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ORIGINAL RESEARCH

The Efficacy of the Systemic Immune-Inflammation Index and Prognosis Nutritional Index for the Diagnosis of Venous Thromboembolism in Gastrointestinal Cancers

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Purpose: This study aimed to analyze the association between venous thromboembolism (VTE) and inflammatory markers like systemic immune-inflammation index (SII) and prognosis nutritional index (PNI), and to evaluate their efficacy for the diagnosis of VTE in patients with gastrointestinal malignancies.

Patients and Methods: A total of 1326 patients with the initial diagnosis of gastrointestinal cancer in the First Affiliated Hospital of Anhui Medical University (AHMU) were enrolled in the training cohort. Univariate and multivariate analysis was used to pinpoint independent predictors of VTE, which were eventually visualized as the nomogram models. The Akaike Information Criterion (AIC) was used to screen the best model. The receiver operating characteristic curve (ROC) and the clinical decision curve analysis (DCA) were utilized to evaluate the models' predictive performance in the training queue and another external sample of 250 patients at the Second Affiliated Hospital of AHMU.

Results: A total of 476 patients were complicated with VTE in the training cohort. Multifactorial analysis of clinical characteristics and inflammatory markers showed that PNI, SII, age, tumor location, and therapy were independent risk factors of VTE, visualized as model A. Another model B was constructed by adding coagulation markers to the previous analysis. Model B was the best prediction model with the minimum AIC value, followed by model A with an AUC of 0.806 (95% CI 0.782~0.830) which was similar to model B's 0.832 (95% CI 0.810~0.855) but significantly higher than the currently widely used Khorana score's 0.592 (95% CI 0.562~0.621) and the CATS score's 0.682 (95% CI 0.653~0.712). The external verification yielded similar findings, with the AUC being 0.792 (95% CI 0.734~0.851), 0.834 (95% CI 0.778~0.890), 0.655 (95% CI 0.582~0.729), and 0.774 (95% CI 0.699~0.849) respectively. The DCA curves demonstrated that new models had excellent usefulness in screening patients with a high VTE risk.

Conclusion: The SII and PNI were simple and viable inflammatory markers associated with VTE, and the nomogram based on them and clinical features had a meaningful clinical utility for VTE in patients with gastrointestinal malignancies.

Keywords: venous thromboembolism, gastrointestinal cancers, inflammation, systemic immune-inflammation index, nomogram

Introduction

Venous thromboembolism (VTE) is considered a common complication and the leading cause of non-oncologic death in cancer patients, which is suffering patients' quality of life and survival prospects.[1,2] With a VTE prevalence rate of 20%, gastrointestinal malignancies are the most frequently reported tumor types with thrombotic events, mainly including pancreatic cancer, gastric cancer, esophageal cancer, and hepatobiliary malignancies.[3] It is critical to evaluate and screen individuals with high-risk VTE, and the guidelines recommend The Khorana score[4] and the Vienna Cancer and Thrombosis Study (CATS) score[5] for the management of cancer patients. The Khorana score is the most traditional

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and authoritative assessment tool, which consists of peripheral blood cells, tumor location, and nutritional status. And the CATS score is another predictive system involving tumor location and coagulation status.[6] Nonetheless, several studies have observed mediocre performance of these strategies in VTE risk stratification for patients with gastrointestinal malignancies. Therefore, it's essential to seek simple but effective biomarkers for tumor-associated VTE, as well as to develop screening tools for people with gastrointestinal cancer.[7]

Substantial clinical studies have revealed that the first six months after the initial diagnosis was the most dangerous period for thrombosis.[8,9] At this stage, tumor burden and injurious therapies lead to the body's hypercoagulable state and vascular endothelial damage that synergistically promote thrombosis. Furthermore, there is mounting evidence that thrombosis is linked to the inflammatory response in cancer patients. It has been reported that the neutrophil to lymphocyte ratio (NLR),[10] platelet to lymphocyte ratio (PLR)[11] were closely related to thromboembolic incidents in cancer patients. The systemic immune-inflammation index (SII),[12] and prognosis nutritional index (PNI),[13] as novel inflammatory markers, accurately represent the body's inflammatory response, but their efficacy for the diagnosis of tumor-associated VTE remains unclear.

The primary goal of this study was to clarify the association between the aforementioned inflammatory markers and VTE in gastrointestinal cancers and identify potential biomarkers, which were eventually visualized as the prediction model. Given that the D-dimer was the undisputed thrombosis marker, another model was developed. This study eventually evaluated the diagnostic utility of the proposed model for VTE in patients with gastrointestinal malignancies by comparing the efficacy of various predictive tools.

Materials and Methods

Study Population

This study was a retrospective cohort study, of which the overall flow was shown in Figure 1. We reviewed the data of 1326 patients with gastrointestinal malignancies admitted to the First Affiliated Hospital of Anhui Medical University (AHMU) from January 2019 to December 2020, which were defined as the training cohort to construct the model. In addition, data on 250 patients admitted to the Second Affiliated Hospital of AHMU from January 2021 to December 2021 was obtained as an external validation cohort. Inclusion criteria were as follows: (1) patients with the initial diagnosis of gastrointestinal malignancies based on cytology or histopathology; (2) patients receiving at least once Doppler vascular ultrasound examination or computed tomography pulmonary angiography (CTPA) during the first six months after diagnosis; (3) patients with baseline laboratory tests before antineoplastic therapy; (4) patients with no serious infections or bone marrow dysfunction. Exclusion criteria were as follows: (1) patients with second primary carcinoma; (2) patients with autoimmune disease or on hormone therapy; (3) patients with incomplete clinical data. This research was sanctioned by the medical ethics committee of the First Affiliated Hospital of Anhui Medical University (Reference number: Quick-PJ 2022-06-34). All procedures adhered to the Helsinki Declaration. Taking into account the retrospective nature of the study, the patients' consents were waived by the ethics committee. Furthermore, the confidentiality of all patient data was guaranteed.

