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Comparison of 5 acute pulmonary embolism mortality risk scores in patients with COVID-19

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ABSTRACT

Objective: Pulmonary embolism (PE) is a common complication of SARS-CoV-2 infection. We aimed to explore the short-term outcomes among patients with acute PE and COVID-19 and to further determine and compare the performance of the different prognostic scores (PESI, sPESI, BOVA, FAST and ESC scores) for risk-stratification in this scenario.

Methods: Retrospective single-centre study of 85 patients with SARS-CoV-2 infection and PE admitted to the Emergency Department (ED). The diagnostic accuracy of each above-mentioned prognostic score was calculated post hoc, and their discriminative power was evaluated through an AUC curve.

Results: Among the 85 patients, all-cause death occurred within 7 days for 6 patients (7.1%) and within 30 days for 14 patients (16.5%). Despite being older and having a higher percentage of altered mental status on presentation, non-survivors patients did not differ from survivors regarding comorbidities, traditional risk factors for venous thromboembolism and signs and symptoms at the ED presentation.

Each risk stratification tool had modest discriminative power for 7-day mortality (AUC range, 0.601–0.730) with slightly lower discrimination for 30-day mortality (AUC range, 0.543–0.638). The pair-wise comparison of ROC curves showed that PESI had better predictive value for short-term mortality than ESC score (z test = 3.92, p = 0.001) and sPESI (z test = 2.43, p = 0.015); there is no significant difference between PESI and BOVA score (z test = 1.05, p = 0.295) and FAST score (z test = 0.986, p = 0.324).

Conclusion: The most common risk-stratification tools for PE had modest discriminative power to predict short-term mortality in patients with acute PE and COVID-19.

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged at the end of 2019 and spread rapidly, becoming a significant public health problem worldwide [1].

The SARS-CoV-2 infection has been recognized as a hyper-inflammatory and prothrombotic state, with pulmonary embolism (PE) being one of the most common complications of COVID-19 [2].

Accumulating evidence has shown an increased risk of thrombotic complications in patients with COVID-19 whose prevalence of thromboembolism is up to 20–25% compared with a lifetime risk of 8% in the general population [3].

The predilection for thrombosis in COVID-19 may be driven by at least two distinct, but interrelated, processes: a hypercoagulable state responsible for large-vessel thrombosis and direct vascular and endothelial injury responsible for in situ microvascular thrombosis [4].

Because of the overlap of signs and symptoms between both conditions, the diagnosis and risk-stratification of PE in COVID-19 can be challenging.

In contemporary cohorts of patients with PE without COVID-19, an estimated 5–15% of patients were at high risk of death or hemodynamic collapse [5].

Prognostically, thromboembolism is believed to contribute to mortality and morbidity in patients infected with COVID-19.

Multiple risk assessment models have been developed to identify patients at risk for these complications and to stratify them. In the era pre-COVID-19, these risk scores were widely recommended in various

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treatment guidelines and expert recommendations [6]. However, when calculating these scores, we must keep in mind that both PE and COVID-19 influence patients' prognoses, and several comorbidities are identified as risk factors for both conditions [7,8]. Additionally, SARS-CoV2-infection could have an unpredictability clinical course with different grades of respiratory insufficiency. Thus, prognostic scores may underestimate the real patient's risk [3].

Some prognostic risk scores are primarily used to identify low-risk patients for whom outpatient treatment may be appropriate. Meanwhile, other scores aim to identify patients at high risk for mortality and hemodynamic deterioration.

The most widely recognised prognostic risk-scores include the Pulmonary Embolism Severity Index (PESI), the simplified PESI (sPESI), Bova and H- FABP (or high-sensitivity troponin T), Syncope, Tachycardia (FAST) scores.

The PESI [9] and sPESI [10] have demonstrated the ability to discriminate between high and low risk for 30-day all-cause mortality. However, these scores were derived from retrospective cohorts, and did not consider the eligibility for home treatment based on patients' social and ambulatory conditions, which could limit its value to guide clinical decision-making at the time of PE diagnosis [11].

BOVA [12] (include four parameters) and FAST [13] (include three parameters) scores are easier to calculate and have been validated in prospective cohort studies. However their implications for patient's management remain unclear. A fifth system, outlined in the 2019 European Society of Cardiology (ESC) guidelines [6], recommends using PESI or the sPESI scores and adds biomarker and radiological findings to the risk stratification scheme.

The accuracy of the above-mentioned risk tools for COVID-19 patients stratification in the setting of PE is unclear. Considering that these scores could identify patients at higher risk that should be hospitalized against those that could be treated at home (relieving the pressure that COVID-19 made on hospital capacity), it is imperative to evaluate the accuracy of the different prognostic scores.

This study aimed to explore the short-term outcomes among patients with acute PE and COVID-19 and to further determine and compare the performance of these prognostic scores for risk-stratification in this scenario.

