Predictive Value of Preoperative Thromboelastography, C-Reactive Protein, and Thrombomodulin for Postoperative Complications Following Hepatectomy in Patients With Hepatocellular Carcinoma

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AIM: Postoperative complications following hepatectomy remain common and are closely associated with patient prognosis. Conventional preoperative assessment may not adequately capture perioperative coagulation disturbances, systemic inflammation, and endothelial injury. This study aimed to develop and internally validate a multidimensional preoperative prediction model integrating thromboelastography (TEG)-related parameters with inflammatory and endothelial biomarkers.

METHODS: This single-center retrospective cohort study included 195 consecutive patients who underwent elective hepatectomy between March 2022 and May 2025. The cohort was randomly divided into a training set (n = 136) and a validation set (n = 59) at an approximate 7:3 ratio. The primary outcome was the occurrence of Clavien–Dindo grade ≥II complications within 30 days postoperatively. All clinically relevant candidate variables were entered into a least absolute shrinkage and selection operator (LASSO) regression model for feature selection. Variables retained by LASSO were further evaluated before inclusion in the multivariable model. Two multivariable logistic regression models were subsequently constructed: a baseline clinical model (Model 1) and an extended biomarker model (Model 2), which additionally incorporated C-reactive protein (CRP), thrombomodulin (TM), and thromboelastography maximum amplitude (MA). Model discrimination, reclassification, calibration, and potential clinical utility were assessed, and Shapley Additive exPlanations (SHAP) were applied as a supplementary interpretability analysis.

RESULTS: A total of 195 patients were included, of whom 56 (28.72%) developed postoperative complications. The final model retained seven predictors: albumin, prothrombin time, portal hypertension, surgical approach, CRP, TM, and MA. Model 2 demonstrated superior discriminative performance compared with Model 1 in the training cohort (area under the curve (AUC) 0.88 vs. 0.74, $p = 0.006$); a similar advantage was observed in the validation cohort (AUC 0.84 vs. 0.67, $p = 0.001$). Model 2 also achieved higher net reclassification improvement (NRI) and integrated discrimination improvement (IDI) values in both cohorts. Incremental value analysis indicated that the performance gain of Model 2 was primarily attributable to MA, while CRP and TM provided only limited additional predictive value. Calibration and decision curve analyses further supported the overall performance and potential clinical utility of Model 2.

CONCLUSIONS: The extended preoperative prediction model demonstrated superior overall predictive performance compared with the model based solely on conventional clinical indicators. This improvement was driven primarily by MA, while CRP and TM, included as exploratory biomarkers within the extended framework, contributed only modest incremental value. These findings should be considered preliminary and require confirmation in larger multicenter studies with external validation before broader clinical implementation.

Keywords: hepatectomy; postoperative complications; thromboelastography; C-reactive protein; thrombomodulin; prediction model

Introduction

Primary liver cancer (PLC) is a common malignant tumor that poses a significant threat to global health. More than 70% of affected patients are middle-aged and elderly individuals [1]. Hepatectomy remains the primary curative treatment for primary liver cancer and other hepatic space-occupying lesions. Although perioperative safety has improved considerably over the past two decades due to advances in surgical techniques and perioperative management, the incidence of postoperative complications remains above 20% [2,3]. Severe complications, including post-hepatectomy liver failure, hemorrhage, and infection, are closely associated with patient prognosis [4]. These findings suggest that, in addition to advances in surgical techniques, establishing an accurate preoperative risk-prediction system is essential to reduce postoperative complications and improve clinical outcomes.

The Child–Pugh score, which is widely used in clinical practice, remains a cornerstone of preoperative assessment in patients with cirrhosis. However, it is primarily applicable to patients with established cirrhosis and has limited utility in a substantial proportion of patients with chronic hepatitis, fatty liver disease-related hepatocellular carcinoma, or early-stage liver cancer accompanied by mild fi-

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brosis [5]. Furthermore, the Child–Pugh system categorizes continuous variables, such as serum albumin and bilirubin, into discrete grades, potentially leading to loss of prognostic information and reduced discriminatory power [6]. Similarly, although the Model for End-Stage Liver Disease (MELD) score is widely used in liver transplantation, it primarily reflects short-term prognosis in chronic liver disease and may be insufficiently sensitive to dynamic physiological alterations induced by acute surgical stress [7]. Consequently, these conventional assessment tools primarily evaluate static hepatic synthetic function while inadequately capturing dynamic coagulation disturbances, systemic inflammatory responses, and vascular endothelial injury induced by hepatectomy itself, all of which may contribute to postoperative complications [8,9].

Thromboelastography (TEG) is a whole-blood assay that evaluates coagulation function by dynamically monitoring clot initiation, propagation, stabilization, and fibrinolysis. It can provide information regarding coagulation status that may not be identified by conventional coagulation tests, such as prothrombin time (PT) and activated partial thromboplastin time (APTT), thereby potentially facilitating earlier risk identification and clinical intervention [10,11]. Studies by Di *et al*. [12] and He *et al*. [13] have suggested that TEG parameters are associated with perioperative bleeding risk. Furthermore, a prospective study by Gaspari *et al*. [14] demonstrated that thromboelastography may be more accurate than conventional coagulation tests in characterizing the actual coagulation status of patients undergoing hepatectomy. C-reactive protein (CRP), an acute-phase reactant, reflects the presence of a pre-existing inflammatory state when elevated before surgery, and previous studies have shown that preoperative CRP levels are associated with postoperative infectious complications following hepatectomy [15,16]. Thrombomodulin (TM) is a specific biomarker of endothelial injury, and elevated serum TM levels may indicate systemic microvascular inflammation [17]. Wei *et al*. [18] reported that TM levels are markedly elevated in patients with decompensated cirrhosis and are associated with long-term prognosis. However, evidence supporting the incorporation of TM into preoperative risk assessment systems for hepatectomy remains limited. Collectively, TEG, CRP, and TM reflect perioperative physiological disturbances from three complementary dimensions—coagulation function, inflammatory status, and endothelial injury—during surgical stress. However, most existing studies have evaluated coagulation-, inflammation-, or endothelial injury-related biomarkers independently, and few have integrated these multidimensional biomarkers into a unified preoperative predictive model for postoperative complications after hepatectomy.

Therefore, the present study aimed to develop and internally validate a multidimensional prediction model integrating hepatic synthetic function, dynamic coagulation status, systemic inflammatory response, and endothelial inflammatory injury. By comparing the predictive performance of a novel model incorporating TEG parameters, CRP, and TM with that of a conventional clinical model, and by quantifying the incremental predictive value of these biomarkers using net reclassification improvement (NRI) and integrated discrimination improvement (IDI), we aimed to establish a preoperative risk stratification tool with potential applicability across a broad spectrum of liver disease etiologies and clinical backgrounds.

Methods

Study Design

This was a single-center retrospective cohort study including consecutive patients who underwent hepatectomy at The First Hospital of Jiaxing, Affiliated Hospital of Jiaxing University, between March 2022 and May 2025. The surgical procedures were performed in the Department of Hepatobiliary Surgery of the same hospital. The study protocol was approved by the Ethics Committee of The First Hospital of Jiaxing, Affiliated Hospital of Jiaxing University (approval number: 2026-LP-070). Written informed consent was obtained from all patients before surgery, and the study was conducted in accordance with the Declaration of Helsinki.

Study Population

The inclusion criteria were as follows: (1) age $\geq$18 years; (2) elective hepatectomy for primary liver cancer or other hepatic space-occupying lesions (including both open and laparoscopic approaches); (3) completion of comprehensive preoperative laboratory and imaging evaluations; and (4) availability of complete clinicopathological data.

The exclusion criteria were: (1) presence of acute infection, sepsis, or refractory ascites before surgery; (2) coexistence of other systemic malignancies or a history of liver transplantation; (3) intraoperative findings of unresectable tumors with biopsy only performed; and (4) missing key preoperative variables (e.g., thromboelastography parameters or liver function indicators) or incomplete postoperative follow-up data.

