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Rapid Prediction of Adverse Outcomes for Acute Normotensive Pulmonary Embolism: Derivation of the Calgary Acute Pulmonary Embolism (CAPE) Score

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ABREVIATIONS LIST

AIC = Akaike Information Criterion

BPM = beats per minute

BNP = brain natriuretic peptide

CAPE = Calgary Acute Pulmonary Embolism Score

CT = computed tomography

DAD = discharge abstract data

DVT = deep vein thrombosis

ED = emergency department

ESC = European Society of Cardiology

hs-TnT = high-sensitivity troponin

IQR = interquartile range

IVC = inferior vena cava

PA = pulmonary artery

PE = pulmonary embolism

RIETE = European Registro Informatizado de la Enfermedad TromboEmbolica

RV = right ventricle

ROC = receiver operating characteristic

sPESI = Simplified Pulmonary Embolism Severity Index

SD = standard deviation

SBP = systolic blood pressure

TTE = transthoracic echocardiogram

TRIPOD = Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis

VQ = ventilation/perfusion

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 multicenter retrospective cohort study of acute PE patients admitted from emergency departments in Calgary, Canada, between 2012-2017 was used to develop a refined acute PE risk score. The composite primary outcome of in-hospital PE-related death or hemodynamic 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 2,067 patients with normotensive acute PE, the primary outcome (hemodynamic decompensation or PE related death) occurred in 32 patients (1.5%). In sPESI 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, & heart rate ≥100 BMP 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 4-variable risk score using clinical data immediately available after CT diagnosis of acute PE predicts in-hospital adverse outcomes. External validation of the CAPE score is required.

INTRODUCTION

The spectrum of acute pulmonary embolism (PE) outcomes is broad with early mortality ranging from 1% up to 50% in patients who are hemodynamically unstable at presentation(1). High-risk PE patients with hypotension or shock should be considered for urgent revascularization(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). Individually however, these have a low positive predictive value for PE-related outcomes. The 2019 European Society of Cardiology (ESC) guidelines proposes 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 hypothesized that optimizing the cutoffs 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 optimized cut-points for independent risk variables, 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 (TRIPOD)(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 (≥18 years) with a confirmed diagnosis of acute PE admitted via emergency departments (ED) at 4 hospitals (collectively >325,000 emergency department visits annually) in Calgary, Alberta, Canada between January 1st, 2012 and March 31st, 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, radiologic/diagnostic imaging , nursing notes and physician transfer/discharge notes. PE diagnosis was confirmed by CT angiography, ventilation/perfusion (VQ) 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. hemodynamically unstable at presentation (systolic blood pressure <90 mmHg or requiring

vasopressor support); 3. PE diagnosis was made >24 hours after admission; 4. recurrent PE <6 months from presentation; 5. incidental/asymptomatic PE; 5. reperfusion therapy at presentation; 7. not admitted to hospital; 8. palliative goals of care.

Vital signs, symptoms and comorbidities on ED arrival and laboratory tests performed with 24-hours 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 previously described(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 (IVC) filter use, admitting medical service, and hospital length of stay.

The sPESI score was calculated as low (<1) or high-risk (≥1)(5). The Bova score(7) and European Society of Cardiology (ESC) classification (4) were calculated from data at ED presentation and then converted into three risk stages (I-III) (eTable 1, Supplement).

Outcomes

The primary outcome was in-hospital PE-related death or hemodynamic decompensation (systolic blood pressure <90 mmHg for >15 minutes, 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. Thirty-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 ± standard deviation (SD) for normally distributed continuous variables and median (interquartile range (IQR), 25% to 75%) for nonnormally distributed variables. Skewness and normality were assessed using the Kolmogorov-Smirnov test. Differences between groups were assessed with 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 modeling 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 modeling used covariates as both continuous variables and dichotomized 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 (ROC) 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) and Stata 14.2 (StataCorp, Texas, 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 with CT in 1906 (92.2%) patients, by ventilation-perfusion imaging in 158 patients (7.6%) and TTE in 3 patients (0.2%). Baseline patient characteristics are presented in **Table 1**. The median age was 63 years (IQR 50-76) and 1054 (50.9%) were male. A total of 1611 patients (77.9%) had hs-TnT measured at admission, which was elevated in 824 patients (51.2%). RV dilatation was assessed on CT angiography in 1906 patients (92.2%) and present (CT RV to LV ratio >1.0) in 922 patients (48.4%).