2. Methods

Single-centre retrospective study performed at a tertiary hospital from 1st April 2020 to 31st March 2021. We selected consecutive adult outpatients with confirmed SARS-CoV-2 infection admitted to the ED, in whom the diagnosis of PE on computed tomography pulmonary angiography (CTPA). Only patients with confirmed SARS-CoV-2 infection in the previous ten days before the ED admission were included. The diagnosis of SARS-CoV-2 was based on a positive result of real-time reverse transcriptase-polymerase chain reaction assay of nasopharyngeal and pharyngeal swabs or, in patients with prior diagnosis, by consulting the national registration platform of COVID-19 patients. Patients without a laboratory assay or with an inconclusive CTPA were excluded.

Demographic, clinical and laboratory data were extracted from a blinded investigator for CTPA reports from electronic medical records.

2.1. Scores and algorithms assessment

The items comprising the prognostic prediction models were calculated *post hoc* by the authors based on the clinical data records at the time of CTPA request. If there was no documentation for a component of any score, it was considered absent.

The PESI score ranges from 0 to >125 points, based on the following criteria: age in years, male sex (10 points), cancer (30 points), chronic heart failure (10 points), chronic pulmonary disease (10 points), pulse rate ≥110 bpm (20 points), systolic blood pressure <100 mmHg (30 points), respiratory rate >30 breaths per min (20 points), temperature <36 °C (20 points), altered mental status (60 points), arterial oxyhaemoglobin saturation <90% (20 points). Patients were categorized according to a risk-stratification of mortality in 5 classes: class I: <65 points (very low 30 day mortality risk: 0–1.6%); Class II: 66–85 points (low mortality risk: 1.7–3.5%); Class III: 86–105 points (moderate mortality risk: 3.2–7.1%); Class IV: 106–125 points (high mortality risk: 4.0–11.4%); Class V: >125 points (very high mortality risk: 10.0–24.5%).

The sPESI score classifies the patients in low risk (30-day mortality risk 1.0% (95% CI 0.0–2.1%)) or high risk (30-day mortality risk 10.9% (95% CI 8.5–13.2%)) according to the presence of 0 points and ≥1 point, respectively. The sPESI is based on six clinical characteristics, attributing 1 point for each: age, cancer, chronic heart failure or pulmonary disease, pulse rate ≥110 bpm, systolic blood pressure (BP) <100 mmHg and arterial oxyhaemoglobin saturation <90%.

The BOVA score includes four parameters (1 point for each): elevated cardiac troponin, right ventricular (RV) dysfunction (documented on transthoracic echocardiogram or CTPA), heart rate ≥110 bpm, systolic BP 90–100 mmHg. The Bova score categorizes patients into three risk groups: group I (0–2 points), group II (3–4 points), and group III (>4points). This score excludes patients presenting with hypotension. To properly compare an individual's risk between different scores, we modified the Bova score using two methods. First, we created a fourth risk group for patients with a systolic BP < 90 mmHg at presentation. Second, we included all patients with systolic BP < 90 mm Hg into the high-risk group (class IV).

FAST score include 3 parameters: elevated cardiac troponin (1.5 point), syncope (1.5 point), heart rate ≥ 100 bpm (2 points). Based on this, the patients were split into low risk (<3 points) and intermediate-high risk (≥3 points).

2.2. CT protocol

Computed tomography (CT) was obtained with a 16-slice multidetector CT (Siemens®) after intravenous injection of 60–90 mL of iodinated contrast agent. The CTPA scans were interpreted by an attending radiologist and reviewed at the time of study inclusion by a second radiologist, blinded for the clinical information.

Pulmonary embolism diagnosis was based on filling defects of the pulmonary artery on at least two consecutive axial sections. In addition, PE was classified according to the location of the thrombus and the presence of right heart strain (defined as right/left ventricle ratio > 1 or interventricular septal bowing).

2.3. Statistical analysis

Categorical variables were presented as frequency rates and percentages and continuous variables as median with interquartile range. Categorial and continuous variables were compared using Pearson chi-square and Mann-Whitney tests, respectively. Sensitivity, specificity, positive and negative predictive values, likelihood ratios and diagnostic odds ratio were calculated and compared among the different prognostic scores. The discriminative power of each score to stratify the prognosis was determined by receiver operating characteristic (ROC) curve analysis, and the area under the curve (AUC) was calculated. ROC curves were compared using the De-Long method.

Statistical significance was defined as a p-value < 0.05. The statistical software used to analyze the data was SPSS®v.26 (IBM).

3. Results

A total of 1477 CTPAs for the suspicion of PE were performed during the study period, 315 of them in patients with a confirmed SARS-CoV-2 infection.

After applying the exclusion criteria, eighty-five patients with

COVID-19 and PE were included in the final analysis. The study flowchart is summarized in Fig. 1.

The demographic, clinical and laboratory features of patients comparing survivors and non-survivors are shown in Table 1.

The vascular allocation of emboli showed a predominantly central distribution (54%), affecting main and lobar arteries (19% and 35%, respectively). Most PE had bilateral involvement (54%), and 23% of patients had evidence of right heart strain. Non-survivors' patients had a significantly higher incidence of bilateral involvement incidence than the survivors. Anticoagulation was done in almost all patients (83 patients with low-molecular-weight heparin and 1 patient with non-fractioned heparin), one of the patients wasńt anticoagulated.

There was no difference in the time between symptoms of COVID-19 and the diagnosis of PE and between RT-PCR confirmation test and the diagnosis of PE (median of 5 days).

