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ORIGINAL ARTICLE

Identification of hemodynamically stable patients with acute pulmonary embolism at high risk for death: external validation of different models

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Abstract

Background: The optimal strategy for identification of hemodynamically stable patients with acute pulmonary embolism (PE) at risk for death and clinical deterioration remains undefined.

Objectives: We aimed to assess the performances of currently available models/scores for identifying hemodynamically stable patients with acute, symptomatic PE at risk of death and clinical deterioration.

Methods: This was a prospective multicenter cohort study including patients with acute PE (NCT03631810). Primary study outcome was in-hospital death within 30 days or clinical deterioration. Other outcomes were in-hospital death, death, and PE-related death, all at 30 days. We calculated positive and negative predictive values, c-statistics of European Society of Cardiology (ESC)-2014, ESC-2019, Pulmonary Embolism Thrombolysis (PEITHO), Bova, Thrombo-embolism lactate outcome study (TELOS), fatty acid binding protein, syncope and tachicardia (FAST), and National Early Warning Scale 2 (NEWS2) for the study outcomes.

Results: In 5036 hemodynamically stable patients with acute PE, positive predictive values for the evaluated models/scores were all below 10%, except for TELOS and NEWS2; negative predictive values were above 98% for all the models/scores, except for FAST and NEWS2. ESC-2014 and TELOS had good performances for in-hospital death or clinical deterioration (c-statistic of 0.700 and 0.722, respectively), in-hospital death (c-statistic of 0.713 and 0.723, respectively), and PE-related death

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* A complete list of the COPE investigators is provided in the Appendix (online only).

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(c-statistic of 0.712 and 0.777, respectively); PEITHO, Bova, and NEWS2 also had good performances for PE-related death (c-statistic of 0.738, 0.741, and 0.742, respectively).

Conclusion: In hemodynamically stable patients with acute PE, the accuracy for identification of hemodynamically stable patients at risk for death and clinical deterioration varies across the available models/scores; TELOS seems to have the best performance. These data can inform management studies and clinical practice.

KEYWORDS
mortality, pulmonary embolism, right ventricle, risk stratification

1 | INTRODUCTION

Acute pulmonary embolism (PE) is a common and potentially fatal disease [1–4]. The risk of death differs substantially across patients with acute PE according to a continuum spectrum of severity at clinical presentation [5]. Patients presenting in shock or with hemodynamic instability have the highest short-term risk for death, and this makes these patients a clinical emergency [2,5]. However, the vast majority of patients with acute PE are hemodynamically stable at presentation. Short-term mortality in these patients varies from less than 1% to more than 10%, mainly as the result of clinical features at presentation, right ventricle overload, troponin levels, and other biomarker abnormalities (brain natriuretic peptide and others) [6,7]. In hemodynamically stable patients, clinical prediction models based on vital parameters at presentation and medical history can accurately identify patients with acute PE at low risk for death [8]. The combination of clinical features and right ventricle dysfunction (RVD) by imaging or biomarkers has been proposed to select patients at risk for death or clinical deterioration who could be candidates for reperfusion strategies despite hemodynamic stability [9–12].

In this scenario, several models and scores have been proposed for risk stratification in hemodynamically stable patients, including different clinical items and different methods for RVD assessment [13–20]. More than including different items, these models often include the same item with different cutoff values, and this contributes to increasing the uncertainty.

International scientific societies endorse the use of validated risk stratification models to drive the clinical management of patients with acute PE [9–12]. However, none of the proposed models has been used in management studies. As for today, the better strategy to identify hemodynamically stable patients at high risk for death or clinical deterioration remains a matter of debate.

We have recently conducted a prospective, multicenter study including adult patients with acute, symptomatic, objectively diagnosed PE (COPE) [21]. The aim of the present analysis performed in hemodynamically stable patients with acute PE included in the COPE study is to externally validate the Bova, Thrombo-embolism lactate outcome study (TELOS), fatty acid binding protein, syncope and tachicardia (FAST), and National Early Warning Scale 2 (NEWS2) scores and the European Society of Cardiology (ESC)-2014, ESC-2019, and Pulmonary Embolism Thrombolysis (PEITHO) models for identification of patients at high risk for death and clinical deterioration.

2 | METHODS

2.1 | Study design

COPE (clinicaltrial.gov identifier: NCT03631810) is a prospective, multicenter study of adult patients with acute PE (either first or recurrent episode) [22]. Diagnostic work-up, risk stratification, and treatment strategies were left at the discretion and responsibility of the attending physicians, who were encouraged to manage patients according to their usual standard of care. The study was conducted in accordance with the Declaration of Helsinki and adhered to applicable national laws and regulations. The study protocol was approved by the Ethical Committee and Institutional Review Board at the coordinating center and then at each site according to local policies and procedures.

The COPE study was supported by an unrestricted grant from Daiichi Sankyo Europe and Daiichi Sankyo Italy. The members of the Steering Committee had full responsibility for the study design and oversight as well as for data analysis and interpretation. The present analysis was conducted without any specific funding.

2.2 | Patients

Patients aged 18 years or older with symptomatic objectively confirmed PE were included in the study after release of informed consent; patients participating in controlled trials on the management of acute PE were excluded. Diagnosis of PE was confirmed according to validated tests and algorithms [22].

For the purpose of the present analysis, patients were included if they were hemodynamically stable at admission, and those who were in shock or had hemodynamic instability at hospital admission were

excluded. Systolic blood pressure ≥90 mm Hg was identified as criterion for hemodynamic stability.

2.3 | Risk stratification strategies

Seven different risk stratification strategies were applied to the hemodynamically stable patients included in the COPE study: the ESC-2014, ESC-2019, and PEITHO models, and the Bova, TELOS, FAST, and NEWS2 scores [13–20]. Models and scores are described in Table 1. In the main analyses, the ESC-2014 and ESC-2019 models were calculated by the use of the simplified PE severity index (sPESI). The performance of the ESC-2014 and ESC-2019 models, calculated by the use of the PESI score, is reported in the Supplementary material.

2.4 | Study outcomes

The primary outcome of the study was the composite of in-hospital death within 30 days or clinical deterioration. Other outcomes were a) in-hospital death, b) death at 30 days, and c) death due to PE at 30 days.

