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A Risk of Venous Thromboembolism Algorithm as a Predictor of Venous Thromboembolism in Patients with Colorectal Cancer

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Abstract

Cancer patients experience an increased risk of venous thromboembolism (VTE). In this study, we investigated a risk of venous thromboembolism algorithm (RVTA) in patients with colorectal cancer and evaluated its ability to predict the prognosis of colorectal cancer. We retrospectively analyzed clinical data from 345 patients with colorectal cancer from January 2015 to December 2018 at the Shanghai Cancer Center to develop the RVTA. Additionally, the 345 patients were followed until December 2020 for prognostic analysis. The RVTA included the following variables: (a) platelet count, (b) blood transfusion history, (c) metastasis, (d) multiple chemotherapy regimens, and (e) the D-dimer level. Good predictive efficiency was observed for the RVTA (AUC was 0.825; 95% CI was 0.721 to 0.930). The median progression-free survival (PFS) of patients who had a score less than 4 (0-3), defined as the low-risk group, was significantly longer than that of the high-risk group, which included patients who had a score greater than 4 (4-8) (26 vs ten months, $P < .001$). The RVTA was a valuable predictor for VTE risk and had prognostic value in colorectal cancer.

Keywords

venous thromboembolism, colorectal cancer, d-dimer, RVTA

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Introduction

Venous thromboembolism (VTE) significantly raises the risk of death and reduces the quality of life. The risk of VTE is increased in patients with colorectal cancer due to hypercoagulability.[1] Based on the retrospective analysis report, the occurrence rate of symptomatic VTE among patients with colorectal cancer is approximately 5.5%.[2,3] Moreover, it has been established that deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE) are critical factors that contribute to poor tumor prognosis.[4,5] Thus, a reliable assessment to identify patients at high risk for VTE is recommended. The aim of this study was to investigate the risk of venous thromboembolism algorithm (RVTA) in patients with colorectal cancer.

D-dimer has been widely used as a sensitive marker for indicating thrombogenesis.[6] Elevated D-dimer levels are closely correlated with VTE events in patients with colorectal cancer.[7] The plasma D-dimer level is often elevated in patients with cancer due to coagulation and fibrinolysis disorders that can be produced by tumor progression. The upper limit of plasma D-dimer levels for ordinary individuals cannot be taken as the prediction criterion for VTE patients with cancer. Therefore, the D-dimer cut-off level should be redefined for patients with colorectal cancer.

In addition to the sensitive biomarker, clinical risk factors for VTE should be considered. It was reported that transfusion was

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associated with venous thromboembolism.[8] Chemotherapy[9] and surgery history[10] were determined to be risk factors for VTE. Thus, a risk assessment tool needs to be established by analyzing the clinical data, including underlying condition, tumor stages, treatment measures and laboratory data, to evaluate the risk of VTE and predict the prognosis of patients with colorectal cancer.

The risk of VTE increases by sixfold in ambulatory cancer patients receiving chemotherapy.[11] However, few available VTE risk assessment models have been evaluated for patients undergoing anti-cancer treatment. The best-known model, proposed by Khorana et al. was obtained using a chemotherapy research group database for neutropenia.[12] The Khorana score is suitable to evaluate of patients with solid tumors before chemotherapy but not patients on anti-cancer treatments. The clinical prediction indicators used in the Khorana model include hemoglobin, blood platelet count and white cell count. However, the sensitive biomarker, D-dimer, is not included. In a SAVE ONCO trial, among patients with a high risk defined by the Khorana score, only 4 of 271 patients in the placebo group and 15 of 279 patients in the semuloparin group developed a VTE.[13] The Khorana score was unable to predict most of the VTE events in the study by George et al. and most of the cancer-associated thrombosis occurred among patients with an intermediate Khorana score (64%). Among the 3212 patients randomized, the majority had lung (36.6%) or colorectal (28.9%) cancer, indicating an improved VTE risk assessment method was needed for this group of patients. Therefore, it is of clinical significance to develop a more accurate risk evaluation tool for predicting thrombosis and estimating the prognosis for ambulatory patients with colorectal cancer.

