Derivation and validation of a clinical prediction rule for thrombolysis-associated major bleeding in patients with acute pulmonary embolism: the BACS score

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The BACS score, based on easily available patient characteristics, could support physicians in their assessment of the risk of bleeding with systemic thrombolysis for acute pulmonary embolism
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ABSTRACT

Background: Improved prediction of the risk of major bleeding in patients with acute pulmonary embolism (PE) receiving systemic thrombolysis is crucial to guide the choice of therapy.

Methods: The study included consecutive patients with acute PE who received systemic thrombolysis in the RIETE registry. We used multivariable logistic regression analysis to create a risk score to predict 30-day major bleeding episodes. We externally validated the risk score in patients from the COMMAND VTE registry. In addition, we compared the newly created risk score against the Kuijer and RIETE scores.

Results: Multivariable logistic regression identified four predictors for major bleeding: recent major bleeding (3 points), age >75 years (1 point), active cancer (1 point) and syncope (1 point) (BACS). Among 1172 patients receiving thrombolytic therapy in RIETE, 446 (38%) were classified as having low risk (none of the variables present, 0 points) of major bleeding according to the BACS score, and the overall 30-day major bleeding rate of this group was 2.9% (95% CI 1.6–4.9%), compared with 44% (95% CI 14–79%) in the high-risk group (>3 points). In the validation cohort, 51% (149 out of 290) of patients were classified as having low risk, and the overall 30-day major bleeding rate of this group was 1.3%. In RIETE, the 30-day major bleeding event rates in the Kuijer and RIETE low-risk strata were 5.3% and 4.4%, respectively.

Conclusions: The BACS score is an easily applicable aid for prediction of the risk of major bleeding in the population of PE patients who receive systemic thrombolysis.

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Introduction

Pulmonary embolism (PE) remains a worldwide major health issue [1]. PE is among the most common causes of vascular death after myocardial infarction and stroke, and is the leading preventable cause of death in hospitalised patients [2].

The cornerstone of PE management includes rapid, effective anticoagulation [3]. In patients with acute symptomatic PE, systemic thrombolytic therapy has been shown to reduce short-term all-cause and PE-specific mortality, but is associated with increased risk of major bleeding (including intracranial haemorrhage (ICH)) [4]. Since the net clinical benefit in unselected patients remains uncertain, clinical practice guidelines recommend the use of thrombolytic therapy for 1) patients with acute symptomatic PE and haemodynamic instability who do not have major contraindications owing to bleeding risk, and 2) patients without hypotension who experience haemodynamic deterioration while receiving anticoagulant therapy [5]. Therefore, improved prediction of the risk of major bleeding in patients with acute PE receiving systemic thrombolysis is crucial to guide the choice of therapy [6]. However, unfortunately, no risk scores have been derived to predict major bleeds in PE patients treated with thrombolytics, and only one risk score has been developed, based on administrative claims data, to predict ICH in this group (PE-CH score) [7].

The Registro Informatizado de la Enfermedad TromboEmbólica (RIETE) registry is an ongoing, multicentre, international, prospective registry of consecutive patients with symptomatic, objectively confirmed, acute venous thromboembolism (VTE) [8, 9]. We derived and externally validated a clinical prediction score for major bleeding in PE patients treated with thrombolysis, identifying patients with either high or low probability of having a major bleed.

Methods

Study design

We performed a derivation and validation study of a clinical scoring system to identify major bleeding events in PE patients treated with thrombolysis.

Derivation cohort

We used the data from the RIETE registry, which prospectively collects information on patients with confirmed acute VTE (ClinicalTrials.gov identifier NCT02832245). All patients, or their healthcare proxy provided written or oral informed consent for participation in the registry in accordance with local ethics committee requirements. Previous publications have described the design and conduct of the RIETE registry [10].

Patient selection

Confirmatory testing for PE consisted of high-probability ventilation–perfusion scintigraphy [11], positive contrast-enhanced, PE-protocol, helical chest computerised tomography (CT) (single- or multi-detector CT) for PE [12], or lower-limb venous compression ultrasonography positive for proximal deep vein thrombosis in a patient presenting with chest symptoms [13]. This study included patients who were

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enrolled in RIETE, and underwent systemic thrombolytic therapy (⩾50% of the recommended dose of the thrombolytic agent) for acute PE from January 1, 2001 through January 31, 2019.

Study end-point

The primary outcome used for derivation and validation of the prediction rule was major bleeding 30 days after diagnosis of acute symptomatic PE. We defined major bleeding episodes as those that required a transfusion of at least two units of blood, were retroperitoneal, intrapericardial, intraocular, spinal or intracranial, or were fatal [14].