Data Collection and Assessment

Perioperative data were extracted from the institutional electronic medical record system. Preoperative baseline characteristics included age, sex, body mass index (BMI), and American Society of Anesthesiologists (ASA) classification [19]. Comorbidities, including hypertension and diabetes mellitus, were also recorded.

Laboratory assessments included complete blood cell count; liver function tests (total bilirubin, albumin, alanine aminotransferase [ALT], and aspartate aminotransferase [AST]); coagulation parameters (prothrombin time [PT], international normalized ratio [INR], activated partial thromboplastin time [APTT], thrombin time [TT], and fibrinogen); tumor markers (alpha-fetoprotein [AFP]); and

inflammatory markers (C-reactive protein [CRP]). Hepatitis B virus DNA (HBV-DNA) levels were measured to assess virological status, because HBV-related liver disease is highly prevalent in patients with hepatocellular carcinoma and may reflect the underlying viral background of the study cohort.

Hepatic functional reserve was evaluated using two key indicators: the indocyanine green 15-minute retention rate (ICG R15), which reflects hepatic metabolic and excretory function; and the future liver remnant (FLR), calculated based on preoperative contrast-enhanced CT three-dimensional reconstruction. The FLR-to-standard liver volume (FLR/SLV) ratio was subsequently derived, with standard liver volume used as a reference to guide safe surgical planning.

Thromboelastography (TEG) parameters were used to assess coagulation function, including reaction time (R time), clot formation time (K time), α-angle, maximum amplitude (MA), and lysis at 30-minute (LY30). Thrombomodulin (TM) was simultaneously measured as a biomarker of vascular endothelial injury. Surgery-related variables included surgical approach (laparoscopic or open) and extent of hepatic resection. Major hepatectomy was defined as resection of three or more liver segments or hemihepatectomy, while all other procedures were classified as minor hepatectomy.

Outcome Definition

The primary outcome was the occurrence of postoperative complications within 30 days after surgery, assessed using the Clavien–Dindo classification system [20]. Complications of grade II or higher, requiring pharmacological treatment, blood transfusion, interventional procedures, or reoperation, were defined as clinically significant events. This composite endpoint included postoperative complications such as infection, bile leakage, hemorrhage, post-hepatectomy liver failure, and other clinically relevant adverse events. Because the study cohort included both cirrhotic and non-cirrhotic patients and the Child–Pugh score is applicable only to cirrhotic populations, this composite scoring system was not utilized. Instead, its individual components (albumin and PT) and portal hypertension were analyzed separately to enable a more refined assessment of hepatic functional reserve across the entire cohort.

Sample Size Consideration

As this was a retrospective cohort study aimed at developing a prediction model, sample size adequacy was evaluated using the events-per-variable (EPV) principle commonly applied in predictive modeling studies. In this cohort, postoperative complications (Clavien–Dindo grade $\geq$II) occurred in 56 patients. The final multivariable logistic regression model included seven predictors selected via least absolute shrinkage and selection operator (LASSO) regression, yielding an EPV of approximately 8 [21]. Although this value was slightly below the traditional threshold of 10, regularization techniques, model parsimony, and additional bootstrap-based internal validation were employed to mitigate overfitting and provide more realistic estimates of model performance.

Statistical Analysis

Data analysis was performed using R software (version 4.5.1, R Core Team). The total sample was randomly divided into a training cohort (n = 136) for model development and a validation cohort (n = 59) for internal validation, at an approximate ratio of 7:3. First, baseline characteristics were compared between the two cohorts to ensure comparability. Subsequently, clinical characteristics were compared between the complication and the non-complication groups within the training cohort.

Univariable logistic regression was used to evaluate crude associations between candidate variables and postoperative complications. All clinically relevant candidate variables were then entered into a least absolute shrinkage and selection operator regression model [22] in the training cohort. The optimal penalty parameter was determined using 10-fold cross-validation, and variables with non-zero coefficients at the selected λ value were considered candidate predictors. Final variable selection was determined by integrating LASSO results with prespecified clinical interpretability, control for redundancy among clinically overlapping predictors, and model parsimony. Subsequently, two multivariable logistic regression models were constructed: a baseline clinical model (Model 1: albumin, PT, portal hypertension, and surgical approach) and an extended biomarker model (Model 2: Model 1 + CRP + TM + MA). Multicollinearity was assessed using variance inflation factors (VIFs), and all VIF values were <3.

Model discrimination was evaluated using receiver operating characteristic (ROC) curves and the area under the curve (AUC) in both the training and validation cohorts, with DeLong tests used for between-model comparisons. Net reclassification improvement (NRI) [23] and integrated discrimination improvement (IDI) [24] were calculated to assess the incremental predictive value of the extended model. Calibration was evaluated using calibration curves, and the Brier score. The held-out validation cohort was used for split-sample validation, whereas 1000 bootstrap resamples within the training cohort were used to estimate optimism-corrected discrimination, calibration slope, and Brier score. Clinical utility was assessed using decision curve analysis (DCA). Shapley Additive exPlanations (SHAP) [25] were employed as a supplementary interpretability analysis for the final multivariable model for model interpretability. A two-sided p-value < 0.05 was considered statistically significant.

Table 1. Baseline characteristics of patients in the training and validation cohorts.

