Abstract

Background: Pulmonary embolism (PE) patients with right ventricular (RV) involvement are a heterogenous group who mandate further risk stratification. Our objective was to evaluate the efficacy of the PE severity index (PESI) for predicting adverse clinical outcomes among PE patients with RV involvement.

Methods and Results: Consecutive normotensive PE patients with RV involvement were allocated according to admission PESI score (PESI <4 vs. PESI ≥4). The primary outcome included hemodynamic instability and in-hospital mortality. Secondary outcomes included each component of the primary outcome as well as mechanical ventilation, thrombolytic therapy, acute kidney injury, and major bleeding. Multivariable logistic regression model was performed to assess the independent association between the PESI score and primary outcome. C-Statistic was used to compare the PESI with the BOVA score. A total of 253 patients were evaluated: 95 (38%) with a PESI of ≥4. Of them, 82 (32%) patients were classified as intermediate-low risk and 171 (68%) as intermediate-high risk. Fifty (20%) patients had at least 1 adverse event. Multivariate analysis demonstrated the PESI to be an independent predictor for the primary outcome (HR 4.81, CI 95%, 1.15-20.09, P=0.031), which was increased with a concomitant increase of the PESI score (PESI 1:4.2%, PESI 2: 3.4%, PESI 3:12%, PESI 4: 16.3%, PESI 5:23.1%, P for trend <0.001). C-Statistic analysis for the PESI score yielded an AUC-0.746 (0.637-0.854), P=0.001, compared to the BOVA score: AUC-0.679 (0.584-0.775), P=0.011.

Conclusion: PESI score was found to predict adverse outcomes among normotensive PE patients with RV involvement**.**

Key words: Pulmonary embolism, PESI score, Risk Stratification, RV dysfunction

Background

The European Society of Cardiology (ESC) guidelines [1] divide pulmonary embolism (PE) patients into risk stratification groups based on their 30-day mortality risk. In addition to laboratory and imaging signs of right ventricular (RV) dysfunction, important consideration has been given to patients' co-morbidities and clinical presentation.

The pulmonary emboli severity index (PESI) score, first described by Aujeski et al [2], consists of 11 variables which can be easily obtained upon patients' admission. The score has been well validated to predict both short (30- and 90-day) [3] and long-term mortality (up to 12 months) in non-selective PE patients [4].

While the PESI score exhibits the practical function of identifying patients with low risk who can be managed ambulatory without hospital admission [5], some have questioned its ability to identify those patients prone to clinical deterioration, and as such it is recommended only for initial risk stratification [6].

Intermediate-risk PE patients pose a therapeutic dilemma. On the one hand, these patients are at increased risk of recurrent venous thromboembolism, hemodynamic compromise and death [1], while on the other hand, routine thrombolysis is contraindicated because of bleeding risk, and in particular intracranial hemorrhage. Therefore, there is a growing need to identity that particular subgroup of patients prone to clinical deterioration who might benefit from early more aggressive treatment.

Our objective was to investigate the efficacy of the PESI score to further predict adverse clinical outcomes among intermediate-risk PE patients admitted to an intensive care cardiac unit (ICCU) with evidence of right ventricular (RV)

involvement, either on imaging (echocardiography and/or computed tomography), and/or positive troponin, regardless of their PESI score.

Methods

We analyzed consecutive patients admitted to the ICCU of the Sheba Medical Center with a diagnosis of intermediate risk PE [7]. Data were collected for prior medical history, presenting signs and symptoms, in-hospital findings, in-hospital treatment and course, including clinical deterioration, and mortality, both in-hospital and at 30 days. Patients were included in the current study if they were over the age of 18, found to have PE, were hemodynamically stable upon presentation, and demonstrating at least one of the following: 1. Evidence of RV enlargement or strain upon computed tomography angiography (CTA) and/or evidence of RV dysfunction upon echocardiography. 2. Evidence of elevated cardiac troponin suggesting RV myocardial damage.

We calculated the PESI score of intermediate-risk PE patients admitted to the ICCU who were stratified to low-risk PESI (<4) and high risk-PESI$_{\geq}$ (≥4). As previously stated [7], all patients hospitalized in our ICCU are subject to rigorous monitoring including continuous invasive blood pressure monitoring and daily echocardiographic evaluation of RV morphology and function.