Risk factors for bleeding

The following variables were examined: age (>75 years *versus* ⩽75 years), sex (male/female), weight (>70 kg *versus* ⩽70 kg), previous use of nonsteroidal anti-inflammatory or antiplatelet therapy (yes/no), chronic heart or lung disease (yes/no), recent (<30 days before PE) major bleeding (yes/no), active cancer (defined as newly diagnosed cancer or cancer being treated (*i.e.* surgery, chemotherapy, radiotherapy, hormonal or support therapy)) (yes/no), recent immobility (defined as nonsurgical patients assigned to bed rest with bathroom privileges for ⩾4 days in the 2 months before VTE diagnosis) (yes/no), surgery (defined as those who had undergone major surgery in the 2 months before VTE) (yes/no), heart rate (⩾110 beats·min^{-1} *versus* <110 beats·min^{-1}), syncope (yes/no), haemoglobin (<13 g·dL^{-1} *versus* ⩾13 g·dL^{-1} in males, <12 g·dL^{-1} *versus* ⩾12 g·dL^{-1} in females), platelet count (⩾100×10^{9}·L^{-1} *versus* <100×10^{9}·L^{-1}) and serum creatinine (>2 mg·dL^{-1} *versus* ⩽2 mg·dL^{-1}).

The RIETE registry restricted all values of these variables to the nearest recorded to the time of PE diagnosis. We imputed missing values where necessary, as described later.

Validation cohort

The validation cohort for this study consisted of the subset of 290 patients enrolled in the Contemporary Management and Outcomes in Patients with Venous Thromboembolism (COMMAND VTE) registry who had acute symptomatic PE, received thrombolytic therapy and had complete baseline and follow-up data required for this study [15]. The COMMAND VTE registry defined major bleeding episodes in a way comparable to RIETE (those that were fatal and/or occurred in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome) and/or those associated with a reduction in the haemoglobin level by ⩾2 g·dL^{-1} or leading to transfusion of at least two units of blood) [16].

Statistical analysis

We used a stepwise logistic regression model with backward elimination to determine the contribution of all candidate covariates, with a threshold for candidate elimination of >0.05. Variable selection was based on clinical (see Risk factors for bleeding section) and statistical significance. Candidate variables that were associated with 30-day major bleeding complications on univariable analysis ($p<0.20$) were included as potential covariates in the multivariable logistic regression model. Our main analyses used multiple imputation to replace missing values for nonsteroidal anti-inflammatory use (5.5%), antiplatelet use (5.0%), heart rate (1.3%) and creatinine levels (26.8%). Our final model was fitted based on 10 multiply imputed datasets using Rubin's rules to combine effect estimates and standard errors to allow for the uncertainty due to imputing missing data [17]. We assessed performance of the model by the area under the receiver operating characteristic (ROC) curve [18]. The study used the Brier score to quantify the overall accuracy of predictions, and used bootstrapping to calculate 95% bias-corrected bootstrap confidence intervals for the c-index. Investigators evaluated model calibration with the modified Hosmer–Lemeshow Chi-squared statistic, where values <20 indicate good calibration [19]. Model for 30-day major bleeds was assessed for possible overfit using linear shrinkage estimators [20, 21].

A score-based prediction rule for the primary end-point at 30 days was developed from the logistic regression model by using a regression coefficient-based scoring method [22, 23]. Integer scores were assigned by dividing risk-factor coefficients by the lowest coefficient and rounding up to the nearest unit for categorical variables [24]. The overall risk score was calculated by adding each component together. We validated the 30-day end-point model internally using the bootstrap in the derivation dataset by sampling with replacement for 200 iterations [25–27]. To assess the robustness of the findings, we estimated the test and performance characteristics of the new risk score in the subgroups of patients with and without haemodynamic instability, and in the subgroup of patients with complete data on renal function. In addition, we examined rates of major bleeding events within 7 days following the diagnosis of PE.

We also compared the newly created risk score against the Kuijer and RIETE bleeding scores (supplementary table S1), which were developed and have been validated for predicting the bleeding risk

in VTE patients on anticoagulant therapy [28, 29]. We examined the proportion of patients who would be reclassified into higher- or lower-risk categories between the new rule and the Kuijer and RIETE scores, and calculated the values of the net reclassification improvement (NRI) comparing the prognostic models.

Statistical significance was defined as a two-tailed p-value of <0.05 for all analyses. Analyses were performed using Stata, version 12.1 (StataCorp, College Station, TX, USA) for Windows.

Results

Study derivation sample

The study cohort consisted of 1172 patients (570 males and 602 females) with confirmed PE who received thrombolytic therapy (figure 1). Of 927 patients with complete information on the type and thrombolytic dose, 463 (50%) received tissue plasminogen activator, 282 (30%) reteplase, 121 (13%) urokinase, 36 (3.9%) streptokinase and 25 (2.7%) tenecteplase. 42 (4.5%, 95% CI 3.3–6.1%) patients received reduced doses of lytics (*i.e.* 50–75% of the standard regimen).

Table 1 shows the clinical symptoms, predisposing conditions and relevant findings at presentation among the included patients. Median (interquartile range) age was 63 (47–74) years. Of the 1172 patients, 265 (23%, 95% CI 20–25%) were aged >75 years, 147 (13%, 95% CI 11–15%) had cancer and 14 (1.2%, 95% CI 0.7–2.0%) had a history of recent major bleeding. At baseline, 69 (5.9%, 95% CI 4.6–7.4%) patients were receiving nonsteroidal anti-inflammatory drugs and 149 (13%, 95% CI 11–15%) patients were receiving antiplatelet agents. Overall, 359 patients (31%, 95% CI 28–33%) had anaemia, 34 (2.9%, 95% CI 2.0–4.0%) had thrombocytopenia and 64 (5.5%, 95% CI 4.2–6.9%) had creatinine levels >2 $mg{\cdot}dL^{-1}$. Patients from the validation cohort had older age, less comorbidity (*e.g.* immobilisation, chronic pulmonary disease, chronic heart disease), fewer signs of haemodynamic severity (*e.g.* syncope, tachycardia, hypotension) and more risk factors for bleeding (*e.g.* recent major bleeding, thrombocytopenia) compared to those from the RIETE cohort (table 1).

