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Construction of Risk Assessment Model for Venous Thromboembolism After Colorectal Cancer Surgery: A Chinese Single-Center Study

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Abstract

Objective: A retrospective study was carried out to construct a postoperative venous thromboembolism (VTE) risk assessment model (RAM) applicable for Chinese colorectal cancer patients.

Methods: 541 Patients who underwent colorectal cancer surgery from June 2019 to May 2020 at Sir-Run-Run-Shaw Hospital affiliated to Zhejiang University School of Medicine were enrolled in this study. Multi-factor analysis was used to determine the independent risk factors of VTE. A novel RAM of VTE which we called Sir-Run-Run-Shaw VTE RAM were constructed basing on the independent risk factors. Another study cohort consisted of 287 colorectal cancer patients underwent surgery from January 2021 to June 2021was used for model evaluation.

Results: The incidence of VTE after colorectal cancer surgery was 12.0%(65/541). Among the 65 VTE Patients, DVT accounted for 92.3% (60/65) and DVT + PE accounted for 7.7% (5/65). Multi-factor analysis showed that age $\geq$ 69 years ($P < 0.01$), preoperative plasma D-dimer $\geq$ 0.49 mg/L ($P = .004$), stage IV of cancer ($P = .018$) and transfusion ($P = .004$) are independent risk factors of VTE after surgery. Sir-Run-Run-Shaw VTE RAM includes the above 4 factors, and the total score is 4 points. The score of the low, medium and high risk groups are 0, 1 and $\geq$2 points. The area under the ROC curve (AUC) of Sir-Run-Run-Shaw VTE RAM is 0.769, while Caprini RAM is 0.656. There is statistical difference between the two risk score tables ($Z = 2.337$, $P = .0195$).

Conclusion: A VTE RAM is constructed basing on a single center retrospective study. This score table may be applicable for Chinese patients with colorectal cancer surgery.

Keywords

colorectal cancer, surgery, venous thromboembolism, risk assessment model, retrospective study

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Introduction

Venous thromboembolism (VTE) is a series of diseases caused by abnormal coagulation and obstruction of blood vessels in the venous system,[1] clinically presenting as Pulmonary embolism (PE) or Deep vein thrombosis (DVT), is globally the third most frequent acute cardiovascular syndrome behind myocardial infarction and stroke.[2] Patients with cancer are at high risk of VTE. According to statistics,[3] the incidence of VTE in cancer patients is 4 to 7 times higher than that in non-cancer patients.[3,4] Cancer patients who underwent surgery are more

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than three times higher at risk of fatal PE than non-cancer patients who underwent similar surgery.[5] VTE is one of the most important causes of deathin cancer patients.[6] It is reported that VTE increases the risk of death in cancer patients by 2 to 6 times, which is the primary cause of death within 30 days after surgery.[7] Therefore, Thrombosis and Cancer (ITAC-CME), American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), International Society on Thrombosis and Haemostasis (ISTH), American Society of Hematology (ASH) all suggest that cancer patients should pay attention to VTE risk assessment and prevention.[4,6–9] Existing evidence prompts that effective risk assessment and prevention could reduce the absolute risk of VTE in cancer patients by 50%.[10]

The incidence of VTE is four times higher in patients with colorectal cancer surgery than that in patients with general abdominal surgery,[11] therefore, an effective VTE risk assessment for these patients is required. At present, there is no simple, fast and efficient postoperative VTE RAM suitable for Chinese colorectal cancer patients. We reviewed the case data of colorectal cancer patients who underwent colorectal cancer surgery at Sir-Run-Run-Shaw Hospital affiliated to Zhejiang University School of Medicine, searched the independent risk factors of VTE, and constructed a postoperative VTE assessment model and score table which we called Sir-Run-Run-Shaw VTE RAM.

