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Rapid prediction of adverse outcomes for acute normotensive pulmonary embolism: derivation of the Calgary Acute Pulmonary Embolism score

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ABSTRACT

Background: Acute pulmonary embolism (PE) has a wide spectrum of outcomes, but the best method to risk-stratify normotensive patients for adverse outcomes remains unclear.

Methods: A multicentre retrospective cohort study of acute PE patients admitted from emergency departments in Calgary, Canada, between 2012 and 2017 was used to develop a refined acute PE risk score. The composite primary outcome of in-hospital PE-related death or haemodynamic decompensation. The model was internally validated using bootstrapping and the prognostic value of the derived risk score was compared to the Bova score.

Results: Of 2067 patients with normotensive acute PE, the primary outcome (haemodynamic decompensation or PE-related death) occurred in 32 (1.5%) patients. In simplified Pulmonary Embolism Severity Index high-risk patients (n=1498, 78%), a multivariable model used to predict the primary outcome retained computed tomography (CT) right–left ventricular diameter ratio ⩾1.5, systolic blood pressure 90–100 mmHg, central pulmonary artery clot and heart rate ⩾100 beats·min^{-1} with a C-statistic of 0.89 (95% CI 0.82–0.93). Three risk groups were derived using a weighted score (score, prevalence, primary outcome event rate): group 1 (0–3, 73.8%, 0.34%), group 2 (4–6, 17.6%, 5.8%), group 3 (7–9, 8.7%, 12.8%) with a C-statistic 0.85 (95% CI 0.78–0.91). In comparison the prevalence (primary outcome) by Bova risk stages (n=1179) were stage I 49.8% (0.2%); stage II 31.9% (2.7%); and stage III 18.4% (7.8%) with a C-statistic 0.80 (95% CI 0.74–0.86).

Conclusions: A simple four-variable risk score using clinical data immediately available after CT diagnosis of acute PE predicts in-hospital adverse outcomes. External validation of the Calgary Acute Pulmonary Embolism score is required.

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Derivation of a simple four-variable risk score that uses parameters available at the time of PE diagnosis to risk stratify acute normotensive PE patients, which may help clinicians better decide how to monitor and treat patients https://bit.ly/37PdyrM

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Introduction

The spectrum of acute pulmonary embolism (PE) outcomes is broad, with early mortality ranging from 1% to 50% in patients who are haemodynamically unstable at presentation [1]. High-risk PE patients with hypotension or shock should be considered for urgent revascularisation [2–4]. Normotensive patients identified as low-risk for adverse outcomes, using the simplified Pulmonary Embolism Severity Index (sPESI), can be treated with outpatient anticoagulation [5, 6]. However, there remains an intermediate group of normotensive patients at higher risk of adverse outcomes which has not been adequately defined in the literature, with data especially lacking for North American populations [7, 8].

Factors predicting mortality in acute PE include signs and symptoms (*e.g.* heart rate or syncope) [5, 9], markers of myocardial injury such as elevated troponin [10], right ventricular (RV) dysfunction or dilatation assessed by echocardiography, computed tomography (CT) angiography scan or brain natriuretic peptide (BNP) levels [11–14], pulmonary arterial clot burden [15], concurrent lower extremity deep vein thrombosis (DVT) [16, 17] and lactate [18]. However, individually, these have a low positive predictive value for PE-related outcomes. The 2019 European Society of Cardiology (ESC) guidelines propose a stepwise algorithm to risk-stratify normotensive PE, beginning with the sPESI followed by assessment of RV dysfunction and cardiac biomarkers [4]. However, risk stratification using only RV dysfunction and cardiac troponin, while sensitive, lacks specificity in identifying normotensive patients at higher risk of mortality [19, 20].

Multivariable risk models, such as the Bova score, have primarily been developed and validated in European populations [7, 17, 21]. Currently used risk scores use dichotomous factors based on the presence or absence of an abnormality (*e.g.* RV dysfunction or cardiac troponin), but do not consider the degree of abnormality. We hypothesised that optimising the cut-offs of known prognostic variables would improve the identification of an intermediate–high risk subgroup of normotensive PE patients [22]. Our objectives were to 1) determine the outcomes of acute normotensive PE in a contemporary North American cohort; 2) develop a risk score to improve identification of intermediate–high risk PE patients using optimised cut-points for independent risk variables; and 3) to comparatively evaluate the performance of a new risk score to the Bova score in a North American population.

Methods

We followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis [23] statement for the development and reporting of this study's multivariable prognostic model. The University of Calgary conjoint health research ethics board approved the study protocol and all modifications (REB15-2549).

Patient cohort and study design

A retrospective cohort design was used to study patients (aged ⩾18 years) with a confirmed diagnosis of acute PE admitted *via* emergency departments at four hospitals (collectively >325 000 emergency department visits annually) in Calgary (AB, Canada) between 1 January 2012 and 31 March 2017.

