

An Original Risk Score to Predict Early Major Bleeding in Acute Pulmonary Embolism



The Syncope, Anemia, Renal Dysfunction (PE-SARD) Bleeding Score

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BACKGROUND: Improved prediction of the risk of early major bleeding in pulmonary embolism (PE) is needed to optimize acute management.

RESEARCH QUESTION: Does a simple scoring system predict early major bleeding in acute PE patients, identifying patients with either high or low probability of early major bleeding?

STUDY DESIGN AND METHODS: From a multicenter prospective registry including 2,754 patients, we performed post hoc multivariable logistic regression analysis to build a risk score to predict early (up to hospital discharge) major bleeding events. We validated the endpoint model internally, using bootstrapping in the derivation dataset by sampling with replacement for 500 iterations. Performances of this novel score were compared with that of the VTE-BLEED (Venous Thrombo-Embolism Bleed), RIETE (Registro informatizado de la enfermedad tromboembólica en España; Computerized Registry of Patients with Venous Thromboembolism), and BACS (Bleeding, Age, Cancer, and Syncope) models.

RESULTS: Multivariable regression identified three predictors for the occurrence of 82 major bleeds (3.0%; 95% CI, 2.39%-3.72%): Syncope (+1.5); Anemia, defined as hemoglobin <12 g/dL (+2.5); and Renal Dysfunction, defined as glomerular filtration rate <60 mL/min (+1 point) (SARD). The PE-SARD bleeding score was calculated by summing all the components. Overall, 52.2% (95% CI, 50.29%-54.11%) of patients were classified as low bleeding-risk (score, 0 point), 35.2% (95% CI, 33.39%-37.04%) intermediate-risk (score, 1-2.5 points), and 12.6% (95% CI, 9.30%-16.56%) high-risk (score >2.5 points). Observed bleeding rates increased with increasing risk group, from 0.97% (95% CI, 0.53%-1.62%) in the low-risk to 8.93% (95% CI, 6.15%-12.44%) in the high-risk group. C-index was 0.74 (95% CI, 0.73-0.76) and Brier score 0.028 in the derivation cohort. Similar values were calculated from internal bootstrapping. Performance of the PE-SARD score was better than that observed with the VTE-BLEED, RIETE, and BACS scores, leading to a high proportion of bleeding-risk reclassification in patients who bled and those who did not.

INTERPRETATION: The PE-SARD bleeding risk score is an original, user-friendly score to estimate risk of early major bleeding in patients with acute PE.

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KEY WORDS: bleeding; pulmonary embolism; score

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ABBREVIATIONS: BACS = Bleeding, Age, Cancer, and Syncope; eGFR_{CKD-EPI} = Chronic Kidney Disease Epidemiology Collaboration formula; ESC = European Society of Cardiology; ICH = intracranial hemorrhage; PE = pulmonary embolism; RIETE = Registro informatizado de la enfermedad tromboembólica en España; Computerized Registry of Patients with Venous Thromboembolism; SARD =

syncope, anemia, and renal dysfunction; VTE-BLEED = Venous Thrombo-Embolism Bleed

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Take-home Points

Study Question: Does a simple scoring system predict early major bleeding in acute PE patients, identifying patients with either a high or low probability of experiencing early major bleeding?

Results: We developed and internally validated the PE-SARD bleeding score for the prediction of early major bleeding in acute pulmonary embolism, including anemia, +2.5 points; syncope, +1.5 points; renal dysfunction, +1 point from 2,754 patients (C-index, 0.74; 95% CI, 0.73-0.76).

Interpretation: The PE-SARD bleeding risk score is an efficient and user-friendly score to estimate the risk of early major bleeding, which might lead to optimization of acute PE management.

Anticoagulation aims to reduce mortality, morbidity related to thrombus extension, and recurrence in acute pulmonary embolism (PE).¹ Moreover, patients with high-risk PE, and those with intermediate-risk PE who develop secondary hemodynamic collapse, typically require emergency reperfusion therapy.²⁻⁴

Bleeding events are the main unwanted consequence of antithrombotic therapy. Mortality linked to major bleeding events is as high as 20%, that is, twice as high as the rate of death from recurrent PE.⁵ Major bleeding has been reported to be a predictor of mortality⁵⁻⁷ and to

occur more frequently within the first 7 days.^{5,8} The latest guidelines focus on appraisal of bleeding risk in candidates for extended-duration anticoagulation, whereas consensus is lacking for acute phase assessment.^{3,9}

Improved prediction of the major bleeding risk in acute PE is needed to guide management. Several bleeding risk scores have been developed to assess bleeding risk in stable PE patients receiving long-term anticoagulation.¹⁰⁻¹² Their ability to Pulmonary Embolism Syncope-Anemia-Renal Dysfunction early bleeding is poorly documented and remains debated.^{6,13} Moreover, the BACS score was recently developed to predict major bleeding in PE patients receiving systemic thrombolysis, without data regarding its usefulness in the overall PE population.¹⁴

Using data from a multicenter prospective registry, we derived and internally validated a prediction score for major bleeding in acute PE patients, identifying patients with either a high or low probability of experiencing early major bleeding. We compared the performance of this novel score with that of the VTE-BLEED (Venous Thrombo-Embolism Bleed), RIETE (Registro informatizado de la enfermedad tromboembólica en España; Computerized Registry of Patients with Venous Thromboembolism), and BACS (Bleeding, Age, Cancer, and Syncope) models.

