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# Validation of the HAS-BLED Scale for the Assessment of Bleeding Risk in Patients on Anticoagulation Therapy with a Diagnosis of Venous Thromboembolic Disease

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## ABSTRACT

**Background:** Several models have been developed to assess bleeding risk in patients with venous thromboembolism, such as HAS-BLED, but their external validity has not been adequately assessed. **Objective**: The objective of the study was to evaluate the discriminative ability and calibration of the HAS-BLED scale for predicting 1-month bleeding risk in patient's anticoagulated for venous thromboembolism. **Materials and Methods:** External validation study of a prediction model based on a retrospective cohort of patients with venous thromboembolism treated between November 2019 and January 2022. Calibration of the HAS-BLED scale was evaluated using the Hosmer–Lemeshow test and the ratio of observed to expect events within each risk category. Discriminatory ability was assessed using the area under the curve (AUC) of a receiver operating characteristic curve. **Results:** We included 735 patients (median age 64 years, female sex 55.2%), pulmonary embolism was diagnosed in most patients (60.7%), and 4.9% presented bleeding events. Regarding calibration, the HAS-BLED scale systematically underestimates the risk both in the general population (ROE 3.76, $p < 0.001$) and in cancer patients (ROE 4.16). The Hosmer–Lemeshow test rejected the hypothesis of adequate calibration ($p < 0.001$). Discriminatory ability was limited both in the general population (AUC = 0.57, 95% confidence interval [CI]: 0.48-0.66) and in the subgroup with active cancer (AUC = 0.53, 95% CI: 0.36-0.69). **Conclusion:** The HAS-BLED scale in patients with venous thromboembolism underestimates the risk of bleeding at 1 month and has a low ability to discriminate high-risk patients. Cautious interpretation of the scale is recommended until additional evidence is available. (REV INVEST CLIN. 2024;76(4):199-204)

**Keywords:** Anticoagulation. Bleeding risk. Prediction models. Venous thromboembolism.

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## INTRODUCTION

Venous thromboembolic disease (VTE) represents a significant cause of morbidity and mortality, ranking as the third leading cause of vascular disease globally and the primary cause of preventable death in hospitals[1]. The annual incidence of deep vein thrombosis (DVT) is estimated to be up to 162/100,000 population, while that of pulmonary embolism (PE) is estimated to be up to 115/100,000 population[2].

The primary treatment for VTE is anticoagulation, which aims to prevent recurrence, embolization, and mortality. The risk of these complications is particularly elevated during the first 3-6 months following diagnosis[3-5]. Nevertheless, anticoagulant treatment confers an important bleeding risk of up to 3% per year with warfarin, which is lower with direct-acting oral anticoagulants (DOAC)[6,7]. The 1st month of treatment is associated with the highest risk of bleeding[8].

Given the importance of determining the bleeding risk of each patient to individualize treatment, various prediction models have been developed. One such model is the HAS-BLED scale, which was initially developed to assess bleeding risk in patients with atrial fibrillation[9]. This scale has recently been employed to assess the risk of bleeding in patients with VTE, demonstrating satisfactory predictive validity, provided that the presence of cancer is considered as an additional independent bleeding risk factor[10]. To date, the external validity of this scale has not been evaluated in other populations with VTE. This is particularly important given that patients treated with DOAC have been poorly represented in the studies performed to date.

The objective of this study is to validate the HAS-BLED scale for estimating 30-day bleeding risk in patients with VTE receiving anticoagulant treatment. This will include evaluating the scale's ability to discriminate between high- and low-risk patients and assessing the relationship between observed and predicted events in a cohort of patients managed in a referral hospital in Colombia.

## MATERIALS AND METHODS

### Study design and participants

This study is an external validation of a prognostic model based on a retrospective cohort. Patients enrolled in the institutional Anticoagulation Registry of Hospital Universitario San Ignacio were included in the study. Inclusion criteria were patients over 18 years of age, treated at Hospital Universitario San Ignacio in Bogotá, Colombia, between November 5, 2019, and January 27, 2022, with an indication for anticoagulation due to acute PE and/or DVT, using anticoagulation with warfarin, DOAC or low-molecular-weight heparin (LMWH), and with at least 1 month of follow-up. Patients who did not give verbal consent to participate by telephone, those who discontinued anticoagulation for medical reasons, and those who died before hospital discharge were excluded from the study. The Institutional Research Ethics Committee approved the study (approval number FM-CIE-0171-22). Study data were collected and managed using REDCap electronic data capture tools hosted at Hospital Universitario San Ignacio[11,12].