Outcomes

The primary outcome occurred in 32 (1.5%) patients (**Table 2**). PE-related death occurred in 16 patients (0.8%) and hemodynamic decompensation occurred in 16 (0.8%). The time to primary outcome from the initial presentation to the ED is shown cumulatively in **Figure 2**. The median time to the primary outcome was 22.5 hours (IQR 6.5-44.5) with a range of 4 to 84 hours. In addition to 16 PE-related deaths, 19 patients (0.9%) 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 6 (31.6%), major hemorrhage (not secondary to thrombolysis) in 4 (21.1%), respiratory failure not related to PE in 3 (15.7%), and other causes in 6 patients (31.6%). All of the patients with major hemorrhage had do-not-resuscitate orders and the sites of major hemorrhage were retroperitoneal in 2, gastrointestinal in 1 and intracranial in 1. All-cause mortality within 30-days occurred for 64 patients (3.1%).

Risk Stratification by the simplified PESI and Bova score

Complete data were available to calculate the sPESI for 2067 patients (100%), of which 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 modeling were done using the high-risk sPESI group. The Bova score was calculable, with complete data for all 4 components, for 1179 patients (73.9%). In the 449 patients with missing Bova variables, 4 patients (0.9%) had an in-hospital adverse outcome and 20 (4.5%) patients died within 30-days. The Bova score classified 586 patients (49.8%) as low risk (score 0-2), 376 patients (31.9%) as intermediate-low risk (score 3-4), and 217 patients (18.4%) as intermediate-high risk (score ≥5) (**Table 3**). Primary outcomes occurred for 1 (0.2%), 10 (2.7%), 17 (7.8%) patients in Bova stage 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, ≥1.5, and ≥100 BPM, respectively. A 4-variable model (model 2) including CT RV/LV ratio, heart rate, central pulmonary artery clot, and 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 4-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 4-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 cutoff of the score (**eFigure 1, supplement**): Low (0-2), Intermediate-low (3-4), 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 intermediate-low (3.0%) group. The CAPE risk groups showed similar discrimination compared to the 4-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 categorized more patients as low-risk compared to the Bova score (74.3% vs. 49.7%) and there were fewer patients in the intermediate-high risk group (10.3% vs. 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 4-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 hemodynamic decompensation). The independent variables were: 1) right-to-left ventricle ratio ≥ 1.5 on CT pulmonary angiogram, 2) presence of central pulmonary artery clot, 3) heart rate ≥100 BPM, and 4) systolic blood pressure 90-100 mmHg at ED 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 also 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 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 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 revascularization therapies, as such interventions may have more favorable benefit-risk tradeoffs 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 (**eFigure 2, supplement**). Patients with a CT RV/LV ratio >1.5 would more likely 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 ED presentation and more likely 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 ICU, to promptly recognize evolving hemodynamic 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, more than 75% of the adverse PE outcomes occurred within 48 hours after presentation to the ED. 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 hours. These data

suggest that close monitoring of intermediate-high risk patients should occur for a minimum of 48-72 hours. 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% vs. 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 2006-2009 compared to 1.1% between 2010-2013, 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 multicenter American study found an in-hospital PE-mortality rate of 1.1% in 1880 patients admitted from the ED, including unstable patients, which is similar to the 0.8% rate in our study(8). We hypothesize 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 ED. Indeed, we found short delays between ED presentation, PE diagnosis and initiation of treatment, especially in normotensive, intermediate-high risk PE (**eTable 2, supplement**).

The main strengths of this study are the large cohort size, the inclusion of patients from tertiary care EDs 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, NT-proBNP, and lower extremity DVT, which precluded consideration in multivariable analysis. Although we used methods to optimize internal validity, our 4-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 VQ 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 BPM (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 revascularization therapy.

