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Comparison of Performances among Four Bleeding-Prediction Scores in Elderly Cancer Patients with Venous Thromboembolism

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Abstract

The performances of RIETE, VTE-BLEED, SWITCO65+, and Hokusai-VTE scores for predicting major bleeding events in hospitalized elderly cancer patients with venous thromboembolism (VTE) have not been evaluated. This study validated the performances of these scoring systems in a cohort of elderly cancer patients with VTE. Between June 2015 and March 2021, a total of 408 cancer patients (aged ≥ 65 years) with acute VTE were consecutively enrolled. The overall rates of in-hospital major bleeding and clinically relevant bleeding (CRB) were 8.3% (34/408) and 11.8% (48/408), respectively. RIETE score could categorize patients with increasing rate of major bleeding and CRB into low-/intermediate- and high-risk categories (7.1 vs. 14.1%, $p = 0.05$ and 10.1 vs. 19.7%, $p = 0.02$, respectively). The discriminative power of the four scores for predicting major bleeding was poor to moderate, indicated by areas under the receiver operating characteristic curves (0.45 [95% confidence interval, CI: 0.35–0.55] for Hokusai-VTE, 0.54 [95% CI: 0.43–0.64] for SWITCO65+, 0.58 [95% CI: 0.49–0.68] for VTE-BLEED, and 0.61 [95% CI: 0.51–0.71] for RIETE). RIETE score might be used to predict major bleeding in hospitalized elderly cancer patients with acute VTE.

Keywords
- cancer
- venous thromboembolism
- elderly patients
- bleeding-prediction score

Introduction

The risk of venous thromboembolism (VTE) is four- to sevenfold higher in cancer patients than in other patients.[1] Approximately 15 to 20% of cancer patients are expected to experience VTE at some point during the course of their illness,[2] and VTE is the leading cause of death among these patients after the cancer itself.[3] The annual incidence of VTE sharply increases with age, with 4.5 to 6 cases per 1,000 person-years in individuals aged ≥65 years, and 10 cases per 1,000 person-years in individuals aged ≥75 years.[4,5]

Notably, when receiving anticoagulant treatment, elderly patients with cancer-associated VTE have higher risks of recurrent VTE and bleeding.[6,7] Several studies have reported that the rate of major bleeding in cancer-associated VTE patients is 3 to 9% during the first 6 months of treatment,[8–10] and the highest risk of bleeding is within the first

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7 days.[7,11–13] Moreover, there is fourfold greater risk of life-threatening and fatal bleeds in patients aged ≥80 years.[7,14,15] Not only the treatment of cancer-associated VTE is more complicated but also recurrent VTE and bleeding are potentially fatal. The case fatality rate of recurrent VTE is higher than the case fatality rate of major bleeding in cancer patients receiving anticoagulation (14.8%; 95% confidence interval [CI]: 6.6–30.1% vs. 8.9%; 95% CI: 3.5–21.1%).[16] Therefore, it is important to achieve a balance between the risks of recurrent VTE and bleeding in these patients, which remains challenging for physicians.

Current treatment guidelines recommend low-molecular-weight heparins (LMWH) for the treatment of cancer-associated VTE.[17,18] However, vitamin K antagonists (VKAs) and rivaroxaban are at least equally utilized in clinical practice.[19] There is evidence that bleeding risk in hospitalized patients varies according to cancer type and anticoagulant strategy (e.g., type, dose, and duration).[10,20–23] Therefore, personalized anticoagulant therapy has been proposed.

As a new prediction model, CT-BLEED score was developed for estimating bleeding risk especially in cancer-associated thrombosis patients.[24] It was developed for cancer-associated thrombosis patients randomly treated by edoxaban or dalteparin. The calculation of "CAT-BLEED" score includes the prediction of "if the patient has gastrointestinal cancer and is prescribed edoxaban treatment." Because edoxaban is not available in China, it is difficult to validate the score in a contemporary Chinese cohort of elderly hospitalized cancer patients with acute VTE. Meanwhile, four existing bleeding-prediction scores have been developed to estimate the risk of major bleeding in the general population of VTE patients during short- (first 3 months) or long-term (extended treatment) anticoagulant therapy. These are the RIETE, VTE-BLEED, SWITCO65+ (the Swiss VTE cohort), and Hokusai-VTE scores.[25–28] All of these scores were derived mainly from patients treated with LMWH/VKAs/dabigatran. These scores were developed without any consideration of advanced age; it remains unknown whether these scores could predict major bleeding in elderly cancer patients with acute VTE during the most vulnerable period of hospitalization. This article aimed to evaluate whether these four scores could predict in-hospital major bleeding in a real-world cohort of elderly cancer patients with acute VTE.

