Original Research

Comparative Performance of Bleeding Risk Scores in Critically Ill and Non-Critically Ill Patients Receiving Prophylactic Enoxaparin Admitted at a Tertiary Hospital: A Prospective Cohort Study

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DISCLOSURE: None

Abstract

BACKGROUND: Balancing the benefits of preventing venous thromboembolism (VTE) against the risks of bleeding is important for patients who need prophylactic anticoagulants. This study compared which of the bleeding scores (IMPROVE and HAS-BLED BRS scores) is better at predicting anticoagulant-related bleeding events in critically ill and non-critically ill patients at a tertiary hospital who received prophylactic enoxaparin.

METHODOLOGY: Sixty-nine (69) patients in the ICU and ward who received prophylactic enoxaparin were included in the study and followed until discharge. Demographic data, comorbidities and IMPROVE and HAS-BLED BRS scores were recorded, and bleeding events monitored.

RESULTS: During the study, 16% (11/69) of the study population experienced bleeding events, both major and minor. Patients with IMPROVE BRS ≥7 (high risk) were more likely to bleed than those with scores of <7 (low risk) (p<0.001). The average HAS-BLED BRS was 2.20 (±1.09). Patients with higher HASBLED BRS scores had a slightly higher rate of bleeding (bleeding event, 2.73 [±1.19] versus no bleeding event, 2.09 [±1.04]), but this difference was not statistically significant (p = 0.079). The IMPROVE BRS had a higher area under the curve (AUC) (0.96) than the HAS-BLED BRS (0.67) in predicting anticoagulant-related bleeding events.

CONCLUSION: In patients receiving prophylactic anticoagulants for VTE, the IMPROVE BRS was better at predicting major anticoagulant-related bleeding events than the HAS-BLED BRS, with higher sensitivity, specificity and accuracy. Both risk scoring systems are useful for assessing bleeding risk before starting pharmacologic VTE prophylaxis, but the IMPROVE BRS is more accurate.

KEYWORDS: Bleeding risk score, venous thromboembolism, prophylactic anticoagulant

ABBREVIATIONS: IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile International Normalized Ratio (INR), Elderly, Drugs or alcohol use; VTE, venous thromboembolism

INTRODUCTION

Venous thromboembolism (VTE) anticoagulation is the primary treatment and preventive measure for VTE. It reduces the risk of recurrent thrombosis, embolism and death, which is highest in the first three to six months after diagnosis.[1] Anticoagulants can also increase the risk of bleeding, so it is essential to assess this risk for each patient before deciding whether or not to prescribe them.[2]

The IMPROVE bleeding risk score has been validated in Western populations and recommended by the American College of Chest Physicians (CHEST) guideline, but there is limited evidence for its use in Asian populations, especially in Filipinos.[3] None of the existing scores has been validated locally.

This prospective cohort study compared which of the bleeding scores [IMPROVE BRS and Hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile International Normalized Ratio (INR), Elderly, Drugs or alcohol use (HAS-BLED) bleeding risk scores] was better in critically ill and non-critically ill patients who received a prophylactic dose of anticoagulant in critical care units and wards.

METHODOLOGY

Between March 16, 2022 and June 15, 2022, a prospective cohort study was conducted at a tertiary hospital. The study included adult patients (18+) admitted to COVID-19 and non-COVID critical care units and wards, who were at high risk for VTE. This time period coincided with the COVID-19 pandemic, which may have affected the results due to its influence on the patient population and hospital environment. All patients, including those with coronary artery disease (CAD) who had undergone revascularization, received a prophylactic dose of enoxaparin. The study was approved by an institutional review board and informed consent was obtained. The decision to administer VTE prophylaxis was made by the attending physicians, independent of the author.

The study excluded patients with a diagnosis of VTE, atrial fibrillation (AF), acute limb ischemia (ALI), valvular heart disease (VHD) or acute coronary syndrome (ACS) without revascularization, who needed a therapeutic dose of enoxaparin or were bleeding at admission.