Materials and Methods

Patients

From 1 June 2019 to 31 May 2020, 605 patients over 18 years underwent colorectal cancer surgery at Sir-Run-Run-Shaw Hospital affiliated to Zhejiang University School of Medicine. Patients who had preoperative VTE and those with preoperative preventive anticoagulation or without complete data were excluded from the study. Finally, 541 patients were enrolled and the clinical data of these patients were collected to construct the risk assessment model (RAM) and risk score table. Another study cohort consisted of 287 patients (includes 51 postoperative VTE patients) who underwent colorectal cancer surgery at Sir-Run-Run-Shaw Hospital affiliated to Zhejiang University School of Medicine from 1 January 2021 to 30 June 2021 was used for model evaluation. This retrospective study complies with the relevant provisions of the Declaration of Helsinki on protecting the rights of subjects and was approved by the Medical Ethics Committee of Sir-Run-Run-Shaw Hospital affiliated to Zhejiang University School of Medicine (ID:20211018-34).

Data Collection and Definition of Terms

The medical records of patients who underwent colorectal cancer surgery were reviewed. And the information of age, gender, BMI, preoperative Serum CEA, preoperative plasma D-dimer, tumor maximum diameter, postoperative Caprini score, transfusion, postoperative length of stay, stage of cancer, operative time, Operative procedures, Pathology, Intraoperative bleeding were collected. BMI equal to body weight (kg) divided by height^2 (m^2). The ELISA method was performed for measurement of D-dimer. The staging in tumor was based on the tumor node metastasis (TNM) clinical staging system. Patients with distant metastasis were identified as stage IV. The operative procedures are divided into open and laparoscopic operation. Highly differentiated, highly-moderately differentiated and moderately differentiated adenocarcinoma were regard as differentiated carcinoma, while signet ring cell carcinoma, moderately-poorly differentiated and poorly differentiated adenocarcinoma were undifferentiated carcinoma.

VTE Confirmation

Lower limbs Doppler ultrasonography was performed before surgery for all patients to exclude preoperative VTE. Patients with lower limb pained, swelled and skin color changed after surgery were immediately performed lower limbs Doppler ultrasonography. Patients with unexplained chest tightness, chest pain, blood hemoptysis, dyspnea or syncope after surgery were immediately performed computer tomography pulmonary angiography (CTPA). Patients without any VTE-related symptom also routinely performed lower limbs Doppler ultrasonography within 1 week after surgery. Lower limbs Doppler ultrasonography suggested that endovascular thrombosis is confirmed as DVT, and CTPA suggested that filling defect of pulmonary artery and its branches was confirmed as pulmonary thromboembolism (PTE).

Statistical Analysis

SPSS 19.0 software for Windows were used for statistical analysis. Categorical variables are expressed as frequency and percentage, and compared by χ^2 test or Fisher's exact test; Continuous variables are represented as mean $\pm$ standard deviation ($\bar{x} \pm s$) or median (interquartile spacing) M (P25,P75), and compared by student's t test or the Mann-Whitney U's test. In our model, the variables were selected based on the results of the univariate analysis, and in order to avoid risk factor omission, the variables for $P <$ .2 in the univariate analysis were included into the multivariate logistic regression analysis. The model variables were screened by a stepwise regression method to simplify the model. The regression method was set to "forward: LR", risk factors for $P \geq 0.05$ were deleted, and risk factors for $P < .05$ were retained in the model as independent risk factors of VTE. $P < .05$ was considered as being statistically different.

Model Construction and Evaluation

The VTE independent risk factors were used to construct the model risk assessment and risk score table, with regression

coefficients divided by the minimum one in them and rounded to integer values to determine the score for each item. The X-tile 3.6.1 software for Windows was used to identify the critical score value for risk stratification. The MedCalc19.6 software for Windows was used to draw receiver operating characteristic curve (ROC) of Sir-Run-Run-Shaw RAM and Caprini RAM. Larger area under curve (AUC) means higher accuracy of the RAM. In this study, AUC of 0.5 to 0.7, 0.7 to 0.9 and >0.9 were considered as low, moderate and high discrimination, respectively.

