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Research paper

Validation of the IMPROVE bleeding risk score in Chinese medical patients during hospitalization: Findings from the dissolve-2 study

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ABSTRACT

Background: Venous thromboembolism (VTE) prophylaxis remains suboptimal in China due to the bleeding risk associated with pharmacologic prophylaxis. We used data from the Dissolve-2 study to report the risk factors for bleeding and validated the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) bleeding risk score (BRS).

Methods: In-hospital major bleeding incidence in medical patients from the Dissolve-2 study were assessed by Kaplan-Meier method. Risk factors associated with clinically relevant bleeding (CRB) were analysed using Cox regression model. Sensitivity, specificity, positive predictive value, negative predictive value and receiver-operating characteristic (ROC) curve was used to compute the diagnostic accuracy of IMPROVE BRS in the study cohort.

Findings: Of the 6623 medical patients, 5076 patients with all relevant clinical details were included for the validation cohort. Overall, 127 CRB events (38 major and 89 clinically relevant non-major bleeding events) occurred in this cohort, with a cumulative incidence rate of 2.6% (95% confidence interval [CI], 2.3–3.4). Application of IMPROVE BRS revealed significantly higher hazards of CRB (hazard ratio [HR]: 7.17, 95% CI, 5.05–10.18) and major bleeding (HR: 13.95, 95% CI, 7.28–26.73) in patients with IMPROVE BRS ≥ 7 . Comparison of predictive parameters revealed higher sensitivity (44.1 vs 35.9) and positive predictive value (10.9 vs 2.6) for CRB in our study than the IMPROVE study, which was substantiated by the area under the curve (0.73, $p < 0.0001$) from the ROC curve analysis.

Interpretation: IMPROVE BRS is a simple model for estimating bleeding risk in Chinese medical patients and could be used in conjunction with VTE risk assessment models to decide prophylactic treatment for VTE.

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1. Introduction

Venous thromboembolism (VTE) is a complex disease resulting from the interaction among clinical, genetic and environmental risk factors, which include deep vein thrombosis (DVT) and pulmonary embolism (PE)¹. Hospitalization is a known risk factor that increases the probability of acquiring VTE by at least 8-fold, which is also influenced by patient- and disease-specific factors². Various international guidelines recommend thrombo-prophylaxis for the prevention of VTE in case of hospitalised, non-surgical patients, based on the presence of risk factors for VTE and bleeding³. The American College of Chest Physicians (ACCP) evidence-based guidelines recommend thrombo-prophylaxis in acute medical ill, hospitalised patients who are at high risk for VTE, and the prophylactic modality should be decided based on the bleeding risk⁴.

The prophylactic treatment for the prevention of VTE in hospitalised patients is frequently based on the stratification of risk factors for acquiring VTE and the risk of bleeding⁴. Clinical prediction models based on the established risk factors are frequently used for stratifying patients into high, medium and low risk for VTE and bleeding⁵. Scoring systems such as the Padua prediction score and the Caprini risk assessment model (RAM) have been used to predict VTE in hospitalised patients^{6–10}. In the Venous Thromboembolism Risk and Prophylaxis in the Acute Hospital Care Setting (ENDORSE) study and The Identification of Chinese Hospitalized Patients' Risk Profile for Venous Thromboembolism-2 (Dissolve-2) study, the rates of VTE prophylaxis were low which could be due to physicians' fear of bleeding^{10,11}. This emphasises the urgent clinical necessity to assess the risk of bleeding in patients with VTE for selecting appropriate therapeutic management in patients at risk of VTE¹².

The established risk factors for bleeding in hospitalised patients have been reported in previous studies^{13–16}. The International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) study identified risk factors and set a model to predict the bleeding risk for hospitalised patients who are at risk for VTE. The study revealed a total of 11 patient- and disease-related factors assessed at hospital admission to be independently associated with higher bleeding rates. On the basis of the incidence of bleeding in their cohort of patients, the study recommended a bleeding risk score (BRS) threshold of seven to categorize patients into high- (≥ 7) and low-risk (< 7) categories¹⁷.

To date, the IMPROVE RAM remains the only BRS in medical patients that was validated in a large cohort of American patients^{18,19}, however, it was not yet validated in other ethnic groups. Dissolve-2 study was designed to identify the risk factors for VTE and bleeding in a large cohort of Chinese medical and surgical inpatients. Herein, we sought to report the risk factors for bleeding and to perform external validation of the IMPROVE BRS in Chinese medical patients in the Dissolve-2 study.

2. Methods

2.1. Study design and participants

We used data from the Dissolve-2 study to report the risk factors and externally validate the IMPROVE BRS. Dissolve-2 is a retrospective, multicentre, observational study (ChiCTR-OOC-16010187) that included patient data from 60 teaching hospitals with >500 beds in 44 major cities across China. These hospitals were randomly selected from six regions of China (Northeast, North, East, Northwest, Southwest and South-Central China)¹⁰. The study was approved by the institutional ethics board, and the requirement of written consent from the included patients was waived off as it was a retrospective study.

