Original, simplified, and modified pulmonary embolism severity indices in risk stratification of pulmonary embolism

Maha Yousif[a], Sabah A. Hussein[b]

Background Acute pulmonary embolism (PE) is a potentially fatal disease. Prognostic assessment is needed for proper management. Several prognostic models have been proposed.

Aim The aim was to validate the original pulmonary embolism severity index (o-PESI) with its simplified version (s-PESI) and modified version (m-PESI) as predictors of in-hospital mortality and homeostatic morbidities (nonlethal repeated venous thromboembolism, and/or nonlethal serious hemorrhage) in patients with PE.

Patients and methods Patients proved to have acute PE admitted to Menoufia and Cairo University Hospitals between March 2017 and March 2019 were included in the study. The o-PESI, s-PESI, and m-PESI were calculated for each patient. In-hospital mortality, homeostatic morbidities, and major adverse events (mortality and homeostatic morbidities) were registered.

Results One hundred and two patients were recruited. In-hospital mortality rate was 13.7%, morbidity rate was 21.6%, whereas major adverse events rate was 31%. The s-PESI classified 31.4% of patients as low risk, and none of them had in-hospital mortality. The frequencies of major adverse events in the low-risk groups were 31.2, 9.1, and 75% for o-PESI, s-PESI, and m-PESI, respectively. Difference between adverse events and non-adverse events groups was significant when s-PESI was applied (P=0.008). The s-PESI had the highest sensitivity and negative predictive value in detecting mortality, morbidity, and major adverse events compared with o-PESI and m-PESI. The area under the curve for s-PESI was significantly above the other two indices (area under the curve=0.78, P=0.04).

Conclusion In addition to its easy application, the s-PESI has a preferably superior prognostic accuracy than o-PESI and m-PESI in prognostication of low-risk patients with acute PE.
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[a]Chest Department, Faculty of Medicine, Menoufia University, Shebin Elkom, [b]Chest Department, Faculty of Medicine, Cairo University, Cairo, Egypt

Correspondence to Maha Yousif, MD, 10 Elhay Elleiby Street, Elbatabon, Shebin Elkom, Menoufia, Egypt. Tel: +20 100 881 8827; fax: +20 482 233 521;
e-mail: drmahayousif@med.menofia.edu.eg

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Introduction

Pulmonary embolism (PE) is a fairly common variant of venous thromboembolism (VTE) with diverse clinical presentations ranging from asymptomatic to life-threatening [1,2]. Approximately 1% of all hospitalized patients and 10% of all in-hospital mortalities are PE related [3]. Adding to this, acute PE is linked to comparatively high (≥13%) short-term mortalities that occur either in hospital or within 30 days [4]. The occurrence of such early PE-related fatality is affected primarily by the clinical scenarios in addition to the underlying diseases [5]. Some studies have demonstrated that PE may indicate increased 1-year mortality rates up to 25% [6–8]. Therefore, PE is considered a potentially fatal disease, although patients who escape a PE-related death are still endangered by hematologic mishaps, especially recurrence of VTE and/or PE, or on the contrary, serious hemorrhage [8].

Risk classification of PE can discriminate low-risk patients, who can be medicated as outpatients, from others at high risk, in whom a profit from intensive care unit admission or even in-hospital thrombolytic therapy is expected [9]. Valid and accurate prognostic models could help clinicians evaluate and classify patients with PE according to their complication risk. Furthermore, establishing prognostic models that work best may improve clinical decisions and research results [10].

Various clinical outcome predictors have been suggested for use in established acute PE despite their practical limitations [11–16]. One of those is named 'original Pulmonary Embolism Severity Index' (o-PESI), intended primarily to assess 30-day fatality. At present, it is one of the top comprehensively justified scores [12]. According to the research studies, this index can point out low mortality-hazard patients sustaining outpatient management [17,18]. Unfortunately, the o-PESI may be practically inappropriate to use in the busy emergency rooms because it is stemmed from 11 variables, for each of which there is a diverse categorical value. So, Jimenez and his research group [19] established the short simplified version of that original score and named it simplified-PESI (s-PESI), whereas Ostovan *et al.* [20]

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used arterial blood gases (ABG) and the ECG available in the emergency health cares, and developed another shortened version named modified-PESI (m-PESI).