Variables	Overall cohort (n = 195)	Validation cohort (n = 59)	Training cohort (n = 136)	Test statistic	*p*-value
Age (years), mean ± SD	58.12 ± 11.33	59.36 ± 11.32	57.58 ± 11.34	$t = 1.00$	0.316
BMI (kg/m^2), mean ± SD	23.79 ± 3.96	23.59 ± 3.54	23.88 ± 4.13	$t = –0.46$	0.645
FLR/SLV (%), mean ± SD	50.24 ± 7.34	50.67 ± 6.77	50.06 ± 7.59	$t = 0.53$	0.595
Albumin (g/L), mean ± SD	38.87 ± 6.36	38.88 ± 6.63	38.87 ± 6.26	$t = 0.01$	0.990
Fibrinogen (g/L), mean ± SD	2.96 ± 0.68	3.10 ± 0.64	2.90 ± 0.69	$t = 1.91$	0.058
TBIL (μmol/L), M (Q_1, Q_3)	33.20 (27.35, 47.60)	35.40 (28.35, 51.35)	32.50 (27.17, 45.80)	$Z = –1.15$	0.249
ALT (U/L), M (Q_1, Q_3)	77.00 (55.00, 111.00)	82.00 (58.00, 113.00)	74.50 (54.00, 107.50)	$Z = –1.11$	0.267
AST (U/L), M (Q_1, Q_3)	90.00 (63.00, 114.50)	83.00 (57.00, 114.00)	94.00 (66.75, 115.25)	$Z = –0.91$	0.365
AFP (ng/mL), M (Q_1, Q_3)	227.50 (97.00, 600.55)	282.60 (115.90, 593.00)	212.90 (88.92, 594.88)	$Z = –0.63$	0.531
ICG R15 (%), M (Q_1, Q_3)	12.30 (10.10, 16.85)	12.70 (10.00, 17.35)	12.25 (10.17, 16.45)	$Z = –0.47$	0.640
Tumor size (cm), M (Q_1, Q_3)	5.50 (4.40, 6.85)	5.50 (4.50, 7.15)	5.50 (4.30, 6.80)	$Z = –0.22$	0.829
Platelet count ($\times 10^9$/L), M (Q_1, Q_3)	173.00 (128.00, 202.00)	170.00 (113.50, 200.00)	178.00 (129.75, 208.50)	$Z = –1.48$	0.140
INR, M (Q_1, Q_3)	1.08 (1.04, 1.13)	1.07 (1.05, 1.15)	1.08 (1.04, 1.13)	$Z = –0.52$	0.605
PT (s), M (Q_1, Q_3)	13.90 (13.40, 14.55)	13.80 (13.50, 14.75)	13.90 (13.40, 14.50)	$Z = –0.52$	0.605
APTT (s), M (Q_1, Q_3)	38.20 (34.35, 42.00)	38.30 (35.05, 40.65)	38.15 (34.25, 42.52)	$Z = –0.22$	0.825
TT (s), M (Q_1, Q_3)	17.20 (15.20, 18.95)	17.10 (15.05, 18.80)	17.25 (15.28, 19.12)	$Z = –0.31$	0.759
CRP (mg/L), M (Q_1, Q_3)	5.60 (2.95, 12.20)	6.40 (3.10, 11.60)	5.40 (2.90, 12.35)	$Z = –0.72$	0.469
TM (ng/mL), M (Q_1, Q_3)	6.30 (5.30, 7.60)	6.60 (5.10, 7.80)	6.30 (5.30, 7.40)	$Z = –0.02$	0.980
R time (minutes), M (Q_1, Q_3)	4.50 (4.00, 5.00)	4.50 (3.95, 4.95)	4.45 (4.00, 5.00)	$Z = –0.31$	0.754
K time (minutes), M (Q_1, Q_3)	2.00 (1.70, 2.30)	1.90 (1.70, 2.30)	2.00 (1.70, 2.30)	$Z = –0.93$	0.352
MA (mm), M (Q_1, Q_3)	63.50 (57.05, 69.80)	64.00 (55.00, 69.90)	63.45 (58.27, 69.62)	$Z = –0.12$	0.903
α-angle (°), M (Q_1, Q_3)	60.60 (54.35, 66.80)	62.10 (55.75, 70.25)	60.25 (53.20, 64.93)	$Z = –1.76$	0.078
LY30 (%), M (Q_1, Q_3)	0.80 (0.40, 1.50)	0.80 (0.40, 1.75)	0.80 (0.40, 1.50)	$Z = –0.10$	0.922
Sex, n (%)				$\chi^2 = 0.05$	0.824
Female	55 (28.21)	16 (27.12)	39 (28.68)		
Male	140 (71.79)	43 (72.88)	97 (71.32)		
Hypertension, n (%)				$\chi^2 = 0.08$	0.776
No	148 (75.90)	44 (74.58)	104 (76.47)		
Yes	47 (24.10)	15 (25.42)	32 (23.53)		
Diabetes mellitus, n (%)				$\chi^2 = 0.48$	0.490
No	164 (84.10)	48 (81.36)	116 (85.29)		
Yes	31 (15.90)	11 (18.64)	20 (14.71)		
Cirrhosis, n (%)				$\chi^2 = 0.10$	0.755
No	39 (20.00)	11 (18.64)	28 (20.59)		
Yes	156 (80.00)	48 (81.36)	108 (79.41)		
Portal hypertension, n (%)				$\chi^2 = 0.03$	0.862
No	101 (51.79)	30 (50.85)	71 (52.21)		
Yes	94 (48.21)	29 (49.15)	65 (47.79)		
High HBV-DNA level (≥4log), n (%)				$\chi^2 = 0.08$	0.775
No	135 (69.23)	40 (67.80)	95 (69.85)		
Yes	60 (30.77)	19 (32.20)	41 (30.15)		
ASA classification, n (%)				$\chi^2 = 4.05$	0.132
I	67 (34.36)	20 (33.90)	47 (34.56)		
II	75 (38.46)	28 (47.46)	47 (34.56)		
III	53 (27.18)	11 (18.64)	42 (30.88)		
Laparoscopic surgery, n (%)				$\chi^2 = 0.03$	0.854
No	84 (43.08)	26 (44.07)	58 (42.65)		
Yes	111 (56.92)	33 (55.93)	78 (57.35)		
Major hepatectomy, n (%)				$\chi^2 = 0.37$	0.541
No	143 (73.33)	45 (76.27)	98 (72.06)		
Yes	52 (26.67)	14 (23.73)	38 (27.94)		

Table 1. Continued.

Variables	Overall cohort (n = 195)	Validation cohort (n = 59)	Training cohort (n = 136)	Test statistic	*p*-value
Clavien–Dindo grade ≥II complications, n (%)				$\chi^2 = 1.95$	0.162
No	139 (71.28)	38 (64.41)	101 (74.26)		
Yes	56 (28.72)	21 (35.59)	35 (25.74)		

Note: Data are presented as mean ± standard deviation (SD), median (Q_1, Q_3), or n (%), as appropriate. Continuous variables were compared using an independent-samples *t*-test or Mann-Whitney *U* test, and categorical variables were compared using the chi-square test.

For skewed variables summarized as median (Q_1, Q_3), identical median values between groups may occur despite differences in interquartile ranges, reflecting the underlying data distribution rather than data-entry, duplication, or formatting errors.

Abbreviations: M, median; Q_1, 1st quartile; Q_3, 3rd quartile; BMI, body mass index; FLR, future liver remnant; SLV, standard liver volume; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; ICG R15, indocyanine green 15-minute retention rate; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; CRP, C-reactive protein; TM, thrombomodulin; MA, maximum amplitude; ASA, American Society of Anesthesiologists; LY30, lysis at 30-minute; HBV-DNA, Hepatitis B virus DNA; R time, reaction time; K time, clot formation time.

Results

Baseline Characteristics and Cohort Comparability Analysis

A total of 195 patients who underwent hepatectomy were included in this study. The patients were randomly assigned to a training cohort (n = 136) and a validation cohort (n = 59) at an approximate ratio of 7:3. No significant differences were observed between the two cohorts in age, sex, BMI, ASA classification, liver-related disease characteristics and systemic comorbidities (cirrhosis, portal hypertension, hypertension, and diabetes mellitus), preoperative laboratory indicators (albumin, total bilirubin, INR, and ICG R15), TEG parameters, TM level, tumor size, surgical approach (laparoscopic or open), or extent of resection, and other baseline variables ($p > 0.05$), indicating good comparability between the cohorts (Table 1).

In the overall cohort, 56 patients developed Clavien–Dindo grade ≥II complications. The composite endpoint comprised a heterogeneous spectrum of postoperative adverse events, most commonly infection, liver failure, and hemorrhage (**Supplementary Table 1**).

In the training cohort, 35 patients (25.74%) developed Clavien–Dindo grade ≥II complications, whereas 101 patients (74.26%) did not. Compared with patients without complications, those who developed complications had lower mean albumin levels (35.99 ± 6.54 vs. 39.87 ± 5.87 g/L, $p = 0.001$) and higher median total bilirubin levels [45.76 (27.80, 56.90) vs. 30.90 (27.00, 36.20) μmol/L, $p = 0.017$]. Among TEG-related markers, the median MA value was lower [53.60 (47.00, 60.80) vs. 65.90 (61.40, 70.10) mm, $p < 0.001$], whereas the median TM level was higher [7.50 (5.60, 9.55) vs. 6.10 (5.30, 7.10) ng/mL, $p = 0.004$]. Patients with complications also exhibited higher proportions of cirrhosis and portal hypertension, as well as a lower proportion of laparoscopic procedures (Table 2). Notably, for some skewed variables, such as CRP, identical median values were observed between groups despite differences in interquartile ranges. These findings reflected the underlying data distribution rather than duplication or rounding.

Univariate logistic regression analysis demonstrated that total bilirubin (TBIL) (odds ratio (OR) = 1.02, $p = 0.021$), albumin (OR = 0.90, $p = 0.002$), PT (OR = 1.67, $p = 0.018$), INR (OR = 1.66, $p = 0.018$), TM (OR = 1.42, $p < 0.001$), MA (OR = 0.88, $p < 0.001$), CRP (OR = 1.06, $p = 0.011$), ICG R15 (OR = 1.09, $p = 0.047$), portal hypertension (OR = 2.69, $p = 0.016$), and laparoscopic surgery (OR = 0.45, $p = 0.047$) were associated with postoperative complications (Table 3).

Variable Screening and Model Construction

Based on the training cohort data, all clinically relevant candidate variables were entered into the LASSO regression model. The optimal λ value was determined to be 0.034 through 10-fold cross-validation. At this λ value, 13 variables with non-zero coefficients were initially retained, including BMI, albumin, INR, PT, CRP, TM, MA, LY30, sex, portal hypertension, ASA classification, laparoscopic surgery, and major hepatectomy. Because the training cohort was small, not all LASSO-selected variables were included in the final multivariable model. Final variable selection was further guided by redundancy control, clinical interpretability, model parsimony, and the predefined study objective.