Sociodemographic data, comorbidities, diagnostic test reports, anticoagulation use, and pharmacologic choice were collected from the institutional anticoagulation registry, where information is systematically collected at the point of care using standardized instruments, and then periodic audits of the data collection process are performed to identify areas for improvement and ensure data quality. When missing information was identified, it was supplemented by a retrospective review of institutional electronic medical records. Bleeding outcomes were assessed by telephone follow-up 1 month after hospital discharge. Missing information on patients lost to follow-up was obtained by reviewing the institutional electronic medical record.

The HAS-BLED scale, which has been validated in VTE[10], was used to estimate bleeding risk. The data required to calculate the scale (age, uncontrolled arterial hypertension, renal disease, liver disease, previous cerebrovascular event, previous major bleeding, alcohol consumption, labile INR, or use of medications predisposing to bleeding) corresponded to the time of diagnosis of VTE. Major bleeding was defined as bleeding requiring hospitalization, hemoglobin drop

> 2 g/dL, transfusion requirement ≥ 2 units of red blood cells, critical site bleeding (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome), or fatal bleeding according to the International Society on Thrombosis and Hemostasis guidelines[13]. Non-major bleeding was defined as any bleeding that did not meet the previously described criteria.

## Statistical analysis

Absolute and relative frequencies were used to describe qualitative variables. Measures of central tendency and dispersion were calculated for quantitative variables, mean and standard deviation for variables with normal distribution, and median with interquartile range for variables with non-normal distribution. The Shapiro–Wilk test was used to assess the normality assumption.

The HAS-BLED scale was then validated by assessing its calibration and discriminative ability. Calibration was assessed by comparing the number of bleeding events observed at 1-month follow-up with the number of events predicted by each score. The expected proportions of bleeding events were obtained from the original study by Brown in the derivation sample for each HAS-BLED score[10]. Expected events were calculated by multiplying the expected proportions by the number of patients in each class. The hypothesis of adequate calibration was evaluated using the Hosmer–Lemeshow statistical test[14]. Discriminatory ability (ability of the prognostic model to discriminate between patients with different outcomes) was assessed with a receiver operating characteristic curve, considering an adequate area under the curve (AUC) > 0.7. Results were reported according to the recommendations of the PROBAST tool[15].

Statistical analysis was performed using STATA (Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

## RESULTS

Table 1 summarizes the demographic and clinical characteristics of the 735 patients included in the analysis. The median age was 64 years, with a higher prevalence female sex (55.2%). The main diagnosis was PE (60.7%), 85 patients (11.6%) had concomitant DVT and PE, and most cases of DVT were distal (74.3%). Active cancer was the most common comorbidity (28%). DOAC was the most commonly prescribed anticoagulants (54.1%), followed by LMWH (38%) and warfarin (7.6%). We identified 3.5% of patients at high risk for major bleeding (HAS-BLED ≥ 3).

Table 1. Sociodemographic characteristics of patients with VTE

| Variable | n = 735 (%) |
|---|---|
| Female sex, n (%) | 406 (55.2) |
| Age in years, median (IQR) | 64 (51-74) |
| Indication for anticoagulation n (%) | |
| DVT | 374 (50.9) |
| PE | 446 (60.7) |
| GFR mL/min n (%) | |
| < 30 | 16 (2.3) |
| 30–60 | 65 (9.3) |
| Diabetes mellitus n (%) | 97 (13.2) |
| Uncontrolled hypertension n (%) | 43 (5.9) |
| Liver disease n (%) | 11 (1.5) |
| Kidney disease * n (%) | 15 (2.0) |
| Previous stroke n (%) | 26 (3.5) |
| Previous major bleeding n (%) | 29 (4.0) |
| Alcohol consumption n (%) | 7 (1.0) |
| Medications, n (%) | |
| ASA | 97 (13.2) |
| P2Y12 inhibitors | 8 (1.1) |
| NSAID | 27 (3.7) |
| Active cancer n (%) | 206 (28.0) |
| Previous VTE n (%) | 6 (0.82) |
| Mortality n (%) | 44 (6.0) |

