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Original article

Definition of tachycardia for risk stratification of pulmonary embolism

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ABSTRACT

Background: Tachycardia is a reliable predictor of adverse outcomes in normotensive patients with acute pulmonary embolism (PE). However, different prognostic relevant heart rate thresholds have been proposed. The aim of the study was to investigate the prognostic performance of different thresholds used for defining tachycardia in normotensive PE patients.

Methods: We performed a post-hoc analysis of normotensive patients with confirmed PE consecutively included in a single-centre and a multi-centre registry. An adverse outcome was defined as PE-related death, need for mechanical ventilation, cardiopulmonary resuscitation or administration of catecholamines.

Results: Of 1567 patients (median age: 72 [IQR, 59–79] years; females: 46.1%) included in the analysis, 78 patients (5.0%) had an in-hospital adverse outcome. The rate of an adverse outcome was higher in patients with a heart rate ≥100 bpm (7.6%) and ≥110 bpm (8.3%) compared to patients with a heart rate <100 bpm (3.0%). A heart rate ≥100 bpm and ≥110 bpm was associated with a 2.7 (95% CI 1.7–4.3) and 2.4-fold (95% CI 1.5–3.7) increased risk for an adverse outcome, respectively. Receiver operating characteristics analysis revealed a similar area under the curve with regard to an adverse outcome for all scores and algorithm (ESC 2019 algorithm, modified FAST and Bova score) if calculated with a heart rate threshold of ≥100 bpm or of ≥110 bpm.

Conclusions: Defining tachycardia by a heart rate ≥100 bpm is sufficient for risk stratification of normotensive patients with acute PE. The use of different heart rate thresholds for calculation of scores and algorithm does not appear necessary.

1. Introduction

Acute pulmonary embolism (PE) is the most serious manifestation of venous thromboembolism (VTE) and a major cause of mortality, morbidity and hospitalization in Western countries [1]. Acute right ventricular (RV) dysfunction due to pressure overload is the critical determinant of outcome in acute PE. Accordingly, clinical symptoms and signs of RV dysfunction such as persistent arterial hypotension, RV dilatation an imaging modalities and elevated cardiac biomarkers indicate a higher risk of early mortality [2,3]. Further, pulmonary artery

Abbreviation: AUC, Area under the curve; CI, Confidence interval; ESC, European society of cardiology; FAST score, H-FABP, Syncope and tachycardia; GFR, Glomerular filtration rate; H-FABP, Heart-type fatty acid-binding protein; IPER, Italian pulmonary embolism registry; hsTnT, High-sensitivity troponin t; IQR, Interquartile range; LV, left ventricular; NPV, negative predictive value; OR, Odds ratio; PE, pulmonary embolism; PPV, positive predictive value; RV, right ventricular; ROC, receiver operating characteristics; (s)PESI, (simplified) Pulmonary Embolism Severity Index; TTE, transthoracic echocardiography; VTE, venous thromboembolism

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Table 1
Baseline characteristics, medical history and initial presentation of 1567 normotensive patients with pulmonary embolism stratified according a heart rate of 100 bpm.

	All study patients (n = 1567)	Heart rate ≥100 bpm (n = 688)	Heart rate <100 bpm (n = 879)	p-value
Sex (male)	723/1567 (46.1%)	290/688 (42.2%)	433/879 (49.3%)	**0.006**
Age (years)	72 (59–79)	71 (57–79)	72 (61–79)	0.107
Risk factors for VTE and comorbidities				
Previous VTE	375/1566 (23.9%)	154/688 (22.4%)	221/878 (25.2%)	0.210
Cancer*	297/1557 (19.1%)	140/684 (20.5)	157/873 (18.0%)	0.218
Chronic pulmonary disease	273/1566 (17.4%)	88/687 (12.8%)	185/879 (21.0%)	**<0.001**
Chronic left heart disease	144/1566 (9.2%)	50/687 (7.3%)	94/879 (10.7%)	**0.022**
Symptoms and clinical findings on admission				
Syncope	209/1564 (13.4%)	100/686 (14.6%)	109/878 (12.4%)	0.231
Systolic blood pressure (mmHg)	130 (120–144)	130 (110–140)	130 (120–145)	**<0.001**
Mild hypotension†	37/1567 (2.4%)	19/688 (2.8%)	18/879 (2.0%)	0.403
Hypoxia††	742/1129 (65.7%)	397/529 (75.0%)	345/600 (57.5%)	**<0.001**
RV dysfunction on imaging	1075/1567 (68.6%)	548/688 (79.7%)	509/879 (57.9%)	**<0.001**
Elevated troponin	611/1567 (39.0%)	368/688 (53.5%)	243/879 (27.6%)	**<0.001**
Treatment and Outcomes				
Thrombolysis	157/1565 (10.0%)	98/688 (14.2%)	59/877 (6.7%)	**<0.001**
Adverse outcome	78/1567 (5.0%)	52/688 (7.6%)	26/879 (3.0%)	**<0.001**
PE-related death	30 /1567 (1.9%)	23/688 (3.3%)	7/879 (0.8%)	**<0.001**
All-cause death	61/1567 (3.9%)	41/688 (6.0%)	20/879 (2.3%)	**<0.001**
In-hospital stay (days)	8 (5–13)	9 (6–14)	8 (4–12)	**<0.001**