The cohort was identified using the inpatient discharge abstract database (DAD), which includes the International Classification of Diseases, tenth revision (ICD-10), coding for up to 25 diagnoses per hospital admission. Patients were screened using the ICD-10 code for PE (I26.0 or I26.9) as the primary diagnosis or the first-listed secondary diagnosis to capture misclassified primary PE admissions. This approach has a reported sensitivity of >90% [24, 25]. All patients screened positive for PE using ICD-10 codes underwent detailed review of their electronic medical chart, including vital signs, medications, laboratory tests, radiological/diagnostic imaging, nursing notes and physician transfer/discharge notes. PE diagnosis was confirmed using CT angiography, ventilation/perfusion (V'/Q') scan, or a clinical diagnosis was made using RV dysfunction on transthoracic echocardiography (TTE) and the presence of DVT on duplex Doppler ultrasound. Exclusion criteria were 1) PE was not the primary diagnosis; 2) haemodynamically unstable at presentation (systolic blood pressure <90 mmHg or requiring vasopressor support); 3) PE diagnosis was made >24 h after admission; 4) recurrent PE <6 months from presentation; 5) incidental/asymptomatic PE; 6) reperfusion therapy at presentation; 7) not admitted to hospital; 8) palliative goals of care.

Vital signs, symptoms and comorbidities on emergency department arrival and laboratory tests performed with 24 h of presentation were recorded. Blinded assessment of right ventricular dilatation was made on CT pulmonary angiography by measurement of the right to left ventricular short axis (RV/LV) ratio, as described previously [26]. Central clot was defined as the presence of a thrombus within a main pulmonary artery proximal to the lobar artery. Lower extremity DVT was recorded if the patient had a positive duplex Doppler ultrasound. Initial anticoagulation choice and time of first dose were recorded, as was inferior vena cava filter use, admitting medical service and hospital length of stay.

The sPESI score was calculated as low (<1) or high (⩾1) risk [5]. The Bova score [7] and European Society of Cardiology (ESC) classification [4] were calculated from data at emergency department presentation and then converted into three risk stages (I–III) (supplementary etable 1).

Outcomes

The primary outcome was in-hospital PE-related death or haemodynamic decompensation (systolic blood pressure <90 mmHg for >15 min, catecholamine administration for hypotension, endotracheal intubation or cardiopulmonary resuscitation). Two of the authors (KS and JW) independently adjudicated all outcome events. Death was considered PE-related if documentation stated the patient's death was secondary to PE or if there was no other obvious explanation. Secondary outcomes were in-hospital all-cause mortality and 30-day all-cause mortality. 30-day mortality was obtained through linkage to a provincial government registry (Alberta Vital Statistics). Investigators were blinded to the exposure variables while assessing outcomes.

Statistical analysis

Descriptive statistics were performed using mean±SD for normally distributed continuous variables and median (interquartile range (IQR)) for non-normally distributed variables. Skewness and normality were assessed using the Kolmogorov–Smirnov test. Differences between groups were assessed using the t-test and Chi-squared test for continuous and discrete variables, respectively.

To derive a risk model for normotensive, non-low-risk PE (sPESI ⩾1) patients, candidate variables were selected based on prior literature and clinical relevance, then assessed for their association with adverse PE outcomes using logistic regression. Variables were considered in multivariable modelling if data were available for >70% of patients. Clinically relevant variables were selected for the final model using stepwise backwards selection with $p<0.20$. Multivariable modelling used covariates as both continuous variables and dichotomised at optimal cut-points according to Youden's index (greatest sum of sensitivity and specificity) [27]. Goodness-of-fit was assessed using the Akaike information criterion (AIC). Model discrimination was evaluated using receiver operating characteristic curves and C-statistics. Model calibration was assessed by the modified Hosmer–Lemeshow Chi-squared statistic. The model was internally validated using bootstrapping in the derivation dataset by sampling with replacement for 400 iterations. To develop a weighted risk score, the final logistic model variable coefficients were divided by the lowest coefficient to create an integer score for each covariate that could be summed into a total score [7]. Risk groups were generated by evaluating sensitivity and specificity at each score cut-point. Statistical analyses were performed by using SAS 9.4 (SAS Institute, Cary, NC, USA) and Stata 14.2 (StataCorp, College Station, TX, USA) with a two-tailed p-value <0.05 deemed statistically significant.

