Received: 19 March 2024 | Revised: 29 April 2024 | Accepted: 9 May 2024

https://doi.org/10.1016/j.rpth.2024.102441

ORIGINAL ARTICLE

Validation of the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) risk scores for venous thromboembolism and bleeding in an independent population

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Handling Editor: Vania M. Morelli

Abstract

Background: Multiple guidelines recommend assessment of bleeding and venous thromboembolism (VTE) risk in adult medical inpatients to inform prevention strategies. There is no agreed-upon method for VTE and bleeding risk assessment.

Objectives: To validate the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE and bleeding risk scores in an independent population.

Methods: In this retrospective study, we calculated the IMPROVE VTE and bleeding risk scores in medical inpatients admitted between 2010 and 2019 at the University of Vermont Medical Center (UVMMC). Patients were followed for in-hospital bleeding events while hospitalized and VTE events while hospitalized and for 3 months after discharge. We assessed calibration of the risk models by comparing the observed incidence of events in the UVMMC and IMPROVE populations across the published risk categories. We also assessed performance of the IMPROVE risk factors after refitting the models in the UVMMC population. Discrimination was assessed using the area under the receiver operating characteristic curve (AUC).

Results: VTE occurred in 270 (1.1%) of 23,873 admissions, with 92 (34%) occurring during admission, and bleeding occurred in 712 (4.7%) of 15,240 admissions. When the IMPROVE-VTE risk factors were refitted to the UVMMC data, the AUC was 0.64. When the IMPROVE bleeding risk factors were refitted to the UVMMC data, the AUC was 0.67. The IMPROVE-VTE score tended to overestimate risk at higher scores, and the IMPROVE bleeding score underestimated risk at lower scores and overestimated risk at higher scores.

Conclusion: While the refitted IMPROVE VTE and bleeding risk scores had reasonable model fit, the scores were poorly calibrated and did not reliably identify or differentiate patients at risk for VTE and bleeding. Different methods are needed for risk assessment of medical inpatients for VTE and bleeding risk.

KEYWORDS
adult, bleeding, inpatients, risk assessment, venous thrombosis

Essentials

- Clinicians use the IMPROVE risk scores to assess VTE and bleeding risk in medical inpatients.
- We assess the performance of the IMPROVE VTE and bleeding risk scores in an independent population.
- The IMPROVE risk scores show modest discrimination but poor accuracy in an independent population.
- New approaches are needed to assess thrombosis and bleeding risk in medical inpatients.

1 | INTRODUCTION

Venous thromboembolism (VTE) and bleeding are known complications of medical (nonsurgical) hospitalizations [1–3]. Traditionally, emphasis has been placed on prevention of VTE rather than bleeding, perhaps because there are known pharmacologic interventions to reduce VTE risk in hospitalized patients, including low-dose anticoagulation or pharmacologic VTE prophylaxis [4–8]. In randomized controlled trials, pharmacologic prophylaxis reduces VTE risk in medical patients at elevated risk for VTE, but the impact in real-world patients is less clear [9]. This has led professional societies to call for clinicians to use an evidence-based risk stratification system to determine whether a patient should receive pharmacologic VTE prophylaxis [10–13].

The International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) study has developed and validated risk assessment scores for hospital-associated VTE (VTE not present at admission occurring during hospitalization or within 3 months after discharge) and hospital-acquired bleeding (bleeding occurring during hospitalization and not present at admission) [14–18]. In theory, these scores can be used to identify patient populations who would benefit from pharmacologic VTE prophylaxis. In practice, however, risk assessment for VTE and bleeding rarely happens [19]. The reasons are likely complex, but the lack of robust validation efforts for many published scores likely plays a role [13,20–22].

We assessed the ability of the IMPROVE VTE [17] and bleeding [18] risk scores to predict VTE and bleeding risk in an independent, unselected medical inpatient population at the time of hospital admission. Through our retrospective analysis, we sought to determine whether there was evidence that application of these scores in general clinical practice would allow for prediction of hospital-associated VTE or hospital-acquired bleeding risk and, by extension, help determine the risk-benefit ratio of pharmacologic VTE prophylaxis in hospitalized medical patients.

2 | METHODS

2.1 | Cohort

The University of Vermont (UVM) Health Network is an integrated inpatient and outpatient health system in northwestern Vermont, United States. The health system has used Epic (Epic Systems) as an electronic health record for both inpatient and outpatient care since 2010. The UVM Medical Center (UVMMC), a tertiary care hospital in Burlington, Vermont, United States, is the only hospital in Chittenden County, Vermont, and also serves the surrounding counties. More than half the adults in the area (ie, roughly 80,000 adults) receive their primary care from UVM Health Network providers. During the period of the current study, there were no other imaging centers or urgent care centers within a 26-mile radius that were able to diagnose VTE. Given the unique healthcare geography of the region, we can capture both the inpatient and outpatient care of individuals who have UVM Health Network primary care providers [1,3]. Individuals aged ≥18 years residing in Chittenden County, Vermont, or surrounding counties who had a UVM Health Network primary care provider entered the cohort at the time of their first primary care visit on or after October 1, 2010, and remained in the cohort until change to a non-UVM Health Network primary care provider, death, or September 30, 2019, whichever occurred first. For bleeding outcomes, we required at least 1 year of outpatient observation time prior to the first hospitalization to allow for complete risk factor ascertainment. A full description of the cohort has been previously published [1].