Methods

Study Design

We derived and internally validated a scoring system to predict major bleeding in acute PE patients, based on individual patient data from the BFC-FRANCE registry. All patients were included between January 2011 and September 2019. Briefly, the BFC-FRANCE registry is an ongoing, noninterventional, multicenter

registry (five French centers, including two tertiary care facilities and three general hospitals) that prospectively records baseline characteristics and follow-up of consecutive patients with a confirmed diagnosis of acute PE.¹⁵ The registry received approval from the national data privacy commission. This study was conducted in accordance with the Declaration of Helsinki. Our institutional review board approved the study. All patients provided written or oral consent for participation in accordance with ethics committee requirements. If the patient was unable to give oral consent at admission, for example, because of cardiac arrest, consent was obtained from a family member, surrogate, or legal guardian to collect and use clinical and outcome data.

Patient Selection

Inclusion criteria were patients ≥ 18 years of age with confirmed diagnosis of PE by CT pulmonary angiography or ventilation-perfusion scan.^{16,17} There were no exclusion criteria. Management was at the discretion of the physician in charge and was in accordance with the guidelines in place at the time of the study.^{3,9,18,19} According to the guidelines, it was suggested that fibrinolytic treatment should not be used in patients with hemodynamically stable PE.^{3,9,18,19} PE was risk-stratified according to the European Society of Cardiology (ESC) guidelines as low, intermediate-low, intermediate-high, and high risk.³

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Study Endpoints

The primary outcome used for derivation and validation of the prediction rule was early major bleeding after the diagnosis of acute PE. Early bleeding was defined as a bleeding event occurring during the hospital stay. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis criteria, namely: (i) fatal bleeding or (ii) symptomatic bleeding in a critical area or organ (intracranial [ICH], intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or IM with compartment syndrome); or (iii) bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.²⁰ All suspected outcome events were classified by a central adjudication committee (R. C. and N. M.). Disagreement was resolved by a third author (F. S.).

Statistical Methods

Model Construction: Continuous variables are expressed as mean (SD). Categorical variables are expressed as number (percentage). Unadjusted differences between groups were compared using the χ^2 or Student *t* test as appropriate. Candidate variables for the penalized logistic regression model were chosen from the list of variables collected at baseline, based on physiological relevance and potential to be associated with bleeding. The full list of candidate covariates is available in e-Table 1. Continuous variables that were statistically significant were categorized, choosing the most discriminative cutoff points, based on best-subset selection.²¹ In particular, syncope was self-reported by the patient (or witnesses), anemia was defined as hemoglobin <12 g/dL, and renal dysfunction was defined as an estimated glomerular function rate calculated with the Chronic Kidney Disease Epidemiology Collaboration formula (eGFR_{CKD-EPI}) < 60 mL/min, according to the Kidney Disease: Improving Global Outcomes guidelines.²² The use of multiple imputation was not required because the rate of missing data was <2% for all covariates.²³ Candidate variables that were associated with major bleeding with *P* < 0.10 by univariable analysis were selected for inclusion in the multivariable logistic regression models. We applied penalization in the logistic regression model to take account of rare events.²⁴ The potential for covariate multiple collinearity was tested using the variance inflation factor and condition number, with variance inflation factor < 10 and condition number < 30 as reference values.²⁵ Because variable selection procedures may produce unstable results, we applied stepwise

elimination selection on 1,000 bootstrap samples. Final model variables were those selected in more than 50% of bootstrap samples.²⁶ Global model fit of the score was assessed by calculation of Nagelkerke's *R*², Bayes information criterion, and Akaike information criterion. The study used the Brier score to quantify overall accuracy of prediction. Model discrimination was evaluated by Harrell's C-index derived from receiver operator characteristic analysis. Calibration was determined with the Hosmer-Lemeshow parameters.

A score-based prediction rule for early major bleeding in PE patients was developed from the logistic regression model, using a regression coefficient-based scoring method. Integer scores were assigned by dividing risk-factor coefficients by the lowest coefficient and rounding up to the nearest unit for categorical variables.²⁷ The overall risk score was calculated by summing all components.

Internal Validity: We validated the endpoint model internally by using bootstrapping in the derivation dataset by sampling with replacement for 500 iterations.²⁸

Sensitivity Analyses: To assess robustness of the findings, we performed sensitivity analyses by estimating the test and performance characteristics of the new risk score in the following subgroups: (1) patients with high-risk PE, and those with intermediate or low-risk; (2) patients aged < and \geq 75 years; (3) for the prediction of major bleeding within the first 30 days in 2,695 patients (96.6%) with complete follow-up. Moreover, to further investigate the impact of defining early major bleeding events with an absolute rather than relative cutoff, we conducted a series of non-prespecified post hoc analyses, including only those events that occurred within 3 and 7 days after hospital admission.

Comparison With Existing Scores: The VTE-BLEED, RIETE, and BACS scores, and staging systems for risk of major bleeding complications, are given in e-Table 2. We compared Harrell's C-indexes between the new rule and the VTE-BLEED, RIETE, and BACS scores and calculated integrated discrimination improvement and net reclassification improvement, comparing the prognostic models.^{29,30}

A *P* < .05 was considered significant. Analyses were performed using SAS 9.4 (SAS Institute).

Results

In total, 2,757 patients were admitted to participating centers during the study period, with an objective diagnosis of acute PE. In-hospital data were not recorded for three patients (0.1%). The remaining 2,754 patients constituted the study population. Mean age was 67.3 \pm 17.4 years; 1,414 (51.3%) were women. One hundred thirty-three patients (4.8%) had high-risk PE, 584 patients (21.2%) intermediate-high risk PE, 1,594 patients (57.9%) intermediate-low risk PE, and 443 patients (16.1%) low-risk PE. Of the 2,754 patients, 203 (7.4%) had syncope as presentation of PE, 726 patients (26.4%) had anemia at admission, and 825 (29.9%) had renal dysfunction. At baseline, 45 patients (1.6%) were receiving nonsteroidal antiinflammatory drugs, and 93 patients (3.4%) were receiving antiplatelet agents

(Table 1 and e-Table 3). Parenteral anticoagulation was initiated at admission in 2,333 patients (84.7%) and single-approach direct oral anticoagulant in 613 patients (22.2%). One hundred thirty-seven patients (5.3%) were treated with advanced therapy, including 107 (3.9%) who received systemic thrombolysis (e-Table 4). Among these, 26 (24.2%) received a half-dose of the standard lytic regimen. Median duration of hospital stay was 2.8 days (Q1-Q3, 1.2-3.9; range, 1-21) (e-Fig 1). None of the patients included in the current analysis was discharged directly from the emergency room. All of them stayed at least 24 hours in a ward.