This study tried to validate o-PESI, s-PESI, and the m-PESI scores in a cohort of our patients with PE, comparing their accuracy in predicting mortality, nonlethal repeated VTE, and nonlethal serious hemorrhage during hospital admission.

Patients and methods

The study patients were prospectively included from Pulmonology, Emergency, and Intensive Care Departments in Menoufia and Cairo University Hospitals admitted with PE between March 2017 and March 2019. A confirmed PE diagnosis was established by computerized tomographic pulmonary angiography with contrast in accordance with internationally validated criteria [21]. Patients who were hospital admitted later than 24 h after symptom beginning or with a past medical history of PE, in addition to patients suffering from a disease that may shorten their expected life to a 1 month or less as major trauma or high-grade cancer (histopathological types known to have rapid growth and spread hence low survival rates) were excluded. Those on therapeutic anticoagulants for more than 24 h were also excluded. All recruited patients gave an informed consent for research participation, and the Local Ethics Committee gave their study approval before patient recruitment.

The parameters in Table 1 were collected. According to the strategy used in the development of the o-PESI, missing value for any prognostic parameter was supposed to be normal. For o-PESI calculation, a total patient score was obtained by addition of the age of the patient (years) to the points for every parameter (if present). Then each patient was assigned to certain risk class as follows: class I for those with a score less than or equal to 65, class II for a score 66–85, class III for a score 86–105, class IV for a score 106–125, and class V for a score more than 125. Low-risk patients were those in classes I or II [12].

For s-PESI calculation, the collected data are presented in Table 1, where both heart failure and chronic lung disease histories were summarized into one variable named 'chr0nic cardiopulmonary disease.' Each present variable was given 1 point with a score range from 0 to 6. Patients were classified as low-risk if they did not meet any of the score variables, whereas those matching any of the score variables were considered high risk [19].

Table 1 Variables of original, simplified, and modified pulmonary embolism severity indices

Variables	Original PESI	s-PESI	m-PESI
Age (years)	>80	1	1
Male sex	+10	–	–
History of cancer	+30	1	1
History of heart failure	+10	1	1
History of chronic lung disease	+10		
Pulse ≥110 beats/min	+20	1	1
Systolic blood pressure <100 mmHg	+30	1	1
Respiratory rate ≥30 breaths/min	+20	–	–
Temperature <36°C	+20	–	–
Altered mental status	+60	–	–
Arterial oxyhemoglobin saturation level <90%	+20	1	–
$PaO_2/PaCO_2 \leq 1.8$	–	–	1
Electrocardiographic evidence of right ventricular strain	–	–	1

m-PESI, modified pulmonary embolism severity index; s-PESI, simplified pulmonary embolism severity index.

For calculation of m-PESI, the first ECG recorded upon patient presentation was interpreted by the attendant cardiologist who was unaware of the study nature or outcomes. The ECG was evaluated for evidence of right ventricular strain, that is, greater than or equal to 1 mm elevation of ST segment in lead aVR or greater than or equal to 1 mm depression of ST segment in V1–V3 chest leads. The first analyzed ABG was used to calculate the ratio of PaO_2 over $PaCO_2$, where the $PaO_2/PaCO_2$ less than or equal to 1.8 replaced the less than 90% oxygen saturation criterion in the variables of s-PESI, and ECG evidence of RV strain was added as the seventh variable to calculate the m-PESI [20]. One point was given for any present criterion and 0 if it was absent. The resultant range of m-PESI was from 0 to 7. Using the m-PESI, patients with a score less than 2 were considered low risk and those with a score more than or equal to 2 were considered high risk.