Data Collection

In this study, VTE mainly included deep vein thrombosis (DVT), superficial thrombophlebitis, and pulmonary embolism (PE). The Doppler vascular ultrasound (GE VividE9/Mindray Resona7s) showed that veins would not compress fully and contained echogenic materials but no flow signals, which was diagnosed as venous thrombosis (Supplementary Figure 1). The clinical symptoms and imaging features of vascular filling defects, such as the "cutoff sign" and "tram-track sign" observed by the CTPA (GE Lightspeed VCT256) were diagnosed as PE. All images were checked separately by two senior radiologists and documented in the patients' electronic medical records.

The demographic characteristics (gender, age, body mass index (BMI), smoking, etc.), clinical features (ascites, tumor location, metastasis, anti-tumor therapy, etc.), and laboratory indicators were obtained. The peripheral blood was acquired and tested within one week after being diagnosed and before anti-tumor medication. Laboratory parameters such as white blood cell count (WBC), neutrophil count (N), lymphocyte count (L), platelet count (PLT), hemoglobin (HB), D-dimer, fibrin

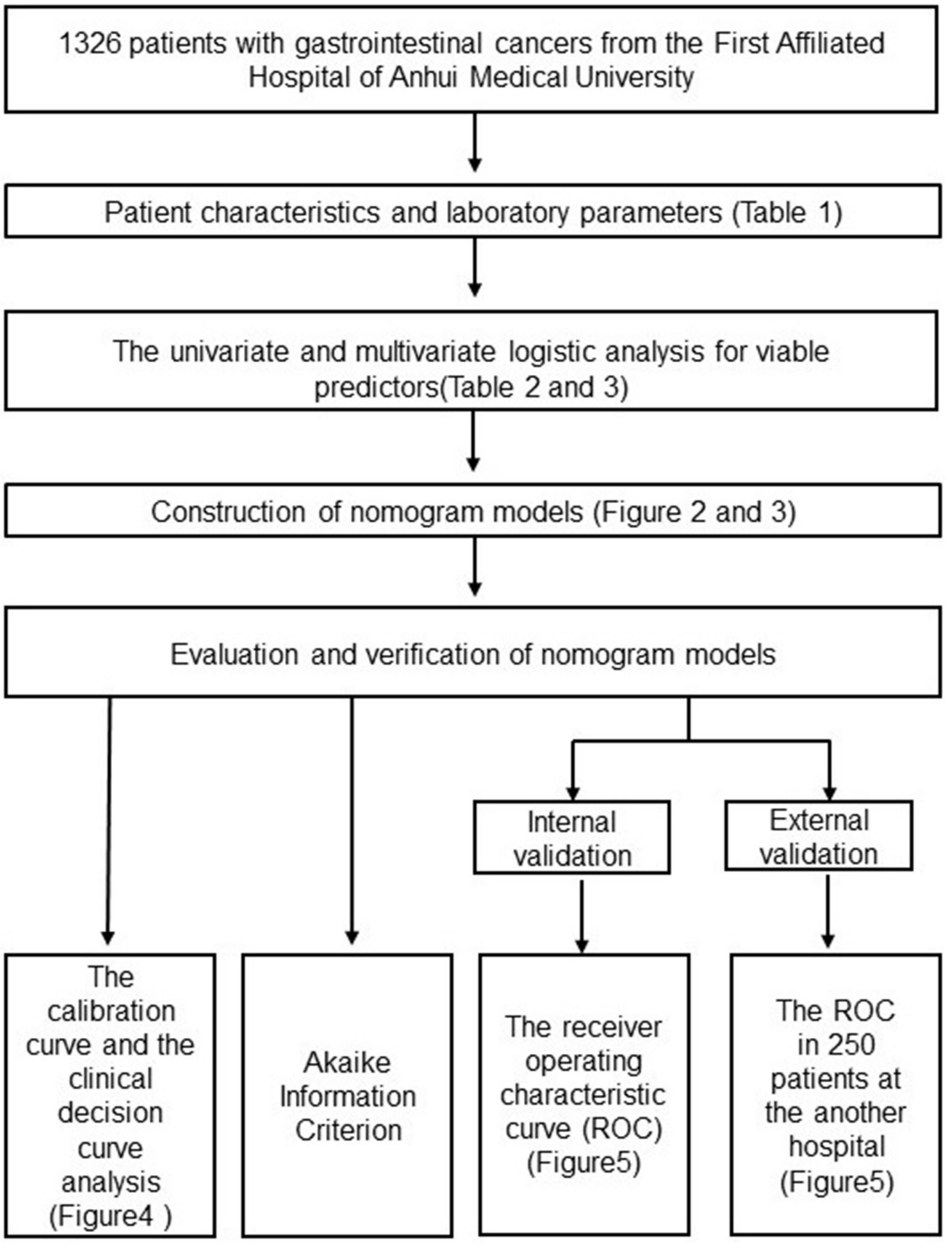

Figure 1 The overall flow of the study.

degradation product (FDP), and serum albumin (ALB) were all included in our study. The calculation formulas were as follows: NLR = N/L; PLR = PLT/L; SII = PLT×N/L; PNI = 10 × ALB (g/dL) + 0.005 × L (/mm^3).

