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Prediction of in-hospital bleeding in acutely ill medical patients: External validation of the IMPROVE bleeding risk score

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ABSTRACT

Introduction: Pharmacological thromboprophylaxis slightly increases bleeding risk. The only risk assessment model to predict bleeding in medical inpatients, the IMPROVE bleeding risk score, has never been validated using prospectively collected outcome data.

Methods: We validated the IMPROVE bleeding risk score in a prospective multicenter cohort of medical inpatients. Primary outcome was in-hospital clinically relevant bleeding (CRB) within 14 days of admission, a secondary outcome was major bleeding (MB). We classified patients according to the score in high or low bleeding risk. We assessed the score's predictive performance by calculating subhazard ratios (sHRs) adjusted for thromboprophylaxis use, positive and negative predictive values (PPV, NPV), and the area under the receiver operating characteristic curves (AUC).

Results: Of 1155 patients, 8 % were classified as high bleeding risk. CRB and MB within 14 days occurred in 0.94 % and 0.47 % of low-risk and in 5.6 % and 3.4 % of high-risk patients, respectively. Adjusted for thromboprophylaxis, classification in the high-risk group was associated with an increased risk of 14-day CRB (sHR 4.7, 95 % confidence interval [CI] 1.5–14.5) and MB (sHR 4.9, 95%CI 1.0–23.4). PPV was 5.6 % and 3.4 %, while NPV was 99.1 % and 99.5 % for CRB and MB, respectively. The AUC was 0.68 (95%CI 0.66–0.71) for CRB and 0.73 (95%CI 0.71–0.76) for MB.

Conclusion: The IMPROVE bleeding risk score showed moderate to good discriminatory power to predict bleeding in medical inpatients. The score may help identify patients at high risk of in-hospital bleeding, in whom careful assessment of the risk-benefit ratio of pharmacological thromboprophylaxis is warranted.

1. Introduction

Hospital acquired venous thromboembolism (VTE) is a known complication and one of the leading preventable causes of death in hospitalized patients [1,2]. Pharmacological thromboprophylaxis reduces the risk of VTE up to two-thirds, but leads to a slightly increased bleeding risk [3,4]. Therefore, guidelines recommend the use of pharmacological thromboprophylaxis only in patients at high VTE risk [5]. Despite the known benefits of VTE prophylaxis, previous studies suggest a suboptimal and often inappropriate use of pharmacological thromboprophylaxis, especially in acutely ill medical patients [6–8]. One of the reasons for the suboptimal clinical use of VTE prophylaxis is the fear of bleeding [9–11].

To help determine a patient's bleeding risk and assist in clinical decision-making, the IMPROVE bleeding risk score was developed to predict the short-term in-hospital bleeding risk at admission [9]. The

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score has been derived using data from 10,866 patients from the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE), a multinational, observational study. The score consists of 11 variables and classifies patients into two bleeding risk classes: high risk (≥7 points) and low risk (<7 points) [9]. In the derivation cohort, the risk of 14-day in-hospital major bleeding (MB) was 0.4 % in the low-risk group and 4.1 % in the high-risk group [9]. Three external validation studies showed moderate to good discriminatory power for predicting MB or clinically relevant bleeding (CRB) within 14 days after admission, with an area under the receiver operating characteristic (AUROC) curve ranging from 0.63 to 0.73 [12–14].

The external validation studies were retrospective analyses [12,14] or assessed bleeding events retrospectively based on administrative codes [13], potentially resulting in an underestimation of bleeding events and a lower specificity of the score compared to the derivation sample [12]. Moreover, generalizability of the results of these external validation studies to the European population may be limited, as they were conducted in the United States and in China. Thus, external validation of the IMPROVE bleeding risk score with prospective and accurate assessment of bleeding predictors and outcomes has not been performed yet, and whether the score may help to adequately assess the risk of bleeding in a European population of hospitalized medical patients remained to be evaluated.

Therefore, we externally validated the IMPROVE bleeding risk score using prospectively collected data from a Swiss multicenter cohort of acutely ill hospitalized medical patients.

2. Methods

2.1. Study design and population

We used data from the RIsk Stratification for hospital-acquired vEnous thromboembolism in medical patients (RISE) Study, a prospective multicenter cohort study assessing VTE risk in medically ill patients. We followed the recommendations of the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) initiative and the Prediction model Risk Of Bias ASessment Tool (PROBAST) when possible [15,16].

Study participants were recruited between June 2020 and January 2022 in three Swiss university hospitals. Inclusion criteria were age 18 years or older and admission for hospitalization for >24 h on an internal medicine ward due to acute medical illness. Exclusion criteria were the need for therapeutic anticoagulation (e.g., atrial fibrillation), life expectancy <30 days, insufficient proficiency of the German or French language, and prior enrollment in the study. For patients unable to give informed consent (e.g., due to mental illness or cognitive impairment), permission to participate in the study was obtained from a legally authorized representative. For the purpose of this analysis and similar to the IMPROVE bleeding risk score derivation study [9], we additionally excluded patients with major surgery or trauma in the last month, patients that presented with bleeding at admission or with missing information on bleeding prior to admission. Out of 1353 patients enrolled in the RISE cohort, we excluded 198 patients, of which some patients had multiple exclusion criteria. One patient withdrew consent and did not allow the use of data, the other patients were excluded due to major surgery ($n = 51$) or trauma ($n = 84$) in the last month or due to bleeding at admission ($n = 89$), leading to a study sample of 1155 patients (Fig. 1). The study was approved by the ethics committees of participating sites. The detailed methods of the RISE study have been published previously [17].