Clinical deterioration was defined according to previous studies as occurrence of at least 1 of the following: 1. need for cardiopulmonary resuscitation, 2. systolic blood pressure < 90 mm Hg for at least 15 minutes, or drop of systolic blood pressure by at least 40 mm Hg for at least 15 minutes, with signs of end-organ hypoperfusion (cold extremities, urinary output < 30 mL/h, or mental confusion), 3. need for catecholamine infusion (except for dopamine at a rate of <5 μg kg^{-1} min^{-1}) to maintain adequate organ perfusion and a systolic blood pressure of >90 mm Hg [23].

In the COPE study, the cause of death was reported by the investigators and documented for central adjudication by an independent Clinical Event Committee unaware of risk adjudication made by the attending physician. PE-related death was defined as one of following: death where PE was the most probable cause or diagnosis based on objective diagnostic testing performed before death or as assessed at autopsy.

2.5 | Data collection

Data on demographic patient features, clinical status at presentation (first medical visit for suspicion of PE), imaging, and laboratory results were electronically collected at presentation, at hospital discharge, and at 30 days (±4) after the index event via a secure website.

2.6 | Statistical analysis

Categorical variables are presented as numbers and frequencies, continuous variables as means and SDs, or median and IQR. Patients' features and outcomes are described in the overall population and by cancer group.

The primary analyses included all hemodynamically stable patients and missing values were managed using multiple imputation methodology [24,25]. We compared individuals with complete and incomplete data to search for important differences and confirm the "missing at random" assumption. Imputation of missing values was performed by using the noniterative method if the data showed a monotone pattern of missing values; otherwise, the iterative Markov Chain Monte Carlo method with a default number of 10 iterations was used. Results across the imputed data set were pooled using Rubin's rule. This was defined as the "primary study population." At a second stage, as the majority of models included the assessment of right ventricle overload by means of echocardiography, troponin, or both, all patients with missing echocardiography and/or troponin were excluded from the analyses. This was defined as the "complete-case" population [25]. For the NEWS2 score, the "complete-case" population was counted as all patients with known oxygen saturation. All the analyses are reported for completeness and comparisons.

The association between any individual item of each score or model with the study outcome events was calculated by means of univariate logistic regression. Results were reported as odds ratio and 95% CI. Irrespective of the results of univariate analyses, multivariate analyses were separately performed for each score or model to assess the independent predictive value of the included items. Finally, the performance of each risk stratification score or model was assessed by the following parameters: discrimination by calculating the concordance index (c-statistic) with 95% CI, calibration by calculating calibration belts and by applying the Hosmer–Lemeshow test ($P > .05$ indicating no significant differences between observed and predicted values), and positive and negative predictive values [26,27]. The positive predictive values were calculated for each model in the highest risk group and the negative predictive value for the lowest risk group. The risk for study outcome events by risk categories according to individual models/scores was calculated using logistic regression model.

We followed the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement for reporting [28].

Statistical analysis was performed with SPSS software (version 22, IBM, SPSS Inc) and R Project (version 4.3.1, R Foundation for Statistical Computing) for statistical computing.

3 | RESULTS

Overall, 5036 hemodynamically stable patients with acute, symptomatic, objectively confirmed PE were included in the COPE study and composed the primary study population. PE was confirmed by computed tomography (CT) angiography in 96% of the patients. The main features of the study population have been previously reported [21]. Of these patients, 3544 had echocardiography performed, and troponin assessed and were included in the complete-case population. The main patient features of the primary and complete-case populations, as well as the prevalence of the items included in the analyzed models, are reported in Supplementary Table S1.

TABLE 1 Models and scores for risk stratification in patients with acute pulmonary embolism.

ESC-2014 model[a] [10]	**Low risk**	**Intermediate low**		**Intermediate high**
sPESI	0	>0		>0
Echocardiography and troponin	–	Both normal/1 abnormal		Both abnormal
ESC-2019 model[a] [11]	Low risk	Intermediate low		**Intermediate high**
sPESI	0	≥0		≥0
Echocardiography and troponin	Both normal	Both normal or 1 abnormal		Both abnormal
PEITHO model [14]	**Group I**	**Group II**	**Group IIIa**	**Group IIIb**
Echocardiography and troponin	Both normal	1 abnormal	Both abnormal	Both abnormal
Systolic BP ≤ 110 mm Hg, RR > 20 breaths/min−1, cancer or chronic heart failure	–	–	None present	≥1 present
BOVA score [15]	**0 points**	**1 point**	**2 points**	
Systolic BP	>100 mm Hg	–	90-100 mm Hg	
Elevated cardiac troponin	No	–	Yes	
RV dysfunction	No	–	Yes	
Heart rate, beats/min	<110	≥110	–	
Patients are divided into 3 groups: class I if 0 to 2 points, class II if 3 to 4 points, and class III if >4 points.				
TELOS score [17]	**0 points**	**1 point**	**2 points**	**3 points**
Systolic BP	>100 mm Hg	–	90-100 mm Hg	–
Elevated cardiac troponin	No	–	Yes	–
RV dysfunction	No	–	Yes	–
Heart rate, beats/min	<110	≥110	–	–
Elevated plasma lactate	No	–	–	Yes
Patients are divided into 3 groups: class I if 0 to 2 points, class II if 3 to 5 points, and class III if >5 points.				
FAST score [20]	**Points**			
Heart rate ≥ 100 bpm	1.5			
Syncope at presentation	1.5			
Elevated troponin	2			
Patients are divided into 2 groups: low risk for adverse in-hospital outcome <3 points and intermediate-high risk for adverse in-hospital outcome ≥3 points.				
NEWS2 score [18,19]	**3**	**2**	**1**	**0**
Respiratory rate, apm	≤8 or ≥25	21-24	9-11	12-20
Oxygen saturation, %	≤91	92-93	94-95	≥96
Supplemental oxygen		Yes		No
Systolic BP, mm Hg	≤90 or ≥130	91-100	101-110	111-219
Heart rate, bpm	≤40 or ≥131	91-100	41-50	51-90
Level of consciousness	V, P, or U			Awake
Patients are divided into 3 groups: i. NEWS2 score < 5 points; ii. NEWS2 score ≥ 5 and >7 points; iii. NEWS2 score ≥ 7 points				

BP, blood pressure; ESC, European Society of Cardiology; NEWS2, National Early Warning Scale 2; RR, respiratory rate; sPESI, simplified PE severity index; FAST, fatty acid binding protein, syncope and tachicardia; PEITHO, Pulmonary Embolism Thrombolysis; TELOS, Thrombo-embolism lactate outcome study; RV, right ventricle.