* defined as active or anti-tumour therapy within the last 6-months, or metastatic state.
† defined as systolic blood pressure between 90 and 100 mmHg on admission.
†† defined as oxygen saturation <90%
Bold values indicate statistical significance ($p < 0.05$).
Abbreviations: VTE, venous thromboembolism; PE, pulmonary embolism; bpm, beats per minute; RV, right ventricular.

obstruction due to embolized thrombotic material leads to an abrupt increase in pulmonary vascular resistance and RV wall tension, consecutively resulting in inotropic and chronotopic cardiac stimulation to maintain cardiac output [4,5]. Thus, tachycardia is an early indicator of haemodynamic compromise and a reliable predictor of PE-related complications in normotensive patients with acute PE. Consequently, tachycardia is used as a risk marker in the majority of risk assessment models such as the (simplified) Pulmonary Embolism Severity Index ([*s*]PESI), Bova and modified FAST score [6-9]. However, different prognostic relevant thresholds for tachycardia have been proposed in these different risk assessment models. In the derivation study of the PESI, a heart rate ≥110 beats per minute (bpm) was identified as predictor of 30-day all-cause mortality. On the other hand, the FAST score identified a heart rate of ≥100 bpm as prognostic relevant [10,11]. In the current European Society of Cardiology (ESC) [12] and American College of Chest Physicians (ACCP) [13] guidelines a recommendation on which heart rate threshold to use is missing.

The aim of the present study was to investigate the prognostic value of different tachycardia thresholds and to compare their impact on the prognostic performance of different scores and algorithm used for risk stratification of normotensive patients with acute PE.

2. Material and methods

2.1. Patient cohort and study design

Consecutive normotensive patients aged ≥18 years with objectively confirmed acute PE were included in the observational multicentre Italian Pulmonary Embolism Registry (IPER) between January 2006 and November 2010 and in the single-centre Pulmonary Embolism Registry of Göttingen (PERGO) between October 2005 and January 2018. The study protocols have been described in detail before [14,15]. Patients were excluded from the present analysis if they fulfilled at least one of the following criteria: 1) missing heart rate, 2) missing troponin plasma concentrations on admission or 3) missing information on RV function on transthoracic echocardiography (TTE) or computed tomography pulmonary angiography (CTPA). In PERGO, the assessment of RV dysfunction was based on TTE and/or CTPA. RV dysfunction on TTE was defined as RV/LV end-diastolic diameter ratio >1.0 combined with absence of the inspiratory collapse of the inferior vena cava or a RV/RA pressure gradient >30 mmHg, in the absence of significant left ventricular (LV) or mitral valve disease. RV dysfunction on (diagnostic) CTPA was defined as RV/LV axial diameter ratio ≥1.0 [7].

In IPER, RV dysfunction was assessed on TTE. RV dysfunction was defined as at least one of the following findings: 1) RV/LV end-diastolic diameter ratio >1.0 in apical 4-chamber view; 2) RV/LV end-diastolic diameter ratio >0.6 in parasternal long-axis or subcostal 4-chamber view; 3) RV/RA pressure gradient >30 mmHg. Signs of RV dysfunction were not considered acute in the presence of RV wall thickness >7 mm or documentation of RV enlargement or pulmonary hypertension at previous examinations [14].

TTE was performed as soon as possible after admission and results of RV function were only included in the analysis, if it was done within 48 h after PE diagnosis. Troponin elevation was defined as troponin I or troponin T plasma concentrations above the assay-specific cut-off value, respectively. In the IPER registry, several ECG parameters were collected. Amongst these, the presence of tachycardia was documented, but not the exact heart rate in beats per minute. Thus, for the current analysis, we used heart rate assessed on clinical examination (auscultation) and not from ECG. In PERGO, heart rates were obtained from ECG performed on admission / at the time of diagnosis of PE.

Patients were stratified post-hoc in risk classes according to the sPESI [16], the modified FAST [7] and Bova score [6,17] and the algorithm proposed by the ESC 2019 guidelines [12]. For calculation of all algorithms and scores, missing values were considered to be normal [18].

All patients were followed for the in-hospital stay. The primary outcome was an in-hospital adverse outcome defined as PE-related death, need for mechanical ventilation, cardiopulmonary resuscitation or the administration of catecholamines (except for dopamine at an infusion rate of ≤5 μg/kg of body weight per minute). The secondary outcome was in-hospital all-cause death.

Treatment decisions were made by the physicians caring for the patient according to current guidelines and local standard operating procedures and were not influenced by the study protocol. Study results were not communicated to the clinicians and thus not used to guide the

Table 2a
Prognostic performance of different heart rate thresholds with regard to an in-hospital adverse outcome.