Result

Form the Department of Anorectal surgery, Sir-Run-Run-Shaw Hospital affiliated to Zhejiang University School of Medicine, 541 patients were enrolled in this study, including 336 male patients and 205 female patients. The mean age and BMI of the patients was 63.2 years and 23.2 kg/m^2. The incidence of VTE after colorectal cancer surgery was 12.0%(65/541). Among the 65 VTE patients, 92.3%(60/65) were DVT and 7.7%(5/65) were DVT + PE. The mean age and BMI of the VTE patients was 68.6 years and 22.7 kg/m^2.

The univariate analysis shows that, age ($P < .01$), gender ($P = .024$), preoperative Serum CEA ($P = .007$), preoperative plasma D-dimer ($P < .01$), tumor maximum diameter ($P = .006$), postoperative Caprini score ($P = .004$), transfusion ($P < .01$), Postoperative length of stay ($P = .044$), stage of cancer ($P = .004$) were associated with VTE, the difference were statistically significant. There was no difference in terms of BMI ($P = .259$), operative time ($P = .902$), Operative procedures ($P = .319$), degree of pathological differentiation ($P = .967$) and the amount of intraoperative bleeding ($P = .655$) between patients with and without VTE (Table 1).

Multivariate logistic regression analysis showed that age ≥ 69 years ($P < .001$), preoperative plasma D-dimer ≥0.49 mg/L ($P = .004$), stage IV of cancer ($P = .018$), transfusion ($P = .004$) were independent risk factors of postoperative VTE in colorectal cancer patients. The VTE risk scoring table for colorectal cancer (Sir-Run-Run-Shaw VTE RAM) is consisted of the above four scoring items, which is 1 point per item and the total score is 4 points (Table 2). The risk stratification of the Sir-Run-Run-Shaw VTE RAM was as follows: low risk group (0 score), medium risk group (1 score), high risk group (≥ 2 scores).

Table 1. Univariate analysis of postoperative VTE-related risk factors in 541 patients with colorectal cancer.

Variable	VTE (-) (n = 476)	VTE (+) (n = 65)	Z value/t value/χ^2 value	*P* value
Age (years)	62.48 ± 11.87	68.57 ± 11.20	17.064	<.001
Gender			5.100	.024
Male	304 (63.9%)	32 (49.2%)		
Female	172 (36.1%)	33 (50.8%)		
BMI (kg/m^2)	23.21 ± 3.15	22.74 ± 3.12	1.272	.259
preoperative Serum CEA (μg/L)			7.317	.007
≥5	159 (33.4%)	33 (50.8%)		
<5	317 (66.6%)	32 (49.2%)		
preoperative plasma D-dimer (mg/L)			16.853	<.001
Median	0.405	0.68		
Quartile range	0.22 to 0.68	0.42 to 1.21		
Tumor maximum diameter (cm)	3.90 ± 1.77	4.46 ± 2.12	7.507	.006
Postoperative Caprini score	6.50 ± 1.39	7.05 ± 1.56	8.120	.004
Operative time (min)	179 ± 49	180 ± 51	0.015	.902
Transfusion			15.083	<.001
Yes	48 (12.2%)	18 (27.7%)		
No	428 (87.8%)	47 (72.3%)		
Postoperative length of stay (day)	11.0 ± 5.6	12.6 ± 7.0	4.060	.044
Operative procedures			0.993	.319
Open operation	39 (7.8%)	3 (4.6%)		
laparoscopic operation	437 (92.2%)	62 (95.4%)		
Stage of cancer (TNM)			8.260	.004
Stage I-III	440 (90.9%)	52 (80.0%)		
Stage IV	36 (9.1%)	13 (20.0%)		
Pathology			0.002	.967
Undifferentiation carcinoma	65 (13.7%)	9 (13.8%)		
Differentiation carcinoma	411 (86.3%)	56 (86.2%)		
Intraoperative bleeding (ml)			0.200	.655
Median	50	50		
Quartile range	50 to 100	50 to 100		

VTE: venous thromboembolism.

Table 2. Multivariate analysis and risk assessment model of postoperative VTE-related risk factors in 541 patients with colorectal cancer.