[a] In case the PESI score is used for model calculation, PESI classes I to II identify low-risk patients, and PESI classes III to V non–low-risk patients.

In-hospital death within 30 days or clinical deterioration occurred in 206 patients (4.1%) in the primary population; death occurred in-hospital and at 30 days in 141 and 208 of these patients (2.8% and 4.1%), respectively, and death due to PE in 61 patients (1.2%). Among patients in the complete-case population, in-hospital death or clinical deterioration occurred in 129 (3.6%), death in-hospital and at 30 days occurred in 77 (2.2%) and 114 patients (3.2%), respectively, and death due to PE occurred in 39 patients (1.1%).

3.1 | Predictors of study outcome events

In univariate analysis, the majority of the individual items were significantly associated with study outcome events (Supplementary Table S2). At multivariable analyses conducted separately for each score and outcome (Table 2 and Supplementary Table S3), all the components of the ESC-2014, ESC-2019, PEITHO, and Bova models were predictors of in-hospital death within 30 days of clinical deterioration. For the TELOS score, heart rate ≥ 110 bpm, and for the FAST score, syncope was not significantly associated with in-hospital death or clinical deterioration. Concerning the NEWS2 score, none of the intervals of heart rate and oxygen saturation were predictors of in-hospital death or clinical deterioration. The association between individual items and secondary outcomes is reported in Table 2.

When the analyses were performed in the complete-case population (Supplementary Table S4), all the components of the ESC-2014 and 2019 and PEITHO models were predictors of in-hospital death or clinical deterioration. In the FAST score, syncope was not associated with the primary study outcome. For the Bova and TELOS scores, heart rate ≥ 110 bpm was not significantly associated with in-hospital death or clinical deterioration. None of the intervals of heart rate or oxygen saturation of the NEWS2 score was significantly associated with in-hospital death or clinical deterioration. Results for secondary study outcomes are reported in Supplementary Table S3.

3.2 | Performance of models and scores

Rates of in-hospital death or clinical deterioration linearly increased according to increasing risk class as assessed by each individual model, except for PEITHO (Table 3 and Supplementary Tables S5 and S6). Similarly, linear associations were observed between rates of in-hospital death, death at 30 days, death due to PE, and increasing risk class as assessed by each analyzed model, except for PEITHO. Associations between rates of clinical outcomes and risk class were confirmed for all models when the analyses were performed in the complete-case population (Supplementary Table S6).

The distribution of patients in different risk classes according to the individual models is reported in Table 3, Supplementary Tables S5 and S6, Figure 1, and Supplementary Figure S1. The proportion of patients classified at low risk varied across models from 17.7% by ESC-2019 to 53.2% with Bova and 73.6% with FAST; similarly, the proportion of patients classified at high risk varied across models and scores, from 9.4% with NEWS2, 14.3% with Bova, to 40.3% with ESC-2019 (Table 3 and Supplementary Tables S5 and S6).

ESC-2019 had the highest negative predictive value for in-hospital death or clinical deterioration (99.7%); ESC-2014, PEITHO, Bova, and TELOS had negative predictive values above 98% (Table 4 and Supplementary Table S7). All the models had a negative predictive value over 99% for death due to PE, except for FAST and NEWS2 scores. The positive predictive values for in-hospital death or clinical deterioration were below 10% for all models except TELOS and NEWS2.

The performance of the analyzed models in terms of discrimination is reported in Table 5, Supplementary Tables S6 and S7, Figure 2, and Supplementary Figure S2. ESC-2014 and TELOS had good performance for in-hospital death or clinical deterioration (c-statistic ≥ 0.700). The 95% CI of c-statistic for each model tended to overlap, excluding significant differences across the models, except for FAST, which revealed the lowest discriminatory power in almost all the analyses and for the ESC models calculated by the use of the PESI and not sPESI score. All the models had a good performance for death due to PE with area under the curve (AUC) above 0.700, except for the ESC-2019 model and the FAST score. The ESC-2014 and TELOS models also had good performance for in-hospital death. All the models had their worst performance for death at 30 days.

Calibration was good for the ESC-2014, ESC-2019, PEITHO, and NEWS2 models, while miscalibration for some predicted intervals was shown for TELOS, FAST, and Bova models (Supplementary Figure S3).

4 | DISCUSSION

Our study in a large cohort of hemodynamically stable patients with acute PE shows that currently available models/scores for identification of patients at high risk for in-hospital death or clinical deterioration have modest positive predictive values, below 10%, except for TELOS and NEWS2. The negative predictive values of TELOS, NEWS2, PEITHO, Bova, and ESC-2019 models/scores are definitely reliable. ESC-2014 and TELOS have good performance in risk stratification for in-hospital death or clinical deterioration. All the analyzed tools had the best performance in the prediction of death due to PE and the worst in the prediction of death at 30 days.

Acute PE is a life-threatening disease. Contemporary in-hospital and 30-day mortalities continue to be higher than 20% in patients with acute PE and hemodynamic compromise [22]. In these patients—less than 5% of over 5200 patients with acute PE—pulmonary artery reperfusion is essential to reduce mortality [9,11]. The remaining 95% of patients with acute PE are hemodynamically stable at admission and present rates of short-term death ranging from about 1% to 12% or 15%; risk stratification is essential in this context to drive clinical decision on early discharge, monitoring for prompt identification of deterioration, and need for reperfusion therapies. However, the optimal method for risk stratification is still undefined, and international guidelines have drawn different conclusions on this issue [9,11,12].

TABLE 2 Multivariable analysis by score or model for study outcome events in the primary population (N = 5036 patients).

