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ORIGINAL PAPER

Machine learning to predict major bleeding during anticoagulation for venous thromboembolism: possibilities and limitations

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Summary

Predictive tools for major bleeding (MB) using machine learning (ML) might be advantageous over traditional methods. We used data from the Registro Informatizado de Enfermedad TromboEmbólica (RIETE) to develop ML algorithms to identify patients with venous thromboembolism (VTE) at increased risk of MB during the first 3 months of anticoagulation. A total of 55 baseline variables were used as predictors. New data prospectively collected from the RIETE were used for further validation. The RIETE and VTE-BLEED scores were used for comparisons. External validation was performed with the COMMAND-VTE database. Learning was carried out with data from 49 587 patients, of whom 873 (1.8%) had MB. The best performing ML method was XGBoost. In the prospective validation cohort the sensitivity, specificity, positive predictive value and F1 score were: 33.2%, 93%, 10%, and 15.4% respectively. F1 value for the RIETE and VTE-BLEED scores were 8.6% and 6.4% respectively. In the external validation cohort the metrics were 10.3%, 87.6%,

A full list of the RIETE investigators is given in the Appendix.

†Deceased.

3.5% and 5.2% respectively. In that cohort, the F1 value for the RIETE score was 17.3% and for the VTE-BLEED score 9.75%. The performance of the XGBoost algorithm was better than that from the RIETE and VTE-BLEED scores only in the prospective validation cohort, but not in the external validation cohort.

KEYWORDS
haemorrhage, machine learning, outcomes, pulmonary embolism, venous thrombosis

INTRODUCTION

Major bleeding (MB) is the most feared complication of anticoagulant therapy in patients with venous thromboembolism (VTE).[1–5] Its incidence within the first 3 months of therapy is ~2.3% and that of fatal bleeding 0.55%.[6,7] To prevent these complications, considerable efforts have been made during recent decades to identify patients at increased risk of bleeding, and a number of prognostic scores have been built.[8–13] However, their individual predictive value 'at patient level' was rather low, particularly if one focuses on positive predictive value (PPV).[14–17] In a recent study on 743 elderly patients, both the VTE-BLEED and Registro Informatizado de Enfermedad TromboEmbólica (RIETE) scores were adequate to identify 'low-risk' patients, but performed relatively poorly to identify the 'high-risk' subgroup.[18] When the aim of the score is to characterise a low-risk subgroup (i.e. for extended anticoagulation) the tool should select a subgroup of patients with few bleeding episodes and in whom the score has a high negative predictive value (NPV). However, when high-risk patients are targeted (i.e. reduce the intensity of anticoagulants early on, or for use of proton pump inhibitors, or consideration of a vena cava filter) the approach is different and metrics should focus on the combination of sensitivity and PPV. Thus, there is a need for better prognostic tools for decision making in clinical practice.

Supervised machine learning (ML) methods of artificial intelligence may learn from large databases and predict outcomes with better metrics than traditional linear models.[19] In a study using data from the RIETE, a neural network accurately predicted the risk of VTE recurrences after early discontinuation of anticoagulant therapy in patients with pulmonary embolism (PE).[20] In the present study, we used data from the RIETE to assess the prognostic ability of ML algorithms to identify patients at increased risk of MB during the first 3 months of anticoagulation and compared the best of them to that of the RIETE and VTE-BLEED scores for high-risk patients.

METHODS

Source of data

The RIETE is an ongoing international registry of patients with objectively confirmed VTE. The methodology of the registry has been described previously.[21] The RIETE enrolled consecutive patients with VTE from 184 hospitals in 27 countries. All patients were diagnosed using imaging tests (compression ultrasonography for suspected deep vein thrombosis [DVT]; helical computed tomography scan, ventilation/perfusion lung scintigraphy or conventional angiography for suspected PE), and followed-up for ≥3 months. Data were recorded on to a computer-based case report form at each participating hospital and submitted to a centralised co-ordinating centre through a secure website. Patients were excluded if they were participating in a clinical trial with a 'blinded' medication. All patients (or healthcare decision-makers) provided informed consent to their participation in the registry, in accordance with local Ethics Committee requirements. The central Institutional Review Board was approved at the Comité de Ética de Investigación Clínica, Hospital Germans Trias i Pujol de Badalona (project approval number, PI-17-053).

Design of the study

The study population for learning was composed of patients with VTE recruited in the registry from March 2010 to January 2020. The study population for prospective validation included patients with VTE recruited from January 2020 to December 2021. The primary outcome was the assessment of a ML algorithm to predict MB within the first 3 months of anticoagulation, evaluated by the confusion matrix metrics and the area under the receiver operating characteristics curve (AUC). In the RIETE, bleeding events were classified as 'major' if they were overt and required a transfusion of ≥2 units of blood, or were retroperitoneal, spinal or intracranial or when they were fatal. This definition preceded but closely resembles the definition by the International Society on Thrombosis and Haemostasis (ISTH).[22] Only the first episode of MB in a patient was evaluated. Fatal bleeding was defined as any death occurring within 7 days of a MB episode, in the absence of an alternative cause of death. If a patient died due to a second MB episode, this event would be considered in the fatal bleeding analysis.