	Elevated heart rate (n;%)	In-hospital adverse outcome (n;%)	Sensitivity (%; 95% CI)	Specificity (%; 95% CI)	PPV (%; 95% CI)	NPV (%; 95% CI)	OR (95% CI) p-value
Heart rate ≥ 115 bpm	295 (18.8%)	26 (8.8%)	0.33 (0.24–0.44)	0.82 (0.80–0.84)	0.09 (0.06–0.13)	0.96 (0.95–0.97)	**2.3 (1.4–3.7) $p = 0.001$**
Heart rate ≥ 110 bpm	432 (27.6%)	36 (8.3%)	0.46 (0.36–0.57)	0.73 (0.71–0.76)	0.08 (0.06–0.11)	0.96 (0.95–0.97)	**2.4 (1.5–3.7) $p < 0.001$**
Heart rate ≥ 105 bpm	515 (32.9%)	39 (7.6%)	0.50 (0.39–0.61)	0.68 (0.66–0.70)	0.08 (0.06–0.10)	0.97 (0.95–0.97)	**2.1 (1.3–3.4) $p = 0.001$**
Heart rate ≥ 100 bpm	688 (43.9%)	52 (7.6%)	0.67 (0.56–0.76)	0.57 (0.55–0.60)	0.08 (0.06–0.10)	0.97 (0.96–0.98)	**2.7 (1.7–4.3) $p < 0.001$**
Heart rate ≥ 95 bpm	785 (50.1%)	54 (6.9%)	0.69 (0.58–0.78)	0.51 (0.48–0.53)	0.07 (0.05–0.09)	0.97 (0.95–0.98)	**2.3 (1.4–3.8) $p = 0.001$**
Heart rate ≥ 90 bpm	933 (59.5%)	57 (6.1%)	0.73 (0.62–0.82)	0.41 (0.39–0.44)	0.06 (0.05–0.08)	0.97 (0.95–0.98)	**1.9 (1.1–3.2) $p = 0.014$**

Abbreviations: OR, odds ratio; AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.
Bold values indicate statistical significance ($p < 0.05$).
The threshold reference is different in each subgroup and relates in each case to all patients which not fulfil the mentioned cut-off.

patient management or to monitor the effects of treatment at any time. The study protocol was conducted in accordance with the amended Declaration of Helsinki and was approved by the local independent Ethic Committees at the study centres, and all patients gave informed written consent for participation in the study.

2.2. Statistical analysis

The Fisher´s exact test or the Chi^2 test were used to compare categorical variables, which are expressed as absolute numbers or percentages. Continuous variables were found not to follow a normal distribution if tested with the modified Kolmogorov-Smirnov test (Lilliefors test); therefore, these variables are expressed as medians with the corresponding interquartile range (IQR) and were compared using the unpaired Mann-Whitney-U test. Receiver operating characteristics (ROC) curve analysis was performed to determine the area under the curve (AUC) of algorithms and scores (absolute points) with regard to study outcomes. To allow comparison of algorithms and scores, the three-level ESC 2019 algorithm and Bova score were dichotomized as low- and intermediate-low-risk ("low-risk") versus intermediate-high-risk ("intermediate-high-risk"). Comparison of the prognostic performance of dichotomous algorithms and scores was performed by calculation of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). The prognostic relevance of dichotomous algorithms and scores as well as single predictors with regard to study outcomes was tested using univariate logistic regression analysis and presented as Odds ratios (OR) with corresponding 95% confidence intervals (CI). A two-sided significance level of $\alpha < 0.05$ was defined appropriate to indicate statistical significance. Statistical analyses were performed using the SPSS software (version 21.0, SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1. Baseline findings and clinical outcomes

Between January 2005 and November 2018, 2273 normotensive patients ≥18 years with objectively confirmed PE were included in two registries. Of those, 706 (30.1%) patients were excluded from the present analysis because of missing information on heart rate, troponin plasma concentrations or RV function on TTE / CTPA (**Figure S1 in the supplementary material**). Thus, 1567 PE patients (median age: 72 [IQR, 59–79] years; males: 46.1%) were analysed and their baseline characteristics are shown in Table 1, **left column**. Troponin plasma concentrations were elevated in 611 (39.0%) patients, RV dysfunction was detected on imaging in 1075 (68.6%) patients and 157 (10.0%) patients received systemic thrombolysis. In PERGO, RV function was evaluated in 362 (51.8%) patients by CTPA alone and in 194 (27.7%) patients by TTE alone. In 143 (20.5%) patients, both imaging modalities were performed to assess RV function. In 26 (3.7%) patients included in PERGO and in 75 (8.6%) patients included in IPER, the diagnosis of PE was based on ventilation / perfusion (V/P) lung scintigraphy. During the in-hospital stay, 78 (5.0%) patients had an adverse outcome and 61 (3.9%) patients died; PE was the cause of death in 30 (1.9%) patients.