Subjects and Methods

Study Design and Subjects

The clinical data from 345 patients with colorectal cancer treated at the Fudan University Shanghai Cancer Center from January 2015 to December 2018 were retrospectively analyzed to explore the relevant risk factors for VTE and develop a risk assessment model for patients with colorectal cancer. Patients were recruited into the study when they were diagnosed with VTE or non-VTE. Written informed consent was obtained from each patient. A definitive diagnosis of VTE was required, including one of the following criteria: (a) The deep venous thrombosis was definitively diagnosed via compression venous ultrasonography (CUS) or (b) pulmonary thromboembolism was definitively diagnosed via computed tomography angiography (CTA). Exclusion criteria included the following: (a) Patients with a history of embolism or continuously taking drugs such as heparin or a vitamin K antagonist that affected coagulation function or (b) patients whose clinical data, such as baseline laboratory data at diagnosis of colon cancer, were unknown. The patients included in this study were receiving a recommended anti-cancer treatment. We retrospectively analyzed the existing patient clinical information and developed a risk assessment model. Furthermore, the 345 patients were followed until December 2020 for survival analysis to evaluate the prognostic value of the RVTA.

Establishment and Validation of the RVTA

The D-dimer level was measured by STA-R Evolution® (STAGO, Asnières, France) using the STA® - Liatest® D-Di kit (STAGO, Asnières, France) and analyzed to define the cut-off level for VTE high-risk patients with colorectal cancer. In the modeling cohort, clinical information was analyzed retrospectively when the patients were enrolled in the study, including age, gender, BMI, tumor stages, metastasis, pelvic or peritoneal effusion, underlying diseases, blood transfusion history (within three months prior to inclusion), surgery history (within three months prior to inclusion), therapeutic regimens and baseline laboratory data at diagnosis of colon cancer (carcinoembryonic antigen, hemoglobin, platelet count, white-cell count, D-dimer). The validation cohort was analyzed according to the RVTA scores, with several statistical indexes evaluated for prediction effectiveness. To further evaluate the calibration, the validation cohort was grouped based on the RVTA scores, and the number of expected VTE events in each group was compared to the number of observed VTE events. Subsequently, correlation analysis was conducted.

Survival Analysis Based on the RVTA

Based on the RVTA scores, the prognosis of the 345 patients with colorectal cancer was evaluated retrospectively. Follow-up information included imaging or pathological evidence to estimate tumor recurrence or metastasis. The deadline for the inclusion of follow-up information was December 2020. Progression-free survival (PFS) was defined as the interval from the date of inclusion to the date of local relapse or observation of distant metastasis. The survival curve and the difference between groups were tested using statistical analysis.

Statistical Analysis

SPSS software (version 19.0) and R software (version 4.1.1) were used for statistical analyses. Due to a non-normal distribution, the significant difference in D-dimer levels between the VTE and non-VTE groups was verified using the Mann-Whitney *U* test. A ROC curve for predicting VTE was drawn based on D-dimer levels. The optimal threshold was defined as the D-dimer cut-off level with the maximum YOUDEN index. Data in the modeling cohort were analyzed by univariate analysis using the chi-square test or Fisher's exact test to screen thrombosis-related risk factors. The variance inflation factor (VIF) was used to assess the multicollinearity of laboratory parameters prior to the multivariable model. Logistic regression analysis was performed for modeling of VTE risk assessment, using the specific method, Backward-LR. The rule of thumb, so-called events per variables (EPV) 1 to 10, was followed in the logistic regression analysis. Each variable

corresponding to 10 outcome events in the modeling cohort was put forward in the analysis described by Peduzzi P et al.[14] The RVTA was then established based on the regression coefficient in the model. The assignment of variables was taken as 0 or 1 (0 for No and 1 for Yes). Risk stratification was classified according to the ROC curve, taking the maximum YOUDEN index as the optimum cut-off score for the high-risk layer. Data in the validation cohort were used to verify the predictive effectiveness. The area under the curve (AUC), specificity, sensitivity, and overall accuracy were analyzed. The metrics of net reclassification index (NRI) was calculated to evaluate the improvement in prediction accuracy. A Kaplan-Meier curve was drawn for survival analysis, and significant differences were tested via the log-rank test. A P value <.05 was considered to be statistically significant.