Development of the model

Learning

Five supervised ML methods were used for training: Support Vector Machine,[23] k-Nearest Neighbours,[24] Neural

Network,[25] Decision Tree[26] and XGBoost.[27] They were implemented by using the statistics and ML MATLAB toolbox and deep learning MATLAB toolbox (MATLAB 2019a, The Mathworks Inc.). The main hyperparameters used for these methods are shown in Table S1. Overall, 70% of the patients were randomly sorted for training and the remaining 30% were used for testing and internal validation (Figure 1). In this process, patient data were not shared across training and testing subsets. A 10-fold cross validation in training sets was used to reduce overfitting. Bootstrap re-sampling (100 times) was used to assess the algorithm performance. The metrics released by the program are the mean values of those obtained in the boot-strapped test samples used in the internal validation.

A model was developed using 55 baseline variables that were considered, a priori, of clinical or prognostic value based on the medical literature. The list of variables appears in the Table S2. Missing values were handled according to consensus among co-authors, and prior to conducting statistical analyses. For some categorical variables (such as Crohn's disease 'Yes'/'No'; Dementia 'Yes'/'No') were assumed to be 'No'. In contrast, a specific category of 'unknown' was assigned for relevant unperformed tests, such as the right ventricular function or D-dimer assessment at baseline. Missing quantitative values were not imputed. The range of missing values in predictors ranged from 0% to 34%, with a mean of 0.82%. The highest proportion (34%) corresponds to D-dimer levels. The ML system was able to recognise missing values and worked properly without this information. Binary logistic regression models based on the 55 variables were developed to calculate the probability pre-test for the calibration study. In this assessment, 757 patients with missing values for logistic regression analysis were not included. Of note, only seven of the 757 patients had a MB event.

Validation

A prospective validation of the best performing ML algorithm was carried out with the new cohort of patients not involved in anyway in the learning process. For this assessment, the system operators handled the dataset and released the predictions without knowing the real outcomes and the verifications were carried out by other researchers. In this cohort, the algorithm sensitivity per site of bleeding was calculated.

The RIETE[10] and the VTE-BLEED[11] scores (Table 1) were calculated for all patients using available variables. To contrast the performance of these scores with ML methods, a prediction of MB was considered when patients were categorised as high risk using these scores (RIETE >4 points; VTE-BLEED ≥2 points) and the net re-classification improvement (NRI) was calculated.