Despite being older and having a higher percentage of altered mental status on presentation, non-survivors' patients did not differ from survivors regarding comorbidities, traditional risk factors and signs and symptoms at the ED presentation.

Regarding the laboratory results, the only difference between survivors and non-survivors was that the last had lower haemoglobin and higher d-dimer levels.

In univariate analysis, only age (OR: 1.092, 95%CI 1.030–1.158, p = 0.003), haemoglobin values (OR: 0.708, 95%CI 0.510–0.982, p = 0.039) and altered mental status (OR: 0.261, 95%CI 0.071–0.957, p = 0.043) were identified as predictors of death in 30 days. None of the comorbidities or traditional risk factors for VTE was identified as predictors of mortality in this cohort. A multivariate logistic regression analysis was performed for mortality based on these three variables, and only age was identified as an independent predictor of mortality in this cohort (OR: 1.079, 95%IC 1.018–1.143, p = 0.010).

Among the 85 patients, all-cause death occurred within 7 days for 6 patients (7.1%) and within 30 days for 14 patients (16.5%). The causes of death were multifactorial but all had respiratory failure with different degrees of interstitial pneumonia (from 10% to 100% involvement of the lung parenchyma). One of the patients died from complication associated with an major stroke. Intensive care unit admission was observed in 16 patients (18.8%; 10 patients in the survivor group) and mechanical ventilation was needed in 12 patients (12.1%; 8 patients in the survivor group). Two of the patients died in the first 24 h of observation in the emergency department.

As seen in Table 2, 7-day mortality in the low-risk groups ranged from 0.0% (0 patients; sPESI, PESI and ESC score) to 3.5% (3 patients; Bova and FAST score), whereas 30-day mortality ranged from 0.0% (0 patients; PESI) to 9.4% (8 patients; FAST score); the rate was 2.4% (2 patients) for sPESI. Among patients in the highest-risk groups, the 7-day mortality ranged from 2.4% (2 patients; BOVA - class III and IV) to 7.1% (6 patients; sPESI), whereas 30-day mortality ranged from 14.4% (37 patients; sPESI) to 7.1% (6 patients; FAST score).

ROC analysis comparing the accuracy of ESC score, PESI, sPESI, BOVA and FAST score to predict mortality in 7 and 30 days is shown in Table 2 and Fig. 2.

Each risk stratification tool had modest discrimination for 7-day mortality (AUC range, 0.601–0.730) with slightly lower discrimination for 30-day mortality (AUC range, 0.543–0.638).

The pair-wise comparison of ROC curves showed that PESI had better predictive value for short-term mortality than ESC score (z test = 3.92, p = 0.001), sPESI (z test = 2.43, p = 0.015); and there is no significant difference between PESI and BOVA score (z test = 1.05, p = 0.295) and FAST score (z test = 0.986, p = 0.324).

4. Discussion

Our analysis demonstrates that all PE-risk scores had modest discriminative power to predict 7- and 30-day mortality, and that most of them are better for estimating the shorter-term outcomes.

To the best of our knowledge, this is the first study to validate these scores as predictors of mortality in COVID-19 patients admitted to the ED with PE, whether they were hospitalized or not, and to further evaluate its prognostic value as a predictor of short-term mortality.

The *ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic* [14] *and the CHEST* [15] recommend that when acute PE is confirmed, treatment should be guided by risk stratification following the current ESC guidelines. However, risk scores performance may be impaired in this particular population due to several reasons: first, the symptoms of PE may mimick or overlap with those of COVID-19 infection, making it challenging to identify causality; second, the overlap between comorbidities and risk factors of this two pathologies may underestimate the real impact of each factor on the final prognosis; third, either the use of biomarkers as troponin/NT-proBNP may be seen in COVID-19 infection, therefore possibly confounding its clinical utility; fourth, COVID-19-associated cardiomyopathy may be an alternative cause of RV dysfunction, and the presence of cardiomyopathy does not exclude concurrent PE and may, indeed, be an independent risk factor for PE based on poor cardiac output.

Risk stratification must consider the relative contribution of COVID-19 lower respiratory tract infection, versus that of PE, as the cause of respiratory failure. The respiratory and hemodynamic compromise from both the viral pneumonia and the PE need to be fully investigated to determine which disorders have the greatest impact and to determine optimal treatment [4,15].

According to the current guidelines, the indication for hospitalization and treatment options (eg, anticoagulation alone, thrombolysis, or thrombectomy) should be based on this initial risk assessment [6].

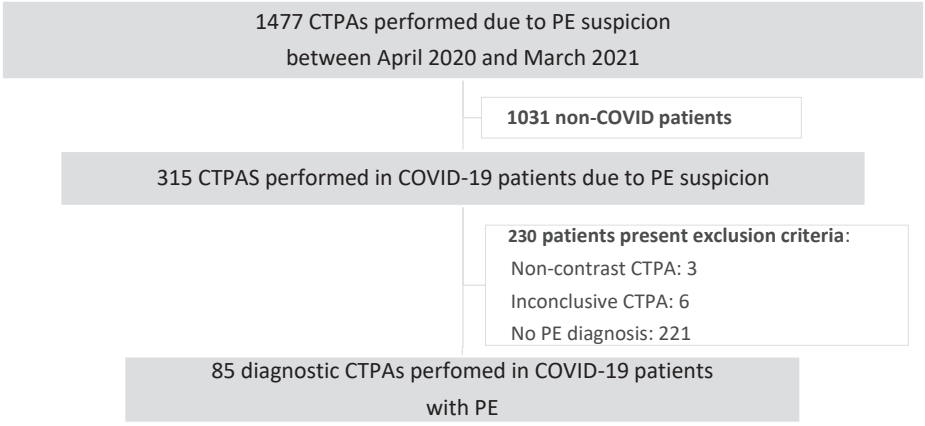

Fig. 1. xxx.