Models and items	In-hospital death or clinical deterioration OR (95% CI)	In-hospital death OR (95% CI)	Death at 30 d OR (95% CI)	Death due to PE OR (95% CI)
ESC				
sPESI ≥ 1	4.064 (2.69-6.14)	5.534 (3.19-9.60)	7.096 (4.42-11.40)	3.365 (1.64-6.92)
RVD or increased troponin	2.632 (1.27-5.47)	2.145 (0.94-4.88)	1.761 (0.92-3.37)	6.408 (0.90-45.71)
RVD and increased troponin	4.453 (2.33-8.50)	3.555 (1.72-7.35)	2.00 (1.12-3.59)	14.336 (1.89-108.62)
PEITHO				
Systolic BP ≤ 110 mm Hg	2.020 (1.49-2.74)	1.481 (1.01-2.16)	1.288 (0.92-1.79)	2.126 (1.25-3.61)
Cancer	2.746 (2.00-3.77)	4.218 (2.95-6.03)	6.404 (4.77-8.60)	1.720 (0.92-3.20)
Heart failure	1.961 (1.30-2.96)	2.248 (1.40-3.62)	2.475 (1.64-3.73)	1.248 (0.56-2.80)
RR > 20 breaths·min^{-1}	2.091 (1.50-2.91)	2.288 (1.58-3.31)	1.866 (1.36-2.56)	3.309 (1.68-6.51)
RVD or increased troponin	2.613 (1.26-5.41)	2.145 (0.95-4.82)	1.864 (0.99-3.52)	6.020 (0.84-43.03)
RVD and increased troponin	4.444 (2.28-8.45)	3.813 (1.86-7.83)	2.477 (1.39-4.42)	12.195 (1.53-96.8)
FAST score				
Heart rate ≥ 100 bpm	1.729 (1.30-2.30)	1.609 (1.14-2.27)	1.508 (1.13-2.01)	1.743 (1.04-2.91)
Syncope	0.843 (0.54-1.31)	0.378 (0.18-0.78)	0.512 (0.30-0.88)	0.648 (0.28-1.52)
Increased troponin	2.939 (1.94-4.46)	2.945 (1.80-4.83)	2.185 (1.48-3.23)	5.675 (2.43-13.27)
Bova score				
Systolic blood pressure 90-100 mm Hg	2.963 (2.08-4.22)	2.144 (1.37-3.36)	1.928 (1.30-2.87)	3.413 (1.90-6.12)
Heart rate ≥ 110 bpm	1.430 (1.04-1.97)	1.476 (1.01-2.15)	1.471 (1.07-2.03)	1.264 (0.71-2.23)
Increased troponin	2.166 (1.38-3.39)	2.141 (1.25-3.67)	1.821 (1.22-2.72)	3.982 (1.65-9.60)
RVD	1.958 (1.31-2.92)	1.859 (1.14-3.03)	1.290 (0.91-1.82)	2.135 (0.81-5.61)
TELOS score				
Systolic BP 90-100 mm Hg	2.556 (1.79-3.65)	1.826 (1.16-2.88)	1.673 (1.12-2.51)	2.850 (1.57-5.19)
Heart rate ≥ 110 bpm	1.286 (0.93-1.77)	1.315 (0.90-1.93)	1.328 (0.96-1.84)	1.108 (0.62-1.97)
Increased troponin	1.923 (1.34-2.75)	1.834 (1.07-3.13)	1.593 (1.07-2.37)	3.337 (1.39-7.98)
RVD	1.638 (1.13-2.37)	1.651 (1.00-2.72)	1.162 (0.82-1.65)	1.842 (0.69-4.93)
Increased lactate	2.426 (1.80-3.26)	2.567 (1.75-3.77)	2.314 (1.61-3.32)	2.938 (1.30-6.64)
NEWS2 score (n = 5009[a])				
Systolic BP 101-110 mm Hg	1.451 (0.95-2.23)	1.241 (0.74-2.09)	1.093 (0.70-1.71)	1.215 (0.53-2.79)
Systolic BP 91-100 mm Hg	2.839 (1.84-4.38)	2.891 (1.77-4.71)	2.593 (1.69-3.98)	4.843 (2.54-9.22)
Systolic BP ≤ 90 or ≥220 mm Hg	2.786 (1.56-4.98)	0.365 (0.09-1.53)	0.256 (0.06-1.06)	0.420 (0.05-3.18)
Heart rate 41-50 or 91-110 bpm	1.178 (0.85-1.64)	1.106 (0.75-1.63)	1.252 (0.91-1.72)	1.081 (0.60-1.95)
Heart rate 111-130 bpm	1.311 (0.85-2.01)	1.056 (0.62-1.78)	1.116 (0.71-1.75)	0.863 (0.38-1-95)
Heart rate ≤ 40 bpm or ≥131 bpm	1.504 (0.71-3.17)	1.398 (0.57-3.42)	1.632 (0.78-3.42)	0.873 (0.19-4.03)
Oxygen saturation 94%-95%	1.294 (0.81-2.08)	1.685 (0.94-3.01)	1.545 (1.00-2.38)	0.555 (0.19-1.61)
Oxygen saturation 92%-93%	1.426 (0.87-2.34)	1.966 (1.07-3.60)	1.299 (0.79-2.14)	1.325 (0.54-3.26)
Oxygen saturation ≤ 91%	1.161 (0.77-1.76)	1.477 (0.88-2.49)	1.127 (0.75-1.70)	1.093 (0.52-2.29)
Supplemental oxygen	3.724 (2.34-5.93)	3.564 (2.02-6.28)	2.674 (1.78-4.02)	2.958 (1.20-7.27)
Consciousness	3.049 (1.96-4.75)	3.596 (2.17-5.96)	3.227 (2.04-5.10)	7.096 (3.75-13.43)

(Continues)

TABLE 2 (Continued)

Models and items	In-hospital death or clinical deterioration OR (95% CI)	In-hospital death OR (95% CI)	Death at 30 d OR (95% CI)	Death due to PE OR (95% CI)
RR 9-11 apm	2.182 (0.43-11.02)	NA	NA	NA
RR 21-24 apm	1.653 (1.07-2.55)	1.693 (1.05-2.73)	1.347 (0.86-2.12)	3.104 (1.42-6.81)
RR ≤ 8 or ≥25 apm	1.698 (1.09-2.64)	1.822 (1.14-2.91)	1.579 (0.99-2.50)	2.268 (1.04-4.95)