3.2. Prognostic performance of different heart rate thresholds

Overall, 688 (43.9%) patients had a heart rate ≥100 bpm and 432 (27.6%) patients a heart rate ≥110 bpm. Patients with tachycardia (heart rate ≥100 bpm) presented more often with signs indicating severe PE such as hypoxia, elevated troponin levels and RV dysfunction on imaging, received more often systemic thrombolysis and reached more often the primary and secondary outcome compared to patients with a heart rate <100 bpm (Table 1, **right column**). Similar findings were obtained if tachycardia was defined by a heart rate ≥110 bpm

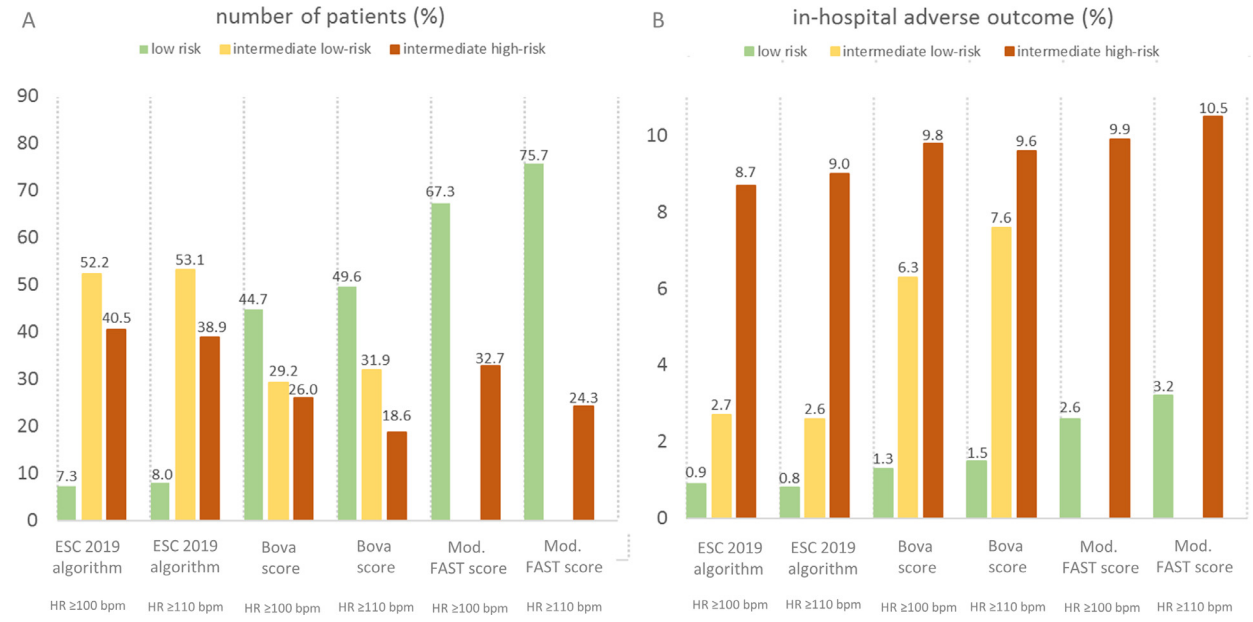

Fig. 1. Performance of algorithms and score calculated by the use of different heart rate thresholds for risk assessment of acute PE.
Classification in risk classes (A) and rate of an in-hospital adverse outcome (B)
Abbreviations: sPESI, simplified Pulmonary Embolism Severity Index, ESC, European Society of Cardiology; Mod., modified; FAST, H-FABP, syncope, tachycardia; H-FABP, heart-type fatty acid-binding protein.

(**Table S1, right column**). As shown in Table 2a, a heart rate ≥100 bpm was associated with a prognostic sensitivity of 67%, a specificity of 57%, a PPV of 8% and a NPV of 97% for reaching the primary outcome. The rate of an adverse outcome increased with increasing heart rate (Table 2a). Using univariate logistic regression analysis, patients with a heart rate ≥100 bpm and ≥110 bpm had the highest risk of an adverse outcome compared to patients stratified according other heart rate thresholds (Table 2a).

3.3. Comparison of algorithms and scores calculated by the use of different heart rate thresholds

Using a heart rate threshold of ≥100 bpm, scores and algorithm classified a smaller number of patients in the low-risk classes compared to scores and algorithm calculated by the use of a heart rate threshold of ≥110 bpm (Fig. 1**a**). The rate of an in-hospital adverse outcome was similar in scores and algorithm calculated based on a heart rate threshold of ≥100 bpm compared to ≥110 bpm (Fig. 1**b**). ROC analyses revealed a similar AUC with regard to an adverse outcome for scores and algorithm calculated using a heart rate of ≥100 bpm and of ≥110 bpm (Table 2b and Fig. 2). Patients stratified to the intermediate-high risk classes by scores calculated with a heart rate ≥100 bpm had a slightly higher risk for an adverse outcome compared to scores calculated with a heart rate ≥110 bpm, except of the ESC 2019 algorithm (Table 2b). Patients classified in low-risk classes by the modified FAST and the Bova score showed a lower rate of in-hospital adverse outcomes if using a heart rate threshold of ≥100 bpm for calculation compared to ≥110 bpm (Fig. 1**b**).