2.2. Study population

The selection of the patient population, sample size calculation, inclusion and exclusion were reported previously¹⁰. Eligible patients were >18 years, had a hospital stay ≥ 72 h, admitted for treatment of a serious acute medical illness listed in the ACCP 8th and 9th Edition. The following patients were excluded: patients admitted solely for diagnostic testing or haemodialysis; patients receiving medicinal anticoagulation treatment; patients admitted for treatment of VTE (began within 24 h of admission); patients with a major traumatic event, requiring or not requiring an operation, including closed head injury; pregnancy; patients who are hospitalised for a chronic condition, rather than an acute medical illness; and patients from the following wards: psychiatric, pediatric, palliative care, maternity, ear, nose and throat units, burn units, dermatological, ophthalmologic services, alcohol/drug treatment wards and rehabilitation unit/ward. Since the main aim of the study was to validate IMPROVE BRS, patients with missing platelet count, international normalised ratio (INR), and glomerular filtration rate (GFR) and surgical patients were excluded from the validation data set as well.

2.3. Data collection and procedure

The incidences of in-hospital major bleeding and clinically relevant non-major bleeding (CRNMB) in medical patients were collected. Data were collected using a case report form for patients who met inclusion criteria on the day of visit to hospital from the medical records of the patients (appendix 1). Data from eligible patients' medical charts were collected by using an electronic case report form, de-identified, and entered into an electronic data capture system by trained data management personnel. The collected data included demographic information, type of medical illness based on admission and discharge diagnoses, treatment/procedural details, risk factors for VTE and bleeding during hospitalization, details of VTE prophylaxis administered as described in the CHEST guidelines, 9th edition^{4,20,21}, and clinical outcome of the patient at discharge.

Risk level of VTE was assessed in medical inpatients using Padua prediction scoring. Based on the risk factors, patients were categorised into low or high risk according to the CHEST guidelines, 9th edition^{4,20,21}.

2.4. Outcomes

The definition of major bleeding was a bleeding event contributing to death, clinically overt bleeding associated with a fall in hemoglobin level by ≥ 2 g/dL or leading to transfusion of at least two units of packed red blood corpuscles (RBCs), or bleeding within a critical organ (including intracranial, retroperitoneal, intraocular or pericardial bleeding). CRNMB was defined as haemorrhoidal bleeding, gross haematuria lasting for >24 h, epistaxis or bleeding gums >5 min, subcutaneous haematoma >25 cm², haematoma requiring drainage or other bleeding. Major bleeding and CRNMB were collectively referred to as clinically relevant bleeding (CRB). The primary outcomes were to estimate the risk factors for CRB/major, and to perform external validation of the IMPROVE BRS. The secondary outcome was to assess the role of VTE prophylaxis in the IMPROVE BRS. Bleeding events were categorised as related or unrelated to anticoagulant usage depending on the occurrence of bleeding within 24 h of administration of anticoagulant. This was interpreted and supervised by an independent adjudication committee.

2.5. Statistical analysis

Continuous variables were described as number of observations, normally distributed variables were expressed as mean and standard deviation (SD) and non-normally distributed variables were expressed as median and interquartile range (IQR). Exploratory hypothesis testing was performed at the two-sided $\alpha = 0.05$ level unless otherwise specified; two-sided 95% confidence intervals (CIs) are presented where specified. Distribution of risk level of VTE in hospitalised patients and proportion of patients receiving any VTE prophylaxis were summarised separately in terms of percentage with 95% CIs. The cumulative bleeding rate within 14 days from the day of admission till any bleeding (or till the day of discharge in case of absence of major bleeding) was determined using Kaplan-Meier (KM) analysis. Univariate and multivariate analyses were performed by Cox regression model to analyze the risk factors associated with bleeding events. Hazards ratio and 95% CI for major bleeding and CRB for different risk stratification factors were computed from the Cox regression.

The rating of patients based on IMPROVE BRS is provided in appendix 2. Based on the presence of risk factors, the patients were dichotomously categorised into low risk (score <7) and high risk (score ≥ 7), and the incidence of major and any bleeding events were analysed in the low-risk and high-risk groups. On the basis of our definition of a positive test (one in which the incidence of bleeding occurred in patients with IMPROVE BRS ≥ 7), we calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) using standard formula. Receiver-operating characteristic (ROC) curve was also plotted to understand the predictive ability of the IMPROVE BRS in our cohort of patients. Statistical analyses were performed by using Statistical Analysis System (SAS) version 9.4 (SAS Institute, Inc).

2.6. Role of the funding source

This study was funded by Sanofi, and editorial support in the preparation of this publication was provided by Sanofi. The authors individually and collectively are responsible for all content and editorial decisions and received no payment from Sanofi related to the development/ presentation of this publication.