Sir-Run-Run-Shaw VTE RAM risk fackors	score	B	S.E.	Wald	OR	95% CI for OR		*P* value
						Lower	Upper	
Age ≥ 69 years (YES = 1 or NO = 0)	1	0.978	0.281	12.144	2.660	1.534	4.612	0.000
Stage of cancer (stage I-III = 0 or stage IV = 1)	1	0.929	0.391	5.641	2.531	1.176	5.446	0.018
Preoperative plasma D-dimer ≥ 0.49mg/L (YES = 1 or NO = 0)	1	0.859	0.297	8.389	2.362	1.320	4.225	0.004
Transfusion (YES = 1 or NO = 0)	1	0.956	0.332	8.280	2.601	1.356	4.987	0.004

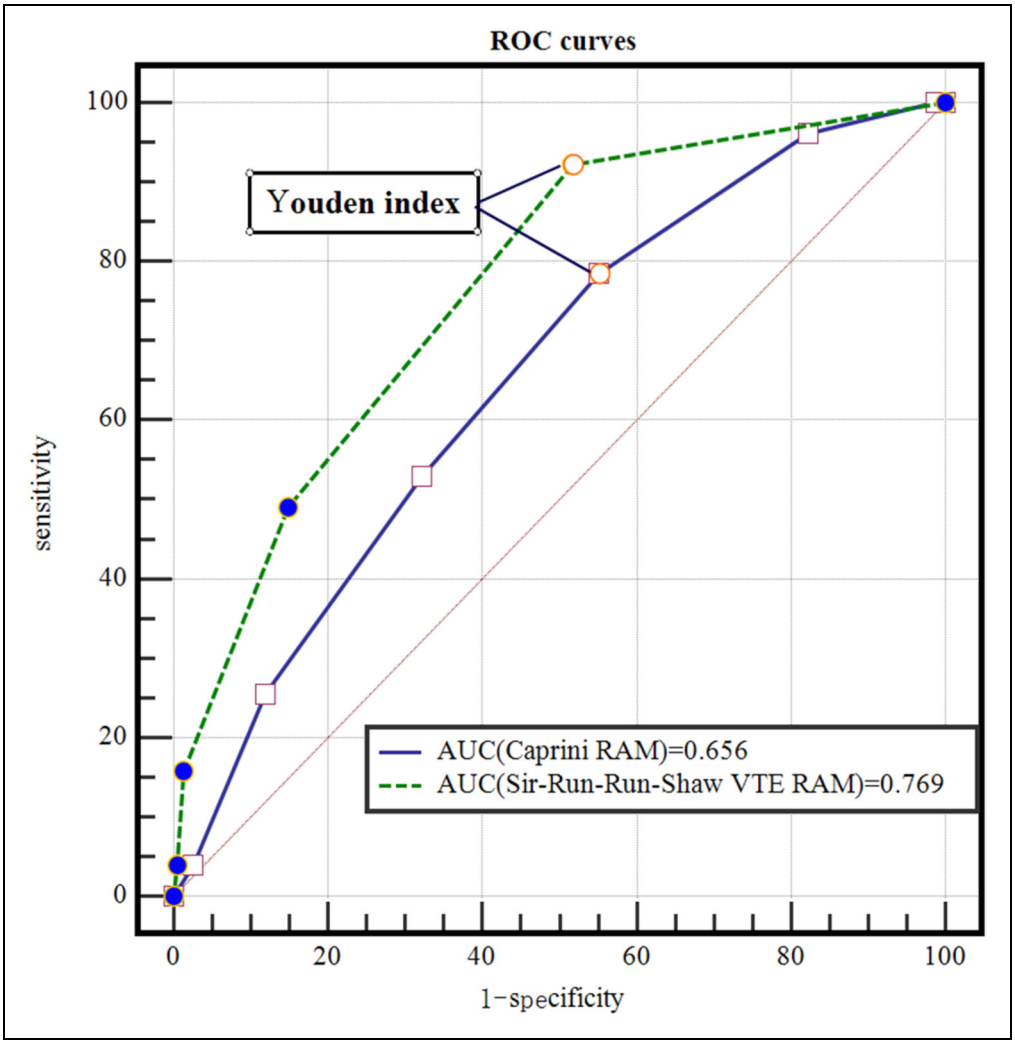

Figure 1. ROC curves of Sir-Run-Run-Shaw VTE RAM and Caprini RAM.