2.2. Baseline data collection

Trained study personnel prospectively collected data on baseline demographic characteristics of all enrolled patients, items of the IMPROVE bleeding risk score and selected VTE risk assessment models (i.e., the simplified and original Geneva score, Padua score and IMPROVE score), comorbidities, VTE and bleeding risk factors, laboratory findings (e.g., platelet count, hemoglobin, INR, creatinine), medications at admission with a potential antithrombotic effect, and treatments during hospital stay including data on pharmacological and mechanical thromboprophylaxis, start of therapeutic anticoagulation, and presence of a central venous catheter. Baseline data were collected within 72 h of admission from electronic medical records or at the patient's bedside.

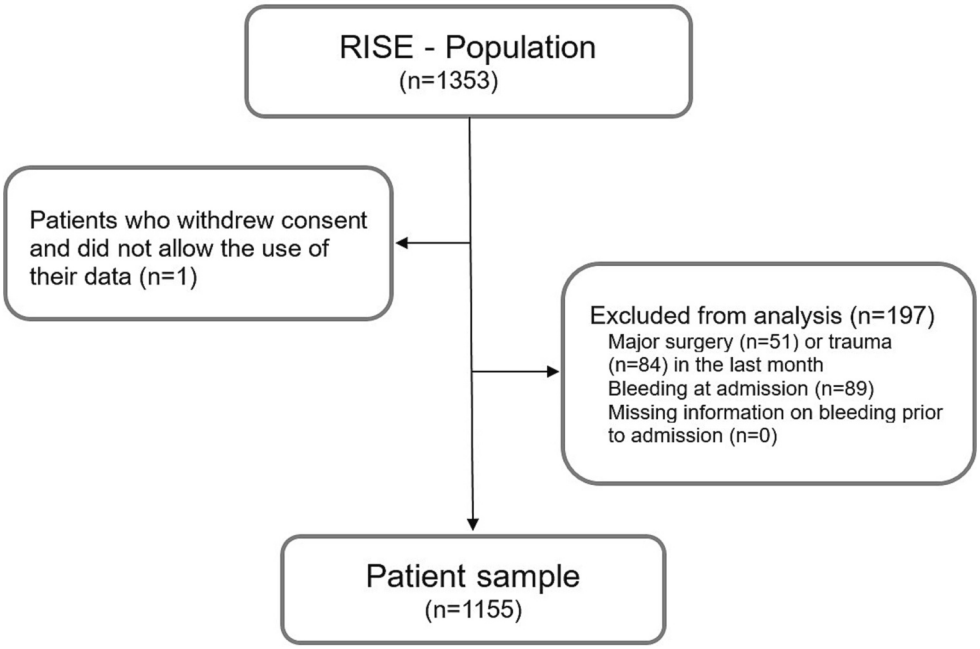

Fig. 1. Flow chart. Some of the excluded participants had multiple exclusion criteria.

2.3. IMPROVE bleeding risk score

We calculated the IMPROVE bleeding risk score using baseline variables for each patient (Supplementary Table 1). Patients with an IMPROVE bleeding risk score of <7 points were classified as low risk and those with a score of ≥7 points as high risk of bleeding. Whenever possible we used the same variable definition as the derivation study [9]. When the original variable definition was not clearly specified or differed from the available data in our database, we used proxy variables with the following definitions. We defined moderate and severe renal failure as a creatinine clearance of 30-59 ml/min and < 30 ml/min according to the Cockcroft-Gault formula, respectively. Current cancer was defined as metastatic cancer, or cancer treated with radiotherapy, chemotherapy, immunotherapy, or cancer surgery within the last 6 months (including myeloma or myelodysplastic syndrome). We used connective tissue diseases such as systemic lupus erythematosus (SLE), polymyositis, mixed connective tissue disease, polymyalgia rheumatica, and moderate to severe rheumatoid arthritis to define presence of rheumatic disease. For bleeding within 3 months before admission, we considered MB or clinically relevant non-major bleeding (CRNMB). We used a diagnosis of peptic ulcer disease (e.g., gastric ulcer or duodenal ulcer) to define active gastroduodenal ulcer.

2.4. Study outcomes

The primary outcome was 14-day in-hospital CRB, defined as combined MB or CRNMB during hospital stay within 14 days after admission. MB was defined according to the definition of the International Society of Thrombosis and Haemostasis as a fatal bleeding and/or a symptomatic bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome) and/or a bleeding with a reduction of hemoglobin ≥20 g/l, or leading to the transfusion ≥2 units of packed red blood cells [18]. Fatal bleeding referred to death following an intracranial hemorrhage or a bleeding episode leading to hemodynamic deterioration [19]. CRNMB was defined as overt bleeding that does not meet criteria for MB but is associated with a medical intervention, bleeding important enough to be documented in the medical chart for inpatients, or bleeding resulting in pain or impairment of activities of daily living [17]. Secondary outcomes were any in-hospital CRB from admission to discharge, in-hospital MB within 14 days of admission, and any in-hospital MB from admission to discharge.