BP, blood pressure; ESC, European Society of Cardiology; NA, not available; NEWS2, National Early Warning Scale 2; OR, odds ratio; RR, respiratory rate; RVD, right ventricle dysfunction at echocardiography; sPESI, simplified PE severity index; FAST, fatty acid binding protein, syncope and tachicardia; PEITHO, Pulmonary Embolism Thrombolysis; TELOS, Thrombo-embolism lactate outcome study).
[a] Patients with oxygen saturation available

We assessed the performance of different models and scores for risk stratification in hemodynamically stable patients with acute PE. All the assessed models and scores were derived and validated in patients with acute PE, except for the NEWS2 score. NEWS2 was set up to standardize the assessment of and response to acute illnesses by clinical parameters routinely measured in-hospital and prehospital care without instrumental or laboratory tests [18,19]. All the strategies derived in patients with acute PE included echocardiography for the assessment of RVD and/or tests for troponin or lactate. These tools were originally derived to risk stratify patients with acute PE for different clinical outcomes at different time points. The ESC models were proposed for risk stratification for short-term death in all comers with acute PE [10,11,29,30]; PEITHO was obtained from a post hoc analysis of the randomized, placebo-controlled PEITHO study to identify additional predictors for death from any cause or hemodynamic decompensation at 7 days in hemodynamically stable patients with RVD and increased troponin [14]; the Bova score is aimed at risk stratifying hemodynamically stable patients for the risk of death due to PE, hemodynamic collapse, or recurrent PE at 30 days [15]; in the TELOS score, lactate levels are added to the Bova score to risk stratify for death due to PE and hemodynamic collapse at 7 days [17]; the modified FAST score was validated to predict in-hospital death due to PE or clinical deterioration [20]. Of note, despite the examined models/scores aim at identifying intermediate-high-risk PE at risk for death and decompensation, almost all of them have been derived in cohorts of hemodynamically stable patients, including the low-risk category [10,11,15,17,20,29,30]. Differences in the derivation process of the individual tools could explain different performances across study outcomes.

The positive predictive values of the examined tools were modest and probably not high enough to select candidate patients for reperfusion strategies. Selection for reperfusion strategies should be based on the balance between the risk for death—or PE-related death, would it be accurately identifiable—and that of severe side effects. Thrombolysis increases the risk for intracranial bleeding by about 10-fold in comparison with anticoagulation alone in patients with acute PE [21]. None of the assessed models or scores seems to have positive predictive value high enough to afford the increase in the risk for intracranial bleeding. Two randomized clinical trials are ongoing aimed at assessing the efficacy and safety of thrombolysis (NCT04430569) [31] or ultrasound-facilitated catheter-directed thrombolysis (NCT04790370) [32] in hemodynamically stable patients with acute PE. Patient selection in these studies is performed by means of PEITHO and NEWS scores, respectively. While systemic and locoregional reperfusion therapies primarily aim to reduce PE-related mortality, both the ongoing trials encompass all-cause mortality within their primary outcome measures. In fact, accurately determining the cause of death in clinical practice poses challenges, thus emphasizing the importance of a comprehensive evaluation. Furthermore, having all-cause death will allow for balance for fatal side effects of interventions, particularly major bleeding. The results of these trials are essential to definitively assess the role of reperfusion strategies in hemodynamically stable patients with acute PE.

All the models and scores had their best performance in predicting the risk for death due to PE and their worst performance for death at 30 days. These results are plausible as all the examined models/scores except for NEWS2 were created to specifically measure the severity of acute PE by including disease-specific predictors. This may explain the poor performance of all the tools for death at 30 days, as this event was mainly due to cancer. NEWS2 includes extremely high or low values of blood pressure or heart rate as predictors. However, only low blood pressure and high heart rate are predictors of severity in acute PE. This could explain differences in the performance of NEWS2 in comparison with PE-specific tools. Whether including marked hypoxia in the existing models or scores would improve their positive predictive value should be further evaluated [33]. The best performances were those of ESC-2014 calculated by the sPESI score and TELOS for almost all the study outcomes; PEITHO, Bova, and ESC-2019 obtained very close results. The performance of NEWS2 is relevant as this score is only based on clinical variables. However, the overlap of 95% CIs excluded substantial differences in performance, except for the FAST score.

Overall, TELOS score appears to be the most promising tool. Despite simple, this score includes 2 laboratory and 1 imaging tests. The laboratory tests (troponin assessment and lactate by blood gas analysis) are quite basic and available around the clock in the acute setting. Echocardiography is included in the TELOS score and in the majority of the examined tools except for FAST and NEWS2 scores. It should be considered that echocardiography is not available worldwide around the clock, which could limit the value of scores and models in clinical practice.

TABLE 3 Rates of study outcome events according to individual scores or model for risk stratification in the primary analysis population (*N* = 5036).

