Nomogram for the Prediction of Delayed Colorectal Post-Polypectomy Bleeding

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ABSTRACT

Background: *Delayed colorectal post-polypectomy bleeding (PPB) is a fairly common complication after polypectomy. The present study aimed to build a novel nomogram-based model of delayed PPB.*

Methods: *A cohort of 2494 patients who had undergone colonoscopic polypectomy between January 2016 and April 2020 were consecutively enrolled. The patient demographics, polyp characteristics, laboratory factors, and pathological parameters were collected. The least absolute shrinkage and selection operator (LASSO) regression was applied for selecting potential variables. Multivariate logistic regression was used to develop the nomogram. A bootstrapping method was employed for internal validation. The performance of the nomogram was evaluated on the basis of its calibration, discrimination, and clinical usefulness.*

Results: *Of 2494 patients undergoing colonoscopic polypectomy, 40 (1.6%) developed delayed PPB. The LASSO regression identified 6 variables (age, gender, polyp location, polyp morphology, antithrombotic medication use, and modality of polypectomy), and a predictive model was subsequently established. The area under the curve (AUC) of the predictive model and the internal validation were 0.838 (95% CI: 0.775-0.900) and 0.824 (95% CI: 0.759-0.889), respectively. The predictive model provided acceptable calibration, and a decision curve analysis (DCA) showed its clinical utility.*

Conclusion: *This predictive model may enable clinicians to predict the risk of delayed PPB and optimize preoperative decision-making, for effective treatment.*

Keywords: *Nomogram, polypectomy, colorectal, bleeding*

INTRODUCTION

Colonoscopic polypectomy is an effective method for removal of colonic polyps.[1] Despite the efficacy of polypectomy in decreasing the incidence of and mortality from colorectal cancer,[2-4] complications can occur, including post-polypectomy bleeding (PPB), perforation, and post-polypectomy coagulation syndrome. Among these complications, PPB is the most common, with an incidence of 0.3-6.1% of all cases.[3-5] Post-polypectomy bleeding can be classified as immediate or delayed. Delayed PPB is less common (approximately 0.4-1.1%), and usually manifests hours and days after polypectomy.[6-8] Although most cases of delayed PPB can be successfully controlled, the development of delayed PPB may potentially require rehospitalization, repeat colonoscopy, and blood transfusion. Moreover, the difficulty of emergency endoscopic treatment increases once bleeding has occurred.[9] Minor bleeding, which is often self-limiting, may also cause discomfort and anxiety among patients.

A spectrum of studies exists regarding risk factors for delayed PPB, with inconsistent results. Several risk factors including polyp size, shape, location, and antithrombotic use have been well established, whereas others (e.g., age, comorbidity) are less obvious.[3,4,6,10,11] Therefore, the precise prediction of delayed PPB will help clinicians identify the high-risk population from among those undergoing polypectomy, to further optimize perioperative management approaches such as prophylactic clipping, extending the observation period, and more rigorous education following discharge. The nomogram has recently been recognized as a useful clinical tool to predict clinical events and outcome. A nomogram is a graphical predictive model that incorporates clinical variables and allows the user to quantitatively predict the risk of a specific event. To the best of our knowledge, no model for the prediction of delayed PPB has been reported to date. This study aimed to develop a predictive model for delayed PPB.

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MATERIALS AND METHODS

Patients

This study was a retrospective cohort study analyzing patients who had undergone colonoscopic polypectomy at our institution, a 2600-bed tertiary hospital, between January 2016 and April 2020. The study was approved by the institutional ethics committee of the hospital (No. 2020000054). Signed informed consent was waived, because patient information was kept anonymous. Delayed PPB was defined as more than 1 incidence of melena or hematochezia occurring 6 hours or later after the procedure.[8,12] Patients were excluded if they had inflammatory bowel disease, familial adenomatous polyposis, or non-epithelial neoplasms. The current ESGE guidelines consider polypectomy as a high-risk procedure.[13] Before polypectomy, patients on antiplatelet or anticoagulant therapy were evaluated and stratified as having low or high thrombotic risk, based on ESGE guidelines. In our institution, the cases involving patients with high thrombotic risk are discussed in detail with cardiologists, and the polypectomies are carried out in a different clinical setting (operating room) under a surgeon's surveillance. Therefore, these patients were not within the range of the present study. The patients with low thrombotic risk were required to discontinue anticoagulant or antiplatelet medicines a week before the procedure and resume using these agents 3-5 days after the procedure.[14]