PT was retained instead of INR because both variables reflect overlapping aspects of coagulation function. MA was prioritized over LY30 because both are thromboelastography-derived indicators, and MA was considered more representative of clot strength. Likewise, laparoscopic surgery was retained rather than a major hepatectomy because both are surgical variables, and simultaneous inclusion could increase model redundancy. In addition, broader background variables, such as BMI, sex, and ASA classification, were not retained in the final model. These variables demonstrated relatively limited crude asso-

Table 2. Comparison of preoperative clinical and perioperative characteristics between patients with and without postoperative complications in the training cohort.

Variables	Overall cohort (n = 136)	No postoperative complications (n = 101)	Postoperative complications (n = 35)	Test statistic	*p*-value
Age (years), mean ± SD	57.58 ± 11.34	57.90 ± 10.39	56.66 ± 13.84	t = 0.49	0.629
BMI (kg/m^2), mean ± SD	23.88 ± 4.13	24.28 ± 4.16	22.70 ± 3.88	t = 1.97	0.051
FLR/SLV (%), mean ± SD	50.06 ± 7.59	49.54 ± 7.66	51.55 ± 7.25	t = –1.35	0.178
Albumin (g/L), mean ± SD	38.87 ± 6.26	39.87 ± 5.87	35.99 ± 6.54	t = 3.27	0.001
Fibrinogen (g/L), mean ± SD	2.90 ± 0.69	2.91 ± 0.70	2.86 ± 0.66	t = 0.31	0.760
TBIL (μmol/L), M (Q_1, Q_3)	32.50 (27.17, 45.80)	30.90 (27.00, 36.20)	45.76 (27.80, 56.90)	Z = –2.38	0.017
ALT (U/L), M (Q_1, Q_3)	74.50 (54.00, 107.50)	73.00 (53.00, 107.00)	78.00 (54.50, 106.00)	Z = –0.10	0.917
AST (U/L), M (Q_1, Q_3)	94.00 (66.75, 115.25)	96.00 (71.00, 115.00)	77.00 (57.00, 115.00)	Z = –1.06	0.291
AFP (ng/mL), M (Q_1, Q_3)	212.90 (88.92, 594.88)	224.30 (101.00, 625.80)	163.50 (51.05, 379.90)	Z = –1.31	0.190
ICG R15 (%), M (Q_1, Q_3)	12.25 (10.17, 16.45)	11.80 (10.10, 14.60)	15.20 (10.65, 17.55)	Z = –1.88	0.061
Tumor size (cm), M (Q_1, Q_3)	5.50 (4.30, 6.80)	5.60 (4.50, 6.80)	5.00 (4.15, 7.00)	Z = –1.15	0.251
Platelet count ($\times 10^9$/L), M (Q_1, Q_3)	178.00 (129.75, 208.50)	176.00 (136.00, 205.00)	185.00 (114.00, 219.50)	Z = –0.06	0.952
INR, M (Q_1, Q_3)	1.08(1.04, 1.13)	1.07 (1.04, 1.12)	1.10 (1.04, 1.18)	Z = –1.84	0.066
PT (s), M (Q_1, Q_3)	13.90 (13.40, 14.50)	13.80 (13.40, 14.40)	14.20 (13.45, 15.24)	Z = –1.84	0.066
APTT (s), M (Q_1, Q_3)	38.15 (34.25, 42.52)	38.40 (34.10, 42.90)	38.00 (34.40, 41.75)	Z = –0.28	0.776
TT (s), M (Q_1, Q_3)	17.25 (15.28, 19.12)	17.20 (15.30, 19.20)	17.60 (15.30, 18.80)	Z = –0.09	0.929
CRP (mg/L), M (Q_1, Q_3)	5.40 (2.90, 12.35)	5.40 (3.00, 10.70)	5.40 (2.35, 21.80)	Z = –1.06	0.291
TM (ng/mL), M (Q_1, Q_3)	6.30 (5.30, 7.40)	6.10 (5.30, 7.10)	7.50 (5.60, 9.55)	Z = –2.88	0.004
R time (minutes), M (Q_1, Q_3)	4.45 (4.00, 5.00)	4.40 (4.00, 4.90)	4.50 (3.80, 5.30)	Z = –0.28	0.776
K time (minutes), M (Q_1, Q_3)	2.00 (1.70, 2.30)	1.90 (1.70, 2.20)	2.20 (1.60, 2.30)	Z = –0.89	0.376
MA (mm), M (Q_1, Q_3)	63.45 (58.27, 69.62)	65.90 (61.40, 70.10)	53.60 (47.00, 60.80)	Z = –5.12	<0.001
α-angle (°), M (Q_1, Q_3)	60.25 (53.20, 64.93)	60.30 (55.00, 64.90)	60.10 (48.65, 66.75)	Z = –0.85	0.393
LY30 (%), M (Q_1, Q_3)	0.80 (0.40, 1.50)	0.80 (0.40, 1.50)	1.10 (0.65, 1.45)	Z = –1.48	0.139
Sex, n (%)				χ^2 = 0.78	0.377
Female	39 (28.68)	31 (30.69)	8 (22.86)		
Male	97 (71.32)	70 (69.31)	27 (77.14)		
Hypertension, n (%)				χ^2 = 1.07	0.301
No	104 (76.47)	75 (74.26)	29 (82.86)		
Yes	32 (23.53)	26 (25.74)	6 (17.14)		
Diabetes mellitus, n (%)				χ^2 = 0.22	0.637
No	116 (85.29)	87 (86.14)	29 (82.86)		
Yes	20 (14.71)	14 (13.86)	6 (17.14)		
Cirrhosis, n (%)				χ^2 = 4.16	0.041
No	28 (20.59)	25 (24.75)	3 (8.57)		
Yes	108 (79.41)	76 (75.25)	32 (91.43)		
Portal hypertension, n (%)				χ^2 = 6.07	0.014
No	71 (52.21)	59 (58.42)	12 (34.29)		
Yes	65 (47.79)	42 (41.58)	23 (65.71)		
High HBV-DNA level (≥4log), n (%)				χ^2 = 0.04	0.848
No	95 (69.85)	71 (70.30)	24 (68.57)		
Yes	41 (30.15)	30 (29.70)	11 (31.43)		
ASA classification, n (%)				χ^2 = 2.61	0.271
I	47 (34.56)	33 (32.67)	14 (40.00)		
II	47 (34.56)	33 (32.67)	14 (40.00)		
III	42 (30.88)	35 (34.65)	7 (20.00)		
Laparoscopic surgery, n (%)				χ^2 = 4.05	0.044
No	58 (42.65)	38 (37.62)	20 (57.14)		
Yes	78 (57.35)	63 (62.38)	15 (42.86)		
Major hepatectomy, n (%)				χ^2 = 1.48	0.224
No	98 (72.06)	70 (69.31)	28 (80.00)		
Yes	38 (27.94)	31 (30.69)	7 (20.00)		

Note: Postoperative complications were defined as Clavien–Dindo grade ≥II occurring within 30 days after surgery. Data are presented as mean ± standard deviation (SD), median (Q_1, Q_3), or n (%), as appropriate. Continuous variables were compared using the independent-samples *t*-test or Mann-Whitney *U* test, whereas categorical variables were compared using the chi-square test.

For skewed variables summarized as median (Q_1, Q_3), identical median values between groups may occur despite differences in interquartile ranges, reflecting the underlying data distribution rather than duplication, rounding, or data-entry errors.

Table 3. Univariable logistic regression analysis of factors associated with postoperative complications in the training cohort.