2.2 | Definitions

Hospitalizations lasting for at least 1 midnight were captured from the electronic health record at UVMMC. Medical hospitalizations were defined as nonsurgical hospitalizations in which a patient was admitted to and discharged from general or family medicine, cardiology, hematology–oncology, or a medical or cardiac intensive care unit.

Supplementary Table S1 provides the definitions used in this study for elements of the IMPROVE bleeding and VTE risk scores. Briefly, risk factors associated with past medical history, such as prior VTE, were identified if they were documented in the problem list or past medical history before admission or within the first 12 hours of admission. Prior bleeding was defined as any hospital-acquired bleeding event or present-on-admission bleeding event associated with a hospital admission that was within 90 days prior to the current admission. To identify some IMPROVE risk factors, such as cancer, that require an active status at admission, we used discharge

diagnoses from hospital billing records that had a present-on-admission indicator equal to "yes." Laboratory values on the day of admission were defined using the first nonmissing value from that day.

Hospital-associated VTE included VTE events occurring either during hospitalization (hospital-acquired VTE) or within a 3-month period after discharge (postdischarge VTE). Hospital-acquired VTE events were defined using a previously developed and validated computable phenotype [23]. Briefly, VTE events were identified using relevant diagnosis codes and corresponding imaging procedure codes during the hospital admission. The timing of the event was determined from present-on-admission flags accompanying the VTE diagnosis codes, the time of the imaging study, and anticoagulant prescription records at the time of admission. Individuals free of VTE at admission were defined as having a hospital-acquired VTE if they were diagnosed with a VTE after the first day of admission. After discharge, individuals were followed for up to 90 days for VTE. Postdischarge hospital-associated VTE events included in-hospital readmissions with VTE present on admission or outpatient diagnosed and managed VTE. The latter events were defined as ≥2 outpatient VTE diagnosis codes separated by 7 to 180 days (the first code had to be within 90 days of discharge), which is similar to validated algorithms used in previous analyses of insurance claims [3,24–26]. These prior studies have demonstrated that the positive predictive value for this definition is >85%, with a negative predictive value >99% [23].

We identified hospital-acquired bleeding events occurring only during hospitalization, consistent with the outcomes examined in the IMPROVE studies [18], using a previously developed and validated computable phenotype [1]. Briefly, bleeding was identified using relevant diagnosis codes and corresponding imaging procedure codes in addition to hemoglobin laboratory results and blood transfusions that occurred during the hospitalization. The phenotype corresponds to clinically relevant bleeding, which is a composite of major bleeding and clinically relevant nonmajor bleeding based on the International Society on Thrombosis and Hemostasis definition [27–29]. Admissions with bleeding identified within the first day were defined as present-on-admission bleeding and were not included in the study. Hospital-acquired bleeding was defined as bleeding occurring after the first admission day and before discharge. Because postdischarge bleeding was not included in the development of the IMPROVE bleeding risk score [18], we did not assess this outcome in the UVMMC population. A prior study demonstrated that the positive predictive value for this definition of hospital-acquired bleeding is 77% (95% CI, 67.0%, 87.8%) with a sensitivity of 99% (95% CI, 98.0%, 100%) [1].

2.3 | Statistical analysis

Hospital admissions were the unit of analysis in this study. For the VTE analysis, we calculated the IMPROVE-VTE risk score for all hospitalizations without VTE at the time of admission. In the original IMPROVE publication, the risk score for hospital-associated VTE was developed using Cox proportional hazards regression [17]. The risk score for a given patient admission ranges from 0 to 8 points based on information from 4 risk factors, as shown in Table 1 [17]. In the present study, we applied the IMPROVE risk score and summarized categories of 0, 1, 2, 3, 4, and 5 to 8 risk score points, analogous to the presentation in the original IMPROVE publication. We calculated the observed 3-month cumulative incidence of VTE using the Kaplan–Meier method. In a secondary analysis, we assessed hospital-acquired and postdischarge VTE separately to determine the performance of the score for each event type. Finally, we used Cox proportional hazard regression to refit a risk model for hospital-associated VTE in the UVMMC cohort using the original IMPROVE risk factor variables and included use of anticoagulation (modeled as full, prophylactic, or none) on the day of or day after admission as previously described [30].

