A Nomogram Model Based on Preoperative Coagulation-Fibrinolysis Biomarkers for Predicting Postoperative Hemorrhage After Pancreaticoduodenectomy: A Retrospective Study With Internal Validation

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AIM: Post-pancreaticoduodenectomy hemorrhage (PPH) remains a life-threatening complication. However, conventional coagulation assays fail to capture the dynamic hemostatic disturbances preceding overt bleeding. This study aimed to evaluate whether preoperative coagulation-fibrinolysis biomarkers could improve PPH risk stratification and support the development of an interpretable predictive model.

METHODS: We retrospectively analyzed 315 adults who underwent elective pancreaticoduodenectomy, randomly allocated to a training cohort (n = 220) and an internal validation cohort (n = 95). Preoperative variables included routine coagulation indices and molecular markers, including thrombin-antithrombin complex (TAT), plasmin-α2-plasmin inhibitor complex (PIC), and D-dimer. Multivariable logistic regression was used to identify independent predictors and construct a predictive nomogram. Model performance was assessed in terms of discrimination (area under the curve [AUC]), calibration (Brier score and Hosmer-Lemeshow goodness-of-fit test), and decision curve analysis (DCA).

RESULTS: In the training cohort, patients who developed PPH exhibited significantly higher levels of TAT, PIC, and D-dimer, and lower fibrinogen (FIB). Multivariable analysis identified four independent predictors: FIB (odds ratio (OR) = 0.46), PIC (OR = 1.79), D-dimer (OR = 1.59), and TAT (OR = 1.15). The nomogram demonstrated good discrimination, with an AUC of 0.81 in the training cohort and 0.75 in the validation cohort. Calibration performance was acceptable, with Brier scores of 0.11 (training) and 0.15 (validation). Although the Hosmer-Lemeshow test indicated no statistically significant lack of fit ($p > 0.05$ in both cohorts), visual inspection of the validation calibration curve suggested moderate deviations in the intermediate-risk range, likely reflecting the limited sample size. Shapley Additive exPlanations (SHAP) analysis identified PIC as the most influential predictor in the model output.

CONCLUSIONS: Preoperative coagulation-fibrinolysis "process markers" may provide additional information for assessing PPH risk. The four-marker nomogram (PIC, TAT, D-dimer, and FIB) offers an interpretable framework for perioperative risk stratification and demonstrates satisfactory overall performance. However, external validation in larger, independent cohorts is warranted to confirm model generalizability and calibration stability.

Keywords: post-pancreaticoduodenectomy hemorrhage; thrombin–antithrombin complex; plasmin-α2-plasmin inhibitor complex; D-dimer; fibrinogen

Introduction

Pancreaticoduodenectomy (PD) is the definitive surgical treatment for many periampullary and pancreatic head malignancies. However, it remains among the most technically demanding abdominal procedures. Despite advances in operative techniques and perioperative critical care that have reduced postoperative mortality to <5%, overall morbidity remains high, with complication rates approaching 50% [1]. Among these complications, post-pancreaticoduodenectomy hemorrhage (PPH) is particularly severe. Although the reported incidence varies depending on definitions, PPH affects a clinically meaningful proportion of patients and is associated with a disproportionately high case-fatality rate [2]. The International Study Group of Pancreatic Surgery (ISGPS) has standardized reporting by classifying PPH according to onset (early vs. late), location (intraluminal vs. extraluminal), and severity [3]. Compared with early bleeding, which typically reflects technical or immediate hemostatic failure, delayed PPH is frequently driven by local inflammation and enzymatic injury, especially in the presence of postoperative pancreatic fistula, where exposure to activated pancreatic juice may erode adjacent vessels [2]. These observations underscore the need to identify earlier physiological and clinical precursors to facilitate the timely identification of patients at risk for delayed hemorrhage.

Current PPH surveillance remains largely reactive, relying on late clinical manifestations such as blood-stained

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drainage, declining hemoglobin levels, or hemodynamic instability, signs that may appear only after substantial blood loss [4]. Conventional coagulation assays, including prothrombin time (PT) and activated partial thromboplastin time (APTT), are routinely obtained. However, they provide a static, plasma-based, and incomplete representation of hemostasis, and are poorly suited to capturing dynamic whole-blood processes (e.g., platelet contribution to clot strength and fibrinolysis) or subtle changes in thrombin generation [5,6]. Following PD, surgical injury and systemic inflammation, often compounded by infection or sepsis, can markedly disrupt the balance between coagulation activation and fibrinolysis, potentially masking early pathophysiological alterations that precede clinically evident hemorrhage [7,8,9].

Hemostatic homeostasis depends on tightly regulated interactions between thrombin generation and fibrinolysis; dysregulation of either pathway may predispose to thrombosis or bleeding. Molecular biomarkers that reflect these dynamics, including the thrombin-antithrombin complex (TAT) and the plasmin-α2-plasmin inhibitor complex (PIC), have been proposed as time-sensitive indicators of coagulation activation, plasmin generation, and endothelial injury, potentially providing a more "real-time" representation of coagulation-fibrinolysis balance than conventional screening assays [10,11,12,13]. Notably, fibrinolytic activation markers may increase early in inflammatory endotheliopathy models, in some settings preceding elevations in thrombin activation markers such as TAT [14]. We therefore hypothesize that a subset of patients enters a "prehemorrhagic" state characterized by enhanced fibrinolysis relative to effective fibrin stabilization, manifesting as subclinical hyperfibrinolysis and/or coagulation factor consumption before overt bleeding.

However, evidence supporting the clinical application of these biomarkers in pancreatic surgery, particularly for predicting PPH, remains limited, and robust predictive tools that integrate dynamic molecular indicators into clinically interpretable risk models are lacking [2,15,16]. Given the heterogeneity of perioperative pathophysiology following PD, reliance on single biomarkers is unlikely to achieve reliable risk stratification [17]. Accordingly, we conducted a retrospective analysis of 315 patients undergoing PD to evaluate associations between preoperative coagulation-fibrinolysis biomarkers and PPH, identify independent predictors using multivariable regression, and develop a visual nomogram. Additionally, we applied explainable machine-learning approaches, including Shapley Additive exPlanations (SHAP) analysis, to quantify the relative contribution of each biomarker to bleeding risk, to support individualized perioperative management and facilitate a shift from reactive interventions to proactive risk stratification and early prevention.