The patients who met the inclusion criteria and had completed the tertiary hospital VTE thrombosis risk assessment form were provided with information and informed consent was obtained. The patient or their legally authorized representative (LAR) was asked for consent. Once consent was obtained, the patient's demographic characteristics, use of VTE prophylaxis and clinical report, ancillary procedures, laboratory reports and standard comorbidities were assessed. Medical records including electronic health records (MEDTRAK) and charts were reviewed to collect demographic data, laboratory results, diagnostic imaging results and clinical information. This data was used to calculate the IMPROVE and HAS-BLED bleeding risk scores. Patients were followed up during their admission and until discharge to monitor for bleeding events. The study conformed with institutional and other applicable protocols and guidelines.

This study required at least 49 patients to accurately diagnose any bleeding event using the IMPROVE bleeding risk score with an AUC of 0.73, a significance level of 5% and a desired half-width of the confidence interval of 12.5%.

Descriptive statistics was used to summarize the demographic and clinical characteristics of patients. Frequency and proportion was used for categorical variables, median and inter-quartile range for non-normally distributed continuous variables, and mean and SD for normally distributed continuous variables. Independent sample T-test, Mann-Whitney U and Fisher's exact/Chi-square test was used to determine the difference of mean, rank and frequency, respectively, between patients with and without anticoagulant-related bleeding events. Area under the receiver operating characteristics curve as well as its diagnostic parameters was determined in the diagnostic accuracy of different bleeding risk scores to accurately diagnose anticoagulant-related bleeding events. All statistical tests were two-tailed tests. Shapiro-Wilk was used to test the normality of continuous variables. Missing variables were neither replaced nor estimated. Null hypothesis was rejected at 0.05α-level of significance. STATA 13.1 was used for data analysis.

Result Tables

The demographic profile of patients is shown in Table 1. Among the 69 patients in the study, 11 (16%) had bleeding. The mean age of all patients was 67.4 years (± 14.05). Most patients (86%) were aged 40-84 years and 72% bleeding events occurred in this age group. More than half (52.2%) of the patients were females.

The mean basic metabolic index (BMI) was 25.7 kg/m^2 (±4.32). Fewer than 15% (9 patients) were obese. Thirty-five percent (24 patients) were smokers and 25 per cent (17 patients) were alcoholic beverage drinkers.

More bleeding occurred in patients with increased creatinine of 110 to 240 mol/L ($p = 0.019$), impaired renal function (decreased creatinine clearance) ($p = 0.043$), those admitted to the ICU/CCU ($p = 0.043$) and those with central venous catheters ($p<0.001$).

The three most common preexisting comorbidities were hypertension (55, 79.71%), diabetes mellitus (26, 37.68%) and CAD (18, 26.09%). Intubated and shock-laden patients were significantly more likely to experience bleeding events ($p = 0.002$ and $p = 0.019$, respectively). Additionally, more patients developed anticoagulant-related bleeding events ($p = 0.019$).

In table 2, the incidence of bleeding events among hospitalized patients is 16%. According to the International Society on Thrombosis and Haemostasis (ISTH):

In this study, major bleeding was defined as fatal bleeding, symptomatic bleeding in a critical area or organ, and/or bleeding that caused a hemoglobin level drop of 20 g/L or more, or that required a transfusion of at least 2 U of whole blood or red cells. Any reported bleeding that did not meet these criteria was classified as minor bleeding.