Outcomes

The study had complete primary outcome information for all (100%) patients at the end of the 30-day follow-up. Within the first 30 days of follow-up, 8.0% of patients died (94 out of 1172; 95% CI 6.5–9.7%). 62% (58 out of 94; 95% CI 51–72%) of deaths were attributed to PE. Bleeding (eight (8.5%) out of 94), other miscellaneous diseases (24 (26%) out of 94) and unknown disorders (four (4.3%) out of 94) caused the other deaths. A major bleeding episode occurred in 69 (5.9%) of the 1172 (95% CI 4.6–7.4%) PE patients who received thrombolysis in RIETE. The most frequent sites of major bleeding were intracranial (18 (26%) out of 69 patients), subcutaneous (15 (22%) out of 69 patients) and gastrointestinal (10 (14%) out of 69 patients), and the highest mortality occurred after intracranial bleeding (eight (44%) out of 18 major bleeds).

Predictors for 30-day major bleeding

The study assessed predictors for 30-day major bleeding complications in 1084 patients who had complete baseline data required for this study. Results of univariable analysis for all potential predictors are shown

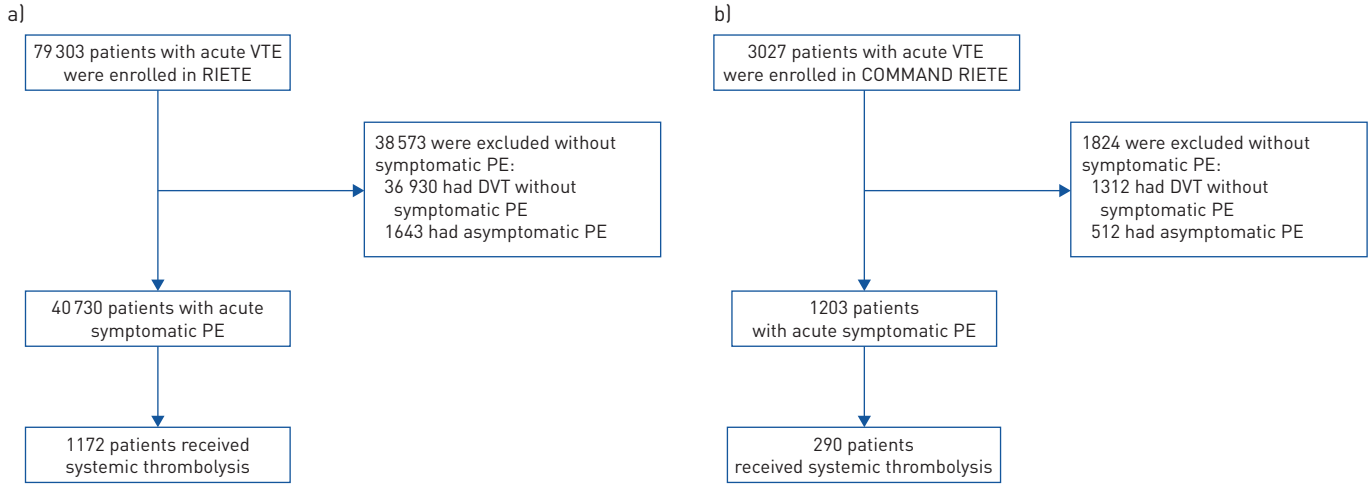

FIGURE 1 Study cohort flow diagram. a) Registro Informatizado de la Enfermedad Tromboembólica (RIETE) derivation cohort; b) Contemporary Management and Outcomes in Patients with Venous Thromboembolism (COMMAND VTE) validation cohort. VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep vein thrombosis.

in table 2. Significant predictors of major bleeding through 30 days after the diagnosis of PE in multivariable analysis included recent major bleeding (adjusted odds ratio (OR_a) 10.4, 95% CI 3.2–33.6), age >75 years (OR_a 2.0, 95% CI 1.2–3.4), active cancer (OR_a 2.1, 95% CI 1.1–3.9) and syncope as presentation of PE (OR_a 1.7, 95% CI 1.0–2.9). Thrombolytic dosing, body mass index and creatinine clearance were not predictors of major bleeding in the univariable analysis. Additionally, there was not a significant interaction between thrombolytic dosing and body weight. Notably, although weight, previous use of nonsteroidal inflammatory or antiplatelet therapy, anaemia and thrombocytopenia were associated with the primary end-point in univariable analysis (table 2), there was no significant effect after adjustment for other factors in the multivariable model.