Outcomes and information on survival status were collected during follow-up assessments, which took place as a face-to-face contact and by consultation of electronic medical records a day prior to or on the day of discharge. In case of an event, study personnel obtained medical records and other available information relating to the event (e.g., laboratory results). A committee of three clinical experts adjudicated all outcome events. Full consensus of the committee was needed for final classification.

2.5. Statistical analysis

Characteristics of patients are presented as n (%) for categorical, and medians with interquartile range (IQR) for continuous variables. To allow comparison with the IMPROVE bleeding risk derivation study, characteristics between patients with and without CRB within 14 days of admission were compared using chi-squared tests for categorical variables, and Wilcoxon rank sum tests for continuous variables, as appropriate. Similarly, we compared characteristics of patients with high versus low bleeding risk according to the IMPROVE bleeding risk score. Bleeding outcomes were presented by IMPROVE bleeding risk categories with percentage and its Wilson 95 % confidence interval (CI). The cumulative incidence of bleeding outcomes in low and high bleeding risk patients was analyzed using Kaplan-Meier estimator; survivor functions across the score's risk groups were compared by the log-rank test. A time to event analysis using a subdistribution hazard model by Fine and Gray was used to assess the prognostic performance of the IMPROVE bleeding risk score and its association with bleeding outcomes [20], with non-bleeding-related death representing the competing risk. Subhazard ratios (sHRs) with 95 % CIs were first calculated in unadjusted analyses, and then after adjustment for the use of pharmacological thromboprophylaxis as a time-varying variable. Subgroup analyses were performed according to receipt of pharmacological thromboprophylaxis. To determine the score's accuracy we assessed the sensitivity, specificity, the positive and negative predictive value, and the positive and negative likelihood ratio for high- versus low-risk patients to predict the outcomes. To assess the score's discriminatory power, the AUROC curve was calculated for all outcomes. We calculated the score's calibration using the Hosmer-Lemeshow statistic. In addition, we described observed bleeding incidences according to IMPROVE bleeding risk score points. For all analyses, patients who were started on full dose anticoagulation during follow-up (n = 35) were censored on the date of starting the corresponding treatment. To investigate the clinical usefulness of the score, the proportion of patients at high risk of VTE and bleeding was determined according to the IMPROVE VTE risk score and IMPROVE bleeding risk score, respectively, because this relates to the population in whom assessment of bleeding risk is particularly important given that thromboprophylaxis is indicated. Missing values were assumed to be normal. All analyses were done using Stata version 17.0 (Stata Corporation, College Station, TX, USA).

3. Results

3.1. Study sample

Among the 1155 patients included in this analysis, median age was 66 years (IQR 53–77 years), and 57 % were men. In-hospital CRB events within 14 days of admission were observed in 15 (1.3 %) patients. Compared to patients without CRB, those with CRB were older (median age 73 vs. 66 years) and more often male (80 % vs. 56 %). They were more likely to have active cancer, a central venous catheter, blood dyscrasia, Aspirin therapy, and a longer time of pharmacologic VTE prophylaxis during hospitalization (Table 1). They further tended to be at higher risk for both thrombosis and bleeding according to the IMPROVE VTE risk score (Supplementary Table 2) and IMPROVE bleeding risk score, respectively (Table 1). We did not observe significant differences in the prevalence of bleeding within the last 3 months, active gastroduodenal ulcer, rheumatic disease, low platelet count, hepatic failure, and renal dysfunction in patients with and without in-hospital CRB events within 14 days of admission (Table 1). Characteristics according to high and low bleeding risk are presented in Supplementary Table 3.

3.2. Bleeding risk according to the IMPROVE bleeding risk score

According to the IMPROVE bleeding risk score, 1066 (92 %) patients were classified as low and 89 (8 %) patients as high bleeding risk (Table 1). Thirty percent of the patients had a score of 2.5 points, of which 79 % were men aged 40 to 84 years (Supplementary Table 4). Overall, 15 (1.3 %) patients experienced in-hospital CRB within 14 days of admission, and any in-hospital CRB was observed in 36 (3.1 %) patients. In-hospital MB within 14 days of admission, and any in-hospital MB occurred in 8 (0.7 %) and 16 (1.4 %) patients, respectively. The incidence of a first bleeding event was higher in patients classified at high risk of bleeding (Table 2). The proportion of patients with in-hospital CRB and MB within 14 days was 0.9 % and 0.5 % in the low bleeding risk category and 5.6 % and 3.4 % in the high bleeding risk category, respectively. The proportion of patients with any in-hospital CRB and MB was 2.6 % and 1.2 % in the low-risk and 9.0 % and 3.4 % in the high-risk category, respectively (Table 2). The cumulative incidence of bleeding events was significantly higher in the high-risk

Table 1
Baseline characteristics according to in-hospital bleeding status.

