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A nomogram predicting venous thromboembolism risk in primary liver cancer patients

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Abstract

Cancer frequently causes venous thromboembolism (VTE), a leading cause of cancer-related mortality. Primary liver cancer (PLC) is prevalent and highly fatal, with an increased risk of venous thrombotic complications. Thus, we aimed to develop a nomogram model for predicting VTE in patients with PLC. We retrospectively analyzed 1,565 patients diagnosed with PLC between January 2018 and December 2022 at Chongqing University Cancer Hospital. Univariate logistic analysis and multivariate logistic regression identified eight significant risk factors: activated partial thromboplastin time (APTT) $\leq$ 32.20 s, D-dimer > 1.44 mg/L, lymphocyte count (LYM) $\leq 1.18 \times 10^9$/L, monocyte count (MONO) $> 0.42 \times 10^9$/L, transarterial chemoembolization (TACE), surgical intervention, immunotherapy, and β2-microglobulin. The nomogram model exhibited strong discriminatory power, with C indices of 0.753 and 0.710 for the training and validation cohorts, respectively. The calibration curve showed a strong correlation between predicted and actual probabilities. Additionally, decision curve analysis (DCA) and clinical impact curves (CIC) confirmed the model's clinical utility. This nomogram facilitates the identification of high-risk PLC patients, allowing for timely preventive and therapeutic interventions to reduce the risk of thrombosis.

Keywords Nomogram · Venous thromboembolism · Primary liver cancer · Predictive model

Introduction

Cancer frequently leads to venous thromboembolism (VTE), a major cause of cancer-related mortality [1, 2]. VTE encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE) [3]. Primary liver cancer (PLC) is a widespread disease with a high mortality rate. In China, which has the highest PLC incidence globally, there are 8 cases per 100,000 individuals [4]. PLC is associated with an increased risk of thrombotic venous complications. Notably, three extensive studies have assessed the frequency of VTE complications in such patients [5–7]. According to these studies, the highest incidences of VTE occur in patients diagnosed with pancreatic, liver, lung, ovarian, and brain carcinomas."

Various predictive models, including the Caprini [8], Padua [9], RAM [10], and Khorana scores [11], have been developed to forecast the probability of VTE events in patients. These models are widely utilized in clinical settings and have been successful in identifying individuals at increased risk of VTE. However, it is essential to recognize that each model is specifically tailored for different patient populations. The primary goal of the Caprini model was to predict VTE risks in cancer patients undergoing the insertion of peripherally inserted central catheters [8]. In contrast, the Khorana Risk Score has been demonstrated to be ineffective in predicting VTE formation in patients with PLC [11]. Patients with PLC constitute a unique subgroup characterized by distinct attributes, including specific mechanisms related to blood clotting and therapeutic approaches. There are significant limitations in utilizing these existing models to predict VTE risk in PLC patients because they do

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not account for all associated risk factors. Therefore, developing a VTE prediction algorithm specifically designed for PLC patients is crucial to guide clinical decision-making.

Nomogram models, which are graphical tools, offer an intuitive method for accurately predicting the probability of clinical occurrences in various individuals [12].This predictive approach effectively transforms traditional regression models into visual assessments of individual risks, thereby enhancing practicality and precision.This improvement is evidenced by the creation of easily interpretable graphs. Research has confirmed the accuracy of nomograms in predicting the prognosis of various types of carcinomas, including lung carcinoma [13], lymphoma [14], ovarian carcinoma [15], breast carcinoma [16], and spinal metastasis tumors [17].

Therefore, we developed a nomogram model to precisely estimate the likelihood of VTE risk in the overall population with PLC. Utilizing this model allows physicians to accurately identify patients at risk of VTE and implement early preventive and therapeutic measures to reduce the incidence of thrombosis.

Materials and methods

Patient population

Data were obtained from the medical records of patients at the Chinese Chongqing University Cancer Hospital. Following the previously mentioned selection criteria [18], eligible participants were: (1) individuals aged 18 years or older; (2) those admitted to the hospital at least once; (3) patients diagnosed with PLC through histological or radiological methods; and (4) patients hospitalized between January 2018 and December 2022. Exclusion criteria included: (1) VTE occurring prior to the diagnosis of PLC, (2) death within 48 h of admission, and (3) insufficient patient data. To enhance the relevance and validity of our findings, we utilized comprehensive data from the database. For patients with multiple hospital admissions, only the initial case was included in the analysis.

Development of the nomogram and statistical analysis

To create and validate the nomogram, we randomly divided all patients into a training cohort ($n=1096$) and a validation cohort ($n=469$), adhering to a 7:3 ratio. Within the training cohort, the relationship between clinical factors and venous thromboembolism (VTE) was examined using univariable logistic regression analyses. Variables deemed clinically significant and showing statistical significance at $P<.05$ were subsequently included in multivariable logistic regression analyses.This multivariable approach identified independent predictors of VTE. Based on the results of the multivariable analyses, a predictive nomogram was constructed.

Categorical variables were described using totals and frequencies. The optimum threshold values for Neutrophil to Lymphocyte Ratio (NLR), Neutrophil to Albumin Ratio (NAR), and Patient-Generated Subjective Global Assessment (PG-SGA) scores were determined using X-tile software (Yale University, New Haven, CT, USA) [19]. The internal and external accuracy of the nomogram was validated in both the training and validation cohorts. The discriminative ability of the nomogram was assessed using the area under the receiver operating characteristic (ROC) curve (AUC) and Harrell's C-index. Calibration curves, generated through bootstrap resampling with 1000 replicates, validated the nomogram in both the training and validation cohorts. Variable scores were calculated using the 'nomogramEx' package in R, with cumulative scores for each patient derived by summing scores across all variables. Decision Curve Analysis (DCA) and Clinical Impact Curves (CIC) were illustrated using the 'rmda' package, evaluating the clinical utility of the Nomogram.