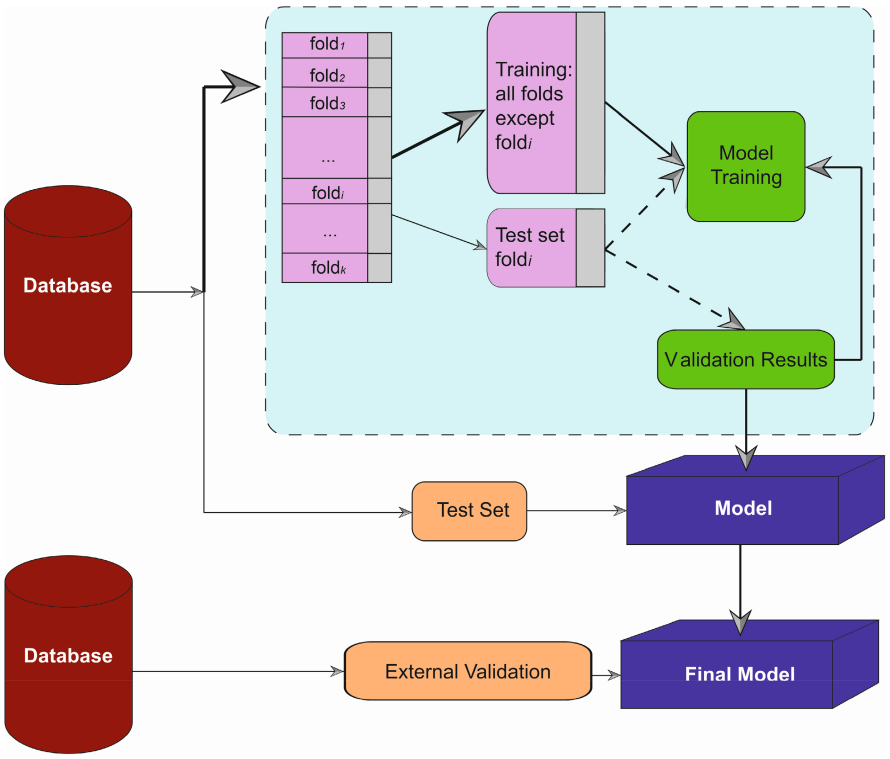

FIGURE 1 Training and validation scheme for machine learning methods. The database is split, and 70% of the data were used for training the method and 30% for testing. The dataset is randomly split up into '*k*' folds ('*k*-fold cross-validation'). One fold is used to test data and the rest are used to train the system. The model is scored on the test set (30%) and then the process is repeated 100 times (bootstrap re-sampling). The output of the resulting algorithm is binary, with two values indicating whether or not there are complications. After this training and internal validation, the model discrimination is tested in a different new subset of prospectively collected patients.

TABLE 1 The Registro Informatizado de Enfermedad TromboEmbólica (RIETE)[10] and venous thromboembolism (VTE)-BLEED[11] scores.

RIETE	Points	VTE-Bleed	Points
Age >75 years	1	Age ≥60 years	1.5
Renal dysfunction (creatinine >106 μmol/L)	1	Renal dysfunction (CrCl <60 mL/min)	1.5
Anaemia[a]	1.5	Anaemia[a]	1.5
History of cancer	1.5	Active cancer[b]	2
Recent major bleeding (<1 month)	2	History of bleeding[c]	1.5
Clinically overt pulmonary embolism	1	Male with uncontrolled hypertension[d]	1

Note: RIETE high-risk category: >4 points. VTE-BLEED high-risk category: ≥2 points.

[a]Anaemia: haemoglobin <130 g/L in men or <120 g/L in women.

[b]Active cancer: cancer diagnosed within the 6 months before diagnosis of venous thromboembolism (VTE) (excluding basal-cell or squamous-cell carcinoma of the skin), recently recurrent or progressive cancer or any cancer that required anti-cancer treatment within 6 months before the VTE was diagnosed.

[c]History of bleeding: including prior major or non-major clinically relevant bleeding event, rectal bleeding, frequent nose bleeding, or haematuria.

[d]Males with uncontrolled arterial hypertension were defined by values of systolic blood pressure ≥140 mmHg at baseline.

External validation was carried out with the COMMAND-VTE[28] cohort of patients with VTE recruited until December 2020.

Statistical analysis

We reported median with interquartile range for quantitative variables, and comparisons were performed using non-parametric tests. Categorical variables were reported as frequency counts and percentages, and the chi-squared test or the Fisher's exact test were used for comparisons. Discrimination was measured using the most familiar metrics: sensitivity, specificity, PPV, NPV, accuracy, F1 score (harmonic mean of sensitivity and PPV) and AUC. The bootstrapped cohort was used to calculate mean values of these parameters and 95% confidence intervals (CIs). Calibration was assessed graphically: patients were ordered according to the event probability determined by logistic regression and then divided into deciles (10 blocks of roughly the same number of patients and similar probability of bleeding). The higher the decile, the higher the probability of bleeding. The Statistical Package for the Social Sciences (SPSS®), version 20 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis and a two-sided $p < 0.01$ was considered as statistically significant.

RESULTS

Overall, 49 587 patients receiving anticoagulant therapy for VTE were recruited in the RIETE from March 2010 to January 2020, and 873 (1.76%) had a MB event within the first 3 months, of whom 125 had fatal bleeding. The most frequent sites of bleeding were: gastrointestinal, 277 (fatal, 34); haematoma, 220 (fatal, 15); intracranial, 124 (fatal, 46); retroperitoneal, 69 (fatal, 15); genitourinary, 76 (fatal, one); other sites, 107 (fatal, 14). Their clinical characteristics at baseline are shown in Table 2. Most of the variables included in the models were significantly associated with bleeding on univariable analysis. There were significant differences in long-term anticoagulation between the learning and validation cohorts regarding the use of vitamin K antagonists (53.7% vs. 24.6%, respectively) and direct oral anticoagulants (DOACs; 12.9% vs. 38.8%, respectively).

The discriminative ability of the five methods of ML is shown in Figure 2. The XGBoost had the best metrics achieving 91.2% sensitivity, 91% specificity, 90.4% PPV, 90.3% NPV and an AUC of 0.91. The relative contribution of the predictors in the model is shown in Figure S1.