Outcomes

During the in-hospital stay, 82 patients (3.0%; 95% CI, 2.39%-3.72%) had a major bleeding event, with a median

TABLE 1] Baseline Characteristics and Clinical Data of 2,754 Study Patients According to the Occurrence of Early Major Bleeding or Not

Characteristics	All (N = 2,754)	Missing Values (%)	No Major Bleeding (n = 2,672)	Major Bleeding (n = 82)	P
Age, years	67.3 ± 17.4	0	67.2 ± 17.4	70.2 ± 14.4	.12
Female sex, No. (%)	1,414 (51.3)	0	1,362 (50.1)	52 (63.4)	.03
BMI	27.4 ± 5.9	0.2	27.4 ± 5.9	27.8 ± 7.4	.59
Comorbidities, %					s
Chronic pulmonary disease	236 (8.6)	0.3	23 (8.6)	5 (6.1)	.41
Active cancer ^a	507 (18.4)	0.1	490 (18.3)	17 (20.7)	.58
Prior bleeding	42 (1.5)	0.3	38 (1.4)	4 (4.9)	.07
Recent surgery ^b	192 (7.0)	0.2	181 (6.8)	11 (13.4)	.02
Low-risk for long-term recurrence	702 (25.6)	0.3	678 (25.4)	24 (29.3)	.42
Associated DVT	1,120 (40.7)	1.1	1,082 (40.5)	38 (46.3)	.30
Clinical characteristics					
Syncope (%)	203 (7.4)	0.7	186 (7.0)	17 (20.7)	<.001
HR at admission, bpm	89.9 ± 19.1	0.6	89.8 ± 19.1	94.1 ± 19.9	.04
SBP at admission, mm Hg	137.7 ± 23.6	0.1	138.0 ± 23.4	131.6 ± 24.0	.01
SaO ₂ at admission, %	93.4 ± 5.6	1.1	93.5 ± 9.8	90.5 ± 5.3	<.001
Biological data					
Anemia, ^c %	726 (26.4)	...	676 (25.3)	50 (61.0)	<.001
Platelet count (×103/μL)	295.2 ± 35.6	1.1	296.5 ± 32.7	252.9 ± 35.8	.88
Renal dysfunction ^d	825 (29.9)	...	781 (29.2)	44 (53.7)	<.001
Positive troponin	981 (35.6)	0.9	938 (35.1)	43 (52.4)	.002
Echo data					
RV dysfunction	911 (33.1)	1.1	871 (32.6)	40 (48.8)	.003
sPESI, median (Q1-Q3)	2 (1-3)	0.9	2 (1-3)	2 (2-3)	.009
ESC-defined risk PE category (%)					<.001
Low-risk	443 (16.1)	...	438 (16.4)	5 (6.1)	
Intermediate-low risk	1,594 (57.9)	...	1,550 (58.0)	44 (53.7)	
Intermediate-high risk	584 (21.2)	...	563 (21.1)	21 (25.6)	
High-risk	133 (4.8)	...	121 (4.5)	12 (14.6)	

ESC = The European Society of Cardiology; HR = heart rate; RV = right ventricle; SBP = systolic BP; sPESI = simplified Pulmonary Embolism Severity Index.

^aActive or anti-tumor therapy within the last 6 months, or metastatic state, according to the 2019 European Society of Cardiology guidelines.

^bwithin the past 4 weeks.

^cdefined by a hemoglobin level < 12 g/dL.

^ddefined by an eGFR_{CKD-EPI} < 60 mL/min (estimated glomerular filtration rate calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula).

time to event of 2.0 days (Q1-Q3, 1.0-5.0, ranging from 0 to 11 days) (e-Fig 1). Bleeding events were classified as major because of the occurrence of at least one of the following criteria: bleeding-related death, nine patients (10.9%); symptomatic bleeding in a critical area or organ, 28 patients (34.1%); bleeding requiring surgery, 13 patients (15.8%); bleeding causing a drop of 20 g/L in hemoglobin level, 58 patients (70.7%); and bleeding leading to transfusion, 48 patients (58.5%). Bleeding

events in a critical area or organ were ICH for 18 patients (21.9%), intraspinal for one patient (1.2%), intraocular for one patient (1.2%), retroperitoneal for two patients (2.4%), and IM for six patients (7.3%). Overall, patients who suffered early bleeding were more frequently women, had a more severe hemodynamic profile, more frequent RV dysfunction, and positive troponin, resulting in a more severe ESC-defined risk stratification (Table 1).

