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Early Warning Models to Estimate the 30-Day Mortality Risk After Stent Placement for Patients with Malignant Biliary Obstruction

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Abstract

Purpose To develop, validate, and compare early warning models of the 30-day mortality risk for patients with malignant biliary obstruction (MBO) undergoing percutaneous transhepatic biliary stent placement (PTBS).

Materials and Methods Between January 2013 and October 2018, this multicenter retrospective study included 299 patients with MBOs who underwent PTBS. The training set consisted of 166 patients from four cohorts, and another two independent cohorts were allocated as external validation sets A and B with 75 patients and 58 patients, respectively. A logistic model and an artificial neural network (ANN) model were developed to predict the risk of 30-day mortality after PTBS. The predictive performance of these two models was validated internally and externally.

Results The ANN model had higher values of area under the curve than the logistic model in the training set (0.819 vs 0.797), especially in the validation sets A (0.802 vs 0.714) and B (0.732 vs 0.568). Both models had high accuracy in the three sets (75.9–83.1%). Along with a high specificity, the ANN model improved the sensitivity. The net reclassification improvement and integrated discrimination improvement also demonstrated that the ANN model led to improvements in predictive ability compared with the logistic model.

Conclusions Early warning models were proposed to predict the risk of 30-day mortality after PTBS in patients with MBO. The ANN model has higher accuracy and better generalizability than the logistic model.

Keywords Malignant biliary obstruction · Biliary stent · 30-Day mortality · Prediction · Artificial neural network

Abbreviations

ANN	Artificial neural network
MBO	Malignant biliary obstruction
PTBS	Percutaneous transhepatic biliary stent placement
AUC	Area under the curve
NRI	Net reclassification improvement
IDI	Integrated discrimination improvement
ECOG	Eastern Cooperative Oncology Group

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NLR	Neutrophil-to-lymphocyte ratio
CA	Cancer antigen
CEA	Carcinoembryonic antigen
OR	Odds ratio
CI	Confidence interval

Introduction

Malignant biliary obstruction (MBO) is mainly caused by biliary tract cancers, pancreatic cancer, and metastasis disease and has a poor prognosis [1]. Percutaneous transhepatic biliary stent placement (PTBS) has become the standard palliative treatment for MBO because the procedure is easy to perform and has a high success rate [2]. However, the 30-day mortality rate after stent placement is as high as 30% among patients with MBO [3]. The postprocedural 30-day mortality rates vary across different patient selection and referral patterns [4]. Early death may be related to the general condition of patients and the underlying nature of the malignant disease itself, rather than directly caused by the interventional procedure [4–6]. Two population-based studies conducted at a national scale showed that MBO is one of the major predictors of 30-day mortality after endoscopic retrograde cholangiopancreatography for all kinds of stenosis [6, 7]. The 30-day mortality rate is similarly high between percutaneous intervention and endoscopic strategies in the management of MBO [5, 8–10]. Early mortality indicates that PTBS is futile and may cause unnecessary patient discomfort and avoidable costs from this interventional procedure, which increases the economic burden of disease worldwide. Therefore, predicting the probability of early death and avoiding futile PTBS procedures are highly demanded.

Considering the high rate of early mortality after biliary interventions, the British Society of Interventional Radiology has suggested developing a preprocedural scoring system to predict risk of mortality [11]. Although Rai et al. identified two laboratory risk factors (blood urea and hemoglobin) related to 30-day mortality after PTBS in MBO patients, tumor-associated factors and general conditions were not explored [12]. Tapping et al. also reported several laboratory factors to predict risk of early mortality in patients with obstructive jaundice treated with percutaneous interventions, but benign diseases were also included in the population [13]. These studies included limited features without evaluating and validating predictive performance. To accurately and objectively obtain an early warning for 30-day mortality, a new model should be developed and validated based on comprehensive preprocedural factors, including laboratory indices, tumor-associated features, and other individual conditions. In patients with MBO, several types of cancer with diverse and correlational characteristics can exist. Usually, traditional statistical methods, such as logistic regression, can be applied to build a predictive model. An artificial neural network (ANN), an advanced method of machine learning, can learn intricate relationships between features and outcomes from complex and heterogeneous data [14].