Table 1. Demographic, Clinical Profile and Outcome of Patients

	Anticoagulant-Related Bleeding Events			P-value
	Total (n=69)	**With (n=11, 16%)**	**Without (n=58, 84%)**	
	Frequency (%); Mean ± SD; Median (IQR)			
Age, years <40 years old 40 to 84 years old ≥85 years old	67.39 ± 14.05 3 (4.35) 59 (85.51) 7 (10.14)	72.27 ± 14.29 0 8 (72.73) 3 (27.27)	66.47 ± 13.94 3 (5.17) 51 (87.93) 4 (6.9)	0.211 0.136
Gender Male Female	 33 (47.83) 36 (52.17)	 6 (54.55) 5 (45.45)	 27 (46.55) 31 (53.45)	0.747
Unit COVID unit Non-COVID unit	 4 (5.8) 65 (94.2)	 2 (18.18) 9 (81.82)	 2 (3.45) 56 (96.55)	0.117
Weight, kg	66.36 ± 11.96	68.91 ± 10.56	65.88 ± 12.23	0.445
Height	160.75 ± 8.26	161.27 ± 7.82	160.65 ± 8.40	0.822
BMI	25.73 ± 4.32	26.68 ± 3.94	25.55 ± 4.40	0.431
Weight Category Normal Overweight Obese I Obese II	 32 (46.38) 27 (39.13) 9 (13.04) 1 (1.45)	 4 (36.36) 5 (45.45) 2 (18.18) 0	 28 (48.28) 22 (37.93) 7 (12.07) 1 (1.72)	0.772
Smoking history	24 (34.78)	3 (27.27)	21 (36.21)	0.736
Alcohol beverage drinker	17 (24.64)	2 (18.18)	15 (25.86)	0.719
Creatinine (mol/L)	110 (70 to 150)	140 (110 to 240)	110 (70 to 150)	**0.019**
Baseline creatinine clearance (mL/min)	46.6 (30 to 66)	33 (17 to 47)	54.5 (32 to 67)	**0.007**
Abnormal renal function	11 (15.94)	3 (27.27)	8 (13.79)	0.364
INR	1.03 (0.98 to 1.14)	1.08 (0.95 to 1.21)	1.03 (0.98 to 1.14)	0.750
Platelet count	260 (198 to 324)	243 (181 to 330)	263 (198 to 324)	0.611
Type of admission CCU/ICU Ward	 43 (62.32 26 (37.68)	 10 (90.91) 1 (9.09)	 33 (56.9) 25 (43.1)	**0.043**

(*Continued*)

Table 1. Demographic, Clinical Profile and Outcome of Patients (Continued)

	Anticoagulant-Related Bleeding Events			P-value
	Total (n=69)	**With (n=11, 16%)**	**Without (n=58, 84%)**	
	Frequency (%); Mean ± SD; Median (IQR)			
Central Venous Catheter	7 (10.14)	7 (63.64)	0	**<0.001**
Liver enzyme	28 (22 to 58)	48 (24 to 89)	28 (21 to 54)	0.139
Labile INR, Unstable/high INRs, time in therapeutic range <60%	2 (2.90)	0	2 (3.45)	1.000
Alcohol intake	11 (15.94)	3 (27.27)	8 (13.79)	0.364
Use of antiplatelet/NSAIDs	46 (66.67)	5 (45.45)	41 (70.69)	0.161
Bleeding disorder	0	0	0	-
Active gastric or duodenal ulcer	0	0	0	-
Prior bleeding within previous 90 days	0	0	0	-
Rheumatic disease	0	0	0	-
Active malignancy	0	0	0	-
Comorbid conditions				
Hypertension	55 (79.71)	10 (90.91)	45 (77.59)	0.440
Diabetes mellitus	26 (37.68)	4 (36.36)	22 (37.93)	1.000
CAD	18 (26.09)	2 (18.18)	16 (27.59)	0.715
Stroke history	16 (23.19)	3 (27.27)	13 (22.41)	0.708
CKD	12 (17.39)	4 (36.36)	8 (13.79)	0.090
COPD	3 (4.35)	0	3 (5.17)	1.000
Atrial fibrillation, intermittent	4 (5.8)	0	4 (6.9)	1.000
Complications				
Intubated	16 (23.19)	7 (63.64)	9 (15.52)	**0.002**
Shock	8 (11.59)	4 (36.36)	4 (6.9)	**0.019**
Prolonged hospital stay Yes No	 61 (88.41) 8 (11.59)	 11 (100) 0	 50 (86.21) 8 (13.79)	0.338
Disposition				
Mortality Expired Discharged	 8 (11.59) 61 (88.41)	 4 (36.36) 7 (63.64)	 4 (6.9) 54 (93.1)	**0.019**

covid- coronavirus disease; BMI- body mass index; INR- international normalized ratio; ICU- intensive care unit; CCU- coronary care unit; NSAID- nonsteroidal antiinflammatory drug; CAD- coronary artery disease; CKD- chronic kidney disease; COPD- chronic obstructive pulmonary disease

Results showed that 14.5% of patients experienced major bleeding, while 1% had minor bleeding. The overall incidence of bleeding (both major and minor) was 16% and one patient died as a result of major bleeding. Major bleeding events can be life-threatening and often require interventions such as blood transfusions, reversal of anticoagulation, or surgery. While less severe, minor bleeding events can still cause discomfort and may require dose adjustments or discontinuation of anticoagulation.