The Khorana score was as follows: 2 points for stomach or pancreatic cancer;1 point for the baseline platelet count of 350×10^9 /L or higher;1 point for hemoglobin less than 100g/L; 1 point for the leukocyte count more than 11×10^9 /L or higher; and 1 point for BMI of 35 kg/m^2 or higher. The CATS score consisted of tumor category and D-dimer concentration. In this study, continuous data like age, blood count, and BMI were converted into categorical variables for statistical analysis referring to two authoritative scores mentioned above. The optimal thresholds for FDP and D-dimer were controversial and previous studies had suggested that D-dimer of three times above normal level might be the optimal cutoff. So the two coagulation indicators here were grouped based on their elevated multiples.[14,15]

Statistical Analysis

All statistical analysis was conducted using IBM SPSS Statistics (version 22.0) and R software (4.1.3). Continuous variables with normal distribution were presented as mean (standard deviation) and compared by the Student's *t*-test. Serial numbers with non-normal distribution were expressed as median with interquartile range and compared by the Mann–Whitney test. Categorical variables were represented by cases and ratios and compared by chi-square or Fisher's exact test. Univariate and multivariate logistic regression analyses were used to determine independent predictors. The nomogram model was built through the "RMS" package. The receiver operating characteristic (ROC) curve, calibration curve, and clinical decision curve analysis (DCA) were conducted using the "proc", "resource selection", and "rmda" packages. A P-value <0.05 indicated that the difference was statistically significant.

Results

Patient Characteristics

A total of 1326 patients were enrolled in the training cohort, and 476 patients were complicated with VTE. This study covered 850 males and 476 females, with a median age of 60 [53, 65]. There were 96 cases of esophageal cancer, 338 cases of gastric cancer, 533 cases of colorectal cancer, 136 cases of pancreatic cancer, and 222 cases of hepatobiliary malignancies. A total of 160 patients received hospice care, 584 patients underwent surgical resection, and 482 patients had chemotherapy as their first treatment. The levels of hematologic parameters such as WBC, N, L, PLT, NLR, PLR, and SII were greater ($P < 0.05$) in the VTE group than those in the non-VTE group, whereas HB and PNI were the polar opposite ($P < 0.05$). The clinical features and laboratory indexes of the two groups were shown in Table 1.

Table 1 Comparison of Clinical Data Between VTE Group and Non-VTE Group in the Training Cohort

Variable	Non-VTE Group (N=850)	VTE Group (N=476)	χ2/U	P-value
Gender			3.598	0.058
Female	281 (60.7%)	182 (39.3%)		
Male	569 (65.9%)	294 (34.1%)		
Age			104.214	0.001
<50	188 (84.7%)	34 (15.3%)		
50–60	320 (72.7%)	120 (27.3%)		
60–70	284 (53.2%)	250 (46.8%)		
>70	58 (44.6%)	72 (55.4%)		
BMI			5.338	0.021
≤28	794 (63.4%)	470 (36.6%)		
>28	56 (76.7%)	17 (23.3%)		
Smoking			3.837	0.050
No	488 (61.9%)	301 (38.1%)		
Yes	210 (68.2%)	98 (31.8%)		
Vessel diseases			2.360	0.124
No	782 (64.7%)	426 (35.3%)		
Yes	68 (57.6%)	50 (42.4%)		
Tumor location			54.686	0.001
Hepatobiliary system	178 (80.2%)	44 (19.8%)		
Esophagus	66 (68.8%)	30 (31.3%)		
Stomach	188 (55.6%)	150 (44.4%)		
Colorectum	353 (66.3%)	180 (33.7%)		
Pancreas	64 (47.1%)	72 (52.9%)		
Ascites			1.106	0.293
No	772 (64.7%)	422 (35.3%)		
Yes	78 (60.0%)	52 (40.0%)		

(*Continued*)

Table 1 (Continued).

Variable	Non-VTE Group (N=850)	VTE Group (N=476)	χ2/U	P-value
Metastasis			5.389	0.020
No	582 (66.3%)	296 (33.7%)		
Yes	268 (59.8%)	180 (40.2%)		
Therapy				
No therapy	178 (68.5%)	82 (31.5%)	174.396	0.001
Surgical	266 (45.5%)	318 (54.5%)		
Medical*	406 (84.2%)	76 (15.8%)		
CVC			1.148	0.700
No	606 (63.9%)	342 (36.1%)		
Yes	242 (65.1%)	130 (34.9%)		
Stay in bed>72h			0.298	0.585
No	842 (64.2%)	470 (35.8%)		
Yes	8 (57.1%)	6 (42.9%)		
Albumin (g/L)	39.5[36.8, 41.5]	38.30[35.30, 40.50]	−5.389	0.001
FDP	2.30[1.50, 3.89]	3.75[2.79, 8.00]	−12.187	0.001
D-dimer	1.53[0.90, 2.46]	2.43[1.60, 3.88]	−11.485	0.001
WBC (×10^9/L)	5.14[4.18, 6.43]	5.28[4.34, 6.63]	−2.050	0.040
HB (g/L)	130[116, 144]	123[111, 134]	−6.575	0.000
PLT (×10^9/L)	219[174, 273]	226[182, 292]	−2.239	0.025
PNI	47.52[44.03, 50.55]	45.65[42.26, 50.04]	−4.300	0.001
NLR	1.78[1.27, 2.77]	2.01[1.30, 3.19]	−2.731	0.007
PLR	137.46[103.47, 179.59]	151.20[111.05, 204.72]	−3.628	0.001
SII (×10^9/L)	391.11[257.21, 624.71]	460.54[285.50, 745.06]	−4.123	0.001

Notes: As the training cohort to construct the model, the data of 1326 patients with gastrointestinal cancers admitted to the First Affiliated Hospital were retrospectively collected. Here are the clinical features and laboratory indexes of the two groups. Smoking history was unclear in 229 patients. *The medical therapy group is a population of patients receiving non-surgical treatment modalities such as chemotherapy, targeted therapy, or radiotherapy.