4. Discussion

We performed a post-hoc analysis of a pooled Italian multicentre and German single-centre registry to investigate the prognostic value of different tachycardia thresholds and to compare their impact on the prognostic performance of different established scores and algorithm used for risk stratification in 1576 in normotensive patients with PE. The main study finding can be summarized as follows: defining tachycardia by a heart rate ≥100 bpm demonstrated good prognostic performance for accurate risk assessment of PE-related complications across all scores and algorithm.

In patients with acute PE who appear haemodynamically stable at diagnosis, single parameters have not been shown to predict risk of an in-hospital adverse outcome that could be considered high enough to justify reperfusion treatment. Thus, during the past years, multiple algorithm and scores have been developed to optimize risk stratification of the large patient subgroup with normal blood pressure and heterogeneous short-term prognosis. The majority of studies focused on the prognostic importance of different definitions of RV dysfunction on imaging testing [19,20] and prognostic relevant cut-off values of laboratory cardiac biomarkers [18,21-24]. Interestingly, most risk assessment models (such as the [s]PESI, Bova and modified FAST score) developed aiming to identify PE patients with a higher risk of short-term complications include tachycardia as a prognostic relevant variable [6,7,11,25]. However, thresholds for defining tachycardia are heterogenous in those risk assessment models. While the (s)PESI and Bova score use a heart rate threshold of 110 bpm, the modified FAST score uses the “textbook definition” of tachycardia defined by a heart rate ≥100 bpm. Large studies investigating the optimal heart rate thresholds for risk assessment in patients with acute PE are lacking. While Aujesky et al. demonstrated in a derivation and validation study with 15531 PE patients that a heart rate of ≥110 bpm is an important prognostic predictor with an 1.8-fold increased risk for 30-day all-cause mortality [16], smaller cohort studies identified a heart rate of ≥100 bpm to predict PE-related complications associated with a 4.5 to 8.3-fold risk for an in-hospital adverse outcome [7,11,26,27]. In the present study, patients with a heart rate ≥100 bpm and ≥110 bpm had a 2.7 and 2.4-fold increased risk for an in-hospital adverse outcome, respectively.

As recommended by the current ESC 2019 guidelines, the use of clinical prediction rules integrating PE severity and comorbidity, preferably the (s)PESI, should be considered for risk assessment in the acute phase in normotensive PE patients [12,28]. Further, in patients without haemodynamic instability, the use of validated scores combining clinical, imaging and laboratory PE-related prognostic factors (such as the Bova or modified FAST score) may be considered to further stratify the severity of the acute PE episode. The Bova score was

Table 2b
Prognostic performance of different risk assessment models with regard to an in-hospital adverse outcome.

	Elevated heart rate (n; %)	In-hospital adverse outcome (n;%)	Sensitivity (%; 95% CI)	Specificity (%; 95% CI)	PPV (%; 95% CI)	NPV (%; 95% CI)	OR (95% CI) p-value	AUC (95% CI) p-value
Mod. FAST score (heart rate ≥110 bpm)	381 (24.3%)	40 (10.5%)	0.51 (0.40–0.62)	0.77 (0.75–0.79)	0.10 (0.08–0.14)	0.97 (0.96–0.98)	**3.5 (2.2–5.6) $p<0.001$**	**0.69 (0.64–0.75) $p<0.001$**
Mod. FAST score (heart rate ≥100 bpm)	513 (32.7%)	51 (9.9%)	0.65 (0.54–0.75)	0.69 (0.67–0.71)	0.10 (0.08–0.13)	0.97 (0.96–0.98)	**4.2 (2.6–6.8) $p<0.001$**	**0.70 (0.64–0.76) $p<0.001$**
Bova score (heart rate ≥110 bpm)	291 (18.6%)	28 (9.6%)	0.36 (0.26–0.47)	0.82 (0.80–0.84)	0.10 (0.07–0.14)	0.97 (0.95–0.97)	**2.6 (1.6–4.3) $p<0.001$**	**0.70 (0.65–0.75) $p<0.001$**
Bova score (heart rate ≥100 bpm)	408 (26.0%)	40 (9.8%)	0.51 (0.40–0.62)	0.75 (0.73–0.77)	0.10 (0.07–0.13)	0.97 (0.96–0.98)	**3.2 (2.0–5.1) $p<0.001$**	**0.71 (0.66–0.76) $p<0.001$**
ESC 2019 incl. sPESI (heart rate ≥110 bpm)	609 (38.9%)	55 (9.0%)	0.71 (0.59–0.79)	0.63 (0.60–0.65)	0.09 (0.07–0.12)	0.98 (0.96–0.98)	**4.0 (2.5–6.6) $p<0.001$**	**0.68 (0.62–0.73) $p<0.001$**
ESC 2019 incl. sPESI (heart rate ≥100 bpm)	635 (50.5%)	55 (8.7%)	0.71 (0.59–0.79)	0.61 (0.59–0.63)	0.09 (0.07–0.11)	0.98 (0.96–0.98)	**3.7 (2.3–6.2) $p<0.001$**	**0.67 (0.61–0.72) $p<0.001$**

The three-level ESC 2019 algorithm and Bova score were dichotomized.
Bold values indicate statistical significance ($p<0.05$).
Abbreviations: ESC, European Society of Cardiology; FAST, H-FABP, syncope, tachycardia; H-FABP, heart-type fatty acid-binding protein; OR, odds ratio; AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.
The threshold reference is different in each subgroup and relates in each case to all patients which not fulfil the mentioned cut-off.