*Defined as creatinine > 2.26 mg/dL, renal replacement therapy, or renal transplantation according to HAS-BLED scale.
IQR: interquartile range; DVT: deep vein thrombosis; PE: pulmonary embolism; GFR: glomerular filtration rate; ASA: acetylsalicylic acid; NSAID: non-steroidal anti-inflammatory drug; VTE: venous thromboembolic disease.

In terms of outcomes of interest, there were 36 events classified as "any bleeding" (4.8%). Of these, 47.2% corresponded to major bleeding with the most common site being gastrointestinal (41.7%). Table 2 shows the calibration of the model for predicting total bleeding. Evaluation of the calibration of the HAS-BLED scale showed that the observed bleeding events were higher than expected with a ratio of observed to expected events was 3.76, suggesting that the scale underestimates the risk ($p < 0.01$). This result holds for each of the scores. The Hosmer–Lemeshow statistic suggests that the model is not calibrated (HL = 0.87 $p = 0.64$).

Table 2. Calibration of HAS-BLED prognostic model as predictor of 30-day total bleeding in patients with venous thromboembolic disease

| Score | n | % total | Expected events | Observed events | Expected ratio | Proportion observed | O/E ratio |
|---|---|---|---|---|---|---|---|
| 0 | 310 | 42.2 | 3.7 | 11 | 1.2 | 3.55 | 2.95 |
| 1 | 280 | 38.1 | 3.9 | 15 | 1.4 | 5.36 | 3.82 |
| 2 | 119 | 16.2 | 1.7 | 9 | 1.5 | 7.56 | 5.04 |
| 3 | 25 | 3.4 | 0.3 | 1 | 1.5 | 4 | 2.66 |
| 4 | 1 | 0.1 | 0.025 | 0 | 2.5 | 0 | NE |
| Total | 735 | 100 | 9.62 | 36 | 1.3 | 4.89 | 3.76 |

Hosmer–Lemeshow test = 0.87; p = 0.64. NE: not evaluable. Expected proportion of bleeding was obtained from the original study by Brown[10]. Expected events were calculated by multiplying the expected proportions by the number of patients in each class.

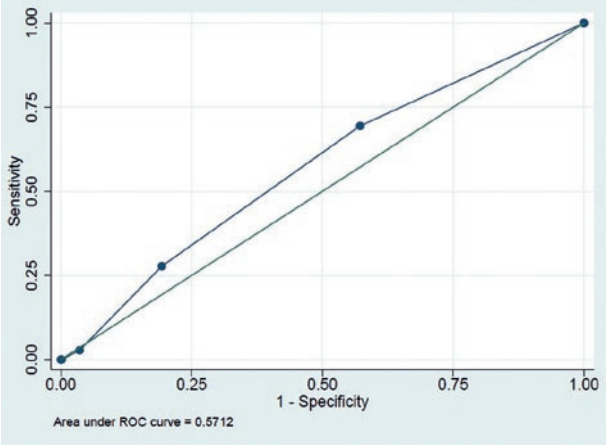
Table 3. Calibration of HAS-BLED prognostic model as predictor of 30-day total bleeding in patients with venous thromboembolic disease in cancer patients

| Score | n | % total | Expected events | Observed events | Expected ratio | Proportion observed | O/E ratio |
|---|---|---|---|---|---|---|---|
| 0 | 73 | 35.4 | 0.88 | 5 | 2.5 | 6.85 | 2.74 |
| 1 | 96 | 46.6 | 1.82 | 5 | 1.9 | 5.25 | 2.76 |
| 2 | 31 | 15.1 | 0.58 | 4 | 1.9 | 12.9 | 6.78 |
| 3 | 6 | 2.9 | 0.08 | 0 | 1.4 | 0 | NE |
| 4 | 0 | 0 | 0 | 0 | 2.9 | 0 | NE |
| Total | 206 | 100 | 3.36 | 14 | 1.6 | 6.7 | 4.18 |

Hosmer–Lemeshow test = 0.03 p = 1. NE: not evaluable. Expected proportion of bleeding in cancer patients was obtained from the original study by Brown[10]. Expected events were calculated by multiplying the expected proportions by the number of patients in each class.