Table 3 shows that the mean IMPROVE risk score was significantly higher in patients with bleeding events (8.04 ± 1.01) compared to those without (4.55 ± 1.82), with a p-value of <0.001. While the HAS-BLED score was not statistically significant (p = 0.079).

Table 4 shows the diagnostic accuracy of the scores. The IMPROVE score has a higher accuracy (90.91%) than the HAS-BLED score (68.75%). The IMPROVE score also has higher sensitivity (100%) and specificity (89.09%) compared to HAS-BLED.

Table 2. In-hospital Incidence of Bleeding Events

	Frequency (%) Total (n=69)
Major bleeds	10 (14.49)
Minor bleeds	1 (1.45)
All bleeds (overall)	11 (16%)

Figure 1 shows the Area Under the ROC Curve (AUC). The IMPROVE risk score has an outstanding AUC of 0.9626, while the HAS-BLED risk score has an acceptable AUC of 0.6702. A higher AUC indicates better predictive ability.

The values for sensitivity, specificity and accuracy, along with the AUC from the ROC curve analysis suggest the use of Receiver Operating Characteristic (ROC) curve analysis to determine the optimal cut-off.

The IMPROVE risk score was significantly better at predicting major anticoagulant-related bleeding events (in Table 3) than the HAS-BLED risk score, as evidenced in Table 4 by higher accuracy (90.91% vs 68.75%), sensitivity (100% vs 81.25%), specificity (89.09% vs 53.13%) and in Figure 1 an AUC (0.9626 vs 0.6702).

DISCUSSION

Categorizing medical inpatients based on their bleeding and VTE risk helps clinicians to select patients for VTE prophylaxis and modify bleeding risks. The IMPROVE BRS, which was developed and validated for medical inpatients, is recommended by the CHEST guideline.[3] The HAS-BLED score which was developed for AF patients has been used in our institution to predict bleeding events. In our study, we found that IMPROVE BRS, with a cut-off of ≥7, was a better predictor of clinically relevant bleeding events than the HASBLED BRS ≥3.