Methods

Study Design

This study was approved by the Ethics Committee of The First Hospital of Jiaxing, Affiliated Hospital of Jiaxing University (Approval No.: 2026-LP-094) and analyzed data collected from 1 May 2020 to 30 June 2025. Written informed consent was obtained from all participants. The study protocol adheres to the Declaration of Helsinki.

Participant Selection

A total of 315 patients who underwent pancreaticoduodenectomy were included in this study. The overall cohort was randomly divided into a training cohort (n = 220) and a validation cohort (n = 95) in an approximate 7:3 ratio. Inclusion criteria were: (1) age ≥18 years; (2) elective pancreaticoduodenectomy for pancreatic or periampullary tumors; (3) availability of complete preoperative coagulation and fibrinolysis biomarker data; and (4) complete clinical and laboratory data sufficient for the diagnosis and ISGPS grading of postoperative hemorrhage following pancreaticoduodenectomy. Exclusion criteria were: (1) history of primary hematologic disorders or severe coagulation dysfunction; (2) concurrent severe hepatic or renal impairment affecting coagulation factor metabolism; and (3) missing data on the primary outcome (postoperative hemorrhage) or loss to follow-up.

Data Acquisition and Clinical Assessments

Perioperative patient data were extracted from the hospital's electronic medical record system using standardized data collection procedures. Preoperative baseline characteristics included age, sex, body mass index (BMI), and American Society of Anesthesiologists (ASA) classification, along with documentation of smoking history and comorbidities such as hypertension and diabetes. Given the potential influence of medications on the coagulation system, preoperative use of antithrombotic agents was recorded separately and incorporated into the analysis.

Laboratory examinations were categorized into conventional coagulation parameters and specific molecular biomarkers. Conventional parameters included platelet count, PT, APTT, thrombin time (TT), and fibrinogen (FIB). Preoperative data on molecular biomarkers of the coagulation-fibrinolysis system, including TAT to reflect thrombin generation, PIC to assess fibrinolytic activation, and D-dimer as a marker of secondary hyperfibrinolysis, were retrieved from medical records.

Statistical Analysis

All statistical analyses were performed using R software (version 4.3.3; R Foundation for Statistical Computing, Vienna, Austria). The study cohort was randomly divided into a training cohort (n = 220) and a validation cohort (n = 95) for internal validation. Normality of continuous variables was assessed using the Shapiro-Wilk test. Normally dis-

tributed variables were expressed as mean ± standard deviation (SD) and compared between groups using the independent samples *t*-test. Non-normally distributed variables were expressed as median (interquartile range) [M (Q1, Q3)] and compared using the Mann-Whitney *U* test. Categorical variables were presented as frequencies (percentages) and compared using the chi-square (χ^2) test or Fisher's exact test as appropriate.

During model development, univariate logistic regression was first conducted in the training cohort to identify potential risk factors. Variables with $p < 0.10$ in univariate analyses were subsequently entered into multicollinearity diagnostics, with variance inflation factor (VIF) calculated; variables with VIF >5 were considered indicative of significant collinearity and were excluded. The remaining variables were then included in a multivariable logistic regression model to identify independent predictors, and a nomogram for predicting PPH was constructed based on these predictors. Continuous variables were analyzed using their original measurement units and were not log-transformed or standardized in the primary model to preserve clinical interpretability.

Model performance was evaluated across discrimination, calibration, and clinical utility. Discrimination was quantified by the area under the curve (AUC). For logistic regression, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using the Wald method. For receiver operating characteristic (ROC) analysis, the 95% CIs of AUCs were estimated using the DeLong method, and statistical significance was also assessed. The optimal cut-off value was determined based on the maximum Youden index, and the corresponding sensitivity and specificity were calculated.

Calibration was assessed using calibration curves with bias correction performed using 1000 bootstrap resamples. To further evaluate model stability and potential overfitting, bootstrap-based internal validation was conducted in the training cohort using 1000 resamples. The average optimism in discrimination was calculated, and a bootstrap-derived calibration slope was used to evaluate overfitting and the need for shrinkage. Quantitative calibration performance was evaluated using the Brier score, with lower values indicating better predictive accuracy. The Hosmer-Lemeshow goodness-of-fit test (g = 10) was used as a supplementary measure of model fit.

Clinical net benefit was evaluated using decision curve analysis (DCA). The distribution of continuous biomarkers was additionally examined for skewness. To assess the robustness of model specification, a sensitivity analysis was performed by refitting the multivariable logistic regression model using log-transformed biomarker values. However, the primary model was retained in the original clinical units to maintain clinical interpretability. Additionally, SHAP values were computed to quantify the contribution of coagulation-fibrinolysis biomarkers and other features to individual predictions. All statistical tests were two-tailed, and $p < 0.05$ was considered statistically significant.

Results

Baseline Characteristics and Cohort Comparability

A total of 315 patients who underwent pancreaticoduodenectomy were included in this study, with a mean age of 64.37 ± 9.26 years; 59.68% were male, and the mean BMI was 23.19 ± 3.04 kg/m^2. The cohort was randomly divided into a training cohort (n = 220) and a validation cohort (n = 95) in a 7:3 ratio. As shown in Table 1, the two cohorts were well-balanced with respect to demographic characteristics (age, sex, BMI), comorbidities (diabetes mellitus and hypertension), smoking history, and preoperative antithrombotic use, with no statistically significant differences (all $p > 0.05$). ASA classification was similarly distributed, predominantly grades II and III, with no significant between-group differences ($p > 0.05$). Surgical anatomical factors, including pancreatic texture and main pancreatic duct diameter, were also comparable between cohorts. Regarding coagulation-fibrinolysis markers, baseline levels were comparable between the two cohorts. Conventional coagulation parameters (PT, APTT, TT, FIB) and platelet count exhibited no significant differences. Key molecular markers (TAT, PIC, and D-dimer) likewise did not differ significantly between groups. These findings indicate that the training and validation cohorts were derived from a homogeneous population, supporting the validity of the data split for subsequent model development and internal validation.