Patient feature	Patients, *n* (%)	Clinical outcome events, *n* (%)			
		In-hospital death or clinical deterioration	In-hospital death	30-d death	Death due to PE
ESC-2014 (sPESI)					
Low	2258 (44.8)	29 (1.3)	15 (0.7)	20 (0.9)	9 (0.4)
Intermediate-low	1395 (27.7)	60 (4.3)	44 (3.1)	85 (6.1)	13 (0.9)
Intermediate-high	1383 (27.5)	117 (8.4)	82 (5.9)	103 (7.4)	39 (2.8)
ESC-2019 (sPESI)					
Low	899 (17.8)	3 (0.3)	2 (0.2)	2 (0.2)	1 (0.1)
Intermediate-low	2105 (41.8)	68 (3.2)	48 (2.3)	91 (4.3)	15 (0.7)
Intermediate-high	2032 (40.3)	135 (6.6)	91 (4.5)	115 (5.6)	45 (2.2)
PEITHO					
Low	1434 (28.5)	16 (1.1)	13 (0.9)	27 (1.9)	2 (0.1)
Intermediate-low	1570 (31.2)	55 (3.5)	37 (2.4)	66 (4.2)	14 (0.9)
Intermediate-high	653 (13.0)	17 (2.6)	9 (1.4)	12 (1.8)	5 (0.8)
Intermediate very high	1379 (27.4)	118 (8.5)	82 (5.9)	103 (7.5)	40 (2.9)
FAST score					
Low risk	3706 (73.6)	115 (3.1)	87 (2.3)	133 (3.6)	30 (0.8)
Intermediate-high risk	1330 (26.4)	91 (6.8)	54 (4.1)	75 (5.6)	31 (2.3)
Bova score					
Class I	2679 (53.2)	40 (1.5)	29 (1.1)	62 (2.3)	8 (0.3)
Class II	1635 (32.5)	99 (6.1)	72 (4.4)	96 (5.9)	29 (1.8)
Class III	722 (14.3)	67 (9.2)	40 (5.6)	50 (6.9)	24 (3.3)
TELOS score					
Class I	2240 (44.5)	27 (1.2)	17 (0.7)	41 (1.8)	5 (0.2)
Class II	1767 (35.1)	72 (4.1)	52 (2.9)	77 (4.3)	18 (1.0)
Class III	1029 (20.4)	107 (10.4)	72 (7.0)	90 (8.7)	38 (3.7)
NEWS2 score					
i. Score < 5 points	3636 (72.2)	82 (2.3)	54 (1.5)	97 (2.7)	17 (0.5)
ii. Score ≥ 5 and >7 points	928 (18.4)	59 (6.3)	46 (4.9)	62 (6.7)	20 (2.1)
iii. Score ≥ 7 points	472 (9.4)	65 (13.8)	41 (8.7)	49 (10.4)	24 (5.1)

ESC, European Society of Cardiology; NEWS2, National Early Warning Scale 2; PE, pulmonary embolism; sPESI, simplified PE severity index; FAST, fatty acid binding protein, syncope and tachicardia; PEITHO, Pulmonary Embolism Thrombolysis; TELOS, Thrombo-embolism lactate outcome study).

In our study, the distribution of patients in the lowest and highest risk classes hugely varied across tools. This issue is of critical value if we consider the potential influence of risk stratification in the clinical management of patients with acute PE. According to international guidelines, low-risk patients could be managed as outpatients or by early discharge, while hemodynamically stable patients at increased risk for death should be monitored or admitted to high-care units for prompt identification of clinical deterioration [9–11]. Categorization of considerable proportion of patients as intermediate-high risk can induce inappropriate admission to high-care units, potentially overcoming surge capacity. In clinical trials, having large high-risk classes can dilute the event rate and lead to suboptimal performance. In this view, it should be noted that PEITHO, Bova, and TELOS had the lowest prevalence of high-risk patients with the highest event rates. On the other hand, the ESC-2019 model calculated by the use of sPESI score had the lowest rate of in-hospital death or clinical deterioration in low-risk patients, with the highest negative predictive value. These data suggest that different scores could be used for different purposes

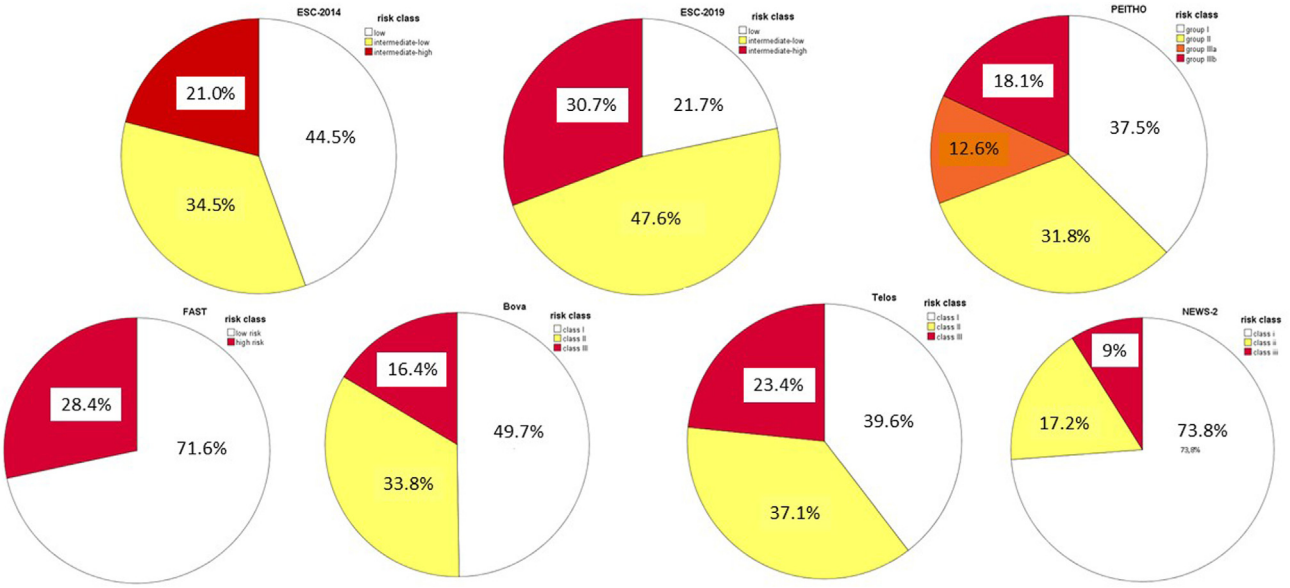

FIGURE 1 Distribution in risk classes according to different models in the overall study population (*N* = 5036). ESC, European Society of Cardiology; NEWS2, National Early Warning Scale 2; FAST, fatty acid binding protein, syncope and tachicardia; PEITHO, Pulmonary Embolism Thrombolysis; TELOS, Thrombo-embolism lactate outcome study).

in clinical practice—for instance, the ESC model to identify patients suitable for outpatient management and a separate score (PEITHO, Bova, and TELOS) for selecting who needs interventional therapy.

We had PE-related death as a secondary study outcome. The cause of death was centrally assessed by the Adjudication Committee. The definition of PE-related death used in the COPE study is very

TABLE 4 Positive and negative predictive values of different scores/models in the primary analysis population (*N* = 5036).