Results

Criteria Used to Define Subject Groups

Three hundred forty-five colorectal cancer patients, including 86 patients with VTE (24.9%) and 259 patients without VTE (75.1%), were definitively diagnosed via CUS or CTA examination. The patients were randomly divided into a modeling cohort ($n = 245$) or a validation cohort ($n = 100$). Sixty-one patients (24.9%) were diagnosed with VTE, and 184 patients (75.1%) did not experience VTE in the modeling cohort. The events were PE for 10 patients, lower extremity DVT for 48 patients (proximal DVT for 26 and distal DVT for 22), and 3 patients of DVT combined with PE. In the validation cohort, 25 patients (25.0%) were diagnosed with VTE, and 75 patients (75%) did not suffer from VTE. PE was confirmed for 5 patients and DVT for 20 patients (proximal DVT for 12 and distal DVT for 8). The VTE events observed in the study were PE and lower extremity DVT, and no patient died of the thrombosis during the study period.

Establishment of the RVTA Based on the D-Dimer Levels

After analysis of the modeling cohort, we observed that the D-dimer levels were significantly higher in the VTE group compared to the non-VTE group (Figure 1), confirming that D-dimer is a reliable marker for VTE. The ROC curve for predicting VTE was drawn according to the D-dimer levels of patients with colorectal cancer. The AUC was 0.855 (95% CI was 0.807 to 0.904), and the optimal threshold was 1.7 μg/mL with the maximum YOUDEN index. The result suggested that D-dimer could be considered an essential variable in the RVTA when 1.7 μg/mL was defined as the cut-off level. In addition, more risk factors for thrombosis were investigated to establish the RVTA and enhance prediction efficiency.

The clinical data from the 245 patients with colorectal cancer included in the modeling cohort were analyzed statistically. Thrombosis-related risk factors included: basic information, tumor stages, treatment measures, and experimental data of the patients. A total of 18 variables were analyzed by univariate

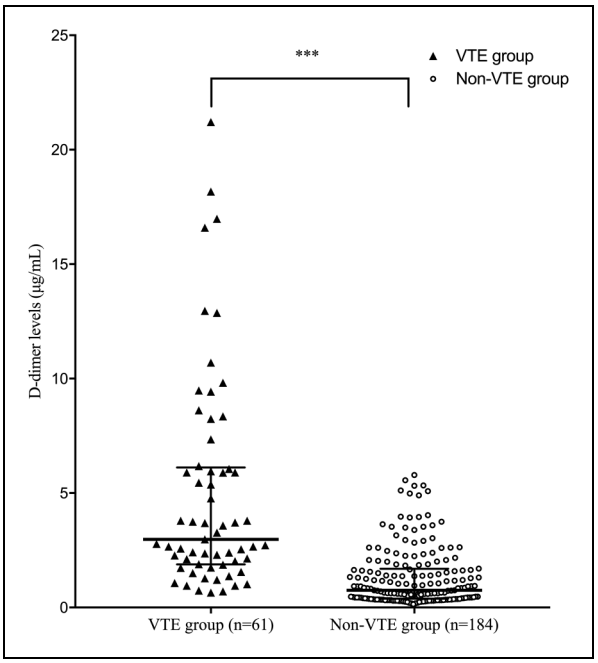

Figure 1. Comparison of D-dimer levels between VTE group and non-VTE group for patients with colorectal cancer. ***, $P < .001$.

analysis using the chi-square test. Nine risk factors with statistical significance were identified: stage of cancer, D-dimer ≥1.7 μg/mL, hemoglobin <100 g/L, platelet count ≥350*10^9/L, surgery history (within three months prior to inclusion), blood transfusion history (within three months prior to inclusion), metastasis, pelvic or peritoneal effusion and multiple chemotherapy regimens (Table 1). Common chemotherapy drug combinations for intestinal cancer included: XELOX (Capecitabine; Oxaliplatin), XELIRI (Capecitabine; Irinotecan), FOLFOX (Oxaliplatin; Calcium folinate; Fluorouracil), and FOLFIRI (Irinotecan; Calcium folinate; Fluorouracil). Multiple chemotherapy regimens included combinations of two or more of the chemotherapies mentioned above. The multicollinearity of laboratory parameters was accessed prior to the logistic regression. The VIF value ranged from 1.022 to 1.135, which we considered acceptable to include these variables in the model. The result showed that no severe multicollinearity was observed among the laboratory parameters.