The primary outcome included hemodynamic instability defined as any one of the following: either a drop in systolic blood pressure to <90 mmHg for at least 15 minutes with signs of end organ hypo-perfusion or the need for vasopressor support to maintain adequate organ perfusion, or blood pressure of >90 mmHg as well as the need for cardiopulmonary resuscitation and in-hospital mortality. Secondary outcomes were adverse events which included: each component of the primary

outcome, as well as mechanical ventilation, thrombolytic therapy (either pharmacological or surgical embolectomy), acute kidney injury (defined as an absolute increase in serum creatinine >0.3mg/dl), a relative increase in serum creatinine >50%, or a reduction of urine output defined as <0.5mk/kg/hour for more than 6 hours, as well as major bleeding during admission (defined as a decrease in hemoglobin by at least 2 g/l, or life-threatening bleeding). Comparisons were made between patients presenting with low versus high PESI scores.

informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee

Statistical Analysis

Continuous variables were expressed as means ± standard deviation (SD) and categorical variables as percentages. Continuous parameters of the study groups were compared using the Student's T test. For comparison of exact data, we used Fischer's exact test and Mantel-Haenszel test. Univariable logistic regression models were used to identify the relationship between individual risk factors that were not included in the PESI score and predefined composite outcome. Clinically significant variables that were found to be independently associated with the composite outcome in the univariable model were incorporated into the multivariable logistic regression model. We constructed an additional multivariable model that included the BOVA score [8] and parameters that were independently associated with composite outcome in the first multivariable model. All analyses were performed with SPSS Software (version 20). An association was considered statistically significant for a two-sided p-value of < 0.05.

Results

Patients' baseline characteristics are shown in Table 1. A total of 253 intermediate-risk PE patients were evaluated, of whom 95 (38%) presented with a PESI score ≥4, and 193 (77%) with elevated troponin levels. The mean age was 65±16 years, with a female predominance of 138 patients (54.5%). A total of 154 patients (61%) had PE involving the main pulmonary artery upon CTA. Echocardiographic RV dysfunction was found in 171 patients (68%), while 149 (61%) had RV dilatation upon CTA. Overall, according to current ESC guidelines [1], 82 patients (32%) were defined as intermediate-low and 171 (68%) as intermediate-high risk. A total of 50 patients (20%) had at least 1 adverse event during hospitalization (Table 2).

Patients with a higher PESI score (≥4) were older (age 73±12vs. 60±17 years, P<0.001), had a higher prevalence of active malignancy (35% vs. 8%, P<0.001), lower creatinine clearance (68.1±33.1 vs. 88.7±32, P<0.001), and lower body mass index (27.7±5.62 vs. 30.7±9.53, P=0.002). At presentation, those with a higher PESI score (≥4) had a higher prevalence of syncope (32% vs 13%, P<0.001), were more tachycardic (103±21vs.95±19, p-0.002) and had lower systolic blood pressure (117±30 vs. 132±18, P<0.001).

Laboratory and ECG Findings (Table 1- Supplementary)

Patients in the higher PESI score group (≥4) had a higher prevalence of new onset atrial fibrillation (9% vs 2%, P=0.022), sinus tachycardia (65% vs 50%, P=0.032), as well as higher troponin levels (1.2±2.00µg/l vs.0.70±1.54µg/l, P=0.041).

Imaging and Echocardiography Findings (Table 1- Supplementary)

CTA demonstrated no significant differences in RV dilation, deviation of the interventricular septum, main pulmonary artery thrombus, or inferior vena cava reflux between the higher and lower PESI groups.

Echocardiography revealed a higher degree of tricuspid regurgitation (TR) among the higher-risk PESI score group (≥4). No difference was found in the severity of RV dysfunction and dilation or in the presence of elevated systolic pulmonary artery pressure (SPAP) >35mmhg.