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KS, JW, JEA, AF, PB, EH and DH conceived and designed the study. KS, CH, and GP collected data. KS, ZY, and JW analyzed the data. KS and JW wrote the first draft of the manuscript. All authors made significant contributions to data interpretation and the final manuscript.

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TABLES

Table 1. Baseline patient characteristics

Variable	All patients n=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 the last 2 months of PE diagnosis	235 (11.3)
Symptoms and clinical findings at admission	
Dyspnea	1581 (78.3)
Chest pain	1109 (53.7)
Syncope	137 (6.6)
Heart rate ≥ 100 BPM	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 cutoff [a]	824 (51.2)
NT-proBNP ≥ 300 pg/ml	240 (71.4)
Serum lactate > 2.2 mmol/L	163 (24.9)
D-dimer > 0.50 mg/L	1170 (97.8)
RV dilatation on CT angiography [b]	922 (48.4)
RV dysfunction on TTE [c]	419 (39.6)
Central pulmonary artery clot	376 (19.7)
Lower extremity DVT at presentation [d]	476 (52.4)

Initial treatment at time of diagnosis	
Unfractionated heparin, IV infusion	543 (26.3)
LMWH, subcutaneous	1473 (71.3)
DOAC, per oral	40 (1.9)
IVC filter insertion	108 (5.2)
Time to initiation of anticoagulation from ED presentation, hours	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 (%) or median (interquartile range) unless otherwise stated. hs-TnT: high-sensitivity troponin; NT-proBNP: N-terminal pro B-type natriuretic peptide; RV: Right ventricle; CT: Computer tomography; TTE: Transthoracic echocardiogram; DVT: Deep venous thrombosis; IV: intravenous; LMWH: Low molecular weight heparin; DOAC: Direct oral anticoagulant; IVC: Inferior vena cava; ED: Emergency department. [a]: ≥14 pg/mL for patients <75 years and ≥45 pg/mL for patients ≥75 years; [b]: Right to the left ventricle axial ratio>1.0; [c]: Moderate or greater right ventricle dysfunction or dilatation; [d]: Duplex ultrasound for DVT of the bilateral extremities. Data available: Hs-TnT: n=1611; NT-proBNP: n=336; Serum lactate: n=654; D-dimer: n=1196; CT angiography: n=1906, TTE: n=1058, Duplex ultrasound for DVT: n=908.

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

Outcome	Patients
Adverse in-hospital PE outcome [a]	32 (1.5)
Hemodynamic decompensation in-hospital [b]	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 presented as n (%) unless otherwise stated. [a]: Death secondary to PE, hemodynamic decompensation; [b]: systolic blood pressure <90mmHg for >15minutes, catecholamine administration for hypotension, endotracheal intubation or cardiopulmonary resuscitation.

Table 3. Risk stratification of normotensive acute pulmonary embolism (PE) by the simplified PESI and Bova Score

Score	n (%)	Adverse in-hospital PE outcome [a]	All cause 30-day mortality
Simplified PESI (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)[b]			
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 (%) unless otherwise stated. PESI: Pulmonary Embolism Severity Index; [a]: Death secondary to PE, hemodynamic decompensation (systolic blood pressure <90 mmHg for >15 minutes, catecholamine administration for hypotension, endotracheal intubation or cardiopulmonary resuscitation); [b]: Simplified PESI score=0 excluded from calculation.

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 PESI

Predictor	**Univariable models, Odds Ratio (95% CI)**	**p-value**	**Multivariable models, Odds Ratio (95% CI)**			
			1. hs-TnT ≥50 pg/ml, CT RV/LV ≥1.5, Heart rate ≥100 BPM, Central PA embolism, Systolic BP 90-100mmHg n=1179	**2. CT RV/LV ≥1.5, Heart rate ≥100 BPM, Central PA embolism, Systolic BP 90-100mmHg n=1498**	**3. CT RV/LV ≥1.5, Heart rate ≥100 BPM, Central PA embolism n=1498**	**4. CT RV/LV ≥1.5, Heart rate ≥100 BPM n=1498**
Age, per year increase	0.98 (0.96-0.99)	0.049				
Lower extremity DVT present [a]	9.61 (2.24-41.196)	0.002				
Elevated lactate > 2.2 mmol/L	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 [b]	8.37 (3.58-19.57)	<0.001	1.90 (0.67-5.40) p=0.223			
CT RV/LV ratio, ≥ 1.5 [b,c]	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 [d]	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 BPM [b]	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 Criteria			217.0	216.6/228.9 [e]	230.4	234
C statistic			0.88	0.88/0.89 [e]	0.89	0.87