Polypectomy Procedure and Data Collection

The colon was cleansed with 4 L of polyethylene glycol solution. Propofol was used for intravenous sedation and pethidine was used to reduce pain. The polypectomies were performed by using a flexible colonoscope (CF-H290I/CF-H260AI; Olympus Optical Co., Tokyo, Japan). The modality for polypectomy was determined by the discretion of the endoscopists, based on the feature of each polyp. An electrosurgical unit (VIO 300 D; ERBE, Tübingen, Germany) was used, adjusted according to the manufacturer's manual.

The following variables of patient data were collected: age, gender, body mass index (BMI), comorbidities (yes or no; hypertension, diabetes, or cardiovascular disease), smoking and alcohol history (yes or no), antithrombotic medication use (yes or no; aspirin, clopidogrel, or warfarin); polyp features including histopathologic diagnosis (hyperplastic/inflammatory, adenoma), location (left or right hemicolon), size, morphology (sessile or pedunculated), resection method (snare/forceps polypectomy or endoscopic mucosal resection (EMR)), and prophylactic clipping (yes or no). The following parameters of laboratory tests were also recorded: prothrombin time (PT), activated partial thromboplastin time (APTT), hemoglobin (Hb) at admission, platelet (PLT) counts, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), triglyceride, total cholesterol, high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) levels.

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics. Continuous variables were presented as mean ± standard deviation and categorical variables were expressed as numbers with percentages. Unpaired *t*-tests (normal distribution) or the Kruskal–Wallis rank-sum test (non-normal distribution), Pearson chi-squared tests, or Fisher's exact test were applied for intergroup comparisons, as appropriate. For variables with missing data, the multiple imputation technique was used for further estimation.[15] The least absolute shrinkage and selection operator (LASSO) regression method was employed for predictor selection and regularization. Logistic regression analysis was used to establish the predictive model for delayed PPB, and a nomogram was constructed according to the model. The area under the curve (AUC) was calculated to assess the discrimination capacity of the model, and internal validation was performed using bootstrapping with 1000 iterations.[16] Calibration was assessed by the unreliability test and calibration curve. Decision curve analysis (DCA) was performed to assess the clinical utility of the model.[17] Statistical analyses were performed using R software (version 3.6.3; https://www.r-project.org). A value of $P < .05$ was considered statistically significant.

MAIN POINTS

- *Post-polypectomy bleeding (PPB) is the most common complication, with an incidence of 0.3-6.1% of all colonic polypectomies. Moreover, delayed PPB could be more severe due to its unpredictable onset.*
- *Accurate prediction of delayed PPB will be beneficial to stratify the high-risk population undergoing polypectomy and further contribute to perioperative management. However, no model for the prediction of delayed PPB has been reported or is available to date.*
- *Our prediction model showed good discriminatory ability and potential clinical efficacy. A nomogram was developed for facilitating individualized prediction of delayed PPB.*

RESULTS

Incidence of Delayed Post-Polypectomy Bleeding and Patients' Characteristics

The patients' baseline characteristics are shown in Table 1. Of the 2494 patients, 40 (1.6%) patients experienced delayed PPB following polypectomy. The factors of age, gender, polyp location, size, morphology, and modality (EMR) differed significantly, as evaluated by univariate analyses.

Predictors Entering the Model

A total of 25 variables were reduced to the 6 most potential predictors, with non-zero coefficients according to the LASSO logistic regression. These variables were age (coefficient: −0.03), gender (coefficient: 0.764), antithrombotic medication use (coefficient: aspirin, 0.12; clopidogrel, 0.768; warfarin, 3.18), polyp location (coefficient: 1.175), polyp morphology (coefficient: 0.25), and modality (coefficient: 0.314).