In this study, we identified clinical predictors and built a visible model to predict the risk of 30-day mortality in patients with MBO who underwent PTBS. In addition, we tried to develop a simple ANN model, to evaluate its predictive performance and compare the ANN model with the traditional model.

Materials and Methods

This multicenter retrospective study was approved by the institutional review boards of all participating centers. The need for informed consent was waived due to the study's retrospective nature.

Patients

Between January 2013 and October 2018, the data of 616 consecutive patients with MBO from six centers were retrospectively reviewed, and 299 of these patients who underwent PTBS with an uncovered self-expanding metal stent were included in this study (181 males, 118 females; mean age, 66 years ± 13 [standard deviation]). Four centers contributed to the training set (n = 166), and another two centers contributed to the two independent external validation sets A (n = 75) and B (n = 58). The study design is illustrated in Supplementary Figure S1.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (a) age 18 years or older, (b) clinical or histopathological diagnosis of MBO, (c) unresectable disease due to extensive lesions, metastases, poor medical condition, or refusal to undergo surgery, and (d) percutaneous approach for the initial placement of an uncovered self-expanding metal stent. The exclusion criteria were as follows: (a) presence of severe infection or organ failure before stent placement, (b) Eastern Cooperative Oncology Group (ECOG) score of 4 before stent placement, (c) any other anticancer therapy, except for supportive treatment after stent placement

within 30 days, (d) incomplete clinical data or (e) unknown 30-day outcomes.

Data Collection

The following clinical characteristics were recorded: (a) demographics, including sex, age, and body mass index; (b) preprocedural status, including prior biliary catheter, duration between diagnosis and stent, duration between prior catheter placement and stent placement, abdominal pain, ECOG performance status, Child–Pugh classification, prior abdominal surgeries, history of chemotherapy, history of radiotherapy, and degree of ascites; (c) blood biochemical indices, including total bilirubin, direct bilirubin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, albumin, white blood cell, neutrophil-to-lymphocyte ratio (NLR), hemoglobin, prothrombin time, levels of cancer antigen (CA) 19-9, CA125, and carcinoembryonic antigen (CEA); and (d) parameters related to malignancies, such as the tumor etiology, distant metastasis, hepatic metastasis, location of obstruction, and length of obstruction. A standard procedure of PTBS was performed under fluoroscopic guidance with or without ultrasonographic guidance by interventional radiologists with more than 15 years of experience. The biliary stent was an uncovered self-expanding metal stent (Nanjing Micro-Tech Co., Ltd., Nanjing, China). The primary outcome of this study was 30-day mortality.

Statistical Analysis

For the training sample size, at least 10 events per-predictor were required to produce reasonably stable estimates [15]. Two features were selected for the logistic model in this study, and the minimum size for the training data was 104, with 20 events and 84 nonevents. For the validation sample size, a power calculation to estimate the sample size was performed in PASS 15 (NCSS, LLC., Kaysville, Utah, USA), and the minimum sample size was 40, with 8 events and 32 nonevents [16, 17]. In this study, the numbers in the training and validation cohorts were 166 (32 events; 134 nonevents), 75 (17 events; 58 nonevents), and 58 (9 events; 49 nonevents), respectively, all of which were sufficient.

Statistical analysis was performed using SPSS 22.0 (IBM Corporation, Somers, NY, USA) and the R package (version 3.4.3; R Package for Statistical Computing; www.r-project.org). 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 by the Mann–Whitney *U* test for continuous variables and by Pearson's Chi-squared or Fisher's exact test for categorical variables. Factors associated with 30-day mortality were selected by univariate analysis in the training set. A P value < 0.05 was considered statistically significant. Because of the few patients with an ECOG score of 0 in this study, patients with ECOG scores of 0 and 1 were merged in the same category of good performance status. An ECOG score of 4 was considered unsuitable for stent placement. Therefore, three categories were divided according to the ECOG score (0/1, 2, and 3).

The logistic model was developed based on the multivariate logistic regression analysis with forward selection, and predictors with a P value < 0.05 stayed in the model. The odds ratios (OR) and the 95% confidence interval (CI) of each predictor were found in the multivariate analysis. A nomogram was formulated to visualize the logistic model.