All statistical analyses were performed using R software, version 4.1.2 (http://www.r-project.org). Statistical significance was established at a P-value of less than 0.05, with tests being two-tailed.

Results

Clinicopathologic characteristics of patients

From 2018 to 2022, a total of 1,726 patients diagnosed with PLC were initially screened for inclusion in this study (Fig. 1). Of these, 1,565 patients met the eligibility criteria and were included in the analysis. Using a random split-sample technique with a split ratio of 7:3, participants were divided into a training group ($n=1,096$) and a validation group ($n=469$). Within the training cohort, VTE was observed in 107 patients (9.8%) during hospitalization. In the validation cohort, VTE occurred in 50 patients (10.7%). Table 1 outlines the initial clinicopathological characteristics of the participants and their correlations with various clinicopathological factors.

Independent predictors in the training data

Table 2 presents the results of the univariate logistic regression analysis. An increased incidence of VTE was observed with elevated monocyte counts (MONO) ($P<.001$).

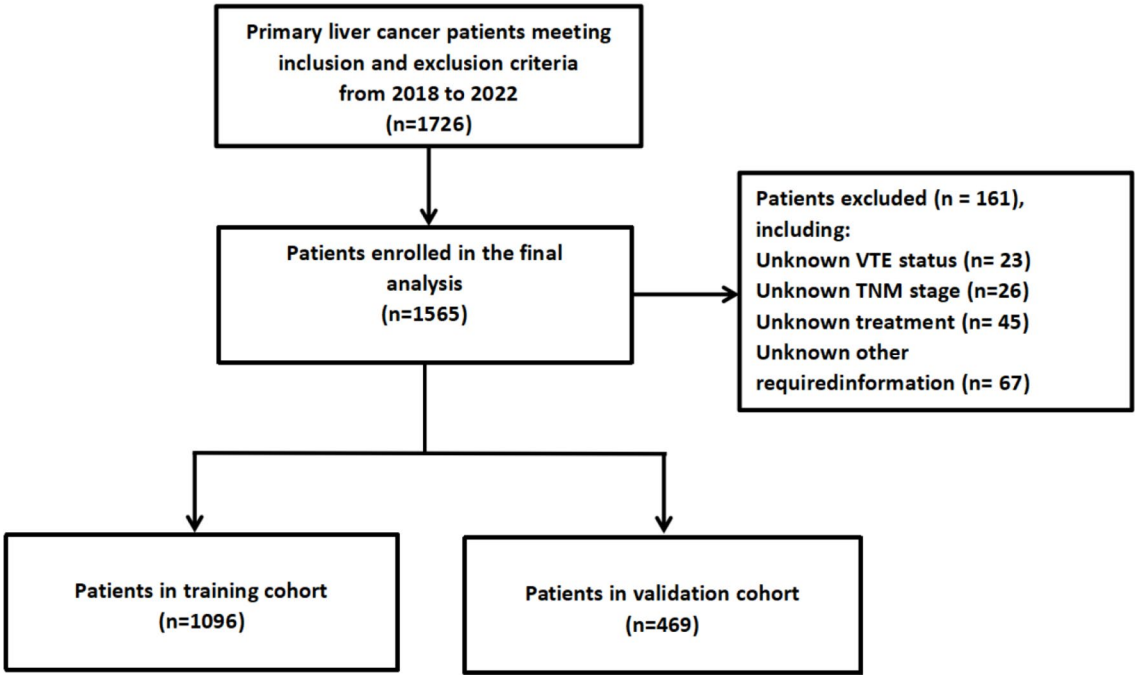

Fig. 1 Flowchart detailing the inclusion and exclusion criteria that resulted in the fnal study cohorts

Patients with prolonged activated partial thromboplastin time (APTT) exhibited a higher likelihood of developing VTE compared to those with shorter APTT durations ($P = .003$). Analysis of treatment factors influencing VTE incidence revealed significant beneficial effects associated with transarterial chemoembolization (TACE) ($P < .001$), immunotherapy ($P < .001$), and targeted therapy ($P < .001$). The univariate model included all statistically significant variables alongside those of clear clinical importance, employing a stepwise logistic regression approach for analysis. In the subsequent multivariate logistic regression model (Table 2), APTT ($P = .007$), D-dimer ($P = .019$), lymphocyte count (LYM) ($P = .012$), MONO ($P = .002$), TACE ($P < .001$), surgical intervention ($P = .010$), and immunotherapy ($P = .010$) were identified as significant independent predictors of VTE.

Nomogram for predicting VTE

A nomogram incorporating critical predictive and clinically relevant factors was developed (Fig. 2). This nomogram identified TACE as making the largest contribution to the prediction of VTE, followed by significant impacts from APTT, immunotherapy, D-dimer levels, MONO, surgical treatment, LYM, and β2-microglobulin. Model selection and optimization adhered to principles aimed at minimizing the Akaike Information Criterion/Bayesian Information Criterion (AIC/BIC). Although the inclusion of β2-microglobulin level showed marginal significance ($P = .053$), it was retained in the analysis. Each factor was assigned a score, and by summing these scores on the overall scoring scale, the approximate likelihood of VTE occurrence could be determined. Additionally, to facilitate the convenient prediction of VTE probability among patients with PLC, a web-based tool was developed using the R package 'DynNom', accessible at https://cqchlivervte.shinyapps.io/liver/. Users can estimate the likelihood of VTE by inputting values into this tool and clicking on the 'predict' button.

Validation and calibration of the nomogram

In the training cohort, the nomogram demonstrated a Concordance index (C-index) of 0.753, accompanied by a 95% confidence interval (CI) ranging from 0.706 to 0.799. For the validation cohort, the C-index was observed at 0.710, with a 95% CI of 0.641 to 0.779 (Fig. 3). Notably, the calibration plots for the nomogram revealed an excellent agreement between the predicted and observed risks of venous thromboembolism (VTE) in both the training (Fig. 4A) and validation cohorts (Fig. 4A)..