Logistic Regression Analysis for Risk Factors of VTE in Patients with Digestive Malignancies

As shown in Table 2, the univariate logistic analysis revealed that 13 candidate variables with $P < 0.05$ were linked to VTE. Age, BMI, tumor location, metastasis, and therapy were summarized as clinical features. The albumin, WBC, NLR, PLR, SII, and PNI were inflammatory marks. The D-dimer and FDP were regarded as coagulation indexes. As shown in Table 3, multifactorial analysis of 11 variables (clinical characteristics and inflammatory markers) showed that PNI, SII, age, tumor location, and therapy were independent risk factors, visualized as model A. Multifactorial analysis of 13 variables (clinical characteristics, inflammatory markers, and coagulation indicators) showed that PNI, SII, age, tumor location, therapy, and D-dimer were determined to be independent risk factors, visualized as model B. We observed the two most prominent laboratory items linked to thrombotic events, which may be used as potential biomarkers of VTE. Higher SII levels made the risk of VTE higher, while the PNI was negatively correlated with thrombosis, of which the risk in the low group was 1.943 times higher than that in the high set. The risk of VTE increases with age, especially among patients above 70 years being 7.931 times more likely to experience VTE than individuals younger than 50 years. The tumor location was connected to VTE: the pancreas, stomach, esophagus, colorectum, and hepatobiliary system are all ranked in terms of their risk. Various therapies substantially impact VTE occurrence, with surgical patients having the most severe trouble. Last, D-dimer was the strongest predictor of VTE consisting with previous studies.

Construction of Nomogram Models for VTE in Gastrointestinal Malignancies

First, clinical features and inflammatory indicators were multifactorial analyzed to identify potential predictors, which were then visualized as predictive model A. Second, considering that coagulation indicators were indisputable thrombotic

Table 2 Univariate Logistic Regression Analysis Between VTE Group and Non-VTE Group

Variate	OR (95% CI)	P-value
Female	1.254(0.992–1.583)	0.058
Age 50–60	2.074(1.361–3.160)	0.001
Age 60–70	4.867(3.253–7.282)	0.001
Age>70	6.864(4.151–11.351)	0.001
BMI>28	0.525(0.302–0.915)	0.023
Smoking	0.757(0.572–1.001)	0.050
Vessel Diseases	1.350(0.920–1.981)	0.126
Hepatobiliary system	1	
Esophagus	1.839(1.068–3.166)	0.028
Stomach	3.228(2.177–4.785)	0.001
Colorectum	2.057(1.413–2.994)	0.001
Pancreas	4.551(2.840–7.292)	0.001
Ascites	1.220(0.842–1.766)	0.294
Metastasis	1.321(1.044–1.671)	0.020
Surgical	2. 595(1.907–3.532)	0.001
Medical*	0. 406(0.284–0.581)	0.001
CVC	0. 952(0.741–1.223)	0.700
Stay in bed>72h	1. 344 (0.463–3.896)	0.587
FDP elevated 1–2fold	2.565(1.883–3.494)	0.001
FDP elevated>2fold	4.400(3.080–6.287)	0.001
D-dimer elevated1–3fold	2.332(1.715–3.170)	0.001
D-dimer elevated>3 fold	6. 557(4.696–9.156)	0.001
Albumin<40 (g/L)	1.794(1.414–2.276)	0.001
WBC≥11×10^9/L	3.301(1.511–7.212)	0.003
HB≤100 (g/L)	1.059(0.722–1.553)	0.770
PLT≥350×10^9/L	1.030(0.703–1.508)	0.881
PNI<45.57	1.943(1.546–2.443)	0.001
NLR>2.82	1.544(1.205–1.978)	0.001
PLR>186.99	1.815(1.413–2.952)	0.001
SII≥504.80	1.749(1.391–2.200)	0.001

Notes: The logistic regression analysis in this study comprised 21 variables, of which continuous ones are converted to categorical variables. FDP and D-dimer were classified based on multiples of the normal value. WBC, HB, and PLT were grouped according to the Khorana score. NLR, PLR, PNI, and SII were classified based on the optimal cutoff values determined by the ROC curves. *The medical therapy group is a population of patients receiving non-surgical treatment modalities such as chemotherapy, targeted therapy, or radiotherapy.

Table 3 Multivariate Logistic Regression Analysis Between Two Groups in Model a and Model B

Variate	Model A			Model B		
	β	OR (95% CI)	P-value	β	OR (95% CI)	P-value
Constant	−3.436		0.032	−4.276		0.014
Age<50		1				
Age50–60	0.605	1.083(1.154–2.904)	0.010	0.599	1.821(1.128–2.938)	0.014
Age60–70	1.476	4.377 (2.798–6.849)	0.001	1.480	4.392(2.761–6.986)	0.001
Age>70	2.066	7.897 (4.451–14.010)	0.001	2.122	8.344(4.594–15.155)	0.001
Hepatobiliary		1				
Esophagus	0.660	1.934(1.059–3.534)	0.032	1.000	2.718(1.446–5.108)	0.002
Stomach	1.049	2.855(1.808–4.507)	0.001	0.898	2.456(1.532–3.936)	0.001
Colorectum	0.651	1.917(1.241–2.962)	0.003	0.623	1.882(1.203–2.945)	0.004

(*Continued*)

Table 3 (Continued).

