

A New Index for the Prediction of In-Hospital Mortality in Patients with Acute Pulmonary Embolism: The Modified Shock Index

ABSTRACT

Background: Pulmonary embolism severity index, its simplified version, and shock index have been used for risk stratification in acute pulmonary embolism. In this study, we proposed a modification in severity index and evaluated the correlates and prognostic value of modification in severity index in this setting.

Methods: The study group comprised retrospectively evaluated 181 patients with acute pulmonary embolism. Systematic workup including pulmonary embolism severity index, its simplified version, shock index, biomarkers, and echocardiographic and multidetector computed tomography assessments was performed in all patients. Moreover, we calculated modification in severity index by multiplying original shock index (heart rate/systolic blood pressure ratio) and a third component, 1/pulse oxymetric saturation (pSat O₂%) ratio. The primary endpoint was defined as all-cause mortality and hemodynamic collapse during the hospital stay.

Results: On the basis of initial risk stratification, ultrasound-assisted thrombolysis, systemic tissue-type plasminogen activator, and unfractionated heparin therapies were utilized in 83 (45.9%), 37 (20.4%), and 61 (33.7%) patients, respectively. The primary endpoint occurred in 13 (7.2%) patients. Receiver-operating curve analysis revealed that modification in severity index had the highest area under the curve of 0.739 (0.588–0.890, $P = .002$) compared with shock index, pulmonary embolism severity index, or its simplified version. The modification in severity index > 0.989 predicted primary endpoint with 73% sensitivity and 54% specificity.

Conclusions: The modification in severity index seems to be a simple, quick, and comprehensive risk assessment tool for bedside evaluation at initial stratification, in monitoring the clinical benefit from therapies, and decision-making for escalation to other reperfusion strategies in patients with acute pulmonary embolism. However, the prognostic value of modification in severity index needs to be validated with further studies.

Keywords: Pulmonary embolism, risk stratification, thrombolytic therapy

INTRODUCTION

Venous thromboembolism (VTE) is the third most common acute cardiovascular syndrome worldwide.^{1,2} In-hospital mortality rate of acute pulmonary embolism (PE) is approximately 7% and may increase up to 30% in patients presenting with unstable hemodynamic status due to obstructive shock and acute-onset, severe right heart failure.^{1–6} Currently available risk stratification models using clinical scores, biomarkers, and imaging aids have been utilized in risk-based treatment strategies in acute PE.^{1–14} Various validated risk assessment models including shock index (SI), pulmonary embolism severity index (PESI), and its simplified version (sPESI) based on clinical parameters have been shown to predict 30-day mortality in patients with acute PE.^{1–13} Approximately one-third of acute PE patients are at low risk (LR) of an early adverse outcome, whereas patients with PESI Class III–V had a 30-day mortality rate of up to 24.5%, and those with an sPESI ≥ 1 up to 11%.^{1–13}

In our single-center study based on retrospective analysis of patients with acute PE, we proposed a modification in SI with the addition of pulse oxymetric saturation (pSat O₂%) into the original index (MSI) and compared our MSI with the

ORIGINAL INVESTIGATION

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original SI, PESI, and sPESI values in terms of clinical, echocardiographic, neurohumoral, and hemodynamic correlates and prognostic value for in-hospital mortality in this setting.

METHODS

This single-center study comprised retrospectively evaluated 181 patients (female 106, aged 61.7 ± 17.6 years) referred to our tertiary cardiovascular center with confirmed diagnosis of acute PE from August 2012 to December 2015. The diagnosis of acute PE and the definition of risk subgroups have been based on the criteria as recommended by the European Society of Cardiology/European Respiratory Society (ESC/ERS) 2014 PE Guidelines¹ and reclassified according to the recommendations by ESC/ERS 2019 PE Guidelines.² Inclusion criteria were acute symptomatic PE confirmed by contrast-enhanced computed tomography (CT) with embolus located in at least one main or proximal lower lobe plasminogen activator (PA).^{1,2,14} Lower extremity venous Doppler ultrasound (US) and echocardiographic data were also available for all patients.