Characteristics	Total	CRB within 14 days	No CRB within 14 days	p-value
	N (%) or median [IQR]			
Total	1155	15	1140	
Age, years	66 [53, 77]	73 [67, 81]	66 [53, 77]	0.034
Age, years				0.46
<40	140 (12)	0 (0)	140 (12)	
40–84	902 (78)	14 (93)	888 (78)	
≥85	113 (10)	1 (6.7)	112 (10)	
Male sex	653 (57)	12 (80)	641 (56)	0.07
BMI, kg/m^2	25 [22, 29]	25 [21, 28]	25 [22, 29]	0.64
Medical conditions				
Bleeding in the last 3 months	29 (2.5)	1 (6.7)	28 (2.5)	0.32
Active gastroduodenal ulcer	22 (1.9)	1 (6.7)	21 (1.8)	0.25
Active cancer[a]	223 (19)	7 (47)	216 (19)	0.014
Rheumatic disease	47 (4.1)	1 (6.7)	46 (4.0)	0.47
Central venous catheter	72 (6.2)	3 (20)	69 (6.1)	0.06
ICU/CCU stay[b]	0 (0)	0 (0)	0 (0)	
History of VTE	72 (6.2)	0 (0)	72 (6.3)	0.62
Thrombophilia/ hypercoagulable state	12 (1.0)	1 (6.7)	11 (1.0)	0.15
Lower extremity paralysis/ paresis	24 (2.1)	0 (0)	24 (2.1)	1.0
Immobilization ≥3 days	317 (27)	6 (40)	311 (27)	0.26
Immobilization ≥7 days	93 (8.1)	2 (13)	91 (8.0)	0.34
Charlson comorbidity index	4.0 [2.0, 6.0]	6.0 [3.0, 8.0]	4.0 [2.0, 6.0]	0.043
Blood dyscrasia[c]	22 (1.9)	2 (13)	20 (1.8)	0.031
Anemia	469 (41)	9 (60)	460 (40)	0.18
Cardiac or respiratory failure	276 (24)	1 (6.7)	275 (24)	0.14
Laboratory findings				
Platelets <50 × 10^9 cells/L	21 (1.8)	0 (0)	21 (1.8)	1.00
Hepatic failure (INR >1.5)	10 (0.9)	0 (0)	10 (0.9)	1.00
Renal function				0.12
GFR ≥60 ml/min/m^2	756 (65)	7 (47)	749 (66)	
GFR 30–59 ml/min/m^2	298 (26)	5 (33)	293 (26)	
GFR <30 ml/min/m^2	101 (8.7)	3 (20)	98 (8.6)	
Concomitant treatment				
Aspirin	303 (26)	8 (53)	295 (26)	0.032
other antiplatelet therapy	78 (6.8)	0 (0)	78 (6.8)	0.62
NSAID	71 (6.1)	0 (0)	71 (6.2)	1.00
Any VTE-prophylaxis[d]	766 (66)	11 (73)	755 (66)	0.78
Any pharmacological prophylaxis	745 (65)	11 (73)	734 (64)	0.59
LMWH	657 (57)	11 (76)	646 (57)	0.29
UFH	86 (7.4)	1 (6.7)	85 (7.5)	1.00
Other pharmacological prophylaxis	33 (2.9)	1 (6.7)	32 (2.8)	0.35
Mechanical prophylaxis[e]	62 (5.4)	1 (6.7)	61 (5.4)	0.57
Days during hospitalization with pharmacological prophylaxis, if any	4.5 [2.0, 8.0]	16 [4.0, 25]	4.0 [2.0, 8.0]	0.005
IMPROVE bleeding risk score				0.004
Low risk (<7 points)	1066 (92)	10 (67)	1056 (93)	
High risk (≥7 points)	89 (7.7)	5 (33)	84 (7.4)	
IMPROVE VTE risk score				0.08
Low risk (0–1 points)	813 (70)	7 (47)	806 (71)	
Greater risk (≥2 points)	342 (30)	8 (53)	334 (29)	

Abbreviations: BMI = body mass index, CCU = coronary care unit, CRB = clinically relevant bleeding, GFR = glomerular filtration rate, ICU = intensive care unit, INR = international normalized ratio, IQR = interquartile range, LMWH = low-molecular-weight heparin, NSAID = nonsteroidal anti-inflammatory drug, UFH = unfractionated heparin, VTE = venous thromboembolism.

Missing data (only in the following two variables): Platelets <50 × 109 cells/L: total 1 (0.1%), CRB within 14 days 0 (0%), no bleeding 1 (0.1%); Hepatic failure: total 99 (9%), CRB within 14 days 1 (7%), no bleeding 98 (9%).

[a] Active cancer was defined as metastatic cancer, or cancer treated with radiotherapy/chemotherapy/immunotherapy, or cancer surgery within last 6 months (also relates to myeloma or myelodysplastic syndrome).

[b] Only patients newly admitted for hospitalization >24 h on a general internal medicine ward were eligible, therefore patients previously hospitalized at the ICU or CCU were not eligible.

[c] Blood dyscrasia was defined as the presence of any bleeding disorder except for liver disease, e.g., hemophilia, von Willebrand disease, idiopathic thrombopenia.