Variate	Model A			Model B		
	β	OR (95% CI)	P-value	β	OR (95% CI)	P-value
Pancreas	1.991	7.325(4.233–12.674)	0.001	1.916	6.796 (3.853–11.988)	0.001
No-therapy		1				
Surgical	1.412	4. 104 (2.769–6.082)	0.001	1.687	5.405(3.541–8.250)	0.001
Medical*	−0.626	0. 535 (0.354–0.807)	0.003	−0.302	0.739(0.479–1.141)	0.173
PNI<45.57	0.633	1.673(1.259–2.222)	0.001	0.460	1.584 (1.176–2.133)	0.002
SII≥504.80	0.515	1.883(1.417–2.502)	0.001	0.382	1.465 (1.090–1.969)	0.011
D-dimer elevated1–3fold	-	-	-	0.589	1.801(1.269–2.557)	0.001
D-dimer elevated>3 fold	-	-	-	1.687	5.404(3.627–8.051)	0.001

Notes: Multivariate analysis revealed 6 independent risk factors. Model A and Model B were built based on including D-dimer or not. *The medical therapy group is a population of patients receiving non-surgical treatment modalities such as chemotherapy, targeted therapy, or radiotherapy.

markers, another model B was built by adding coagulation indicators. Model A and Model B were satisfactorily developed as shown in Figures 2 and 3.

Evaluation and Verification of Nomogram Models

The calibration curves in Figure 4A with no departure and the Hosmer-Lemeshow Goodness-of-Fit test of 0.067 and 0.350 (P> 0.05) indicated that the models' calibration was satisfactory. The DCA curve showed the threshold ranged from 0.01 to 0.70 in Figure 4B. The Akaike Information Criterion (AIC) was used to screen the best model and showed that the AIC values were 1618.64, 1531.19, 1782.05, and 1768.47. This meant that model B was the best prediction model, followed by the new model A. Two nomogram models were validated using Bootstrap in internal validation. The areas under the ROC curve (AUC) for model A, model B, the Khorana score, and the CATS score in the training set were 0.806 (95% CI 0.782~0.830), 0.832 (95% CI 0.810~0.855), 0.592 (95% CI 0.562~0.621), and 0.682 (95% CI 0.653~0.712), as shown in Figure 5A and C. The accuracy of model A was 75.2%, with 76.5% sensitivity and 73.2% specificity; The accuracy of model B was 77.2%, with 73.5% sensitivity and 78.1% specificity.

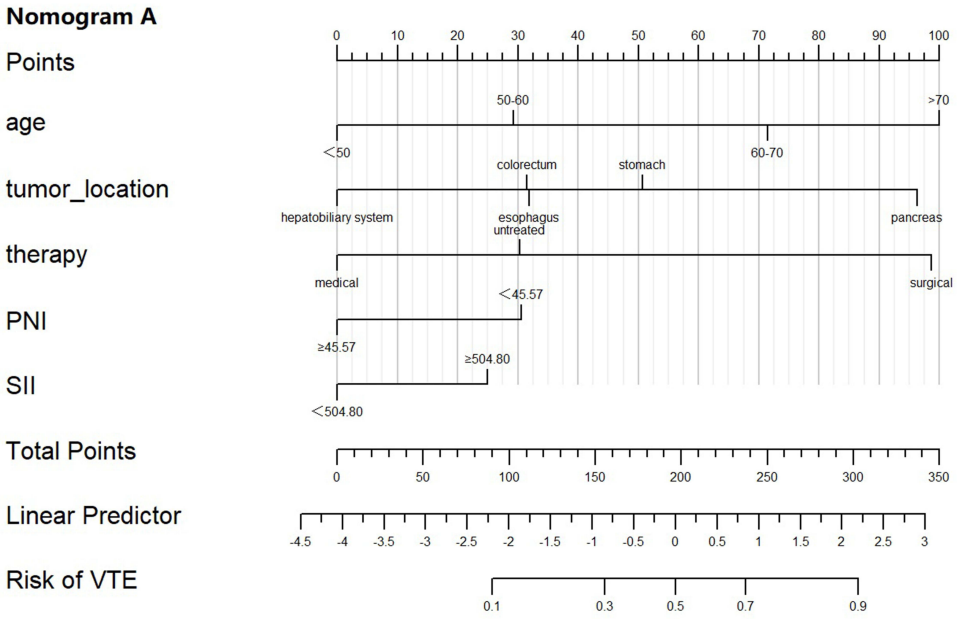

Figure 2 The nomogram of the model A.
Notes: Here's nomogram model A with five elements. Each line indicates a factor; for example, age under 50 and over 70 receive scores of 0 and 100, respectively; however, the scores for the 50–60 and 60–70 categories are 30 and 70, respectively.