3. Results

3.1. Demographic characteristics, prevalence of VTE risk and pharmacologic prophylaxis

The study screened a total of 51,835 patients, of which 14,000 were enrolled. After removing surgical patients, a total of 6623 medical patients were included for assessing the VTE risk. The mean age of the medical patients was 63 years (SD: 16), and 58% of the patients were males. The other baseline parameters are provided in Supplementary Table 1. Out of the 6623 patients, 1547 patients were excluded from the analysis because of missing values for platelet count or INR or GFR. Risk factors for major/CRB and validation of the IMPROVE BRS was done in the remaining 5076 patients (validation cohort) (Supplementary Figure 1). Risk stratification for VTE by Padua scoring revealed 37% (95% CI: 35–38) of the patients to be at high risk and 63% of the patients to be at low risk (95% CI: 62–65). The corresponding bleeding rates in patients with high and low risk of VTE were 1.4% and 3.4%, respectively (Supplementary Table 2). Of 5076 patients, only 519 patients (8%) received any pharmacologic prophylaxis. Low-molecular-weight heparin (LMWH) was the most frequently used pharmacologic prophylaxis (158/519; 30%). The other pharmacologic prophylactic drugs used, their dosage/day and routes of administration are provided in Supplementary Table 3.

3.2. Type of in-hospital bleeding, clinical consequence and reasons for bleeding

A total of 140 bleeding events were reported in the medical patients from the Dissolve-2 study out of which 42 bleeding events were major and 98 bleeding events were CRNMB. The various types of major and CRNMB in medical patients include bleeding requiring blood transfusion ≥ 2 units (21%), intracranial bleeding (7%), bleeding leading to a fall in hemoglobin level by ≥ 2 g/dL (2%), epistaxis (5%), gross haematuria (2%), haemorrhoidal bleeding (1%) and others bleeding events important enough to be recorded on the hospital chart (63%; Supplementary Table 4). Different clinical consequences of bleeding in medical patients in the validation cohort included improvement (58%), cure (8%), death (8%), aggravation (3.2%), department transference (0.8%) and unknown (22.1%). The incidence of bleeding was unrelated to anticoagulation in 87.4% of the patients and was related to anticoagulation in 2.4% of the patients (Supplementary Table 5).

3.3. Cumulative incidence of bleeding in the validation cohort

The cumulative bleeding rate from the day of hospital admission until the 14th day of hospital admission, as evaluated by the KM curve, revealed a cumulative incidence of 2.6% (95% CI: 2.3–3.4) in the validation cohort (Fig. 1). A total of 38 (1%) major bleeding events and 89 (2%) CRNMB were recorded in the validation cohort. Patient- and disease-related factors in the validation cohort stratified according to incidence of major bleeding and CRNMB are provided in Table 1.

3.4. Validation of IMPROVE BRS

A total of 11 factors that had higher odds of bleeding in the IMPROVE BRS were evaluated for their association in medical patients. Among the factors, active gastrointestinal ulcer (HR: 7.08), bleeding in 3 months before admission (HR: 7.21), platelet count $<50 \times 10^9$ (HR: 5.70), GFR (moderate renal failure, HR: 2.07; severe renal failure, HR: 3.02) and ICU/CCU admission (HR: 2.67) were significantly associated with CRB (Table 2).

A total of 4564 (90%) and 512 (10%) patients had an IMPROVE BRS of <7 and ≥ 7 , respectively (Fig. 2A), and the incidence of CRB was 2% and 11%, respectively (Fig. 2B). The hazards of CRB event were 7.17 times more in patients with an IMPROVE BRS of ≥ 7 , whereas the hazards of major bleeding event were 13.95 times more in patients with an IMPROVE BRS of ≥ 7 (Supplementary Table 6). There seems to be a direct proportionality between the IMPROVE BRS and the bleeding rates (CRB and major bleeding) as the bleeding rate in patients with a score of 0 to 1 increased from 1% to 26% in patients with BRS >12 for CRB. The corresponding change in bleeding rates for major bleeding was 0% to 21% (Table 3, Supplementary Figure 2A and 2B). Further, a total of 318 patients with an IMPROVE BRS >7 was also considered as patients at high risk for VTE as per the Padua score (Supplementary Table 7).

The predictive ability of the IMPROVE BRS in medical patients revealed a high specificity and NPV for both CRB (specificity: 90.8%; NPV: 98.4%) and major bleeding (specificity: 90.3%; NPV: 99%) events. Comparison of predictive parameters of the medical patients in the current study with the IMPROVE patient cohort (calculated from the reported bleeding rates), revealed a higher sensitivity (44.1 vs 35.9) and PPV (10.9 vs 2.6) for CRB (Supplementary Table 8). The ROC curve plotted with the predictive parameters (sensitivity and specificity) revealed an area under the curve value of 0.73 (95% CI: 0.68–0.78, $p < 0.0001$; Fig. 3).