	Percentage negative predictive value (95% CI)			
Score/model	In-hospital death or clinical deterioration	In-hospital death	30-d death	Death due to PE
ESC-2014 (sPESI)	98.7 (98.2-99.2)	99.3 (99.0-99.7)	99.1 (98.7-99.5)	99.6 (99.3-99.9)
ESC-2019 (sPESI)	99.7 (99.3-100)	99.8 (99.5-100)	99.8 (99.5-100)	99.9 (99.7-100)
PEITHO	98.9 (98.3-99.4)	99.1 (98.6-99.6)	98.1 (97.4-98.8)	99.9 (99.7-100)
FAST score	96.9 (96.3-97.4)	97.6 (97.2-98.1)	96.4 (95.4-97.4)	99.2 (98.9-99.5)
Bova	98.5 (98.0-99.0)	98.9 (98.5-99.3)	97.7 (97.1-98.2)	99.7 (99.5-99.9)
TELOS	98.8 (98.3-99.2)	99.2 (98.9-99.6)	98.2 (97.6-98.7)	99.8 (99.6-100)
NEWS2 score	97.7 (97.3-98.2)	98.5 (98.1-98.9)	97.3 (96.8-97.8)	94.9 (92.9-96.9)
Score/model	**Percentage positive predictive value (95% CI)**			
	In-hospital death or clinical deterioration	**In-hospital death**	**30-d death**	**Death due to PE**
ESC-2014 (sPESI)	8.4 (7.0-9.9)	5.9 (4.7-7.2)	7.4 (6.1-8.8)	2.8 (1.9-3.7)
ESC-2019 (sPESI)	6.6 (5.6-7.7)	4.5 (3.6-5.4)	5.6 (4.6-6.7)	2.2 (1.6-2.8)
PEITHO	8.5 (7.1-10.0)	5.9 (4.7-7.2)	7.5 (6.1-8.8)	2.9 (2.0-3.8)
FAST score	6.8 (5.5-8.2)	4.1 (3.0-5.1)	5.6 (4.4-6.9)	2.3 (1.5-3.1)
Bova	9.3 (7.2-11.4)	5.5 (3.9-7.2)	6.9 (5.1-8.8)	3.3 (2.0-4.6)
TELOS	10.4 (8.5-12.3)	7.0 (5.4-8.5)	8.7 (7.0-10.5)	3.7 (2.5-4.8)
NEWS2 score	13.8 (10.7-16.9)	8.7 (6.1-11.2)	10.4 (7.6-13.1)	5.0 (3.1-7.1)

ESC, European Society of Cardiology; NEWS2, National Early Warning Scale 2; PE, pulmonary embolism; sPESI, simplified PE severity index; FAST, fatty acid binding protein, syncope and tachicardia; PEITHO, Pulmonary Embolism Thrombolysis; TELOS, Thrombo-embolism lactate outcome study).