The selected variables were entered into the logistic regression test, and the risk model was established using the Back-LR method. Finally, five independent risk factors were incorporated into the model, including platelet count ≥ 350*10^9/L, blood transfusion history (within three months prior to inclusion), metastasis, multiple chemotherapy regimens, and D-dimer ≥1.7 μg/mL (Table 2). Variables were assigned as 0 or 1 (0 for No and 1 for Yes). The VTE risk prediction model for patients with colorectal cancer was as follows: risk = −4.047 + (2.421* [D-dimer ≥ 1.7 μg/mL]) + (0.938* [multiple chemotherapy regimens]) + (1.298* [platelet count ≥ 350*10^9/L]) + (1.835* [metastasis]) + (1.197* [blood transfusion history]). A Hosmer-Lemeshow test was applied to verify the goodness of fit for the parameters. The result, $P = .9 > .05$, was considered as passing, which confirmed

Table 1. Univariate analysis of VTE related risk factors for patients with colorectal cancer.

Variables	Modelin cohortg (n = 245), n (%)		Non-VTE (n = 184), n	VTE (n = 61), n	χ^2	*P*
Gender					1.95	.163
Female	94	(38.4)	66	28		
Male	151	(61.6)	118	33		
Age (years)					2.54	.111
Age < 60	114	(46.5)	91	23		
Age ≥ 60	131	(53.5)	93	38		
BMI					2.56	.110
BMI < 30	231	(94.3)	176	55		
BMI ≥ 30	14	(5.7)	8	6		
Basis diseases					0.40	.939
Hypertension	47	(19.2)	34	13		
Diabetes	17	(6.9)	13	4		
Hypertension with Diabetes	19	(7.8)	14	5		
Others	15	(6.1)	10	5		
N/A	147	(60.0)	113	34		
Stage of cancer					12.78	<.001*
I or II	82	(33.5)	73	9		
III or IV	163	(66.5)	111	52		
Distant metastasis					34.54	<.001*
No	128	(52.2)	116	12		
Yes	117	(47.8)	68	49		
Pelvic/peritoneal effusion					5.02	.025*
No	176	(71.8)	139	37		
Yes	69	(28.2)	45	24		
CEA (ng/mL)					0.26	.612
CEA < 5.2	91	(37.1)	70	21		
CEA ≥ 5.2	154	(62.9)	114	40		
Hemoglobin (g/L)					6.39	.011*
Hemoglobin ≥ 100	172	(70.2)	137	35		
Hemoglobin < 100	73	(29.8)	47	26		
Platelet count (10^9/L)					8.77	.003*
Platelet count < 350	218	(89.0)	170	48		
Platelet count ≥ 350	27	(11.0)	14	13		
White-cell count (10^9/L)					1.47	.226
White-cell count < 11	219	(89.4)	167	52		
White-cell count ≥ 11	26	(10.6)	17	9		
D-dimer (μg/mL)					60.48	<.001*
D-dimer < 1.7	151	(61.6)	139	12		
D-dimer ≥ 1.7	94	(38.4)	45	49		
Surgery history[a]					8.97	.003*
No	221	(90.2)	172	49		
Yes	24	(9.8)	12	12		
Radiotherapy					0.32	.570
No	195	(79.6)	148	47		
Yes	50	(20.4)	36	14		
Blood transfusion history[a]					14.40	< .001*
No	220	(89.8)	173	47		
Yes	25	(10.2)	11	14		
Interventional therapy					0.39	.531
No	211	(86.1)	157	54		
Yes	34	(13.9)	27	7		
Multiple chemotherapy regimens					20.26	<.001*
No	200	(81.6)	162	38		
Yes	45	(18.4)	22	23		
Targeted therapy					0.13	.721