Results

Patient selection and characteristics

A total of 3246 patients were identified in the DAD and after complete medical file review; 2067 (63.6%) patients were eligible (figure 1). Diagnosis of acute PE was made using CT in 1906 (92.2%) patients, by V'/Q' imaging in 158 (7.6%) patients and TTE in three (0.2%) patients. Baseline patient characteristics are

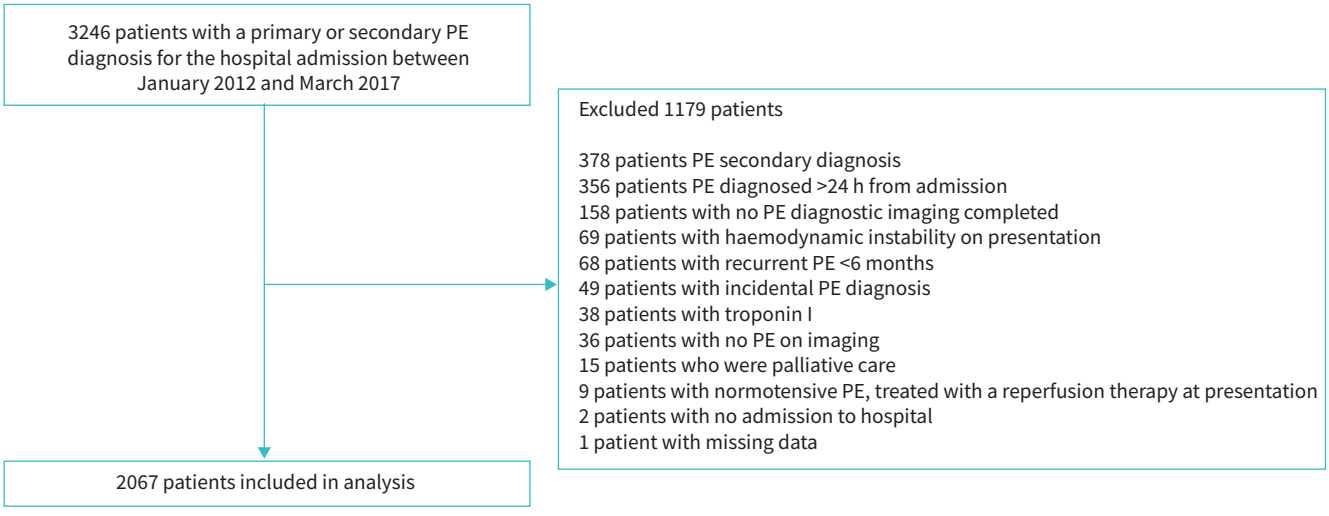

FIGURE 1 Patient inclusion and exclusion flow diagram. PE: pulmonary embolism.

TABLE 1 Baseline patient characteristics

Patients	2067
Clinical characteristics	
Age years	63 (50–76)
Male	1054 (51)
Comorbidities and VTE risk factors	
Chronic lung disease	373 (18.1)
Chronic heart disease	316 (15.2)
Chronic kidney disease	137 (6.6)
Type 2 diabetes	280 (13.6)
Charlson comorbidity index score ⩾1	781 (37.8)
Cancer diagnosis within 2 years of PE diagnosis	371 (18.0)
Metastatic cancer at time of PE diagnosis	176 (9.4)
History of venous thromboembolism	405 (19.6)
Surgery within 2 months of PE diagnosis	235 (11.3)
Symptoms and clinical findings at admission	
Dyspnoea	1581 (78.3)
Chest pain	1109 (53.7)
Syncope	137 (6.6)
Heart rate ⩾100 beats·min^{-1}	797 (38.6)
Systolic blood pressure 90–100 mmHg	71 (3.4)
Oxygen saturation <90%	1070 (51.8)
Biomarkers and imaging at presentation	
Hs-TnT >age-adjusted cut-off$^{\#}$ (n=1611)	824 (51.2)
NT-proBNP ⩾300 pg·mL^{-1} (n=336)	240 (71.4)
Serum lactate >2.2 mmol·L^{-1} (n=654)	163 (24.9)
D-dimer >0.50 mg·L^{-1} (n=1196)	1170 (97.8)
RV dilatation on CT angiography¶ (n=1906)	922 (48.4)
RV dysfunction on TTE^{+} (n=1058)	419 (39.6)
Central pulmonary artery clot	376 (19.7)
Lower extremity DVT at presentation§ (n=908)	476 (52.4)
Initial treatment at time of diagnosis	
Unfractionated heparin, *i.v.* infusion	543 (26.3)
LMWH, *s.c.*	1473 (71.3)
DOAC, *p.o.*	40 (1.9)
IVC filter insertion	108 (5.2)
Time to initiation of anticoagulation from ED presentation h	5.8 (3.7–8.0)
Admitting medical service	
Intensive care unit	76 (3.7)
Hospitalist	566 (27.4)
Cardiology	37 (1.8)
General internal medicine	888 (43.0)
Pulmonary medicine	467 (22.5)
Other	33 (1.6)
Hospital length of stay days	4.5 (2.7–7.1)