Table 1
Demographic and clinical characteristics of patients admitted with COVID-19 and PE at baseline (all patients) and according to the outcome (survivors and non-survivors at 30 days). Data are reported as *n* (%) or median (IQR). Abbreviations: PE, pulmonary embolism; ED, emergency department; RT-PCR, real-time reverse transcriptase-polymerase chain reaction; NT-proBNP, N-terminal prohormone B-type natriuretic peptide.

Variable	All patients		Survivors		Non-survivors		p value
	(n = 85)		(n = 71)		(n = 14)		
Age, median (Q1-Q3) (years)	72	(63–83)	71	(59–80)	83.5	(77–90)	**p = 0.002**
Gender - Male, n (%)	45	(52.9%)	39	(54.9%)	6	(42.9%)	p = 0.408
Comorbidities							
Obesity, n (%)	9	(10.6%)	6	(8.5%)	3	(21.4%)	p = 0.149
Arterial hypertension, n (%)	53	(62.4%)	42	(59.2%)	11	(78.6%)	p = 0.171
Dyslipidemia, n (%)	26	(30.6%)	23	(32.4%)	3	(21.4%)	p = 0.416
Diabetes mellitus, n (%)	23	(27.1%)	20	(28.2%)	3	(21.4%)	p = 0.604
Chronic heart failure, n (%)	5	(5.9%)	5	(7.0%)	0	(0.0%)	p = 0.306
Ischemic heart disease, n (%)	6	(7.1%)	4	(5.6%)	2	(14.3%)	p = 0.248
Atrial fibrillation, n (%)	9	(10.6%)	7	(9.9%)	2	(14.3%)	p = 0.623
Chronic kidney disease, n (%)	21	(24.7%)	16	(22.5%)	5	(35.7%)	p = 0.296
Chronic obstructive pulmonary disease, n (%)	14	(16.5%)	12	(16.9%)	2	(14.3%)	p = 0.809
Chronic respiratory insufficiency, n (%)	2	(2.4%)	2	(2.8%)	0	(0.0%)	p = 0.525
Apnea syndrome, n (%)	3	(3.5%)	3	(4.2%)	0	(0.0%)	p = 0.434
Smoking (active or past smoker), n (%)	10	(11.8%)	7	(9.9%)	3	(21.4%)	p = 0.431
Cerebrovascular disease, n (%)	16	(18.8%)	12	(16.9%)	4	(28.6%)	p = 0.307
Active malignancy, n (%)	4	(4.7%)	4	(5.6%)	0	(0.0%)	p = 0.363
ED presentation							
Progressive dyspnea, n (%)	54	(63.5%)	45	(63.4%)	9	(64.3%)	p = 0.949
Chest pain, n (%)	15	(17.6%)	14	(19.7%)	1	(7.1%)	p = 0.259
Syncope, n (%)	6	(7.1%)	5	(7.0%)	1	(7.1%)	p = 0.989
Dry cough, n (%)	26	(30.6%)	19	(26.8%)	7	(50.0%)	p = 0.085
Fever, n (%)	28	(32.9%)	22	(31.0%)	6	(42.9%)	p = 0.388
Altered mental status, n (%)	14	(16.5%)	9	(12.7%)	5	(35.7%)	**p = 0.034**
Clinical status							
Systolic blood pressure, median (Q1-Q3) (mmHg)	130	(115.5–148.0)	130	(116.0–148.0)	133	(111.3–159.3)	p = 0.666
Heart rate, median (Q1-Q3) (beats/min)	89	(79.5–106.0)	87	(79–105)	96.5	(81.0–113.3)	p = 0.387
Respiratory rate, median (Q1-Q3) (breaths/min)	18	(16.0–22.0)	18	(16–21)	19.5	(16.0–22.3)	p = 0.927
SpO2, median (Q1-Q3) (%)	95	(91.5–97.5)	95	(92.0–98.0)	92.5	(87.8–95.8)	p = 0.175
Oxygen apport, median (Q1-Q3) (L/min)	1	(0.0–3.0)	0.0	(0.0–2.0)	2.0	(0.0–6.0)	p = 0.833
Temperature, median (Q1-Q3) (°C)	37	(36.0–38.0)	37.0	(36.0–38.0)	37.0	(36.0–38.0)	p = 0.823
Laboratory results							
Hemoglobin, median (Q1-Q3) (g/dL)	13.2	(12.0–14.1)	13.2	(12.2–14.3)	12	(11.3–13.2)	**p = 0.020**
D-dimer, median (Q1-Q3) (ng/mL)	5860	(1190–22895)	4550	(1170–22000)	16,470	(1913–37918)	**p = 0.026**
Platelets, median (Q1-Q3) ($x10^3$)	217	(155.5–278.5)	221	(159–284)	182	(133–243)	p = 0.119
hs Troponin T, median (Q1-Q3) (ng/L)	17	(9–66)	17	(9–55)	18	(9–134)	p = 0.262
NT-proBNP, median (Q1-Q3) (pg/mL)	413	(73–1574)	347	(67–1368)	508	(306–2531)	p = 0.425
Creatinine, median (Q1-Q3) (mg/dl)	0.90	(0.72–1.17)	0.91	(0.73–1.14)	0.84	(0.62–1.55)	p = 0.915
eGFR, median (Q1-Q3) (mL/min/1.73 m^2)	78	(57.5–91)	78	(59–92)	63.5	(38–84)	p = 0.147
Time between COVID-19 symptoms and CTPA, median (Q1-Q3) (days)	5.0	(2–10)	5	(2–10)	5	(1–19)	p = 0.398
RT-PCR positive to CTPA, median (Q1-Q3)(days)	5.0	(1–12.5)	5	(1–12)	8	(1–18)	p = 0.636
Localization and affection of PE							
Main arteries, n (%)	16	(18.8%)	15	(21.1%)	1	(7.1%)	p = 0.221
Lobar arteries, n (%)	30	(35.3%)	23	(32.4%)	7	(50.0%)	p = 0.208
Subsegmentar arteries, n (%)	39	(45.8%)	33	(46.5%)	6	(42.9%)	p = 0.591
Bilateral involvement, n (%)	46	(54.1%)	35	(49.3%)	11	(78.6%)	**p = 0.045**
Right heart disfunction, n (%)	19	(22.4%)	16	(22.5%)	3	(21.4%)	p = 0.428