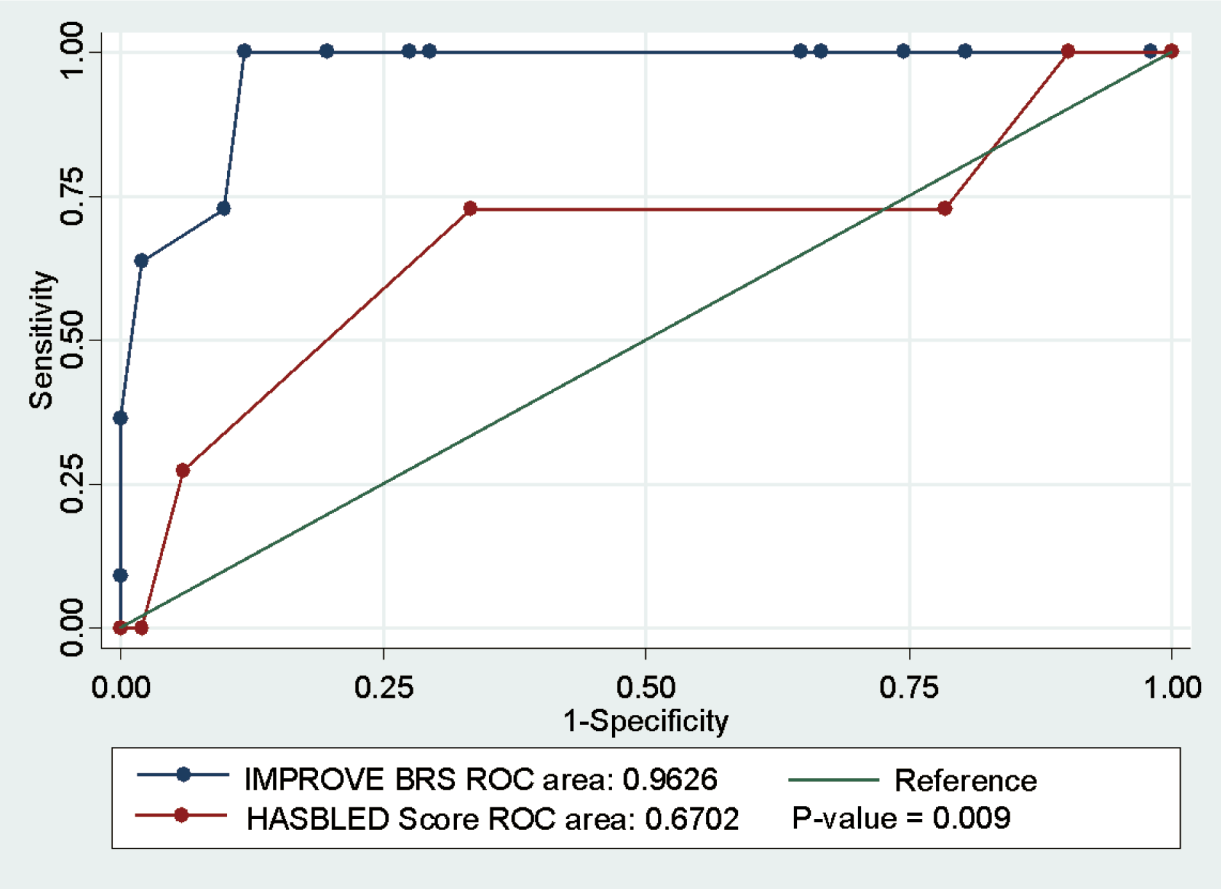
Our study differed from previous cohorts in several ways, even though we used similar selection criteria. Our cohort required admission to the ICU or CCU, which likely explains the higher

Table 3. IMPROVE and HAS-BLED Bleeding Risk Score and Anticoagulant-Related Bleeding Events

	Anticoagulant-Related Bleeding Events			**P-value**
	Total	**With**	**Without**	
	Frequency (%); Mean ± SD			
IMPROVE Bleeding Risk Score <7 not at increased risk of bleeding ≥7 increased risk of bleeding	5.14 ± 2.15 49 (74.24) 17 (25.76)	8.04 ± 1.01 0 11 (100)	4.55 ± 1.82 49 (89.09) 6(10.91)	**<0.001** **<0.001**
HAS-BLED Bleeding Risk Score <3 not at increased risk of bleeding ≥3 increased risk of bleeding	2.20 ± 1.09 39 (60.94) 25 (39.06)	2.73 ± 1.19 3 (27.27) 8 (72.73)	2.09 ± 1.04 36 (67.92) 17 (32.08)	0.079 **0.018**

Table 4. Optimal Cut-off Score of IMPROVE and HAS-BLED Bleeding Risk Score to Correctly Diagnose Anticoagulant-Related Bleeding Events

Bleeding risk score	**Cut-off**	**Accuracy**	**Sensitivity**	**Specificity**	**LR+**	**LR-**
IMPROVE	≥7	90.91%	100%	89.09%	9.1667	0.0000
HAS-BLED	≥3	68.75%	72.73%	67.92%	2.2674	0.4015



ROC- receiver operating characteristic;

Figure 1. Area Under the ROC Curve of Different Bleeding Risk Score to Accurately Diagnose Anticoagulant-Related Bleeding Events

percentage of patients with an IMPROVE BRS ≥7 and the higher overall bleeding rate in our study. This reinforces the rationale for our study as our inpatients are a diverse group. The corresponding major bleeding incident rates in our study were 14.5% vs 4.5% in Hostler, et al., done in American patients, while with IMPROVE BRS the incidence rates of major bleeding were lower,[5] although analysis of patients with VTE prophylaxis in the current study revealed no significant difference.