(continued)

Table 1. (continued)

Variables	Modelin cohortg (n = 245), n (%)		Non-VTE (n = 184), n	VTE (n = 61), n	χ^2	*P*
No	216	(88.2)	163	53		
Yes	29	(11.8)	21	8		

Abbreviations: VTE, venous thromboembolism; BMI, body mass index; CEA, carcinoembryonic antigen.
[a], Data collected within three months prior to inclusion; *, $P < 0.05$.

that the equation was sufficient to evaluate the risk of VTE, with an overall accuracy of 85.3%. To simplify the model, the index of each variable in the RVTA was set based on the regression coefficient in the model (Table 3). The D-dimer level was included in the RVTA when 1.7 μg/mL was defined as the cut-off level, using the STA® - Liatest® D-Di kit (STAGO, Asnières, France).

Stratification for the RVTA in Patients with Colorectal Cancer

We established the RVTA as a risk assessment tool for VTE in patients with colorectal cancer by analyzing data from the 245 patients in the modeling cohort. Notably, an RVTA score threshold of 0 to 8 was calculated by adding the individual component indexes. The optimal cut-off score for the stratification was defined as 4 using the maximum YOUDEN index. The sensitivity was 78.7%, specificity was 87.5%, positive predictive value was 67.6%, and negative predictive value was 92.5%. The AUC of the ROC curve was 0.883 (95% CI was 0.833 to 0.934), and the overall accuracy was 85.3%. Patients with an RVTA score ≥ 4 were defined as the high-risk group, while those with an RVTA score < 4 were classified as the low-risk group. The NRI of 0.602 (95%CI: 0.469-0.734; $P < .001$) indicated that the RVTA score had an improved prediction performance compared to the Khorana score in the modeling cohort. Forty-eight patients were reclassified correctly and 13 patients were reclassified incorrectly for the VTE group. One hundred and sixty-one patients were reclassified correctly and 23 patients were reclassified incorrectly for the non-VTE group using the RVTA. Also, we observed that the number of patients with VTE (67.6%) in the high-risk group was significantly greater than the number (7.5%) in the low-risk group. However, we needed to analyze data from the validation cohort to verify the reliability and effectiveness of the established prediction tool.

Table 2. Regression coefficients and odds ratios for variables that were significantly associated with the risk of VTE using logistic regression

Variables	B	*P*	OR	95% CI for OR Lower limit	95% CI for OR Upper limit
D-dimer ≥ 1.7 μg/mL	2.421	<.001	11.252	5.019	25.224
Multiple chemotherapy regimens	0.938	.045	2.556	1.023	6.387
Platelet count ≥ $350*10^9$/L	1.298	.017	3.663	1.266	10.599
Metastasis	1.835	<.001	6.268	2.645	14.858
Blood transfusion history[a]	1.197	.035	3.311	1.088	10.072
Constant	−4.047	<.001	0.017		

Abbreviations: CI, confidence interval; B, regression coefficient; OR, odds ratio.
a, Data collected within three months prior to inclusion.

Validation of the Predictive Efficiency of the RVTA

We verified the predictive performance of the RVTA based on data from the 100 patients included in the validation cohort. The ROC curve reflected the specificity and sensitivity relative to a certain threshold. The prediction accuracy was positively correlated with the size of the area under the curve (AUC). The AUC was 0.825 (95% CI was 0.721 to 0.930) based on the RVTA scores. In contrast, the AUC was 0.709 (95% CI was 0.580 to 0.838) based on the Khorana scores (Figure 2). When patients with RVTA scores above 4 were considered as the high-risk group, the calculated indexes were as follows: 80% sensitivity, 80% specificity, a positive predictive value of 57.1%, a negative predictive value of 92.3%, and an overall accuracy of 80%. We computed the NRI for the RVTA score versus the Khorana score, which showed an improved prediction performance for the RVTA score, with the NRI of 0.573 (95%CI: 0.384-0.763; $P < .001$) in the validation cohort. Twenty patients were reclassified correctly and 5 patients were reclassified incorrectly for the VTE group. Sixty patients were reclassified correctly and 15 patients were reclassified incorrectly for the non-VTE group using the algorithm. The layering results of the validation cohort indicated that the proportion of VTE patients in the high-risk group was 57.1%, and the proportion was 7.7% in the low-risk group (Figure 3A). The RVTA prediction results agreed with the diagnostic results from the CUS and CTA examination. To evaluate the calibration capacity of the RVTA further, the validation cohort was grouped based on the RVTA scores. We plotted the expected VTE events against the observed VTE events in each score group and observed a good correlation ($r^2 = 0.9$, Figure 3B). Based on the comparative analysis, data from the validation cohort indicated that the RVTA scores exhibited a robust predictive result.