However, our data suggest that no single risk score is highly accurate or superior to another for estimating 30-day mortality. Regarding short-term (7 days) mortality, we had a slighter better accuracy of the different scores, especially PESI, which showed to be slightly better than the others (AUC 0.73). This difference between the two periods of time is concordant with other studies of patients with PE without COVID-19 [5]. The better accuracy of PESI score could be explained by the fact that this score considers a higher number of variables that will better stratify each patient in the different risk strata.

Regarding mortality risk, except for older patients, we found no differences in comorbidities or risk factors for VTE between survivors and non-survivors patients, which may justify the absence of predictive value of the different risk scores for PE mortality. This data highlights the difficulty of PE risk stratification in COVID-19 patients, probably because inflammation, endothelial dysfunction and coagulopathy play a major role in its pathophysiology [4,16]. Accordingly, caution is recommended when interpreting the impact of PE on mortality in COVID-19 patients, as it is difficult to distinguish the mortality directly attributed to the lung disease from which that results from the PE. Thus, it is necessary to use both prognostic risk scores for PE and for COVID-19 mortality to better predict the prognosis in those patients. However as *Lombardi Y* [17] et al showed that the prognostic scores for COVID-19 were only fairly accurate to predict death in hospitalised COVID-19 patients.

Table 2
Pulmonary Embolism Risk Scores and Associated 7- and 30-Day Mortality. Abbreviation: AUC, area under the receiver operator curve.

Risk score	All patients, no.	Death within 7 days			Death within 30 days		
		Patiens, No. (%)	*P value*	AUC (95% CI)	Patiens, No. (%)	*P value*	AUC (95% CI)
European Society of Cardiology risk score							
Low risk	21 (24.7)	0 (0.0)	0.011	0.648 (0.460–0.835)	3 (3.5)	0.352	0.543 (0.375–0.712)
Intermediate-low	45 (52.9)	4 (4.7)			7 (8.2)		
Intermediate-high	19 (22.4)	2 (2.4)			4 (4.7)		
High	0 (0.0)	0 (0.0)			0 (0.0)		
Pulmonary embolism severity index							
Class I	7 (8.2)	0 (0.0)	0.001	0.730 (0.580–0.880)	0 (0.0)	0.047	0.638 (0.476–0.800)
Class II	16 (18.8)	0 (0.0)			3 (3.5)		
Class III	27 (31.8)	1 (1.2)			2 (2.4)		
Class IV	17 (20.0)	3 (3.5)			4 (4.7)		
Class V	18 (21.2)	2 (2.4)			5 (5.9)		
Simplified pulmonary embolism severity index							
Low risk	16 (18.8)	0 (0.0)	0.001	0.601 (0.502–0.801)	2 (2.4)	0.131	0.527 (0.365–0.689)
Intermediate-high risk	69 (81.2)	6 (7.1)			12 (14.1)		
BOVA							
Class I	58 (68.2)	3 (3.5)	0.012	0.634 (0.472–0.896)	6 (7.1)	0.041	0.627 (0.456–0.799)
Class II	18 (21.2)	1 (1.2)			4 (4.7)		
Class III	8 (9.4)	2 (2.4)			3 (3.5)		
Class IV	1 (1.2)	0 (0.0)			1 (1.2)		
Fast score							
Low risk	65 (76.5)	3 (3.5)	0.013	0.642 (0.495–0.890)	8 (9.4)	0.049	0.616 (0.444–0.787)
Intermediate-high risk	20 (23.5)	3 (3.5)			6 (7.1)		