Clinical Outcomes

Univariable analysis (Table 3) showed that the higher PESI score group had a significantly higher prevalence of the combined primary outcome (consisting of hemodynamic instability and in-hospital mortality) (HR 9.6, C.I 2.7-34.2, $p<0.001$). Furthermore, the combined outcome was significantly greater with a concomitant increase of the PESI score (PESI 1: 4.2%, PESI 2: 3.4%, PESI 3:12%, PESI 4: 16.3%, PESI 5:23.1%, P for trend <0.001) (Figure 1). Additionally, for the higher PESI group, there was a higher prevalence of hemodynamic instability (15% vs 2%, $p<0.001$), need for inotropic support (11% vs 1%, $p<0.001$), mechanical ventilation (11% vs 1%, $p<0.001$), and in-hospital mortality (6% vs 0, $p=0.03$). No differences were observed in the need for thrombolysis or thrombectomy between the two PESI groups (Table 2, Figure 1- Supplementary).

Additional predictors of adverse clinical outcomes upon univariable analysis were syncope at presentation, elevated troponin levels, higher lactate upon admission, increased TR severity, main pulmonary artery thrombus, and a higher BOVA score (Table 3).

After performing multivariate analysis, a higher PESI score (≥4) was still found to be the most significant predictor associated with an adverse primary outcome (HR 4.81, CI 95%, 1.15-20.09, p-0.031) (Table 4a). Higher troponin levels, syncope at presentation, and increased TR severity were also independently associated with the primary outcome.

After adjustment to the BOVA score (Table 4b), a higher PESI score (HR 4.9, CI 95%, 1.2-19.9, p=0.025) and a TR grade >2 (HR 6.4, CI 95%, 1.65-25.2, p=0.007) showed an increased risk for adverse outcomes.

Performing C-Statistic for the PESI score yielded an AUC-0.746 (0.637-0.854), P=0.001 compared to the BOVA score of AUC-0.679 (0.584-0.775), P=0.011 (Figure 2).

Discussion

In the current study we demonstrated that a higher PESI score (defined as PESI ≥4) was associated with a higher prevalence of adverse clinical outcomes among PE patients. These findings were also found to be consistent by multivariable analysis after correcting to the well-validated BOVA scoring system.

Intermediate-risk patients account for about 60% of PE patients. As stated by Becattini et al [9-10], this group of patients can be highly heterogenous in regard to both their clinical features and PE severity. Current guidelines [1] have attempted to stratify PE patients based on clinical, imaging, and laboratory parameters upon admission. However, as postulated by Jimenez et al [11], an important finding of the PEITHO study [12] was that current guideline recommendations incorporating signs of RV dysfunction and myocardial injury might be insufficient for identifying normotensive patients prone to clinical deterioration. Hence, it is essential to have a

reliable clinical score that can identify those patients who might benefit from early rigorous monitoring combined with possible escalation of therapy.

Several risk scores have been proposed to identity high-risk features among normotensive PE patients. The PROTECT multimarker [11] model described the high predictive ability of brain natriuretic peptide (BNP) levels, the simplified PESI score, troponin, and lower extremity ultrasound to further stratify normotensive PE patients prone to adverse outcomes. The BOVA score [8] (systolic blood pressure 90-100 mmHg, elevated troponin level, RV dysfunction upon echo or CT, and heart rate >110 mmHg) has been prospectively validated to predict PE-related complications.

Finally, in order to define those patients who will not deteriorate despite the presence of RV involvement, a previous study by our group [7] proposed a clinical score consisting of 4 predictors of adverse outcomes among intermediate-risk PE patients: syncope, severe RV dysfunction on echocardiography, an RV/LV ratio >1.425 upon CTA, and elevated troponin levels. Patients with a score of ≤1 had a rather benign clinical course. While some of these studies have focused on a non-selective population of normotensive PE patients [8,13,14], others [7,15] focused on patients with imaging and laboratory findings suggestive of RV dysfunction.

In order to overcome the heterogenic characteristics of normotensive PE patients, we focused on a specific subgroup of PE patients with evidence of RV involvement either by the presence of positive cardiac troponin, and/or by the evidence of positive imaging signs suggestive of RV involvement either by echocardiography or CT. In view of the critical clinical dilemma among these patients, improved risk stratification tools are warranted.

