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

Kevin Solverson, Christopher Humphreys, Zhiying Liang, Graeme Prosperi-Porta, James E. Andruchow, Paul Boiteau, Andre Ferland, Eric Herget, Doug Helmersen, and Jason Weatherald

Affiliations: 1Dept of Critical Care Medicine, University of Calgary, Calgary, AB, Canada. 2Dept of Medicine, University of Calgary, Calgary, AB, Canada. 3Libin Cardiovascular Institute of Alberta, Calgary, AB, Canada. 4Dept of Emergency Medicine, University of Calgary, Calgary, AB, Canada. 5Dept of Radiology, University of Calgary, Calgary, AB, Canada. 6Section of Respirology, Dept of Medicine, University of Calgary, Calgary, AB, Canada.

Correspondence: Jason Weatherald, Peter Lougheed Centre, 3500 26 Ave NE, Calgary, Alberta, T1Y 6J4, Canada. E-mail: jcweathe@ucalgary.ca

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.

This article has supplementary material available from openres.ersjournals.com

Received: 24 Nov 2020 | Accepted after revision: 18 Feb 2021

Copyright ©The authors 2021. This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org
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.](https://doi.org/10.1183/23120541.00879-2020)
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 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.
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

---

**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.
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 3 Risk stratification of normotensive acute pulmonary embolism (PE) by the simplified Pulmonary Embolism Severity Index (sPESI) and Bova score |
|-----------------|-----------------|-----------------|
| sPESI (n=2035)  | Adverse in-hospital PE outcome | All cause 30-day mortality |
| 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.

https://doi.org/10.1183/23120541.00879-2020
### 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)

| Patients n | Age per year increase | Lower extremity DVT present<sup>#</sup> | Elevated lactate >2.2 mmol·L<sup>−1</sup> | Oxygen saturation <90% | Syncope | hs-TnT ≥50 pg·mL<sup>−1</sup> | CT RV/LV ratio ≥1.5<sup>+</sup> | Central PA embolism§ | Heart rate ≥100 beats·min<sup>−1</sup> | SBP 90–100 mmHg | Model performance measures |
|------------|-----------------------|----------------------------------------|----------------------------------------|------------------------|--------|----------------------------|----------------------------|--------------------------|--------------------------|----------------------|---------------------------------|
| 1179       | 0.98 [0.96–0.99]      | 9.61 [2.24–41.196]                     | 5.06 [2.17–11.81]                     | 2.86 [1.09–7.46]       | 1.30 [0.39–4.32] | 8.37 [3.58–19.57]          | 22.92 [8.68–60.52]         | 9.85 [4.32–22.46]         | 4.90 [2.19–10.96]           | 3.26 [1.11–9.56] | Akaike information criterion 217.0 216.6/228.9<sup>f</sup> 230.4 234 |
| 1498       |                       |                                        |                                        |                        |        |                           |                            |                          |                          |                      | C-statistic 0.88 0.88/0.89<sup>f</sup> 0.89 0.87 |
| 1498       |                       |                                        |                                        |                        |        |                           |                            |                          |                          |                      | Model performance measures  |                  |
| 1498       |                       |                                        |                                        |                        |        |                           |                            |                          |                          |                      |                                  |

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. <sup>#</sup>: documented positive if reported on duplex ultrasound of the lower extremities; <sup>+</sup>: cut-points determined by Youden’s index; <sup>§</sup>: defined as thrombus present within the central pulmonary arteries proximal to a lobar artery; <sup>f</sup>: 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 (sPESI) patients.

| Risk factor                  | Patients (n=1498) | Adverse in-hospital PE outcome\(\#\) | All cause 30-day mortality |
|------------------------------|-------------------|--------------------------------------|-----------------------------|
| CT RV/LV ratio \(\geq 1.5\)  | 3                 | 326 [21.8]                           |                             |
| Central PA clot†             | 1                 | 330 [22.0]                           |                             |
| Heart rate \(\geq 100\) beats·min\(^{-1}\) | 1                 | 702 [43.1]                           |                             |
| SBP 90–100 mmHg              | 1                 | 71 [4.4]                             |                             |

| Risk group                  | Patients (%)      | Adverse in-hospital PE outcome (%) |
|------------------------------|-------------------|-----------------------------------|
| Low-risk                     | 1168 [78.0]       | 4 [0.3]                           |
| Intermediate–low risk        | 199 [13.3]        | 9 [4.5]                           |
| Intermediate–high risk       | 131 [8.7]         | 16 [12.2]                         |

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 \(\geq 1\) and a complete Bova score (n=1179). Total adverse in-hospital PE outcomes were 28.

https://doi.org/10.1183/23120541.00879-2020
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 inhospital 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.