TABLE 2] Univariable and Multivariable Predictors of In-Hospital Major Bleeding

Variable	OR (95% CI)	P	OR (95% CI)	P
	Univariable analysis		Multivariable analysis	
Female sex	1.6 (1.05-2.6)	.03
Age > 80, y	1.6 (1.05-2.56)	.03
Weight < 60 kg	1.6 (1.01-2.6)	.04
Recent surgery ^a	2.2 (1.2-4.2)	.02
Syncope	3.5 (2.0-6.2)	<.001	2.3 (1.3-4.2)	.003
Heart rate > 100 beats/min	1.7 (1.0-2.8)	.05
Major oxyhemoglobin saturation < 90, %	1.5 (1.0-2.4)	.05
Positive troponin ^b	2.0 (1.3-3.2)	.001
Platelet count < 150, 1,000/mm ³	2.0 (1.3-3.4)	.006
Renal dysfunction ^c	2.8 (1.8-4.3)	<.001	1.7 (1.0-2.8)	.03
Anemia ^d	4.6 (2.9-7.2)	<.001	3.7 (2.3-5.9)	<.001
RV dysfunction ^e	1.9 (1.3-3.0)	.002
Concomitant medication usage predisposing to bleeding ^f	2.1 (1.2-3.6)	.002

^aWithin the past 4 weeks.

^bDefined as a value >99th percentile of healthy subjects with a coefficient of variation of 10%.

^cDefined by an estimated glomerular filtration rate calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula $eGFR_{CKD-EPI} < 60$ mL/min.

^dDefined by a hemoglobin level < 12 g/dL.

^eDefined by the presence of at least one of the following on echography: increased end-diastolic right ventricle/left ventricle diameter ≥ 1.0 in the apical four-chamber view, flattened intraventricular septum, decrease tricuspid annular plane systolic excursion < 16 mm, or right heart thrombus detected in right heart cavities.⁶

^fAnti-platelet therapy or nonsteroidal antiinflammatory drugs.

Predictors of Early Major Bleeding

Results of univariable analysis for all potential predictors are shown in Table 2. Multivariable predictors of major bleeding in >50% of bootstrap samples included anemia

(OR, 3.89; 95% CI, 2.41-6.28), syncope (OR, 2.32; 95% CI, 1.28-4.21), and $eGFR_{CKD-EPI}$ -defined renal dysfunction (OR, 1.74; 95% CI, 1.08-2.81) (Table 2). e-Figure 2 summarizes crude incidence of ICH and

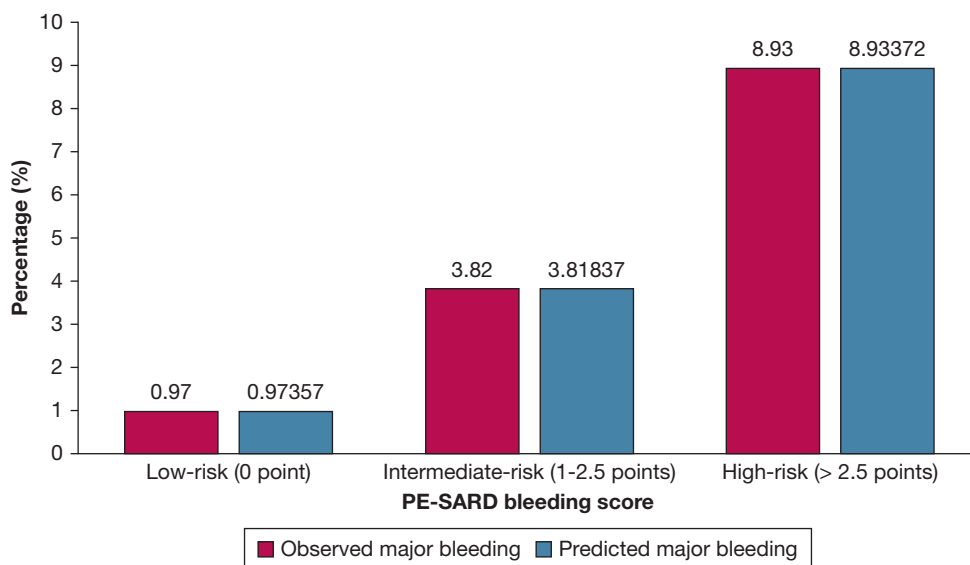


Figure 1 – Observed and predicted rates of early major bleeding according to PE-SARD score-defined risk classification. PE-SARD risk staging increased with point totals: low-risk (0 point), intermediate-risk (1-2.5 points), or high-risk (>2.5 points). PE-SARD = Pulmonary Embolism Syncope-Anemia-Renal Dysfunction.

