO, such as tumor etiology, length of obstruction, and location of obstruction (low level, high level). High-level obstruction is located at or above the common hepatic duct. Low-level obstruction is located below the insertion of the cystic duct, which involves the common bile duct.

APPENDIX B. ADMINISTRATION OF ANTIBIOTICS

Antibiotics selection depended on individual conditions, such as drug allergies, comorbidities, renal function, hepatic function, hospital-acquired or community-acquired infection, and the severity of cholangitis. Empiric antibiotics should be broad-spectrum antibiotics that cover both Gram-negative and anaerobic organisms. The initial choices were piperacillin-tazobactam, ticarcillin-clavulanate, and ceftriaxone plus metronidazole. If a patient was sensitive to penicillin, ciprofloxacin plus metronidazole, carbapenems, or gentamicin plus metronidazole were good choices. Antibiotics adjustment was further evaluated by blood culture and antimicrobial susceptibility results. Once the source of infection was controlled, antibiotic therapy should be continued for 4–7 days. If bacteremia with Gram-positive cocci was present, the minimum duration was 2 weeks. If liver abscess was present, antimicrobial therapy should be continued until complete resolution of the abscess demonstrated by clinical, biochemical, and radiological follow-up.

Table E1. Classification of EBI in Both Cohorts*

Classification	Training Cohort (n = 182)	Validation Cohort (n = 61)
Cholangitis	8 (4.4%)	2 (3.3%)
Cholecystitis	7 (3.8%)	1 (1.6%)
Liver abscess	3 (1.6%)	1 (1.6%)
Cholangitis and liver abscess	2 (1.1%)	0
Cholecystitis and liver abscess	2 (1.1%)	0
Unclassified infections†	19 (10.4%)	7 (11.5%)
Total	41 (22.5%)	11 (18.0%)

EBI = early biliary infection; PTBS = percutaneous transhepatic biliary stent.
*EBI after PTBS is defined as biliary infection within 30 days after PTBS by leukocytosis, fever (>38°C), exacerbation of jaundice or epigastric pain, and excluding the presence of other infections, plus positive bile culture or imaging findings of biliary inflammation.
†Of the EBI patients, it is considered as unclassified infections if they have negative bile culture and undefined imaging findings of biliary inflammation.

Table E2. Diagnostic Efficacy of the Nomogram for EBI

Values	Training cohort (n = 182)	Validation cohort (n = 61)
Cutoff risk	0.25	0.25
Sensitivity (%)	68.3	81.8
Specificity (%)	80.1	72.0
Positive predictive value (%)	50.0	39.1
Negative predictive value (%)	89.7	94.7

EBI = early biliary infection.

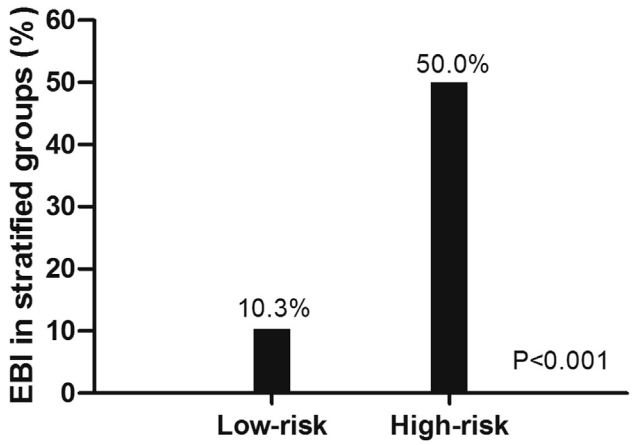

Figure E1. Comparison of EBI occurrences in the stratified groups. In the training cohort, the high-risk group had significantly more EBI patients than the low-risk group (50.0% vs 10.3%; $P < .001$).