Prospective validation was performed using data collected from 10 337 patients who had 227 MB episodes (fatal, 26): gastrointestinal, 73 (fatal, eight); haematoma, 47 (fatal, one); intracranial, 36 (fatal, 12); retroperitoneal, 17 (fatal, three); genitourinary, 24; other sites, 30 (fatal, two). XGBoost algorithm classified correctly 76 (8.7%) episodes of MB (fatal, seven) in 872 high-risk patients, and failed to predict 151 (1.6%; fatal 19, of which eight were intracranial) in 9465 low-risk patients (odds ratio [OR] 5.9, 95% CI 4.4–7.8). The odds for the end-points fatal bleeding, intracranial bleeding, and intracranial or fatal bleeding estimated by the XGBoost algorithm are shown in Table 3. Sensitivity was similar across all bleeding sites, with highest values for retroperitoneal bleeding (65%) and lowest (12%) for uterine bleeding (Table 4). The algorithm classified correctly 12 (of 36) intracranial bleeds. Overall, the sensitivity, specificity, PPV and NPV were 33.2%, 93.0%, 10.0% and 98.3% respectively (Figure 3A). These metrics varied depending on the probability of bleeding (pre-test) of the patient's subsets: Sensitivity and PPV increased from 11% and 7.7% in decile 2 (D2) to 40.8% and 14.7% respectively in D10 (Figure 3B and Table S3).

Calibration was assessed graphically by dividing patients into deciles in which the probability of bleeding increased progressively. A calibration plot is shown in Figure S2, with the predictions on the *y*-axis and the observed proportion of MB events on the *x*-axis. The correlation between observed (real) and predicted probability across deciles was high (R^2 0.87; slope 0.94).

In the same prospective validation cohort, the cut-point for patients at high risk of bleeding in the RIETE score (high threshold for bleeding that selected 614 patients)

TABLE 2 Clinical characteristics of the patients.

Characteristic	Learning		Validation	
	Major bleeding (*N* = 873)	No major bleeding (*N* = 48 714)	Major bleeding (*N* = 227)	No major bleeding (*N* = 10 110)
Age, years, median (Q1–Q3)	75 (65–83)**	68 (53–79)	70 (59–80)**	66 (53–77)
Male sex, *n* (%)	357 (41)**	23.871 (49)	117 (52)	5.317 (53)
Weight, kg, median (Q1–Q3)	72 (61–82)**	75 (65–85)	75 (65–85)	77 (67–88)
VTE diagnosis during hospitalisation, *n* (%)	321 (37)**	13.578 (28)	96 (43.4)**	3.190 (33)
Heart rate, beats/min, median (Q1–Q3)	90 (78–105)**	85 (74–100)	90 (77–102)	85 (75–100)
Systolic blood pressure, mmHg, median (Q1–Q3)	124 (110–141)**	130 (117–143)	126 (113–140)	130 (117–143)
NSAIDs treatment at baseline, *n* (%)	80 (9.2)**	3.302 (6.8)	15 (6.6)	497 (4.9)
Anti-platelet drugs at baseline, *n* (%)	211 (24)**	8029 (17)	36 (16)	1.443 (14)
Hospitalised due to VTE, *n* (%)	447 (51)	23.595 (48)	103 (45)	4.107 (41)
Recent (<30 days) major bleeding, *n* (%)	68 (7.8)**	973 (2.0)	21 (9.3)**	213 (2.1)
Prior myocardial infarction, *n* (%)	101 (12)**	3.218 (6.6)	15 (6.6)	536 (5.3)
Prior ischaemic stroke, *n* (%)	71 (8.1)	2965 (6.1)	18 (7.9)	548 (5.4)
Peripheral artery disease, *n* (%)	44 (5.0)	1.682 (3.5)	10 (4.4)	275 (2.7)
Arterial hypertension, *n* (%)	500 (57)**	22.320 (46)	126 (56)**	4.469 (44)
Oesophagitis[a], *n* (%)	13 (1.5)*	328 (0.7)	1 (0.4)	102 (1.0)
Hiatal hernia[a], *n* (%)	41 (4.7)**	1.371 (2.8)	9 (4.0)	370 (3.7)
Oesophageal varicosities[a], *n* (%)	7 (0.8)**	54 (0.1)	3 (1.3)**	12 (0.1)
Gastroduodenal ulcer[a], *n* (%)	22 (2.5)**	539 (1.1)	4 (1.8)	119 (1.2)
Gastric erosions[a], *n* (%)	13 (1.5)**	291 (0.6)	0 (0)	75 (0.7)
Ulcerative colitis[a], *n* (%)	2 (0.2)	204 (0.4)	1 (0.4)	50 (0.5)
Crohn's disease[a], *n* (%)	2 (0.2)	187 (0.4)	1 (0.4)	44 (0.4
Angiodysplasia[a], *n* (%)	6 (0.7)**	36 (0.1)	0 (0)	13 (0.1)
Liver cirrhosis (biopsy proven), *n* (%)	19 (2.2)**	200 (0.4)	6 (2.6)**	45 (0.4)
Chronic liver disease (other)[a], *n* (%)	10 (1.1)	532 (1.1)	0 (0)	91 (0.9)
Dementia, *n* (%)	62 (7.1)**	2.364 (4.9)	21 (9.3)**	490 (4.8)
Heavy alcohol intake, *n* (%)	12 (1.4)	568 (1.2)	2 (0.9)	113 (1.1)
Haemoptysis, *n* (%)	29 (3.3)	1.472 (3.0)	8 (3.5)	274 (2.7)
Abnormal mental status, *n* (%)	94 (11)**	2.087 (4.3)	24 (11)**	371 (3.7)
Right ventricular hypokinesis[d], *n* (%)	83 (9.5)**	2.477 (5.1)	21 (9.3)**	429 (4.2)
Proximal vs. distal DVT, *n* (%)	385 (44)**	24.314 (50)	67 (30)	4.109 (41)
Active cancer, *n* (%)	283 (33)**	9.150 (19)	53 (23)**	1.508 (15)
Recent surgery (<2 months), *n* (%)	120 (14)**	5.237 (11)	25 (11)	857 (8.5)
Recent immobilisation, *n* (%)	269 (31)**	10.290 (21)	109 (48)**	2.959 (29)
Prior DVT or PE, *n* (%)	110 (13)	7.283 (15)	22 (9.7)	1.276 (13)
Hormonal treatment, *n* (%)	34 (3.9)**	3.124 (6.4)	9 (4.0)	493 (4.9)