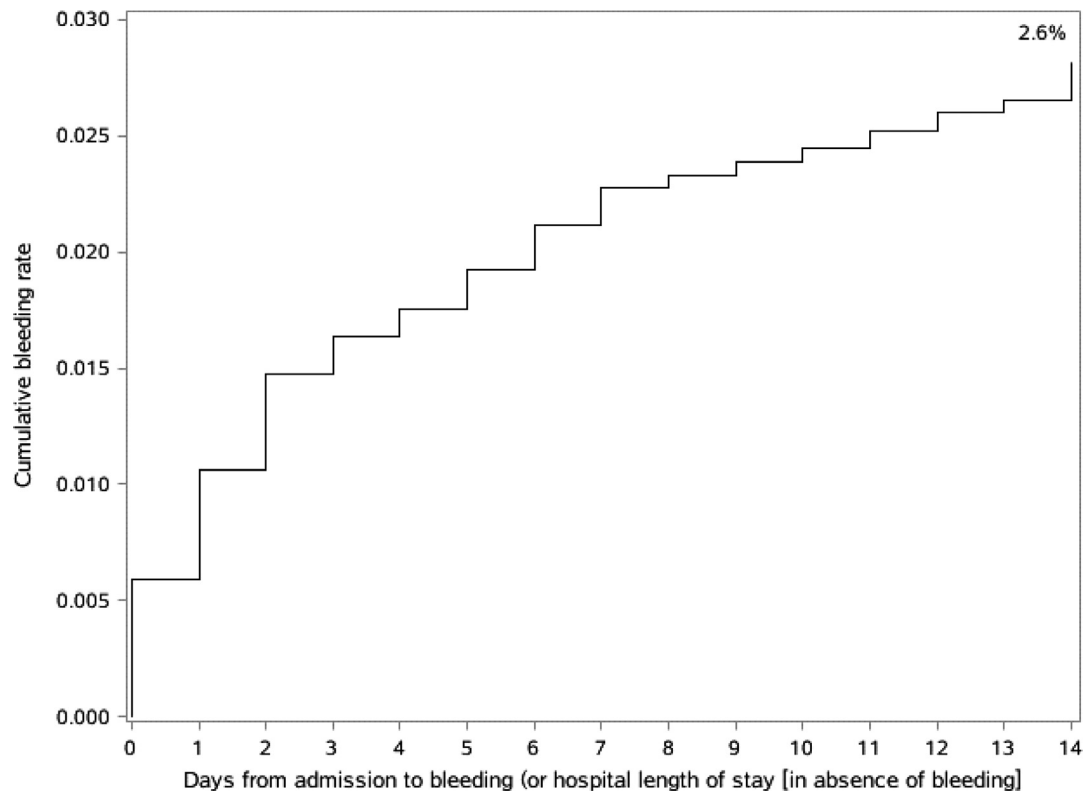


Fig. 1. Kaplan-Meier plot showing the cumulative incidence rate of clinically relevant bleeding from within 14 days from admission in medical patients ($n = 5076$). Major bleeding and clinically relevant non major bleeding were collectively referred to as clinically relevant bleeding.A.

Table 1
Patient - and disease-related risk factors stratified by bleeding status.

	Total Patients N = 5076		Major Bleeding N = 38		CRNM Bleeding N = 89		No Bleeding N = 4949	
	n	(%)	n	(%)	n	(%)	n	(%)
Patient characteristics								
Age in years								
<40	401	(7.9)	5	(13.2)	7	(7.9)	389	(7.9)
≥40 and <85	4362	(85.9)	31	(81.6)	75	(84.3)	4256	(86.0)
≥85	313	(6.2)	2	(5.3)	7	(7.9)	304	(6.1)
Male								
	2946	(58.0)	22	(57.9)	58	(65.2)	2866	(57.9)
Medical conditions								
Active gastroduodenal ulcer	52	(1.0)	3	(7.9)	6	(6.7)	43	(0.9)
Bleeding in 3 mo before admission	121	(2.4)	9	(23.7)	13	(14.6)	99	(2.0)
Platelet count $<50 \times 10^9$	101	(2.0)	8	(21.1)	8	(9.0)	85	(1.7)
Hepatic failure (INR>1.5)	115	(2.3)	5	(13.2)	1	(1.1)	109	(2.2)
Severe renal failure								
GFR <30 mL/min/m ²	234	(4.6)	11	(29.0)	8	(9.0)	215	(4.3)
GFR 30–59 mL/min/m ²	590	(11.6)	9	(23.7)	17	(19.1)	564	(11.4)
GFR ≥ 60 mL/min/m ²	4252	(83.8)	18	(47.4)	64	(71.9)	4170	(84.3)
ICU/CCU	340	(6.7)	12	(31.6)	16	(18.0)	312	(6.3)
Central venous catheter	319	(6.3)	14	(36.8)	12	(13.5)	293	(5.9)
Rheumatic disease	277	(5.5)	3	(7.9)	4	(4.5)	270	(5.5)
Current cancer	1196	(23.6)	10	(26.3)	29	(32.6)	1157	(23.4)
VTE prophylaxis	432	(8.5)	1	(2.6)	10	(11.2)	421	(8.5)
Median hospital length of stay (days)	11	(IQR 8–16)	16	(IQR 11–25)	12	(IQR 8–18)	11	(IQR 8–16)

CRNM, clinically relevant nonmajor; INR, international normalized ratio; GFR, glomerular filtration rate; ICU, intensive care unit; CCU, cardiac care unit.