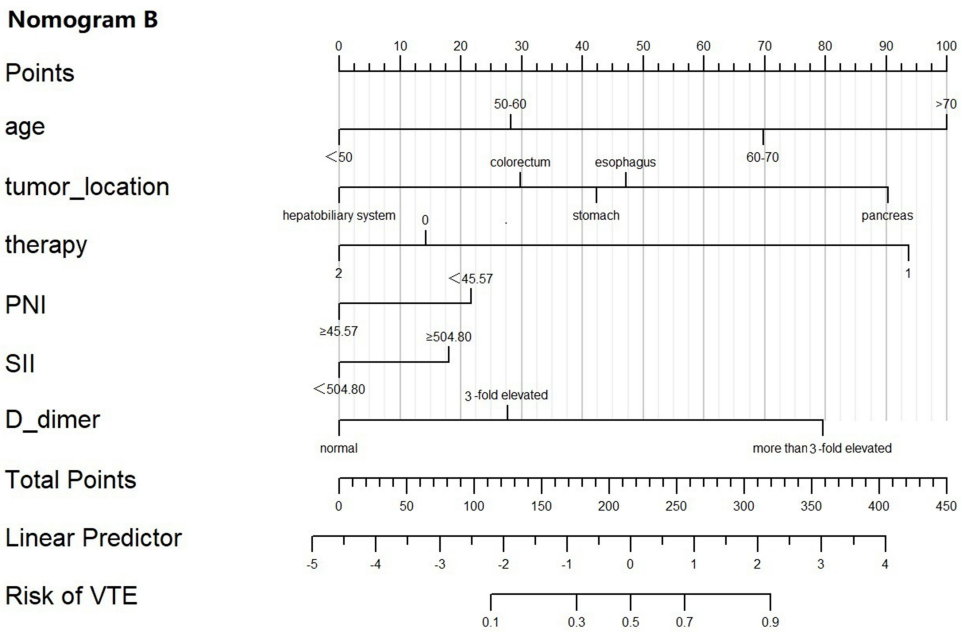

Figure 3 The nomogram of the model B.
Notes: This is the nomogram model B with six factors. There is some discrepancy in the scores of distinct tumor sites. The severity of stomach and esophageal cancer varies.

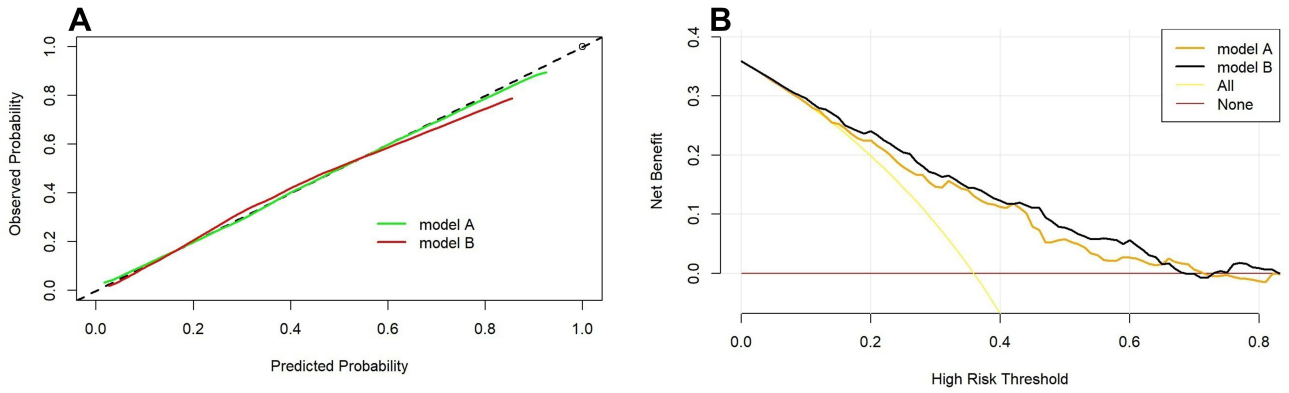

Figure 4 (**A**) The calibration curve of nomogram of model A and B in the training cohort (bootstrap 1000 repetitions); (**B**) the clinical decision curve analysis of nomogram of model A and B in the training cohort.

Finally, we gathered data from 250 patients admitted to the Second Affiliated Hospital of AHMU from January 2021 to December 2021 as an external validation cohort. There were 60 patients with VTE. The AUCs in Figure 5B and D for model A, model B, the Khorana model and the CATS score were 0.773 (95% CI 0.711~0.836), 0.822 (95% CI 0.764~0.881), 0.655 (95% CI 0.582~0.729), and 0.774 (95% CI 0.699~ 0.849), respectively. The accuracy of model A was 77.2%, with 85.0% sensitivity and 61.6% specificity; The accuracy of model B was 81.2%, with 77.7% sensitivity and 87.9% specificity.

Discussion

This study confirmed that SII and PNI were potential biomarkers associated with thrombotic events and conducted two nomogram models for VTE in patients with gastrointestinal malignancies. The ROC curve analysis of the training and testing team revealed that new models could effectively predict VTE events. Model B, including numerous