Materials and Methods

Study Population and Selection Criteria

This retrospective cohort study included cancer patients aged ≥65 years who were consecutively admitted to the Aerospace Center Hospital, Beijing, China, between June 2015 and March 2021, with a definitive diagnosis of acute VTE (pulmonary embolism [PE], lower extremities proximal or distal deep vein thrombosis [DVT], or upper extremities DVT).[17,18] Cancer patients aged 65 years or older were eligible for inclusion if they met one of the following criteria: they were admitted due to acute VTE or they were admitted due to other reasons and acute VTE occurred during hospitalization. Meanwhile, cancer patients comprised patients with active cancer or cancer diagnosed within 2 years before enrollment. Active cancer was defined as solid or hematologic cancer treated with chemotherapy, radiotherapy, or surgery; or recurrent or metastatic disease; or palliative care during the preceding 3 months.[27] All patients were identified based on the diagnostic codes (ICD-10) and medical records through electronic patient records. Patients were excluded if they met one of the following criteria: bleeding on admission, missing risk score variables, thrombolytic treatment, and death within 48 hours of hospital arrival (unrelated to bleeding). All patients were treated at the discretion of their attending physicians during hospitalization, in accordance with the most recent clinical guidelines.[17,18]

Complete data were collected regarding the enrolled patients, including baseline demographics; clinical, hemodynamic, and laboratory parameters; diagnostic procedures; VTE-related treatment; concomitant antiplatelet therapy; bleeding events; and all-cause mortality during hospitalization. The study protocol was approved by the Clinical Research Ethics Committee of the Aerospace Center Hospital (No. 20190528-JT-15).

Bleeding Events

Major bleeding was assessed using the International Society on Thrombosis and Hemostasis criteria.[29] Major bleeding included fatal bleeding; symptomatic bleeding in a critical area or organ, including intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, and intramuscular bleeds with compartment syndrome; and bleeding causing a ≥20 g/L (1.24 mmol/L) decrease in the hemoglobin level, or requiring the transfusion of ≥2 units of whole blood or red cells. According to the International Society on Thrombosis and Hemostasis criteria,[30] clinically relevant non-major bleeding requires intervention by a healthcare professional, leads to hospitalization or increased level of care, or prompts a face-to-face evaluation. Clinically relevant bleeding (CRB) was defined as major bleeding or clinically relevant non-major bleeding.[31] All bleeding events were assessed by a blinded, independent central committee of three to five experts. For patients who experienced multiple bleeding events, only the most severe event was included in the final analysis.

Bleeding Score Calculation

Based on the critical review of the literature, the RIETE, VTE-BLEED, SWITCO65+, and Hokusai-VTE scores, developed specifically for the prediction of bleeding risk among VTE patients, were calculated for all patients. To calculate the RIETE or SWITCO65+ scores, recent or previous major bleeding was defined as a major bleeding event that occurred fewer than 15 days prior to VTE.[25] The definition of anemia was consistent with the RIETE, VTE-BLEED, and SWITCO65+ scores.[25–27] Creatinine clearance (Ccr) was calculated using the Cockcroft–Gault formula.[26] Patients with Ccr less than 30 mL/minutes were also included; for this parameter, they were given 1.5 points in the VTE-BLEED score.

Statistical Analysis

Continuous variables are described as means ± standard deviations (SDs); they were compared using Student's *t*-test. Categorical variables are reported as numbers and percentages (*n*, %); they were compared using the chi-squared test or Fisher's exact test, as appropriate. The RIETE, VTE-BLEED, SWITCO65, and Hokusai-VTE scores were converted into corresponding points; the patient scores were calculated by summing all of the points of their variables. Within each category, the proportions of low-, intermediate-, and high-risk patients, as well as the major bleeding and CRB rates during hospitalization, were described along with 95% CIs; they were compared using the chi-squared test or Fisher's exact test.