Systematic workup including PESI, sPESI, SI, MSI, biomarkers, and echocardiographic and multidetector CT (MDCT) assessments was performed in all patients. For the calculation of MSI, we multiplied the original SI (heart rate/systolic blood pressure ratio) with $1/\text{pSat O}_2\%$ ratio.

Our proposed formula for MSI was as follows:

$$\text{MSI} = (\text{heart rate/systolic blood pressure}) \times (1/\text{SatO}_2\%).$$

Based on the ESC/ERS 2014 PE Guidelines, the patients were separated into 4 risk groups. While hypotensive patients were in the high-risk (HR) group, normotensive patients were evaluated based on right ventricular (RV) dilatation and elevation in troponin values.

Normotensive patients with RV dilatation and a positive troponin value were classified as intermediate-high-risk (IHR) group, while those meeting one of these conditions were in the intermediate-low-risk (ILR) group. Patients who did not have RV dilatation or troponin elevation were considered LR.

The MSI was calculated for all patients before and after treatment, and its role in determining treatment response and prognosis was investigated.

HIGHLIGHTS

- The modified shock index (MSI) showed significant correlations with previously validated risk tools including shock index (SI), pulmonary embolism severity index (PESI) score and class, and simplified pulmonary embolism severity index (sPESI) score and class.
- The MSI provided the highest area under the curve in predicting the primary endpoint compared with SI, PESI, and sPESI.
- The MSI is a simple and quick tool for assessing the initial risk and can also be used to monitor the benefit of specific therapies.

Echocardiographic Assessment

A short-axis view was used to evaluate the presence of a D-shaped interventricular septum, and an apical four-chamber view was used for the estimation of PA systolic pressure (PASP) from tricuspid regurgitation jet, M-mode measurement of tricuspid annular plane systolic excursion (TAPSE), and tissue velocity of tricuspid annular longitudinal systolic motion (St).¹⁵⁻¹⁷

Contrast-Enhanced Chest Computed Tomography

For baseline assessment, either pre-referral CT images or initial CT evaluation images acquired immediately after arrival at our hospital were utilized. In our hospital, MDCT angiographic images were obtained using a 64-slice helical CT scanner with angiographic contrast material (Omnipaque 350; Toshiba Aquilion 64™, Toshiba Medical Systems Corp. Tokyo, Japan) for evaluation of PA thrombotic obstructive burden; we utilized a score dedicated to CT pulmonary angiography proposed by Qanadli (Qanadli Score).¹⁸ Non-obstructive thrombus located in a lobar or main PA received score points equal to the number of arising segmental PA branches (maximum 10 points per lung). A segmental PA containing non-obstructive thrombus without any thrombus in its proximity received 1 score point, and score points were multiplied by 2 in case of an occlusive clot (ranging from 0-40 points, maximum 20 points per lung).

Treatment

In accordance with current Pulmonary embolism (PE) guidelines and depending on the patient's individual risk status, the treatment of choice was as follows: unfractionated heparin (UFH) or low-molecular-weight heparin for patients at LR or ILR status, standard systemic full-dose tissue-type plasminogen activator (t-PA) infusion for 1-2 hours, or single or repeated low-dose, slow-infusion(s) of t-PA up to 4-6 hours, or percutaneous treatments with ultrasound-assisted thrombolysis (USAT) for patients at HR or rapidly deteriorating IHR status. Absolute and relative thrombolytic contraindications were questioned in all patients receiving systemic thrombolytic therapy and USAT. The procedural details of USAT therapy were given in our previously published studies.¹⁹⁻²²

Study Outcome Measures

The primary endpoint (PEP) of our study was all-cause death and hemodynamic collapse during hospital stay. The optimal cut-off value of MSI was 0.989 for all-cause mortality and hemodynamic collapse.

Safety Measures

The safety endpoints of our study were major bleeding within 7 days (bleeding that causes a decrease of 2 g/dL in hemogram or requiring 2 units or more of erythrocyte suspension replacement or life-threatening bleeding due to its localization in the body), minor bleeding within 7 days (with another bleeding that does not have the characteristics of major bleeding), and ischemic or hemorrhagic stroke within 7 days.