For the bleeding analysis, we calculated the IMPROVE bleeding risk score for all hospitalizations without bleeding at the time of admission. In the original IMPROVE publication, a risk score for hospital-acquired bleeding was developed using logistic regression [18]. The risk score for a given patient admission ranges from 0 to 30.5 points based on the presence of 11 risk factor categories, described in Figure 1. We also summarized low vs high risk of bleeding based on a risk score cut of <7 or ≥7, respectively, as described in the original study [18]. We then used logistic regression to refit the risk model for hospital-acquired bleeding in the UVMMC cohort using the original IMPROVE risk factor variables, including use of full, intermediate, or no anticoagulation on the day of or day after admission [30]. We also examined hospital-acquired bleeding events separately by anatomic site of bleeding (gastrointestinal, genitourinary, intracranial, pulmonary, nasal, and other sites).

Model calibration was assessed by comparing the observed vs predicted incidence of events in the UVMMC and IMPROVE populations across the published risk categories. Model discrimination was assessed by estimating the area under the receiver operating curve (AUC) with 95% CIs calculated by bootstrapping. In sensitivity analyses, we excluded admissions who received full or intermediate anticoagulation on the day of or the day after admission and adjusted for use of prophylactic anticoagulation.

The research reported here conforms to the tenets of the Declaration of Helsinki and was determined exempt by the UVM Institute Review Board based on exemption category 4 under the 2018 Common Rule in the United States [31].

3 | RESULTS

Figure 2 presents the derivation of the cohorts for the hospital-associated VTE and hospital-acquired bleeding analyses. Overall, there were 193,974 admissions, of which 62,468 were medical admissions. For the hospital-associated VTE population, 37,211 admissions were outside of the primary catchment area of UVMMC, 1346 admissions had VTE present on admission, and 38 admissions either were missing VTE risk factors or were after the first identified VTE for the patient, leaving 23,873 admissions at risk for hospital-associated VTE. For bleeding, 43,545 admissions had less than 1 year of outpatient observation time prior to their first hospitalization or resided

TABLE 1 Baseline characteristics of University of Vermont cohorts at risk of hospital-associated venous thromboembolism and hospital-acquired bleeding.

Admission characteristics	Cohort at risk of VTE (validation population), *n* (%)[a]	Cohort at risk of bleeding (validation population), *n* (%)[a]
No. of admissions	23,873	15,240
No. of events	270 (1.1)	712 (4.7)
Hospital-acquired	92 (34.1)	712 (100)
Postdischarge	178 (65.9)	
Age, y (mean ± SD)	67 ± 17	67 ± 16
Male	10,950 (45.9)	6849 (44.9)
Race		
Black	283 (1.2)	122 (0.8)
Hispanic	8 (0.1)	6 (0.04)
White	22,616 (94.7)	14,499 (95.1)
Other/unknown	966 (4.0)	613 (4.0)
Length of stay days, median (IQR)	3 (2, 5)	3 (2, 5)
Maximum anticoagulation level day of or day after admission		
Full/intermediate		4215 (27.7)
Prophylactic		7.065 (46.4)
None		3.960 (26.0)
IMPROVE-VTE risk score variables		
Previous VTE	1417 (5.9)	-
Known thrombophilia	399 (1.7)	-
Active cancer	6938 (29.1)	-
Age >60 y	16,160 (67.7)	-
IMPROVE bleeding risk score variables		
Moderate renal failure	-	3660 (24.0)
Age, 40-84 y	-	11,877 (77.9)
Current cancer	-	4382 (28.7)
Rheumatic disease		1462 (9.6)
Central venous catheter	-	930 (6.1)
Intensive care unit admission	-	942 (6.2)
Severe renal failure	-	1587 (10.4)
Hepatic failure	-	942 (6.2)
Age ≥85 y	-	2411 (15.8)
Platelet count $<50 \times 10^9$ cells/L	-	192 (1.3)
Bleeding in prior 3 mo	-	443 (2.9)
Active gastrointestinal ulcer	-	656 (4.3)

IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; VTE, venous thromboembolism.
[a]Unless otherwise specified.

outside of the primary catchment area of UVMMC. Bleeding at admission excluded a further 1857 admissions, and missing bleeding risk factors excluded a further 1826 admissions, leaving the final at-risk population of 15,240 admissions for hospital-acquired bleeding.

Table 1 presents the baseline characteristics of the cohorts at risk of hospital-associated VTE and hospital-acquired bleeding at UVMMC. In the former cohort, there were 270 (1.1%) hospital-associated VTE events among 23,873 admissions, of which 92 (34.1%) occurred during hospitalization, and 178 (65.9%) occurred in the 3 months after discharge. Twenty-eight (14%) of the VTE events were detected the day after admission. In the latter cohort, there were 712 hospital-acquired bleeding events among 15,240 admissions (4.7%). Overall demographics were similar in the 2 cohorts, with a mean age of 67 years, ~45% male, and ~95% White. The median (IQR) length of stay was 3 (2, 5) days.