3.5. Effect of VTE prophylaxis on the performance of IMPROVE BRS

A total of 374 (8%) and 58 (11%) patients with an IMPROVE BRS of <7 and ≥ 7 , respectively, underwent VTE prophylaxis (Supplementary Figure 3). A total of 11 patients who underwent VTE prophylaxis experienced CRB, of whom seven patients had an IMPROVE BRS <7 and 4 patients had an IMPROVE BRS ≥ 7 . The bleeding rate for CRB event was more in patients without any prophylaxis, with an IMPROVE BRS ≥ 7 (12% vs 7%), although there was no statistically significant difference suggesting that the VTE prophylaxis did not alter the performance of IMPROVE BRS (Supplementary Table 9).

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4. Discussion

Bleeding and VTE risk stratifications in hospitalised medical patients assist in selecting patients for VTE prophylaxis. The IMPROVE

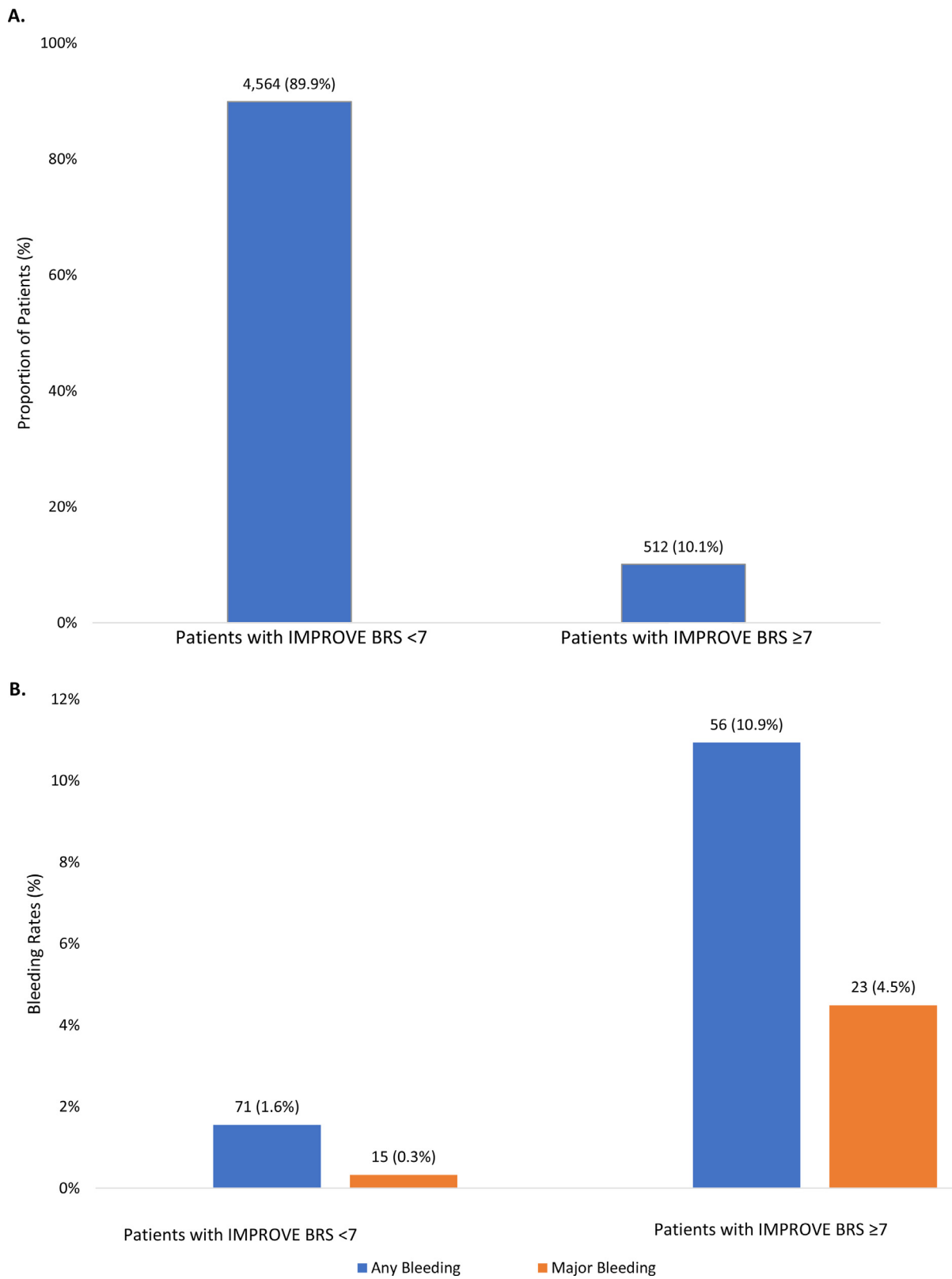


Fig. 2. Implications of IMPROVE bleeding risk score for clinical decision making. A. Proportion of medical patients with IMPROVE BRS of <7 and ≥7. B. rates of clinically relevant bleeding in patients with IMPROVE BRS <7 and ≥7. BRS: bleeding risk score.