Variables	β	SE	Z	p-value	OR (95% CI)
Sex					
Female					1.00 (Reference)
Male	0.40	0.46	0.88	0.379	1.49 (0.61–3.66)
Hypertension					
No					1.00 (Reference)
Yes	–0.52	0.50	–1.03	0.305	0.60 (0.22–1.60)
Diabetes mellitus					
No					1.00 (Reference)
Yes	0.25	0.53	0.47	0.637	1.29 (0.45–3.65)
Cirrhosis					
No					1.00 (Reference)
Yes	1.26	0.65	1.94	0.052	3.51 (0.99–12.45)
Portal hypertension					
No					1.00 (Reference)
Yes	0.99	0.41	2.42	0.016	2.69 (1.21–6.01)
High HBV-DNA level					
No					1.00 (Reference)
Yes	0.08	0.42	0.19	0.848	1.08 (0.47–2.49)
ASA classification					
I					1.00 (Reference)
II	0.00	0.45	0.00	1.000	1.00 (0.41–2.42)
III	–0.75	0.52	–1.44	0.150	0.47 (0.17–1.31)
Laparoscopic surgery					
No					1.00 (Reference)
Yes	–0.79	0.40	–1.99	0.047	0.45 (0.21–0.99)
Major hepatectomy					
No					1.00 (Reference)
Yes	–0.57	0.47	–1.21	0.228	0.56 (0.22–1.43)
BMI	–0.10	0.05	–1.93	0.054	0.91 (0.82–1.00)
TBIL	0.02	0.01	2.30	0.021	1.02 (1.01–1.05)
Age	–0.01	0.02	–0.56	0.575	0.99 (0.96–1.02)
ALT	–0.00	0.01	–0.02	0.985	1.00 (0.99–1.01)
AST	–0.00	0.01	–0.59	0.556	1.00 (0.99–1.01)
AFP	0.00	0.00	0.03	0.972	1.00 (1.00–1.00)
ICG R15 (%)	0.09	0.04	1.99	0.047	1.09 (1.01–1.18)
FLR/SLV (%)	0.04	0.03	1.35	0.178	1.04 (0.98–1.09)
Tumor size	–0.10	0.10	–0.99	0.323	0.90 (0.74–1.11)
Albumin	–0.10	0.03	–3.05	0.002	0.90 (0.85–0.96)
Platelet count	–0.00	0.00	–0.25	0.806	1.00 (0.99–1.01)
INR	0.51	0.22	2.36	0.018	1.66 (1.09–2.54)
PT	0.51	0.22	2.36	0.018	1.67 (1.09–2.56)
APTT	–0.02	0.04	–0.38	0.701	0.98 (0.91–1.07)
TT	–0.01	0.08	–0.16	0.874	0.99 (0.84–1.16)
Fibrinogen	–0.09	0.29	–0.31	0.758	0.92 (0.52–1.60)
CRP	0.06	0.02	2.55	0.011	1.06 (1.01–1.11)
TM	0.35	0.10	3.41	<0.001	1.42 (1.16–1.75)
R time	0.18	0.22	0.83	0.407	1.20 (0.78–1.86)
K time	0.32	0.49	0.65	0.519	1.37 (0.52–3.61)
MA	–0.13	0.03	–4.84	<0.001	0.88 (0.83–0.92)
α-angle	–0.02	0.02	–0.68	0.495	0.98 (0.94–1.03)
LY30 (%)	0.31	0.18	1.76	0.079	1.37 (0.96–1.94)

Note: Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using univariable logistic regression analyses. Postoperative complications were defined as Clavien–Dindo grade II or higher occurring within 30 days after surgery.

ciations with postoperative complications and were therefore not prioritized, thereby helping to control the number of predictors while preserving variables more directly related to hepatic reserve, coagulation status, inflammation, endothelial injury, and perioperative complexity. Ultimately, seven predictors were retained in the final model: albumin, PT, CRP, TM, MA, portal hypertension, and laparoscopic surgery (Fig. 1). All variance inflation factors in the final model were <3 (portal hypertension, 1.11; laparoscopic surgery, 1.07; PT, 1.03; albumin, 1.18; TM, 1.45; CRP, 1.28; and MA, 1.20), indicating no substantial multicollinearity.

These seven variables were subsequently included in multivariable logistic regression analyses to construct two prediction models. Model 1 included albumin, PT, portal hypertension, and laparoscopic surgery, whereas Model 2 included C-reactive protein (CRP), TM, and MA, in addition to the variables in Model 1. In Model 1, albumin (OR = 0.93, 95% CI: 0.87–0.99, p = 0.032) and PT (OR = 1.64, 95% CI: 1.03–2.59, p = 0.036) were significantly associated with the risk of postoperative complications. Portal hypertension showed a marginal positive association with postoperative complications (OR = 2.28, 95% CI: 0.94–5.52, p = 0.068), whereas laparoscopic surgery demonstrated a protective trend (OR = 0.45, 95% CI: 0.19–1.08, p = 0.075). In Model 2, portal hypertension (OR = 3.10, 95% CI: 1.02–9.41, p = 0.046), PT (OR = 2.32, 95% CI: 1.30–4.13, p = 0.004), and MA (OR = 0.88, 95% CI: 0.82–0.93, $p < 0.001$) remained statistically significant predictors. Albumin (OR = 0.92, p = 0.055) showed a marginal association with postoperative complications. Laparoscopic surgery (OR = 0.53, p = 0.247), CRP (OR = 1.05, p = 0.134), and TM (OR = 1.12, p = 0.459) did not reach conventional statistical significance (Table 4). The nomogram derived from Model 2 may be used to predict individualized risk (Fig. 2).

Model Discrimination and Incremental Value Evaluation

Receiver operating characteristic (ROC) curve analysis demonstrated that, in the training cohort, the AUC of Model 2 was 0.88 (95% CI: 0.81–0.96), which exceeded that of Model 1 [0.74 (95% CI: 0.64–0.84)]. In the validation cohort, the AUC of Model 2 was 0.84 (95% CI: 0.73–0.95), and that of Model 1 was 0.67 (95% CI: 0.53–0.82) (Fig. 3). The DeLong test demonstrated that the difference in AUC between the two models was statistically significant in both the training (p = 0.006) and validation (p = 0.001) cohorts. NRI analysis showed that, compared with Model 1, the category-based NRI of Model 2 in the training cohort was 0.66 ($p < 0.001$), whereas the continuous NRI was 1.01 ($p < 0.001$). In the validation cohort, the category-based NRI was 0.74 ($p < 0.001$), and the continuous NRI was 1.25 ($p < 0.001$). IDI analysis showed IDI values of 0.27 ($p < 0.001$) in the training cohort and 0.32 ($p < 0.001$) in the validation cohort (Table 5). Given the relatively small size of the validation cohort (59 patients, including 21 events),

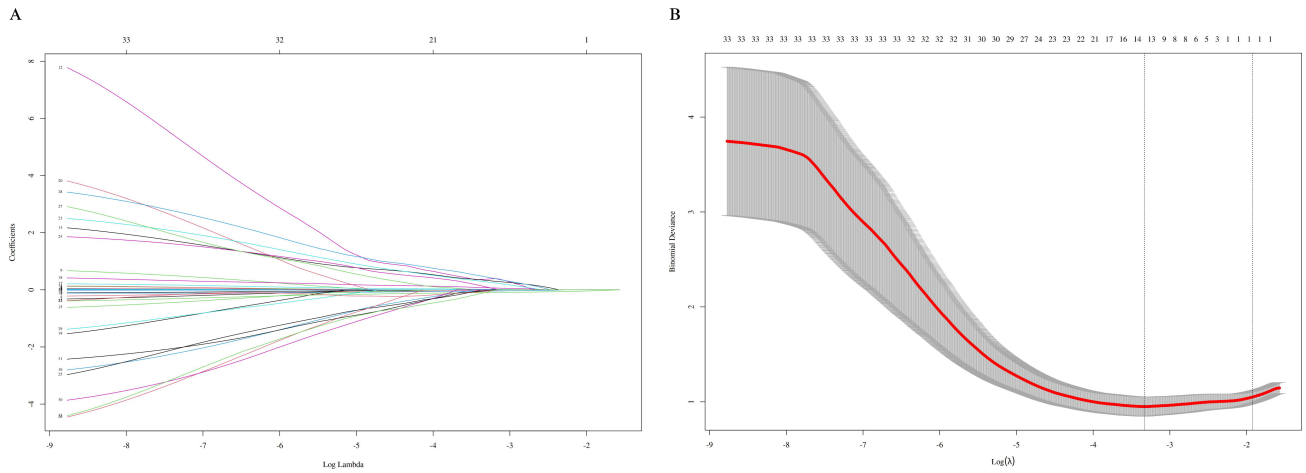

Fig. 1. Feature selection using the least absolute shrinkage and selection operator (LASSO) regression. (A) LASSO coefficient profiles showing the shrinkage of regression coefficients as the penalty parameter log(λ) increased. (B) A ten-fold cross-validation curve was used to determine the optimal λ value based on the minimum binomial deviance. The left vertical dashed line indicates the value of λ corresponding to the minimum cross-validation error (λmin), which was selected for the final model. The right vertical dashed line indicates the largest value of λ within one standard error of the minimum criterion (λ1se).