PESI: Pulmonary Embolism Severity Index; Hs-TnT: High-sensitivity troponin; CT RV/LV: Computed tomography right ventricle to left ventricle ratio; BPM: beats per minute; PA:

pulmonary artery; SBP: systolic blood pressure; DVT: Deep venous thrombosis. [a]: DVT documented positive if reported on duplex ultrasound of the lower extremities; [b]: Cut-points determined by the Youden's index; [c]: Measured by dividing the RV and LV ventricle diameter at the valvular level of the CT angiogram axial cuts; [d]: Defined as thrombus present within the central pulmonary arteries proximal to a lobar artery; [e]: The first value is calculated using a model limited to the 1179 patient in model 1, the second value is calculated using the 1498 patients in models 2-4. There were 29 adverse in-hospital outcomes 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 PESI

	Score	Patients (n=1498)	Adverse in-hospital PE outcome [a]	All cause 30-day mortality
Risk Factor [b]				
CT RV/LV ratio, ≥ 1.5	3	326 (21.8)		
Central PA clot	1	330 (22.0)		
Heart rate, ≥100 BPM	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 (%) unless otherwise stated. PESI: Pulmonary Embolism Severity Index; CT RV/LV: Computed tomography angiogram right ventricle to left ventricle ratio; BPM: beats per minute [a]: Death secondary to PE, hemodynamic decompensation (systolic blood pressure <90mmHg for >15minutes, catecholamine administration for hypotension, endotracheal intubation or cardiopulmonary resuscitation); [b]: See table 4 footnote for risk factor definitions

FIGURE LEGENDS

Figure 1. Patient inclusion and exclusion flow diagram. PE, pulmonary embolism.

Figure 2. Cumulative in-hospital adverse PE outcomes.

Figure 3. Risk stratification performance of the CAPE score, Bova score and ESC classification (see table 5, eTable 1 and (4) for definitions) for normotensive acute pulmonary embolism (PE) patients who are high-risk simplified PESI. 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 statistic calculated on patients who had sPESI≥1 and a complete Bova score, n=1179. Total adverse in-hospital PE outcomes were 28.