Establishment of the Model and Nomogram

Accordingly, a predictive model for delayed PPB was developed on the basis of the aforementioned 6 predictors. The coefficient of each predictor entering the model was as follows: age, −0.053; gender, 1.679; antithrombotic medication use, 1.092 (aspirin), 2.336 (clopidogrel), 3.457 (warfarin); polyp location, 1.604; polyp morphology, 0.806; and modality, 0.862. As shown in Figure 2, the AUC of the model (black line) was 0.838 (95% CI: 0.775-0.900) and it was 0.824 (95% CI: 0.759-0.889) in the internal validation using bootstrapping (resampling = 1000 times). The sensitivity and specificity of the receiver operating characteristic (ROC) curve were 0.900 and 0.667, respectively. The optimal cutoff was 0.011 according to the ROC curve. To provide physicians with a quantitative tool for individualized prediction of delayed PPB, a nomogram was constructed according to multivariable logistic regression (Figure 3). The formula based on the model was presented as follows: $- 4.015 - 0.053 \times \text{age} + 1.679 \times (\text{gender} = \text{male}) + 1.092 \times (\text{antithrombotic medication use} = \text{aspirin}) + 2.336 \times (\text{antithrombotic medication use} = \text{clopidogrel}) + 3.457 \times (\text{antithrombotic medication use} = \text{warfarin}) + 1.604 \times (\text{polyp location} = \text{right hemicolon}) + 0.806 \times (\text{polyp morphology} = \text{pedunculated}) + 0.862 \times (\text{modality} = \text{EMR})$.

Calibration of the Model

The calibration plot for the probability of delayed PPB showed good agreement between the predicted and observed rates in the model (Figure 4). The *P*-value for the Hosmer–Lemeshow test was .957, with an Emax value of 0.156 and an Eavg value of 0.003, suggesting that this model was a perfect fit.

Decision Curve Analysis of the Nomogram

The DCA of the model is shown in Figure 5. With a threshold probability of <40%, this model would provide additional value relative to either the treat-all or the treat-none schemes.

DISCUSSION

In the present study, a risk prediction model for delayed PPB was developed and evaluated in patients undergoing colonoscopic polypectomy. This model incorporated age, gender, polyp location, polyp morphology, antithrombotic medication use, and modality for polypectomy. The model showed good discrimination (AUC = 0.838, 95% CI: 0.775-0.900) and calibration performance. Additionally, a nomogram was developed according to the predictors for facilitating individualized prediction of delayed PPB. This model showed potential clinical utility.

Colonoscopic polypectomy is considered a standard procedure that significantly decreases the incidence of colorectal carcinoma. It is well documented that the majority of colonic adenocarcinomas originate from preexisting colonic adenomas.[2-4,18,19] Despite remarkable improvements in the hemostatic equipment and techniques employed, PPB remains the most significant adverse event of endoscopic polypectomy.[20-22] Delayed PPB can cause serious clinical consequences requiring blood transfusion, endoscopic hemostasis, embolization, or surgery, which often manifest after the patient has been discharged from the hospital.[12]

Although our data also showed that polyp size was the most conspicuous risk factor in the univariate analyses,[3,4,6,9,12] they were subsequently filtered by LASSO regression. Moreover, polyp morphology (pedunculated) and location (right hemicolon) were identified as potential variables for predicting delayed PPB. However, results regarding polyp morphology have been inconsistent according to previous reports.[11,23,24] These studies demonstrated that sessile polyps were more likely to bleed due to the increasing depth of polypectomy sections and the added risk of visible blood vessels in the submucosa during the procedure. In our study, more cases of delayed PPB with pedunculated polyps were observed. We considered the long, large-caliber feeding vessels inside the stalk of the pedunculated polyps