Stratified Analysis of Prognostic Determinants

In the training cohort (n = 220), patients were stratified according to the occurrence of PPH, and clinical characteristics, as well as preoperative coagulation-fibrinolysis markers, were compared between groups (Table 2). The results showed that median TAT levels in the PPH group were 5.27 ng/mL, significantly higher than 3.08 ng/mL in the non-PPH group ($Z = –4.33$, $p < 0.001$). For fibrinolysis-related markers, PIC levels (median 1.64 mg/L vs. 0.94 mg/L; $Z = –4.25$, $p < 0.001$) and D-dimer levels (median 1.12 mg/L vs. 0.71 mg/L; $Z = –3.51$, $p < 0.001$) were also significantly elevated in the PPH group. Among conventional coagulation parameters, FIB levels were significantly lower in the PPH group (median 2.94 g/L) compared to the non-PPH group (median 3.19 g/L; $Z = –2.04$, $p = 0.041$). However, no statistically significant differences were observed between groups for platelet count, PT, APTT, or thrombin time (TT) (all $p > 0.05$). Baseline characteristics, including age, sex, BMI, diabetes mellitus, hypertension, preoperative antithrombotic use, smoking history, ASA classification, pancreatic texture, and duct diameter, were comparable between groups, with no statistically significant differences (all $p > 0.05$).

Table 1. Baseline characteristics and comparability between training and validation cohorts.

Variables	Total (n = 315)	Validation cohort (n = 95)	Training cohort (n = 220)	Statistic	*p*-value
Age (years), mean ± SD	64.37 ± 9.26	64.07 ± 8.85	64.49 ± 9.45	$t = -0.37$	0.714
Gender, n (%)				$\chi^2 = 0.01$	0.940
Female	127 (40.32)	38 (40.00)	89 (40.45)		
Male	188 (59.68)	57 (60.00)	131 (59.55)		
BMI (kg/m^2), mean ± SD	23.19 ± 3.04	23.33 ± 3.19	23.13 ± 2.98	$t = 0.54$	0.592
Diabetes mellitus, n (%)				$\chi^2 = 0.16$	0.689
No	227 (72.06)	67 (70.53)	160 (72.73)		
Yes	88 (27.94)	28 (29.47)	60 (27.27)		
Hypertension, n (%)				$\chi^2 = 0.11$	0.737
No	200 (63.49)	59 (62.11)	141 (64.09)		
Yes	115 (36.51)	36 (37.89)	79 (35.91)		
Antithrombotic use, n (%)				$\chi^2 = 2.57$	0.109
No	270 (85.71)	86 (90.53)	184 (83.64)		
Yes	45 (14.29)	9 (9.47)	36 (16.36)		
Smoking status, n (%)				$\chi^2 = 0.40$	0.526
No	238 (75.56)	74 (77.89)	164 (74.55)		
Yes	77 (24.44)	21 (22.11)	56 (25.45)		
ASA grade, n (%)				$\chi^2 = 0.17$	0.919
1	12 (3.81)	3 (3.16)	9 (4.09)		
2	160 (50.79)	49 (51.58)	111 (50.45)		
3	143 (45.40)	43 (45.26)	100 (45.45)		
Pancreatic texture, n (%)				$\chi^2 = 0.09$	0.764
Soft	130 (41.27)	38 (40.00)	92 (41.82)		
Hard	185 (58.73)	57 (60.00)	128 (58.18)		
Duct diameter (mm), M (Q_1, Q_3)	3.00 (2.20–4.25)	3.10 (2.25–4.20)	2.95 (2.20–4.30)	$Z = -0.16$	0.876
Platelet ($\times 10^9$/L), M (Q_1, Q_3)	232.00 (184.00–273.50)	226.00 (182.50–265.00)	233.50 (185.75–278.25)	$Z = -0.90$	0.369
FIB (g/L), M (Q_1, Q_3)	3.10 (2.65–3.62)	3.04 (2.53–3.60)	3.13 (2.70–3.62)	$Z = -1.26$	0.207
PT (s), M (Q_1, Q_3)	13.30 (12.58–13.98)	13.19 (12.59–14.01)	13.33 (12.58–13.98)	$Z = -0.17$	0.868
APTT (s), M (Q_1, Q_3)	33.06 (30.82–35.71)	33.14 (30.86–35.77)	33.05 (30.79–35.71)	$Z = -0.24$	0.810
TT (s), M (Q_1, Q_3)	16.89 (15.89–17.80)	16.97 (15.98–17.98)	16.86 (15.88–17.74)	$Z = -1.10$	0.270
TAT (ng/mL), M (Q_1, Q_3)	3.53 (2.05–5.61)	3.60 (2.21–5.74)	3.49 (1.99–5.59)	$Z = -0.40$	0.687
PIC (mg/L), M (Q_1, Q_3)	1.07 (0.65–1.71)	1.11 (0.66–1.68)	1.06 (0.65–1.70)	$Z = -0.31$	0.760
D-dimer (mg/L), M (Q_1, Q_3)	0.76 (0.49–1.34)	0.80 (0.48–1.50)	0.76 (0.50–1.27)	$Z = -0.40$	0.686
PPH, n (%)				$\chi^2 = 0.61$	0.435
No	260 (82.54)	76 (80.00)	184 (83.64)		
Yes	55 (17.46)	19 (20.00)	36 (16.36)		

Notes: Data are presented as mean ± standard deviation (SD) for normally distributed continuous variables, median (interquartile range [IQR], Q1–Q3) for non-normally distributed variables, or frequency (percentage) for categorical variables. *p*-values were calculated using the independent student's *t*-test (*t*) for normally distributed variables, the Mann-Whitney *U* test (*Z*) for non-normally distributed variables, and the chi-square (χ^2) test for categorical variables. No statistically significant differences were observed between the training and validation cohorts (all $p > 0.05$), indicating good baseline comparability.

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists; PPH, post-pancreaticoduodenectomy hemorrhage; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; FIB, fibrinogen; TAT, thrombin-antithrombin complex; PIC, plasmin-α2-plasmin inhibitor complex.