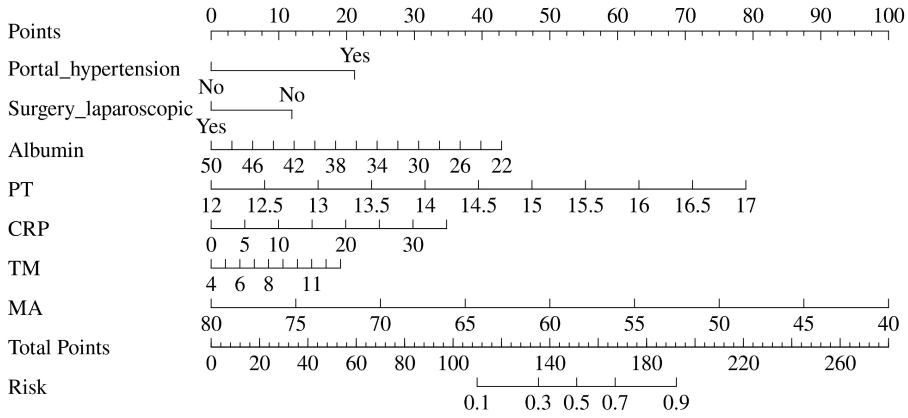

Fig. 2. Nomogram for predicting postoperative complications after hepatectomy.

the validation-cohort AUC and reclassification estimates should be interpreted cautiously.

To further disentangle the respective contributions of MA and CRP/TM, additional incremental model comparisons were performed (**Supplementary Table 2**). Compared with the base clinical model, the addition of MA alone (Base + MA) significantly improved discrimination and reclassification performance, whereas the addition of CRP and TM without MA (Base + CRP + TM) yielded a more modest improvement. The full model (Base + MA + CRP + TM) demonstrated the highest apparent performance. However, its incremental benefit beyond the Base + MA model was limited.

Model Calibration and Clinical Utility

The calibration curve demonstrated good agreement between the predicted and observed probabilities for Model 2 in both the training and validation cohorts (Fig. 4). The Hosmer-Lemeshow test yielded *p*-values of 0.463 for the training cohort and 0.082 for the validation cohort. The corresponding Brier scores were 0.104 and 0.150, respectively. To further evaluate potential overfitting and optimism in model performance estimation, an additional 1000 bootstrap resampling internal validation was performed within the training cohort. The apparent AUC of the final model was 0.885, whereas the optimism-corrected AUC was 0.874. The optimism-corrected calibration slope was 0.785. The apparent Brier score was 0.104, and the optimism-corrected Brier score was 0.115. These findings suggest that, although the model exhibited some optimism bias, it maintained acceptable discrimination and calibration after correction.

Decision curve analysis showed that the net benefit of Model 2 exceeded that of the "treat-all" and "treat-none" strategies across a clinically relevant range of threshold probabilities in both the training and validation cohorts (Fig. 5).

Table 4. Multivariable logistic regression models for predicting postoperative complications.

Variables	Model 1		Model 2	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Portal hypertension				
No	1.00 (Reference)		1.00 (Reference)	
Yes	2.28 (0.94–5.52)	0.068	3.10 (1.02–9.41)	0.046
Laparoscopic surgery				
No	1.00 (Reference)		1.00 (Reference)	
Yes	0.45 (0.19–1.08)	0.075	0.53 (0.18–1.55)	0.247
Albumin	0.93 (0.87–0.99)	0.032	0.92 (0.85–1.00)	0.055
PT	1.64 (1.03–2.59)	0.036	2.32 (1.30–4.13)	0.004
CRP			1.05 (0.98–1.13)	0.134
TM			1.12 (0.83–1.51)	0.459
MA			0.88 (0.82–0.93)	<0.001

Note: Model 1 included conventional clinical and perioperative variables identified from univariate analyses. Model 2 additionally incorporated the novel biomarkers CRP, TM, and MA. Odds ratios (ORs) and 95% confidence intervals (CIs) are presented.

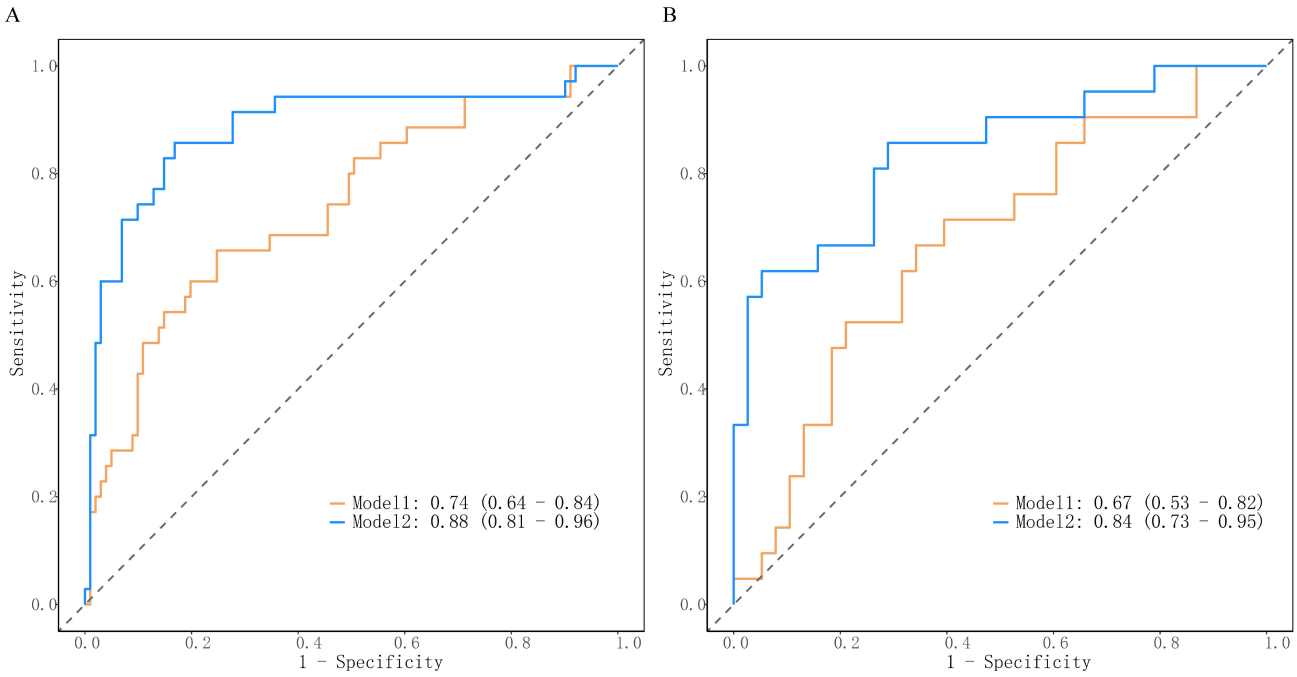

Fig. 3. Discriminative performance of the prediction models in the training and validation cohorts. (A) Receiver operating characteristic (ROC) curves comparing Model 1 and Model 2 in the training cohort. (B) ROC curves comparing Model 1 and Model 2 in the validation cohort.

Model Interpretability Analysis

SHAP analysis was performed as a supplementary interpretability assessment based on the final multivariable model (Model 2), and the included variables were identical to those listed in Table 4. MA exhibited the highest SHAP importance, followed by PT, portal hypertension, albumin, CRP, laparoscopic surgery, and TM (Fig. 6A). The SHAP beeswarm plot further illustrated the direction and magnitude of the effects of individual features on the predicted risk of postoperative complications (Fig. 6B). Overall, the SHAP-based ranking was broadly consistent with the regression-based findings, particularly in identifying MA as the dominant contributor to model predictions.