Figure 1

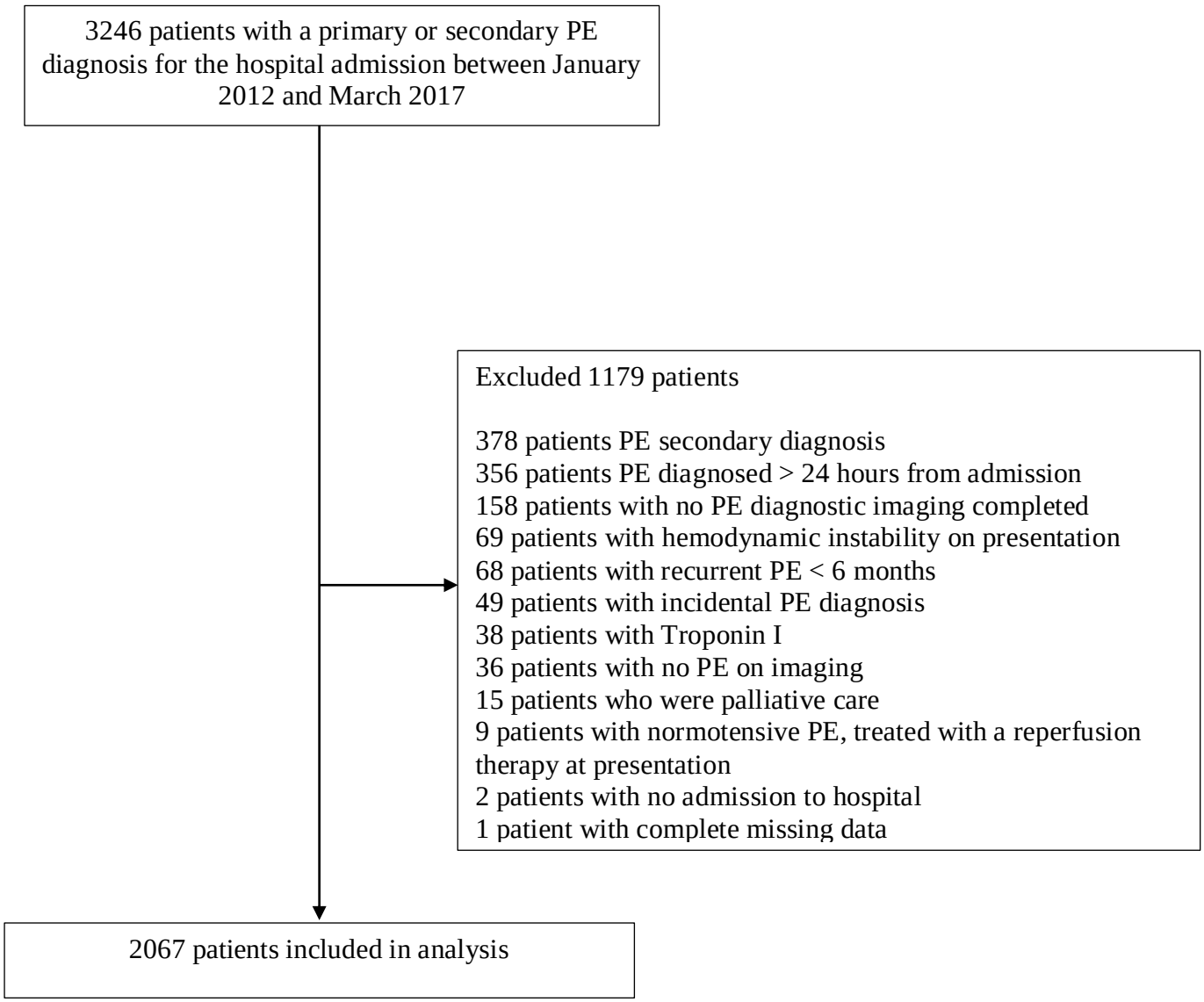

3246 patients with a primary or secondary PE diagnosis for the hospital admission between January 2012 and March 2017
Excluded 1179 patients
378 patients PE secondary diagnosis
356 patients PE diagnosed > 24 hours from admission
158 patients with no PE diagnostic imaging completed
69 patients with hemodynamic instability on presentation
68 patients with recurrent PE < 6 months
49 patients with incidental PE diagnosis
38 patients with Troponin I
36 patients with no PE on imaging
15 patients who were palliative care
9 patients with normotensive PE, treated with a reperfusion therapy at presentation
2 patients with no admission to hospital
1 patient with complete missing data
2067 patients included in analysis