The ANN model was developed based on the factors associated with 30-day mortality. The simplest multilayer perceptron network was established in the training set with one hidden layer and one unit. The covariates were rescaled by standardized method. Seventy percent of the patients in the training set were randomly selected to build the model, and the remaining thirty percent were used for cross-validation to prevent overfitting. The hyperbolic tangent function was applied in the hidden layer, and the softmax function was applied in the output layer.

After establishing the logistic and ANN models, their predictive performances were evaluated, validated, and compared with various indices, such as the area under the curve (AUC) with 95% CI, accuracy, sensitivity, specificity, net reclassification improvement (NRI), and integrated discrimination improvement (IDI). By using these two models, a decision curve analysis was applied to compare the net benefits, and a clinical impact curve was applied to assess the cost–benefit ratio [18].

Results

Patients Characteristics

A total of 299 patients were included in this study. The training set enrolled 166 patients (105 males, 61 females; mean age, 68 years ± 12 [standard deviation]), and the validation sets A and B enrolled 75 patients (45 males, 30 females; mean age, 61 years ± 12 [standard deviation]) and 58 patients (31 males, 27 females; mean age, 67 years ± 12 [standard deviation]), respectively. The clinical characteristics of patients in these three sets are shown in Supplementary Table S1. Most patients had poor performance status with an ECOG score of 2 (51.7–58.7%) or 3 (22.3–33.9%). The causes of mortality and 30-day mortality rates are shown in Supplementary Table S2.

Factors Associated with 30-Day Mortality

The univariate analysis indicated eight clinical factors associated with 30-day mortality for patients with MBO undergoing PTBS, including duration between prior catheter placement and stent placement, ECOG score, Child–Pugh classification, ascites level, prior catheter, NLR, CA19-9 level, and CEA level (all $P < 0.05$, Table 1). In the training set, the CA19-9 level widely varied from 0.6 U/mL to 28,470 U/mL, and the optimum cutoff value for CA19-9 is determined to be 1000 U/mL by maximizing the Youden index in Supplementary Figure S2.

The Logistic Model

According to the multivariate logistic regression analysis, the logistic model was finally developed based on two clinical predictors, an ECOG score of 3 (OR [95% CI]: 9.39 [1.836–47.98]; $P = 0.007$) and a high CA19-9 level (OR [95% CI]: 6.48 [2.67–15.71]; $P < 0.001$) (Table 2). A nomogram was built to visualize the logistic model and for ease of use (Fig. 1).

The ANN Model

The ANN model was developed based on the eight factors selected from univariate analysis. The covariates are NLR and duration between prior catheter placement and stent placement. The other six factors are categorical variables, including the ECOG score, Child–Pugh classification, ascites level, prior catheter, CA19-9 level, and CEA level. The structural diagram of this model is illustrated in Supplementary Figure S3. The importance and standardized importance of these factors selected for the ANN model are listed in Supplementary Figure S4.

Validation and Comparison of Both Models

As shown in Table 3, the predictive performance was validated and compared between the logistic and ANN models internally (in the training set) and externally (in validation sets A and B). The ANN model had a higher AUC (0.819) than the logistic model (0.797) in the training set and especially in validation sets A (0.802 vs 0.714) and B (0.732 vs 0.568) (Fig. 2). Both models had relatively high accuracy in the three sets (75.9–83.1%). Along with a high specificity, the ANN model improved the sensitivity from 28.1–33.3 to 46.9–55.6% in the three sets. The NRI (12.0–16.5%) and IDI (5.9–13.5%) also indicated that the ANN model definitely led to improvements in predictive ability compared with the logistic model.

Clinical Use

By using the two models among all patients ($n = 299$), the decision curve analysis showed the largest overall net benefit in predicting the 30-day mortality for the ANN model compared with the logistic model, the treat-all-patients scheme, and the treat-none scheme if the threshold probability of a patient was > 12.0% (Fig. 3a). Moreover, the clinical impact curve showed the cost–benefit ratio according to different risk thresholds (Fig. 3b).

Discussion

Early mortality after biliary interventions is very common in patients with obstructive jaundice, especially in those with advanced malignancies [4, 6, 7, 11]. Since metal stents are recommended for patients with an expected survival of more than 3 months [19], some costly and invasive treatments may be unsuitable for patients with a high risk of early mortality. Accurate predictions about the likely outcome after biliary decompression is important in the clinical decision-making process for conventional therapy. The early evaluation of 30-day mortality following biliary stent placement is still dependent on empirical judgment. In this study, the logistic and ANN models were established based on clinical factors to estimate the risk of 30-day mortality in patients with MBO undergoing PTBS. These risk factors were easy to acquire before stent placement. Importantly, the predictive performance was validated in two external centers and compared between the two models.