Efficacy of the nomogram in segregating patient risk levels

In the designated training and validation cohorts, both DCA (Fig. 5) and CIC (Fig. 6) depicted favorable clinical utility. The DCA effectively illustrated the model's utility by

Table 1 Patient demographics and clinical characteristics between VTE and clinicopathological aspects

Level	Overall	VTE			Cohort		
		NO-VTE($n=1408$)	YES-VTE($n=157$)	P	Trian($n=1096$)	Validation($n=469$)	P
Age (mean ± SD)	56.65 ± 11.91	56.60 ± 12.07	57.12 ± 10.41	0.601	56.69 ± 11.91	56.57 ± 11.92	0.858
Sex (%)				0.105			0.070
Male	1221 (78.02)	1107 (78.62)	114 (72.61)		841 (76.73)	380 (81.02)	
Female	344 (21.98)	301 (21.38)	43 (27.39)		255 (23.27)	89 (18.98)	
BMI (%)				0.087			0.262
18.5–23.9	972 (62.11)	887 (63.00)	85 (54.14)		695 (63.41)	277 (59.06)	
≥ 24	476 (30.42)	417 (29.62)	59 (37.58)		321 (29.29)	155 (33.05)	
< 18.5	117 (7.48)	104 (7.39)	13 (8.28)		80 (7.30)	37 (7.89)	
Pathological (%)				0.420			0.448
HCC	1297 (82.88)	1171 (83.17)	126 (80.25)		914 (83.39)	383 (81.66)	
ICC/cHCC-CC	268 (17.12)	237 (16.83)	31 (19.75)		182 (16.61)	86 (18.34)	
TNM (%)				0.995			0.072
I-II	422 (26.96)	380 (26.99)	42 (26.75)		300 (27.37)	122 (26.01)	
III	533 (34.06)	479 (34.02)	54 (34.39)		354 (32.30)	179 (38.17)	
IV	610 (38.98)	549 (38.99)	61 (38.85)		442 (40.33)	168 (35.82)	
Basedisease (%)				0.989			0.636
NO	1172 (74.89)	1055 (74.93)	117 (74.52)		825 (75.27)	347 (73.99)	
YES	393 (25.11)	353 (25.07)	40 (25.48)		271 (24.73)	122 (26.01)	
TACE (%)				< 0.0001			0.436
NO	1101 (70.35)	1020 (72.44)	81 (51.59)		778 (70.99)	323 (68.87)	
YES	464 (29.65)	388 (27.56)	76 (48.41)		318 (29.01)	146 (31.13)	
Surgical.treatment (%)				0.381			0.994
O	1063 (67.92)	951 (67.54)	112 (71.34)		745 (67.97)	318 (67.80)	
YES	502 (32.08)	457 (32.46)	45 (28.66)		351 (32.03)	151 (32.20)	
Immunotherapy (%)				< 0.0001			0.655
NO	1447 (92.46)	1316 (93.47)	131 (83.44)		1016 (92.70)	431 (91.90)	
YES	118 (7.54)	92 (6.53)	26 (16.56)		80 (7.30)	38 (8.10)	
Targeted.therapy (%)				< 0.0001			1.000
NO	1208 (77.19)	1110 (78.84)	98 (62.42)		846 (77.19)	362 (77.19)	
YES	357 (22.81)	298 (21.16)	59 (37.58)		250 (22.81)	107 (22.81)	
APTT (%)				0.016			0.636
≤ 32.20 s	1211 (77.38)	1077 (76.49)	134 (85.35)		844 (77.01)	367 (78.25)	
> 32.20 s	354 (22.62)	331 (23.51)	23 (14.65)		252 (22.99)	102 (21.75)	
PT (%)				0.091			0.426
≤ 12.50 s	913 (58.34)	811 (57.60)	102 (64.97)		647 (59.03)	266 (56.72)	
> 12.50 s	652 (41.66)	597 (42.40)	55 (35.03)		449 (40.97)	203 (43.28)	
FIB (%)				0.153			0.020
≤ 1.96 μg/mL	235 (15.02)	218 (15.48)	17 (10.83)		149 (13.59)	86 (18.34)	
> 1.96 μg/mL	1330 (84.98)	1190 (84.52)	140 (89.17)		947 (86.41)	383 (81.66)	
D_dimer (%)				0.287			0.193
≤ 1.44 mg/L	875 (55.91)	794 (56.39)	81 (51.59)		625 (57.03)	250 (53.30)	
> 1.44 mg/L	690 (44.09)	614 (43.61)	76 (48.41)		471 (42.97)	219 (46.70)	
Neutrophil (%)				0.133			0.359
$\leq 4.39\times10^9$/L	959 (61.28)	872 (61.93)	87 (55.41)		663 (60.49)	296 (63.11)	
$> 4.39\times10^9$/L	606 (38.72)	536 (38.07)	70 (44.59)		433 (39.51)	173 (36.89)	
LYM (%)				0.009			0.712
$\leq 1.18\times10^9$/L	827 (52.84)	728 (51.70)	99 (63.06)		583 (53.19)	244 (52.03)	
$> 1.18\times10^9$/L	738 (47.16)	680 (48.30)	58 (36.94)		513 (46.81)	225 (47.97)	
MONO (%)				< 0.0001			0.917
$\leq 0.42\times10^9$/L	819 (52.33)	766 (54.40)	53 (33.76)		575 (52.46)	244 (52.03)	
$> 0.42\times10^9$/L	746 (47.67)	642 (45.60)	104 (66.24)		521 (47.54)	225 (47.97)	
PLT (%)				0.058			0.475
$\leq 91.00\times10^9$/L	269 (17.19)	251 (17.83)	18 (11.46)		183 (16.70)	86 (18.34)	