Data are presented as n, median (interquartile range) or n (%), unless otherwise stated. VTE: venous thromboembolism; PE: pulmonary embolism; hs-TnT: high-sensitivity troponin; NT-proBNP: N-terminal pro-B-type natriuretic peptide; RV: right ventricle; CT: computed tomography; TTE: transthoracic echocardiogram; DVT: deep vein thrombosis; *i.v.*: intravenous; LMWH: low molecular-weight heparin; DOAC: direct oral anticoagulant; IVC: inferior vena cava; ED: emergency department. $^{\#}$: ⩾14 pg·mL^{-1} for patients aged <75 years and ⩾45 pg·mL^{-1} for aged patients ⩾75 years; ¶: right/left ventricle axial ratio >1.0; $^{+}$: moderate or greater right ventricle dysfunction or dilatation; §: duplex ultrasound for DVT of the bilateral extremities.

presented in table 1. The median (IQR) age was 63 (50–76) years and 1054 (50.9%) patients were male. 1611 (77.9%) patients had high-sensitivity troponin (hs-TnT) measured at admission, which was elevated in 824 (51.2%) patients. RV dilatation was assessed on CT angiography in 1906 (92.2%) patients and present (CT RV/LV ratio >1.0) in 922 (48.4%) patients.

Outcomes

The primary outcome occurred in 32 (1.5%) patients (table 2). PE-related death occurred in 16 (0.8%) patients and haemodynamic decompensation occurred in 16 (0.8%) patients. The time to primary

TABLE 2 In-hospital and 30-day adverse outcome and mortality in 2067 normotensive pulmonary embolism (PE) patients

Adverse in-hospital PE outcome[#]	32 (1.5)
Haemodynamic decompensation in hospital[¶]	16 (0.8)
PE-related in-hospital mortality	16 (0.8)
All-cause in-hospital mortality	35 (1.7)
All-cause 30-day mortality	64 (3.1)

Data are presented as n (%). [#]: death secondary to PE, haemodynamic decompensation; [¶]: systolic blood pressure <90 mmHg for >15 min, catecholamine administration for hypotension, endotracheal intubation or cardiopulmonary resuscitation.

outcome from the initial presentation to the emergency department is shown cumulatively in figure 2. The median (IQR) time to the primary outcome was 22.5 (6.5–44.5) h with a range of 4–84 h. In addition to 16 PE-related deaths, 19 (0.9%) patients died of non-PE related causes giving an all-cause in-hospital mortality rate of 1.7%. The cause of death in the 19 patients assessed as non-PE related reasons were cancer in six (31.6%); major haemorrhage (not secondary to thrombolysis) in four (21.1%) respiratory failure not related to PE in three (15.7%); and other causes in six (31.6%) patients. All of the patients with major haemorrhage had do-not-resuscitate orders and the sites of major haemorrhage were retroperitoneal in two, gastrointestinal in one and intracranial in one patient. All-cause mortality within 30-days occurred for 64 (3.1%) patients.

Risk stratification by the sPESI and Bova score

Complete data were available to calculate the sPESI for 2067 (100%) patients, of whom 439 (21.2%) were low-risk (sPESI=0) and 1628 (78.8%) were high-risk (total score ⩾1) (table 3). No patients (0%) in the low-risk category experienced an in-hospital adverse outcome and all were alive at 30 days post-hospital admission. All primary outcomes and 30-day all-cause deaths occurred in the high-risk (sPESI ⩾1) group.

All further analyses and risk modelling were done using the high-risk sPESI group. The Bova score was calculable, with complete data for all four components, for 1179 (73.9%) patients. In the 449 patients with missing Bova variables, four (0.9%) patients had an in-hospital adverse outcome and 20 (4.5%) patients died within 30 days. The Bova score classified 586 (49.8%) patients as low risk (score 0–2), 376 (31.9%) patients as intermediate–low risk (score 3–4) and 217 (18.4%) patients as intermediate–high risk (score ⩾5) (table 3). Primary outcomes occurred for one (0.2%), 10 (2.7%) and 17 (7.8%) patients in Bova stages I, II and III, respectively.

Prediction of adverse PE outcomes

Univariable and multivariable logistic regression models are shown in table 4. Optimal cut-points for hs-TnT, CT RV/LV ratio and heart rate were ⩾50 ng·L^{-1}, ⩾1.5 and ⩾100 beats·min^{-1}, respectively. A four-variable model (model 2) including CT RV/LV ratio, heart rate, central pulmonary artery clot and

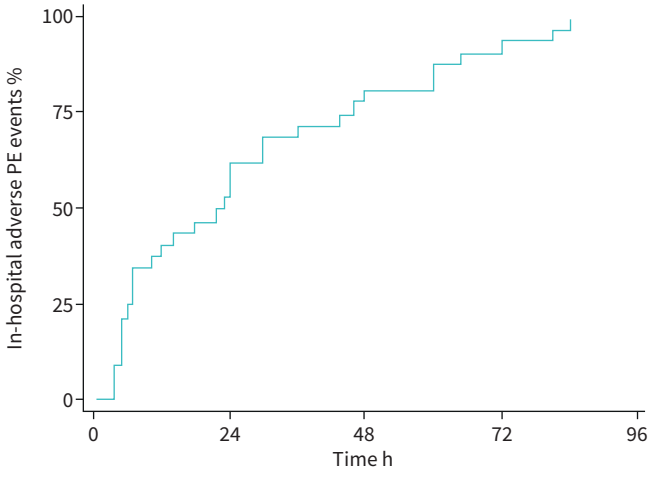

FIGURE 2 Cumulative in-hospital adverse pulmonary embolism (PE) outcomes.