Risk score derivation

Patients with higher risk scores were at higher risk of major bleeding events; the odds ratio for complications per 1-point increase in the score was 1.99 (95% CI 1.55–2.55; p<0.001). Points were assigned to variable categories to create a point-score model (range 0–6) for prediction of major bleeding, as shown in table 3. The total point scores were used to classify patients as low risk (0 points), intermediate risk (1–3 points) or high risk (>3 points). Cumulative incidence of 30-day bleeding events differed substantially among stages for the model (2.9%, 7.3% and 44% for low, intermediate and high risk, respectively) (figure 2, table 3 and supplementary table S2). The study showed 1) an increase in the rate of stage 3 classification in patients who died, compared to the rate of stage 3 classification in patients who survived (positive likelihood ratio (LR) 12.8, 95% CI 3.5–46.6); and 2) a slight decrease in the rate of stage 1 classification in patients who died, compared to the rate of stage 1 classification in patients who survived (negative LR 0.48, 95% CI 0.29–0.79). Of note, only four (0.9%, 95% CI 0.2–2.3%) of the 446 low-risk patients experienced an episode of intracranial bleeding, and none of the low-risk PE patients suffered a fatal bleeding event.

TABLE 1 Baseline characteristics of patients in derivation and validation cohorts

	Derivation cohort	Validation cohort	p-value
Subjects	1172	290	
Clinical characteristics			
Age years	63 (47–74)	66 (57–75)	0.03
Age >75 years	265 (23)	67 (23)	0.93
Male	570 (49)	117 (40)	0.01
Risk factors for VTE			
Cancer[#]	147 (13)	32 (11)	0.55
Recent surgery[¶]	108 (9.2)	23 (7.9)	0.57
Immobilisation[+]	254 (22)	20 (6.9)	<0.001
Concomitant medication			
Nonsteroidal anti-inflammatory drugs	69 (5.9)	12 (4.1)	0.31
Antiplatelet agents	149 (13)	23 (7.9)	0.02
Comorbid diseases			
Recent major bleeding[¶]	14 (1.2)	13 (4.5)	<0.001
COPD	115 (9.8)	9 (3.1)	<0.001
Congestive heart failure	58 (4.9)	4 (1.4)	<0.01
Clinical symptoms and signs at presentation			
Syncope	527 (36)	58 (20)	<0.001
Heart rate ⩾110 beats·min^{-1}	577 (49)	79 (27)	<0.001
Arterial oxyhaemoglobin saturation <90%	365 (31)	239 (82)	<0.001
SBP <90 mmHg	261 (22)	46 (16)	0.02
Simplified PESI			
Low risk	244 (21)	28 (10)	<0.001
High risk	928 (79)	262 (90)	<0.001
Laboratory findings			
Anaemia[§]	359 (31)	94 (32)	0.57
Platelet count <100×10^9·L^{-1}	34 (2.9)	25 (8.6)	<0.001
Creatinine >2 mg·dL^{-1}	64 (5.5)	8 (2.8)	0.07

Data are presented as n, median (interquartile range) or n (%), unless otherwise stated. VTE: venous thromboembolism; SBP: systolic blood pressure; PESI: Pulmonary Embolism Severity Index. [#]: active or receiving treatment in the past year; [¶]: in the previous month; [+]: defined in this analysis as nonsurgical patients who had been immobilised (*i.e.* total bed rest with bathroom privileges) for ⩾4 days in the month prior to pulmonary embolism diagnosis; [§]: <13 g·dL^{-1} in males, <12 g·dL^{-1} in females.

TABLE 2 Factors associated with 30-day major bleeding in 1172 patients with acute symptomatic pulmonary embolism (PE) who received thrombolysis

	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age >75 years	2.04 (1.23–3.41)	<0.01	2.02 (1.19–3.43)	<0.01
Male	0.71 (0.43–1.16)	0.17		
Weight >70 kg	0.99 (0.97–1.00)	0.09		
Nonsteroidal anti-inflammatory therapy	2.30 (1.05–5.03)	0.04		
Antiplatelet therapy	1.86 (1.00–3.45)	0.05		
Chronic heart disease	0.87 (0.26–2.84)	0.81		
Chronic lung disease	1.04 (0.46–2.33)	0.92		
Recent major bleeding[#]	9.50 (3.09–29.16)	<0.001	10.36 (3.20–33.56)	<0.001
Cancer[¶]	2.04 (1.12–3.72)	0.02	2.09 (1.12–3.89)	0.02
Immobilisation[+]	0.75 (0.40–1.42)	0.38		
Recent surgery[#]	1.32 (0.61–2.83)	0.48		
Systolic blood pressure >160 mmHg	2.04 (0.60–6.96)	0.25		
Heart rate ⩾110 beats·min^{-1}	1.25 (0.76–2.03)	0.38		
Syncope	1.71 (1.05–2.80)	0.03	1.72 (1.04–2.85)	0.03
Anaemia[§]	1.49 (0.91–2.46)	0.12		
Thrombocytopenia[f]	2.20 (0.75–6.44)	0.15		
Creatinine >2 mg·dL^{-1}	1.60 (0.66–3.90)	0.30		
Previous use of oral anticoagulation	1.82 (0.17–14.66)	0.57		
Thrombolytic dosing[##]	1.21 (0.36–4.04)	0.76		

Hosmer–Lemeshow goodness-of-fit test statistic was used for the complete case analysis: Chi-squared (3 degrees of freedom) 0.48, p=0.79. [#]: in the previous month; [¶]: active or received treatment in the past year; [+]: defined in this analysis as nonsurgical patients who had been immobilised (*i.e.* total bed rest with bathroom privileges) for ⩾4 days in the month prior to PE diagnosis; [§]: <13 g·dL^{-1} in males, <12 g·dL^{-1} in females; [f]: <100×10^{9}·L^{-1}; [##]: 50–75% *versus* >75% of the standard regimen.