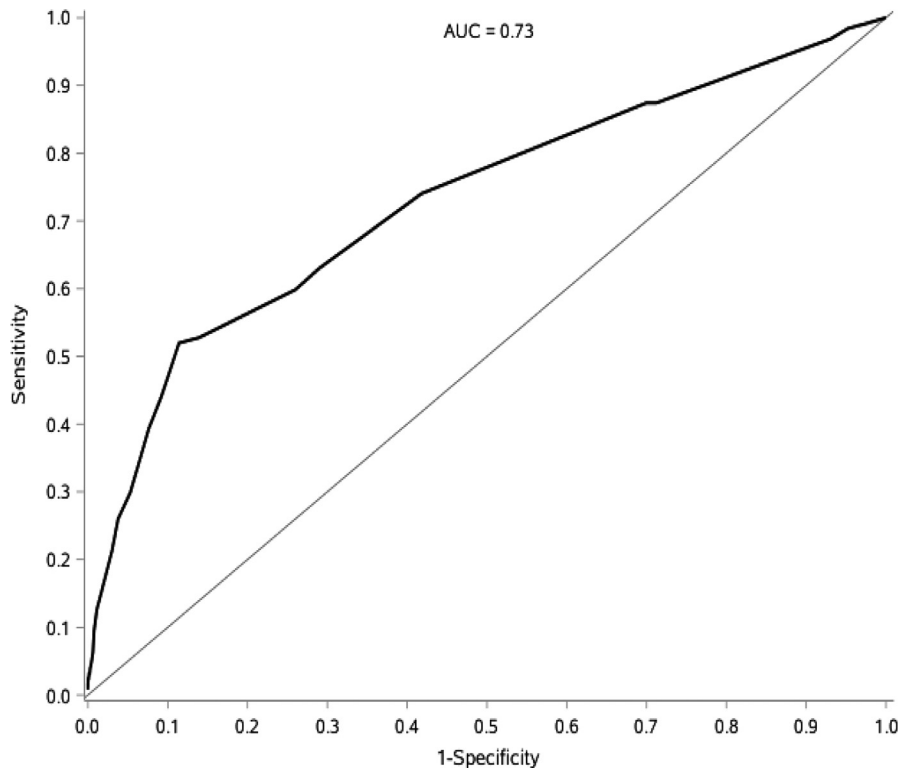


Fig. 3. Receiver-operating characteristic curve to assess the diagnostic accuracy of IMPROVE BRS. Area under the ROC curve value was 0.73 (0.68–0.78, $p < 0.0001$). AUC: Area under the curve.

Table 2
Association between bleedings and IMPROVE bleeding risk factors ($n = 5076$).

	HR	[95% CI]	P-value
Patient characteristics			
Age ≥ 40 and < 85 vs < 40 years	0.82	[0.45–1.51]	0.5216
Age ≥ 85 vs < 40 years	0.65	[0.27–1.60]	0.3481
Male vs Female	1.07	[0.74–1.55]	0.7226
Medical conditions			
Active gastroduodenal ulcer	7.08	[3.54–14.17]	$< 0.0001^*$
Bleeding in 3 mon before admission	7.21	[4.46–11.66]	$< 0.0001^*$
Platelet count $< 50 \times 10^9$	5.70	[3.26–9.96]	$< 0.0001^*$
Hepatic failure (INR > 1.5)	1.08	[0.45–2.58]	0.8615
Severe renal failure			
GFR 30–59 vs ≥ 60 ml/min/m ²	2.07	[1.31–3.29]	0.0019*
GFR < 30 vs ≥ 60 ml/min/m ²	3.02	[1.78–5.13]	$< 0.0001^*$
ICU/CCU	2.67	[1.62–4.40]	0.0001*
Central venous catheter	1.48	[0.89–2.46]	0.1325
Rheumatic disease	1.00	[0.46–2.18]	0.9906
Current cancer	1.34	[0.89–2.03]	0.1607

INR, international normalized ratio; GFR, glomerular filtration rate; ICU, intensive care unit; CCU, cardiac care unit; HR, hazard ratio; CI, confidence interval.
* $p < 0.05$.

Table 3
Model Calibration: bleeding rates by IMPROVE bleeding risk group level.