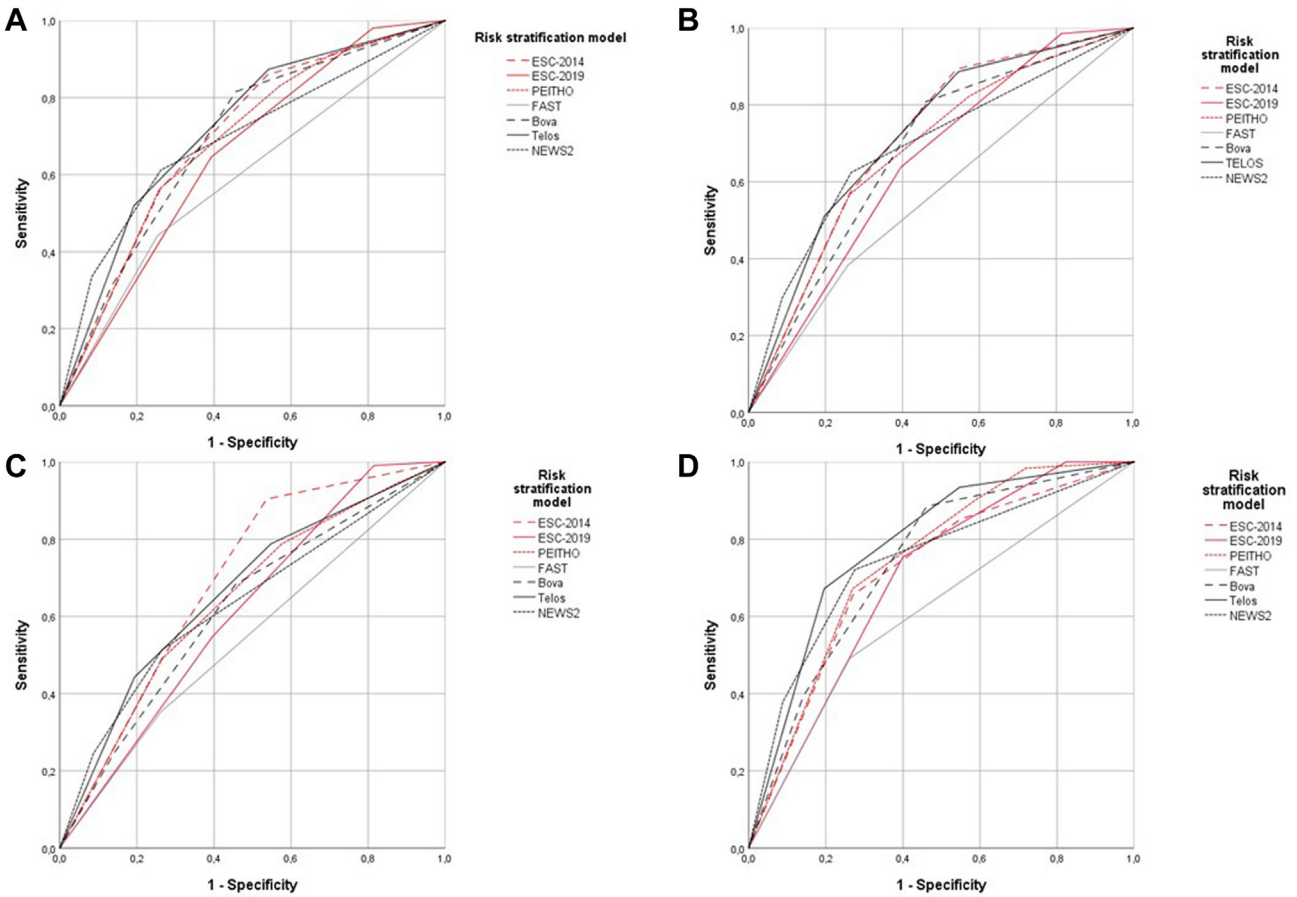

FIGURE 2 Receiver operating characteristic curves for prognostic scores and models in hemodynamically stable patients with acute pulmonary embolism included in the primary analysis population. (A) In-hospital death or clinical deterioration, (B) in-hospital death, (C) death at 30 days, and (D) death due to pulmonary embolism. ESC, European Society of Cardiology; NEWS2, National Early Warning Scale 2; FAST, fatty acid binding protein, syncope and tachicardia; PEITHO, Pulmonary Embolism Thrombolysis; TELOS, Thrombo-embolism lactate outcome study.

close to that proposed by the International Society of Thrombosis and Haemostasis [22,34].

Our study has some limits. First, despite the rate of missing data is minimal for clinical parameters, about one-fifth of the patients had echocardiography or troponin assessment missing at initial evaluation. This required management of missing data by multiple imputations. However, the analysis of patients with complete data included a number of hemodynamically stable patients as high as 3544 and showed consistent results with the primary analysis. In addition, no difference was observed between complete and incomplete cases (age, comorbidities, severity of PE, and management setting), and no systematic explanation was finally found for missing. Based on this, the "Missing at random" assumption was applied [24]. RVD was locally assessed, and no central evaluation was planned. Although this may have influenced the accuracy of the assessment, it is conceivable that our results reflect the role of RVD in clinical practice, thus increasing external validity of our results. In fact, requiring a centralized reading of echocardiograms reduces recruitment and may generate selection bias. Our study has some strengths. By using multiple imputation techniques, we could maintain the full sample of the COPE study for our analyses, thus allowing the validation of different prognostic models in a sample size of over 5000 hemodynamically stable patients with acute PE. In fact, ignoring missing data and using only subjects with complete data can result in biased results [25,35].

In conclusion, prognostic models/scores for identification of hemodynamically stable patients with acute PE at high risk for in-hospital death or clinical deterioration have modest positive predictive values, and this should be considered when using these tools for decision-making concerning reperfusion therapy. Our results may inform management studies and clinical practice.

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AUTHOR CONTRIBUTIONS

C.B. is the guarantor of the content of the manuscript, including the data and analysis.

M.C.V., S.C., S.V., M.G.A., A.B.S., A.M., M.B., M.B., A.F., F.D., A.P.M., G.A., and M.M.G. contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

TABLE 5 Performance of different scores/models for study outcome events in the primary population and in the complete-case population.

	C-statistic (95% CI)			
Prognostic model	In-hospital death or clinical deterioration	In-hospital death	30-d death	Death due to PE
Primary population (*N* = 5036)				
ESC-2014 (sPESI)	0.700 (0.666-0.734)	0.713 (0.675-0.751)	0.696 (0.665-0.726)	0.721 (0.659-0.784)
ESC-2019 (sPESI)	0.657 (0.624-0.690)	0.652 (0.613-0.692)	0.615 (0.582-0.649)	0.701 (0.645-0.756)
PEITHO	0.692 (0.658-0.726)	0.689 (0.647-0.731)	0.652 (0.616-0.689)	0.749 (0.696-0.803)
FAST score	0.594 (0.553-0.636)	0.563 (0.513-0.613)	0.551 (0.510-0.592)	0.623 (0.549-0.698)
Bova score	0.696 (0.662-0.731)	0.681 (0.639-0.723)	0.626 (0.588-0.664)	0.743 (0.687-0.799)
TELOS score	0.722 (0.688-0.756)	0.723 (0.678-0.762)	0.668 (0.626-0.705)	0.780 (0.730-0.829)
NEWS2 score	0.682 (0.641-0.724)	0.682 (0.634-0.730)	0.637 (0.596-0.678)	0.727 (0.657-0.797)
Complete-case population (*n* = 3544)				
ESC-2014 (sPESI)	0.670 (0.631-0.716)	0.697 (0.644-0.750)	0.674 (0.632-0.715)	0.688 (0.609-0.768)
ESC-2019 (sPESI)	0.636 (0.598-0.674)	0.669 (0.617-0.720)	0.617 (0.571-0.662)	0.696 (0.629-0.763)
PEITHO	0.675 (0.636-0.714)	0.708 (0.654-0.762)	0.682 (0.637-0.727)	0.758 (0.694-0.821)
FAST score	0.581 (0.534-0.627)	0.559 (0.492-0.626)	0.549 (0.494-0.604)	0.633 (0.542-0.725)
Bova score	0.675 (0.637-0.714)	0.702 (0.652-0.751)	0.648 (0.601-0.696)	0.744 (0.685-0.803)
TELOS score	0.711 (0.673-0.749)	0.727 (0.678-0.777)	0.680 (0.633-0.728)	0.788 (0.731-0.845)
NEWS2 score	0.674 (0.631-0.716)	0.684 (0.623-0.744)	0.643 (0.590-0.695)	0.749 (0.672-0.826)
NEWS2 score (*n* = 5009)[a]	0.702 (0.665-0.739)	0.692 (0.646-0.737)	0.637 (0.597-0.678)	0.738 (0.669-0.807)

ESC, European Society of Cardiology; NEWS2, National Early Warning Scale 2; PE, pulmonary embolism; sPESI, simplified PE severity index; FAST, fatty acid binding protein, syncope and tachicardia; PEITHO, Pulmonary Embolism Thrombolysis; TELOS, Thrombo-embolism lactate outcome study).
[a] Patients with oxygen saturation available.

DECLARATION OF COMPETING INTERESTS

None of the authors have conflicts of interest related to this manuscript.

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SUPPLEMENTARY MATERIAL

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