The initial research outcome point was to validate the prediction rules for in-hospital overall mortality and homeostatic morbidities (nonlethal repeated VTE and nonlethal serious hemorrhage) after diagnosis of acute PE diagnosis. Death from any cause was used to define overall mortality. Serious hemorrhage was defined as a hemorrhage that was either associated with a drop in hemoglobin more than 2 g%, required a transfusion of at least 2 units of blood, or was intracranial or retroperitoneal [22]. The recruited participants were followed up during their hospital stay to record in-hospital mortality and morbidities. The sum of mortality and homeostatic morbidities was called major adverse events.

Statistical analysis

Data were statistically analyzed using Statistical Package for the Social Sciences (SPSS) version 22 (SPSS Inc., Chicago, Illinois, USA). The scores' variables were in the form of 'mean±SD' for continuous data and of '*n* (%)' for categorical data. The analysis used χ^2-test to compare groups regarding their categorical data. The accuracy, sensitivity, specificity, in addition to, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC) of the three scores were calculated. *P* value less than 0.05 was regarded significant statistically.

Results

After implementing the inclusion and exclusion rules, a total of 102 participants with a confirmed diagnosis of PE were recruited. Of them, 54.9% were males whereas the mean age in years was 55.4±14. The frequency of cancer, chronic lung diseases, and chronic heart diseases were 9.8, 27.5, and 7.8%, respectively. Overall, 45.1% of the patients had ECG changes on presentation, compatible with right ventricular strain, and 1.96% had disturbed consciousness. The mean pulse was 114.35±13.85, the mean oxygen saturation was 87.37±5.77, whereas the mean $PaO_2/PaCO_2$ was 1.744±0.34. All patient characteristics used to calculate the studied scores are presented in Table 2.

Table 2 Patient characteristics used to calculate the studied scores

Studied variables	*N*=102 [*n* (%)] or (mean±SD)
Sex	
Male	56 (54.9)
Female	46 (45.1)
Age	55.42±14.01
History of cancer	
Yes	10 (9.8)
No	92 (90.2)
Chronic lung diseases	
Yes	28 (27.5)
No	74 (72.5)
Chronic heart diseases	
Yes	8 (7.8)
No	94 (92.2)
ECG changes (right ventricular strain)	
Yes	46 (45.1)
No	96 (54.9)
Disturbed conscious level	
Yes	2 (1.96)
No	100 (98.04)
Pulse	114.35±13.85
Systolic blood pressure	107.84±10.06
Temperature	37.03±0.08
Respiratory rate	31.73±3.32
O_2 saturation	87.37±5.77
$PaO_2/PaCO_2$	1.744±0.34

The o-PESI classified 49% of the patients as low risk and 51% as high risk, whereas according to s-PESI, 31.4% of the patients were at low risk and 68.6% were at high risk. The m-PESI showed that 29.4% of the patients were at low risk and 70.6% were at high risk. Mortality rate among the studied patients during hospitalization was 14 (13.7%) of 102 patients. Differences in the classification of participants into low and high risk groups according to o-PESI and s-PESI were significant (*P*=0.048 and 0.045, respectively). The s-PESI classified 31.4% of the patients as low risk and none of them had in-hospital mortality. However, o-PESI and m-PESI recorded a mortality rate of 14.3% among their low-risk patient groups (Table 3).

Twenty two patients out of 102 (21.6%) had at least one homeostatic morbidity (nonlethal repeated VTE and/or nonlethal serious hemorrhage). Morbidity frequencies in the low-risk groups were 36.4, 9.1, and 27.3% for o-PESI, s-PESI, and m-PESI, respectively. Differences in the frequencies of morbidity according to risk stratification of the studied scores were statistically nonsignificant (Table 4).