[d] Any VTE prophylaxis during hospitalization.

[e] Mechanical prophylaxis was defined as lower extremity compression stockings/bandages, intermittent pneumatic compression devices.

Table 2
Outcomes in high- versus low-risk patients according to the IMPROVE bleeding risk score.

Outcomes	High risk		Low risk		All patients	
	n/N	% (95 % CI)*	n/N	% (95 % CI)*	n/N	% (95 % CI)*
In-hospital CRB within 14 days	5/89	5.6 (2.4–12.5)	10/1066	0.9 (0.5–1.7)	15/1155	1.3 (0.8–2.1)
In-hospital MB within 14 days	3/89	3.4 (1.2–9.5)	5/1066	0.5 (0.2–1.1)	8/1155	0.7 (0.4–1.4)
Any in-hospital CRB	8/89	9.0 (4.6–16.8)	28/1066	2.6 (1.8–3.8)	36/1155	3.1 (2.3–4.3)
Any in-hospital MB	3/89	3.4 (1.2–9.5)	13/1066	1.2 (0.7–2.1)	16/1155	1.4 (0.9–2.2)

Abbreviations: CI = confidence interval, CRB = clinically relevant bleeding, MB = major bleeding. High risk is defined as ≥7 points and low risk as <7 points on the IMPROVE bleeding risk score. * Wilson confidence interval.

compared to the low-risk group (Fig. 2).

Bleeding risk adjusted for the use of pharmacological thromboprophylaxis was significantly higher in patients in the high- compared to the low-risk category, with adjusted sHR of 4.7 (95 % CI 1.5–14.5, p = 0.007) and 4.9 (95 % CI 1.0–23.4, p = 0.045) for in-hospital CRB and MB within 14 days, and adjusted sHR of 1.7 (95 % CI 0.7–4.3, p = 0.24) and 1.4 (95 % CI 0.3–6.0, p = 0.67) for any in-hospital CRB and MB, respectively (Table 3). When stratified according to thromboprophylaxis use, the high-risk category remained associated with in-hospital CRB and MB within 14 days in the subgroup of patients with pharmacological thromboprophylaxis, but not in those without (Supplementary Table 5), although the estimates were imprecise due to the low number of events

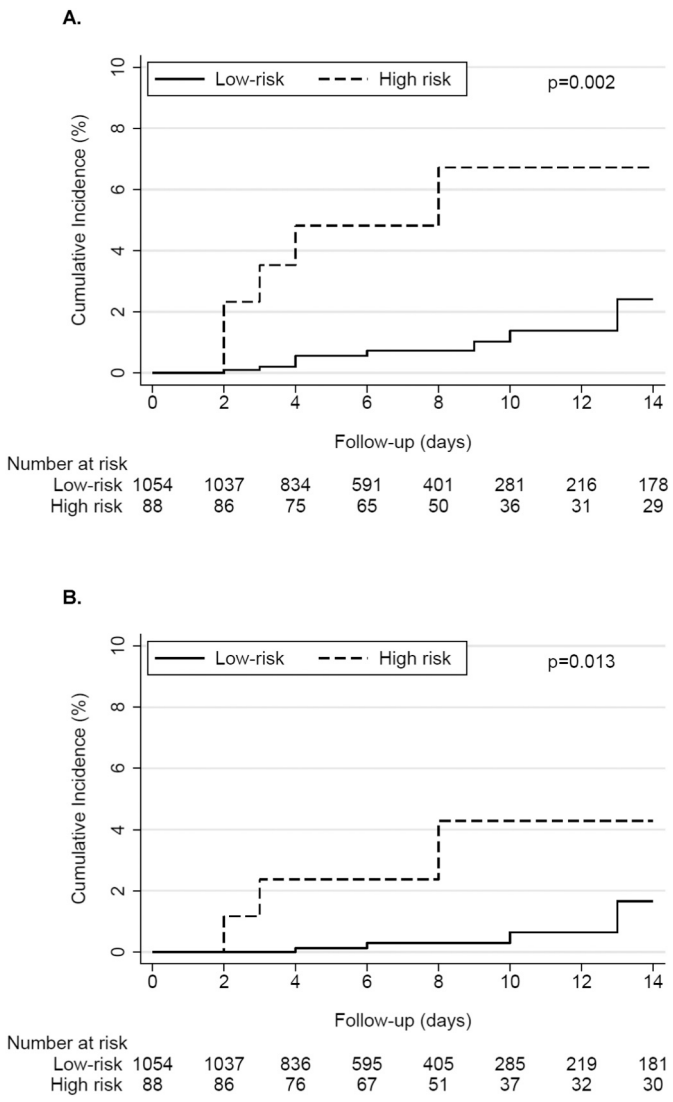

Fig. 2. Kaplan-Meier plot showing the cumulative incidence of bleeding in low- and high-risk patients according to the IMPROVE bleeding risk score.
Panel A. Cumulative incidence of in-hospital clinically relevant bleeding within 14 days of hospital admission. The cumulative incidence was 2.41 % (95 % confidence interval [CI] 1.15–5.02) for low-risk, 6.72 % (95 % CI 2.79–15.72) for high-risk patients ($p = 0.002$).
Panel B. Cumulative incidence of in-hospital major bleeding within 14 days of hospital admission. The cumulative incidence was 1.66 % (95 % confidence interval [CI] 0.63–4.37) for low-risk, 4.28 % (95 % CI 1.35–13.12) for high-risk patients ($p = 0.013$).

in the subgroups.