(Continues)

TABLE 2 (Continued)

Characteristic	Learning		Validation	
	Major bleeding (*N* = 873)	No major bleeding (*N* = 48 714)	Major bleeding (*N* = 227)	No major bleeding (*N* = 10 110)
Postpartum (last 2 months), *n* (%)	1 (0.1)	256 (0.5)	1 (0.4)	37 (0.4)
Haemoglobin levels, g/L, median (Q1–Q3)	119 (102–134)**	131 (117–144)	117 (102–135)**	133 (119–146)
Leucocyte count, $\times 10^9$/L, median (Q1–Q3)	9.7 (7.2–12.6)**	8.8 (6.9–11.2)	9.2 (7.1–12.7)**	8.7 (6.7–11.2)
Platelet count, $\times 10^9$/L, median (Q1–Q3)	211 (160–280)	219 (173–276)	231 (175–309)	224 (178–284)
Abnormal prothrombin time, *n* (%)	106 (12)**	3.190 (6.6)	34 (15)**	760 (7.5)
Increased D-dimer levels[b], *n* (%)	717 (82)	42.115 (87)	168 (74)	6.872 (68)
D-dimer levels at baseline, µg/mL, median (Q1–Q3)	3.53 (1.50–6.83)	3.23 (1.40–6.40)	5.49 (1.95–12.8)	3.85 (1.67–7.93)
Thrombophilia[c], *n* (%)	43 (4.9)	4.794 (9.8)	7 (3.1)	640 (6.3)
Creatinine levels, µmol/L), median (Q1–Q3)	88.42 (68.08–154.74)**	80.46 (64.55–106.1)	79.58 (61.89–112.29)**	77.81 (62.78–97.26)
Vena cava filter (pre-diagnosis), *n* (%)	5 (0.6)	202 (0.4)	0 (0)	36 (0.4)
Symptomatic PE, *n* (%)	585 (67)**	27.223 (56)	168 (74)**	6.460 (64)
Corticosteroids at baseline, *n* (%)	146 (17)**	4.378 (9.0)	42 (19)**	979 (9.7)
Syncope, *n* (%)	126 (14)**	3.907 (8.0)	20 (8.8)	657 (6.5)
Initial therapy with LMWH, *n* (%)	716 (82)**	42.014 (86)	181 (80)	8.204 (81)
Initial therapy with UFH, *n* (%)	75 (8.6)**	2.371 (4.9)	20 (8.8)**	443 (4.4)
Initial therapy with fondaparinux, *n* (%)	22 (2.5)	1.341 (2.8)	3 (1.3)	192(1.9)
Initial therapy with thrombolytics, *n* (%)	46 (5.3)**	698 (1.4)	5 (2.2)	108 (1.1)
Initial therapy with DOACs, *n* (%)	9 (1.0)**	1969 (4.0)	17 (7.5)	1.027 (10)
Initial therapy with AVK, *n* (%)	2 (0.2)	226 (0.5)	0 (0)	68 (0.7)
Initial therapy with other agents, *n* (%)	3 (0.3)	95 (0.2)	1 (0.4)	18 (0.2)

Abbreviations: DOACs, direct oral anticoagulants; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; NS, non-significant; NSAIDs, non-steroidal anti-inflammatory drugs; PE, pulmonary embolism; Proximal (including popliteal vein); UFH, unfractionated heparin; VKAs, vitamin K antagonists. Qualitative variables: number of cases (%); quantitative variables: median (Q1–Q3).