Identification of Independent Predictors

Univariate logistic regression analysis identified significant associations between PPH and specific molecular biomarkers (TAT, PIC, and D-dimer), as well as FIB (all $p < 0.05$). In contrast, conventional demographic variables (e.g., age, sex, BMI) and standard coagulation parameters (PT, APTT, TT, platelet count) were not significantly associated with PPH (all $p > 0.05$).

Multivariable logistic regression analysis identified four independent predictors of PPH (Table 3) including FIB (OR

Table 2. Comparison of clinical and coagulation-fibrinolysis variables stratified by PPH status in the training cohort (n = 220).

Variables	Total (n = 220)	Non-PPH group (n = 184)	PPH group (n = 36)	Statistic	*p*-value
Age (years), mean ± SD	64.49 ± 9.45	64.47 ± 9.53	64.61 ± 9.18	$t = -0.08$	0.934
Gender, n (%)				$\chi^2 = 0.34$	0.562
Female	89 (40.45)	76 (41.30)	13 (36.11)		
Male	131 (59.55)	108 (58.70)	23 (63.89)		
BMI (kg/m^2), mean ± SD	23.13 ± 2.98	23.04 ± 2.97	23.63 ± 3.02	$t = -1.10$	0.275
Diabetes mellitus, n (%)				$\chi^2 = 0.01$	0.941
No	160 (72.73)	134 (72.83)	26 (72.22)		
Yes	60 (27.27)	50 (27.17)	10 (27.78)		
Hypertension, n (%)				$\chi^2 = 0.62$	0.431
No	141 (64.09)	120 (65.22)	21 (58.33)		
Yes	79 (35.91)	64 (34.78)	15 (41.67)		
Antithrombotic use, n (%)				$\chi^2 = 0.87$	0.352
No	184 (83.64)	152 (82.61)	32 (88.89)		
Yes	36 (16.36)	32 (17.39)	4 (11.11)		
Smoking status, n (%)				$\chi^2 = 0.24$	0.626
No	164 (74.55)	136 (73.91)	28 (77.78)		
Yes	56 (25.45)	48 (26.09)	8 (22.22)		
ASA grade, n (%)				$\chi^2 = 2.23$	0.328
1	9 (4.09)	6 (3.26)	3 (8.33)		
2	111 (50.45)	95 (51.63)	16 (44.44)		
3	100 (45.45)	83 (45.11)	17 (47.22)		
Pancreatic texture, n (%)				$\chi^2 = 0.12$	0.727
Soft	92 (41.82)	76 (41.30)	16 (44.44)		
Hard	128 (58.18)	108 (58.70)	20 (55.56)		
Duct diameter (mm), M (Q_1, Q_3)	2.95 (2.20–4.30)	3.00 (2.20–4.40)	2.70 (2.10–3.97)	$Z = -1.24$	0.216
Platelet (×10^9/L), M (Q_1, Q_3)	233.50 (185.75– 278.25)	236.00 (187.00– 277.25)	229.50 (180.50– 290.75)	$Z = -0.35$	0.724
FIB (g/L), M (Q_1, Q_3)	3.13 (2.70–3.62)	3.19 (2.71–3.69)	2.94 (2.62–3.38)	$Z = -2.04$	0.041
PT (s), M (Q_1, Q_3)	13.33 (12.58–13.98)	13.25 (12.58–13.94)	13.44 (12.63–14.35)	$Z = -1.16$	0.247
APTT (s), M (Q_1, Q_3)	33.05 (30.79–35.71)	32.92 (30.68–35.76)	33.39 (32.35–35.18)	$Z = -0.90$	0.369
TT (s), M (Q_1, Q_3)	16.86 (15.88–17.74)	16.80 (15.87–17.65)	17.18 (16.22–18.13)	$Z = -1.34$	0.181
TAT (ng/mL), M (Q_1, Q_3)	3.49 (1.99–5.59)	3.08 (1.85–4.91)	5.27 (3.72–7.62)	$Z = -4.33$	<0.001
PIC (mg/L), M (Q_1, Q_3)	1.06 (0.65–1.70)	0.94 (0.61–1.45)	1.64 (1.01–2.61)	$Z = -4.25$	<0.001
D-dimer (mg/L), M (Q_1, Q_3)	0.76 (0.50–1.27)	0.71 (0.47–1.19)	1.12 (0.79–1.88)	$Z = -3.51$	<0.001

Notes: Data are presented as mean ± standard deviation (SD) for normally distributed continuous variables, median (interquartile range [IQR], Q1–Q3) for non-normally distributed variables, or frequency (percentage) for categorical variables. *p*-values were calculated using the independent student's *t*-test (*t*) for normally distributed variables, the Mann-Whitney *U* test (*Z*) for non-normally distributed variables, and the chi-square (χ^2) test for categorical variables.

0.46, 95% CI 0.24–0.88, $p = 0.019$), PIC (OR 1.79, 95% CI 1.26–2.55, $p = 0.001$), D-dimer (OR 1.59, 95% CI 1.08–2.35, $p = 0.019$), and TAT (OR 1.15, 95% CI 1.03–1.27, $p = 0.012$). Multicollinearity diagnostics indicated that all retained predictors in the final model exhibited low VIF values (FIB: 1.02; PIC: 1.04; D-dimer: 1.03; TAT: 1.01), confirming the absence of meaningful collinearity among model variables. In the training cohort, 36 outcome events were available for the final multivariable model comprising four predictors, corresponding to an event-per-variable (EPV) ratio of 9.0, which is generally considered acceptable for model stability.

Model Performance and Visualization

The nomogram incorporating FIB, PIC, D-dimer, and TAT (Fig. 1) demonstrated robust predictive performance. Discrimination analyses yielded an area under the curve (AUC) of 0.81 (95% CI: 0.74–0.88) in the training cohort and 0.75 (95% CI: 0.63–0.87) in the validation cohort; both values were statistically significant ($p < 0.001$) (Fig. 2). The optimal cut-off value, determined using the maximum Youden index, was 0.126 in the training cohort, corresponding to a sensitivity of 86.1% and a specificity of 67.9%. Application of the same cut-off in the validation cohort yielded a sensitivity of 78.9% and a specificity of 60.5%.