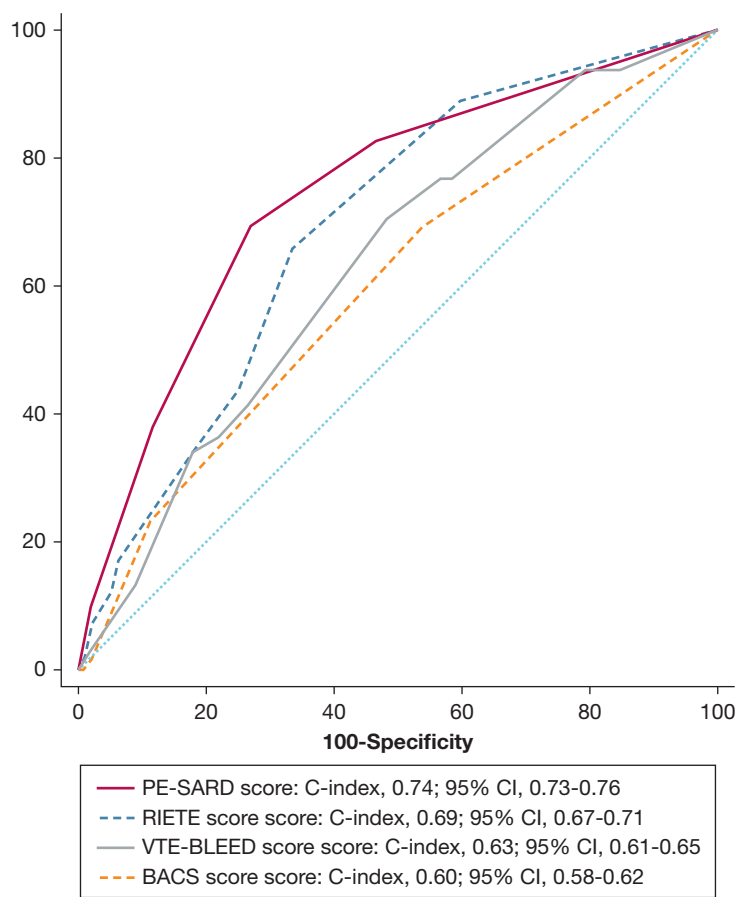


Figure 2 – Receiver operating characteristic curves of the PE-SARD, VTE-BLEED, RIETE and BACS bleeding scores and their corresponding Harrell's C-indexes. BACS = Bleeding, Age, Cancer, and Syncope; PE-SARD = Pulmonary Embolism Syncope-Anemia-Renal Dysfunction; RIETE = Registro informatizado de la enfermedad tromboembólica en España; Computerized Registry of Patients with Venous Thromboembolism; VTE-BLEED = Venous Thrombo-Embolic Bleed.

bleeding-related death according to the occurrence or not of the independent predictors of major bleeding.

Risk Score Construction

Points were assigned to variables to create a point-score model (range, 0-5), namely, the Pulmonary Embolism Syncope-Anemia-Renal Dysfunction (PE-SARD) bleeding score, for prediction of early major bleeding: Anemia, + 2.5 points; syncope, + 1.5 points; renal dysfunction, + 1 point. Patients with higher risk scores were at greater risk for major bleeding events; the OR for complications per 1-point increase in the score was 1.82 (95% CI, 1.51-2.52; $P < .001$). Patients were classified into three risk categories for major bleeding, based on total point scores: low risk (score, 0 point), intermediate risk (score, 1-2.5 points), and high risk (score, >2.5). The largest proportion of patients were classified as low bleeding risk (52.2%; 95% CI, 50.29%-54.11%), followed

by intermediate-risk (35.2%; 95% CI, 32.19%-38.30%), and high-risk (12.6%, 95% CI, 9.30%-16.56%). Observed bleeding rates increased with increasing risk group, from 0.97% (95% CI, 0.53%-1.62%) in the low-risk group to 8.93% (95% CI, 6.15%-12.44%) in the high-risk group (Fig 1). ICH and bleeding-related death occurred in 0.3% and 0.2%, respectively, in the low bleeding risk category, and in 1.7% and 1.2%, respectively, in the high-risk category (e-Table 5).

Risk Score Performance and Internal Validation

Analyses showed that the PE-SARD bleeding score had good predictive performance in the overall population. Predicted bleeding rates were similar to the observed bleeding rates, whatever the risk level (Fig 1). Figure 2 displays the receiver operator characteristic curve of the PE-SARD score. Harrell's C-index was 0.74 (95% CI, 0.73-0.76), and the Brier score was 0.028. The PE-SARD model was well calibrated based on Hosmer-Lemeshow

TABLE 3] Model Performances for the PE-SARD, VTE-BLEED, RIETE, and the BACS Scores

Characteristic	PE-SARD Score	VTE-BLEED Score	RIETE Score	BACS Score
Derivation cohort				
Global fit				
Bayes information criteria	687.4	737.9	724.2	746.0
Akaike information criteria	675.5	726.1	712.4	734.2
Nagelkerke's R^2	23.784	0.6	0.01	0.02
Accuracy of prediction				
Brier score	0.028099	0.026011	0.027887	0.026443
Discrimination				
Harrell's C-index	0.744 (95% CI, 0.72-0.76)	0.633 (95% CI, 0.617-0.65)	0.692 (95% CI, 0.67-0.71)	0.600 (95% CI, 0.58-0.61)
Calibration				
Hosmer-Lemeshow χ^2	1.99	10.4	13.9	1.03

PE-SARD score: Anemia (ie, hemoglobin < 12 g/dL): + 2.5 points; syncope: + 1.5 points; renal dysfunction (ie, GFR_{CKD-EPI} < 60 mL/min): + 1 point. Glomerular filtration rate calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. BACS = Bleeding, Age, Cancer, and Syncope; PE-SARD = Pulmonary Embolism Syncope-Anemia-Renal Dysfunction; RIETE = Registro informatizado de la enfermedad tromboembólica en España; Computerized Registry of Patients with Venous Thromboembolism; VTE-BLEED = Venous Thrombo-Embolism Bleed.

c^2 of 1.19, where values <20 indicate good calibration (Table 3), and on the visual plot of predicted and observed major bleeding (e-Fig 3).

The internal validity of the model was checked by bootstrapping. Optimism, which is the tendency of the model to perform better with the data from which it was constructed than on new data, was low (optimism, -0.00112). The internally validated Harrell's C-index and Brier score were 0.74 and 0.028099, respectively.

Sensitivity Analyses

In total, 1,065 patients (38.7%) were aged >75 years, and 2,621 patients (95.2%) had a low- or intermediate-risk PE. The rate of major bleeding at 3 days, 7 days, and 30 days was 2.4% (66 patients), 3.1% (88 patients), and 4.1% (113 patients), respectively. Prediction performances were similar across subgroups (with or without high-risk PE, and patients younger or older than 75 years) (Fig 3). The PE-SARD bleeding score had good predictive performance for the prediction of 30-day major bleeding with a Harrell's C-index of 0.74 (95% CI, 0.72-0.76) and a Brier score of 0.0354 (Fig 4). Additional nonprespecified post hoc analyses including only bleeding events that occurred within 3 and 7 days after hospital admission showed similarly good performance of the PE-SARD bleeding score (C-index, 0.74 [95% CI, 0.71-0.77], and C-index, 0.74 [95% CI, 0.68-0.76], respectively) (e-Fig 4).