TABLE 3 Risk stratification of normotensive acute pulmonary embolism (PE) by the simplified Pulmonary Embolism Severity Index (sPESI) and Bova score

	Patients	Adverse in-hospital PE outcome[#]	All cause 30-day mortality
sPESI (n=2035)			
Low-risk (score 0)	439 (21.2)	0 (0)	0 (0)
High-risk (score ⩾1)	1628 (78.8)	32 (2.0)	64 (3.9)
Bova risk stage (n=1179)[¶]			
Low risk (score 0–2)	586 (49.8)	1 (0.2)	13 (2.2)
Intermediate–low risk (score 3–4)	376 (31.9)	10 (2.7)	14 (3.7)
Intermediate–high risk (score ⩾5)	217 (18.4)	17 (7.8)	17 (7.8)

Data presented as n (%). [#]: death secondary to PE, haemodynamic decompensation (systolic blood pressure <90 mmHg for >15 min, catecholamine administration for hypotension, endotracheal intubation or cardiopulmonary resuscitation); [¶]: sPESI score=0 excluded from calculation.

systolic blood pressure had the highest C statistic (0.89, 95% CI 0.85–0.93) and the lowest AIC (228.9). Hs-TnT correlated with CT RV/LV ratio (Pearson r=0.48) and was not an independent predictor. The internal validation of the final four-variable model resulted in a bootstrap-corrected C-statistic of 0.89 (95% CI 0.85–0.93) and was well calibrated (Hosmer–Lemeshow Chi-squared 2.71 with 10 groups, p=0.44 for poor fit).

The derived risk score, hereafter called the Calgary Acute Pulmonary Embolism (CAPE) score, and three CAPE risk groups are shown in table 5. Each coefficient from the four-variable model (table 4) was transformed into an integer risk score that can be summed (range 0–6). Three risk groups were developed by assessment of the sensitivity and specificity for each cut-off of the score (supplementary efigure 1): low (0–2), intermediate–low (3–4) and intermediate–high (5–6). The proportion with adverse in-hospital PE outcomes increased with each risk group (0.3%, 4.5%, 12.2%), whereas 30-day all-cause mortality was higher in low (3.8%) and intermediate–high (7.6%) groups compared to the intermediate–low (3.0%) group. The CAPE risk groups showed similar discrimination compared to the four-variable multivariable logistic regression model (C statistic 0.85, 95% CI 0.78–0.92 and 0.89, 95% CI 0.85–0.93, respectively).

For patients with complete data to calculate a Bova score, CAPE score and classify by the ESC algorithm (n=1179), the C-statistic was higher using the CAPE score (0.84, 95% CI 0.76–0.91) compared to the Bova score (0.80, 95% CI 0.75–0.86) and the ESC 2019 risk classification [4] (0.75, 95% CI 0.70–0.81). The C-statistic of the CAPE score was not statistically greater than the Bova score (Chi-squared 0.83, p=0.36). The CAPE score categorised more patients as low-risk compared to the Bova score (74.3% *versus* 49.7%) and there were fewer patients in the intermediate–high risk group (10.3% *versus* 18.4%) (figure 3). The intermediate–high risk group according to the CAPE score had a higher adverse in-hospital PE outcome rate than according to the Bova score (CAPE score 13.3%, 95% CI 7.49–19.11%; Bova score 7.8%, 95% CI 4.23–11.4%; p=0.048) and similar event rates in the low and intermediate–low risk groups combined (p=1.0).

Discussion

We developed a novel four-variable model and risk score for the identification of normotensive acute PE patients at increased risk of in-hospital adverse outcomes (death secondary to PE or haemodynamic decompensation). The independent variables were 1) right/left ventricle ratio ⩾1.5 on CT pulmonary angiogram; 2) presence of central pulmonary artery clot; 3) heart rate ⩾100 beats·min^{-1}; and 4) systolic blood pressure 90–100 mmHg at emergency department presentation, all of which are available at the time of PE diagnosis with CT pulmonary angiogram.