ROC curves of the Sir-Run-Run-Shaw VTE RAM and Caprini RAM were drew by MedCalc19.6 software for Windows (Figure 1). The cutoff values of Sir-Run-Run-Shaw VTE RAM and Caprini RAM was 0.50 and 6.50,Youden index was 0.4046 and 0.2335. When the Youden index were set to the cutoff, both sensitivity was 92.16% and 48.31%, specificity was 78.43% and 44.92% and AUC was 0.769 and 0.656, respectively. There is statistically different among the two ROC curves ($Z = 2.337$, $P = .0195$) (Table 3).

Discussion

VTE is one of the most important complications of cancer, which increases the risk of death in cancer patients.[7] Therefore, it is necessary to conduct effective VTE risk assessment and prevention for cancer patients. For the risk assessment of the VTE, several RAMs were widely used such as Caprini RAM[12] (applicable to surgical patients), Khorana RAM[13] (applicable to outpatient cancer patients), PROTECHT RAM[14] (two therapeutic measures of chemotherapy using

Table 3. ROC curve comparison of Sir-Run-Run-Shaw VTE RAM and Caprini RAM.

RAM	Youden index	cutoff	sensitivity	Specificity	AUC	S.E.	95% CI for OR		*Z* value	*P* value
							Lower	Upper		
									2.337	0.0195
Sir-Run-Run-Shaw VTE RAM	0.4046	0.50	0.9216	0.4831	0.769	0.0348	0.716	0.817		
Caprini RAM	0.2335	6.50	0.7843	0.4492	0.656	0.0400	0.598	0.710		

platinum and gemcitabine chemotherapy were added to the Khorana RAM), Vienna CATS RAM[15] (two biochemical metrics of the D-dimer and soluble P-selection protein were added to the Khorana RAM) and Padua RAM[16] (applicable to medical patients). But nothing is perfect, these RAMs are unable to cover all diseases. Therefore, many scholars focused on personalized assessment of VTE. Simple, quick, and effective are the characteristics of personalized assessment tools. For instance, Marliese Alexander et al.[17] constructed a VTE RAM based on a study cohort containing 129 non-small cell carcinoma (NSCLC) patients, which contains only three items: chemotherapy, D-dimer and fibrinogen. It was validated by a gastrointestinal cancer cohort and demonstrated its effectiveness and scalability. Castellón Rubio VE et al.[18] used soluble P-selectin and factor VIII to construct a Thrombo-NSCLC riskscore based on a prospective study, which is simple and effective for VTE risk assessment in NSCLC patients. Sultan AA et al.[19] constructed a postpartum VTE RAM for women based on the clinical information of nearly one million British and Swedish women, which quantified the absolute risk of postpartum VTE and passed external validation. In China, Bo Tian et al.[20] constructed a VTE RAM based on the clinical information of 533 thoracic surgery patients in Beijing Chao-yang Hospital. It contained 9 scoring items, and showed good VTE risk assessment effect, but the model have not underwent further external verification.

Colorectal cancer is one of the most common abdominal cancers. Altered in pelvic anatomy caused by surgery[21] and systemic hypercoagulation state caused by the disease[22] resulted that patients with colorectal cancer surgery have higher incidence of VTE than those with general abdominal surgery. At present, there is no simple, fast and efficient VTE risk assessment tool for Chinese patients with colorectal cancer surgery, so we conducted this study.

In this study, 12.0% of patients developed VTE after surgery, while retrospective studies in Korea and Hong Kong, China found that the incidence of VTE after colorectal cancer surgery was between 0.18% and 0.85%.[5,23,24] This discrepancy maybe due to the inclusion of asymptomatic DVT in our study while they did not. In our study, 92.3% of VTE patients were DVT alone and 7.7% of VTE patients were DVT + PE, there is no one with PE but without DVT. It indicates that all PE patients were developed from DVT. Therefore, routine limb pressurized ultrasound examination after colorectal cancer surgery is necessary.