The logistic model is presented concisely and visually by a nomogram, but the ANN model seems complicated and inconvenient to use. Although the two models had similarly high specificity values, the sensitivity surprisingly improved from approximately 30% in the logistic model to 50% in the ANN model. According to the NRI and IDI results, the ANN model demonstrated a better predictive ability than the logistic model. Although the ANN model seems difficult to use, it has higher benefits for clinical decision making than the logistic model. In this study, two independent external validation tests were performed to verify the generalizability of both models. Notably, the AUC values were clearly higher for the ANN model (0.802 and 0.732) than for the logistic model (0.714 and 0.568) according to the external validation results, which meant that the ANN model had a higher accuracy and better generalizability than the logistic model. In particular, the logistic model showed an AUC of 0.568 and did not indicate good discrimination in validation set B, which may be because the model was inadequately developed based on limited predictors, and major differences exist between the training and validation populations [20].

Table 1 Clinical features of patients in the training set and results of univariate analysis for factors associated with 30-day mortality

Characteristics	Univariate analysis		
	Death (n = 32)	No death (n = 134)	P value
Gender, No. (%)			0.922
Male	20 (62.5)	85 (63.4)	
Female	12 (37.5)	49 (36.6)	
Age, median (IQR), years	68 (62–81)	67 (59–78)	0.262
BMI, median (IQR), kg/m^2	22.7 (19.6–24.2)	21.7 (19.4–23.6)	0.176
Duration between diagnosis and stent, median (IQR), days	24 (13–50)	23 (13–49)	0.835
Duration between prior catheter and stent, median (IQR), days	4 (0–17)	0 (0–7)	0.047
Length of obstruction, median (IQR), cm	4.0 (4.0–6.0)	4.0 (4.0–4.5)	0.065
Biliary infection, No. (%)			0.109
Yes	7 (21.9)	15 (11.2)	
No	25 (78.1)	119 (88.8)	
Abdominal pain, No. (%)			0.076
Yes	27 (84.4)	92 (68.7)	
No	5 (15.6)	42 (31.3)	
ECOG score, No. (%)			0.003
0/1	2 (6.3)	40 (29.9)	
2	17 (53.1)	70 (52.2)	
3	13 (40.6)	24 (17.9)	
Child–Pugh classification, No. (%)			0.046
A	3 (9.4)	11 (8.2)	
B	19 (59.4)	105 (78.4)	
C	10 (31.3)	18 (13.4)	
Ascites level, No. (%)			0.041
None	19 (59.4)	100 (74.6)	
Mild or moderate	5 (15.6)	22 (16.4)	
Severe	8 (25.0)	12 (9.0)	
Prior catheter, No. (%)			0.023
Yes	21 (65.6)	58 (43.3)	
No	11 (34.4)	76 (56.7)	
Location of obstruction, No. (%)			0.704
High level	16 (50.0)	72 (53.7)	
Low level	16 (50.0)	62 (46.3)	
Tumor etiology, No. (%)			0.168
Biliary tract cancer	11 (34.4)	66 (49.3)	
Pancreatic carcinoma	12 (37.5)	30 (22.4)	
Metastases	9 (28.1)	38 (28.4)	
Distant metastasis, No. (%)			0.941
Yes	21 (65.6)	87 (64.9)	
No	11 (34.4)	47 (35.1)	
Hepatic metastasis, No. (%)			0.318
Yes	16 (50.0)	54 (40.3)	
No	16 (50.0)	80 (59.7)	
Surgeries in gut, No. (%)			0.560
Yes	5 (15.6)	27 (20.1)	
No	27 (84.4)	107 (79.9)	
Chemotherapy, No. (%)			0.181
Yes	6 (18.8)	41 (30.6)	