The CAPE score builds upon recommendations by the ESC to initially use the sPESI to identify intermediate-risk patients, followed by further stratification. Our study provides further external validation of the sPESI and Bova scores. Within our cohort, the CAPE score better identified acute normotensive PE patients at intermediate–high risk of adverse in-hospital outcomes compared to the Bova score. The use of the CAPE score in addition to the sPESI score identifies a select cohort of normotensive PE patients at the highest risk of adverse events. The smaller cohort of patients identified as intermediate–high risk by the CAPE score improves the feasibility of intensively monitoring these patients for adverse events as compared to all high-risk sPESI patients. The increased specificity for adverse short-term outcomes has

TABLE 4 Univariable and multivariable logistic regression of risk factors with optimal cut-points for in-hospital adverse outcomes in normotensive acute pulmonary embolism (PE) patients who are high-risk simplified Pulmonary Embolism Severity Index (sPESI)

	Univariable models OR (95% CI)	p-value	Multivariable models OR (95% CI)			
			1) hs-TnT ⩾50 pg·mL^{-1}, CT RV/LV ⩾1.5, heart rate ⩾100 beats·min^{-1}, central PA embolism, SBP 90–100 mmHg	2) CT RV/LV ⩾1.5, heart rate ⩾100 beats·min^{-1}, central PA embolism, SBP 90–100 mmHg	3) CT RV/LV ⩾1.5, heart rate ⩾100 beats·min^{-1}, central PA embolism	4) CT RV/LV ⩾1.5, heart rate ⩾100 beats·min^{-1}
Patients n			1179	1498	1498	1498
Age per year increase	0.98 (0.96–0.99)	0.049				
Lower extremity DVT present[#]	9.61 (2.24–41.196)	0.002				
Elevated lactate >2.2 mmol·L^{-1}	5.06 (2.17–11.81)	<0.001				
Oxygen saturation <90%	2.86 (1.09–7.46)	0.032				
Syncope	1.30 (0.39–4.32)	0.673				
hs-TnT ⩾50 pg·mL^{-1}[¶]	8.37 (3.58–19.57)	<0.001	1.90 (0.67–5.40) p=0.223			
CT RV/LV ratio ⩾1.5[¶,+]	22.92 (8.68–60.52)	<0.001	5.55 (1.77–17.04) p=0.003	9.02 (3.06–26.58) p<0.001	9.11 (3.09–26.8) p<0.001	15.35 (5.76–40.88) p<0.001
Central PA embolism[§]	9.85 (4.32–22.46)	<0.001	2.93 (1.10–7.80) p=0.031	2.86 (1.13–7.23) p=0.027	2.91 (1.15–7.36) p=0.24	
Heart rate ⩾100 beats·min^{-1}[¶]	4.90 (2.19–10.96)	<0.001	2.61 (1.01–6.72) p=0.047	3.02 (1.18–7.70) p=0.021	2.96 (1.17–7.51) p=0.022	3.36 (1.33–8.43) p=0.010
SBP 90–100 mmHg	3.26 (1.11–9.56)	0.031	3.29 (0.99–10.88) p=0.051	3.51 (1.07–11.50) p=0.038		
Model performance measures						
Akaike information criterion			217.0	216.6/228.9[f]	230.4	234
C-statistic			0.88	0.88/0.89[f]	0.89	0.87

Hs-TnT: high-sensitivity troponin; CT RV/LV: computed tomography right/left ventricle ratio; PA: pulmonary artery; SBP: systolic blood pressure; DVT: deep vein thrombosis. [#]: documented positive if reported on duplex ultrasound of the lower extremities; [¶]: cut-points determined by Youden's index; [+]: measured by dividing the right and left ventricle diameter at the valvular level of the CT angiogram axial cuts; [§]: defined as thrombus present within the central pulmonary arteries proximal to a lobar artery; [f]: the first value is calculated using a model limited to the 1179 patients in model 1; the second value is calculated using the 1498 patients in models 2–4. There were 29 adverse in-hospital outcomes in models 2–4.

TABLE 5 The Calgary Acute Pulmonary Embolism (CAPE) score and risk groups for normotensive acute pulmonary embolism (PE) who are high-risk simplified Pulmonary Embolism Severity Index

	Score	Patients (n=1498)	Adverse in-hospital PE outcome[#]	All cause 30-day mortality
Risk factor				
CT RV/LV ratio ⩾1.5[¶]	3	326 (21.8)		
Central PA clot[+]	1	330 (22.0)		
Heart rate ⩾100 beats·min^{-1}	1	702 (43.1)		
SBP 90–100 mmHg	1	71 (4.4)		
Risk group				
Low-risk	0–2	1168 (78.0)	4 (0.3)	44 (3.8)
Intermediate–low risk	3–4	199 (13.3)	9 (4.5)	6 (3.0)
Intermediate–high risk	⩾5	131 (8.7)	16 (12.2)	10 (7.6)

Data presented as n or n (%). CT RV/LV: computed tomography angiogram right/left ventricle ratio; PA: pulmonary artery; SBP: systolic blood pressure. [#]: death secondary to PE, haemodynamic decompensation (systolic blood pressure <90 mmHg for >15 min, catecholamine administration for hypotension, endotracheal intubation or cardiopulmonary resuscitation); [¶]: measured by dividing the right and left ventricle diameter at the valvular level of the CT angiogram axial cuts; [+]: defined as thrombus present within the central pulmonary arteries proximal to a lobar artery.