Discussion

This study constructed a predictive model for post-hepatectomy complications. The dual-model design allowed us to distinguish the predictive contribution of conventional clinical variables from the additional value of biomarker-based information, with maximum amplitude (MA) emerging as a key predictor. While CRP and thrombomodulin (TM) may provide some auxiliary information

Table 5. Comparison of discrimination and incremental predictive performance between Model 1 and Model 2.

Cohort	DeLong test		*p*-value
	Model 1 AUC (95% CI)	Model 2 AUC (95% CI)	
Training	0.74 (0.64–0.84)	0.88 (0.81–0.96)	0.006
Validation	0.67 (0.53–0.82)	0.84 (0.73–0.95)	0.001
	NRI (categorical)		*p*-value
Training	0.66 (0.41–0.90)		<0.001
Validation	0.74 (0.50–0.98)		<0.001
	NRI (continuous)		
Training	1.01 (0.67–1.35)		<0.001
Validation	1.25 (0.83–1.67)		<0.001
	IDI		*p*-value
Training	0.27 (0.18–0.37)		<0.001
Validation	0.32 (0.21–0.45)		<0.001

Note: Model performance was evaluated using area under the curve (AUC), net reclassification improvement (NRI), and integrated discrimination improvement (IDI). Differences in AUCs between models were assessed using the DeLong test. Both categorical and continuous NRI values are reported.

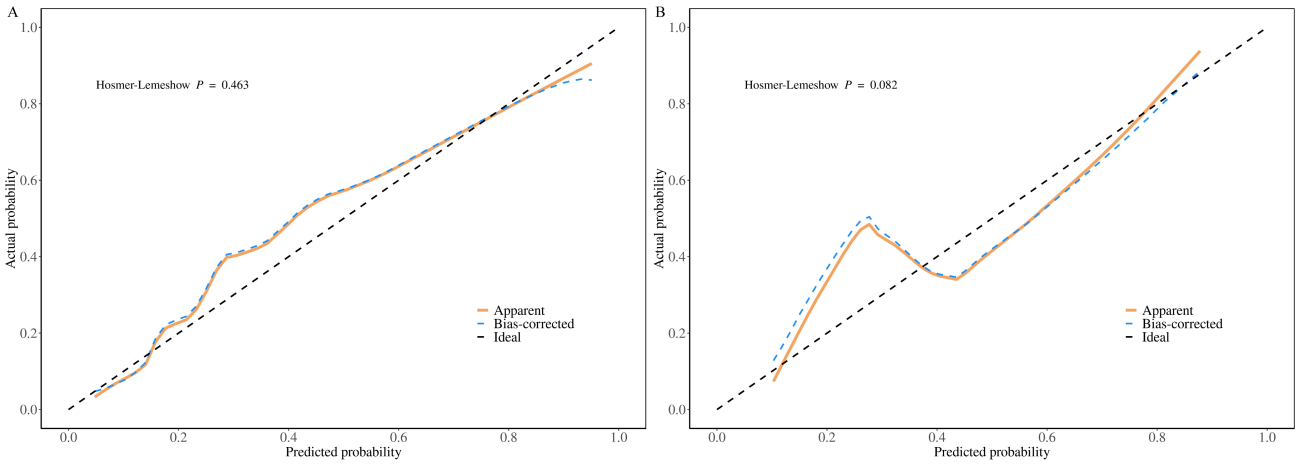

Fig. 4. Calibration performance of Model 2 in the training and validation cohorts. (A) Calibration curve for Model 2 in the training cohort. (B) Calibration curve for Model 2 in the validation cohort. Calibration was evaluated using calibration curves generated from 1000 bootstrap resamples. Model calibration was further assessed using the Hosmer–Lemeshow goodness-of-fit test and Brier scores.

within the model framework, their incremental value beyond MA appears limited. The findings of the present study demonstrated that Model 2, which incorporated these biomarkers, was superior to Model 1, which included only conventional clinical variables, in terms of discrimination, calibration, and clinical utility. These findings suggest that a multidimensional preoperative assessment framework may better capture perioperative vulnerability. However, because the primary endpoint was a heterogeneous composite outcome, the present study cannot determine whether individual biomarkers are preferentially associated with specific complication subtypes.

Among the TEG parameters, MA reflects platelet function and the degree of fibrin cross-linking, thereby representing the maximum strength of a blood clot. In the present study, MA was retained through LASSO regression and identified as the most important biomarker in the multivariable model. The SHAP ranking was broadly consistent with these regression-based findings, further supporting the dominant role of MA in model prediction. This dominant role was also supported by the incremental comparison analysis, which showed that adding MA alone to the baseline clinical model yielded the most pronounced improvement in discrimination and reclassification. The liver is the principal organ responsible for the synthesis of coagulation factors and the clearance of activated coagulation substances. When liver function is impaired, coagulation factor synthesis decreases, while reduced hepatic clearance leads to the accumulation of activated coagulation products, resulting in coagulation dysfunction [26]. A reduced MA value indicates platelet dysfunction or decreased fibrinogen levels [27] and has been associated with an increased risk

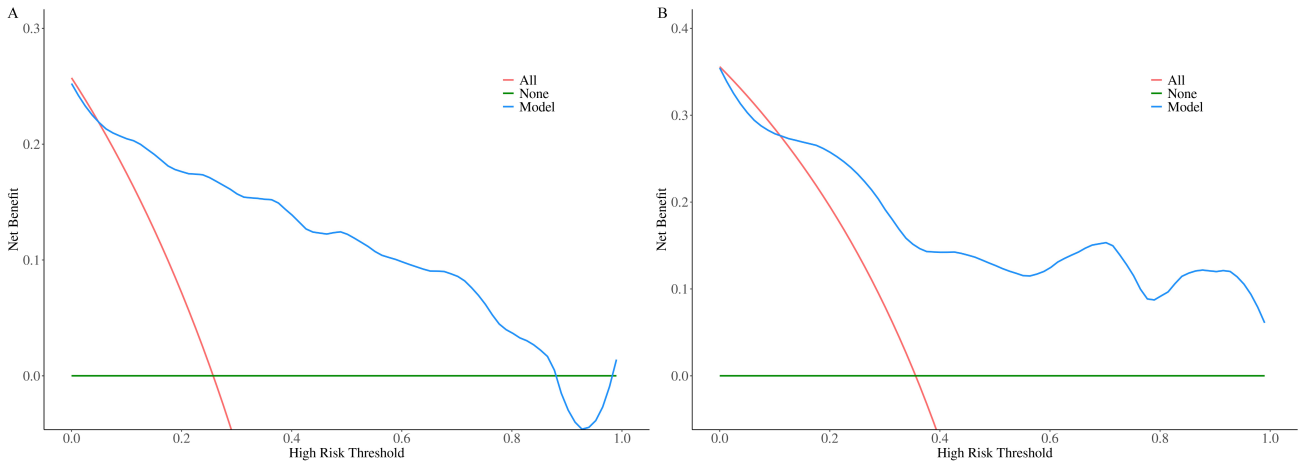

Fig. 5. Decision curve analysis of Model 2 in the training and validation cohorts. (A) Decision curve analysis (DCA) of Model 2 in the training cohort. (B) Decision curve analysis of Model 2 in the validation cohort.