Table 1. Baseline Characteristics of the Study Participants

	Delayed PPB		
Variables	No (n = 2454)	Yes (n = 40)	*P*
Age (years)	58.11 (10.73)	51.98 (11.95)	<.001
Gender (%)			<.001
Male	1576 (64.2)	36 (90.0)	
Female	878 (35.8)	4 (10.0)	
BMI (kg/m^2)	23.77 (4.83)	23.13 (2.47)	.399
Hypertension, n (%)			.773
Yes	789 (32.2)	12 (30.0)	
No	1665 (67.8)	28 (70.0)	
Diabetes, n (%)			.503
Yes	193 (7.9)	2 (5.0)	
No	2261 (92.1)	38 (95.0)	
Cardiovascular disease, n (%)			.844
Yes	107 (4.4)	2 (5.0)	
No	2347 (95.6)	38 (95.0)	
Smoking, n (%)			.657
Yes	818 (33.3)	12 (30.0)	
No	1636 (66.7)	28 (70.0)	
Alcohol, n (%)			.698
Yes	788 (32.1)	14 (35.0)	
No	1666 (67.9)	26 (65.0)	
Antithrombotic medication use, n (%)			<.001
No	2356 (96.0)	33 (82.5)	
Aspirin	83 (3.4)	3 (7.5)	
Clopidogrel	12 (0.5)	1 (2.5)	
Warfarin	3 (0.1)	3 (7.5)	
Pathological results, n (%)			.624
Adenomatous	2213 (90.2)	37 (92.5)	
Inflammatory/hyperplastic	241 (9.8)	3 (7.5)	
Location, n (%)			<.001
Right hemicolon	447 (18.2)	17 (42.5)	
Left hemicolon	2007 (81.8)	23 (57.5)	
Morphology, n (%)			.008
Pedunculated	645 (26.3)	8 (45.0)	
Sessile	1809 (73.7)	22 (55.0)	
Modality, n (%)			.014
EMR	1177 (48.0)	27 (67.5)	
Snare/forceps	1277 (52.0)	13 (32.5)	
Prophylactic clipping			.686

(*Continued*)

Variables	Delayed PPB		P
	No (n = 2454)	Yes (n = 40)	
Yes	1456 (59.3)	25 (62.5)	
No	998 (40.7)	15 (37.5)	
Polyp size (mm)	8.45 (4.88)	10.60 (5.28)	.006
PT (s)	11.26 (0.77)	11.18 (0.62)	.522
APTT (s)	32.79 (8.09)	33.52 (3.34)	.569
Hemoglobin (g/L)	141.19 (34.27)	142.22 (17.65)	.849
Platelets ($\times 10^9$/L)	214.06 (77.27)	203.88 (68.05)	.407
CEA (ng/mL)	2.85 (17.05)	1.36 (0.88)	.580
CA199 (ng/mL)	13.38 (56.04)	8.32 (6.28)	.568
Triglyceride (mmol/L)	1.65 (1.35)	1.52 (0.98)	.537
TC (mmol/L)	4.86 (8.87)	4.49 (0.84)	.794
HDL-C (mmol/L)	1.33 (2.44)	1.21 (0.31)	.754
LDL-C (mmol/L)	3.00 (0.88)	2.95 (0.64)	.739

Continuous variables are shown as mean (SD).
EMR, endoscopic mucosal resection; PT, prothrombin time; APTT, activated partial thromboplastin time; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.

as a possible reason. The potential explanations for delayed PPB in the right hemicolon might be as follows: (1) the abundant fat in the submucosa compared to that in the left hemicolon could reduce the efficacy of the electrosurgical unit's coagulation function; or (2) the thinner wall of the right hemicolon might be associated with more damage of the vessels in the submucosal layer.[25,26] Antithrombotic medication use has shown conflicting results in previous studies.[14,27,28] Our data demonstrated that it is a significant risk factor for delayed PPB. However, the number of the cases was small, which might need further investigation. Of interest is the observation that the younger patients were more susceptible to delayed PPB. Our assumption was that it might possibly be related to social factors. Young patients might resume their normal life, including a heavy workload or habitual intake of alcohol, immediately after polypectomy.