Median length of hospital stay was significantly longer in the high-risk group compared to the low-risk group, with 8 days versus 6 days. Median time to first in-hospital CRB or MB within 14 days tended to be shorter in the high-risk group (3 days) than in the low-risk group (5–10 days), although the difference was not statistically significant (Supplementary Table 6).

3.3. Accuracy, discrimination, and calibration

For prediction of in-hospital CRB within 14 days, the score showed a low sensitivity of 33.3 % but a high specificity of 92.6 % (Table 4). The positive predictive value was 5.6 %, while the negative predictive value was high with 99.1 %; the positive and negative likelihood ratios were 4.52 and 0.72, respectively. Results were similar for in-hospital MB events within 14 days, and for any in-hospital CRB or MB (Table 4), and for patients with and without pharmacological thromboprophylaxis (results not shown). Discriminative power was moderate to good with an AUROC curve ranging from 0.68 (95 % CI 0.66–0.71) for in-hospital CRB within 14 days to 0.76 (95 % CI 0.73–0.78) for any in-hospital MB (Table 5, Fig. 3). The discriminative power of the score was similar for patients receiving pharmacological thromboprophylaxis and those without (Supplementary Table 7). Goodness of fit of the IMPROVE bleeding risk score was generally adequate ($p > 0.05$; Table 5). The observed rate of in-hospital bleeding showed an increasing trend with increasing IMPROVE bleeding risk score (Supplementary Fig. 1).

Table 3
Association between a high IMPROVE bleeding risk score and bleeding events.

Outcomes	High risk	Low risk	Unadjusted SHR	p-value	Adjusted SHR*	p-value
	n events/N		(95 % CI)		(95 % CI)	
In-hospital CRB within 14 days	5/89	10/1066	4.8 (1.5–15.0)	0.007	4.7 (1.5–14.5)	0.007
In-hospital MB within 14 days	3/89	5/1066	5.1 (1.1–24.6)	0.040	4.9 (1.0–23.4)	0.045
Any in-hospital CRB	8/89	28/1066	1.7 (0.7–4.1)	0.27	1.7 (0.7–4.3)	0.24
Any in-hospital MB	3/89	13/1066	1.3 (0.3–5.5)	0.74	1.4 (0.3–6.0)	0.67

Abbreviations: CI = confidence interval, CRB = clinically relevant bleeding, MB = major bleeding, SHR = subhazard ratio.
Subhazard ratios are shown for high-risk (≥7 points) vs. low–risk (<7 points) groups based on the IMPROVE bleeding risk score.
* Adjusted for use of pharmacological thromboprophylaxis as a time-varying covariate.

3.4. Clinical application

To assess the clinical usefulness of the IMPROVE bleeding risk score, we investigated bleeding risk in high and low VTE risk groups. Overall, 342 (30 %) had a high VTE risk (≥2 points according IMPROVE VTE score) and thus qualified for VTE prophylaxis. Among those, 56 (16.4 %, or 4.8 % of the overall study population) had high bleeding risk (≥7 points based on the IMPROVE bleeding risk score; Supplementary Table 3).

4. Discussion

In this external validation study of the IMPROVE bleeding risk score using data of a prospective, multicenter Swiss cohort of acutely ill medical inpatients, bleeding risk was up to 5-times increased in patients in the high compared to those in the low bleeding risk group. The IMPROVE bleeding risk score showed a moderate to good discriminatory power and calibration to predict in-hospital bleeding.

Compared with the population of the derivation study, our patients were slightly younger, more likely to have active cancer, and none had a previous ICU or CCU stay, as only patients newly admitted to a general internal medicine ward were eligible for our study [9]. Compared to the three previously published external validation studies of the IMPROVE bleeding risk score, our population had fewer comorbidities and thus seemed healthier overall than the populations of the two validation studies conducted in the United States [12–14]. These differences can explain the fact that we observed the lowest incidence of bleeding events compared with the other studies: the incidence of in-hospital CRB within 14 days was less than half of the incidence observed in the derivation study (1.3 % vs 3.2 %), and also lower than in other validation studies

Table 4
Predictive accuracy of the IMPROVE bleeding risk score.

Outcomes	Sensitivity (%) (95 % CI)	Specificity (%)	PPV (%)	NPV (%)	Positive LHR	Negative LHR
In-hospital CRB within 14 days	33.3 (15.2–58.3)	92.6 (91.0–94.0)	5.6 (2.4–12.5)	99.1 (98.3–99.5)	4.52 (2.15–9.53)	0.72 (0.50–1.03)
In-hospital MB within 14 days	37.5 (13.7–69.4)	92.5 (90.8–93.9)	3.4 (1.2–9.4)	99.5 (98.9–99.8)	5.0 (2.0–12.52)	0.68 (0.39–1.16)
Any in-hospital CRB	22.2 (11.7–38.1)	92.8 (91.1–94.1)	9.0 (4.6–16.7)	97.4 (96.2–98.2)	3.07 (1.61–5.86)	0.84 (0.70–1.00)
Any in-hospital MB	18.8 (6.6–43.0)	92.4 (90.8–93.8)	3.4 (1.2–9.4)	98.8 (97.9–99.3)	2.48 (0.88–7.03)	0.88 (0.69–1.11)

Abbreviations: CI = confidence interval, CRB = clinically relevant bleeding, LHR = likelihood ratio, MB = major bleeding, NPV = negative predictive value, PPV = positive predictive value.