[a]"History of…' does not necessarily means active disease.

[b]Above the upper normal limit established by sites.

[c]In the learning cohort 11 063 patients were assessed for thrombophilia and in the validation cohort 1545.

[d]In the learning cohort 12 203 patients have right ventricular function data and in the validation cohort 2311.

*$p = 0.01$.; **$p < 0.01$.

yielded a 16.4% sensitivity, 94% specificity, 6% PPV and 98% NPV (Figure 3A). The VTE-BLEED score cut-point for patients at high risk of bleeding (low threshold for bleeding that selected 3813 patients) yielded a 58.2% sensitivity, 63.5% specificity, 3.6% PPV and 98.5% NPV (Figure 3A). The odds for the end-points MB, fatal bleeding, intracranial bleeding, and intracranial or fatal bleeding estimated by the RIETE and VTE-BLEED scores are shown in Table 3 and the sites of bleeding in Table 4. The NRI of the XGBoost algorithm for MB was 15.5% ($p < 0.001$) compared to the RIETE score and 4.8% ($p = 0.28$) compared to the VTE-BLEED score. The F1 scores were 15.4% (XGBoost algorithm), 8.6% (RIETE score) and 6.4% (VTE-BLEED score).

The external validation cohort (COMMAND-VTE) was composed of 3027 patients who had 126 (4.1%) MB events

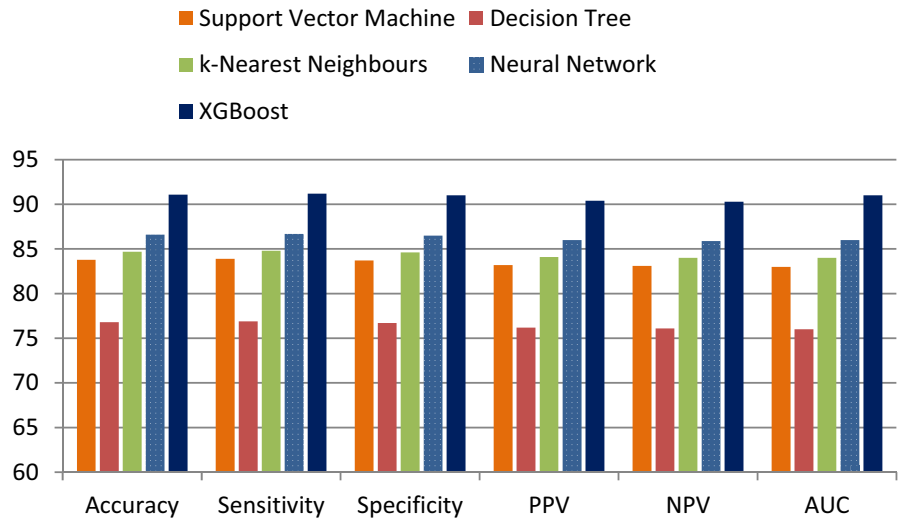

FIGURE 2 Discrimination metrics of the machine learning methods developed with 55 features in the learning set. AUC, area under the receiver operating characteristics curve; NPV, negative predictive value; PPV, positive predictive value.

TABLE 3 Comparative odds for major bleeding, fatal bleeding, intracranial bleeding and intracranial or fatal bleeding during the first 90 days after diagnosis in the validation cohort (10 337 patients).

Outcome	Events, *N*	XGBoost high-risk, OR (95% CI)	RIETE high-risk, OR (95% CI)	VTE-BLEED high-risk, OR (95% CI)
Major bleeding	227	5.89 (4.43–7.83)	3.11 (2.16–4.48)	2.34 (1.79–3.05)
Fatal bleeding	26	3.26 (1.66–6.41)	5.36 (2.78–10.4)	2.87 (1.60–5.15)
Intracranial bleeding	36	5.49 (2.74–11.0)	2.57 (0.99–6.63)	1.71 (0.89–3.30)
Intracranial or fatal bleeding	50	4.72 (2.57–8.67)	3.51 (1.70–7.26)	2.19 (1.25–3.83)

Abbreviations: CI, confidence interval; OR, odds ratio; RIETE, Registro Informatizado de Enfermedad TromboEmbólica; VTE, venous thromboembolism.

TABLE 4 XGBoost algorithm outcomes according to the site of major bleeding in the prospective validation dataset. The correspondent values for the 'high-risk' Registro Informatizado de Enfermedad TromboEmbólica (RIETE) and VTE-BLEED scores are also presented.