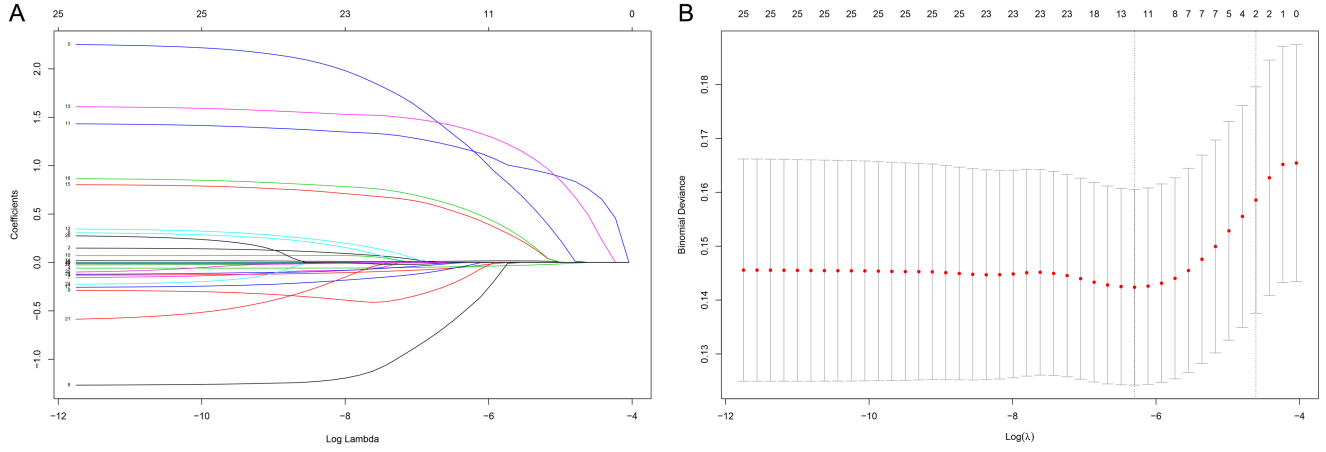

Figure 1. Predictor selection using the LASSO regression analysis. (A) Tuning parameter (lambda) selection in the LASSO regression used 10-fold cross-validation. Binomial deviance was plotted versus log (lambda). The dotted vertical lines were plotted at the optimal values according to the 1-SE criteria; (B) LASSO regression coefficient profiles of variables. A coefficient profile plot was created against the log (lambda) sequence. A total of 6 non-zero coefficients were filtered and used to construct predictive model. SE, standard error.

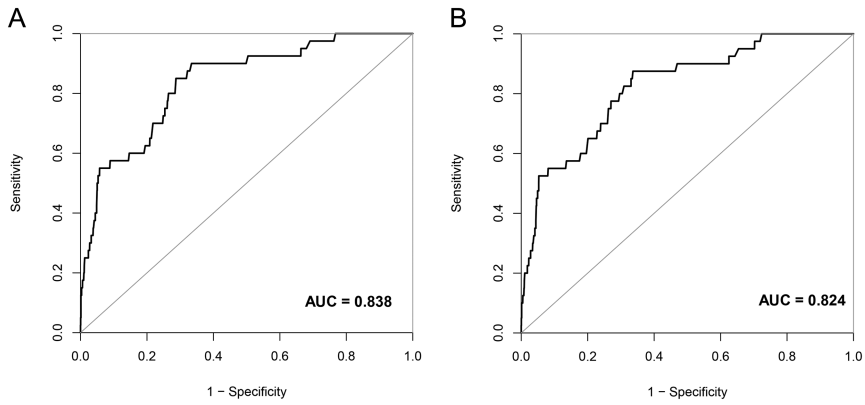

Figure 2. ROC curve of the established model and in the internal validation. AUC (A) shows the discrimination in the model, and AUC (B) of the internal validation. ROC, receiver operating characteristic; AUC, area under the curve.