Statistical Analysis

Numerical variables were expressed as mean \pm standard deviation, and categorical variables were expressed as absolute numbers with percentages. Chi-square or Fisher's exact test was used in the between-group analysis for categorical

variables. Spearman or Pearson correlation analysis was used to test the level and significance of the relationship between numerical variables. The receiver-operating characteristic curve analysis was used to determine the best predictive value, sensitivity, and specificity of formula-1 (modified shock index) in estimating PEP. A 2-tailed *P* value <.05 in all analyses was accepted as the limit for statistical significance. Statistical Package for Social Sciences version 20.0 (IBM Corp., Armonk, NY, USA) package program was used for statistical analysis.

RESULTS

Among the 181 patients with acute PE, the HR, IHR, ILR, and LR status were noted in 18 (9.9%), 135 (74.5%), 22 (12.2%), and 6 (3.3%) patients, respectively. The baseline demographic, clinical, and laboratory characteristics of the PE patients included in the study are given in Table 1. Table 2

Table 1. The Baseline Demographic, Clinical, and Laboratory Characteristics and Treatment Patterns of 181 Patients with PE

Variable	Total Patients (181)
Age, years	61.7 ± 17.6
Sex, female, %	106 (58.6)
Heart rate, minute	105.8 ± 22.1
Baseline vital signs	
Systolic blood pressure (mm Hg)	121.9 ± 28.3
Diastolic blood pressure (mm Hg)	74.3 ± 18.6
Arterial oxyhemoglobin saturation (%)	88.4 ± 6.8
Baseline laboratory variables	
Troponin I (ng/mL)	0.34 ± 0.745
D-dimer (U/mL)	9.7 ± 6.3
Baseline echocardiographic parameters	
TAPSE (mm)	1.8 ± 0.5
St (cm/sn)	11.1 ± 3.01
PASP (mm Hg)	53 ± 16
Risk classification (n, %)	
High-risk PE	18 (9.9)
Intermediate-high-risk PE	135 (74.5)
Intermediate-low-risk PE	22 (12.1)
Low-risk PE	6 (3.3)
Risk scores	
PESI	99.87 ± 34.09
PESI class	3.13 ± 1.42
sPESI	1.27 ± 1.04
sPESI class	0.77 ± 0.42
MSI (t-PA, full-dose + low-dose)	1.3 ± 1.2
MSI (USAT)	1.1 ± 0.4
MSI (UFH)	0.9 ± 0.6
MSI (total patients)	1.1 ± 0.4

MSI, modified shock index; PASP, pulmonary artery systolic pressure; PE, pulmonary embolism; PESI, pulmonary embolism severity index; St, tissue velocity of tricuspid annular longitudinal systolic motion; sPESI, simplified pulmonary embolism severity index; TAPSE, Tricuspid annular plane systolic excursion; t-PA, tissue-type plasminogen activator; UFH, unfractionated heparin; USAT, ultrasound-assisted thrombolysis.

Table 2. Treatment Strategies According to Risk Situation

Risk Situation	Treatment Strategies				Study Population
	t-PA (Full-Dose)	t-PA (Low-Dose)	USAT	UFH	n = 181
High-risk (n)	10	-	8	-	18 (9.9%)
Intermediate-high-risk (n)	-	27	75	33	135 (74.5%)
Intermediate-low-risk (n)	-	-	-	22	22 (12.1%)
Low-risk (n)	-	-	-	6	6 (3.3%)

t-PA, tissue-type plasminogen activator; UFH, unfractionated heparin; USAT, ultrasound-assisted thrombolysis.

demonstrates treatment strategies according to the risk situation. Table 3 demonstrates the echocardiographic parameters of PE patients.

Among the 18 (9.9%) patients who were at HR status, 10 patients were treated with systemic infusion of 100 mg t-PA within 2 hours, 5 of these underwent USAT as initial treatment, and 3 patients were treated with USAT after the failure of initial t-PA therapy. In the HR group, 5 patients died and 3 of them had major bleeding. The remaining 13 patients were discharged without any problem.