The incidence of hospital-associated VTE was slightly lower in the original IMPROVE cohort compared with the UVMMC cohort (9.4 vs 11.3 events per 1000 admissions; Table 2) [17]. The prevalence of each IMPROVE-VTE risk score variable was higher in the UVMMC population compared with the original IMPROVE cohort, with the most notable difference being cancer (10.7% in the IMPROVE cohort vs 29.1% in the UVMMC cohort; Table 2). Comparing hazard ratios (HRs) from the Cox model in the original IMPROVE cohort and a refitted Cox model in the UVMMC cohort, respectively, previous VTE (HR, 5.0 [95% CI, 3.3, 7.8] and 3.9 [95% CI, 2.8, 5.3]) and cancer (HR, 2.0 [95% CI, 1.3, 2.1] and 2.3 [95% CI, 1.8, 3.0]) were associated with higher risk of hospital-associated VTE in both cohorts (Table 2). Known thrombophilia (HR, 5.2 [95% CI, 1.3, 21.5]) and age >60 years (HR, 1.8 [95% CI, 1.2, 2.7]) were associated with higher risk of hospital-associated VTE in the IMPROVE cohort; however, in the UVMMC cohort we did not observe an association between known thrombophilia and risk of VTE (HR, 0.8 [95% CI, 0.4, 1.7]), and age >60 years was associated with lower risk of VTE (HR, 0.8 [95% CI, 0.6, 0.9]; Table 2). The discriminative performance of the IMPROVE risk score was similar for the original IMPROVE cohort (AUC, 0.65) and in the UVMMC cohort (AUC, 0.64 for the refitted model).

Table 3 presents the percentage of admissions falling into 6 categories of the IMPROVE-VTE risk score, as well as the observed 3-month cumulative incidence of hospital-associated VTE in the IMPROVE and UVMMC cohorts [17]. Patient hospital admissions with

IMPROVE VTE Risk Score (Spyropoulos et al[17])	
Risk Factor	**Points**
Previous VTE	3
Known Thrombophilia	3
Cancer	1
Age >60 years	1
Suggested Categories	
Low Risk	0-1
High Risk	2+

IMPROVE Bleeding Risk Score (Decousus et al[18])	
Risk Factor	**Points**
Active gastroduodenal ulcer	4.5
Bleeding in the 3 months before admission	4
Platelet Count <50*10^9cells/L	4
Age: 85+	3.5
40-84	1.5
<40	0
Hepatic Failure (INR >1.5)	2.5
Renal Failure: GFR <30	2.5
GFR 30-59	1
GFR 60+	0
Intensive / Coronary Care Unit	2.5
Central venous catheter	2
Rheumatic disease	2
Current Cancer	2
Sex: Male	1
Female	0
Suggested Categories	
Low Risk	<7.0
High Risk	7.0+

FIGURE 1 International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) venous thromboembolism (VTE) and bleeding scores. GFR, glomerular filtration rate; INR, international normalized ratio.

lower risk scores (eg, a score of 0 or 1) were more common in the IMPROVE cohort (89% of admissions) than in the UVMMC cohort (71% of admissions), whereas admissions with the highest risk scores (a score of 5-8) were more common in the UVMMC cohort (3% of admission) than in the IMPROVE cohort (0.4% of admissions). In the IMPROVE cohort, the observed 3-month cumulative incidence of VTE increased in a graded fashion from 0.5% for admissions with a risk score of 0 up to 11% for admissions with a risk score of 5 to 8. In the UVMMC cohort, the pattern of observed VTE incidence across risk score categories was similar to that of IMPROVE, up to a score of 3, but then declined slightly in the 2 highest risk score categories. However, the sensitivity of the score (the ability to appropriately identify the population at risk) was low. If an IMPROVE score of 0 was designated as low risk, 75% of patients (and 83% of hospital-associated VTE) would be classified as high risk, whereas a cutoff for low risk of 0 or 1 would classify 71% of admissions as low risk and 49% of hospital-associated VTE as low risk (Table 3). Patterns of observed VTE incidence were similar across the range of risk score categories when examining hospital-acquired VTE and post-discharge VTE separately in the UVMMC cohort (Supplementary Table S2).

In the UVMMC cohort, there were 712 hospital-acquired bleeding events among 15,240 admissions, representing an incidence of 46.7 bleeding events per 1000 admissions, which is double the reported incidence in the IMPROVE cohort (21.2 events per 1000 admissions; Table 4) [14,18]. Admissions in the UVMMC cohort had a lower proportion of men than in the IMPROVE cohort (45% vs 49%), a greater prevalence of active cancer (29% vs 11%), and a greater proportion ≥85 years old (16% vs 11%), with other risk factors having a similar prevalence. Generally, the IMPROVE risk factors were more weakly associated with risk of hospital-acquired bleeding in the UVMMC cohort than in the original IMPROVE cohort. Notably, we did not observe an association of current cancer (odds ratio [OR], 1.0; 95% CI, 0.9, 1.2), intensive care unit admission (OR, 0.9; 95% CI, 0.6, 1.2), or low platelet count (OR, 0.8; 95% CI, 0.4, 1.3) with risk of hospital-acquired bleeding in the UVMMC cohort. The AUC of the refitted IMPROVE bleeding model was 0.67 in the UVMMC cohort, which is lower than the performance of the original model in the IMPROVE cohort (0.71).