Calibration curves (Fig. 3) demonstrated good agreement between predicted and observed probabilities. Quantitative

Table 3. Univariate and multivariate logistic regression analysis for predictors of post-pancreaticoduodenectomy hemorrhage.

Variables	Univariate					Multivariate				
	β	SE	Z	*p*-value	OR (95% CI)	β	SE	Z	*p*-value	OR (95% CI)
Age	0.00	0.02	0.08	0.933	1.00 (0.96–1.04)					
Gender										
Female					1.00 (Reference)					
Male	0.22	0.38	0.58	0.562	1.25 (0.59–2.61)					
BMI (kg/m^2)	0.07	0.06	1.09	0.274	1.07 (0.95–1.21)					
Diabetes mellitus										
No					1.00 (Reference)					
Yes	0.03	0.41	0.07	0.941	1.03 (0.46–2.29)					
Hypertension										
No					1.00 (Reference)					
Yes	0.29	0.37	0.79	0.432	1.34 (0.65–2.78)					
Antithrombotic use										
No					1.00 (Reference)					
Yes	–0.52	0.56	–0.92	0.356	0.59 (0.20–1.80)					
Smoking status										
No					1.00 (Reference)					
Yes	–0.21	0.43	–0.49	0.627	0.81 (0.35–1.90)					
ASA grade										
1					1.00 (Reference)					
2	–1.09	0.76	–1.44	0.151	0.34 (0.08–1.49)					
3	–0.89	0.76	–1.18	0.238	0.41 (0.09–1.80)					
Pancreatic texture										
Soft					1.00 (Reference)					
Hard	–0.13	0.37	–0.35	0.727	0.88 (0.43–1.81)					
Duct diameter (mm)	–0.20	0.14	–1.42	0.157	0.82 (0.62–1.08)					
FIB (g/L)	–0.60	0.28	–2.16	0.031	0.55 (0.32–0.95)	–0.79	0.33	–2.35	0.019	0.46 (0.24–0.88)
PT (s)	0.11	0.13	0.82	0.413	1.11 (0.86–1.43)					
APTT (s)	0.02	0.04	0.56	0.573	1.03 (0.94–1.12)					
TT (s)	0.17	0.12	1.41	0.159	1.19 (0.94–1.50)					
Platelet (×10^9/L)	0.00	0.00	–0.36	0.717	1.00 (0.99–1.00)					
PIC (mg/L)	0.67	0.18	3.80	<0.001	1.95 (1.38–2.74)	0.58	0.18	3.24	0.001	1.79 (1.26–2.55)
D-dimer (mg/L)	0.58	0.18	3.28	0.001	1.79 (1.26–2.53)	0.47	0.20	2.35	0.019	1.59 (1.08–2.35)
TAT (ng/mL)	0.17	0.05	3.34	<0.001	1.18 (1.07–1.31)	0.14	0.05	2.51	0.012	1.15 (1.03–1.27)

Note: Univariate and multivariate logistic regression analyses were performed to identify independent predictors of PPH. Results are presented as regression coefficient (β), standard error (SE), *Z* statistic, *p*-value, and odds ratio (OR) with 95% confidence interval (CI). Variables with a univariate *p*-value < 0.1 were entered into the multivariable model. A *p*-value < 0.05 was considered statistically significant.
Abbreviation: OR, odds ratio.

assessment yielded a Brier score of 0.11 in the training cohort and 0.15 in the validation cohort, indicating acceptable overall predictive accuracy. The Hosmer-Lemeshow goodness-of-fit test showed no evidence of significant miscalibration in either the training cohort ($p = 0.374$) or the validation cohort ($p = 0.392$). However, visual inspection of the validation cohort (Fig. 3B) revealed moderate variability within the intermediate-risk range, likely attributable to the limited sample size of the validation set.

Decision curve analysis (DCA) demonstrated clinical utility across a broad spectrum of threshold probabilities, with the model providing greater net benefit than "treat-all" or "treat-none" strategies (Fig. 4). To further evaluate internal validity, bootstrap resampling (1000 iterations) was performed in the training cohort. The estimated optimism for discrimination was 0.016, resulting in an optimism-corrected AUC of 0.795. The bootstrap-derived calibration slope was 0.884, suggesting mild overfitting.

Assessment of variable distributions showed that several coagulation-fibrinolysis biomarkers were right-skewed, particularly PIC, D-dimer, and TAT. Sensitivity analysis using log-transformed biomarker values yielded results consistent with the primary model analysis, with no substantive change in the direction or magnitude of associations. The log-transformed model demonstrated comparable predictive performance, with AUC values of 0.82 in the train-

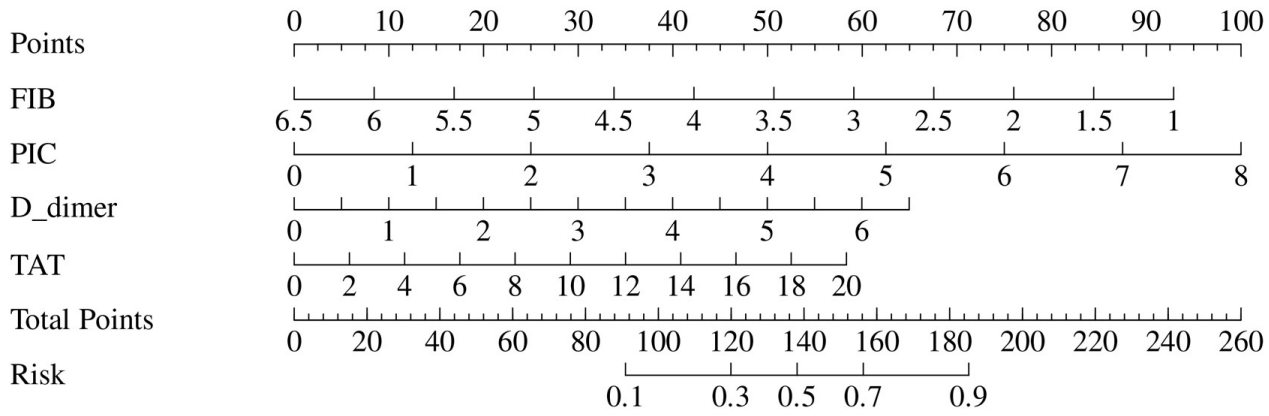

Fig. 1. Predictive nomogram for post-pancreaticoduodenectomy hemorrhage. FIB, fibrinogen; PIC, plasmin-α2-plasmin inhibitor complex; TAT, thrombin-antithrombin complex.