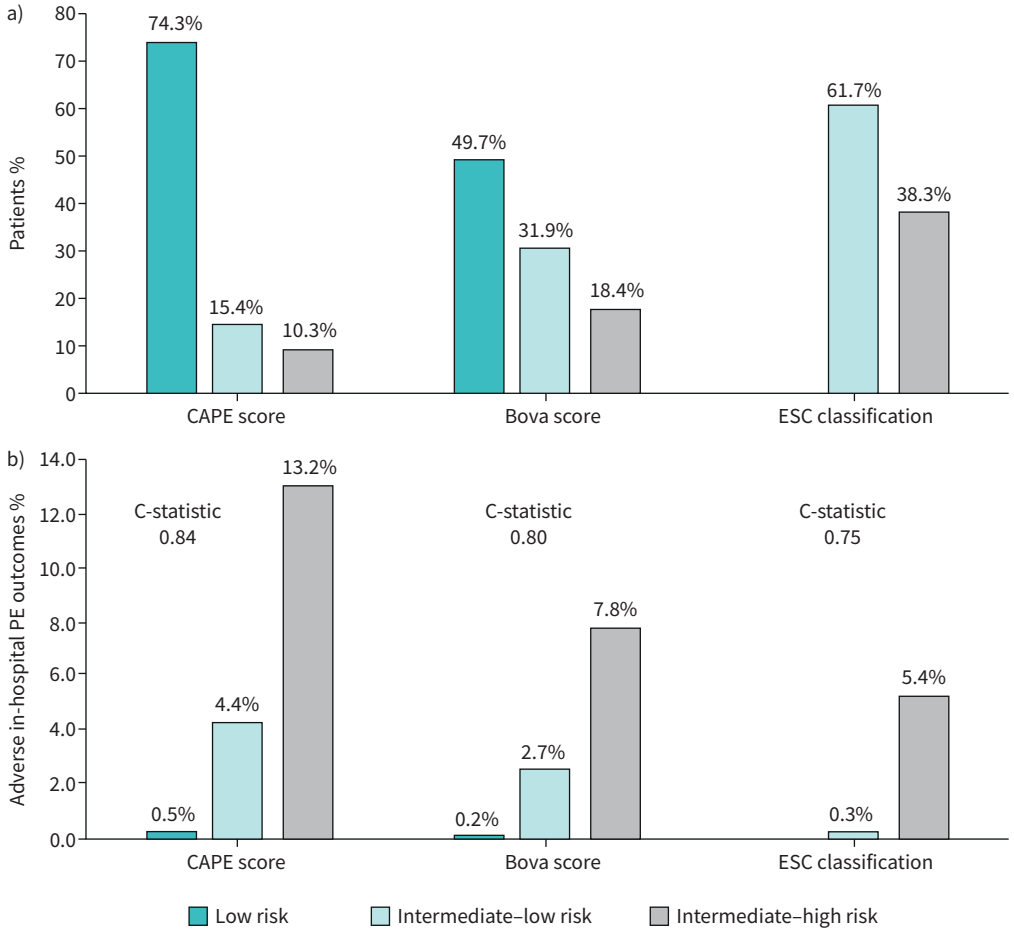

FIGURE 3 Risk stratification performance of the Calgary Acute Pulmonary Embolism (CAPE) score, Bova score and European Society of Cardiology (ESC) classification (see table 5, supplementary etable 1 and [4] for definitions) for normotensive acute pulmonary embolism (PE) patients who are classified as high-risk simplified Pulmonary Embolism Severity Index (sPESI). a) Percentage of patients in each risk stage; b) adverse in-hospital PE outcomes (see table 5 for definitions) by risk stage. Proportions and C-statistics calculated on patients who had sPESI ⩾1 and a complete Bova score (n=1179). Total adverse in-hospital PE outcomes were 28.

implications for future clinical trial design. For example, patients in CAPE risk group 3 (score ⩾5) had twice the rate of adverse outcomes (12.2%) than the placebo group in the recent PEITHO (Pulmonary Embolism Thrombolysis) trial (5.6%), which evaluated the use of systemic thrombolysis in intermediate-risk PE [19]. Thus, the CAPE score could be useful for inclusion criteria to enrich future clinical trials evaluating thrombolytic or other revascularisation therapies, as such interventions may have more favourable benefit–risk trade-offs in higher-risk groups.