Patients in the IHR group comprised 135 (74.5%) patients. Ultrasound-assisted thrombolysis, low-dose systemic t-PA, and unfractionated intravenous heparin treatments were given to this group. One patient died as a result of intracranial hemorrhage while under USAT treatment. Reembolism was observed in 1 patient after USAT treatment and he died. Reembolism was observed in 2 heparin-treated patients, who were given 100 mg of t-PA over 2 hours after hemodynamic decompensation was observed. These patients, who had hemodynamic and echocardiographic improvement, were discharged under oral anticoagulant therapy after a few days of heparin therapy. Three patients died as a result of worsening of their own disease other than pulmonary

Table 3. The Echocardiographic Parameters of PE Patients Before and After Treatment

Echocardiographic Parameters	At Hospital Admission	At Discharge	<i>P</i>
PA systolic pressure (PASP) (mm Hg)	54.3 ± 16.6	38.08 ± 12.6	<.001
Tricuspid annular plane systolic excursion (TAPSE) (cm)	1.8 ± 0.5	2.1 ± 0.45	<.001
Tissue velocity of tricuspid annular longitudinal systolic motion (Sm) (cm/sn)	11.1 ± 3.0	13.3 ± 2.6	<.001
Ejection fraction (%)	63.3 ± 6.2	63.3 ± 6.2	.632
Presence of right ventricular dilatation	59% (n = 103)	28% (n = 49)	<.001

PE, Pulmonary embolism.

Table 4. MSI Values in Patients with PEP in Different Risk Groups

Risk Groups	Patients (n = 13)	Primary Endpoint		Modified Shock Index 1.77 (8.5-0.06)	
		Death	Collapse	Death	Collapse
High-risk	5	5	-	3.06 (8.5-1.17)	-
Intermediate-high-risk	7	5	2	0.86 (1.04-0.63)	0.87
Intermediate-low-risk	-	-	-	-	-
Low-risk	1	1	-	0.06	-

MSI, modified shock index; PEP, primary endpoint.

embolism. The remaining 130 patients were discharged without any problem.

Patients in the ILR group comprised 22 (12.2%) of those who applied to our clinic; all of these patients were treated with heparin as the initial treatment. There were no deaths, bleeding, or adverse events in this group.

Heparin followed by oral anticoagulant treatment was given to all 6 (3.3%) LR patients. In this group, 1 patient with lung cancer died due to clinical worsening of his current disease. Apart from this, no death, bleeding, or adverse event occurred during hospital follow-up.

When the whole group was evaluated, the PEP occurred in 13 (7.2%) patients. In-hospital mortality was observed in 11 (6.1%) patients, while hemodynamic collapse was observed in 2 (1.1%) patients. Both patients who developed hemodynamic collapse under heparin therapy were in the IHR group. Respiratory arrest was observed in 1 of these patients, and palpitations and hypotension were observed in the other. These patients showed hemodynamic and echocardiographic improvement after administration of 100 mg t-PA over 2 hours.

None of the patients in the HR group had contraindications for thrombolytic therapy. Seven patients in the IHR group had contraindications for thrombolytic therapy. Two patients with absolute contraindications and 3 patients with relative contraindications were not given thrombolytic therapy. Twenty-five milligrams of t-PA were administered for over 6 hours to a 9-week pregnant woman who was in the transition zone between IHR and HR status. She had increased clot burden detected on CT angiography and her respiratory rate and heart rate were increasing gradually. A patient with a history of previous stroke had a rapid deterioration and was administered USAT therapy. Thirty-three milligrams of t-PA were given in 24 hours during this time. No major or minor bleeding was observed in all these patients.

For PEP, the USAT and UFH groups were similar, while it was significantly higher in the t-PA group. While the t-PA group had significantly more major bleedings than the USAT group [16.2% (6) vs. 1.2% (1), $P = .003$], there was no significant difference in the minor bleeding groups [0% (0) vs. 8.4% (7), $P = .098$]. Table 4 represents MSI values in patients with PEP in different risk groups.