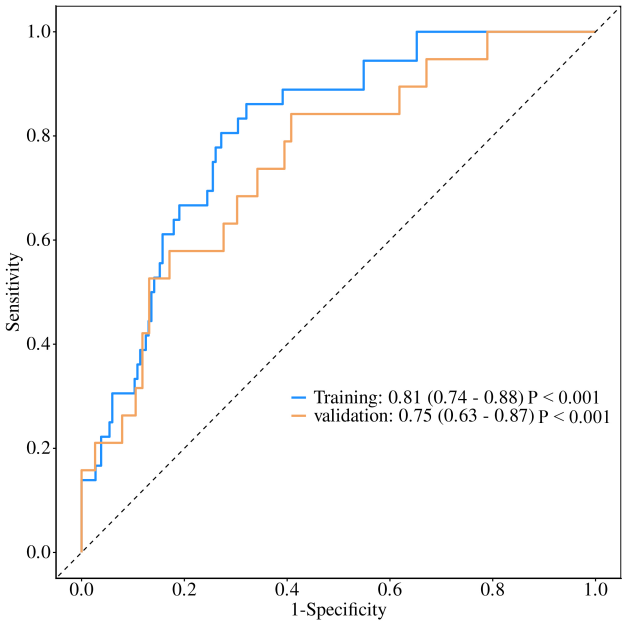

Fig. 2. Receiver operating characteristic (ROC) curves for the predictive nomogram. ROC curve analysis was performed to evaluate the discriminatory performance of the nomogram. The blue curve represents the training cohort, with an area under the curve (AUC) of 0.81 (95% CI: 0.74–0.88). The orange curve represents thevalidation cohort, with an AUC of 0.75 (95% CI: 0.63–0.87), indicating good predictive performance in the internal validation cohort.

ing cohort and 0.78 in the validation cohort, supporting the robustness of the primary modeling strategy.

SHAP analysis further improved model interpretability (Fig. 5), revealing PIC as the most influential prognostic feature. Elevated levels of TAT and D-dimer, together with reduced FIB, were observed to collectively shift individual risk predictions toward adverse outcomes.

The nomogram was developed based on four independent predictors identified in multivariable logistic regression analysis, including fibrinogen (FIB), plasmin-α2-plasmin inhibitor complex (PIC), D-dimer, and TAT. For each variable, the observed value is projected vertically to the "Points" scale to obtain a corresponding score. The sum of all individual scores yields the "Total Points", which corresponds to the estimated probability of postoperative hemorrhage on the bottom axis. Higher total scores indicate an increased predicted risk of postoperative hemorrhage.

Discussion

In the present retrospective cohort of 315 patients undergoing pancreaticoduodenectomy, we evaluated whether preoperative "process-specific" molecular biomarkers of the coagulation-fibrinolysis system could enhance the prediction of PPH. Patients who developed PPH exhibited elevated preoperative TAT, PIC, and D-dimer levels, together with reduced FIB, whereas conventional screening indices (PT, APTT, TT, and platelet count) demonstrated no significant between-group differences. A nomogram incorporating TAT, PIC, D-dimer, and FIB demonstrated good discriminatory performance with acceptable calibration in both the training and validation cohorts, and decision curve analysis indicated a clinically meaningful net benefit. Collectively, these findings support the feasibility of leveraging preoperative molecular hemostatic biomarkers to identify patients at increased risk of PPH before abnormalities become apparent using routine assays.

The observed hemostatic pattern, including concurrent activation of coagulation and enhanced fibrinolysis with relative substrate depletion, is pathophysiologically plausible [18]. TAT reflects *in vivo* thrombin generation and thus the degree of coagulation cascade activation; its elevation is consistent with a procoagulant state driven by inflammation, tissue injury, and endothelial dysfunction [19,20,21]. PIC reflects plasmin generation and fibrinolytic activation

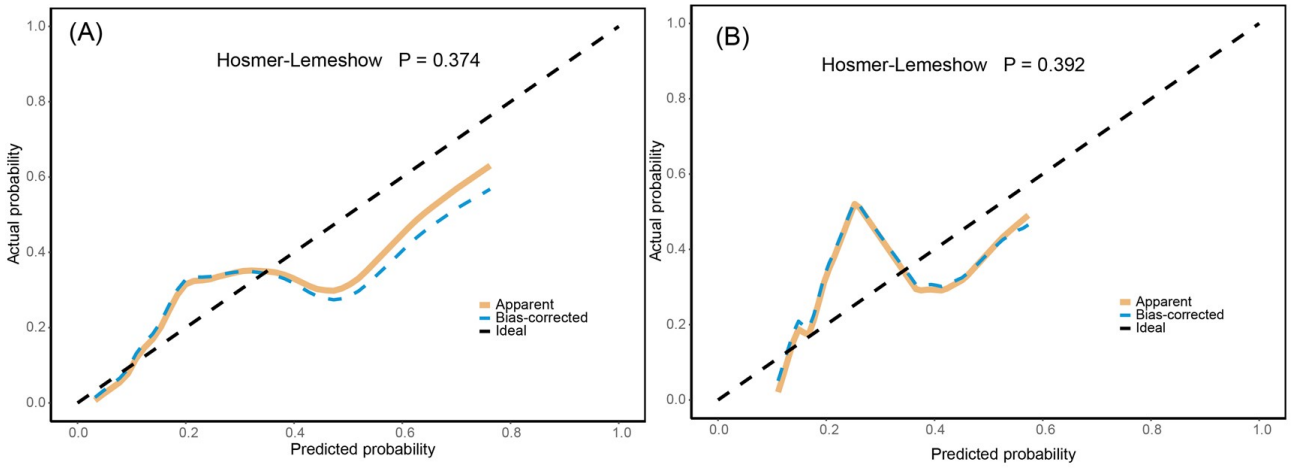

Fig. 3. Calibration curves for the predictive nomogram. (A) Calibration curve for the training cohort. (B) Calibration curve for the validation cohort. The x-axis represents the predicted probability of PPH, and the y-axis represents the observed probability. The diagonal dashed black line represents the ideal reference line representing perfect calibration. The solid orange line represents the apparent performance of the model, while the dashed blue line represents the bias-corrected performance estimated using bootstrap resampling (B = 1000). The Hosmer-Lemeshow test yielded no evidence of significant lack of fit in either cohort ($p > 0.05$), indicating acceptable calibration.