Comparison With the VTE-BLEED, RIETE, and BACS Bleeding Scores

When dichotomized as low- vs intermediate- and high-risk, the PE-SARD bleeding score improved major bleeding prediction compared with the VTE-BLEED, RIETE, and BACS scores, with better global model fit (ie higher Nagelkerke's R^2 , and lower Akaike information criterion and Bayes information criterion), better discriminatory capacity, with a significant increase in Harrell's C-index, and better calibration (Table 3, Fig 2, e-Fig 3). Compared with the VTE-BLEED, RIETE, and BACS scores, net reclassification improvement was estimated at 72.4% ($P < .001$), 58.0% ($P < .001$), and 72.4% ($P < .001$), respectively, with the PE-SARD score, leading to a high proportion of bleeding-risk reclassification in patients who bled and those who did not (Fig 5).

Discussion

Using a large multicenter registry with adjudication of International Society on Thrombosis and Haemostasis-defined outcomes, we identified three easily available factors that are associated with early major bleeding in acute PE and derived the new PE-SARD bleeding score. When collapsed into a three-category risk score, the new score was able to identify a sizeable proportion of patients who fell into the most clinically meaningful categories, that is, low or high risk of hemorrhage. The C-index (0.74) and Brier score (0.028) indicate good

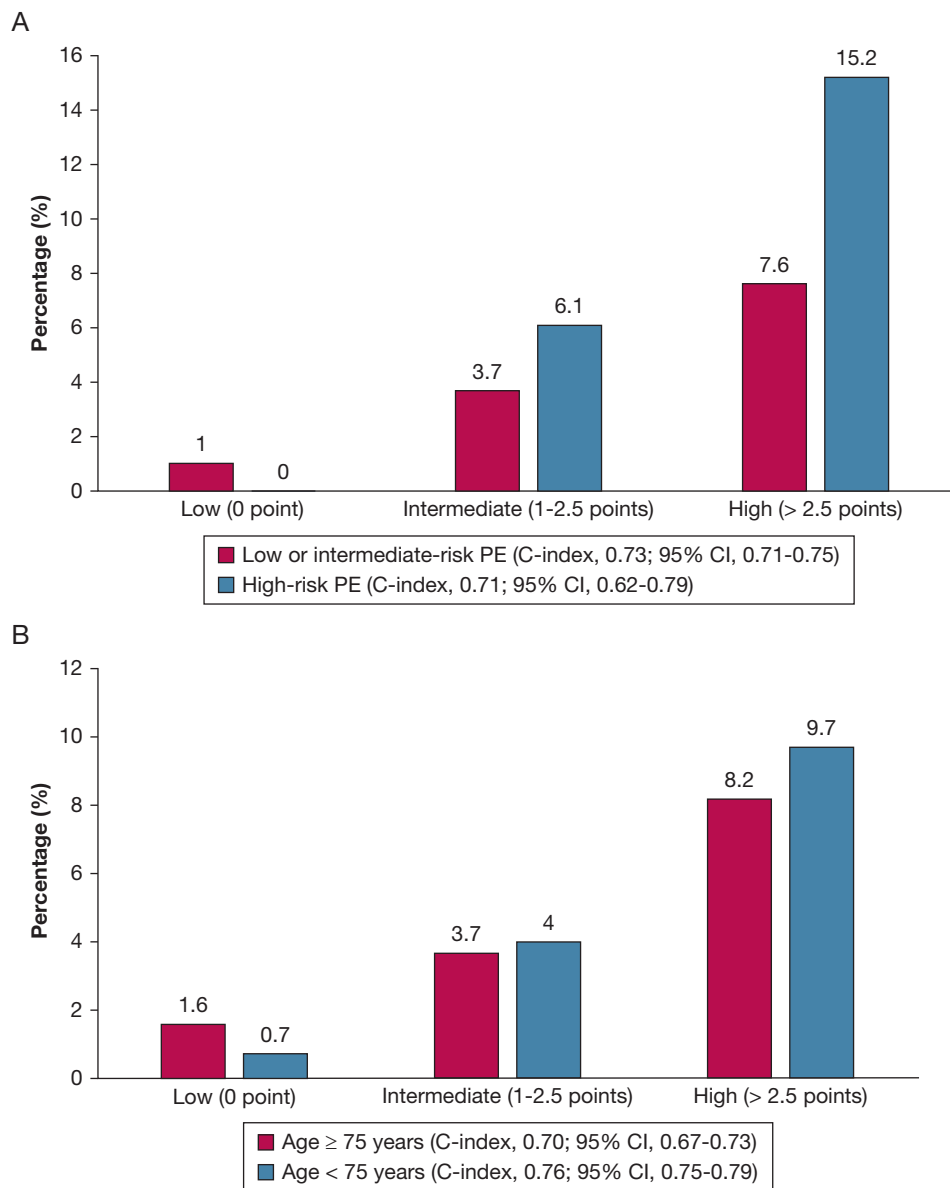


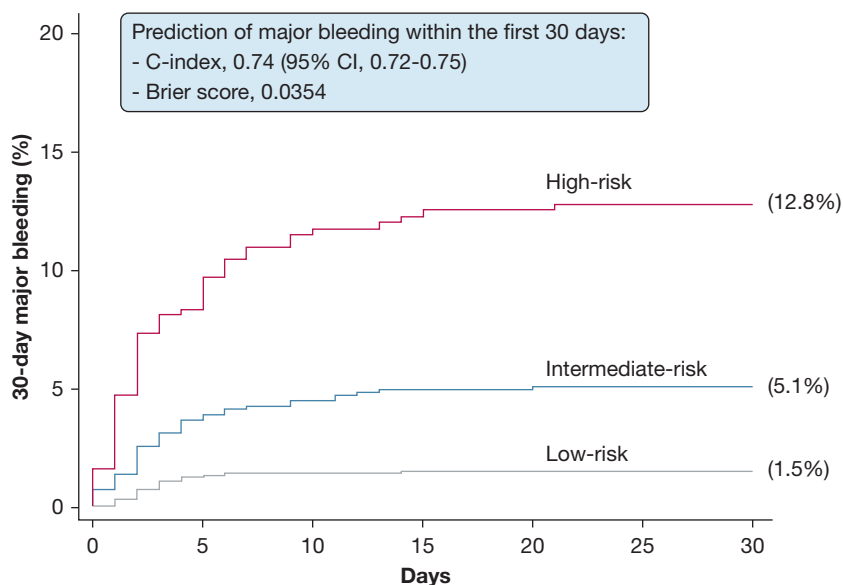
Figure 3 – Observed rates of early major bleeding according to PE-SARD score-defined risk classification in the subgroups of patients with high-risk PE and those with intermediate or low-risk (A), in patients younger or older than 75 years (B), and the corresponding Harrell’s C-indexes of models. PE-SARD risk staging increased with point totals: low-risk (0 point), intermediate-risk (1-2.5 points), or high-risk (>2.5 points). PE-SARD = Pulmonary Embolism Syncope-Anemia-Renal Dysfunction.

performance for a prediction model and compare favorably with other risk stratification rules in the PE setting.

Of the three variables in our model, one reflects the severity of PE (syncope), and the other two reflect patient comorbidities. Anemia was identified as the most powerful predictor of early major bleeding, and, therefore, all high-risk patients must have anemia and at least one of the other variables. All three covariates identified here are individually linked to an increased risk of bleeding in acute PE. First, anemia was associated

with in-hospital bleeding in a cohort of 522 PE patients (OR, 2.60; 95% CI, 1.0-6.90),⁶ and features in existing bleeding risk scores in PE.¹⁰⁻¹² Although we were unable to determine the mechanism of association, anemia may reflect a predisposition to hemorrhage or recent subclinical hemorrhage. Second, recent data suggested a relationship between syncope and bleeding in acute PE.^{14,31} We also observed a significantly higher crude incidence of ICH (3.9% vs 0.4%) and bleeding-related death (2.0% vs 0.2%) in patients with syncope as the initial presentation of PE. Some patients with syncope could have suffered from traumatic head injury and may