The calibration of each score was assessed using the Hosmer–Lemeshow (HL) goodness-of-fit test; a *p*-value < 0.05 was indicative of a poor fit.[32] The discriminative power of each score to predict major bleeding and CRB during hospitalization was determined using the receiver operating characteristic (ROC) curve.[33] Furthermore, the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) with PredictABEL were also used to quantify the discriminative increment of the risk scores.[34,35] All analyses were performed using SPSS Statistics software, version 22.0 (IBM Corp., Armonk, New York, United States).

Results

Study Sample and Baseline Characteristics

A total of 433 consecutive elderly cancer patients with acute VTE were enrolled, of whom 408 (94.2%) were included in the final analysis (►Fig. 1). In-hospital major bleeding was significantly more common in patients with lower hemoglobin levels and patients with digestive system cancers (►Table 1).

Major Bleeding and CRB

During hospitalization (median: 13 days; interquartile range: 9–18 days), 34 patients (8.3%) experienced major bleeding. According to the International Society on Thrombosis and Hemostasis criteria for major bleeding, 8.8% of the patients had fatal bleeding, while 91.2% patients had a ≥20 g/L decrease in hemoglobin levels or required ≥2 units of red blood cell transfusion. Furthermore, 48 patients (11.8%) experienced CRB, including 14 cases of clinically relevant non-major bleeding. In addition, the overall rate of in-hospital mortality was 17.2% (70/408). Among them, death from fatal bleedings occurred in three (0.7%) patients, and PE occurred in three (0.7%) patients.

Because cancer and low physical activity were included as variables in the RIETE and SWITCO65+ scores, respectively, there were no patients classified as low risk using these scores (►Table 2). Using the original risk categories, RIETE and Hokusai-VTE scores classified most patients as low or intermediate risk (82.6 and 75.7%, respectively), whereas VTE-BLEED and SWITCO65+ scores classified most patients as high risk (93.9 and 95.1%, respectively; ►Table 2). Moreover, there was no statistical difference in the rate of major bleeding and CRB in the low- or intermediate-risk and high-risk categories of the VTE-BLEED (0.0 vs. 8.9% [$p = 0.24$] and 4.0 vs. 12.3% [$p = 0.36$], respectively), SWITCO65+ (0.0 vs. 8.8% [$p = 0.33$] and 0.0 vs. 12.4% [$p = 0.19$], respectively), and Hokusai-VTE scores (8.7 vs. 7.1% [$p = 0.60$] and 11.7 vs. 12.1% [$p = 0.90$], respectively). Only the RIETE score was able to categorize patients with increasing rate of major bleeding and CRB as low or intermediate risk and high risk (7.1 vs. 14.1% [$p = 0.05$] and 10.1 vs. 19.7 [$p = 0.02$], respectively; ►Table 2).

Bleeding Prediction Performance

The calibration of each score was adequate to predict in-hospital major bleeding (HL $p > 0.05$) for all patients. The