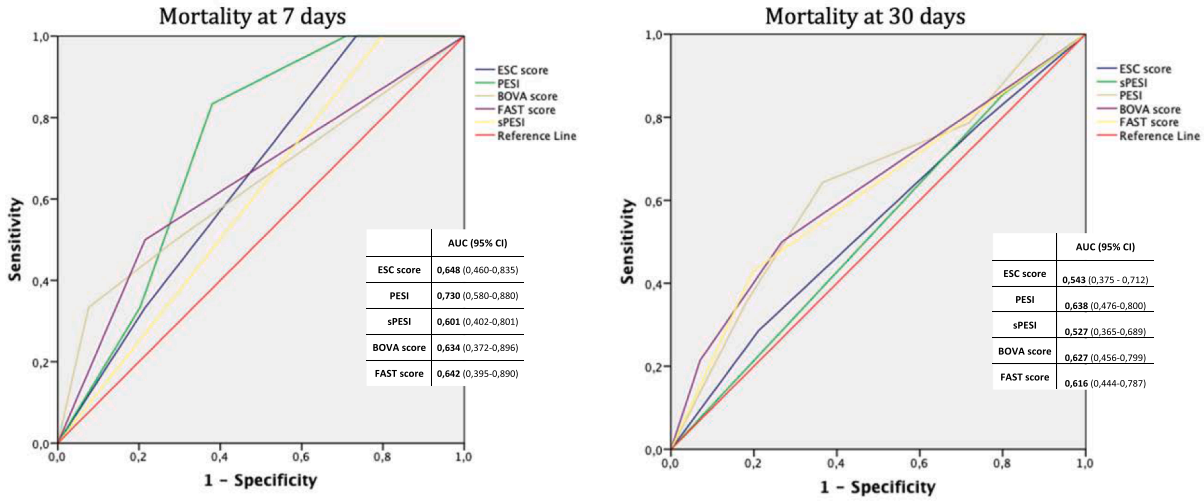

Fig. 2. analysis comparing the predictive accuracy for mortality at 7 and 30 days of ESC score, PESI, sPESI, BOVA and FAST score. Abbreviations: AUC, area under the curve; CI, confidence interval.

In agreement with previous studies [18], we found that non-survivors patients had significantly higher D-dimer levels than survivors. As the degradation product of crosslinked fibrin (by factor XIII), D-dimer reflects an ongoing activation of the haemostatic system and serves as an indicator of thrombosis. Nevertheless, there is no consensus on the optimal cut-off value and the real prognostic significance of this parameter. Some studies show a significant correlation between PE and mortality [8], and others no [3] (which is the case of our cohort).

The mortality rate observed on our cohort (7.1% at 7 days and 16.5% at 30 days) was comparable with the previous reported, regardless of the heterogeneity among populations studied [19,20,21]. Considering that patients' selection was based on CTPA request due to clinical worsening and/or PE suspicion, some patients without symptoms related to PE could be included in our cohort.

It is probable that our cohort excludes the patients that were transferred directly to ICUs, underestimating the real mortality incidence.

A clinical study from Barnes et al. [5] that compared four clinical prognostic risk scores (PESI; sPESI; BOVA and ESC score) in a population with PE without COVID-19 had similar results compared to our study among low-risk patients according to both the PESI (2.6% vs 2.4%) and the sPESI (3.8% vs 2.4%) scores. However, the documented 30-day mortality rates differed from our study among those highest-risk groups for the PESI score (26.3% vs 5.9%) but less so for the sPESI score (14.4% vs 14.1%).

From a research and quality improvement standpoint, the use of any single PE risk stratification tool may not be adequate to appropriately

risk-adjust patient outcomes. This is particularly relevant when comparing clinical outcomes across hospitals or organizations. In addition, the limited ability of any single risk score to estimate mortality may limit its use in identifying patients most likely to benefit from advanced therapies, especially in this specific population of patients with COVID-19. It is possible that currently available treatments (e.g., catheter-directed thrombolysis) may offer mortality benefits only if the patients at higher risk for complications can be easily identified.

4.1. Limitations

Our study must be evaluated in light of some limitations. First, this is a single-centre retrospective observational study. Therefore, prospective larger multicentre studies are needed to draw definitive conclusions. Secondly, only adverse events recorded in the index hospital's medical record were considered. In addition, mortality was assessed as all-cause rather than PE-specific because we are unable to assess death attributable to PE or underlying comorbidities in the data set. Thirdly, clinicians may have incorporated one or more of these scores into their management decisions, which can be potentially associated with mortality outcomes. Fourth, larger validations studies are needed given the small overall number of deaths in our study population. However, we believe this to be the first study that validates these risk tools published to date.

5. Conclusions

Our study demonstrates that the most common risk-stratification tools for PE had only modest discriminative power to predict short-term mortality in patients with acute PE and COVID-19.