In the cohort of stable patients (n=911), 43% (390 out of 911) of patients were classified as having low risk, and the overall 30-day major bleeding rate of this group was 2.7% (95% CI 1.3–4.9%), compared with 5.4% (95% CI 1.1–15%) in the low-risk group (56 (21%) out of 261) of unstable patients. Supplementary table S3 shows the test and performance characteristics of the BACS score in the subgroup of patients who

TABLE 3 The staging system

	Risk classification		
	Low	**Intermediate**	**High**
Points n	0	1–3	>3
RIETE derivation cohort			
Patients	38.1	61.2	0.8
30-day major bleeding	2.9	7.3	44.4
30-day intracranial bleeding	0.9	1.8	11.1
30-day fatal bleeding	0	1.1	22.2
COMMAND VTE validation cohort			
Patients	51.4	46.2	2.4
30-day major bleeding	1.3	6.7	28.6
30-day intracranial bleeding	0	2.2	14.3
30-day fatal bleeding	0	0	0

Data are presented as %, unless otherwise stated. Points are assigned for each variable of the scoring system to obtain a total point score (range 0–6): previous major bleeding (3 points), age >75 years (1 point), cancer (1 point), syncope (1 point). The total point score is used to classify patients as low risk (0 points), intermediate risk (1–3 points) or high risk (>3 points). Model-predicted 30-day major bleeding events are shown by stage. RIETE: Registro Informatizado de la Enfermedad Tromboembólica; COMMAND VTE: Contemporary Management and Outcomes in Patients with Venous Thromboembolism.

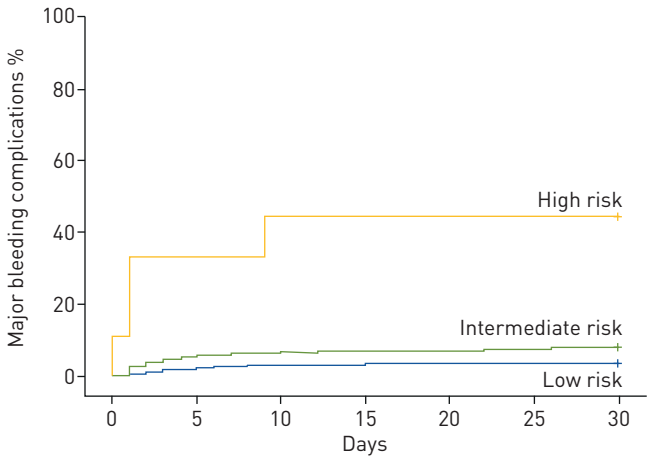

FIGURE 2 Cumulative major bleeding complications stratified by stage for the risk index. BACS score: previous major bleeding (3 points), age >75 years (1 point), cancer (1 point), syncope (1 point). Points are assigned for the presence of each variable. The sum of the variable points produces the total point score (range 0–6). BACS risk staging increased with point totals: low risk (0 points), intermediate risk (1–3 points) or high risk (>3 points).

had complete information on renal function. Consistently, cumulative incidence of 7-day bleeding events differed substantially among stages for the model (2.5%, 6.4% and 33% for low, intermediate and high risk, respectively).

Risk score validation

Analyses suggested that the final model had modest predictive performance (table 4). In the derivation set (n=1084), the area under the ROC curve was 0.67 (0.58–0.72) for 30-day major bleeding events. The internally validated area under the curve and Brier score were 0.66 (95% CI 0.59–0.73) and 0.02, respectively. The final model was well calibrated (Hosmer–Lemeshow Chi-squared statistic 0.48, p-value for the lack of fit 0.79).

Out of the 290 patients included in the COMMAND VTE validation cohort, the BACS score classified 51% (n=149) as low risk, 46% (n=134) as intermediate risk and 2.4% (n=7) as high risk. Cumulative incidence of 30-day major bleeding complications differed substantially among BACS risk classes (two (1.3%) out of 149, nine (6.7%) out of 134 and two (29%) out of seven for low, intermediate and high risk, respectively). None of the 149 low-risk patients experienced an episode of intracranial bleeding or a fatal bleeding event (table 3). The predictive model had a c-index of 0.72 (95% CI 0.60–0.84) in the external validation cohort.

Comparison with previous bleeding scores

When dichotomised as low *versus* intermediate and high risk, the Kuijer and RIETE scores identified 19% and 35% of patients, respectively, in the derivation cohort as low risk. The 30-day major bleeding event

TABLE 4 Model performance

	Study cohort	
	Predicted	**Observed**
C-index (95% CI)	0.67 (0.58–0.72)	
30-day major bleeding events %		
Low risk	3.4	2.9
Intermediate risk	7.8	7.3
High risk	43.7	44.4

BACS score: previous major bleeding (3 points), age >75 years (1 point), cancer (1 point), syncope (1 point). Points are assigned for the presence of each variable. The sum of the variable points produces the total point score (range 0–6). BACS risk staging increased with point totals: low risk (0 points), intermediate risk (1–3 points) or high risk (>3 points).