Score Group	Total Patients		Any Bleeding Rates		Major Bleeding Rates	
	n	(%)	n	(%)	n	(%)
0–1	113	(2.2)	1	(0.9)	0	(0.0)
1.5–2	236	(4.6)	3	(1.3)	2	(0.8)
2.5	1092	(21.5)	12	(1.1)	2	(0.2)
3–4	1565	(30.8)	19	(1.2)	1	(0.1)
4.5–5	708	(13.9)	16	(2.3)	4	(0.6)
5.5–6.5	850	(16.7)	20	(2.4)	6	(0.7)
7	84	(1.7)	6	(7.1)	2	(2.4)
7.5–8	208	(4.1)	17	(8.2)	6	(2.9)
8.5–9.5	120	(2.4)	14	(11.7)	4	(3.3)
10–12	81	(1.6)	14	(17.3)	7	(8.6)
Above 12	19	(0.4)	5	(26.3)	4	(21.1)

BRS was formulated specifically for medical patients not selected for any specific disease state. In the current study, we performed an external validation of IMPROVE BRS with a large multicentric cohort of Chinese hospitalised patients. The inclusion criteria for patients in the Dissolve-2 study were similar to those in the IMPROVE study. The results of our current study revealed comparable specificity (90.8% vs 90.9%) and NPV (98.4% vs 98.2%) in predicting CRB events to the IMPROVE study. The performance of the IMPROVE BRS in our cohort of patients was also better than the IMPROVE cohort in terms of sensitivity (44.1% vs 35.9%) and PPV (10.9% vs 2.6%) in predicting CRB events. The sensitivity in our cohort was also much higher in predicting major bleeding events (60.5% vs 51%). This suggested the applicability of IMPROVE BRS in Chinese medical patients.

In a previous external validation study by Hostler et al., in American patients, the incidence rates of major bleeding were significantly higher in patients with an IMPROVE BRS of ≥ 7 compared with IMPROVE BRS of < 7 (4% vs 1.2%; $p = 0.02$)¹⁸. The corresponding major bleeding incident rates in our study were 4.5% versus 0.3% ($p < 0.0001$). Although the incident rates were significantly higher in both the studies, there was a distinct disparity in incident rates in patients with BRS of ≥ 7 and < 7 in our study. This might be because a majority of the patients in the study by Hostler et al. were on chemical VTE prophylaxis (80% vs 7.8% in the current study). Further, 22% of the patients in the study by Hostler et al. had a BRS ≥ 7 whereas only 10% of the patients in the current study had a BRS ≥ 7 . Although analysis of patients on VTE prophylaxis in the current study revealed no statistically significant difference in the incidence of CRB events in patients with an IMPROVE BRS of < 7 versus ≥ 7 , VTE prophylaxis might attenuate the difference in bleeding rates.

In a large retrospective, single-center study, Rosenberg et al. also validated the IMPROVE BRS, reporting a similar sensitivity and NPV as the IMPROVE cohort, but lower specificity (81.5% vs 90.9%)

in predicting any bleeding events. The sensitivity (33.3% vs 51%) and specificity (81.3% vs 90%) for predicting major bleeding events were also much lower in their validation cohort¹⁹. This could be due to the difference in the proportion of patients undergoing VTE prophylaxis in the IMPROVE cohort (48%) and their validation cohort (82%). This is in contrast to our current study wherein the predictive parameters were comparable or better than those in the IMPROVE cohort. The corresponding AUCs obtained from ROC curve in the study by Rosenberg et al. were also lower than those in the IMPROVE cohort and the current study cohort (0.63 vs 0.71 vs 0.73). The higher AUC value in our study might suggest better performance of the IMPROVE BRS in Chinese patients. Further, in the current study, there was no statistically significant association between the IMPROVE BRS, incidence of CRB and VTE prophylaxis. However, in a study by Rosenberg et al., the predictive parameters (specificity, NPV and PPV) were significantly lower in patients without prophylaxis¹⁹.

In the current study, age, sex, hepatic failure, rheumatic disease and current cancer were not significantly associated with incidence of any bleeding. This is in contrast to the findings from the IMPROVE cohort wherein, except age (40–84 years) and moderate renal failure, all the factors had a significantly higher odds of bleeding. Although in the current study, even moderate renal failure was significantly associated with a higher hazards of CRB (HR: 2.07, $p = 0.0019$), this is in concordance with the IMPROVE cohort. Rosenberg et al. and Hostler et al. did not report the effect estimates for the independent risk factors in their respective patient cohorts^{18,19}.

In the current study, model calibration revealed that the incidence of major bleeding increased exponentially in proportion to the IMPROVE BRS, which is on par with the previous studies reporting different RAMs^{17,22,23}. In a post hoc pooled analysis of two randomised sister trials predicting bleeding events using VTE-BLEED score, in patients with VTE on anticoagulant treatment, the bleeding incidence was high (12.6%) in patients with score >2 compared with those with score <2 (2.8%)²². A retrospective study evaluating the accuracy of HAS-BLED score reported higher bleeding risk in patients with VTE on vitamin K-antagonist treatment with HAS-BLED BRS ≥ 3 (9.6%) than that of patients with HAS-BLED BRS <3 (1.3%)²³.