The MSI showed a positive correlation with PESI score ($r = 0.515$, $P < .01$), PESI class ($r = 0.514$, $P < .01$), sPESI score ($r = 0.584$, $P < .01$), sPESI class ($r = 0.453$, $P < .01$), and with SI

($r = 0.598$, $P < .01$). When echocardiographic parameters were examined, MSI was correlated with PASP ($r = 0.164$, $P < .05$) and excursion of the tricuspid annular planary excursion (TAPSE) ($r = -0.246$, $P < .01$), but not with tricuspid annular tissue Doppler systolic velocity (St). It showed a moderate ($r = 0.279$, $P < .05$) correlation with troponin. When we look at the clinical scores, PESI showed a positive correlation with sPESI ($r = 0.653$, $P < .01$), SI ($r = 0.340$, $P < .01$), PASP ($r = 0.305$, $P < .01$), TAPSE ($r = -0.278$, $P < .01$), and St ($r = -0.238$, $P < .05$). Table 5 represents the correlations of MSI with PESI, sPESI, SI, and echocardiographic measures. Troponin correlated with the SI and MSI, but not with PESI or sPESI measures. D-dimer showed a positive correlation with MSI ($r = 0.282$, $P < .05$). Figure 1 represents the correlation between MSI and D-dimer.

Table 5. The Correlations of MSI with PESI, sPESI, SI, and Echocardiographic Measures

Variable	PESI	sPESI	SI	TAPSE	PASP
MSI	$r = 0.515$ $P < .001$	$r = 0.584$ $P < .001$	$r = 0.598$ $P < .001$	$r = -0.246$ $P < .001$	$r = 0.164$ $P < .001$
PESI		$r = 0.563$ $P < .001$	$r = 0.340$ $P < .001$	$r = -0.278$ $P < .001$	$r = 0.305$ $P < .001$
sPESI	$r = 0.623$ $P < .001$		$r = 0.390$ $P < .001$	$r = 0.249$ $P < .001$	$r = 0.346$ $P < .001$

MSI, modified shock index; PASP, pulmonary artery systolic pressure; PESI, pulmonary embolism severity index; SI, shock index; sPESI, simplified pulmonary embolism severity index; TAPSE, tricuspid annular plane systolic excursion.

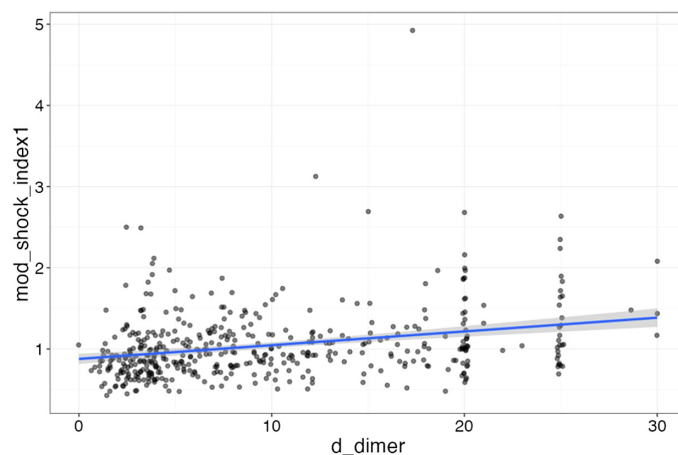


Figure 1. The correlation between MSI and D-dimer value. MSI, modified shock index.

Table 6. The Comparison of MSI, SI, sPESI, and PESI in Predicting the PEP

Variable	Sensitivity (%)	Specificity (%)	NPV (%)	AUC	Cut-off
MSI	73	54	94.8	0.739	0.989
SI	36.3	94.7	95.8	0.602	1.52
SPESI	55.5	69.1	96.6	0.616	2.0
PESI	77.8	68	92.3	0.698	114

AUC, area under the curve; MSI, modified shock index; NPV, negative predictive value; PEP, primary endpoint; PESI, pulmonary embolism severity index; SI, shock index; sPESI, simplified pulmonary embolism severity index.

In predicting the PEP, the AUC of MSI was found to be 0.739 (0.588-0.890, $P = .002$), and MSI > 0.989 had a 73% sensitivity and a 54% specificity.

Table 6 demonstrates the comparisons among MSI, SI, PESI, and sPESI in predicting the PEP.

Figures 2-5 represent the ROC curves of MSI, SI, PESI, and sPESI in predicting PEP.