Table 3. Simplified RVTA score for VTE prediction in patients with colorectal cancer

Variables	Index[a]
D-dimer ≥1.7 μg/mL	3
Multiple chemotherapy regimens	1
Platelet count ≥ $350*10^9$/L	1
Metastasis	2
Blood transfusion history[b]	1

The RVTA score was calculated by adding the individual component index. Low risk: the RVTA score was 0 to 3; high risk: the RVTA score was 4 to 8.
b, Data collected within three months prior to assessment.
a, According to the regression coefficient (B value) in the equation, the weights of variables were obtained as integer indexes based on the minimum value.

Evaluation of the RVTA as a Predictor in Tumor Prognosis

To evaluate the role of the RVTA in tumor prognosis, the 345 patients with colorectal cancer were evaluated using progression-free survival analysis. Kaplan-Meier curves were analyzed according to the RVTA risk stratification based on the RVTA. A log-rank test was performed to verify the difference between high-risk and low-risk groups as defined by the RVTA scores. For patients with an RVTA score greater than 4, the median PFS (10 months, 95% CI was 8.2 to 11.8) was shorter compared to patients who scored less than 4 (26 months, 95% CI was 19.0 to 33.0). Kaplan-Meier curves indicated that a higher RVTA score was associated with a worse patient prognosis ($P < .001$, Figure 4). Thus, the RVTA could be used to assess the prognosis for patients with colorectal cancer.

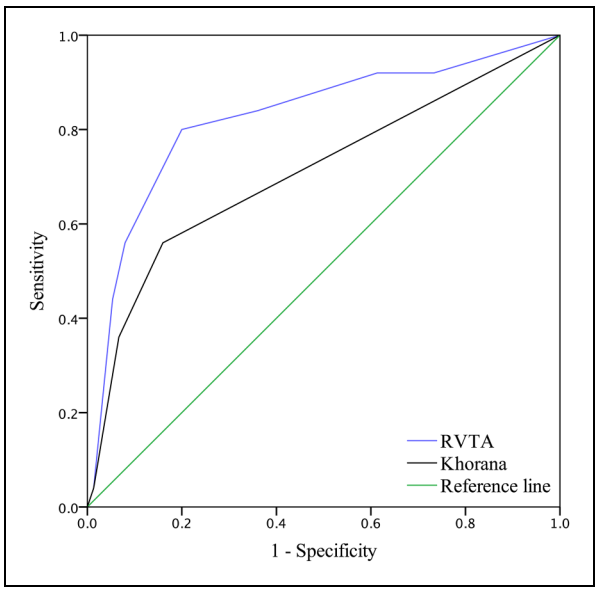

Figure 2. ROC analysis of risk scores to verify the prediction efficiency in the validation cohort. The AUC was 0.825 (95% CI was 0.721 to 0.930) based on the RVTA scores. The AUC was 0.709 (95% CI was 0.580 to 0.838) based on the Khorana scores.

Discussion

VTE is a serious thrombotic complication in patients with colorectal cancer, with a higher incidence correlated with tumor progression.[11,15] The specific internal pathological mechanisms of tumor-related VTE are not well understood. Previous studies have shown that thrombogenesis may be associated with tumor cells overexpressing cytokines such as tissue factor and malignant tumor mucin, leading to disorder of blood coagulation.[16] Conversely, the tumor cell behavior is affected by hypercoagulability, resulting in a poor prognosis in patients with VTE.[17] Thus, to improve tumor prognosis, early screening of VTE in patients with colorectal cancer has important clinical value.