Table 1 (continued)

Level	Overall	VTE			Cohort		
		NO-VTE($n=1408$)	YES-VTE($n=157$)	P	Trian($n=1096$)	Validation($n=469$)	P
$>91.00\times10^9$/L	1296 (82.81)	1157 (82.17)	139 (88.54)		913 (83.30)	383 (81.66)	
β2_microglobulin (%)				<0.0001			0.043
≤2.24 mg/mL	595 (38.02)	563 (39.99)	32 (20.38)		435 (39.69)	160 (34.12)	
>2.24 mg/ml	970 (61.98)	845 (60.01)	125 (79.62)		661 (60.31)	309 (65.88)	
LDH (%)				0.014			0.865
≤268.30 U/L	1058 (67.60)	966 (68.61)	92 (58.60)		739 (67.43)	319 (68.02)	
>268.30 U/L	507 (32.40)	442 (31.39)	65 (41.40)		357 (32.57)	150 (31.98)	
AFP (%)				0.265			0.256
≤2.40 ng/mL	191 (12.20)	167 (11.86)	24 (15.29)		141 (12.86)	50 (10.66)	
>2.40 ng/mL	1374 (87.80)	1241 (88.14)	133 (84.71)		955 (87.14)	419 (89.34)	

BMI: body mass index; TNM: tumor node metastasis; TACE: transarterial chemoembolization; APTT: activated partial thromboplastin time; PT: prothrombin time; FIB: fibrinogen; FDP: fibrinogen degradation products; LYM: lymphocyte; MONO: monocytes; PLT: platelet; LDH: lactate dehydrogenase; AFP: alpha-fetoprotein

graphically representing a range of VTE risk thresholds on the horizontal (X-axis) and the net benefit in comparison to a scenario where no patients are assumed to develop VTE on the vertical axis (Y-axis). This analysis indicated net benefit ranges of 0–38% and 0–43% for the training and validation cohorts, respectively. Similarly, the CIC provided a visual representation of the model's practicability; the red curve demonstrated the number of individuals identified by the model as being at high risk across various probability thresholds, whereas the blue curve illustrated the number of correctly identified positive cases at each threshold.

Discussion

VTE is a significant concern for patients with PLC, notably elevating mortality rates. Through multivariate analysis, Wang et al. identified a hazard ratio (HR) for mortality in patients with PLC who experience VTE events of 3.62 (95% CI = 1.22–10.79, $p = .021$), corroborating earlier studies on the detrimental impact of VTE on survival across various conditions [20]. Nonetheless, patients with PLC represent a distinct subgroup characterized by unique factors. The occurrence of thrombotic complications can be attributed to the severe deterioration of liver function-a crucial organ in the synthesis of various coagulation factors and regulatory proteins integral for maintaining hemostasis. Recent evidence has demonstrated that PLC can precipitate a shift in the hemostatic balance toward hypercoagulability through multiple interconnected mechanisms [21–25]. Consequently, there is an imperative need for a VTE risk model tailored specifically to PLC. The present study identified critical factors associated with VTE risk in PLC patients and developed a reliable nomogram to accurately predict VTE likelihood. To our knowledge, this study boasts the largest sample size to date in devising a prognostic nomogram for estimating VTE probability among individuals with PLC.

The nomogram employs multivariate regression analysis to integrate various predictors, presenting each variable's interrelationships within the prediction model through proportionally scaled line segments arranged on a shared plane [26]. This graphical approach not only simplifies the complex underlying regression formula but also improves outcome comprehensibility of the prediction model. Given their intuitive nature and ease of interpretation, nomograms are widely utilized in cancer prognosis [12]. The recently developed nomogram model has successfully predicted VTE probability in diverse carcinomas including those of the lung [13], lymphoma [14], ovaries [15], breast [16], and spinal metastases [17]. However, its application to PLC remains under-documented, necessitating further exploration. In this study, a prediction model for VTE risk in PLC patients was established, incorporating variables such as APTT, D-dimer, LYM, MONO, TACE, surgical treatments, immunotherapy, and β2-microglobulin levels. The model was internally validated, achieving a C-index of 0.753, which confirms its predictive accuracy. The model's clinical utility was further supported by favorable outcomes in DCA and CIC across both training and validation cohorts. Additionally, a user-friendly online calculator has been developed to aid clinicians in treatment decision-making

Research extensively investigates the correlation between APTT and VTE. Prior studies have identified a significant inverse relationship, highlighting that a reduced APTT is independently associated with an elevated risk of VTE. For instance, patients with the lowest APTT ratios (≤0.80) face a five-fold increase in VTE risk compared to those with ratios exceeding 1.00 [27]. Legnani et al. further corroborated these findings, demonstrating a notably higher likelihood of VTE recurrence with unusually low APTT values [28]. Consistent with these observations, our

Table 2 Univariate and multivariate analysis for overall survival of the training cohort