No	26 (81.3)	93 (69.4)	
Radiotherapy, No. (%)			0.248
Yes	6 (18.8)	15 (11.2)	
No	26 (81.3)	119 (88.8)	
TB, median (IQR), μmol/L	199.60 (94.73–305.00)	189.95 (94.73–308.63)	0.789
DB, median (IQR), μmol/L	167.25 (84.03–244.85)	135.35 (68.45–226.63)	0.397
ALT, median (IQR), IU/L	53 (28–188)	82 (48–138)	0.147
AST, median (IQR), IU/L	58 (47–142)	84 (54–145)	0.194
LDH, median (IQR), IU/L	280 (180–310)	204 (165–255)	0.088
ALP, median (IQR), IU/L	518 (269–893)	424 (259–694)	0.327
ALB, median (IQR), g/L	33.4 (30.2–38.0)	34.0 (30.4–37.7)	0.948
WBC, median (IQR), $\times 10^9$/L	7.31 (5.47–9.38)	6.34 (4.88–8.29)	0.095
NLR, median (IQR)	6.72 (3.17–9.63)	4.25 (2.78–6.31)	0.023
HGB, median (IQR), g/L	113 (97–123)	120 (108–137)	0.825
PT, median (IQR), seconds	12.5 (11.6–14.4)	12.2 (11.2–13.1)	0.069
CA19-9, No. (%)			< 0.001
≥ 1000 U/mL	23 (71.9)	36 (26.9)	
< 1000 U/mL	9 (28.1)	98 (73.1)	
CA125, No. (%)			0.141
≥ 35 U/mL	12 (37.5)	33 (24.6)	
< 35 U/mL	20 (62.5)	101 (75.4)	
CEA, No. (%)			0.006
≥ 5 ng/mL	23 (71.9)	60 (44.8)	
< 5 ng/mL	9 (28.1)	74 (55.2)	

IQR interquartile range; *OR* odds ratio; *CI* confidence interval; *BMI* body mass index; *PTBD* percutaneous transhepatic biliary drainage; *ECOG* Eastern Cooperative Oncology Group; *TB* total bilirubin; *DB* direct bilirubin; *ALT* alanine aminotransferase; *AST* aspartate aminotransferase; *LDH* lactate dehydrogenase; *ALP* alkaline phosphatase; *ALB* albumin; *WBC* white blood cell; *NLR* neutrophil-to-lymphocyte ratio; *HGB* hemoglobin; *PT* prothrombin time; *CA* cancer antigen; *CEA* carcinoembryonic antigen

Table 2 Predictors selected by using multivariate logistic regression model for 30-day mortality in the training set

Characteristics	Multivariate analysis	
	OR (95%CI)	*P* value
ECOG score, No. (%)		
0/1	1	
2	4.54 (0.95–21.59)	0.057
3	9.39 (1.836–47.98)	0.007
CA19-9, No. (%)		
< 1000 U/mL	1	
≥ 1000 U/mL	6.48 (2.67–15.71)	< 0.001

OR odds ratio; *CI* confidence interval; *ECOG* Eastern Cooperative Oncology Group; *CA* cancer antigen

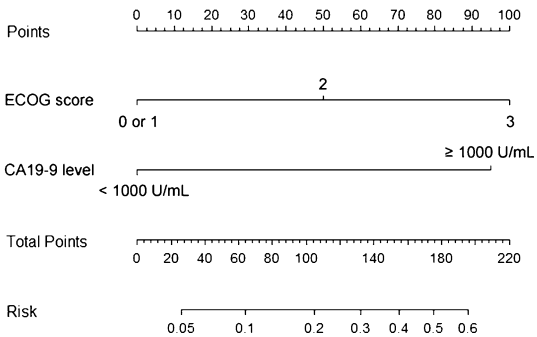

Fig. 1 The nomogram for the logistic model. To use the nomogram, the user locates an individual patient's value on each variable axis and draws a line up to determine the number of points received for each variable value. The sum of these numbers is located on the axis of total points, and a line is drawn at the bottom to determine the 30-day mortality probabilities

Indeed, the patient characteristics in the validation sets were not balanced with those in the training set. Thus, when we use the predictive model in a real-world cohort, the characteristics of the population do not always remain similar to those of the primary training population.