Table 5
IMPROVE bleeding risk score's discrimination and goodness of fit.

Outcomes	AUC (95 % CI)	Goodness of fit[a]
In-hospital CRB within 14 days	0.68 (0.66–0.71)	0.81
In-hospital MB within 14 days	0.73 (0.71–0.76)	0.50
Any in-hospital CRB	0.70 (0.68–0.73)	0.18
Any in-hospital MB	0.76 (0.73–0.78)	0.13

Abbreviations: AUC = area under the receiver operating characteristic curve, CI = confidence interval, CRB = clinically relevant bleeding, MB = major bleeding.
[a] Hosmer-Lemeshow goodness-of-fit test, p-value.

(2.2 %–2.6 %) [9,12–14]. The use of pharmacological thromboprophylaxis varied widely in these studies (8 %–82 %), but higher thromboprophylaxis use did not translate into a higher incidence of bleeding. The IMPROVE bleeding risk score classified a lower proportion of patients as high risk in our study (8 %), the derivation study, and the Chinese validation study (both 10 %), than in the two validation studies from the United States, in which the proportions were twice as high (around 20 %) [12–14].

Previous studies described a two- to five-fold higher incidence of bleeding within 14 days in patients at high (≥7 points) compared to those at low risk of bleeding (<7 points) based on the IMPROVE bleeding risk score [9,12–14]. In line with these findings, we observed at least a five-time increase in incidence of a first CRB and MB event within 14 days of admission in high-risk compared to low-risk patients. This five-fold increase in bleeding risk remained after adjustment for the use of pharmacological thromboprophylaxis, suggesting that differences in the use of thromboprophylaxis do not explain the strong association between the IMPROVE bleeding risk score categories and the risk of in-hospital bleeding within 14 days of hospital admission. Accuracy measures were similar for both types of bleeding outcomes (in-hospital CRB and MB) and follow-up durations (14 days and entire hospital stay), and matched those of previous studies, with high specificities and negative predictive values, and low sensitivities and positive predictive values [9,12,14]. Therefore, potential underestimation of bleeding events due to their retrospective assessment did not seem to have affected specificity of the score in the three previous external score validation studies. The likelihood ratios found in our study suggest little impact of the IMPROVE bleeding risk score on post-test probability [21,22]. The high negative predictive value indicates that patients classified in the low-risk group by the score are unlikely to bleed, but mostly reflects the low bleeding incidence overall. The high specificity, in turn, implies an increased risk of bleeding in patients classified as high-risk. In all four external validation studies the discriminatory performance of the IMPROVE bleeding risk score to predict bleeding within 14 days was moderate to good with AUROC curve varying between 0.63 and 0.73 [12–14]. In summary, the score may help clinicians to identify medical inpatients at increased risk of bleeding.

The IMPROVE bleeding risk score is the only score available to assess short-term bleeding risk in acutely ill medical inpatients. In clinical practice, the score is particularly helpful in identifying patients at high

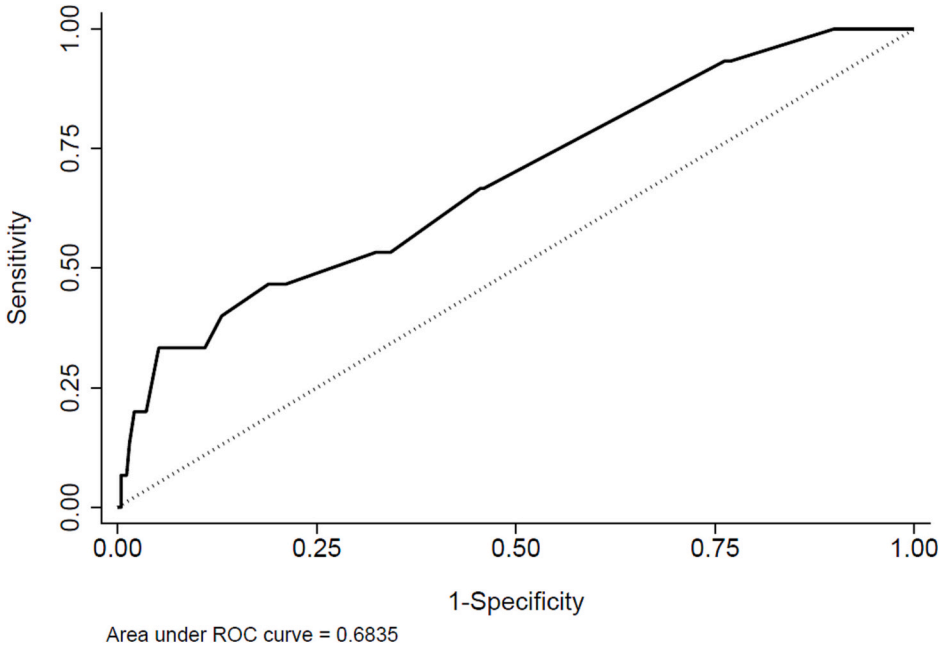

Fig. 3. Receiver operating characteristics (ROC) curves for diagnostic accuracy of the IMPROVE bleeding risk score to predict 14-day in-hospital clinically relevant bleeding.
The area under the ROC curve was 0.68 (95 % CI 0.66–0.71).