Author contributions: K. Solverson, J. Weatherald, J.E. Andruchow, A. Ferland, P. Boiteau, E. Herget and D. Helmerson conceived and designed the study. K. Solverson, C. Humphreys and G. Prosperi-Porta collected data. K. Solverson, Z. Liang and J. Weatherald analysed the data. K. Solverson and J. Weatherald wrote the first draft of the manuscript. All authors made significant contributions to data interpretation and the final manuscript.

Conflict of interest: K. Solverson reports travel grants from Bayer outside the submitted work. C. Humphreys has nothing to disclose. Z. Liang has nothing to disclose. G. Prosperi-Porta has nothing to disclose. J.E. Andruchow reports an unrestricted grant for high-sensitivity troponin research from Roche Diagnostics outside the submitted work. P. Boiteau has nothing to disclose. A. Ferland has nothing to disclose. E. Herget has nothing to disclose. D. Helmerson reports grants and nonfinancial support from Actelion Pharmaceuticals, and grants from Bayer Pharmaceuticals, Gilead, Janssen Inc. and United Therapeutics, outside the submitted work. J. Weatherald reports grants, personal fees and nonfinancial support from Janssen Inc. and Actelion, personal fees and nonfinancial support from Bayer, personal fees from Novartis, and grants from the Alberta Lung Association, the Canadian Vascular Network, the European Respiratory Society and the Canadian Thoracic Society, outside the submitted work.

References
1. Kucher N, Rosset E, De Rosa M, et al. Massive pulmonary embolism. Circulation 2006; 113: 577–582.
2. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J 2019; 54: 1901647.
3. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016; 149: 315–352.
4. Konstantinides SV, Meyer G. The 2019 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2019; 40: 3453–3455.
5. Jiménez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med 2010; 170: 1383–1389.
6. Aujesky D, Roy PM, Verschuren F, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. Lancet 2011; 378: 41–48.
7. Bova C, Sanchez O, Prandoni P, et al. Identification of intermediate-risk patients with acute symptomatic pulmonary embolism. Eur Respir J 2014; 44: 694–703.
8. Pollack CV, Schreiber D, Goldhaber SZ, et al. Clinical characteristics, management, and outcomes of patients diagnosed with acute pulmonary embolism in the emergency department: initial report of EMPEROR (Multicenter Emergency Medicine Pulmonary Embolism in the Real World Registry). J Am Coll Cardiol 2011; 57: 700–706.
9. Delles C, Tschepe M, Seeger V, et al. A novel H-FABP assay and a fast prognostic score for risk assessment of normotensive pulmonary embolism. Thromb Haemost 2014; 111: 996–1003.
10. Lankeit M, Jiménez D, Kostrubiec M, et al. Predictive value of the high-sensitivity troponin T assay and the simplified Pulmonary Embolism Severity Index in hemodynamically stable patients with acute pulmonary embolism: a prospective validation study. Circulation 2011; 124: 2716–2724.
11. Barrios D, Morillo R, Lobo JL, et al. Assessment of right ventricular function in acute pulmonary embolism. Am Heart J 2017; 185: 123–129.
12. Meinel FG, Nance JW Jr, Schoepf UJ, et al. Predictive value of computed tomography in acute pulmonary embolism: systematic review and meta-analysis. Am J Med 2015; 128: 747–759.
13. Jiménez D, Aujesky D, Moores L, et al. Combinations of prognostic tools for identification of high-risk normotensive patients with acute symptomatic pulmonary embolism. Thorax 2011; 66: 75–81.
14. Lankeit M, Jiménez D, Kostrubiec M, et al. Validation of N-terminal pro-brain natriuretic peptide cut-off values for risk stratification of pulmonary embolism. Eur Respir J 2014; 43: 1669–1677.
15. Vedovati MC, Germini F, Agnelli G, et al. Prognostic role of embolic burden assessed at computed tomography angiography in patients with acute pulmonary embolism: systematic review and meta-analysis. J Thromb Haemost 2013; 11: 2092–2102.
16. Quezada CA, Bikdeli B, Barrios D, et al. Assessment of coexisting deep vein thrombosis for risk stratification of acute pulmonary embolism. Thromb Res 2018; 164: 40–44.
17. Jiménez D, Kopcena D, Tapson V, et al. Derivation and validation of multimarker prognostication for normotensive patients with acute symptomatic pulmonary embolism. Am J Respir Crit Care Med 2014; 189: 718–726.
18. Vanni S, Jiménez D, Nazerian P, et al. Short-term clinical outcome of normotensive patients with acute PE and high plasma lactate. Thorax 2015; 70: 333–338.
19. Meyer G, Vlacic E, Danay T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014; 370: 1402–1411.
20. Becattini C, Agnelli G, Lankeit M, et al. Acute pulmonary embolism: mortality prediction by the 2014 European Society of Cardiology risk stratification model. Eur Respir J 2016; 48: 780–786.
21. Hobohm L, Hellenkamp K, Hasenfuß G, et al. Comparison of risk assessment strategies for not-high-risk pulmonary embolism. Eur Respir J 2016; 47: 1170–1178.
Kaeberich A, Seeber V, Jiménez D, et al. Age-adjusted high-sensitivity troponin T cut-off value for risk stratification of pulmonary embolism. *Eur Respir J* 2015; 45: 1323–1331.