Table 3 Predictive performance of the logistic and ANN models

Index	Training set		Validation set A		Validation set B	
	Logistic model	ANN model	Logistic model	ANN model	Logistic model	ANN model
AUC	0.797	0.819	0.714	0.802	0.568	0.723
95% CI of AUC	0.719–0.876	0.738–0.900	0.577–0.851	0.672–0.932	0.352–0.785	0.527–0.920
Accuracy* (%)	81.3	83.1	78.7	81.3	81.0	75.9
Sensitivity* (%)	28.1	46.9	29.4	47.1	33.3	55.6
Specificity* (%)	94.0	91.8	93.1	91.4	89.8	79.6
NRI* (%)	16.5		15.9		12.0	
IDI (%)	5.9		12.6		13.5	

ANN artificial neural network; *AUC* area under the curve; *CI* confidence interval; *NRI* net reclassification improvement; *IDI* integrated discrimination improvement

*Cutoff value of 30-day mortality probability was identified as 0.5 to evaluate the indices of sensitivity, specificity, accuracy, and NRI

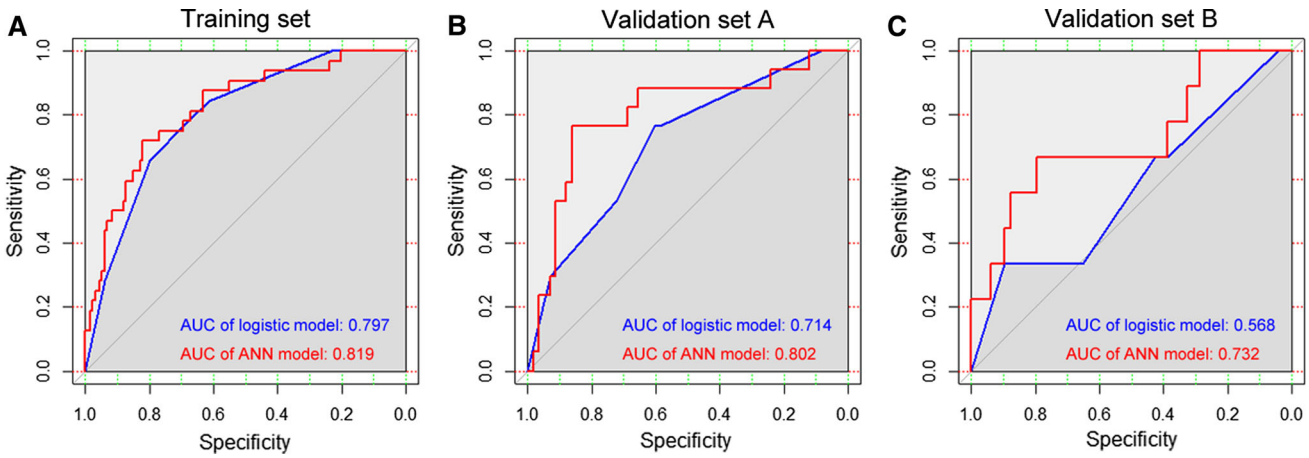

Fig. 2 The receiver operating characteristic curves with the area under the curve (AUC) for both models. The AUC of the logistic and ANN models were compared internally in the training set (**A**, 0.797 vs 0.819), externally in validation set A (**B**, 0.714 vs 0.802), and externally in validation set B (**C**, 0.568 vs 0.732), respectively

Fortunately, patients in the training set of this study were included from a multicenter population. The validation sets were independent of the training set, which may fit the actual application [21].

After the multivariate regression analysis, the preprocedural ECOG score and CA19-9 level were selected for the logistic model. The ECOG performance status is an important factor that may be related to tumor prognosis [22]. Compared to ECOG scores of 0/1, ECOG 2 had a strong trend favoring 30-day mortality (OR [95% CI], 4.54 [0.95–21.59]; $P = 0.057$), and ECOG 3 was a predictor of 30-day mortality (OR [95% CI], 9.39 [1.836–47.98]; $P = 0.007$). Similarly, the ECOG score was identified as a risk factor for overall survival in patients with MBO who underwent PTBS [23]. Serum CA19-9 levels have been proposed as a prognostic predictor in several malignancies, such as pancreatic cancers, bile duct cancers, ampullary cancer, and gastric cancers [22]. A CA19-9 level over 1000 U/mL was demonstrated as a strong predictor of 30-day mortality (OR [95% CI], 6.48 [2.67–15.71]; $P < 0.001$). Other potential risk factors, such as the duration of prior drainage [24], Child–Pugh classification [25], ascites [26], prior catheter [27, 28], NLR [29], and CEA level [30], were previously reported as prognostic predictors for patients with malignancies. These factors were not included in the multivariate logistic regression model, but were considered important variables in the ANN model. The ANN can learn adequate information from a collection of variables to build a model because this algorithm has the ability to calculate complex and abstract nonlinear relationships among the variables [31]. Some variables with P values between 0.05 and 0.1 in the univariate analysis, such as the length of obstruction, abdominal pain, lactate dehydrogenase, white blood cell, and prothrombin time, were not considered to be significantly associated with 30-day mortality in this study and need further exploration.