The independent variables used in our risk model and score are rational and durable, with all having been previously associated with adverse outcomes [7, 28, 29]. The CAPE score is unique in that it exclusively uses CT-derived RV/LV ratio rather than TTE for the assessment of RV dilatation along with higher cut-points for the CT RV/LV ratio (⩾1.5) compared to previous studies (⩾0.9 or ⩾1.0) [11, 30, 31]. The higher CT RV/LV ratio cut-point improved specificity while maintaining sensitivity for adverse in-hospital events (supplementary efigure 2). Patients with a CT RV/LV ratio >1.5 would be more likely to have impaired LV stroke volume, as a consequence of ventricular interdependence, and be farther along the pathophysiologic spiral towards shock [32]. Additionally, the presence of central clot on CT pulmonary angiogram was found to be a significant predictor of adverse PE outcomes in both the univariable and multivariable model, which is consistent with prior studies [28, 33]. Currently used prediction scores do not include the presence of central pulmonary clot as a risk factor [7, 17].

We chose to focus on short-term PE adverse outcomes in contrast to other studies that used 30-day outcomes [7, 17]. Decompensation or death occurring later, after the acute illness phase, is less likely to be driven by risk factors measured at emergency department presentation and more likely to be confounded by patient comorbidities, such as malignancy [28]. Current guidelines recommend that intermediate–high risk patients be considered for close monitoring, such as in the intensive care unit (ICU), to promptly recognise evolving haemodynamic instability and intervene earlier. The immediate availability of the variables in this model may limit the need for further investigations and can facilitate rapid clinical decision-making regarding disposition and monitoring. In our cohort, >75% of the adverse PE outcomes occurred within 48 h after presentation to the emergency department. Similarly, during the PEITHO trial [19] of thrombolysis for intermediate-risk PE patients, the majority of adverse outcome in the control group occurred within 72 h. These data suggest that close monitoring of intermediate–high risk patients should occur for a minimum of 48–72 h. If ICU monitoring is needed for intermediate–high risk patients, our score could prove more cost-effective given the lower proportion of patients identified as intermediate–high risk compared to Bova.

The rate of in-hospital adverse PE outcomes and 30-day all-cause mortality are lower in this cohort compared with prior studies [7, 17, 34, 35]. The in-hospital PE-related mortality and all-cause mortality in the Bova derivation study, which includes a meta-analysis of cohorts from Europe, were 2.7% and 6.1%, respectively, *versus* 0.8% and 3.1% in our cohort [7]. Compared to the Bova derivation study, we had more than three times the proportion of intermediate–high risk patients according to the Bova risk stratification (18.4% *versus* 5.8%, respectively), suggesting our lower overall event rates were not due to less severe patients. Data from the RIETE (European Registro Informatizado de la Enfermedad TromboEmbolica) study showed that the 7-day PE mortality rate was 2.0% between 2006 and 2009, compared to 1.1% between 2010 and 2013, suggesting that mortality is decreasing temporally, which may explain the higher mortality rates in older studies [36]. There are limited data on PE outcomes from North America. To our knowledge, this is the report of acute PE outcomes in Canada. A multicentre American study found an in-hospital PE-mortality rate of 1.1% in 1880 patients admitted from the emergency department, including unstable patients, which is similar to the 0.8% rate in our study [8]. We hypothesise that our low outcome rate may be related to more rapid availability of CT angiography to diagnose PE and prompt initiation of anticoagulation from presentation to the emergency department. Indeed, we found short delays between emergency department presentation, PE diagnosis and initiation of treatment, especially in normotensive, intermediate–high risk PE (supplementary etable 2).

The main strengths of this study are the large cohort size, the inclusion of patients from tertiary-care emergency departments and community-based hospitals, and completeness of data for the variables used in our multivariable model. We acknowledge several limitations given the retrospective nature and missing data for several candidate predictor variables such as lactate, N-terminal pro-BNP and lower extremity DVT, which precluded consideration in multivariable analysis. Although we used methods to optimise internal validity, our four-variable score requires prospective validation, which is now underway in our centre, as well as independent external validation. Our model relies on PE diagnosis by CT pulmonary angiogram, in order to determine presence of central pulmonary clot and RV/LV ratio, precluding its use when PE is diagnosed by V'/Q' or TTE. Although CT measurements were performed blindly with respect to outcomes, the lack of cardiac gating means that RV/LV measurements may not have been obtained at the same point in the cardiac cycle between patients.

Conclusions

The CAPE score consists of CT RV/LV ratio ⩾1.5 (3 points), presence of central clot (1 point), heart rate ⩾100 beats·min^{-1} (1 point) and systolic blood pressure 90–100 mmHg (1 point), which predicted adverse in-hospital outcomes with a high degree of discrimination in patients with acute normotensive PE. A CAPE score of ⩾5 identifies an intermediate–high risk group of patients who may be considered for more intensive monitoring or revascularisation therapy.

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