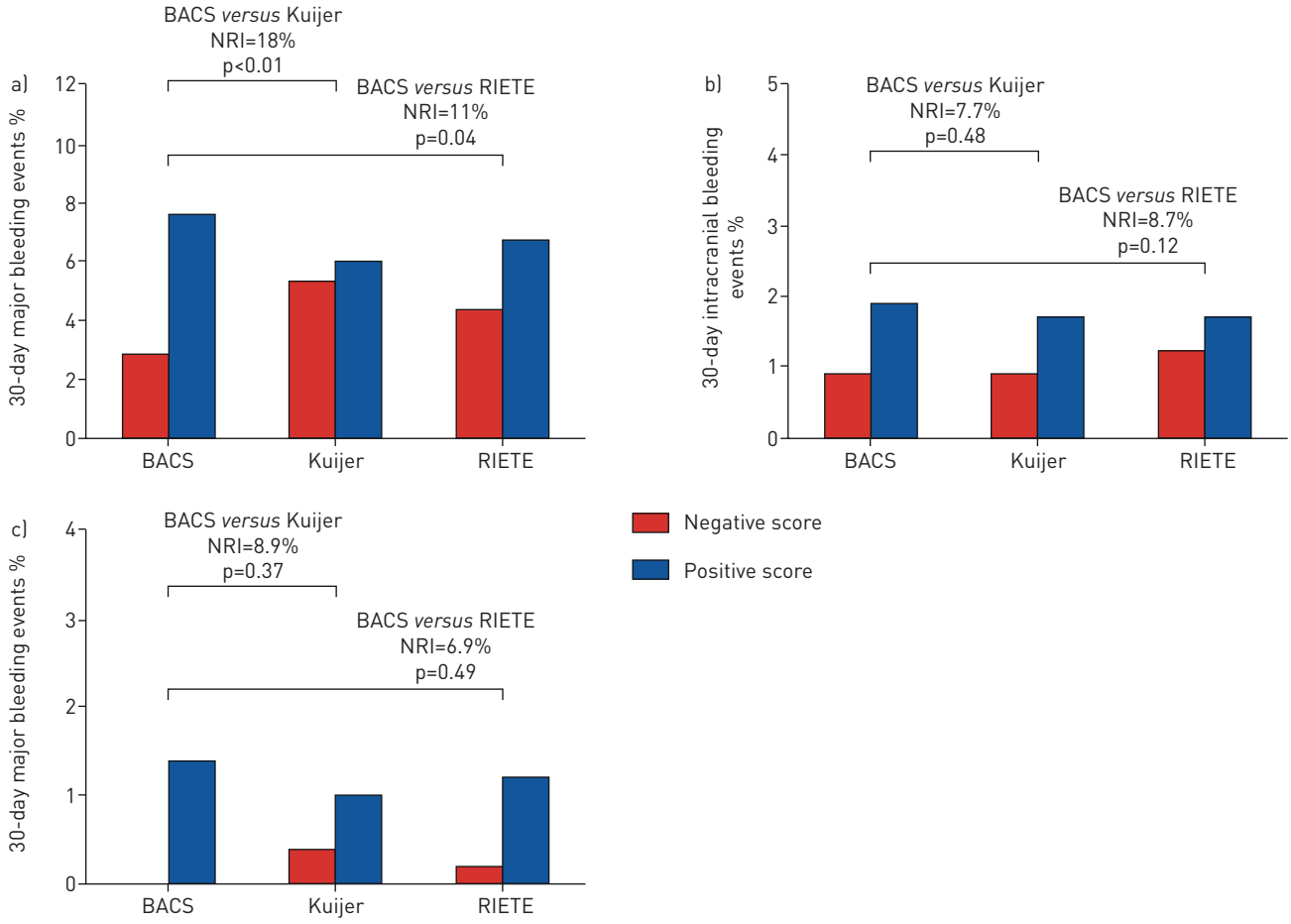

FIGURE 3 Frequency of a) 30-day major bleeding, b) 30-day intracranial bleeding and c) 30-day fatal bleeding events according to baseline prognostic tests. BACS: bleeding, age, cancer, syncope; NRI: net reclassification improvement; RIETE: Registro Informatizado de la Enfermedad Tromboembólica.

rates in the low-risk subgroups were 5.3% and 4.4%, respectively. Two patients (0.9% of 227) in the Kuijer low-risk subgroup and five patients (1.2% of 411) in the RIETE low-risk subgroup experienced an episode of intracranial bleeding; and one patient in the Kuijer low-risk subgroup and one patient in the RIETE low-risk subgroup had a fatal bleed (0.5%, 0.4% and 0.2%, respectively) (figure 3).

Compared with the Kuijer score, the NRI was estimated at 0.18 ($p<0.01$) with the BACS score, resulting from a net 1.5% decrease in patients who bled correctly identified as being at high risk, but a net 19.8% increase in patients who did not bleed correctly identified as at lower risk. Compared with the RIETE score, the NRI was estimated at 0.11 ($p=0.04$) with the BACS score, resulting from a net 7.2% increase in bleeding patients correctly identified as being at high risk and a net 3.6% increase in non-bleeding patients correctly identified as at lower risk (supplementary table S4).