After merging frequencies of mortality and morbidity (frequency of major adverse events), 4 patients had both morbidity and mortality, 10 patients had mortality only, and 18 patients had at least one homeostatic morbidity without mortality. The frequencies of major adverse events in the low risk groups were 31.2, 9.1, and 75% for o-PESI, s-PESI, and m-PESI, respectively. Differences between adverse events group and non-adverse events groups when s-PESI was applied were significant (*P*=0.008), whereas these differences were statistically nonsignificant when o-PESI and m-PESI were applied (*P*=0.078 and 0.453, respectively) (Tables 5 and 6).

The sensitivity of s-PESI in predicting mortality was 63.6%, whereas it was 45.5% for o-PESI and 31.8% for m-PESI. Regarding morbidity, the highest sensitivity was for s-PESI (90.9%), compared with 63.6% for o-PESI and 72.7% for m-PESI. When all major adverse events were considered, s-PESI had the highest sensitivity (93.8%) and NPV (97.8%) compared with o-PESI and m-PESI. The AUC for s-PESI was significantly higher than the other two indices (AUC=0.78, *P*=0.04).

Discussion

Evaluation of PE prognosis is essential for proper management decisions. Accurate risk classification

Table 3 Frequency of in-hospital death according to risk stratification of the studied scores

	Total patients (*N*=102) [*n* (%)]	In-hospital mortality [14 (13.7)] [*n* (%)]	No death [88 (86.3)] [*n* (%)]	χ^2	*P* value
o-PESI					
Low risk	50 (49)	2 (14.3)	48 (54.5)	3.92	0.048*
High risk	52 (51)	12 (85.7)	40 (45.5)		
s-PESI					
Low risk	32 (31.4)	0 (0)	32 (36.6)	3.71	0.045*
High risk	70 (68.6)	14 (100)	56 (63.6)		
m-PESI					
Low risk	30 (29.4)	2 (14.3)	28 (31.8)	0.89	0.344
High risk	72 (70.6)	12 (85.7)	60 (68.2)		

m-PESI, modified pulmonary embolism severity index; o-PESI, original pulmonary embolism severity index; s-PESI, simplified pulmonary embolism severity index. *$P<0.05$.

Table 4 Frequency of homeostatic morbidity according to risk stratification of the studied scores

	Total patients (*N*=102)	In-hospital morbidity [22 (21.6)] [*n* (%)]	No morbidity [80 (78.4)] [*n* (%)]	χ^2	*P* value
o-PESI					
Low risk	50 (49)	8 (36.4)	42 (52.5)	0.90	0.27
High risk	52 (51)	14 (63.6)	38 (47.5)		
s-PESI					
Low risk	32 (31.4)	2 (9.1)	30 (37.5)	3.23	0.07
High risk	70 (68.6)	20 (90.9)	50 (62.5)		
m-PESI					
Low risk	30 (29.4)	6 (27.3)	24 (30)	0.03	0.59
High risk	72 (70.6)	16 (27.7)	56 (70)		

m-PESI, modified pulmonary embolism severity index; o-PESI, original pulmonary embolism severity index; s-PESI, simplified pulmonary embolism severity index.

Table 5 Frequency of in-hospital major adverse events according to risk stratification of the studied scores

	Total patients (*N*=102) [*n* (%)]	Major adverse events [32 (31)] [*n* (%)]	No major adverse events [70 (69)] [*n* (%)]	χ^2	*P* value
o-PESI					
Low risk	50 (49)	10 (31.2)	40 (57.1)	2.95	0.078
High risk	52 (51)	22 (68.8)	30 (42.9)		
s-PESI					
Low risk	32 (31.4)	2 (9.1)	30 (57.1)	6.83	0.008*
High risk	70 (68.6)	30 (93.8)	40 (42.9)		
m-PESI					
Low risk	30 (29.4)	24 (75)	22 (31.4)	0.22	0.453
High risk	72 (70.6)	8 (25)	48 (68.6)		

m-PESI, modified pulmonary embolism severity index; o-PESI, original pulmonary embolism severity index; s-PESI, simplified pulmonary embolism severity index. *$P<0.05$.