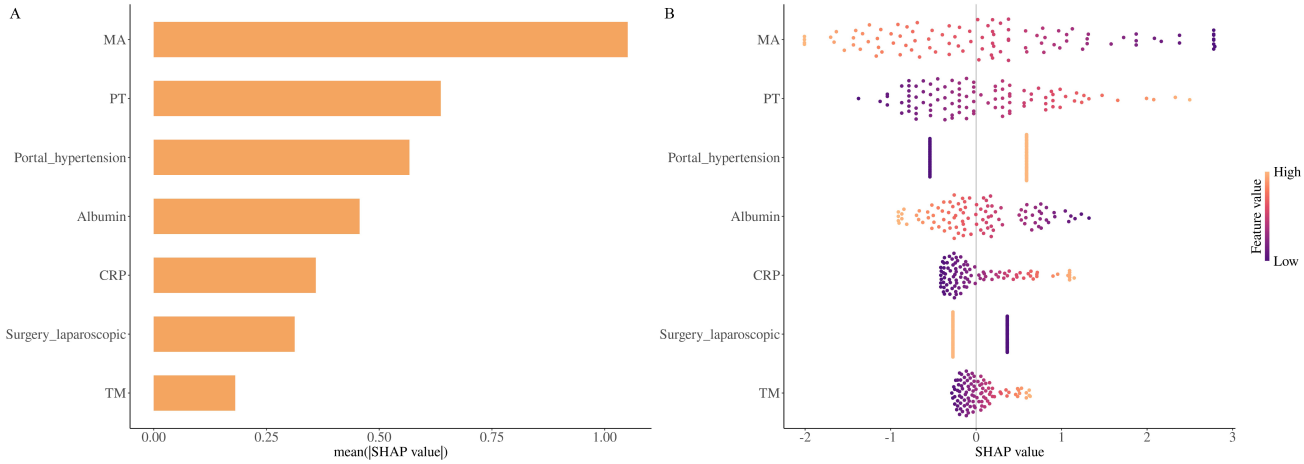

Fig. 6. Shapley Additive exPlanations (SHAP)-based interpretation of predictor contributions in Model 2. (A) SHAP feature importance plot showing the relative contribution of each predictor to model performance. (B) SHAP beeswarm plot illustrating the direction and magnitude of individual predictor effects on the estimated risk of postoperative complications.

of postoperative bleeding, thereby contributing to postoperative complications [28]. Approximately 80% of patients in this cohort had liver cirrhosis. These patients often exhibit a rebalanced hemostatic state, characterized by both increased levels of procoagulant factors, such as factor VIII and von Willebrand factor, and reduced levels of anticoagulant factors, including protein C and antithrombin. Traditional coagulation indices, such as PT and INR, may not fully capture this complexity, while TEG provides a comprehensive assessment of global coagulation function and can better reflect these complex pathophysiological alterations [29]. Accordingly, preoperative TEG, particularly MA, may provide complementary information for risk stratification, although its clinical utility requires confirmation in larger external validation cohorts.

Although univariate analysis showed higher CRP levels in the complication group, consistent with a previous study [30], CRP was not identified as an independent predictor in the multivariate model. This may be because surgical trauma itself induces a systemic inflammatory response, while pre-existing inflammatory conditions may further exacerbate this response, thereby increasing the risk of postoperative complications [16]. CRP typically peaks 2–3 days after surgery and then gradually declines. Persistent elevation or a secondary increase in CRP after surgery may indicate infection or other postoperative complications [31]. In the present study, preoperative CRP was included as one of the model variables, and its potential value may lie in identifying patients with pre-existing inflammatory activation, whose preoperative CRP levels may provide limited auxiliary information within a multidimensional prediction model. However, incremental comparative analyses demonstrated that the predictive gain from adding CRP and TM was smaller than that from adding MA alone, and the additional benefit of incorporating CRP/TM beyond MA was limited. Therefore, the current findings do not sup-

port considering preoperative CRP an independent predictor of postoperative complications. A more cautious interpretation is that CRP primarily reflects baseline systemic inflammatory status and contributes only limited auxiliary information within a multidimensional prediction model.

TM is a glycoprotein expressed on vascular endothelial cells and is commonly considered a marker of endothelial injury or dysfunction [32]. In the perioperative setting, elevated TM levels may be associated with endothelial stress and postoperative vulnerability [33]. Specifically, surgical manipulation and liver traction during hepatectomy may lead to injury of hepatic sinusoidal endothelial cells, followed by hepatic endothelial dysfunction, which may also impair recovery from liver injury [34]. In this study, although TM was associated with postoperative complications in univariate analysis and improved model performance when added to the baseline model with CRP, it failed to maintain an independent association in the fully adjusted model, including MA, and its additional value beyond MA was relatively limited. Therefore, given these limitations, TM should be considered an exploratory biomarker of endothelial injury in this study rather than a confirmed independent predictor. Future studies may explore the value of combining TM with other endothelial injury biomarkers, such as von Willebrand factor (vWF).

Several preoperative assessment indicators widely used in clinical practice, including FLR/SLV, ICG R15, certain TEG parameters, and traditional coagulation indices, did not reach statistical significance in the univariate regression analysis. However, this finding does not negate their clinical significance. FLR and ICG R15 are primarily used to define the safety threshold for hepatectomy, and the patients in this study underwent rigorous preoperative screening. Consequently, individuals at extremely high risk had been excluded before surgery, resulting in limited variability in these indicators within the study population. For TEG parameters, different indicators reflect distinct stages of the coagulation process. MA, as a comprehensive indicator of final clot strength, provides a higher degree of information integration than process-related parameters. Traditional coagulation indices mainly reflect the activity of plasma coagulation factors. In the context of chronic liver disease, compensatory procoagulant mechanisms may lead to discordance between these indices and the real coagulation risk, thereby reducing their predictive sensitivity in univariable analysis. Furthermore, our findings support MA as the most robust biomarker associated with postoperative complications, whereas CRP and TM should be considered exploratory biomarkers retained within the extended prediction framework rather than confirmed independent predictors. Although these indicators are relatively accessible in clinical practice, their routine implementation requires further external validation as well as assessment of feasibility and cost-effectiveness.

HBV-DNA was collected as a baseline virological characteristic because HBV-related liver disease is common in the study population. However, HBV-DNA did not demonstrate a clear association with postoperative complications in this cohort and was therefore not emphasized in the final predictive framework. In addition, the apparent protective effect of laparoscopic surgery should be interpreted with caution. Although laparoscopic surgery showed a protective trend in less-adjusted models, this association was attenuated and no longer statistically significant after the inclusion of additional biomarkers. This finding suggests that the observed association may partially reflect differences in case selection or surgical complexity. Because minimally invasive surgery is more likely to be applied in cases with relatively lower technical complexity, residual confounding related to tumor burden or surgical difficulty cannot be completely excluded in this retrospective cohort. Therefore, the surgical approach may be more appropriately interpreted as a perioperative factor influenced by specific clinical circumstances rather than as an independently established determinant of postoperative outcomes.

This study has several limitations. First, although the final model incorporated regularization, redundancy control, and bootstrap-based optimism correction during model development, the number of events remained relatively limited, with an EPV of approximately 8. Therefore, the possibility of unstable regression coefficients and overfitting cannot be completely ruled out. Second, the validation cohort was relatively small, comprising only 59 patients and 21 events, which may have limited the stability of the AUC and reclassification indicator. Accordingly, the apparent performance advantage of Model 2 should be considered preliminary and interpreted with caution. Third, this study included only preoperative variables and did not evaluate the predictive value of perioperative dynamic changes. Such factors may be closely associated with postoperative complications. In addition, the primary endpoint was a heterogeneous composite outcome, and the available sample size did not allow stable complication-specific modeling. Therefore, whether MA, CRP, or TM preferentially predict specific complication subtypes requires further investigation in larger cohorts. Finally, this was a single-center retrospective study without external validation and is therefore subject to potential selection bias and residual confounding. For example, the observed association between surgical approach and operative outcomes may still be influenced by residual confounding related to case selection and surgical complexity. Consequently, the generalizability and robustness of the proposed model require further confirmation in larger prospective multicenter cohorts.

Conclusions

In summary, in this single-center retrospective cohort, the extended preoperative model demonstrated superior apparent predictive performance compared with the baseline clin-

ical model. This improvement appeared to be driven primarily by MA, whereas CRP and TM provided limited incremental predictive information. These findings should be considered preliminary and require confirmation in larger multicenter studies with external validation before broader clinical application.

Availability of Data and Materials

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

Author Contributions

YLH and DMT designed the research study. YLH and WFS performed the research. YLH and HZ analyzed the data. DMT drafted this 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 number: 2026-LP-070), and all procedures followed the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients before surgery.

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62713/aic.4609.

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