Table 5 presents calibration of the IMPROVE bleeding score in the UVMMC cohort; the bleeding incidence was 4.4% for an IMPROVE bleeding risk score <7 vs 6.5% for a bleeding risk score ≥7 (vs 1.5% and 7.9% in the IMPROVE population, respectively) [18]. In both the IMPROVE and the UVMMC cohorts, >85% of the population was low risk (score <7). Of admissions with hospital-acquired bleeding, 64% in the original IMPROVE population and 80% in the UVMMC population scored as low risk. When the IMPROVE bleeding model was refitted in the UVMMC cohort separately by anatomic bleeding site, model discrimination was lowest for genitourinary (AUC, 0.65) and other unspecified bleeding sites (AUC, 0.64) and the highest for nasal (AUC, 0.76) and gastrointestinal (AUC, 0.79) bleeding (Table 6) [18]. When stratified by IMPROVE bleeding risk score categories, a low vs a high bleeding score was associated with less hospital-acquired bleeding for gastrointestinal (1.4% vs 2.6%) and genitourinary (0.7% vs 1.1%) bleeding, but there was little difference for intracranial (0.3% vs 0.4%), pulmonary (0.3% vs 0.4%), nasal (0.1% vs 0.3%), and other bleeding (1.6% vs 1.8%; Table 6). Excluding individuals on full or intermediate-dose anticoagulation on

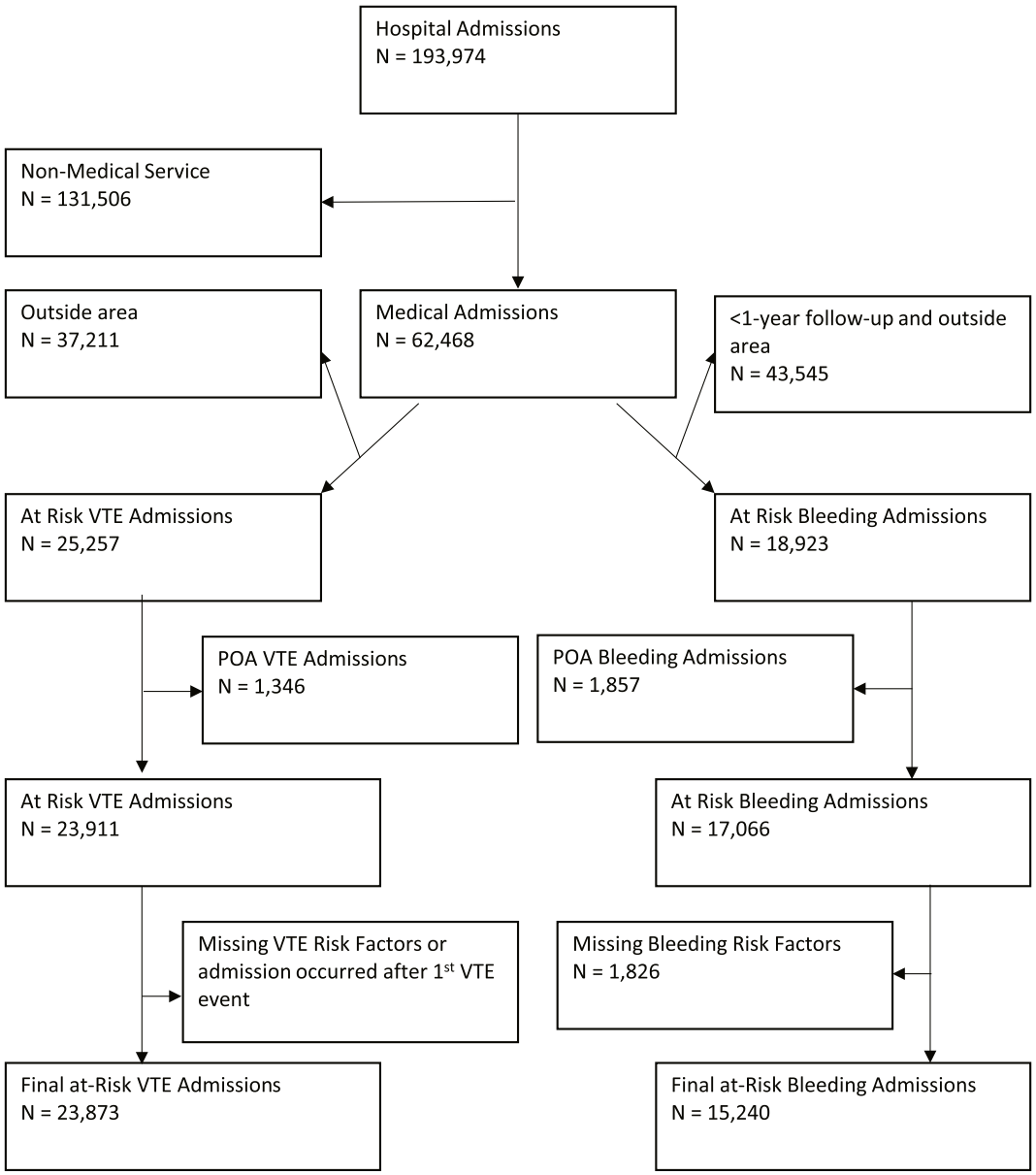

FIGURE 2 Population flow chart. POA, present on admission; VTE, venous thromboembolism.

the day of or the day after admission did not meaningfully affect the results (Supplementary Tables S3 and S4).