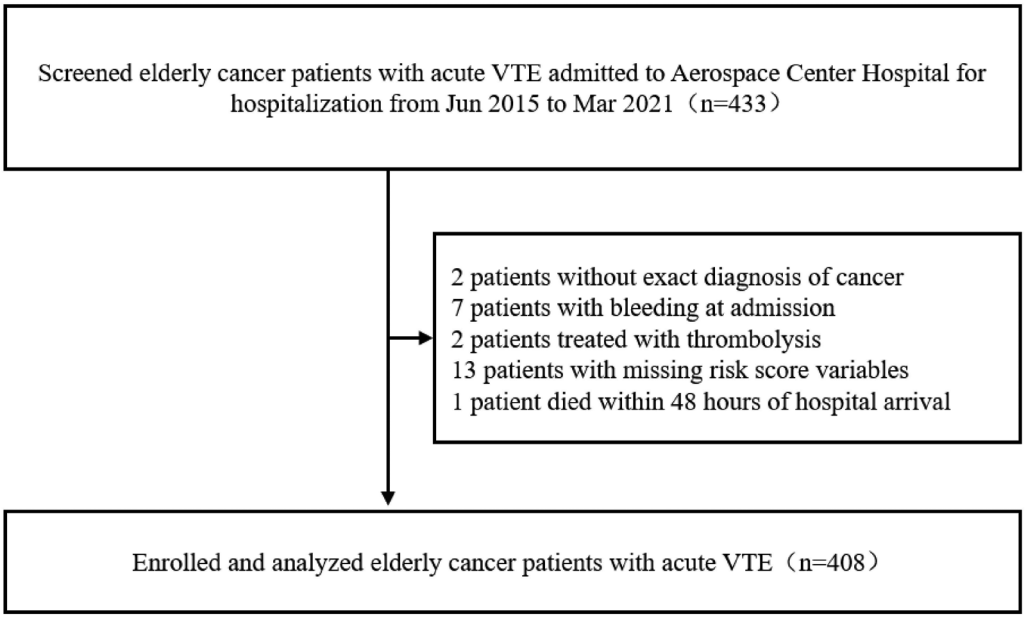

Fig. 1 Study flow chart. VTE, venous thromboembolism.

Table 1 Baseline characteristics, admission data, diagnosis, and treatment

Characteristic	Major bleeding ($n = 34$)	No major bleeding ($n = 374$)	*p*-Value
Demographic data and medical history			
Age (mean ± SD), y	76.7 ± 8.3	76.9 ± 7.6	0.89
>75 y, *n* (%)	17 (50.0)	208 (55.6)	0.53
Women, *n* (%)	14 (41.2)	193 (51.6)	0.24
Prior VTE, *n* (%)	8 (23.5)	67 (17.9)	0.42
Recent major bleeding, *n* (%)	0 (0.0)	7 (1.9)	0.91
Hypertension, *n* (%)	14 (41.2)	202 (54.0)	0.15
Diabetes mellitus, *n* (%)	7 (20.6)	95 (25.4)	0.54
Chronic renal insufficiency, *n* (%)	4 (11.8)	58 (15.5)	0.56
Cerebrovascular disease, *n* (%)	6 (17.6)	107 (28.6)	0.29
Coronary heart disease, *n* (%)	6 (17.6)	118 (31.6)	0.09
Prior coronary revascularization, *n* (%)	2 (5.9)	29 (7.8)	0.96
Atrial fibrillation, *n* (%)	3 (8.8)	55 (14.7)	0.49
Chronic heart failure, *n* (%)	6 (17.6)	71 (19.0)	0.85
Anemia, *n* (%)	11 (32.4)	94 (25.1)	0.36
Prior hemorrhagic disease, *n* (%)	2 (5.9)	18 (4.8)	1.00
Depression, *n* (%)	1 (2.9)	22 (5.9)	0.75
Liver cirrhosis, *n* (%)	1 (2.9)	4 (1.1)	0.89
Admission data			
Systolic blood pressure (mean ± SD), mm Hg	124.4 ± 23.0	127.5 ± 20.2	0.39
Hemoglobin (mean ± SD), (g/L)	91.0 ± 22.7	105.7 ± 21.4	0.00
Platelet count (mean ± SD), 10^9/L	226.1 ± 109.0	212.8 ± 93.3	0.43
Ccr[a] (mean ± SD), mL/min	77.7 ± 63.2	74.3 ± 61.3	0.76
<60 mL/min, *n* (%)	20 (58.8)	181 (48.4)	0.24
Diagnosis			
Type of VTE, *n* (%)			
PE only	3 (8.8)	22 (5.9)	0.25
DVT only	31 (91.2)	332 (88.8)	
Both PE and DVT	0 (0.0)	20 (5.3)	
Cancer type, *n* (%)			
Lung	5 (14.7)	107 (28.6)	0.03
Digestive system	24 (70.6)	140 (37.4)	
Urogenital system	4 (11.8)	74 (19.8)	
Breast	0 (0.0)	28 (7.5)	
Brain	0 (0.0)	3 (0.8)	
Hematological	0 (0.0)	4 (1.1)	
Other	1 (2.9)	18 (4.8)	
Digestive system cancer	24 (70.6)	140 (37.4)	0.00
Active cancer	29 (85.3)	287 (76.7)	0.25
Metastatic malignancy	19 (55.9)	194 (51.9)	0.65
Treatments			
Initial parenteral anticoagulation, *n* (%)	24 (70.6)	306 (81.8)	0.11
Subsequent VKA or DOAC therapy, *n* (%)	2 (5.9)	53 (14.2)	0.28