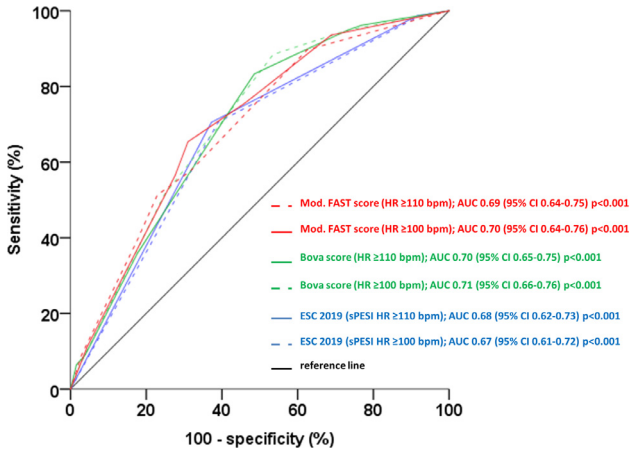

Fig. 2. Receiver operating characteristic analysis of scores and algorithm calculated by the use of different heart rate thresholds regarding an in-hospital adverse outcome.
Original score or algorithm = solid lines
Modified (use of alternative heart rate threshold) score or algorithm = dashed lines
Abbreviations: sPESI, simplified Pulmonary Embolism Severity Index, ESC, European Society of Cardiology; Mod., modified; FAST, H-FABP, syncope, tachycardia; H-FABP, heart-type fatty acid-binding protein; HR, heart rate; AUC, area under the curve, CI, confidence interval.

recently validated in a prospective study: Patients classified in stage III (>4 points, intermediate-high-risk) had a 6.5-fold increased risk for an adverse outcome (95% CI 3.1–13.5; $p<0.001$) as compared to patients stratified to stages I or II [29]. In the present study, patients classified to stage III by the Bova score had a 2.6-fold increased risk for an in-hospital adverse outcome. Importantly, similar results were obtained if tachycardia was defined as heart rate ≥100 bpm for calculation of the Bova score. The modified FAST score indicated a nearly 16-fold and 2.8-fold increased risk for PE-related complications if at least two parameters were positive (intermediate-high risk) in the derivation and validation study, respectively [7,9]. Regardless of the heart rate threshold, in the present study, the modified FAST score demonstrated a good prognostic performance for the prediction of an in-hospital adverse outcome. Although patients stratified to the low-risk class by the modified FAST and the Bova score had a slightly lower rate of complications if a heart rate threshold of ≥100 bpm compared to a threshold of ≥110 bpm was used, the rate of an adverse outcome remained >1.0%. These findings may be explained by the fact that those scores, which were specifically developed to identify patients at higher risk for PE-related complications (and not to identify low-risk patients), do not consider relevant comorbidities such as cancer or cardiopulmonary diseases. Congruently, in the present study, the ESC 2019 algorithm (that considers comorbidities since included in the [s]PESI) classified a lower number of patients as low-risk compared to the other scores. More importantly, the ESC 2019 algorithm allowed safe identification of low-risk patients with a complication rate <1.0% regardless whether a heart rate threshold of ≥100 bpm or ≥110 bmp was used for calculation of the sPESI.

Strengths of our study include the multicentre prospective design and the large sample size. However, our study has limitations that deserve consideration: First, due to the observational study design, only patients with troponin measurements were included; thus, the number of low-risk patients might have been underestimated. Second, the rate of patients with PE-related death (1.9%) was lower compared to other cohort studies limiting the power of statistical analyses [7,17]. Furthermore, due to missing troponin levels and RV assessment a large number of patients (31.1%) were excluded. However, excluded patients were compared to non-excluded patients (**Figure S2 in the supplementary material**) without revealing relevant differences in baseline

characteristics or outcome.

5. Conclusion

In conclusion, the present study demonstrates that defining tachycardia by a heart rate of ≥100 bpm used for calculation of scores and algorithms allows accurate risk stratification of normotensive patients with acute PE. The use of different heart rate thresholds for calculation of scores and algorithm for risk stratification does not appear necessary. This appears of special clinical importance since the availability of different clinical prediction scores and novel biomarkers allowing the prediction of PE-related complications, has made risk stratification of haemodynamically stable PE patients more complex for treating physicians. A uniform definition of tachycardia (by a heart rate ≥100 bpm) may help simplifying the complexity of current risk assessment strategies of normotensive patients with acute PE.