Dependent: VTE		0 ($N=989$)	1 ($N=107$)	OR (univariable)	OR (final)
Age	Mean ± SD	56.7 ± 12.1	56.8 ± 10.5	1.00 (0.98–1.02, $p=.893$)	
Sex	Male	766 (77.5%)	75 (70.1%)		
	Female	223 (22.5%)	32 (29.9%)	1.47 (0.94–2.28, $p=.088$)	
BMI	18.5–23.9	634 (64.1%)	61 (57%)		
	≥ 24	282 (28.5%)	39 (36.4%)	1.44 (0.94–2.20, $p=.095$)	
	< 18.5	73 (7.4%)	7 (6.5%)	1.00 (0.44–2.26, $p=.994$)	
Pathological	HCC	826 (83.5%)	88 (82.2%)		
	ICC/cHCC-CC	163 (16.5%)	19 (17.8%)	1.09 (0.65–1.85, $p=.736$)	
TNM	I-II	273 (27.6%)	27 (25.2%)		
	III	318 (32.2%)	36 (33.6%)	1.14 (0.68–1.93, $p=.614$)	
	IV	398 (40.2%)	44 (41.1%)	1.12 (0.68–1.85, $p=.664$)	
Basedisease	NO	742 (75%)	83 (77.6%)		
	YES	247 (25%)	24 (22.4%)	0.87 (0.54–1.40, $p=.562$)	
TACE	NO	721 (72.9%)	57 (53.3%)		
	YES	268 (27.1%)	50 (46.7%)	2.36 (1.57–3.54, $p<.001$)	3.37 (1.92–5.91, $p<.001$)
Surgical.treatment	NO	670 (67.7%)	75 (70.1%)		
	YES	319 (32.3%)	32 (29.9%)	0.90 (0.58–1.38, $p=.621$)	2.12 (1.19–3.77, $p=.010$)
Immunotherapy	NO	929 (93.9%)	87 (81.3%)		
	YES	60 (6.1%)	20 (18.7%)	3.56 (2.05–6.18, $p<.001$)	2.25 (1.22–4.16, $p=.010$)
Targeted.therapy	NO	778 (78.7%)	68 (63.6%)		
	YES	211 (21.3%)	39 (36.4%)	2.11 (1.39–3.23, $p<.001$)	
APTT	≤ 32.20 s	749 (75.7%)	95 (88.8%)		
	> 32.20 s	240 (24.3%)	12 (11.2%)	0.39 (0.21–0.73, $p=.003$)	0.41 (0.22–0.78, $p=.007$)
PT	#x2264; 12.50 s	576 (58.2%)	71 (66.4%)		
	> 12.50 s	413 (41.8%)	36 (33.6%)	0.71 (0.46–1.08, $p=.106$)	
FIB	≤ 1.96 μg/mL	137 (13.9%)	12 (11.2%)		
	> 1.96 μg/mL	852 (86.1%)	95 (88.8%)	1.27 (0.68–2.38, $p=.451$)	
D_dimer	≤ 1.44 mg/L	573 (57.9%)	52 (48.6%)		
	> 1.44 mg/L	416 (42.1%)	55 (51.4%)	1.46 (0.98–2.17, $p=.065$)	1.73 (1.09–2.73, $p=.019$)
Neutrophil	$\leq 4.39\times10^9$/L	603 (61%)	60 (56.1%)		
	$> 4.39\times10^9$/L	386 (39%)	47 (43.9%)	1.22 (0.82–1.83, $p=.326$)	
LYM	$\leq 1.18\times10^9$/L	518 (52.4%)	65 (60.7%)		
	$> 1.18\times10^9$/L	471 (47.6%)	42 (39.3%)	0.71 (0.47–1.07, $p=.101$)	0.57 (0.36–0.88, $p=.012$)
MONO	$\leq 0.42\times10^9$/L	540 (54.6%)	35 (32.7%)		
	$> 0.42\times10^9$/L	449 (45.4%)	72 (67.3%)	2.47 (1.62–3.78, $p<.001$)	2.06 (1.29–3.27, $p=.002$)
PLT	$\leq 91.00\times10^9$/L	171 (17.3%)	12 (11.2%)		
	$> 91.00\times10^9$/L	818 (82.7%)	95 (88.8%)	1.65 (0.89–3.08, $p=.113$)	
β2_microglobulin	≤ 2.24 mg/mL	409 (41.4%)	26 (24.3%)		
	> 2.24 mg/mL	580 (58.6%)	81 (75.7%)	2.20 (1.39–3.48, $p<.001$)	1.75 (1.08–2.84, $p=.024$)
LDH	≤ 268.30 U/L	677 (68.5%)	62 (57.9%)		
	> 268.30 U/L	312 (31.5%)	45 (42.1%)	1.57 (1.05–2.37, $p=.029$)	
AFP	≤ 2.40 ng/mL	125 (12.6%)	16 (15%)		
	> 2.40 ng/mL	864 (87.4%)	91 (85%)	0.82 (0.47–1.45, $p=.498$)	

BMI: body mass index; TNM: tumor node metastasis; TACE: transarterial chemoembolization; APTT: activated partial thromboplastin time; PT: prothrombin time; FIB: fibrinogen; LYM: lymphocyte; MONO: monocytes; PLT: platelet; LDH: lactate dehydrogenase; AFP: alpha-fetoprotein

analysis confirms that APTT serves as a significant determinant of VTE risk (OR 0.41, 95% CI 0.22–0.78; $P=.007$). This relationship may be attributed to APTT's role in assessing plasma concentrations of key clotting factors, which are integral to the blood coagulation cascade through the contact, intrinsic, and common pathways. These pathways involve factors such as XII, prekallikrein, high-molecular-weight kininogen, IX, VIII, XI, fibrinogen, and II, V, and X. Recent advances have further delineated specific clotting