In this study, 14 potential risk factors of VTE were selected basing on previous literature reports[11,21,25–28] and our clinical observations. It showed that age ≥69 years, preoperative plasma D-dimer ≥0.49 mg/L, stage IV of cancer and transfusion are independent risk factors of VTE after colorectal cancer surgery. Then we constructed Sir-Run-Run-Shaw VTE RAM based on the above 4 independent risk factors. In this score, the stratification of age is similar to Padua score. The two-stage age grouping method make the evaluation faster. Preoperative plasma D-dimer is an independent risk factor for postoperative VTE of colorectal cancer, which is also consistent with mainstream studies.[29–31] Stage IV of cancer is also an independent risk factor for postoperative VTE of colorectal cancer may be due to Tissue Factor. In the study of VTE mechanism, it is found that Tissue Factor starts the exogenous coagulation pathway and participates in thrombosis.[32] The high expression of Tissue Factor in patients with stage IV of cancer may be related to the high incidence of VTE.[33] In addition, this study found that transfusion is also related to postoperative VTE, which is the same as that reported by Xenos ES[25] and Sweeney J.[34] The pro-inflammatory and immunomodulatory effects of stored blood may enhance the inflammatory and hypercoagulable state related to tumor formation and surgery, thereby increasing VTE.[35]

Many Studies showed that risk stratification for patients helps to the implementation of prevention strategies avoiding excessive prevention and insufficient prevention.[36] In our study, 0 point, 1 point and ≥ 2 points were considered as low risk, medium risk and high risk of postoperative VTE, respectively. We recommend mechanical prophylaxis (early activity or lower limb air pressure pumpmechanical prevention) for low risk patients, drug prophylaxis (low molecular heparin or oral anticoagulant) for medium risk patients and mechanical prophylaxis combined with drug prophylaxis for high risk patients.

Finally, we validated the model with another study cohort consisted of 287 colorectal cancer surgery patients which includes 51 postoperative VTE patients. We compared Sir-Run-Run-Shaw VTE RAM and Caprini RAM, with AUC of 0.769 and 0.656, the two are statistically different ($P < .05$). It indicates that Sir-Run-Run-Shaw VTE RAM was better than Caprini RAM for postoperative VTE evaluation in our study cohort. Caprini RAM listed all cancer patients into high risk of VTE, which may lead to excessive prophylaxis. In addition, Sir-Run-Run-Shaw VTE RAM is based on surgical clinical practice, consist of only four scoring items, is easier, faster in use than Caprini RAM.

However, there are some shortcomings in this study. First, a limited sample size may affect the predictive power of the

RAM. Second, the study was conducted at only one center, which may limit its generalization.

Conclusion

In this study, we found that age ≥69 years, preoperative plasma D-dimer ≥0.49 mg/L, stage IV of cancer and transfusion were independent risk factors for postoperative VTE of colorectal cancer. Based on this, we constructed a novel RAM which we called Sir-Run-Run-Shaw VTE RAM which includes only four scoring items, and carried out risk stratification. This RAM performed better in comparison with Caprini RAM for patients with colorectal cancer surgery, and is simple and fast in use. In addition, it has good validity, and the risk stratification is reasonable, which avoids insufficient or excessive prevention of VTE. The scale may have certain clinical value in the evaluation of postoperative VTE of Chinese colorectal cancer patients, but it needs further external verification in multiple centers before it is applied in clinic.

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Author contribution

Jianchang Yao: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Writingoriginal draft (lead). **Yina Lang:** Data curation (equal); Formal analysis (equal); Methodology (equal); Software (equal); **Hua Su:**Data curation (supporting); Investigation (equal); Validation (equal).**Sheng Dai:** Supervision(equal); Writing-review & editing (equal).**Kejing Ying:** Conceptualization (equal); Funding acquisition (lead); Project administration (lead); Supervision (lead); Writing-review & editing (equal).

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

This study was approved by the Medical Ethics Committee of Sir-Run-Run-Shaw Hospital affiliated to Zhejiang University School of Medicine (ID:20211018-34).

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