with objectively precise diagnostic tools is of crucial importance. Previous research studies have demonstrated strong proof that the outcome prediction of acute PE can differ according to body hemodynamics and other clinical parameters [11,23,24]. Several prognostic indices are available, of which the o-PESI and its two shortened versions (the s-PESI and m-PESI) are recently suggested as clinical prognostic models that can help clinicians and researchers identify appropriate participants for safe out-of-hospital management or brief admission and those at high risk who may need closer monitoring or more aggressive therapy. The aim of this research was to assess the validity of o-PESI, s-PESI, and m-PESI scores as predictors of in-hospital mortality and hemostatic morbidities in patients with PE.

In this study, the frequencies of in-hospital death, morbidity, and major adverse events among patients sorted by the s-PESI as having a low clinical hazards were inferior to its corresponding values in the low-risk groups according to o-PESI and m-PESI, without mandating any imaging tool or sophisticated laboratory essay. Furthermore, none of the patients in the low-risk mortality group according to s-PESI had in-hospital mortality. So, s-PESI authentically

Table 6 Accuracy of the studied scores in predicting mortality, morbidity, and major adverse events

	o-PESI (%)	s-PESI (%)	m-PESI (%)
In-hospital mortality			
Sensitivity	45.5	63.6	31.8
Specificity	14.3	22.4	85.7
Positive predictive value	76.9	80	93.3
Negative predictive value	14	19.6	16.7
Accuracy	41.2	54.9	39.2
Area under curve	0.76	0.80	0.69
P value	0.09	0.125	0.46
In-hospital morbidity			
Sensitivity	63.6	90.9	72.7
Specificity	52.5	37.5	30
Positive predictive value	26.9	28.6	22.2
Negative predictive value	84	93.8	80
Accuracy	54.9	49	39.2
Area under curve	0.68	0.74	0.64
P value	0.42	0.15	0.89
In-hospital major adverse events			
Sensitivity	68.8	93.8	25
Specificity	57.1	37.5	31.4
Positive predictive value	42.3	37.3	14.3
Negative predictive value	85	97.8	47.8
Accuracy	60.8	53.6	29.4
Area under curve	0.75	0.78	0.67
P value	0.14	0.04*	0.72

m-PESI, modified pulmonary embolism severity index; o-PESI, Original pulmonary embolism severity index; s-PESI, simplified pulmonary embolism severity index. *$P<0.05$.

labeled low-risk patients who essentially needed a mere short hospitalization or even could be handled as outpatients. This result agrees with that of Jiménez *et al.* [19] who compared the accuracy of o-PESI with s-PESI and showed that the low-risk patients according to s-PESI had a lower death rate (1%) compared with the o-PESI low-risk patients (2.5% death rate) (P=0.25). In addition, three patients only (1%) of the s-PESI low-risk group developed hemostatic morbidities during their follow-up.

This study proves that sensitivity and NPV of s-PESI are above those of o-PESI and m-PESI for detecting mortality, morbidity, and major adverse events. This result is in line with those of Jiménez *et al.* [19] who demonstrated that s-PESI was more sensitive (superior sensitivity, and NPV) than the o-PESI for anticipating 30-day death rate. Such finding was reported by Kilic *et al.* [22], so they concluded that the s-PESI seemed to be more satisfactory for labeling patients who are at low hazard of fatal and nonfatal clinical outcome.