The advantages of the PESI score are based on its extensive clinical validation, as well as being easy to use both upon admission and during follow-up. Yet, its efficacy

to identify PE patients prone to clinical deterioration remains unclear [16] with conflicting results in the literature. Chan et al [3] evaluated 302 PE patients and found a direct correlation between the PESI score and 30-day as well as 90-day mortality. Furthermore, a meta-analysis of 21 studies by Zhou et al [17], found the PESI score to have discriminative power to predict short-term all-cause, and PE-related mortality, as well as clinical adverse outcomes (defined as non-fatal recurrent PE/deep vein thrombosis, non-fatal bleeding, and delayed hemodynamic instability). In contrast, out of the 245 non-selective PE patients evaluated by Hariharan et al [18], those with an adverse clinical course (14%) were categorized as low risk, according to the PESI score.

The main finding of our study was the independent correlation between the PESI score and adverse outcomes among PE patients with evidence of RV involvement who were already prone to clinical deterioration. Patients with a higher PESI score were older, had more co-morbidities and were more likely to present with syncope. These findings, however, are not surprising as age and co-morbidities are integral parameters of the PESI score. Furthermore, several publications have stressed the correlation between syncope and adverse outcomes [7,19-20].

There are several clinical implications arising from the current study: first, among normotensive PE patients with laboratory and/or imaging signs of RV involvement (intermediate-risk patients), the PESI score may be used to predict the risk of adverse outcomes. These patients should receive more rigorous monitoring since they are prone to clinical deterioration and may derive benefit from escalation of therapy. Second, the PESI score, a simple clinical tool without the need of advanced laboratory/imaging data, can further aid in stratifying normotensive PE patients with evidence of RV involvement.

Third, the PESI score was found to be reliable and more accurate for predicting hard outcomes of in-hospital mortality and hemodynamic instability compared to the well-validated BOVA score. Further prospective trials to compare the PESI with other clinical risk scores are mandatory.

Finally, since a significant group of our cohort with laboratory and imaging signs of RV dysfunction had a low PESI score (N=145, 61%), we would like to stress the importance of the PESI score to further stratify these patients after hospitalization, and not only as a tool for the initial triage when there is evidence of RV involvement.

The main limitations of our study lie in its retrospective nature and the fact that it is based on a single-center registry, although our institution is a large tertiary center which also serves as a national referral center for PE patients. As a result, our findings might reflect only local applicability and therefore may be only hypothesis-generating.

In conclusion, we found the PESI score to be a predictor of adverse clinical outcomes among normotensive PE patients with evidence of RV involvement. Further research is needed to establish whether this will have an impact on the decision to escalate therapy.

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Table 1: Baseline characteristics of study cohort

	Total N=253	PESI <4 N=158	PESI ≥4 N=95	P value*
Age (years ± SD)	65 ±17	60±17	73±12	<0.001
Male (%)	115 (46)	72 (46)	43 (45)	1.000
Smoking (%)	39 (17)	23 (16)	16 (17)	0.962
Body mass index (Mean±SD)	30 ± 8	31 ± 10	28± 6	0.002
Hypertension (%)	131 (52)	76 (48)	55 (58)	0.168
Hyperlipidemia (%)	102 (40)	62 (40)	40 (42)	0.751
Diabetes (%)	72 (29)	41 (26)	31 (33)	0.334
Coronary artery disease (%)	30 (12)	17 (11)	13 (14)	0.620
Active malignancy (%)	46 (18)	13 (8)	33 (35)	<0.001
Prior oral anti-coagularion (%)	38 (15)	22 (14)	16 (17)	0.655
Prior venous thromboembolism (%)	48 (19)	28 (18)	20 (21)	0.625
Surgery within 1 month (%)	43 (17)	28 (18)	15 (16)	0.852
Diastolic blood pressure (mmHg, Mean±SD)	80 ± 46	84 ±56	72± 18	0.018
Systolic blood pressure (mmHg, Mean±SD)	126 ± 24	132 ± 18	117 ± 30	<0.001
SpO2, room air (%, Mean±SD)	91 ± 8	92 ± 10	89 ± 7	0.018
Pulse (beats/minute, Mean±SD)	98 ±21	95 ± 19	103 ± 21	0.002
Dyspnea (%)	204 (82)	131 (83)	73(79)	0.595
Pleuritic pain (%)	63 (25)	45 (29)	18 (20)	0.171
Syncope (%)	50 (20)	20 (13)	30 (32)	<0.001
Deep vein thrombosis (%)	61 (24)	39 (25)	22 (24)	1.000

Abbreviation: PESI – Pulmonary embolism severity index.