Abbreviations: Ccr, creatinine clearance; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.
[a]Creatinine clearance was calculated using the Cockcroft–Gault formula.

Table 2 Rates of major bleeding and CRB during hospitalization according to risk categories of bleeding-prediction scores

Bleeding scores	Low risk	Intermediate risk	High risk	*p*-Value
Number of major bleedings/number of patients (%, 95% CI)				
RIETE score	–	24/337 (7.1%, 4.4–9.9%)	10/71 (14.1%, 5.8–22.4%)	0.05
VTE-BLEED score	0/25 (0.0%)	/	34/383 (8.9%, 6.0–11.7%)	0.24
SWITCO65+ score	–	0/20 (0.0%)	34/388 (8.8%, 5.9–11.6%)	0.33
Hokusai-VTE score	27/309 (8.7%, 6.1–12.9%)	/	7/99 (7.1%, 1.9–12.2%)	0.60
Number of CRB/number of patients (%, 95% CI)				
RIETE score	–	34/337 (10.1%, 6.9–13.3%)	14/71 (19.7%, 10.2–29.2%)	0.02
VTE-BLEED score	1/25 (4.0%, 0.0–12.3%)	/	47/383 (12.3%, 9.0–15.6%)	0.36
SWITCO65+ score	–	0/20 (0.0%)	48/388 (12.4%, 9.1–15.7%)	0.19
Hokusai-VTE score	36/309 (11.7%, 8.1–15.2%)	/	12/99 (12.1%, 5.6–18.7%)	0.90

Abbreviations: CI, confidence interval; CRB, clinically relevant bleeding.

areas under the ROC curve ranged from low for Hokusai-VTE (0.45; 95% CI: 0.35–0.55), SWITCO65+ (0.54; 95% CI: 0.43–0.64), and VTE-BLEED (0.58; 95% CI: 0.49–0.68) to moderate for RIETE (0.61; 95% CI: 0.51–0.71); there were no differences between RIETE and the other scores ($p > 0.05$; ►Fig. 2). Furthermore, compared with Hokusai-VTE, the RIETE score reclassified major bleeding risk with a significant IDI of +0.17 ($Z = 11.13$, $p < 0.001$) and a nonsignificant NRI of +0.17 ($Z = 1.55$, $p = 0.06$). Compared with SWITCO65+ and VTE-BLEED, the RIETE score reclassified major bleeding risk with nonsignificant IDIs of +0.08 ($Z = 0.63$, $p = 0.26$) and +0.06 ($Z = 0.47$, $p = 0.32$), and nonsignificant NRIs of +0.08 ($Z = 0.52$, $p = 0.30$) and +0.06 ($Z = 0.42$, $p = 0.34$), respectively.

In terms of CRB prediction, the calibration of each score was adequate for the entire cohort (HL $p > 0.05$). The predictive values of the four scores for CRB, as expressed by areas under the ROC curve, were poor: 0.48 (95% CI: 0.39–0.57) for Hokusai-VTE, 0.56 (95% CI: 0.48–0.64) for SWITCO65 +, 0.60 (95% CI: 0.52–0.68) for VTE-BLEED, and 0.59 (95% CI: 0.50–0.67) for RIETE. There were no differences between RIETE and the other three scores ($p > 0.05$; ►Fig. 3). Moreover, compared with Hokusai-VTE, the RIETE score reclassified CRB risk with a significant IDI of +0.13 ($Z = 16.8$, $p < 0.001$) and a nonsignificant NRI of +0.13 ($Z = 1.28$, $p = 0.10$). Compared with SWITCO65+ and VTE-BLEED, the RIETE score reclassified CRB risk with nonsignificant IDIs of +0.08 ($Z = 0.73$, $p = 0.23$) and +0.09 ($Z = 0.82$, $p = 0.21$), and nonsignificant NRIs of +0.08 ($Z = 0.60$, $p = 0.27$) and +0.09 ($Z = 0.68$, $p = 0.25$), respectively.