risk of bleeding among those with a concurrently high risk of VTE, since thromboprophylaxis is warranted in these patients to decrease their VTE risk [5,23]. This relates to as many as 16 % of patients at high VTE risk according to the IMPROVE VTE score in our study (i.e., 4.8 % of the entire study population). In these patients, the decision concerning the type of thromboprophylaxis should be based on a careful individualized integration of their VTE and bleeding risk [23]. In case of active bleeding or if the risk of MB exceeds the risk of VTE based on clinical judgement, mechanical thromboprophylaxis with graduated compression stockings or intermittent pneumatic compression should be used instead of pharmacological thromboprophylaxis according to the American College of Chest Physicians guidelines [5]. Whether this recommendations should be applied to all patients at high risk of VTE who have an IMPROVE bleeding risk score of $\geq$7 points is unclear. The more recent guidelines from the American Society of Hematology do not specifically comment on this, although they mention the IMPROVE bleeding risk score as a validated tool to assess bleeding risk [23]. If patients classified as high bleeding risk receive pharmacological thromboprophylaxis (as it was the case in 65 % of high bleeding risk patients in our study), modifiable bleeding risk factors should be addressed and these patients should be clinically monitored for bleeding events. Overall, whether the use of the IMPROVE bleeding risk score leads to an improvement in patient outcomes has not been shown to date. One before and after study investigated the clinical impact of the combined use of the Padua Prediction Score and the IMPROVE bleeding risk score, and found no effect on the incidence of major bleeding or VTE [24]. The study was conducted within a short period of time and included only few patients; whether the clinical results would be different in a larger study remains to be investigated.

The risk of bleeding is particularly high in patients with cancer, and cancer is included as a bleeding risk factor in the IMPROVE bleeding risk score. While cancer patients accounted for 19 % of the RISE cohort, almost half of all clinically relevant bleeding events within 14 days occurring in this population. The IMPROVE bleeding risk score was recently validated in patients with advanced gastrointestinal cancer with VTE and showed a significant association between a high score and major bleeding in these patients [25]. However, several bleeding risk models developed to predict bleeding on therapeutic anticoagulation showed only poor to moderate predictive performance when validated in cancer patients with VTE [26], and a separate bleeding risk score specifically for cancer patients without VTE may be needed.

To our knowledge, this is the first study assessing the accuracy and discriminatory performance of the IMPROVE bleeding risk score in a European population, and with prospectively collected predictor and outcome data. Thus, this study addresses previous calls for prospective validation of the IMPROVE bleeding risk score in medical inpatients [12,13]. However, some limitations apply. First, the number of outcome events was low, which may have affected accuracy and reduced the precision of performance measures. The imprecise estimates are reflected by large CIs, particularly for the sHRs. However, even when considering the lower bounds of the 95 % CIs, the risk of CRB in high-risk patients was substantial. Second, because we used proxy variables when the original variable definition was unclear or differed from the available data points in our database, the classification of patients into risk categories may have slightly differed from the derivation study. However, differences in variable definitions were only minimal and thus unlikely to influence the conclusions of our study. Third, we considered missing values to be absent or normal, which may have resulted in patients being classified at lower risk than they actually were. However, this was very unlikely, as we only had missing values in two variables, i.e., low platelet count (1 case, 0 %) and hepatic failure (99 cases, 9 %). Finally, because we lacked the intercept of the socre's original regression model for a calibration plot, we evaluated the calibration with the Hosmer-Lemeshow test, which may overestimate score calibration in smaller samples [16,27–29].

In conclusion, the IMPROVE bleeding risk score has moderate to good discriminatory performance to predict bleeding within 14 days of admission in acutely ill medical inpatients. Our findings confirm a similar performance of the score in a Swiss setting compared to the previously analyzed populations of the United States and China. Calculation of the IMPROVE bleeding risk score at admission may aid clinicians to identify patients at high risk of bleeding, which is of particular relevance in patients at high risk for VTE requiring thromboprophylaxis. In these patients, a careful risk-benefit assessment regarding the optimal type of thromboprophylaxis is warranted, and they should be monitored closely for modifiable bleeding risk factors and occurrence of bleeding events. In addition, the score reinforces in particular the importance of avoiding pharmacological thromboprophylaxis in patients at low risk of VTE and high risk of bleeding.

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Study concept and design: R. Villiger, C. Baumgartner, M. Méan.

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Revision of the manuscript: all authors. All authors approved the final manuscript.

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Declaration of competing interest

None declared.

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