Recently, an increasing number of studies have focused on the relationship between D-dimer levels and tumors.[18–22] D-dimer is a specific degradation product of cross-linked fibrin clots dissolved by fibrinolytic enzymes. D-dimer is at extremely low levels in plasma, and high levels of D-dimer often represent systemic hypercoagulability and fibrinolysis. Based on this biological characteristic, D-dimer has been widely regarded as a sensitive predictor for VTE.[6,22] Data in this study also showed a significant increase in plasma D-dimer levels in patients with VTE, which was consistent with previous studies. Based on ROC analysis, we determined the D-dimer cut-off level for patients with colorectal cancer. Using 1.7 μg/mL as the threshold level, the D-dimer level can be a key variable in the risk model for VTE in patients with colorectal cancer.

In this study, instead of relying solely on the D-dimer level for prediction, additional risk factors leading to thrombosis were included. Treatment-related factors were evaluated to identify patients at high risk for VTE. We found that metastasis, blood transfusion history, multiple chemotherapy regimens, platelet count, and D-dimer levels were independent VTE risk factors in patients with colorectal cancer when applied to the RVTA, which was consistent with previous reports.[8–10,23] The possible mechanism of chemotherapy-related thrombosis is that vascular endothelial injury initiates endothelial coagulation. In addition, 61 VTE patients responded to the above five variables in the modeling cohort, complying with the EPV 1 to 10 rule.[14] By analyzing the validation cohort, the RVTA was confirmed as a useful risk assessment tool for patients with colorectal cancer.

Compared to the Khorana score, which is the existing tumor-related VTE risk assessment tool, the RVTA was better suited for patients with colorectal cancer due to its applicability. According to the Khorana score, a score of 2 was assigned to very high- risk cancer sites (pancreatic or gastric), and a score of 1 was assigned to high-risk cancer sites (lung, lymphoma, gynecologic, bladder, or testicular cancer). However, the score for colon cancer was not evaluated, suggesting the Khorana score was not appropriate to predict VTE in this population. Also, D-dimer, a VTE-sensitive indicator, is not included in the Khorana score, and therapy history is not taken into account, suggesting the need for an improved