* P value between the high- and low-risk PESI groups

Table 2: Clinical Outcomes

	Total N=253	PESI<4 N=158	PESI≥4 N=95	P value*
Inotropes (%)	11 (4)	1(1)	10 (11)	<0.001
Hemodynamic instability (%)	17 (7)	3 (2)	14 (15)	<0.001
Mechanical ventilation (%)	11 (4)	1 (1)	10 (11)	<0.001
Thrombolysis (%)	24 (10)	17 (11)	7 (7)	0.493
Mechanical thrombectomy (%)	5 (2)	2 (1)	3 (3)	0.367
All bleeding (%)	28 (11)	13 (8)	15 (16)	0.09
Major bleeding (%)	15 (6)	8 (5)	7 (7)	0.633
Acute kidney injury (%)	17 (7)	6 (4)	11 (12)	0.033
In-hospital mortality (%)	6 (2)	0 (0.0)	6 (6)	0.003

Abbreviation: PESI – Pulmonary embolism severity index.

Table 3: Univariable logistic regression model for hemodynamic instability and death

Variable	Hazard ratio	Confidence interval	P value
Creatinine clearance <60 ml/min/1.73m^2	1.03	0.25-4.1	0.966
Body mass index	0.958	0.88-1.04	0.314
Syncope	4.16	1.5-11.4	0.006
Troponin	1.4	1.18-1.67	<0.001
BNP	0.998	0.98-1.007	0.63
New atrial fibrillation	1.37	0.16-11.4	0.77
CRBBB	0.56	0.07-4.42	0.58
IVC backflow	0.974	0.37-2.54	0.95
Main PA Thrombus	5.45	1.2-24.3	0.026
Abnormal right ventricle	3.97	0.89-17.8	0.071
TR grade>2	7.03	2.1-23.2	0.001
LVEF	0.97	0.93-1.02	0.28
Lactate	1.038	1.02-1.06	0.001
PESI ≥4	9.6	2.7-34.2	<0.001
BOVA (continuous)	2.1	1.47-3.12	<0.001

Abbreviations: BNP - Brain natriuretic peptide, CRBBB - Complete right bundle branch block, IVC- Inferior vena cava, PA- Pulmonary artery, TR - Tricuspid regurgitation, LVEF- Left ventricular ejection fraction, PESI – Pulmonary embolism severity index.

Table 4a: Multivariable cox proportional hazard model of hemodynamic instability and death

Variable	Hazard Ratio (95%, CI)	P value
PESI ≥4	4.813 (1.15-20.09)	0.031
TR >2	4.57 (1.053-19.866)	0.043
Syncope	4.43 (1.21-16.080)	0.024
Troponin	1.39 (0.99-1.067)	0.011
Lactate	1.033 (0.99-1.067)	0.055

Table 4b: Multivariable cox proportional hazard model of hemodynamic instability and death adjusted for BOVA

Variable	Hazard Ratio (95%, CI)	P value
TR >2	6.4 (1.65-25.2)	0.007
PESI ≥4	4.93 (1.21-19.9)	0.025
Syncope	2.33 (0.69-7.88)	0.173

Figure legends:

Figure 1: Incidence of combined primary outcome according to the PESI score.

PESI – Pulmonary embolism servity index

Figure 2: ROC curve of hemodynamic instability and death according to PESI ≥4 (left) compared to BOVA score (right).

PESI - Pulmonary embolism servity index

Figure 1- Supplementary: Clinical outcomes among PE patients according to PESI score.

PE = Pulmonary embolism, PESI - Pulmonary embolism servity index