4 | DISCUSSION

In a cohort of medical inpatient admissions at UVMMC and outpatients at UVM Health Network, the IMPROVE hospital-associated VTE [17] and hospital-acquired bleeding risk scores [18] did not perform well in identifying people at risk for VTE or bleeding. Nearly half the hospital-associated VTE events occurred among patient admissions with a risk score of 0 or 1, and modeling of hospital-acquired and postdischarge VTE separately did not improve the performance. For hospital-acquired bleeding, ~80% of the bleeding events had a low-risk score. Stratifying by bleeding site revealed different performances for the score by bleeding site.

Prior efforts have been published validating both the IMPROVE VTE [16,32,33] and IMPROVE bleeding risk scores [14,15,34,35] with mixed results. For the IMPROVE-VTE score, the original study developed both a predictive (4-variable) and associative (7-variable) model for hospital-associated VTE [17]. A modified IMPROVE-VTE score incorporating D-dimer has also been published, but D-dimer was measured in a small minority of the UVMMC cohort and is not standard of care to assess at admission in unselected medical inpatients [36]. Current guidelines recommend assessing risk at admission for hospital-acquired VTE, and there is no recommendation for postdischarge prophylaxis—hence; we focused on the 4-variable predictive VTE risk score in the current analysis and did not assess the

TABLE 2 Performance of the International Medical Prevention Registry on Venous Thromboembolism risk factors in the original and University of Vermont cohorts.

Characteristic		IMPROVE cohort [17] (results from Spyropoulos et al. [17])		UVM cohort (validation population)	
Admissions (*N*)		15,156		23,873	
Hospital-associated VTE events (*N*)		143		270	
Hospital-associated VTE per 1000 admissions		9.4		11.3	
AUC (95% CI)		0.65		0.64 (0.60, 0.69)	
Risk Factors	**Prevalence, %**	**HR (95% CI)**	**Assigned points**	**Prevalence, %**	**HR (95% CI)**
Previous VTE	3.6	5.0 (3.3, 7.8)	3	5.9	3.9 (2.8, 5.3)
Known thrombophilia	0.1	5.2 (1.3, 21.5)	3	1.7	0.8 (0.4, 1.7)
Cancer	10.7	2.0 (1.3, 2.1)	1	29.1	2.3 (1.8, 3.0)
Age >60 y	63.6	1.8 (1.2, 2.7)	1	67.7	0.8 (0.6, 0.9)

AUC, area under the receiver operating characteristic curve; HR, hazard ratio; IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; UVM, University of Vermont; VTE, venous thromboembolism.

modified score as it would require a change in current clinical practice [13]. Cobben et al. [32] validated the IMPROVE-VTE predictive score within the Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis study. The reported C-statistic was similar to that reported in the original IMPROVE-VTE derivation cohort and here (~0.65), but the score had poor sensitivity, specificity, and positive and negative predictive values. Due to the methodology of the Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis study, the control population consisted only of 40 individuals, and the calibration of the score could not be assessed. Sensitivity, specificity, and positive and negative predictive values are not the best gauge of the IMPROVE hospital-acquired VTE's score efficacy in clinical practice, as the goal is to assess risk, not determine the presence or absence of disease [37]. The other efforts at validating the IMPROVE-VTE risk score used the associative risk score and are not directly relevant to the current findings [16,33]. In the UVMMC cohort, any IMPROVE-VTE score cutoff that would classify a majority of people who went on to develop hospital-associated VTE would also classify a majority of admissions as high risk, revealing poor sensitivity for the score to identify those at risk (Table 3).

For the IMPROVE bleeding risk score [14], at least 4 previous studies have validated the risk score [14,15,34,35]. In Supplementary Table S5, we present a summary of the previous efforts to validate the IMPROVE bleeding risk score. In contrast to the current study, the conclusion from the previous studies has been that the IMPROVE bleeding risk score was validated or had reasonable calibration and fit. Consistent with the current study, the discrimination was, in general,

TABLE 3 Observed 3-month cumulative incidence of hospital-associated venous thromboembolism using the International Medical Prevention Registry on Venous Thromboembolism risk score in original study and the University of Vermont cohort.