This study demonstrated that s-PESI has a NPV of 97.8% for in-hospital major adverse events in low-risk group. Previous studies [10,22,25] demonstrated a NPV of 100% in the same risk group, and they concluded that s-PESI is reliable in the exclusion of such short-lived adverse events. Ostovan *et al.* [20] study compared m-PESI accuracy to s-PESI in anticipating in-hospital outcomes and 1-year outcomes [mortality or major adverse cardiopulmonary events (as sum of 1-year death rate, treatment with thrombolytics or being mechanically ventilated during hospitalization)] in patients admitted with PE. The study demonstrated that s-PESI had a higher sensitivity (100%) and a lower specificity (35%) in predicting in-hospital death compared with m-PESI (68 and 53%, respectively). However, comparable to the s-PESI, m-PESI has a sensitivity, specificity, PPV, and NPV of 74, 56.5, 35.8, and 87%, respectively, for 1-year fatality and a sensitivity, specificity, PPV, and NPV of 73.2, 65.5, 61.2, and 76.7%, respectively, for cumulative (major adverse cardiopulmonary events) outcome. They concluded that m-PESI shows higher validity than s-PESI for each outcome variable [20]. Differences between this study and their study may be attributed to differences in patient characteristics, as their patients generally had low scores in m-PESI signifying incomplete representation of high-risk patients in their work.

Statisticians consider a statistical test with an AUC in the region of 0.75–0.92 to have good accuracy [26]. In this study, the AUC calculated for s-PESI and o-PESI in death rate fall in that range of 0.80–0.76, correspondingly. The same finding is noted in predicting major adverse events (AUC for s-PESI: 0.78 and AUC for o-PESI: 0.75), whereas the AUC for the m-PESI fall out of that range. So both s-PESI and o-PESI have good accuracy in predicting PE prognosis in terms of in-hospital mortality and in-hospital major adverse events, with higher AUC for s-PESI. These results match those of Zhou *et al.* [27] who showed in their meta-analysis that the o-PESI had AUC for all-cause fatality of 0.78. In s-PESI group, the AUC that predicts all-cause fatality and serious adverse events was also comparable to that in o-PESI group, indicating the equivalent accuracy of o-PESI compared with s-PESI. They explained this that o-PESI was extracted from large population samples derived from multiple centers through validated research methods. However, suitability of o-PESI for clinical practice in emergency rooms is doubtful, as it mandates multiparameter calculations using diverse values [22]. To bypass the weaknesses in o-PESI, the s-PESI score was developed [19]. The

simplified version was derived from logistic regression analysis of the eleven o-PESI elements with omission of the nonsignificant ones and the production of the six-element s-PESI. So, each of the six elements included has already justified to be a good PE outcome predictor [19]. However, s-PESI is easier to use [27].

The AUC of m-PESI was the lowest compared with the other two scores regarding mortality, morbidity, and major adverse events. On the contrary, Ostovan *et al.* [20] found that AUC of m-PESI was above the AUC of s-PESI, and they consider this to be an advancement over s-PESI as a predictor of PE outcome, which could be related to different patient characteristics.

Certain issues support the superiority of the s-PESI to other prognostication indices: first, it is generated from precisely outlined, simple objective clinical data that are regularly got upon patient admission; second, the consideration of both clinical PE severity and concomitant disease burden; third, it does not necessitate costly or time-consuming laboratory assays, such as brain natriuretic peptide and cardiac troponin, or echocardiographic procedures, which require time and expertise [22]; and compared with m-PESI, it does not require an invasive maneuver such as ABG but use the simple noninvasive O_2 saturation.

To the best of our knowledge, the present study is the first English literature research work which prospectively assesses validity of the s-PESI, o-PESI, and m-PESI in a row as predictors of in-hospital mortality, and homeostatic morbidities. However, this study has some limitations that might affect results interpretation, that is, a relatively small sample size. As autopsy was unavailable, the definite cause of death could not be determined in some patients and so the overall mortality was the evaluation aspect. The study results were based on follow-up of the patients during their hospital stay only without postdischarge follow-up to determine long-term outcomes. Lastly, there were no data about the in-hospital management of the patients, so the probable influence of therapy on PE end results could not be determined. This research work demonstrated in conclusion that s-PESI was an easily applicable score that proved superior prognostic accuracy to o-PESI and m-PESI in predicting low-hazard patients with acute PE who can safely be considered for out-of-hospital therapy.

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Conflicts of interest
There are no conflicts of interest.

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