Figure 4 – Cumulative incidence of 30-day major bleeding in acute PE patients according to the PE-SARD risk categories. PE-SARD risk staging increased with point totals: low-risk (0 point), intermediate-risk (1–2.5 points), or high-risk (> 2.5 points). PE-SARD = Pulmonary Embolism Syncope-Anemia-Renal Dysfunction.



be more likely to bleed. These findings might suggest a need for careful neurological workup, including brain imaging, in PE patients who present with syncope; however, further data are needed. Finally, renal dysfunction was associated with higher adjusted rates of 30-day major bleeding (8% vs 5%, respectively; $P < .001$) in a multicenter cohort including 2,875 acute PE patients.³² We assessed renal dysfunction using the $eGFR_{CKD-EPI}$ formula, as recommended by the Kidney Disease: Improving Global Outcomes guidelines.¹⁸

Surprisingly, active cancer was not associated with early major bleeding in our cohort ($P = .58$ in univariable analysis). Cancer is a strong and independent risk factor for VTE. Cancer-associated VTE patients treated with warfarin are at twofold to sixfold higher risk of bleeding.³³ Cancer is included in all bleeding scores derived in the PE setting, including those predicting risk on stable anticoagulation treatment (ie, the RIETE [OR, 3.80; 95% CI, 2.56-5.64; $P < .001$], and the VTE-BLEED [$P = .0002$] scores),¹⁰⁻¹² and the new BACS score, which predicts bleeding events at 30 days in PE patients who received systemic thrombolysis (OR, 2.10; 95% CI, 1.10-3.90).¹⁴

To our knowledge, the PE-SARD score is the first score fully dedicated to assessing bleeding risk at the acute phase of PE. Our new risk score improves risk prediction compared with other scores. Klok et al¹³ reported a low accuracy of the RIETE score for 30-day major bleeding prediction (C-index, 0.60; 95% CI, 0.47-0.72).¹³

Conversely, the VTE-BLEED score was independently associated with in-hospital major bleeding in 522 PE patients with a C-index of 0.69 (95% CI, 0.58-0.80).⁶

Finally, the BACS score was built and validated from 1,172 PE treated with thrombolysis, and 69 bleeding events, with good performances (ie, C-index, 0.67 [95% CI, 0.58-0.72]) in this PE population.¹⁴

The accurate identification of acute PE patients at high bleeding risk with the PE-SARD score, together with individualized decision-making, could prompt alternative therapeutic strategies. Low-molecular-weight heparin might be a preferred option rather than unfractionated heparin in high-risk patients, to avoid suprathreshold anticoagulation when advanced therapy is planned.³⁴ Direct oral anticoagulants have been shown to be associated with a lower risk of bleeding than the standard heparin/vitamin K antagonist regimen.³⁵ The bleeding risk of patients treated with systemic thrombolysis could potentially be overcome by the use of alternative reperfusion strategies, such as ultrasound-facilitated catheter-based therapy or surgical embolectomy.³⁶⁻³⁹ The 2019 ESC guidelines recommend inferior vena cava filter implantation for patients with an absolute contraindication to anticoagulant therapy, based on a lower risk of recurrent PE over the first month compared with patients not receiving this device.^{3,40} Finally, the identification of high-bleeding-risk patients should prompt providers to mitigate other modifiable risk factors such as concomitant antiplatelet therapy or hypertension.⁴¹