Figure 2

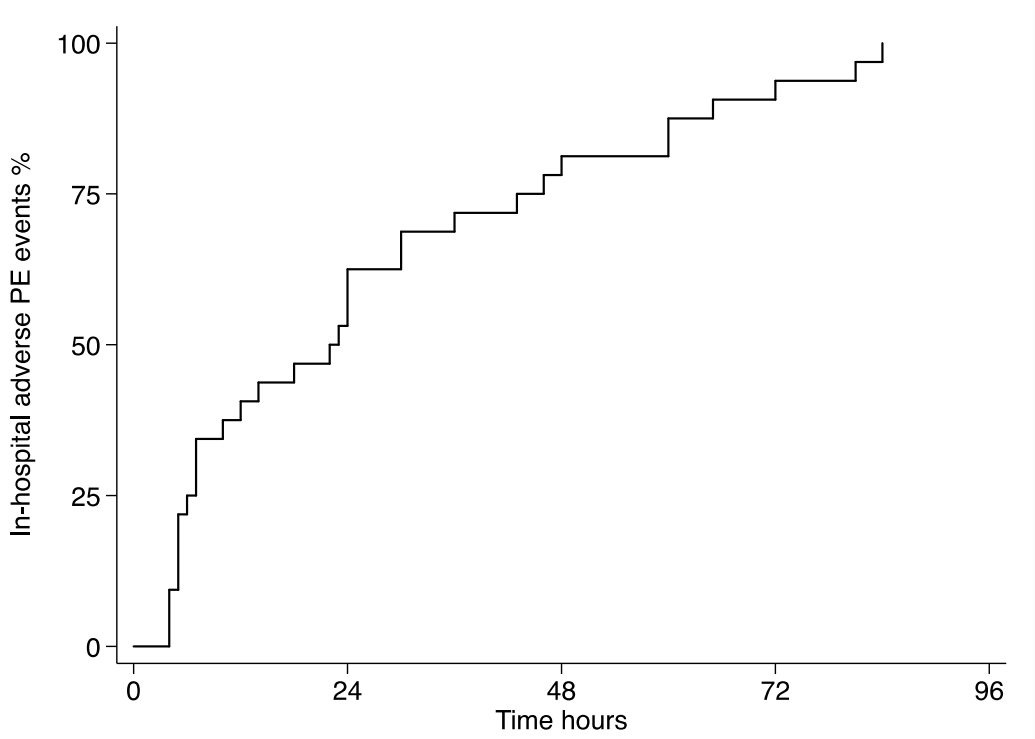
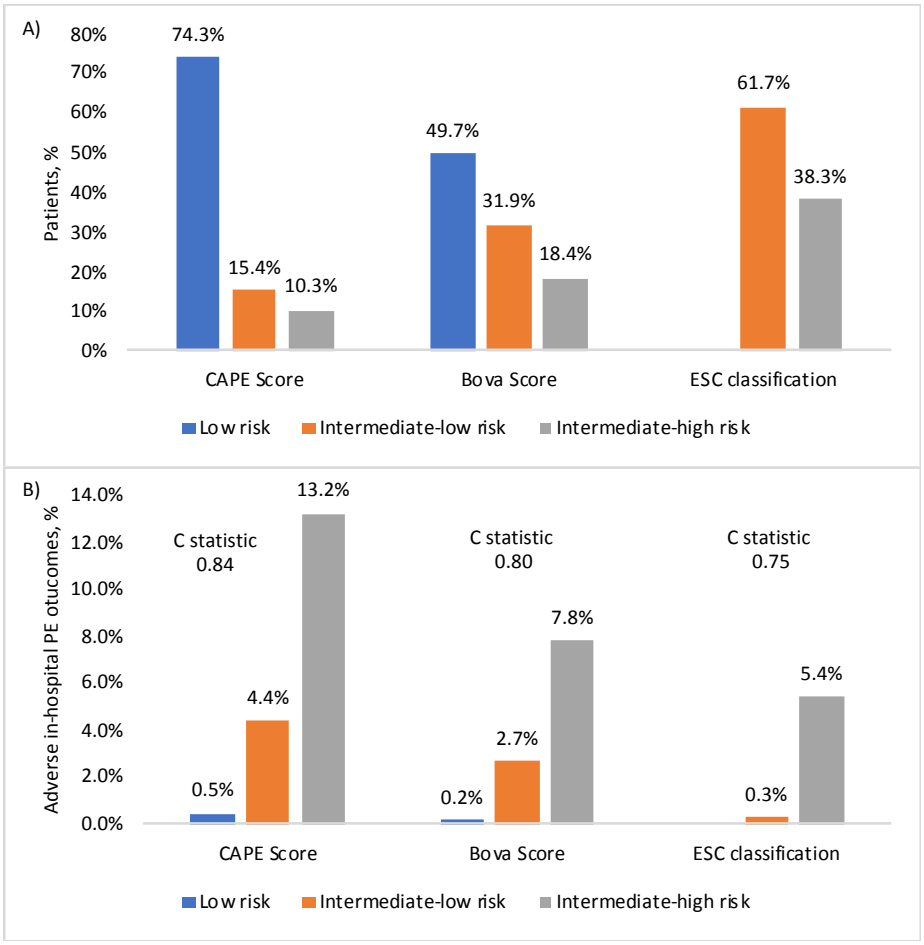