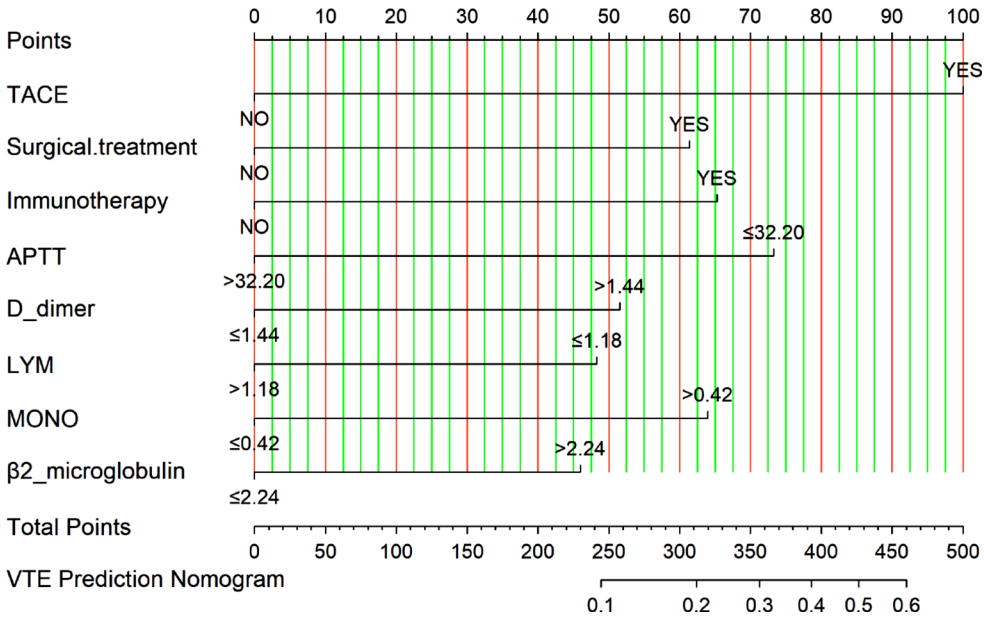

Fig. 2 The construction of the nomogram model was predicated on the identification of independent risk factors obtained through multivariate logistic regression analysis. This nomogram facilitates a visual representation, positioning each variable on its respective axis for clearer interpretability

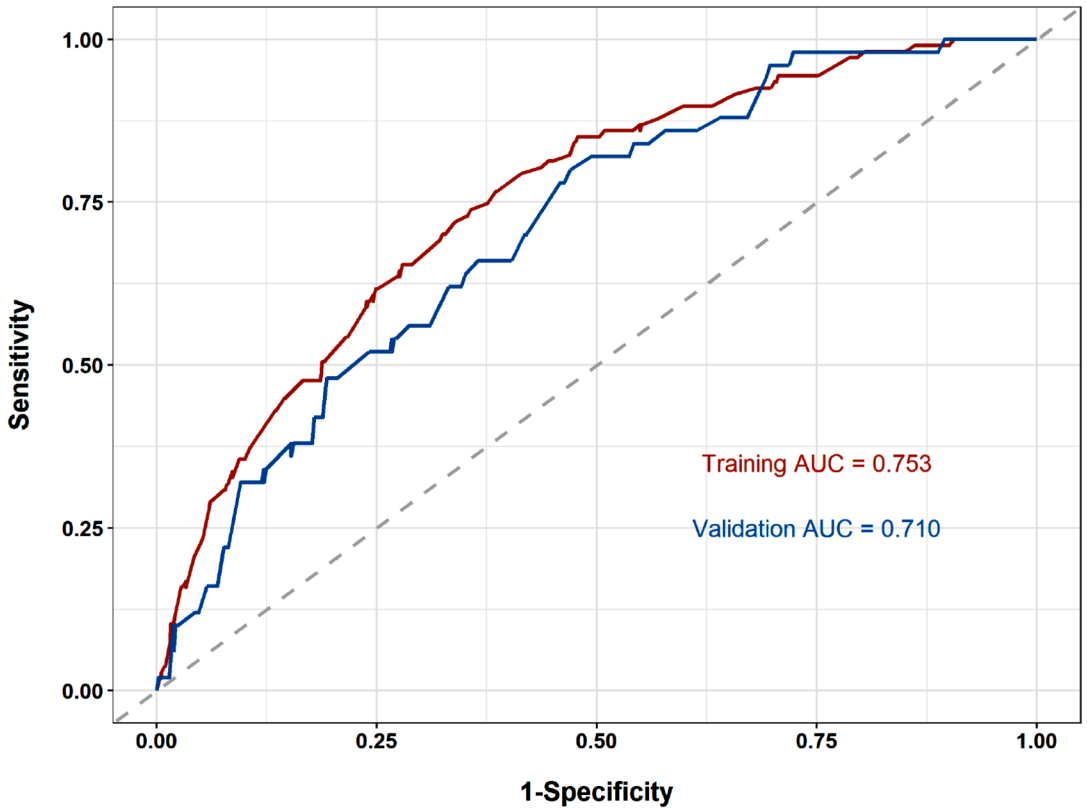

Fig. 3 ROC curves of the nomogram for VTE risk prediction in the training and validation cohorts

factors, including fibrinogen and factors II, VIII, IX, and XI, as distinct contributors to increased VTE risk [29–31].

Our study revealed that elevated D-dimer levels significantly increase the risk of VTE, with individuals displaying higher D-dimer concentrations having a 1.73-fold increased risk of VTE compared to those with lower levels (OR: 1.73, 95% CI: 1.09–2.73, $P = .019$). This finding aligns with the results from recent research. Ay et al. confirmed that initial D-dimer levels are a reliable predictor of VTE risk, noting that a D-dimer threshold of ≥ 1.44 mg/mL is indicative of increased VTE risk [32]. Furthermore, Verhovsek et al. found that D-dimer measurements can predict the risk of