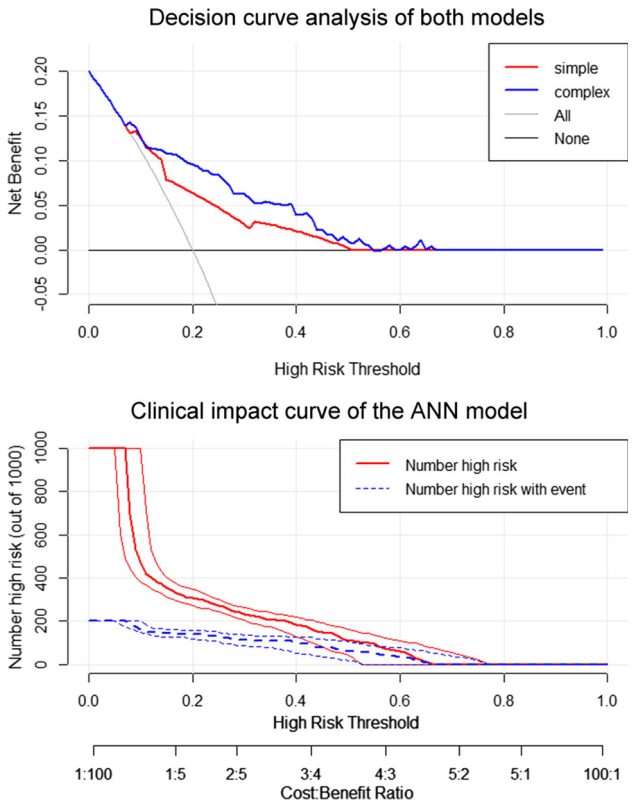

Fig. 3 Clinical use of the logistic and ANN models. To predict the 30-day mortality, the decision curve analysis showed the largest overall net benefit in predicting the 30-day mortality for the ANN model (complex) compared with the logistic model (simple), the treat-all-patients scheme, and the treat-none scheme (**A**), and the clinical impact curve showed the cost–benefit ratio according to different risk thresholds (**B**)

There are several limitations in this study. First, the predictive models were validated with retrospective data, which may be less convincing than in a prospective validation. Second, this study included limited samples and may have patient selection bias. Third, patients who received endoscopic intervention were not included in this study, and whether the models are suitable for such patients remains unknown. Fourth, the ANN model is a preliminary model that requires further optimization. Because of the "black box" nature of the ANN model [32, 33], a simplified software or tool should be constructed to facilitate its ease of use. Therefore, an additional prospective validation sample enrolled from a large population is recommended to optimize the proposed models. More individual preprocedural factors, such as genomics biomarkers, radiomics features, and microbiome characteristics, should be evaluated. Ultimately, and most importantly, a predictive model should maintain high accuracy, good generalizability, and easy application.

Conclusions

In conclusion, this study proposed early warning models based on clinical factors to predict the risk of 30-day mortality post-PTBS in patients with MBO. The ANN model has a higher accuracy and better generalizability than the logistic model.

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Author Contributions All authors contributed to review and critical revision of the manuscript and approved the final version of the manuscript. GJT, HFZ, JL, HDZ, and JHG contributed to study concept and design. JHG, MH, JSJ, WFL, YLL, HX, LC, and GYZ contributed to acquisition of data. HFZ contributed to drafting of the manuscript. GJT, HDZ, and JHG contributed to analysis and interpretation of data. JL contributed to statistical analysis. GJT, HDZ, and JHG supervised and oversaw the study.

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Compliance with Ethical Standards

Conflict of interest None.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent The requirement to obtain informed consent was waived due to the retrospective nature of this study.

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