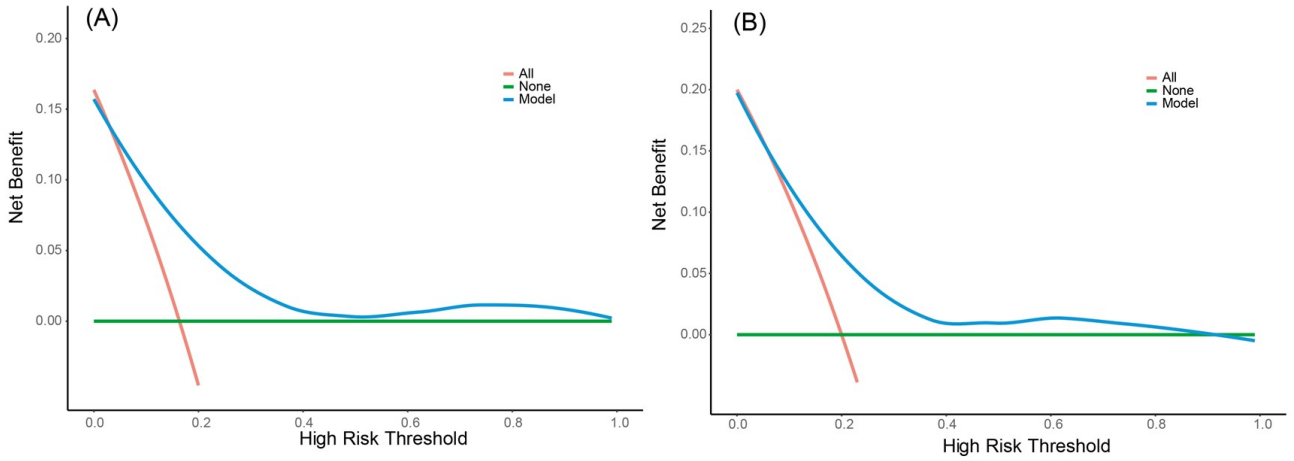

Fig. 4. Decision curve analysis (DCA) for the predictive nomogram. (A) DCA for the training cohort. (B) DCA for the validation cohort. The x-axis represents threshold probability, and the y-axis represents net benefit. The blue curve represents the predictive nomogram. The red curve represents the assumption that all patients experience PPH (treat all strategy), whereas the green curve represents the assumption that no patients experience PPH (treat none strategy). The results indicate that the nomogram provides greater net clinical benefit than either strategy across a broad range of threshold probabilities.

[22], while D-dimer captures the integrated downstream products of fibrin formation and degradation, typically increasing in the setting of active secondary fibrinolysis [23]. Concurrently, reduced FIB may indicate limited hemostatic reserve and/or increased consumption, thereby impairing clot strength and durability [24,25]. When interpreted collectively, these biomarkers suggest that a subset of patients may enter surgery with a preoperative "fragile hemostasis" phenotype: despite activation of coagulation, concurrent hyperfibrinolysis and reduced fibrinogen availability may predispose to clot instability and premature lysis, thereby increasing susceptibility to clinically significant postoperative bleeding. This conceptual framework further provides a mechanistic explanation for the occurrence of severe hemorrhage despite apparently normal routine coagulation test results.

The lack of discriminatory capacity of PT, APTT, TT, and platelet count further underscores the inherent limitations of conventional assays for perioperative bleeding risk stratification in this context [26,27]. These tests are performed under standardized *ex vivo* conditions and are primarily sensitive to coagulation factor deficiencies or prolonged pathway kinetics; they do not adequately capture real-time thrombin generation, endothelial-inflammatory interactions, or dy-