This prospective study compared the IMPROVE BRS with HAS-BLED BRS in critically ill and non-critically ill hospitalized patients receiving prophylactic enoxaparin. The goal was to show that using a risk tool to guide prophylaxis decisions can reduce bleeding and promote VTE prophylaxis. A full-scale evaluation score that integrates bleeding risk should be included in the existing instrument tools used to assess VTE risk and guide prophylaxis decisions.

In the Zhang, et al. study, among the factors that had higher odds of bleeding in the IMPROVE BRS include the glomerular filtration rate (GFR) [moderate renal failure, Hazard ratio (HR) 2.07; severe renal failure, HR 3.02][3] and ICU/CCU admission (HR 2.67) which was significantly associated with clinically relevant bleeding (CRB) just like in our study where more bleeding occurred in patients with increased creatinine levels and with ICU/CCU admission.

More intubated and shock-laden patients in our study experienced bleeding events and more patients who died developed anticoagulant-related bleeding events. The quick Sequential Organ Failure Assessment (qSOFA) score is a tool for assessing morbidity and mortality in patients with sepsis. It includes three criteria: respiratory rate ≥22 breaths/min (or on mechanical ventilation), altered mental status and systolic blood pressure <100 mmHg. A qSOFA score ≥2 suggests sepsis. Although qSOFA has been criticized for being insensitive for sepsis, it may be more specific for mortality and predicting organ dysfunction. In Taslidere, et al., the qSOFA score is for intensive care needs and can be used to estimate the severity of patients with upper gastrointestinal bleeding. A higher qSOFA score predicts in-hospital adverse events, such as mortality, re-bleeding, length of hospital stay, intensive care and the need for blood transfusion.[6] In our cohort, intubated and shock patients had higher qSOFA scores, more bleeding events and increased risk of mortality.

In a retrospective, single center study of Rosenberg, et al., the IMPROVE BRS, reported a lower sensitivity (33.3% vs

100%) and specificity (81.3% vs 89.09%) in comparison to our IMPROVE BRS cohort for predicting major bleeding events.[4] While in the Zhang, et al. study, the IMPROVE BRS still reported a lower sensitivity (44% vs 100%) but this time a higher specificity (90.8% vs 89.09%) in predicting CRB.[3] The IMPROVE BRS performed better in our cohort than in the original IMPROVE BRS cohort in terms of sensitivity and specificity, suggesting that it is applicable to medical inpatients. The IMPROVE BRS also performed better in predicting clinically relevant bleeding events.

For future studies, we recommend increasing the sample size and conducting a multi-centered study to obtain more robust findings. Since critically ill and non-critically ill patients may have different VTE and bleeding risks, it would also be interesting to compare the two groups. Additionally, we suggest investigating factors that can improve the implementation of VTE and BRS protocols, as well as applying BRS in non-critical settings for patients with high IMPROVE VTE risk scores.

This study had several limitations. First, the data may have not reliably captured all diagnoses and procedures for all patients. Additionally, the number of participants was relatively small and they were only followed until discharge.

The bleeding risk scores IMPROVE and HAS-BLED predict overall bleeding risk, not the severity. IMPROVE is better at predicting any bleeding, but not specifically major bleeds. Clinical judgment remains crucial in managing anticoagulation. Future research could develop bleeding risk scores that specifically predict major bleeding events.

CONCLUSION

In this small study of patients receiving anticoagulant for deep venous thrombosis prophylaxis, the IMPROVE BRS was a better predictor of major anticoagulant-related bleeding events than HAS-BLED BRS, with excellent sensitivity, specificity and accuracy. IMPROVE scores ≥7, classified as high risk, had significantly higher rates of bleeding events. Similarly, there were significantly more individuals in the low-risk category (HAS-BLED risk score <3) who did not develop any bleeding events than those in the high-risk category (HAS-BLED risk score ≥3). While HAS-BLED can be used to assess bleeding risk, IMPROVE performs better.

Bleeding risk scoring is important for preventing future bleeding by enabling clinicians to provide alternative preventive strategies and modifying the patient's bleeding risk until they can safely receive chemoprophylaxis. This highlights the need for regular and frequent evaluation of patients for both VTE and bleeding risk, especially among renal and critically ill patients.

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