Collins GS, Reitsma JB, Altman DG, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. *Ann Intern Med* 2015; 162: 55–63.

Casez P, Labarère J, Sevestre MA, et al. ICD-10 hospital discharge diagnosis codes were sensitive for identifying pulmonary embolism but not deep vein thrombosis. *J Clin Epidemiol* 2010; 63: 790–797.

Burles K, Innes G, Senior K, et al. Limitations of pulmonary embolism ICD-10 codes in emergency department administrative data: let the buyer beware. *BMC Med Res Methodol* 2017; 17: 89.

Jiménez D, Lobo JL, Monreal M, et al. Prognostic significance of multidetector computed tomography in normotensive patients with pulmonary embolism: rationale, methodology and reproducibility for the PROTECT study. *J Thromb Thrombolysis* 2012; 34: 187–192.

Youden WJ. Index for rating diagnostic tests. *Cancer* 1950; 3: 32–35.

Kabrhel C, Okechukwu I, Hariharan P, et al. Factors associated with clinical deterioration shortly after PE. *Thorax* 2014; 69: 835–842.

Jiménez D, Díaz G, Molina J, et al. Troponin I and risk stratification of patients with acute nonmassive pulmonary embolism. *Eur Respir J* 2008; 31: 847–853.

Jiménez D, Lobo JL, Monreal M, et al. Prognostic significance of multidetector CT in normotensive patients with pulmonary embolism: results of the protect study. *Thorax* 2014; 69: 109–115.

Becattini C, Agnelli G, Vedovati MC, et al. Multidetector computed tomography for acute pulmonary embolism: diagnosis and risk stratification in a single test. *Eur Heart J* 2011; 32: 1657–1663.

Prosperi-Porta G, Solverson K, Fine N, et al. Echocardiography-derived stroke volume index is associated with adverse in-hospital outcomes in intermediate-risk acute pulmonary embolism: a retrospective cohort study. *Chest* 2020; 158: 1132–1142.

Kwak MK, Kim WY, Lee CW, et al. The impact of saddle embolism on the major adverse event rate of patients with non-high-risk pulmonary embolism. *Br J Radiol* 2013; 86: 20130273.

Vanni S, Nazerian P, Bova C, et al. Comparison of clinical scores for identification of patients with pulmonary embolism at intermediate-high risk of adverse clinical outcome: the prognostic role of plasma lactate. *Intern Emerg Med* 2017; 12: 657–665.

Bova C, Vanni S, Prandoni P, et al. A prospective validation of the Bova score in normotensive patients with acute pulmonary embolism. *Thromb Res* 2018; 165: 107–111.

Jiménez D, de Miguel-Díez J, Guijarro R, et al. Trends in the management and outcomes of acute pulmonary embolism: analysis from the RIETE registry. *J Am Coll Cardiol* 2016; 67: 162–170.