Discussion

We have developed and externally validated a practical risk score (BACS) that predicts a PE patient's risk of major bleeding after systemic thrombolysis on the basis of a set of routinely assessed patient characteristics. We found that the largest amount of prognostic information was contained in four predictors: history of recent major bleeding, older age, active cancer and syncope. The BACS score showed significant improvement on current scores for identification of PE patients at low risk of major bleeding when receiving systemic thrombolytic therapy.

Reliable identification of prognostic factors for major bleeding after thrombolysis for PE management has been difficult, because the number of major bleeding events during follow-up in most individual studies was not large enough for robust analyses [30]. By using data from the large RIETE registry, we were able to include 1172 patients with acute symptomatic PE who received systemic thrombolysis, of whom 69 had a major bleeding episode during the first 30 days of follow-up. This number of haemorrhages enabled us to undertake multivariable analyses. In addition, we were able to externally validate the new score in a

separate population to ensure that the low risk group has low risk of major bleeding events. The results confirmed the robustness of the model, with no evidence of over-fitting.

In our study, recent major bleeding was the most important predictor of haemorrhage in PE patients receiving thrombolytic therapy. This finding was in agreement with previous investigations aiming to predict the risk of major bleeding while on anticoagulant therapy [29]. Prior history of bleeding may reflect on a group of other covariates that collectively increase the risk of bleeding. Our analyses showed that major bleeding under thrombolytic therapy is also related to age [7, 31]. This raises the issue of the net clinical benefit of thrombolytic therapy in elderly *versus* younger patients with acute symptomatic PE [4]. Prior evidence suggests that the risk of major bleeding events is greatly increased among patients with active cancer [32]. We confirmed that, compared with patients with non-cancer-associated PE, those with cancer-associated PE who received thrombolysis had a two-fold increased risk of major bleeding complications. Patients with syncope as the initial presentation of PE had an increased risk of major bleeding (7.6%) and intracranial bleeding (1.7%). The reason for this excess risk is unclear. Some patients with syncope might suffer from head injury, and might be more likely to bleed after thrombolytic therapy. For patients with syncope as the initial presentation of their PE, it might be reasonable to consider a CT scan of the head prior to administration of systemic thrombolysis. However, this issue requires further investigation.

The findings from this study may have practical implications. The technological landscape for management of acute severe PE is evolving rapidly, and novel endovascular procedures are increasingly being used to treat these patients [33, 34]. In the absence of randomised clinical trials to provide a direct comparison of reperfusion strategies, the recent scientific statement from the American Heart Association suggests consideration of catheter-directed therapies for PE patients who have a significant bleeding risk [6]. The BACS score provides clinicians and patients with a framework for discussing therapeutic strategies and researchers with the ability to identify at-risk study populations that maximise the efficiency and power of clinical trials. Additionally, it is important to highlight that this score should supplement, rather than supplant, clinical decision-making. For example, active liver cirrhosis, severe thrombocytopenia or recent intracranial surgery are known to be associated with increased risk of bleeding, and hence, thrombolysis is rarely used in these patients. This might explain, in part, why such factors were not identified as predictors of major bleeding in multivariable analysis in our study.

Our study has some limitations. First, the model proposed had a modest discrimination. However, the BACS score was developed to identify PE patients who might receive systemic thrombolysis with a very low risk of major bleeding, intracranial bleeding and fatal bleeding. In fact, the score was able to identify one-third of PE patients receiving thrombolysis with a <1% risk of intracranial bleeding, and none of these patients experienced a fatal bleeding episode. Second, the RIETE registry did not systematically collect data on some clinical characteristics that had been previously reported as risk factors for bleeding, such as peripheral vascular disease or stroke, and we could not compare the newly created risk score against the PE-CH score [9]. In addition, the score is relevant only to patients with similar characteristics to those who received thrombolysis in the RIETE registry and its generalisability to other patient populations for whom thrombolysis is not selected due to inherently high risk of bleeding (*e.g.* very recent surgery, cirrhosis, severe thrombocytopenia) may be limited. Third, the RIETE registry does use a specific definition for major bleeding episodes, and our study could not test other bleeding classifications (supplementary table S5). Finally, we used dichotomised variables that simplified the creation of a risk score, but may provide less-granular information than continuous variables.

In conclusion, our proposed risk prediction rule, based on easily available patient characteristics, could support physicians in their assessment of the risk of bleeding with systemic thrombolysis and serve as a good starting point for discussing the pros and cons of the available reperfusion options. Future studies should assess the clinical usefulness of this score for patient selection for the choice of reperfusion therapies, and the safety of ensuing outcomes.