Sites of major bleeding	Major bleeding episodes, *N*	XGBoost algorithm, *n* (%)	RIETE high risk, *n* (%)	VTE-BLEED high risk, *n* (%)
Gastrointestinal	73	22 (30)	14 (19)	51 (70)
Urinary	16	6 (38)	7 (44)	15 (94)
Intracranial	36	12 (33)	5 (14)	18 (50)
Retroperitoneal	17	11 (65)	3 (17)	9 (53)
Haematoma	47	15 (32)	4 (8.5)	21 (45)
Uterine	8	1 (12)	0 (0)	2 (25)
Other	30	9 (30)	3 (10)	14 (47)
Total	227	76 (33)	36 (16)	130 (57)

in 3 months. The clinical characteristics of the patients are presented in Table S4. The COMMAND-VTE dataset lacked 14 variables that were part of the XGBoost model. In that cohort the odds to predict a MB event in high-risk patients was 0.81 (95% CI 0.43–1.50). The algorithm's metrics were: 10.3% sensitivity, 87.6% specificity, 3.5% PPV and 5.2% F1 score (Figure 3A).

DISCUSSION

Our findings, obtained from a large cohort of patients with VTE, using baseline variables, reveal that the algorithm identifies patients with VTE at high risk of a MB event within the first 3 months of anticoagulation. In the prospective validation cohort from the same registry the OR for a

(A)

Validation cohort	Sensitivity %	Specificity %	PPV %	NPV %	LR+	LR-	F1 score %
Prospective							
XGBoost	33.2	93.0	10.0	98.3	4.72	0.72	15.4
RIETE sc	16.4	94.0	6.0	98.0	2.72	0.89	8.6
VTE-BLEED sc	58.2	63.5	3.6	98.5	1.50	0.66	6.4
External							
XGBoost	10.3	87.6	3.5	95.7	0.83	1.02	5.2
RIETE sc	31.0	90.1	12.0	96.8	3.13	0.77	17.3
VTE-BLEED sc	84.9	32.3	5.2	98	1.25	0.47	9.75

(B)

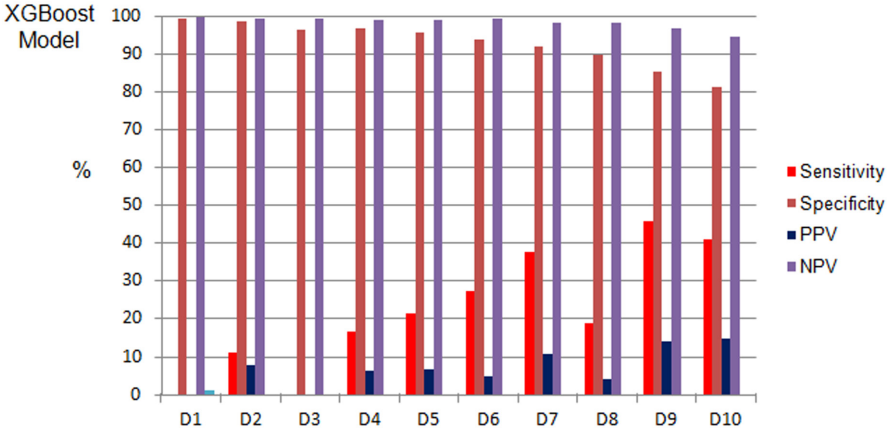

FIGURE 3 (A) Metrics of the XGBoost model and Registro Informatizado de Enfermedad TromboEmbólica (RIETE) and VTE-BLEED scores for 'high risk' patients in the validation dataset and in the external validation cohort (COMMAND-VTE). (B) Metrics of the XGBoost model in patients divided in deciles of probability of bleeding. D1–D10: deciles of probability of bleeding; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

MB event in high-risk patients was 5.89 (95% CI 4.43–7.83) and the metrics were better than those resulting from applying the two scales based on linear models (RIETE and VTE-BLEED scores).

However, the XGBoost algorithm did not perform well in the external validation cohort. In fact, the performance in the COMMAND-VTE patients was worse than that of the RIETE scale (to our knowledge, externally validated for the first time). This external validation with the COMMAND-VTE dataset was suboptimal, because it lacked 14 (25%) predictors included in the algorithm (Table S4). A full external dataset would be necessary for a strict validation. On the other hand, there were differences between the RIETE and COMMAND-VTE databases in type of patients, sites of bleeding and treatments administered. Also, historical differences in patient recruitment may also have played a role. Nevertheless, this may suggest that the more precise the algorithm is, the less exportable it is. The greater the number of predictors, the greater the predictive capacity and the more adjusted it is to the dataset from which it was derived.

Identifying a patient as having a 'high-risk of bleeding' might be useful to the clinician to guide the selection of the most appropriate anticoagulant drug, dose and duration. If the attending doctors might have known the risk earlier and decided to prematurely discontinue anticoagulation of the 731 patients identified by the algorithm around 73 MB events (intracranial, 12) might have been prevented. Of course, this potential benefit must be balanced against the risk of exposing them to a higher risk of VTE recurrences, around 13%–23% during the first month in patients with PE[29,30] and somewhat less afterwards.