	IMPROVE cohort [17] (results from Spyropoulos et al. [17])			UVM cohort (validation population)		
		% (*N*) of admissions with risk score			% (*N*) of admissions with risk score	
Risk score	3-mo cumulative incidence, %	Overall *N* = 15,156	With VTE *N* = 143	3-mo cumulative incidence, % (95% CI)	Overall *N* = 23,873	With VTE *N* = 270
0	0.5	33 (4981)	17 (NR)	0.8 (0.6, 1.1)	25 (6070)	17 (45)
1	1.0	56 (8441)	50 (NR)	0.9 (0.7, 1.1)	46 (11,033)	32 (88)
2	2.1	8 (1166)	14 (NR)	1.9 (1.5, 2.3)	22 (5114)	30 (80)
3	4.0	1 (127)	3 (NR)	5.5 (3.2, 8.7)	1 (298)	5 (15)
4	4.7	2 (376)	11 (NR)	3.7 (2.4, 5.3)	3 (732)	9 (24)
5-8	11	0.4 (65)	4 (NR)	3.2 (2.0, 4.9)	3 (626)	7 (18)

IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; NR, not reported; UVM, University of Vermont; VTE, venous thromboembolism.

TABLE 4 Performance of the International Medical Prevention Registry on Venous Thromboembolism bleeding risk model in the International Medical Prevention Registry on Venous Thromboembolism and University of Vermont cohorts.

Characteristic	IMPROVE cohort (Rosenberg et al. [14] and Decousus et al. [18])		UVM cohort (validation population)	
No. of admissions	10,866		15,240	
No. of HA-bleeding events	230		712	
HA-bleeding events per 1000 admissions	21.2		46.7	
AUC (95% CI)	0.71		0.67 (0.65, 0.69)	
Risk Factors	**Predictor prevalence, %**	**OR (95% CI)**	**Predictor prevalence, %**	**OR (95% CI)**
Moderate renal failure	25.7	1.4 (1.0, 1.9)	24.0	0.9 (0.8, 1.1)
Male	49.4	1.5 (1.1, 2.0)	44.9	1.1 (0.9, 1.2)
Age, 40-84 y	76.1	1.7 (0.9, 3.3)	77.9	1.4 (0.9, 2.0)
Current cancer	10.7	1.8 (1.2, 2.6)	28.8	1.0 (0.9, 1.2)
Central venous catheter	7.5	1.9 (1.2, 2.9)	6.1	0.8 (0.5, 1.1)
Intensive care unit	8.5	2.1 (1.4, 3.1)	5.7	0.9 (0.6, 1.2)
Severe renal failure	11.0	2.1 (1.4, 3.2)	10.4	1.2 (0.9, 1.5)
Hepatic failure	2.0	2.2 (1.1, 4.3)	6.2	1.4 (1.0, 1.8)
Age ≥85 y	10.8	3.0 (1.4, 6.2)	15.8	2.1 (1.4, 3.2)
Platelet count $<50 \times 10^9$ cells/L	1.7	3.4 (1.8, 6.2)	1.3	0.8 (0.4, 1.3)
Bleeding in 3 mo before admission	2.2	3.6 (2.2, 6.0)	2.9	3.3 (2.5, 4.4)
Active gastroduodenal ulcer	2.2	4.2 (2.2, 7.8)	4.3	1.1 (0.7, 1.5)

AUC, area under the receiver operating characteristic curve; HA, hospital-acquired; IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; OR, odds ratio; UVM, University of Vermont.

good, with AUCs ranging from 0.63 to 0.73 (similar to or higher than the original derivation cohort). Calibration was more troublesome, however. The incidence of bleeding in the low-risk group (IMPROVE score <7) ranged from 0.9% to 2.7% compared with 1.5% in the original study and 4.4% reported here. The incidence of bleeding in the high-risk population (IMPROVE score ≥7) ranged from 4.7% to 11%, with 7.9% reported in the original study and 6.6% reported here. In each validation effort, however, most people with bleeding were classified as low risk (ranging from 56% to 80%).

The current and prior findings likely represent loss of information when converting the risk model (where actual risk is predicted) to a score (where disparate groups of individuals are grouped together). For VTE, 2 different outcomes were combined into 1 (hospital-acquired VTE and postdischarge VTE). It is reasonable to hypothesize that events occurring in the hospital might change the risk of postdischarge VTE, and hence, the time to assess risk factors for postdischarge VTE would be at the time of discharge and not at admission. For bleeding, the risk score is performed differently by bleeding site, and different proportions of bleeding events in different validation efforts could affect validation. The IMPROVE study used actual length of hospital stay ≥3 days as an inclusion criterion as individuals were recruited retrospectively. The clinical utility of predictive bleeding and VTE risk models is a prospective estimation of risk at the time of admission. In the current study, we did not exclude individuals with less than a 3-day hospitalization as was done in the original IMPROVE study [17], as clinicians do not know the length of hospitalization at

TABLE 5 Observed hospital-acquired bleeding risk using the International Medical Prevention Registry on Venous Thromboembolism risk score in the International Medical Prevention Registry on Venous Thromboembolism and the University of Vermont cohorts.

	IMPROVE cohort (Decousus et al. [18])			UVM cohort (validation population)		
		Percentage of admissions with risk score			Percentage of admissions with risk score (95% CI)	
Risk score	Observed bleeding risk, %	Overall	With bleeding	Observed bleeding risk, % (95% CI)	Overall	With bleeding
<7	1.5	90.3	64	4.4 (3.9, 5.9)	85.7 (85.1, 86.2)	79.9 (77.0, 82.9)
≥7	7.9	9.7	36	6.5 (5.5, 7.6)	14.3 (13.8, 14.9)	20.1 (17.1, 23.0)

IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; UVM, University of Vermont.