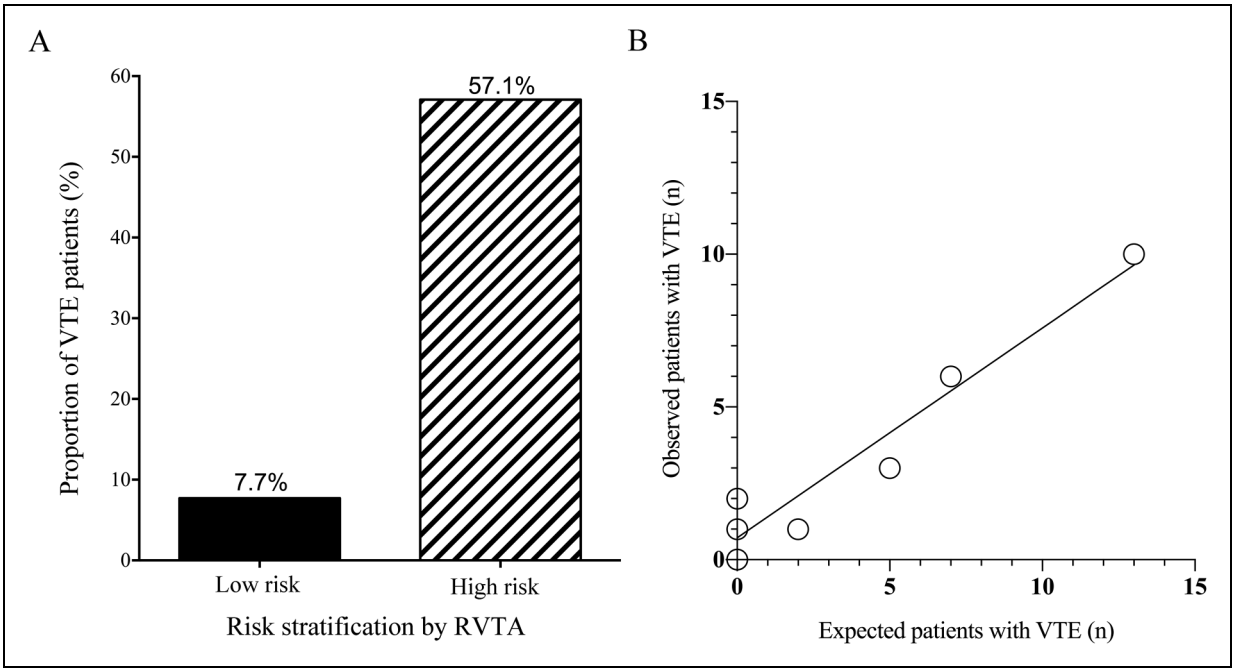

Figure 3. Discrimination performance of the RVTA in the validation cohort: (A) The proportion of VTE patients with different risk stratifications using the RVTA. (B) Correlation between the expected and the observed number of patients with VTE based on the RVTA score groups ($r^2 = 0.9$).

assessment tool. The algorithm for VTE risk in this study utilized basic information, tumor progression, treatment measures, and laboratory data in the retrospective analysis. Consequently, the RVTA was determined to have reliable discrimination capability (the AUC was 0.825; 95% CI was 0.721 to 0.930), while the AUC for Khorana score was 0.709 (95% CI was 0.580 to 0.838). The Khorana score is often used with cancer patients at the initiation of chemotherapy.[24] On the other hand, the RVTA was more reliable to evaluate patients while undergoing the recommended anti-cancer treatment.

The prognostic value of the RVTA was evaluated using survival analysis. In this study, patients with higher RVTA scores were at a greater risk of VTE. VTE has been associated with poor prognosis in several cancer types, including lung cancer, breast cancer, ovarian cancer, and pancreatic cancer.[5,19,20,25] Recent reports suggest that VTE is associated with reduced overall survival (OS) in patients with colorectal cancer.[26] Based on survival analysis, the median PFS was longer in patients with an RVTA score below 4 compared to those with an RVTA score above 4, indicating the prognostic value of the RVTA in patients with colorectal cancer. The follow-up duration for the survival analysis was not long enough to evaluate OS. However, improved PFS is even more beneficial for patients with advanced colorectal cancer.

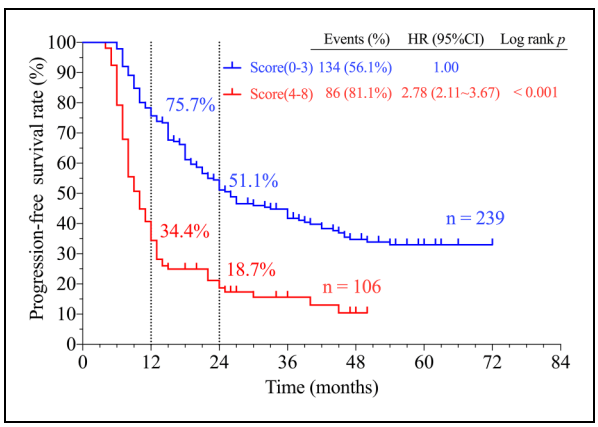

Figure 4. Kaplan-Meier survival curves for the prognostic impact of the RVTA on the progression-free survival were plotted. The risk score was calculated and stratified by RVTA.

Several limitations existed for the present study. The sample size used to develop and validate the model was limited. Of note, the rule of thumb, so-called events per variables (EPV) 1 to 10, was followed in the study. Each variable corresponding to 10 outcome events in the modeling cohort was put forward in the analysis. Although the internal validation was confirmed, it is necessary to enroll patients into the external validation cohort prospectively from an external geographic region before the routine use in clinical practice.

In summary, this study determined the level of 1.7 μg/mL as D-dimer cut-off for patients with colorectal cancer. An RVTA that included the D-dimer variable was established for patients with colorectal cancer and was suitable for screening patients with high-risk VTE as well as those with a poor prognosis.

Authors' Note

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Author Contributions

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