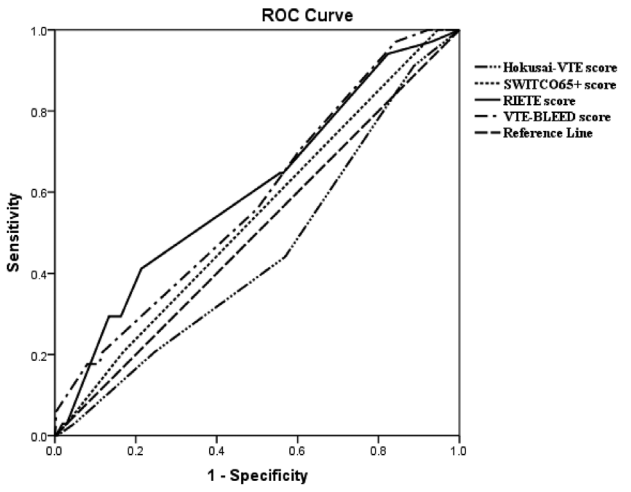

Fig. 2 Receiver-operating characteristic curve for predicting major bleeding during hospitalization in elderly cancer patients with acute venous thromboembolism (VTE) using the RIETE (0.61; 95% CI: 0.51–0.71), VTE-BLEED (0.58; 95% CI: 0.49–0.68), SWITCO65+ (0.54; 95% CI: 0.43–0.64), and Hokusai-VTE scores (0.45; 95% CI: 0.35–0.55). There were no significant differences among scores ($p = 0.45$, $p = 0.29$, and $p = 0.74$ for comparisons between RIETE and Hokusai-VTE, RIETE and SWITCO65 +, and RIETE and VTE-BLEED, respectively).

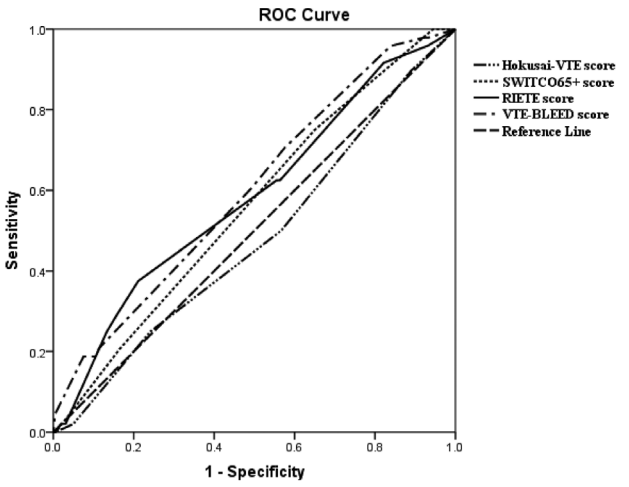

Fig. 3 Receiver-operating characteristic curve for predicting clinically relevant bleeding during hospitalization in elderly cancer patients with acute venous thromboembolism (VTE) using the RIETE (0.59; 95% CI: 0.50–0.67), VTE-BLEED (0.60; 95% CI: 0.52–0.68), SWITCO65+ (0.56; 95% CI: 0.48–0.64), and Hokusai-VTE scores (0.48; 95% CI: 0.39–0.57). There were no significant differences among scores ($p = 0.33$, $p = 0.65$, and $p = 0.79$ for comparisons between RIETE and Hokusai-VTE, RIETE and SWITCO65 +, and RIETE and VTE-BLEED, respectively).

Discussion

The main finding of the present study was that, for predicting in-hospital major bleeding, the discriminative power of the four scores was poor to moderate, as indicated by areas under the ROC curve (0.45, 0.54, 0.58, and 0.61 for Hokusai-VTE, SWITCO65+, VTE-BLEED, and RIETE, respectively). The superiority of RIETE was indicated only by the IDI compared with the Hokusai-VTE score ($p < 0.001$).