We suppose that there are MB events that are currently 'unpredictable', which depend on chance and the circumstances of the patients' lives, and MB events that depend on dynamic predictors (international normalised ratio instability, non-steroidal anti-inflammatory drugs use, invasive procedures, new DOACs use, surgery, new comorbidities, etc.) that cannot be identified at the time of diagnosis but may influence the occurrence of MB events in the future. As an example of the importance of these evolutionary predictors, in the Dresden registry of patients receiving long-term DOACs, it was found that one in every three MB events (35%) occurred after trauma, surgery or interventional treatments.[31] This effect could be counteracted by shortening the observation period, in which the risk of bleeding is highest and the input of new factors or chance is limited.[6] Finally, there are

MB events more conditioned by factors present at the time of diagnosis. This third group probably encompasses only a portion of anticoagulated patients, but it is where traditional scales (i.e. the RIETE and VTE-BLEED) and this study have focused their observations (only with baseline predictors). As this technique uses a high number of variables the expectations of its use in daily practice would likely depend on the ability to incorporate the variables into a computer system (i.e., with Natural Language Processing and the Electronic Health Records Read (EHRead) technology).[32,33]

The ML tools have been used to assess the risk of bleeding in other studies. They have been used to predict the risk of postpartum bleeding or intracranial bleeding in preterm children,[34,35] or the risk of complications after gastrointestinal or subarachnoid bleeding.[36–40] Overall, the discriminative ability measured by c-statistics was ~90%, and ML methods improved prior existing risk scores. However, not all results have been so good and external validation was rarely performed.[36] In a clinical scenario more similar to ours, the prediction of the risk of MB after percutaneous coronary intervention using the XGBoost method achieved a c-statistics of 0.82.[41] In another study performed with datasets from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) and Global Anticoagulant Registry in the Field-Atrial Fibrillation (GARDFIELD-AF) registries, ML techniques trained with 30–32 variables did not improve the prediction of MB compared to stepwise logistic regression.[42] In that cohort, a neural network multilayer showed an AUC of 0.58–0.63. Differences in patients' characteristics, selected variables, duration of follow-up and use of anticoagulants may likely account for the differences among studies. Also, patients with VTE have specific risk factors for bleeding, which are different from those of patients with atrial fibrillation or valve disease (i.e. cancer, anticoagulant choice or the initial loading doses).

There are some limitations of the present study that must be acknowledged. First, the external validation has been suboptimal because it was not carried out with a complete set of variables. Second, the differences in the use of DOACs in the learning and validation cohort could reduce the precision of the results in the validation cohort. In fact, DOACs use was a relevant predictor in the model (Figure S1). Third, ML methods may learn from large databases and classify patients. Their capacity can be so high that they can be overtrained and specifically identify 'patients' rather than 'patterns' of the disease they are studying ('overfitting'). This may represent the greatest threat to the generalisability of the model, even when the characteristics of the external patients or the period of time studied change slightly. Finally, the RIETE definition of MB does not take into account haemoglobin drops of 20 g/L and probably underestimates the incidence of MB episodes when compared to the ISTH definition.[22]

In conclusion, the XGBoost algorithm identified patients with VTE at increased risk of MB during the first 3 months of anticoagulation therapy, slightly improving the results of traditional methods in a prospective validation cohort, but it was not validated in an external cohort. These results show the current performance of a method intended to improve the predictive capability of this elusive event. Future studies focused on the benefit in patient care, as well as improvements in the ML technique, will be necessary to fully evaluate the clinical utility of this technique.

AUTHOR CONTRIBUTIONS

D. Mora, J.A. Nieto, M. Monreal: design the research study. D. Mora, J.A. Nieto, J. Mateo: analysis, interpretation of the data and draft writing. Dr Yamashita provided the COMMAND-VTE database and revised the intellectual content. B. Bikdeli, S. Barco, D. Jiménez: critical writing and revising the intellectual content. All authors approved the final approval of the version.

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CONFLICT OF INTEREST STATEMENT

Dr Bikdeli reports that he is a consulting expert, on behalf of the plaintiff, for litigation related to two specific brand models of inferior vena cava filters. Dr Bikdeli is supported by the Scott Schoen and Nancy Adams IGNITE Award, and the Mary Ann Tynan Research Scientist award through the Mary Horrigan Connors Center for Women's Health and Gender Biology, as well as the Heart and Vascular Center Junior Faculty Award, all at Brigham and Women's Hospital. Dr Bikdeli is a recipient of a Career Development Award by the American Heart Association and VIVA Physicians (no. #938814).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

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