The strengths of our study include the prospective patient recording in different centers, the high rate of consecutive inclusions and follow-up, and adjudication of clinical

A

Patients who did not bleed, (N = 2,672)				
VTE-BLEED score, N (%)				
	Low-risk	High-risk	Total	
PE-SARD score, N (%)	Low-risk	921 (79.8)	503 (33.1)	1,424 (53.3)
	High-risk	233 (20.2)	1,015 (66.9)	1,248 (46.7)
	Total	1,154 (43.1)	1,518 (56.8)	2,672 (100.0)

Reclassification, N (%)	1,424 - 1,154 = 270 (+10.1%)			
Patients who bled, (N = 82)				
VTE-BLEED score, N (%)				
	Low-risk	High-risk	Total	
PE-SARD score, N (%)	Low-risk	6 (31.6)	8 (12.7)	14 (17.1)
	High-risk	13 (68.4)	55 (87.3)	68 (82.9)
	Total	19 (23.2)	63 (76.8)	82 (100.0)

Reclassification, N (%)	68 - 63 = 5 (+6.1%)			
Reclassification parameters				
NRI, % (95% CI; P value)	72.4%; 95% CI, 55.7-89.2; P < .001			
IDI, % (95% CI; P value)	1.0%; 95% CI, 0.7-1.4; P < .001			
Δ C-index, (95% CI; P value)	0.03; 95% CI, 0.02-0.13; P = .004			

B

Patients who did not bleed, (N = 2,672)				
RIETE score, N (%)				
	Low-risk	High-risk	Total	
PE-SARD score, N (%)	Low-risk	1,420 (56.0)	4 (2.9)	1,424 (53.3)
	High-risk	1,114 (44.0)	134 (97.1)	1,248 (46.7)
	Total	2,534 (94.8)	138 (5.2)	2,672 (100.0)

Reclassification, N (%)	1,424 - 2,534 = -1,110 (-41.5%)			
Patients who bled, (N = 82)				
RIETE score, N (%)				
	Low-risk	High-risk	Total	
PE-SARD score, N (%)	Low-risk	14 (19.4)	0 (0)	14 (17.1)
	High-risk	58 (80.6)	10 (14.7)	68 (82.9)
	Total	72 (87.8)	10 (12.2)	82 (100.0)

Reclassification, N (%)	68 - 10 = 58 (+70.7%)			
Reclassification parameters				
NRI, % (95% CI; P value)	58.0%; 95% CI, 38.0-78.1; P < .001			
IDI, % (95% CI; P value)	1.2%; 95% CI, 0.8-1.6; P < .001			
Δ C-index, (95% CI; P value)	0.14; 95% CI, 0.09-0.12; P < .001			

C

Patients who did not bleed, (N = 2,672)				
BACS score, N (%)				
	Low-risk	High-risk	Total	
PE-SARD score, N (%)	Low-risk	921 (34.5)	503 (18.8)	1,424 (53.3)
	High-risk	233 (8.7)	1,015 (38.0)	1,248 (46.7)
	Total	1,154 (43.2)	1,518 (56.8)	2,672 (100.0)

Reclassification, N (%)	1,424 - 1,154 = 238 (+10.1%)			
Patients who bled, (N = 82)				
BACS score, N (%)				
	Low-risk	High-risk	Total	
PE-SARD score, N (%)	Low-risk	5 (6.1)	9 (10.8)	14 (17.1)
	High-risk	20 (24.4)	48 (58.5)	68 (82.9)
	Total	25 (30.5)	57 (69.5)	82 (100.0)

Reclassification, N (%)	68 - 57 = 11 (+13.4%)			
Reclassification parameters				
NRI, % (95% CI; P value)	72.4%; 95% CI, 55.7-89.2 P < .001			
IDI, % (95% CI; P value)	1.2%; 95% CI, 0.8-1.6; P < .001			
Δ C-index, (95% CI; P value)	0.10; 95% CI, 0.04-0.17; P < .001			

Figure 5 – Reclassification of patients who bled or who did not bleed with the PE-SARD score vs the VTE-BLEED score (A), the RIETE score (B), and the BACS score (C) according to low-risk patients who had no observed bleeding event, and high-risk patients who had an observed bleeding event. BACS = Bleeding, Age, Cancer, and Syncope; PE-SARD = Pulmonary Embolism Syncope-Anemia-Renal Dysfunction; RIETE = Registro informatizado de la enfermedad tromboembólica en España; Computerized Registry of Patients with Venous Thromboembolism; VTE-BLEED = Venous Thrombo-Embolic Bleed.

endpoints. Our study has some limitations. First, we used rigorous contemporary statistical approaches, such as the regression coefficient-based scoring method and bootstrap sampling to underwrite internal validity, which are commonly used for research purposes.^{42,43} However,

external validation is warranted to ensure generalizability of the PE-SARD risk score. Second, we dichotomized variables to facilitate creation of a risk score, but this may provide less granular information than when continuous variables are used. Third, according to the simple design

of our bleeding score, which includes only three covariates, anemia at admission is the cornerstone of early major bleeding risk appraisal in our acute PE patient population. Fourth, although our registry collects detailed clinical data on most known risk factors for major bleeding, possibly other important risk factors exist that were not captured in our dataset. Finally, our study was not designed to distinguish between chronic kidney disease and acute kidney injury.

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Interpretation

The PE-SARD bleeding risk score is an original, user-friendly score to estimate the risk of early major bleeding in patients with acute PE. It exhibits better performance compared with existing scoring systems in the PE setting. Further studies are required to externally validate our score and to determine its clinical usefulness for acute PE patient management.

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