In cancer patients, the proportion of patients with "any bleeding event" was 6.8%, of which 64.2% were major bleeding events. Again, the scale overestimated the risk in this population (ratio of observed/expected events: 4.18), demonstrating that the model is not calibrated (Hosmer-Lemeshow = 0.03, p = 1) (Table 3).

Figure 1. Discriminatory capacity of the HAS-BLED as predictor of total bleeding at 30 days in patients with venous thromboembolic disease.




The discriminatory ability of the scale was low, with an AUC of 0.57 (confidence interval [CI] 0.48-0.66) in the general population and even lower in the cancer subgroup (AUC 0.53; 95% CI 0.36-0.69) (Fig. 1).

## DISCUSSION

The aim of our study was to evaluate the predictive ability of the HAS-BLED scale for major bleeding after 1 month of anticoagulation therapy in patients with VTE. Our results suggest that the risk of bleeding is underestimated and that the model has a poor ability to discriminate high-risk patients.

Several validations have been performed in patients with atrial fibrillation. Among them, a study by Pisters et al. concluded that the HAS-BLED scale was able to predict the risk of major bleeding (AUC 0.72)[9]. In a further analysis, Apostolakis et al. found a moderate ability to predict the risk of major bleeding (AUC 0.67)[16,17]. However, the available evidence for VTE is limited and the results are similar to our study. Kooiman et al. evaluated the scale with an AUC of 0.55,

suggesting that it may not be applicable or may have limited ability to predict bleeding risk in this group[16,18].

Brown et al., chose to include cancer as an independent variable in the model because it was found to have the most robust association of all covariates[10]. However, only changes from 3 to 4 points showed significance. Our results suggest that HAS-BLED underestimates the risk of bleeding at any of the cutoff points, especially in patients classified as low risk, both in the general population, and in the subgroup of patients with active cancer.

The limitations of the scale are mainly related to the lack of inclusion of the cancer variable. It should be considered that cancer is a recognized risk factor for both, venous thromboembolism and bleeding, due to various factors inherent to the disease or its treatment. In addition, the criterion of INR (international normalized ratio) liability cannot be evaluated in the context of DOAC, which do not require regular INR monitoring due to their predictable and constant dosing and because they have fewer food and drug interactions than warfarin. Therefore, the use of this variable in patients treated with DOACs is clinically irrelevant and it could lead to an underestimation or overestimation of the true bleeding risk[16].

In addition, we found an AUC value of 0.57 (CI 0.48-0.66), demonstrating that the ability of the HAS-BLED score to discriminate patients at high risk of bleeding at 1 month is limited. This suggests the need to consider other variables to include in the model or to explore other predictive scales in this population. These results are consistent with different research groups that have evaluated the discriminative ability of the scale in different contexts. For example, Poli et al. evaluated 1078 patients over 80 years of age and obtained a C-statistic of 0.55[19]. Other studies conducted in populations treated with Vitamin K antagonists for VTE and atrial fibrillation reported C-statistic values of 0.57 and 0.67[20,21].

One of the strengths of the present study is the close follow-up and telephone contact with our patients, in contrast to the original study in which outcomes were identified by diagnosis code from the insurer's database[10]. This probably allowed us to detect more events and partially explains the large difference found between the number of expected and actual events.

However, it is important to mention the limitations of the study, among which the evaluation of outcomes by patient self-report could lead to misclassification bias, but the evaluation of medical records minimizes this risk, especially in cases of major bleeding. In addition, although we included a large sample, the number of events was relatively small, 36 for total bleeding and 17 for major bleeding, which limits the precision of our estimates. Prospective validation studies with larger numbers of patients are therefore needed to confirm our results.