TABLE 6 Performance of the International Medical Prevention Registry on Venous Thromboembolism bleeding risk score risk factors when refitted to University of Vermont data.

	No. of hospital-acquired bleeding events			No. of hospital-acquired bleeding events stratified by IMPROVE risk score, UVM cohort (validation population)	
Bleeding site	IMPROVE (Decousous et al. [18]), *n* (%)	UVM cohort (validation population), *n* (%)	AUC at UVM	<7 (*n* = 13,057), *n* (%)	≥7 (*n* = 2183), *n* (%)
Overall	230 (100)	712 (100)	0.67 (0.65, 0.69)	569 (4.4)	143 (6.6)
Gastrointestinal	64 (28)	240 (34)	0.79 (0.76, 0.82)	183 (1.4)	57 (2.6)
Genitourinary	22 (10)	109 (15)	0.65 (0.60, 0.70)	86 (0.7)	23 (1.1)
Intracranial	10 (4)	45 (6)	0.67 (0.58, 0.75)	36 (0.3)	9 (0.4)
Pulmonary	0 (0)	42 (6)	0.66 (0.56, 0.75)	33 (0.3)	9 (0.4)
Nasal	14 (6)	23 (3)	0.76 (0.66, 0.84)	17 (0.1)	6 (0.3)
Other	120 (52)	253 (36)	0.64 (0.61, 0.68)	214 (1.6)	39 (1.8)

AUC, area under the receiver operating characteristic curve; IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; UVM, University of Vermont.

the time of admission, and provider-predicted length of stay at admission is notoriously inaccurate, averaging 3 to 4 days shorter than the actual length of stay [38]. Despite including individuals with shorter lengths of stay, we did not observe a lower overall rate of hospital-acquired bleeding or hospital-associated VTE, suggesting these admissions are at risk for adverse outcomes.

The current study has strengths and weaknesses. Firstly, our population was in 1 geographic region and at 1 academic medical center. Given the geography of northwest Vermont, UVMMC has a mix of tertiary care referrals and routine hospitalizations, though requiring a UVM Health Network primary care provider may result in fewer tertiary care cases. While our exclusion of nonprimary care patients may limit the generalizability of the study, it does allow us to capture most events in the population as a high percentage of patients admitted to UVMMC also have a UVM Health Network primary care provider. Further, the UVMMC population had a high level of co-morbid conditions and lacked racial diversity. The lack of racial diversity would limit the applicability of the results had the scores validated, but lack of validation in this homogeneous population raises the concern that the risk scores may not perform as well in more diverse populations. The original IMPROVE study did not report a racial breakdown of the population to compare with the current study [17]. Overall, the population studied here is the population for which the IMPROVE VTE and bleeding risk scores were designed. A strength was using the predictive rather than the associative IMPROVE-VTE risk score, reflecting how the score would be employed in practice. Finally, we would miss fatal outpatient VTE events if they did not make it to the hospital.

In conclusion, the IMPROVE hospital-associated VTE and hospital-acquired bleeding scores would misclassify risk for the population studied here—adults admitted to nonsurgical services in an acute care hospital. While the fit of the models was similar to that reported in the original studies and prior validation efforts, the calibration of the scores was poor, and the clinical utility was limited by difficulty in identifying populations at risk. This may be due to the loss of information by converting a risk assessment model into a score or potentially by combining events with different risk factors to develop the scores (hospital-acquired and postdischarge VTE and bleeding at different anatomic sites). Future directions include developing and validating predictive risk assessment models with information known at admission and refining the outcomes assessed.

ACKNOWLEDGMENTS

The authors appreciate and acknowledge the support and expertise of Mr Michael Gianni, senior measurement analyst, and the Data Management Office at the University of Vermont Health Network. We appreciate the support and guidance of investigators from the Study Design and Molecular Epidemiology Core of the Vermont Center for Cardiovascular and Brain Health. Funding was provided by P20 GM135007 from the National Institute of General Medical Sciences of the National Institutes of Health.

FUNDING

This study was funded by grant R01-HL141290 (N.A.Z.) from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, United States of America. The sponsoring institution was not involved in the analytical approach or data review. The views presented here represent those of the authors and not necessarily of the National Institutes of Health. H.A.-S. is funded by the National Heart, Lung, and Blood Institute (1K23HL159313).

AUTHOR CONTRIBUTIONS

N.A.Z. obtained funding. K.S.W., A.D.S., and N.A.Z. drafted and revised the manuscript. K.S.W., A.D.S., and N.S.R. performed and directed statistical analysis. All authors provided critical scientific input and revised the manuscript.

RELATIONSHIP DISCLOSURE

The authors report no relevant conflicts of interest.

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SUPPLEMENTARY MATERIAL

The online version contains supplementary material available at https://doi.org/10.1016/j.rpth.2024.102441