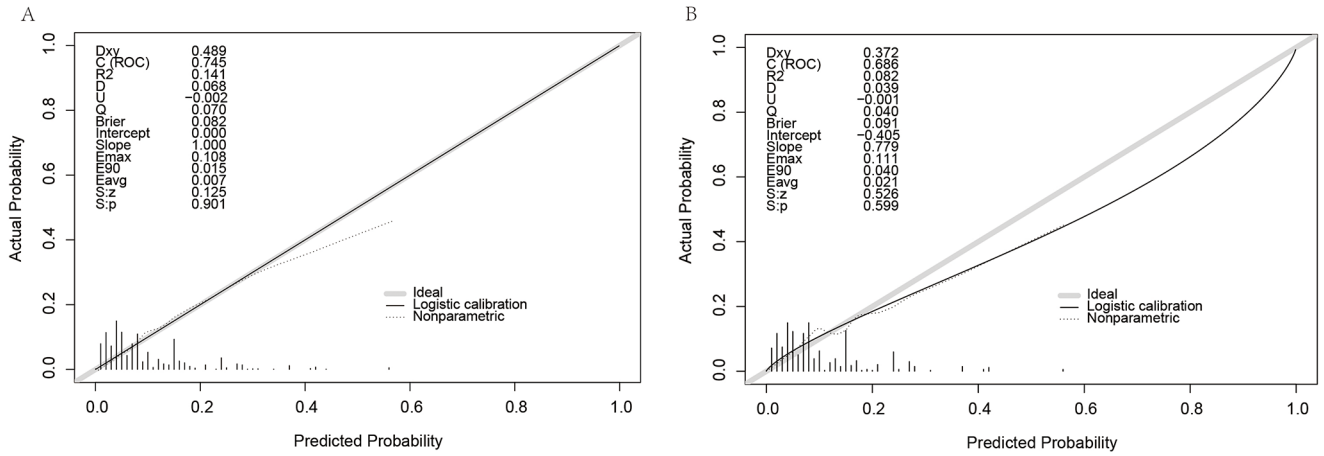

Fig. 4 Calibration plot of the nomogram for VTE risk in the training cohort (**A**) and validation cohort (**B**)

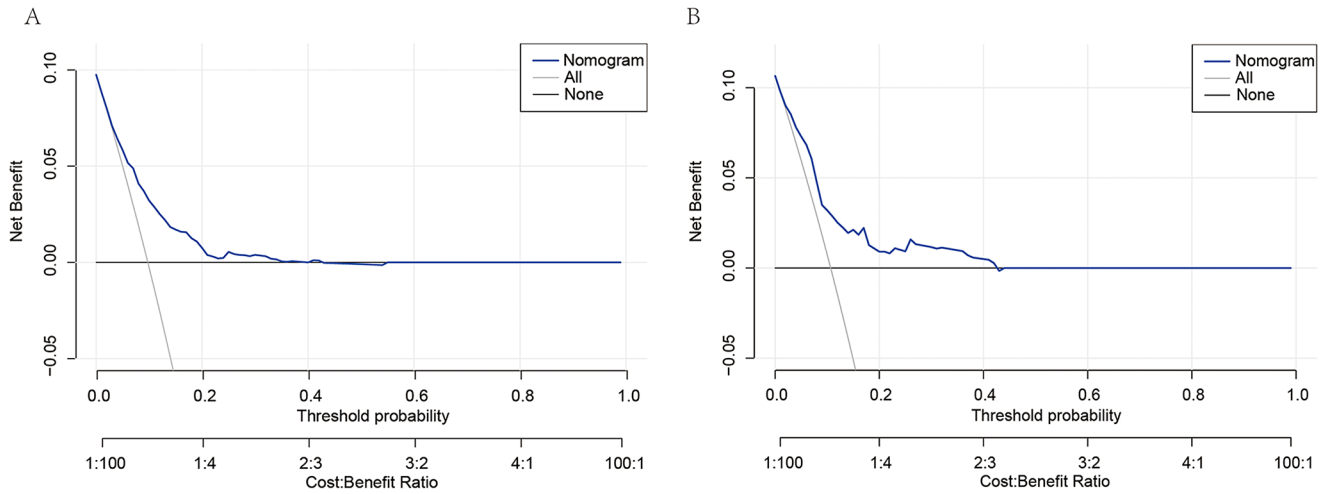

Fig. 5 Decision-curve analysis (DCA) of the nomogram for VTE risk in the training cohort (**A**) and validation cohort (**B**)

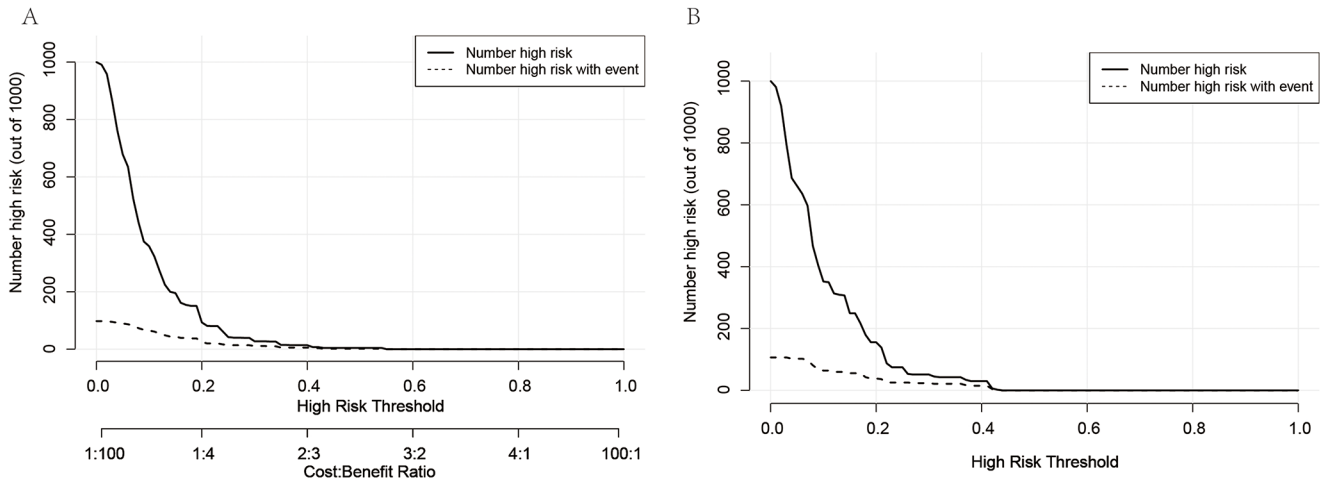

Fig. 6 Clinical Impact Curve(CIC) of the nomogram for VTE risk in the training cohort (**A**) and validation cohort (**B**)

recurrent symptomatic VTE after cessation of anticoagulation therapy in idiopathic VTE patients [33]. In a similar vein, Darzi and colleagues observed that thromboprophylaxis may benefit hospitalized patients at elevated VTE risk with high D-dimer levels [34]. D-dimer, being a soluble degradation product of cross-linked fibrin, offers a non-invasive indication of hypercoagulability and secondary hyperfibrinolysis. High D-dimer levels thus reflect an active fibrinolysis process and the concurrent formation and breakdown of blood clots, underlying the utility of D-dimer as a diagnostic marker in VTE [35].