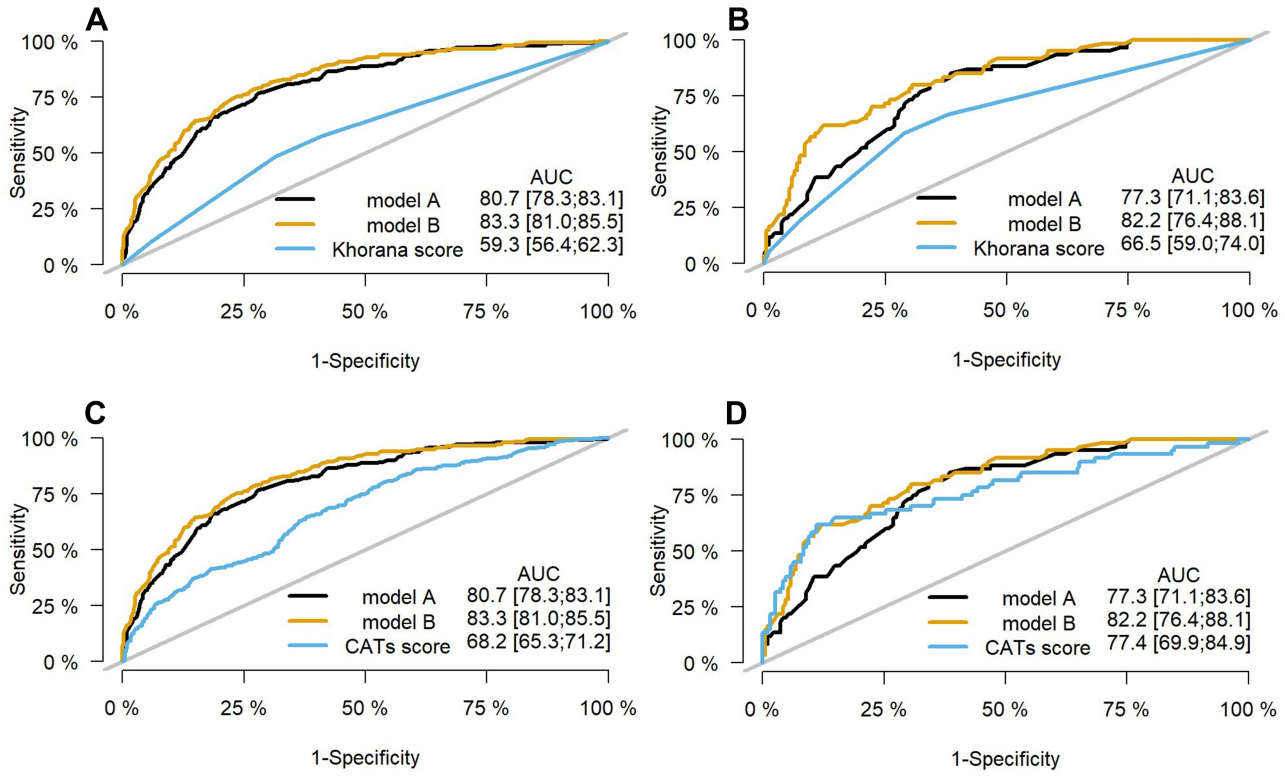

Figure 5 (**A**) The receiver operating characteristic (ROC) curve and the area under the ROC (AUC) of model A, model B, and Khorana score in the training cohort; (**B**) the ROC and AUC of model A, model B, and Khorana score in the testing cohort. (**C**) The ROC and AUC of model A, model B, and CATSs core in the training cohort; (**D**) the ROC and AUC of model A, model B, and CATSs core in the testing cohort.

comprehensive elements, has the best forecasting potency. It is essential to point out that Model A, which just contains inflammatory biomarkers and patient features, can still predict well.

In our study, SII and PNI were involved in VTE-forecasting tools for the first time, which was a distinguishing feature. In recent research, NLR and PLR have been attribute to thrombosis.[16–18] The diagnostic value of SII coupled with PNI in cancer-related VTE has yet to be determined. Our findings showed that SII paired with PNI was the valuable predictor for VTE in gastrointestinal cancer patients, with the cutoff values of 504.80 and 45.57.

SII accurately depicts inflammatory reaction in the body which is easy to calculate from neutrophils, lymphocytes, and platelets.[17] PNI was first utilized to assess the extent of inflammation and nutrition condition of patients[18] and it was calculated from lymphocyte and serum albumin. Reports about thrombosis and two indicators were searched in PubMed, Embase, and Web of Science and then summarized in Table 4. SII has been viewed as a risk factor for acute PE, DVT, cerebral venous thromboembolism, and portal vein thrombosis.[19–22] In addition, Gok et al found that the extent of SII augmentation was associated with the severity of PE.[19] PNI has been described as a predictor of PE, DVT, and cerebral venous sinus thrombosis.[23–25]

Recent researches have also shown that SII and PNI were linked to the prognosis of thrombosis patients.[26–28] Li et al observed the SII level in 270 patients with acute or subacute cerebral venous sinus thrombosis and then found SII was a potential predictor of poor prognosis in those patients (HR = 1.304, 95% CI: 1.101–1.703, P= 0.001), whose cutoff level was 1525.04.[27] Another retrospective study of 51 cases was consistent with the conclusion.[28] Future researches should explore further how these two novel inflammatory indicators affect the prognosis of patients with tumor-associated VTE, as well as construct a prognostic model to help physicians in clinical decision-making.

In reality, the linkage of the immunity, inflammation and thrombosis has been studied. Increased systemic inflammation and mass inflammatory mediators commonly occur in patients with digestive cancers due to the tumor or anti-tumor treatment. At first, inflammation causes monocytes to release tissue factor (TF), which is important for starting the

Table 4 Summary of Exploring the Relationship Between SII, PNI, and VTE

Theme	Study	Year	Country	Study Design	Cases	Age	VTE Type	OR (95% CI)	Cut-off	AUC	Sensitivity	Specificity
SII	Gok[19]	2021	Turkey	Retrospective	442	64.0±16.0	PE	1.005(1.002–1.007)	1161.00	0.957	91.0%	90.0%
	Zhang X[20]	2021	China	Retrospective	150	37.8±15.9	CVT	13.136(5.675–30.407)	496.07	0.827	84.4%	75.1%
	Peng J[22]	2021	China	Retrospective	104	75.6±8.4	DVT	1.004(1.001–1.008)	847.78	0.795	53.8%	92.3%
	Xing Y[21]	2022	China	Retrospective	478	55.4±9.8	PVT	-	268.90	0.612	-	-
PNI	Hayıroğlu Mİ[24]	2018	Turkey	Retrospective	251	64.0±15.0	PE	2.5(0.9–10.4)	38.00	0.79	53.0%	95.0%
	Iguchi T[23]	2020	Japan	Retrospective	100	68.1[24–85]	DVT	31.3(2.0–486.4)	44.30	-	-	-
	Oe S[25]	2020	Japan	Retrospective	285	68.6±8.6	DVT/PE	2.9(1.69–4.93)	50.00	-	-	-