Although multiple risk factors have been proposed in prior studies, it is still challenging to predict the occurrence of delayed PPB. To the best of our knowledge, no model for the prediction of delayed PPB has been reported to date. The predictive model for delayed PPB in the present study was developed on basis of 6 predictors, including age, gender, polyp location, polyp morphology, antithrombotic medication use, and modality of polypectomy. These predictors were filtered by shrinking the regression coefficients with the LASSO regression. This method was considered to surpass the technique of choosing predictors based on the strength of their univariable association with outcome.[29,30] In addition, these selected predictors are clinically accessible. The relevant nomogram served to stratify patients with a higher risk of delayed PPB in a straightforward manner. Therefore, physicians can accordingly adjust the strategies of management for these patients (e.g., prophylactic clipping; using an endoloop for pedunculated polyps; or extending the observation period). Our model showed good discrimination and calibration. Decision curve analysis is recommended as a novel method for assessing the clinical usefulness of a predictive model.[31,32] The DCA of this model suggested that when the threshold probability of an individual was <40%, using the model in the present study to predict delayed PPB could provide additional value relative to either the treat-all or the treat-none schemes.

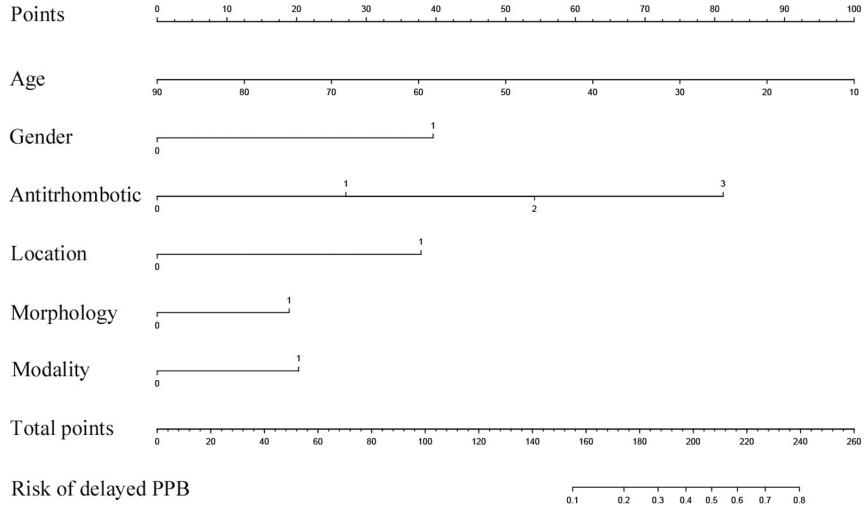

Figure 3. Nomogram for prediction of delayed PPB risk and its predictive performance. First, find the points for each predictor (variable) of a patient on the uppermost rule; then, add all points to calculate the "total points;" finally find the corresponding predicted probability of delayed PPB on the lowest rule. Codes annotation: gender, 0 = female, 1 = male; antithrombotic medication use, 0 = none, 1 = aspirin, 2 = clopidogrel, 3 = warfarin; location, 0 = left hemicolon, 1 = right hemicolon; morphology, 0 = sessile, 1 = pedunculated; modality, 0 = snare/forceps, 1 = EMR. PPB, post-polypectomy bleeding; EMR, endoscopic mucosal resection.