In addition to D-dimer, our study identified LYM, MONO, and β2-microglobulin levels as predictors of VTE risk. These correlations align with findings from similar contemporary studies. Liu et al. reported an association between Fusobacterium nucleatum presence in gastric cancer tissues, decreased lymphocyte counts, and elevated platelet-to-lymphocyte ratios, linking these markers to increased VTE incidence in gastric cancer patients [36]. Furthermore, Tsubata et al. demonstrated that reduced lymphocyte levels could accelerate VTE progression in patients with advanced lung cancer [37]. Research also supports the role of monocytes in VTE, suggesting that the inflammatory actions of these cells contribute to its pathophysiology [38]. Additionally, endothelial cell activation due to abnormal or stagnant venous blood flow-exacerbated by the presence of monocytes and other cells-promotes VTE development in intact veins [39]. Gade et al. found discernible differences in VTE rates based on β2-microglobulin concentrations: over two years, patients with levels exceeding 4 mg/L experienced a VTE rate of 3.0% (95% CI, 1.5-5.5%), whereas those with levels below 4 mg/L had a lower rate of 1.5% (95% CI, 1.1-2.2%), in a cohort of individuals diagnosed with chronic lymphocytic leukemia [40].

For patients with inoperable PLC, TACE emerges as the preferred therapeutic strategy [41, 42]. This procedure entails the use of a catheter to deliver embolic agents, iodized oil, and chemotherapy drugs directly into the hepatic artery, effectively obstructing the tumor's blood supply to impede its growth and dissemination [42]. However, complications such as VTE, including severe PE, commonly occur post-TACE [43]. Our analysis corroborates previous research, suggesting that TACE significantly increases the risk of developing VTE, with an odds ratio of 3.37 (95% CI 1.92–5.91; $P < .001$). The likelihood of lower limb DVT following TACE could be attributable to prolonged immobilization during the procedure, diminished limb blood flow, enhanced blood coagulability, and the influence of chemotherapy agents [44]. Further investigation is warranted to elucidate the precise mechanisms underlying these observations.

It is well-documented that cancer surgery predisposes patients to an increased risk of VTE. Research by Merkow RP, et al. revealed that VTE occurred in 1.6% of oncological surgery patients, with the highest incidence observed following hepatopancreaticobiliary procedures (3.6%). Notably, about 33% of VTE events in this patient cohort occurred post-discharge, highlighting the importance of the surgical intervention type in the risk of postoperative VTE [45]. Our analysis supports this, showing that surgery for PLC independently elevates the risk of VTE, with a probability ratio of 2.12 (95% CI 1.19–3.77, $P = .010$). Similarly, a study by Wei Q, reported an 11.2% incidence of VTE following CRC surgery within a short duration post-operation, comprising 11.0% cases of DVT (95%CI 9.6–12.5) and a mere 0.2% of PE cases (95%CI 0-0.5) [46]. Prior investigations have elucidated the underlying mechanisms. Surgical manipulation and adjustment of anatomical structures lead to local and systemic inflammatory responses, generally in proportion to the degree of tissue trauma [47]. This inflammation can trigger endothelial dysfunction, activate the coagulation system, and foster a hypercoagulable state. Subsequent reduced postoperative mobility exacerbates the risk of VTE development. Furthermore, limb stagnation and vascular injury also promote postoperative inflammation through localized release of cytokines and activation of coagulation factors [48].

Immunotherapy represents a pivotal advancement in cancer treatment, distinguishing itself from traditional therapies such as chemotherapy and radiation by leveraging the immune system's capacity to detect and eliminate cancer cells. This modality has markedly transformed oncological practices over the last decade. Recent evidence suggests that immunotherapy may heighten the risk of VTE, including DVT and PE. A comprehensive meta-analysis involving 12,870 patients with solid tumors identified increased relative risks (RRs) for VTE at 1.46 (95% CI 1.20–1.79) in those treated with cetuximab and 1.46 (95% CI 1.18–1.80) in those administered panitumumab [49]. Additionally, Nalluri et al. reported an 11.9% overall incidence of VTE in patients receiving bevacizumab, with an elevated RR of 1.33 (95% CI 1.13–1.56; $P < .001$) compared to control groups [50].

Our data corroborates these findings, identifying immunotherapy as an independent risk factor for VTE with an odds ratio (OR) of 2.25 (95% CI 1.22–4.16; $P = .010$).

In relation to this research, it's important to be mindful of certain constraints.To begin with, all the cases currently examined originate from a solitary center, leading to an inevitable introduction of bias and a reduction in statistical capability. Furthermore, the existing study is constrained by the retrospective nature of its research design. Hence, to address these crucial issues, it is imperative to conduct

meticulously planned, forward-looking, multicenter extensive research in the future.

Conclusion

In conclusion, we developed and validated a nomogram to predict the risk of VTE in patients with PLC. This nomogram facilitates accurate assessment of VTE risks on an individual basis, allowing for the identification of high-risk patients who may benefit from tailored preventive interventions.

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Data availability The data of this study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval This study was approved by the ethical institutions of the local medical centers (ID: CZLS2023343-A).

Competing interests None.

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