Notes: We systematically searched PubMed, Embase, and Web of Science for relevant reports up to March 2022 with the terms as follows: ("systemic immune-inflammation index" OR "SII") OR ("prognostic nutritional index" OR "PNI") AND ("pulmonary embolism" OR "PE") OR ("deep venous thrombosis" OR "DVT") OR ("venous thromboembolism" OR "VTE".

exogenous coagulation reaction and stopping fibrinolysis from happening.[29,30] Second, neutrophils are incorporated into developing thrombi via the release of neutrophil extracellular traps (NETs), which promote platelet aggregation and activation and factor XII.[31] NETs and Nod-like receptor protein (NLRP)-3 inflammasomes cooperatively promote the destruction of vascular integrity and trigger pathological thrombus development.[32] Severe malnutrition, like dehydration, provokes elevated plasma viscosity and slowed blood flow. Recently, albumin has been verified to suppress platelet activation by blocking the NOX2-mediated response to oxidative stress, and hypoalbuminemia was probably associated with VTE.[33,34]

In addition, thrombosis is preceded by local inflammation termed "immunothrombosis". Vascular inflammation motivates the activation of endothelial cells, platelets, and leucocytes and then triggers the coagulation system.[35] Luther et al demonstrated that thrombosis increased chemokine expression, leading to the recruitment of effector memory T-cells (TEM-cells) into the vessel wall.[36] TEM-cells recruit monocytes and neutrophils and ultimately lead to delayed resolution of the venous clots. Circulating immune cells support the local pro-inflammatory state during thrombosis by directly adhering to the inflamed endothelium membrane and releasing potent pro-inflammatory cytokines.

Furthermore, the new models in this study contained demographics and tumor features, which is consistent with earlier findings. A survey in the Swiss Registry found that age (OR = 2.21, 95% CI: 1.33–3.67), malignancy (OR = 2.01, 95% CI: 1.20–3.35), and recent surgical history (OR = 2.92, 95% CI: 1.80–4.73) were independent risk factors for DVT.[37] Patients with different tumor locations had a variable risk of VTE. Several extensive epidemiologic studies have revealed that pancreatic and stomach cancers had the highest incidence of VTE.[38] The risk scores for pancreatic and stomach cancer were 97.5 and 52.5 in our new nomogram. VTE risk varies among cancer patients getting various therapies. Ratib S discovered that VTE risk in chemotherapy patients was 1.75 times higher than in non-chemotherapy individuals.[39] The risk of VTE in patients undergoing surgery is 2 to 6 folds greater than that in patients undergoing non-surgical treatment.[40] However, a multicenter prospective study in France observed that the incidence of VTE in patients getting radiotherapy was 2% (95% CI: 0.9–3.7), the same as in those not receiving radiotherapy, indicating that radiotherapy might not be a risk factor for thrombosis.[41] We found that patients who underwent surgery had a higher risk of VTE than those who did not receive any anti-tumor treatment, which was higher than those who got medicinal treatment. The following are plausible explanations: 1) Abdominal surgery causes significant trauma where the vascular endothelium is severely damaged. Moreover, postoperative patients' limited activity causes blood stasis, which raises the chances of thrombosis. 2) Untreated cancer patients' substantial tumor load and vascular compression from the abdominal mass facilitate impaired blood flow, easily associated with VTE.[37] 3) Even though chemotherapy and intravenous infusion cause vascular damage, the tumor gets better control, relieving vascular restrictions. 4) Patients in this study who got radiotherapy were classed as a medical treatment group, which might not be related to an increased risk of thrombosis.

Lastly, models A and B were formulated based on whether or not coagulation indexes were included. Patients with malignant tumors are in a state of hypercoagulation and fibrinolytic system activation where the biomarker is D-dimer.[42] Growing D-dimer levels frequently indicate a greater risk of thrombosis, and their increased levels relate to the thrombosis burden.[43,44] Model A with an excellent clinical evaluation despite the absence of D-dimers may be considered for the prediction of VTE in patients lacking coagulation markers.

Even though a suitable sample size was included, our current study had some existing limitations. First and foremost, this was a prediction model constructed with the clinical characteristics of the Asian population. Although it performed well in other medical institutions, its prediction efficiency for other races or regions had not been determined. Second, the models did not include tumor stage as an original variable since more than 10% of data were absent, which rendered the model limited despite the incorporation of metastasis. Last, it was a retrospective and observational study and the objects may be biased. Hence, a multicenter, prospective, and large-scale clinical trial is required for in-depth research and verification.

Conclusion

We analyzed data from patients with gastrointestinal malignancies and concluded that the SII and PNI were potential biomarkers associated with VTE. And then we devised risk prediction models for VTE based on inflammatory

biomarkers and clinical characteristics. The two models had excellent prediction performance higher than the current widespread risk assessment tools. Additionally, VTE can be foreknown satisfactorily in patients lacking coagulation-related markers using the novel prediction system.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the medical ethics committee of the First Affiliated Hospital of Anhui Medical University (Number: Quick-PJ 2022-06-34). All procedures adhered to the Helsinki Declaration. Taking into account the retrospective nature of the study, the patients' consents were waived by the ethics committee. All data about the patients was anonymized or maintained confidentially.

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Disclosure

The authors report no conflicts of interest in this work.

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