In conclusion, the results described in the present study suggest that the HAS-BLED prediction model has poor discriminatory ability and underestimates the risk of bleeding at 1 month in patients with VTE, and this result is consistent in the subgroup of patients with cancer, suggesting that these models have limited utility in our population. Therefore, it may be necessary to recalibrate the scale or consider the evaluation of other risk stratification tools. In the meantime, clinical decisions should be made with caution, using clinical judgment on a case-by-case basis by the treating physician.

## REFERENCES


1. Jimenez-Hernandez S, Ruiz-Artacho P. Enfermedad Tromboembólica Venosa (ETEV) en Urgencias. Barcelona: Sociedad Española de Medicina de Urgencias y Emergencias; 2017.
2. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41:543-603.
3. Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ, et al. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. Chest. 2021;160:e545-608.
4. Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv. 2020;4: 4693-738.
5. Raja AS, Greenberg JO, Qaseem A, Denberg TD, Fitterman N, Schuur JD. Evaluation of patients with suspected acute pulmonary embolism: best practice advice from the clinical guidelines committee of the American college of physicians. Ann Intern Med. 2015;163:701-11.
6. Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of pulmonary embolism. Cochrane Database Syst Rev. 2015;2015: CD010957.
7. Gruenebaum D. How do oral direct thrombin inhibitors and oral factor Xa inhibitors compare with standard anticoagulation for the treatment of pulmonary embolism? Cochrane Clin Answers. 2017. Available from: http://doi.wiley.com/10.1002/cca.1439
8. Kakkos SK, Kirkilesis GI, Tsolakis IA. Editor's choice - efficacy and safety of the new oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban in the treatment and secondary prevention of venous thromboembolism: a systematic review and meta-analysis of Phase III trials. Eur J Vasc Endovasc Surg. 2014; 48:565-75.

9. Pisters R, Lane DA, Nieuwlaat R, De Vos CB, Crijns HJ, Lip GY, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the euro heart survey. Chest. 2010;138:1093-100.
10. Brown JD, Goodin AJ, Lip GY, Adams VR. Risk stratification for bleeding complications in patients with venous thromboembolism: application of the HAS-BLED bleeding score during the first 6 months of anticoagulant treatment. J Am Heart Assoc. 2018; 7:e007901.
11. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform. 2019; 95:103-208.
12. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42: 377-81.
13. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost. 2015;13:2119-26.
14. Kupper LL, Hosmer DW, Lemeshow S. Applied logistic regression. J Am Stat Assoc. 1990;85:901.
15. Moons KG, Wolff RF, Riley RD, Whiting PF, Westwood M, Collins GS, et al. PROBAST: a tool to assess risk of bias and applicability of prediction model studies: explanation and elaboration. Ann Intern Med. 2019;170:W1-33.
16. Klok FA, Huisman MV. How I assess and manage the risk of bleeding in patients treated for venous thromboembolism. Blood. 2020;135:724-34.
17. Klok FA, Kooiman J, Huisman MV, Konstantinides S, Lankeit M. Predicting anticoagulant-related bleeding in patients with venous thromboembolism: a clinically oriented review. Eur Respir J. 2015;45:201-10.
18. Kooiman J, van Hagen N, Iglesias Del Sol A, Planken EV, Lip GY, van der Meer FJ, et al. The HAS-bled score identifies patients with acute venous thromboembolism at high risk of major bleeding complications during the first six months of anticoagulant treatment. PLoS One. 2015;10:e0122520.
19. Poli D, Antonucci E, Testa S, Cosmi B, Palareti G, Ageno W, et al. The predictive ability of bleeding risk stratification models in very old patients on vitamin K antagonist treatment for venous thromboembolism: results of the prospective collaborative EPICA study. J Thromb Haemost. 2013;11:1053-8.
20. Burgess S, Crown N, Louzada ML, Dresser G, Kim RB, Lazo-Langner A. Clinical performance of bleeding risk scores for predicting major and clinically relevant non-major bleeding events in patients receiving warfarin. J Thromb Haemost. 2013;11:1647-54.
21. Donzé J, Rodondi N, Waeber G, Monney P, Cornuz J, Aujesky D. Scores to predict major bleeding risk during oral anticoagulation therapy: a prospective validation study. Am J Med. 2012;125: 1095-102.