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Authorship details

L.H. and M.L. (Guarantor statement) had full access to all of the data in the study, take responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. L.H., C.B. M.E., M.H.L., F.C., G.H. S.V.K. and M.L. contributed substantially to the study design, data analysis and interpretation. L.H., C.B. and M.L. drafted the manuscript. L.H., C.B. M.E., M.H.L., F.C., G.H. S.V.K. and M.L. critically revised the manuscript and approved the final version for submission.

Declaration of competing interest

L.H. reports having received lecture honoraria from MSD and Actelion. C.B. reports having received consultancy and lecture honoraria from Bayer, Bristol Myers Squibb and Daiichi Sankyo. M.E. reports no conflicts. M.H.L. having received consultancy Honoria from Siemens Healthineers. F.C. reports no conflict of interest. G.H. reports having received consultancy and lecture honoraria from AstraZeneca, Berlin Chemie, Corvia, Impulse Dynamics, Novartis, Servier and Vifor Pharma; and editor honoraria from Springer International Publishing AG. S.V.K. reports having received consultancy and lecture honoraria from Bayer, Boehringer Ingelheim, Daiichi-Sankyo, MSD and Pfizer – Bristol-Myers Squibb; and institutional grants from Actelion, Bayer, Boehringer Ingelheim, Daiichi-Sankyo and Pfizer – Bristol-Myers Squibb. M.L. reports having received consultancy and lecture honoraria from Actelion, Bayer, BRAHMS – Thermo Fisher scientific, Daiichi-Sankyo, MSD, Pfizer – Bristol-Myers Squibb and research funding from BRAHMS – Thermo Fisher scientific.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2020.08.009.

References

[1] Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, et al. Venous thromboembolism (VTE) in Europe - The number of VTE events and associated morbidity and mortality. Thromb. Haemost. 2007;98:756–64.
[2] Jimenez D, de Miguel-Diez J, Guijarro R, Trujillo-Santos J, Otero R, Barba R, et al. Trends in the Management and Outcomes of Acute Pulmonary Embolism: analysis From the RIETE Registry. J Am Coll Cardiol 2016;67:162–70. https://doi.org/10.1016/j.jacc.2015.10.060.
[3] Konstantinides SV, Barco S, Lankeit M, Meyer G. Management of Pulmonary Embolism: an Update. J Am Coll Cardiol 2016;67:976–90. https://doi.org/10.1016/j.jacc.2015.11.061.
[4] McIntyre KM, Sasahara AA. The hemodynamic response to pulmonary embolism in patients without prior cardiopulmonary disease. Am J Cardiol 1971;28:288–94.
[5] Lankhaar JW, Westerhof N, Faes TJ, Marques KM, Marcus JT, Postmus PE, Vonk-Noordegraaf A. Quantification of right ventricular afterload in patients with and without pulmonary hypertension. Am J Physiol Heart Circ Physiol 2006;291:H1731–7. https://doi.org/10.1152/ajpheart.00336.2006.
[6] Fernandez C, Bova C, Sanchez O, Prandoni P, Lankeit M, Konstantinides S, et al. Validation of a model for identification of patients at intermediate to high risk for complications associated with acute symptomatic pulmonary embolism. Chest 2015. https://doi.org/10.1378/chest.14-2551. 2107859 [pii][doi].
[7] Hobohm L, Hellenkamp K, Hasenfuss G, Munzel T, Konstantinides S, Lankeit M. Comparison of risk assessment strategies for not-high-risk pulmonary embolism. Eur Respir J 2016;47:1170–8. https://doi.org/10.1183/13993003.01605-2015.
[8] Jimenez D, Aujesky D, Moores L, Gomez V, Lobo JL, Uresandi F, et al. Simplification of the Pulmonary Embolism Severity Index for Prognostication in Patients With Acute Symptomatic Pulmonary Embolism. Arch. Intern. Med. 2010;170:1383–9.
[9] Hobohm LBC, Konstantinides SV, Casazza F, Lankeit M. Validation of a fast prognostic score for risk stratification of normotensive patients with acute pulmonary embolism. Clin Res Cardiol 2020. press.
[10] Donze J, Le Gal G, Fine MJ, Roy PM, Sanchez O, Verschuren F, et al. Prospective validation of the Pulmonary Embolism Severity Index A clinical prognostic model for pulmonary embolism. Thromb. Haemost. 2008;100:943–8.
[11] Lankeit M, Friesen D, Schafer K, Hasenfuss G, Konstantinides S, Dellas C. A simple score for rapid risk assessment of non-high-risk pulmonary embolism. Clinical Research in Cardiology 2013;102:73–80.
[12] Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, Huisman MV, Humbert M, Jennings CS, Jimenez D, Kucher N, Lang IM, Lankeit M, Lorusso R, Mazzolai L, Meneveau N, Ni Ainle F, Prandoni P, Pruszczyk P, Righini M, Torbicki A, Van Belle E, Zamorano JL. Group ESCSD. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2019. https://doi.org/10.1093/eurheartj/ehz405.
[13] Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest 2016;149:315–52. https://doi.org/10.1016/j.chest.2015.11.026.
[14] Casazza F, Becattini C, Bongarzoni A, Cuccia C, Roncon L, Favretto G, Zonzin P, Pignataro L, Agnelli G. Clinical features and short term outcomes of patients with acute pulmonary embolism. The Italian Pulmonary Embolism Registry (IPER). Thromb Res 2012;130:847–52. https://doi.org/10.1016/j.thromres.2012.08.292.
[15] Ebner M, Kresoja KP, Keller K, Hobohm L, Rogge NIJ, Hasenfuss G, Pieske B, Konstantinides SV, Lankeit M. Temporal trends in management and outcome of pulmonary embolism: a single-centre experience. Clin Res Cardiol 2019. https://doi.org/10.1007/s00392-019-01489-9.
[16] Aujesky D, Roy PM, Le Manach CP, Verschuren F, Meyer G, Obrosky DS, et al. Validation of a model to predict adverse outcomes in patients with pulmonary embolism. Eur. Heart J. 2006;27:476–81.
[17] Bova C, Sanchez O, Prandoni P, Lankeit M, Konstantinides S, Vanni S, Jimenez D. Identification of intermediate-risk patients with acute symptomatic pulmonary embolism. European Respiratory Journal 2014;44:694–703.
[18] Lankeit M, Jimenez D, Kostrubiec M, Dellas C, Hasenfuss G, Pruszczyk P, 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;124:2716–300.
[19] Coutance G, Cauderlier E, Ehtisham J, Hamon M, Hamon M. The prognostic value of markers of right ventricular dysfunction in pulmonary embolism: a meta-analysis. Crit Care 2011;15:R103. https://doi.org/10.1186/cc10119.
[20] Becattini C, Agnelli G, Vedovati MC, Pruszczyk P, Casazza F, Grifoni S, Salvi A, Bianchi M, Douma R, Konstantinides S, Lankeit M, Duranti M. Multidetector computed tomography for acute pulmonary embolism: diagnosis and risk stratification in a single test. Eur Heart J 2011;32:1657–63. https://doi.org/10.1093/eurheartj/