Further studies to develop and validate more accurate risk assessment tools should be encouraged to improve clinical care and human resources in the setting of the COVID-19 pandemic.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] N.a. Zhu, D. Zhang, W. Wang, X. Li, B.o. Yang, J. Song, X. Zhao, B. Huang, W. Shi, R. Lu, P. Niu, F. Zhan, X. Ma, D. Wang, W. Xu, G. Wu, G.F. Gao, W. Tan, A novel coronavirus from patients with pneumonia in China, 2019, N. Engl. J. Med. 382 (8) (2020) 727–733.

[2] J. Brito, B.V. Silva, P. Alves et al., Cardiovascular Complications of COVID-19, Published online, 2020, pp. 67–74. doi:10.4103/hm.hm.

[3] C.A. Gómez, C.K. Sun, I.T. Tsai et al., Mortality and risk factors associated with pulmonary embolism in coronavirus disease 2019 patients: a systematic review and meta – analysis (901) (2021) 1–13.

[4] C. Coughlan, S. Rahman, K. Honeyford, et al., Pulmonary thrombosis and thromboembolism in COVID-19, Chest 97 (1) (2021) 4–11, https://doi.org/10.1136/postgradmedj-2021-140086.

[5] G.D. Barnes, A. Muzikansky, S. Cameron, J. Giri, G.A. Heresi, W. Jaber, T. Wood, T. M. Todoran, D.M. Courtney, V. Tapson, C. Kabrhel, Comparison of 4 acute pulmonary embolism mortality risk scores in patients evaluated by pulmonary embolism response teams, JAMA Netw. Open 3 (8) (2020) e2010779, https://doi.org/10.1001/jamanetworkopen.2020.10779.

[6] S.V. Konstantinides, G. Meyer, C. Becattini, 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. 41 (4) (2020) 543–603, https://doi.org/10.1093/eurheartj/ehz405.

[7] Y.J. Suh, H. Hong, M. Ohana, F. Bompard, M.-P. Revel, C. Valle, A. Gervaise, J. Poissy, S. Susen, G. Hékimian, M. Artifoni, D. Periard, D. Contou, J. Delaloye, B. Sanchez, C. Fang, G. Garzillo, H. Robbie, S.H. Yoon, Pulmonary embolism and deep vein thrombosis in COVID-19: a systematic review and meta-analysis, Radiology 298 (2) (2021) E70–E80.

[8] T.P. Velavan, C.G. Meyer, International Journal of Infectious Diseases Mild versus severe COVID-19: Laboratory markers 95 (2020) 304–307. doi.org/10.1016/j.ijid.2020.04.061.

[9] J. Donzé, G. Gal, M.J. Fine, P.-M. Roy, O. Sanchez, F. Verschuren, J. Cornuz, G. Meyer, A. Perrier, M. Righini, D. Aujesky, Prospective validation of the pulmonary embolism severity index, Thromb. Haemost. 100 (05) (2008) 943–948.

[10] M. Righini, P.-M. Roy, G. Meyer, F. Verschuren, D. Aujesky, G. Le gal, The simplified Pulmonary Embolism Severity Index (PESI): validation of a clinical prognostic model for pulmonary embolism, J Thromb Haemost. 9 (10) (2011) 2115–2117, https://doi.org/10.1111/j.1538-7836.2011.04469.x.

[11] P.-M. Roy, A. Penaloza, O. Hugli, et al., Triaging acute pulmonary embolism for home treatment by Hestia or simplified PESI criteria: the HOME-PE randomized trial, Eur. Heart J. 42 (33) (2021) 3146–3157, https://doi.org/10.1093/eurheartj/ehab373.

[12] C. Bova, O. Sanchez, P. Prandoni, M. Lankeit, S. Konstantinides, S. Vanni, D. Jimenez, Identification of intermediate-risk patients with acute symptomatic pulmonary embolism, Eur. Respir. J. 44 (3) (2014) 694–703, https://doi.org/10.1183/09031936.00006114.

[13] C. Dellas, M. Tschepe, V. Seeber, I. Zwiener, K. Kuhnert, K. Schäfer, G. Hasenfuß, S. Konstantinides, M. Lankeit, A novel H-FABP assay and a fast prognostic score for risk assessment of normotensive pulmonary embolism, Thromb. Haemost. 111 (05) (2014) 996–1003, https://doi.org/10.1160/TH13-08-0663.

[14] The European Society for Cardiology. ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic, Eur. Heart J. Published online (2020) 1–115. <https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance> (Last update: 10 June 2020).

[15] R.P. Rosovsky, C. Grodzin, R. Channick, G.A. Davis, J.S. Giri, J. Horowitz, C. Kabrhel, R. Lookstein, G. Merli, T.A. Morris, B. Rivera-Lebron, V. Tapson, T. M. Todoran, A.S. Weinberg, K. Rosenfield, Diagnosis and treatment of pulmonary embolism during the coronavirus disease 2019 pandemic, Chest 158 (6) (2020) 2590–2601, https://doi.org/10.1016/j.chest.2020.08.2064.

[16] S. Shi, M.u. Qin, B.o. Shen, Y. Cai, T. Liu, F. Yang, W. Gong, X.u. Liu, J. Liang, Q. Zhao, H.e. Huang, B.o. Yang, C. Huang, Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China, JAMA Cardiol. 5 (7) (2020) 802, https://doi.org/10.1001/jamacardio.2020.0950.