The RIETE score was developed for predicting major bleeding within the first 3 months of anticoagulant therapy, based on the VTE patients in a large RIETE registry. It could identify elderly cancer-associated VTE patients with a high risk of major bleeding during hospitalization. It performed moderately well in the present study (area under the curve > 0.6). Our results were consistent with the findings in a recent prospective, multicenter study that evaluated the RIETE score in elderly VTE patients (aged ≥65 years), in which the area under the curve was 0.60.[36]

The VTE-BLEED and Hokusai-VTE scores, derived from VTE patients randomized to receive either novel oral anticoagulants or warfarin, were designed to predict long-term major bleeding during the "stable" term of anticoagulation therapy (defined as the treatment period after the first 30 days, or a period of 3–12 months).[26,28] The design of this article differed from both of the derivation studies because it focused on a real-world cohort of elderly cancer-associated VTE patients, most of who were probably much sicker than the patients enrolled in the derivation studies. Furthermore, the present study focused on in-hospital bleeding events, rather than long-term outcomes. The risk factors for bleeding are likely to shift after the early weeks of treatment.[11] Therefore, our results considerably differ from the more optimistic findings of the original score derivation studies.

The SWITCO65+ score, derived from the Swiss VTE cohort (SWITCO65+) of elderly patients (≥65 years) with acute VTE, was developed for predicting major bleeding during extended anticoagulation therapy with VKAs (3–36 months).[27] To our knowledge, the present study is the first externally validated study to evaluate these scores. The area under the curve was 0.54, indicating a poor predictive ability and a much lower accuracy than reported for the derivation cohort (C-statistic: 0.71). However, this unsurprising difference is presumably because our study focused on elderly cancer-associated acute VTE patients; notably, 77.5% of our patients (316/408) were classified as active cancer patients. All patients in our cohort represented a particularly vulnerable group; they received 2 points for "low physical activity" in accordance with the criteria of the derivation study.[6,27] In addition, the risk factors for bleeding change with time; they may have differed between the hospitalization and extended anticoagulation periods.[11] Thus, the different follow-up times may have influenced the predictive values of the scores.

There were some limitations in this study. First, the sample size was small ($n = 408$). However, elderly cancer-associated VTE patients represent a particularly vulnerable group with high rates (8.3%) of major bleeding during hospitalization, which makes this study clinically relevant. Second, the exclusion of patients treated with thrombolytic therapy may have introduced a bias. Third, patients with Ccr less than 30 mL/min were included and received 1.5 points for the VTE-BLEED score; thus, our analysis may have overestimated the bleeding risk with respect to the VTE-BLEED score. Fourth, we calculated only the overall rates of in-hospital major bleeding and CRB, and did not calculate the cumulative rates of major bleeding and CRB according to the method of Kaplan–Meier. However, the rates of in-hospital major bleeding and mortality were comparable to the related studies.[16,37] In-hospital mortality might be a competing risk for major bleeding or CRB, and it would be nice to have the additional analysis for making the conclusion more convincing. Finally, this was a single-center observational study, and the management protocols were uniform for all patients. Therefore, our findings should be viewed with caution, particularly in other centers with different medical facilities and management protocols.

In conclusion, our findings suggested that the RIETE score had a moderate predictive value for in-hospital major bleeding in a real-world cohort of elderly cancer patients with acute VTE. Because bleeding-prevention strategies are clinically important in these vulnerable individuals, the RIETE score may be used to predict the risk of major bleeding during hospitalization.

What is known about this topic?

- Major bleeding risk, conferred a high case fatality as that of recurrent VTE itself, is highly relevant for anticoagulant treatment decisions in elderly cancer patients with VTE.
- Several risk scores for bleeding in patients with VTE exist, but have never been validated in elderly cancer patients with VTE and are not recommended for practice.

What does this paper add?

- RIETE score had moderate predictive value for hospitalized major bleeding in elderly Chinese cancer patients with acute VTE.
- RIETE score also could categorize the patients with increasing rate of major bleeding and CRB according to the low-/intermediate- and high-risk categories.

Conflict of Interest

The authors declare that they have no conflict of interest.

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