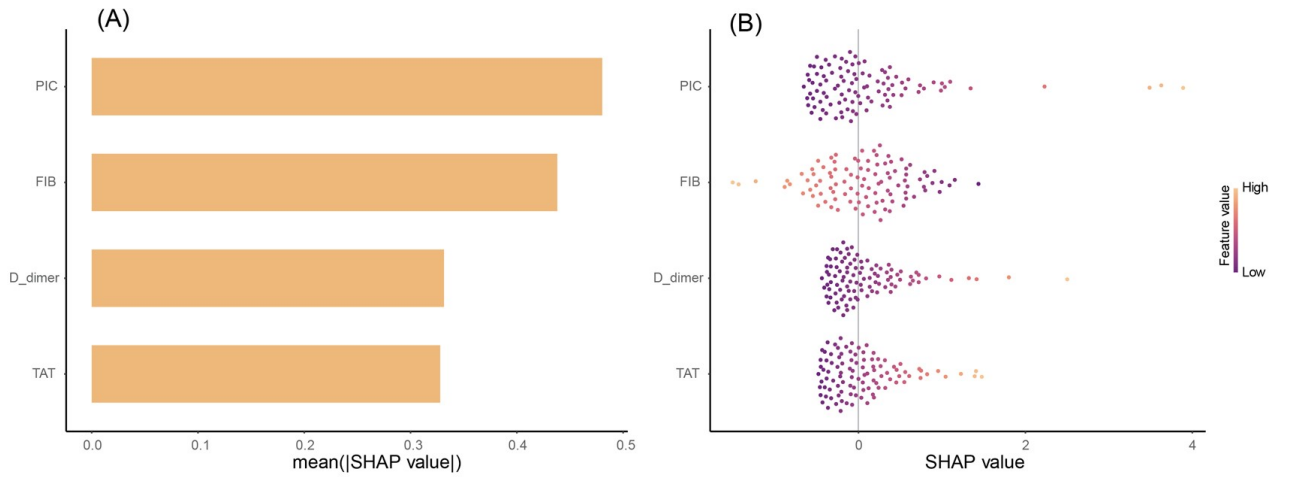

Fig. 5. SHAP visualization of feature importance. (A) Bar plot of the mean absolute SHAP values illustrating the global importance ranking of the four predictors. PIC contributes most strongly to the model output. (B) SHAP (beeswarm) summary plot showing the distribution of SHAP values for each feature across individual patients. Each point represents one patient. Color indicates feature value (red = high, blue = low). The x-axis represents SHAP values, where positive values indicate increased predicted risk of post-pancreaticoduodenectomy hemorrhage (PPH) and negative values indicate decreased risk. The analysis demonstrates that higher levels of PIC, D-dimer, and TAT, as well as lower levels of FIB, are associated with increased predicted risk of post-pancreaticoduodenectomy hemorrhage. PIC, plasmin-α2-plasmin inhibitor complex; FIB, fibrinogen; TAT, thrombin-antithrombin complex; SHAP, Shapley Additive exPlanations.

namic fibrinolytic activity [20,28]. In contrast, TAT and PIC more directly reflect ongoing *in vivo* coagulation and fibrinolysis processes and may therefore detect latent risk trajectories that remain undetected by standard screening approaches [29]. Accordingly, our findings support a risk assessment framework in which molecular "process markers" complement routine indices when evaluating PPH risk.

From an implementation perspective, the proposed model incorporates four preoperative laboratory variables with clear biological interpretability and practical accessibility. However, its clinical applicability should be interpreted with caution. Given that this was a retrospective single-center study with only internal split-sample validation, the generalizability of the model across institutions, patient populations, and perioperative settings remains uncertain. Accordingly, it should currently be regarded as a preliminary preoperative risk-stratification tool rather than a clinically deployable instrument. If validated in external multicenter prospective cohorts, it may facilitate earlier perioperative stratification and allow more tailored surveillance strategies. From a clinical perspective, the proposed cutoff value of 0.126 may serve as a pragmatic reference for preoperative risk stratification rather than an absolute decision threshold. Patients with predicted probabilities exceeding this level may be considered at relatively higher risk of PPH and could therefore warrant closer perioperative surveillance, more intensive postoperative monitoring, and earlier recognition of bleeding-related warning signs. In this context, decision curve analysis further supports the potential clinical utility of the model by demonstrating a net benefit across a range of threshold probabilities, suggesting that its application may improve the identification of patients most likely to benefit from risk-adapted management. In addition, the prominent contribution of PIC suggests that fibrinolytic activation may represent a key axis of risk, although causal inferences cannot be established from the present observational data.

This study extends prior work by shifting prediction upstream, from clinical characteristics or postoperative events to the preoperative coagulation-fibrinolysis baseline. Given that PPH develops within a complex postoperative milieu involving inflammation, infection, vascular erosion, and pancreatic fistula, the present nomogram should be interpreted as a baseline preoperative model rather than a dynamic postoperative early-warning tool. Its value lies in identifying patients who may require closer surveillance once postoperative complications arise, thereby complementing, rather than replacing, dynamic postoperative monitoring.

Several limitations should be acknowledged. First, the retrospective single-center design may have introduced selection bias and limited external generalizability. Second, the model was derived from a single preoperative time point, whereas delayed PPH is strongly influenced by dynamic postoperative processes, including inflammation, infection, and pancreatic fistula. Postoperative measurements and serial trajectories of PT, APTT, TT, fibrinogen, platelet count, TAT, PIC, and D-dimer were not systematically collected and therefore could not be evaluated. Important perioperative variables associated with PPH, including intraoperative

blood loss, operative time, postoperative pancreatic fistula, and postoperative infection, were not included because this study focused on preoperative prediction. Their incremental predictive value should be evaluated in future studies. Third, PPH is not a uniform entity but a heterogeneous complication that varies in timing, location, severity, and underlying mechanism. Early PPH is more likely to reflect technical failure of hemostasis or immediate perioperative coagulation disturbance, whereas delayed PPH is often driven by postoperative events such as pancreatic fistula, infection, local inflammation, and vascular erosion. Accordingly, the present nomogram should be interpreted as a preoperative model reflecting overall susceptibility to PPH rather than a subtype-specific predictor. Future large-scale multicenter studies are warranted to determine whether distinct coagulation-fibrinolysis biomarker profiles are associated with specific clinical phenotypes of PPH. Finally, the limited number of outcome events may have constrained model stability, as suggested by variability in the validation calibration curve, underscoring the need for larger multi-center external validation before routine clinical implementation. Future work should prioritize multi-center prospective validation and evaluate whether integration of postoperative trajectories of TAT, PIC, D-dimer, and FIB, together with key complications such as pancreatic fistula and infection, can enhance time-updated prediction, particularly for delayed PPH. In addition, subtype-specific modeling and mechanistic stratification are warranted to define coagulation-fibrinolysis signatures associated with distinct bleeding phenotypes and to inform the development of rigorously evaluated, risk-adapted intervention strategies.

Conclusions

In conclusion, this study indicates that preoperative coagulation-fibrinolysis molecular biomarkers may provide additional and mechanistically informative indicators for predicting post-pancreaticoduodenectomy hemorrhage. A nomogram based on four markers, including PIC, TAT, D-dimer, and fibrinogen, demonstrated satisfactory discrimination, acceptable calibration, and potential clinical utility for preoperative risk stratification. These findings suggest that assessment of baseline hemostatic imbalance may facilitate identification of patients at increased risk of PPH before surgery. However, given the retrospective single-center design with internal validation only, further external and prospective validation is required before routine clinical application.

Availability of Data and Materials

The data analyzed are available from the corresponding author upon reasonable request.

Author Contributions

YLH designed the research study. YLH and WFS performed the research. DMT and HZ analyzed the data. HZ drafted the article. All authors have been involved in revising the manuscript critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of The First Hospital of Jiaxing, Affiliated Hospital of Jiaxing University (Approval No.: 2026-LP-094), and all procedures followed the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

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Conflict of Interest

The authors declare no conflict of interest.

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