[17] Y. Lombardi, L. Azoyan, P. Szychowiak, A. Bellamine, G. Lemaitre, M. Bernaux, C. Daniel, J. Leblanc, Q. Riller, O. Steichen, P.-Y. Ancel, A. Bauchet, N. Beeker, V. Benoit, R. Bey, A. Bourmaud, S. Bréant, A. Burgun, F. Carrat, C. Caucheteux, J. Champ, S. Cormont, J. Dubiel, C. Duclos, L. Esteve, M. Frank, N. Garcelon, A. Gramfort, N. Griffon, O. Grisel, M. Guilbaud, C. Hassen-Khodja, F. Hemery, M. Hilka, A.S. Jannot, J. Lambert, R. Layese, L. Lebouter, D. Leprovost, I. Lerner, K. L. Sallah, A. Maire, M.-F. Mamzer, P. Martel, A. Mensch, T. Moreau, A. Neuraz, N. Orlova, N. Paris, B. Rance, H. Ravera, A. Rozes, P. Rufat, E. Salamanca, A. Sandrin, P. Serre, X. Tannier, J.-M. Treluyer, D. Van Gysel, G. Varoquaux, J.-J. Vie, M. Wack, P. Wajsburt, D. Wassermann, E. Zapletal, External validation of prognostic scores for COVID-19: a multicenter cohort study of patients hospitalized in Greater Paris University Hospitals, Intensive Care Med. 47 (12) (2021) 1426–1439, https://doi.org/10.1007/s00134-021-06524-w.

[18] B. Valente, C. Jorge, R. Plácido, et al., Pulmonary embolism and COVID-19: A comparative analysis of different diagnostic models performance, Am. J. Emerg. Med. 50 (2020) 526–531, https://doi.org/10.1016/j.ajem.2021.09.004.

[19] M.B. Malas, I.N. Naazie, N. Elsayed, A. Mathlouthi, R. Marmor, B. Clary, Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: a systematic review and meta-analysis, EClinicalMedicine 29-30 (2020) 100639, https://doi.org/10.1016/j.eclinm.2020.100639.

[20] S. Richardson, J.S. Hirsch, M. Narasimhan, J.M. Crawford, T. McGinn, K. W. Davidson, D.P. Barnaby, L.B. Becker, J.D. Chelico, S.L. Cohen, J. Cookingham, K. Coppa, M.A. Diefenbach, A.J. Dominello, J. Duer-Hefele, L. Falzon, J. Gitlin, N. Hajizadeh, T.G. Harvin, D.A. Hirschwerk, E.J. Kim, Z.M. Kozel, L.M. Marrast, J. N. Mogavero, G.A. Osorio, M. Qiu, T.P. Zanos, Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area, JAMA – J. Am. Med. Assoc. 323 (20) (2020) 2052, https://doi.org/10.1001/jama.2020.6775.

[21] G. Grasselli, A. Zangrillo, A. Zanella, M. Antonelli, L. Cabrini, A. Castelli, D. Cereda, A. Coluccello, G. Foti, R. Fumagalli, G. Iotti, N. Latronico, L. Lorini, S. Merler, G. Natalini, A. Piatti, M.V. Ranieri, A.M. Scandroglio, E. Storti, M. Cecconi, A. Pesenti, E. Agosteo, V. Alaimo, G. Albano, A. Albertin, A. Alborghetti, G. Aldegheri, B. Antonini, E. Barbara, N. Belgiorno, M. Belliato, A. Benini, E. Beretta, L. Bianciardi, S. Bonazzi, M. Borelli, E. Boselli, N. Bronzini, C. Capra, L. Carnevale, G. Casella, G. Castelli, E. Catena, S. Cattaneo, D. Chiumello, S. Cirri, G. Citerio, S. Colombo, D. Coppini, A. Corona, P. Cortellazzi, E. Costantini, R. D. Covello, G. De Filippi, M. Dei Poli, F. Della Mura, G. Evasi, R. Fernandez-Olmos, A. Forastieri Molinari, M. Galletti, G. Gallioli, M. Gemma, P. Gnesin, L. Grazioli, S. Greco, P. Gritti, P. Grosso, L. Guatteri, D. Guzzon, F. Harizay, R. Keim, G. Landoni, T. Langer, A. Lombardo, A. Malara, E. Malpetti, F. Marino, G. Marino, M. Mazzoni, G. Merli, A. Micucci, F. Mojoli, S. Muttini, A. Nailescu, M. Panigada, P. Perazzo, G.B. Perego, N. Petrucci, A. Pezzi, A. Protti, D. Radrizzani, M. Raimondi, M. Ranucci, F. Rasulo, M. Riccio, R. Rona, C. Roscitano, P. Ruggeri, A. Sala, G. Sala, L. Salvi, P. Sebastiano, P. Severgnini, I. Sforzini, F.D. Sigurtà,

M. Subert, P. Tagliabue, C. Troiano, R. Valsecchi, U. Viola, G. Vitale, M. Zambon, E. Zoia, Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy, JAMA – J. Am. Med. Assoc. 323 (16) (2020) 1574, https://doi.org/10.1001/jama.2020.5394.