The results of the study substantiate the utility of an evidence-based RAM to predict hospitalised patients who might potentially benefit from prophylactic treatment for VTE without bleeding risk. This might allow more patient-specific, individualised management strategies for reducing VTE risk in acutely ill medical patients. A risk-benefit ratio could also be computed with BRS and VTE risk scores to drive therapeutic management. Although online tools for calculating IMPROVE BRS are already available, including machine learning approaches might increase the predictive ability of the IMPROVE BRS. Machine learning-based approaches have already been used with the Khorana score to predict VTE risk in patients with cancer and has revealed better predictive ability in machine learning-based approaches²⁴.

The IMPROVE bleeding risk score has been validated in western population and was recommended by the CHEST guideline, however, there is a lack of evidence in the Chinese population. Other bleeding risk models, such as NICE and REITE have not been validated extensively. Those models mainly targeted the VTE patients with comorbidities to predict their bleeding risks. There was no bleeding risk score computed in the NICE guidelines and REITE was used in VTE patients treated with anticoagulants^{25,26}. Hence, the IMPROVE BRS may not be comparable to other BRS models.

The current study has some limitations. This was a cross-sectional study and data were collected from patient's medical records, and hence no follow-up data were available. Moreover, the hospitals selected for this study are among the best treatment-

providing hospitals and hence might not represent the general level of care provided to patients. Finally, in this real-world data, only a few patients received pharmacologic prophylaxis. Hence, this might have introduced some bias while assessing the bleeding events associated with pharmacologic prophylaxis. Further, in this study, a total of 31 bleeding events were reported in the 1547 patients excluded from the study which may have introduced a selection bias. However, since the incidence of bleeding in the validation cohort and the overall medical patients is similar (2.6% vs 2.4%), we believe the effect of the selection bias could be negligible.

In conclusion, we validated the IMPROVE BRS with a large, multicentric cohort of hospitalised medical patients and provided evidence for the clinical utility of the IMPROVE BRS in Chinese patients. The main risk factors for bleeding in our cohort of patients were active gastroduodenal cancer, bleeding before hospitalization, platelet count, hepatic failure, severe renal failure, ICU/CCU admission, and central venous catheter. IMPROVE BRS in conjunction with VTE RAMs could be used for selecting patients for VTE prophylaxis. In the future, prospective validation of IMPROVE BRS needs to be performed and integrated scoring systems for VTE and bleeding need to be developed and validated. The IMPROVE VTE scoring system could be integrated with the IMPROVE BRS, and a cumulative scoring system could be designed and validated to alleviate the risk of VTE in medical patients.

Future research could also focus on the applicability of machine learning tools to enhance the bleeding and VTE risk assessments.

Author contributions

Study concept and design: C.W. and Z.G.Z. Data acquisition: Z.G.Z., X.Y.Q., Y.K.S., R.H.X., W.M.L., Y.M.X., J.M.Q., Z.Z. and C.W. Drafting of the manuscript: Z.G.Z., Z.Z. and C.W. Statistical analysis and interpretation: Z.G.Z., Z.Z. and C.W. All authors provided final approval of the version to be published.

Data sharing statement

Qualified researchers may request access to patient-level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: <https://www.clinicalstudydatarequest.com/>.

Notation of prior abstract publication/presentation

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Research in context

Evidence before this study

Hospitalization is a common risk factor for venous thromboembolism. Although thromboprophylaxis is recommended, it is not commonly used due to fear of bleeding. Risk factor-based prediction models are available for predicting VTE in hospitalized patients. IMPROVE bleeding risk score predicts the risk of bleeding in hospitalized patients which has not been extensively validated. A PubMed search with the "IMPROVE bleeding risk score" since inception till 15th July 2020, retrieved only 2 hits wherein the IMPROVE bleeding risk score was validated in North American patients and patients with chronic liver disease.

Added value of this study

We performed an external validation of the IMPROVE bleeding risk score using data from the Dissolve-2 study that included hospitalized, Chinese patients. The results revealed better performance of the IMPROVE bleeding risk score in predicting clinically relevant bleeding events. The sensitivity, specificity, positive predictive value and negative predictive value were similar or better than the performance of IMPROVE bleeding risk score in the original IMPROVE cohort and in other population.

Implications of all the available evidence

IMPROVE bleeding risk score is a simple clinical prediction model that could be used in conjunction with VTE risk assessment models to select patients for VTE prophylaxis. It could be linked to machine learning-based approaches for robust application in clinical practice.

Declaration of Interests

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.lanwpc.2020.100054](https://doi.org/10.1016/j.lanwpc.2020.100054).

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