ehr108.
[21] Klok FA, Mos IC, Huisman MV. Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism: a systematic review and meta-analysis. Am J Respir Crit Care Med 2008;178:425–30. https://doi.org/10.1164/rccm.200803-459OC.
[22] Lankeit M, Jimenez D, Kostrubiec M, Dellas C, Kuhnert K, Hasenfuss G, Pruszczyk P, Konstantinides S. Validation of N-terminal pro-brain natriuretic peptide cut-off values for risk stratification of pulmonary embolism. Eur Respir J 2014;43:1669–77. https://doi.org/10.1183/09031936.00211613.
[23] Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. Circulation 2007;116:427–33. https://doi.org/10.1161/CIRCULATIONAHA.106.680421.
[24] Dellas C, Puls M, Lankeit M, Schafer K, Cuny M, Berner M, Hasenfuss G, Konstantinides S. Elevated heart-type fatty acid-binding protein levels on admission predict an adverse outcome in normotensive patients with acute pulmonary embolism. J Am Coll Cardiol 2010;55:2150–7. https://doi.org/10.1016/j.jacc.2009.10.078.
[25] Aujesky D, Roy PM, Verschuren F, Righini M, Osterwalder J, Egloff M, Renaud B, Verhamme P, Stone RA, Legall C, Sanchez O, Pugh NA, N'Gako A, Cornuz J, Hugli O, Beer HJ, Perrier A, Fine MJ, Yealy DM. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. Lancet 2011;378:41–8. https://doi.org/10.1016/S0140-6736(11)60824-6.
[26] Dellas C, Tschepe M, Seeber V, Zwiener I, Kuhnert K, Schafer K, 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.
[27] Smith SB, Geske JB, Maguire JM, Zane NA, Carter RE, Morgenthaler TI. Early anticoagulation is associated with reduced mortality for acute pulmonary embolism. Chest 2010;137:1382–90. https://doi.org/10.1378/chest.09-0959.
[28] Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, Gibbs JS, Huisman MV, Humbert M, Kucher N, Lang I, Lankeit M, Lekakis J, Maack C, Mayer E, Meneveau N, Perrier A, Pruszczyk P, Rasmussen LH, Schindler TH, Svitil P, Vonk Noordegraaf A, Zamorano JL, Zompatori M. Task Force for the D, Management of Acute Pulmonary Embolism of the European Society of C. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014;35:3033–69. https://doi.org/10.1093/eurheartj/ehu283. 69a-69k.
[29] Bova C, Vanni S, Prandoni P, Morello F, Dentali F, Bernardi E, Mumoli N, Bucherini E, Barbar S, Picariello C, Enea I, Pesavento R, Bottino F, Jimenez D. Bova Score Validation Study I. A prospective validation of the Bova score in normotensive patients with acute pulmonary embolism. Thromb Res 2018;165:107–11. https://doi.org/10.1016/j.thromres.2018.04.002.