100
75
50
25
0
In-hospital adverse PE events %
0
24
48
72
96
Time hours

Figure 3


A)
80%
70%
60%
50%
40%
30%
20%
10%
0%
Patients, %
74.3%
15.4%
10.3%
49.7%
31.9%
18.4%
61.7%
38.3%
CAPE Score
Bova Score
ESC classification
Low risk
Intermediate-low risk
Intermediate-high risk
B)
14.0%
12.0%
10.0%
8.0%
6.0%
4.0%
2.0%
0.0%
Adverse in-hospital PE otucomes, %
C statistic
0.84
0.5%
4.4%
13.2%
C statistic
0.80
0.2%
2.7%
7.8%
C statistic
0.75
0.3%
5.4%
CAPE Score
Bova Score
ESC classification
Low risk
Intermediate-low risk
Intermediate-high risk

Supplemental Data

Rapid Prediction of Adverse Outcomes for Acute Normotensive Pulmonary Embolism: Derivation of the Calgary Acute Pulmonary Embolism (CAPE) Score

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eTable 1. Summary of the Simplified Pulmonary Embolism Index and Bova Score

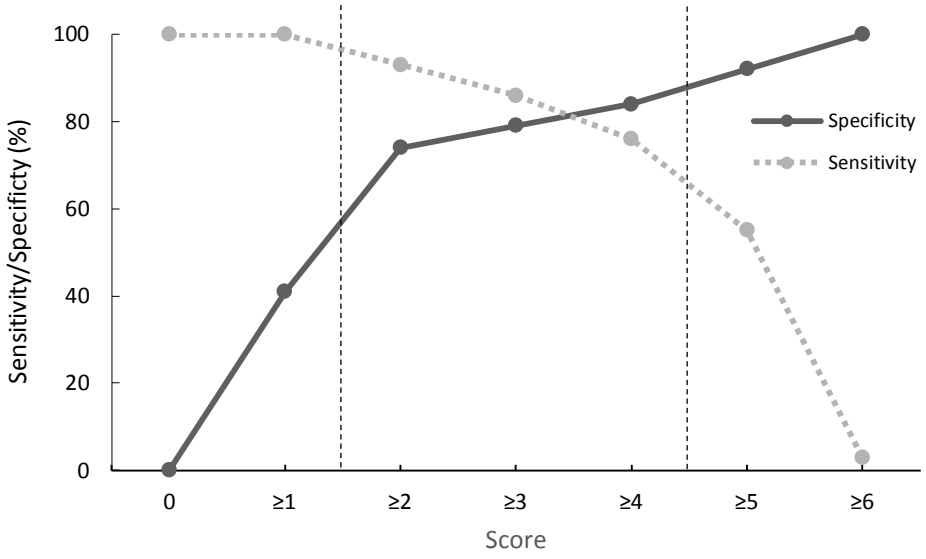
Variables (score)	sPESI	Bova Score
	Age >80 years (1)	
	Cancer (1)	Elevated Hs-TnT (2)
	Cardiopulmonary disease (1)	Right Ventricular Dysfunction (TTE or CT) (2)
	Heart Rate ≥110 BPM (1)	Heart Rate ≥110 BPM (1)
	Systolic BP <100 mmHG (1)	Systolic BP 90-100 mmHG (2)
	Oxygen Saturation <90% (1)	
Risk category	Total score	Total score
Low risk	0	≤2
Intermediate-low-risk		≥3 to ≤4
Intermediate-high-risk	≥1	≥5

sPESI: Simplified Pulmonary Embolism Severity Index; Hs-TnT: High-sensitivity troponin; BP: blood pressure; TTE: Transthoracic echocardiogram; CT: Computed tomography