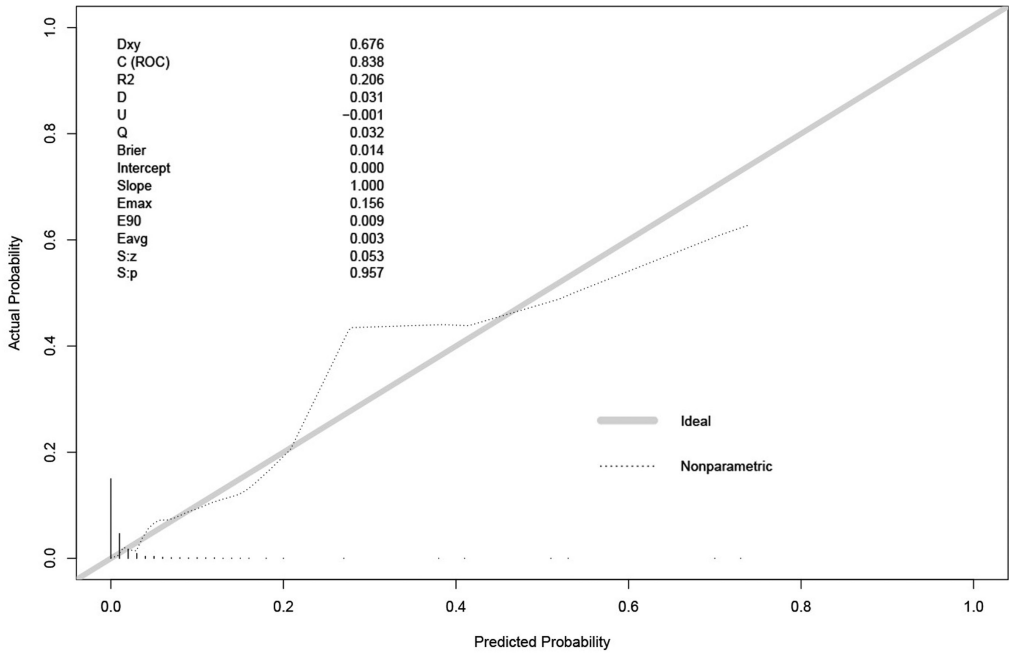

Figure 4. Calibration curve of the model. The calibration of the model in line with the agreement between predicted and observed outcomes of delayed PPB. The Y-axis represents the actual delayed PPB rate. The X-axis represents the predicted risk of delayed PPB. The shadowed line represents a perfect prediction by an ideal model. The dotted line represents the performance of the model, with a closer fit to the shadow line representing a better prediction. PPB, post-polypectomy bleeding.

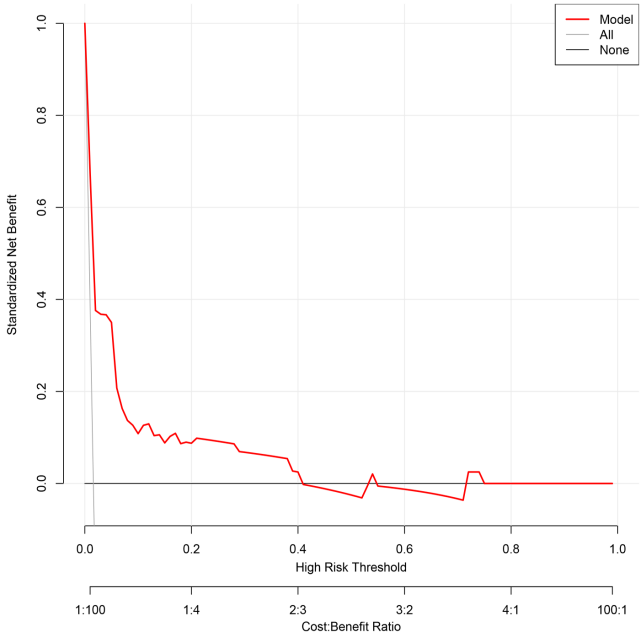

Figure 5. Decision curve analysis for the predictive model. The net benefit was produced against the high-risk threshold. The red solid line represents the predictive model. The decision curve indicates that when the threshold probability is less than 40%, the application of this predictive model would add net benefit compared with either the treat-all or the treat-none strategies.

However, our study has several limitations. First, this model was developed by using retrospective data at a single center, which inevitably suffered from confounding bias. Second, an external validation is warranted to confirm the performance of the nomogram. Since delayed PPB is an infrequent complication, a relatively small number of cases with delayed PPB was examined in this study, which could thus cause ambiguous results.

In summary, a predictive model for delayed PPB has been developed. This model shows good discriminatory performance and significant clinical efficacy, and could thereby facilitate more precise prediction and better management of delayed PPB.

Ethics Committee Approval: The study was approved by the institutional ethics committee of Jinhua Hospital of Zhejiang University (No. 2020000054).

Informed Consent: Signed informed consent was waived, because patient information was kept anonymous.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – X.Y.; Design - X.Y.; Supervision - X.Y., J.D.; Resource - X.Y., J.D.; Materials -J.H.; Data Collection and/or

Processing - J.H.; Analysis and/or Interpretation -J.H.; Literature Search - J.H.; Writing - X.Y.; Critical Reviews - X.Y., J.D.

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Conflict of Interest: The authors involved declared no conflict of interest.

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