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References

1 Barco S, Mahmoudpour SH, Valerio L, *et al.* Trends in mortality related to pulmonary embolism in the European Region, 2000–15: analysis of vital registration data from the WHO Mortality Database. *Lancet Respir Med* 2020; 8: 277–287.
2 ISTH Steering Committee for World Thrombosis Day. Venous thromboembolism: a call for risk assessment in all hospitalised patients. *Thromb Haemost* 2016; 116: 777–779.
3 Konstantinides SV, Meyer G, Becattini C, *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.
4 Chatterjee S, Chakraborty A, Weinberg I, *et al.* Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *JAMA* 2014; 311: 2414–2421.
5 Kearon C, Akl EA, Ornelas J, *et al.* Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016; 149: 315–352.
6 Giri J, Sista AK, Weinberg I, *et al.* Interventional therapies for acute pulmonary embolism: current status and principles for the development of novel evidence: a scientific statement from the American Heart Association. *Circulation* 2019; 140: e774–e801.
7 Chatterjee S, Weinberg I, Yeh RW, *et al.* Risk factors for intracranial haemorrhage in patients with pulmonary embolism treated with thrombolytic therapy: development of the PE-CH Score. *Thromb Haemost* 2017; 117: 246–251.
8 Muriel A, Jiménez D, Aujesky D, *et al.* Survival effects of inferior vena cava filter in patients with acute symptomatic venous thromboembolism and a significant bleeding risk. *J Am Coll Cardiol* 2014; 63: 1675–1683.
9 Jiménez D, de Miguel-Díez J, Guijarro R, *et al.* Trends in the management and outcomes of acute pulmonary embolism: analysis from the RIETE registry. *J Am Coll Cardiol* 2016; 67: 162–170.
10 Bikdeli B, Jiménez D, Hawkins M, *et al.* Rationale, design and methodology of the computerized registry of patients with venous thromboembolism (RIETE). *Thromb Haemost* 2018; 118: 214–224.
11 PIOPED Investigators. Value of ventilation/perfusion scan in acute pulmonary embolism: results of the prospective investigation of the pulmonary embolism diagnosis (PIOPED). *JAMA* 1990; 263: 2753–2759.
12 Remy-Jardin M, Remy J, Wattinne L, *et al.* Central pulmonary thromboembolism: diagnosis with spiral volumetric CT with the single-breath-hold-technique – comparison with pulmonary angiography. *Radiology* 1992; 185: 381–387.
13 Kearon C, Ginsberg JS, Hirsh J. The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. *Ann Intern Med* 1998; 129: 1044–1049.
14 Riera-Mestre A, Jiménez D, Muriel A, *et al.* Thrombolytic therapy and outcome of patients with an acute symptomatic pulmonary embolism. *J Thromb Haemost* 2012; 10: 751–759.
15 Yamashita Y, Murata K, Morimoto T, *et al.* Clinical outcomes of patients with pulmonary embolism *versus* deep vein thrombosis: from the COMMAND VTE Registry. *Thromb Res* 2019; 184: 50–57.

16 Kaatz S, Ahmad D, Spyropoulos AC. 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: 2119–2126.
17 Royston P. Multiple imputation of missing values. *Stata J* 2004; 4: 227–241.
18 Pencina MJ, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. *Stat Med* 2004; 23: 2109–2123.
19 Hosmer DW Jr, Lemeshow S. Applied Logistic Regression. New York, Wiley, 1989.
20 Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996; 15: 361–387.
21 Van Houwelingen JC, Le Cessie S. Predictive value of statistical models. *Stat Med* 1990; 9: 1303–1325.
22 Tu JV, Naylor CD. Clinical prediction rules. *J Clin Epidemiol* 1997; 50: 743–744.
23 Moons KG, Harrell FE, Steyerberg EW. Should scoring rules be based on odds ratios or regression coefficients? *J Clin Epidemiol* 2002; 55: 1054–1055.
24 Fine MJ, Auble TE, Yealy DM, *et al.* A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997; 336: 243–250.
25 Efron B, Tibshirani RJ. An Introduction to the Bootstrap. New York, Chapman & Hall/CRC Press, 1998.
26 Steyerberg EW, Eijkemans MJ, Harrell FE Jr, *et al.* Prognostic modeling with logistic regression analysis: in search of a sensible strategy in small data sets. *Med Decis Making* 2001; 21: 45–56.
27 Steyerberg EW, Harrell FE Jr, Borsboom GJ, *et al.* Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *J Clin Epidemiol* 2001; 54: 774–781.
28 Kuijer PM, Hutten BA, Prins MH, *et al.* Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism. *Arch Intern Med* 1999; 159: 457–460.
29 Ruíz-Giménez N, Suárez C, González R, *et al.* Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE Registry. *Thromb Haemost* 2008; 100: 26–31.
30 Meyer G, Vicaut E, Danays T, *et al.* Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med* 2014; 370: 1402–1411.
31 Stein PD, Matta F, Steinberger DS, *et al.* Intracerebral hemorrhage with thrombolytic therapy for acute pulmonary embolism. *Am J Med* 2012; 125: 50–56.
32 Prandoni P, Lensing AW, Piccioli A, *et al.* Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood* 2002; 100: 3484–3488.
33 Tu T, Toma C, Tapson VF, *et al.* A prospective, single-arm, multicenter trial of catheter-directed mechanical thrombectomy for intermediate-risk acute pulmonary embolism: the FLARE study. *JACC Cardiovasc Interv* 2019; 12: 859–869.
34 Piazza G, Hohlfelder B, Jaff MR, *et al.* A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: the SEATTLE II study. *JACC Cardiovasc Interv* 2015; 8: 1382–1392.