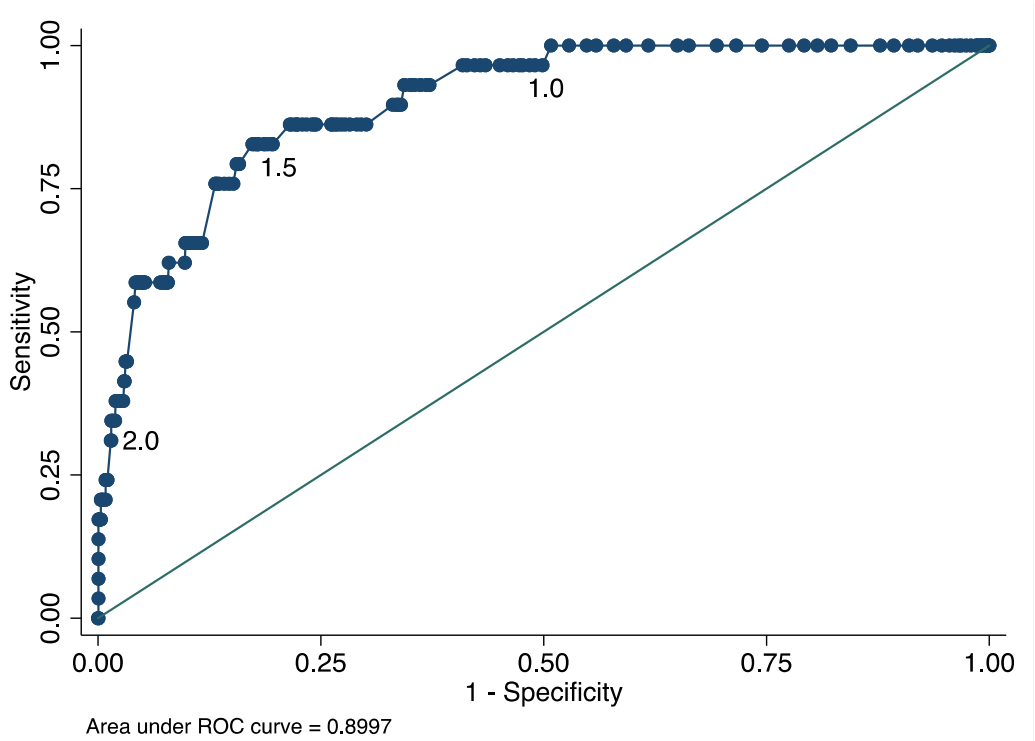
eTable 2. Time of hospital presentation to pulmonary embolism diagnosis and initiation of anticoagulation, stratified by Bova Stage[a] (n=1498)

	All patients, hr	Bova Stage I, hr	Bova Stage II, hr	Bova Stage III, hr	p-value [b]
ED presentation to PE diagnosis [c]	4.1 (2.8-5.9)	4.3 (3.0-6.0)	3.9 (2.7-5.8)	3.7 (2.6-5.0)	0.005
ED presentation to initiation of anticoagulation [d]	5.7 (3.7-8.0)	6.1 (4.2-8.2)	5.2 (3.5-7.3)	4.3 (2.6-6.0)	<0.001
Pulmonary embolism diagnosis to initiation of anticoagulation [d]	1.2 (0.5-2.1)	1.3 (0.7-2.4)	1.1 (0.4-1.8)	0.6 (-0.3-1.3)	<0.001

Data presented median (interquartile range). ED: Emergency Department; hr: hours. [a]: Bova stage I (Bova score 0-2), stage II (Bova score 3-4), stage II (Bova score ≥5), see eTable 1 for Bova score definitions; [b]: Kruskal-Wallis equality-of-populations rank test comparison between Bova stages; [c]: PE diagnosis defined as completion of a computed tomography pulmonary angiogram, ventilation perfusion scan or transthoracic echocardiogram; d: initiation of anticoagulation defined as time of the medical team ordering therapeutic anticoagulation.



eFigure 1. Sensitivities and specificities of the risk score to identify acute PE patients who had an in-hospital adverse event. Three risk groups were defined: (1) risk score ≤2, (2) risk score 3-4, and (3) risk score ≥5.



eFigure 2. Receiver operator characteristics of the CT right to left ventricular ratio for identifying acute PE patients with in-hospital adverse events