In the comparison among all 3 treatment groups, formula-1 (MSI before initial treatment) was found to be 1.10 ± 0.42 , formula-2 (MSI after treatment) was 0.74 ± 0.13 , and median delta change was 0.33 (0.08-0.49) in the USAT group. In the t-PA group, MSI values were 1.3 ± 1.2 for formula-1, 0.74 ± 0.13 for formula-2, and 0.36 (0.11-0.51) for median change, whereas these values were 0.97 ± 0.69 for formula-1, 0.74 ± 0.16 for formula-2, and 0.13 (0.02-0.24) for median change in the UFH group. While there was no MSI difference between all 3 groups for formula-2 ($P = .108$) as post-treatment measure, there was a significant difference for formula-1 ($P = .005$) as initial measure and delta change with treatment ($P = .001$). While pre-treatment MSI (formula-1) was comparable between USAT and UFH groups, this measure

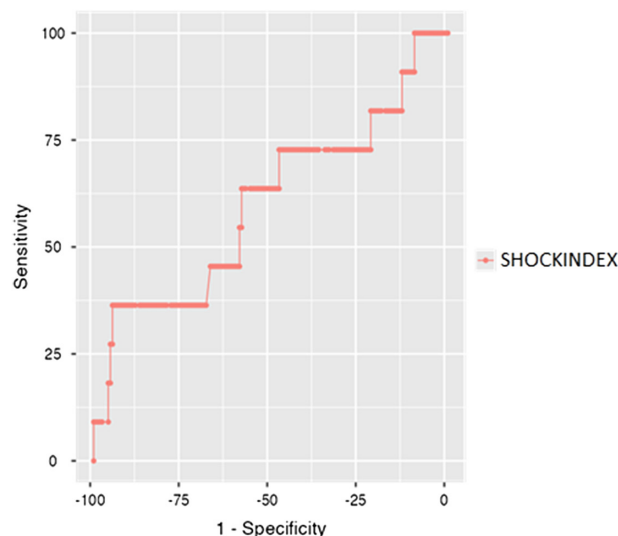


Figure 3. Receiver-operating characteristic curve of the SI. SI, shock index.

was higher in the t-PA group. Figure 6 illustrates the delta changes in USAT, t-PA, and UFH groups. Delta change was similar between the USAT and t-PA groups but was significantly lower in the UFH group.

DISCUSSION

In this study, we proposed a new score in acute PE. The MSI showed significant correlations with previously validated risk tools such as SI, PESI score and class, and sPESI score and class; and the MSI had the highest prediction for mortality and hemodynamic deterioration during hospital stay. The MSI provided the highest AUC in predicting the PEP compared with SI, PESI, and sPESI. Among the patients who underwent USAT, t-PA, and UFH treatments, pre-treatment MSI was the

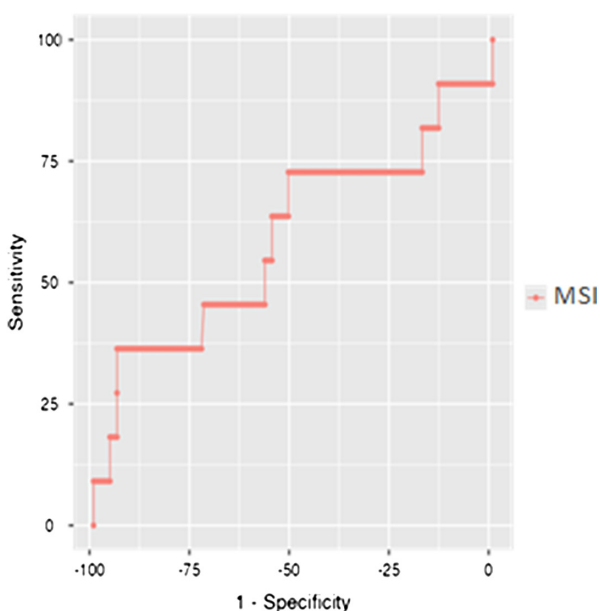


Figure 2. Receiver-operating characteristic curve of the MSI. MSI, modified shock index.

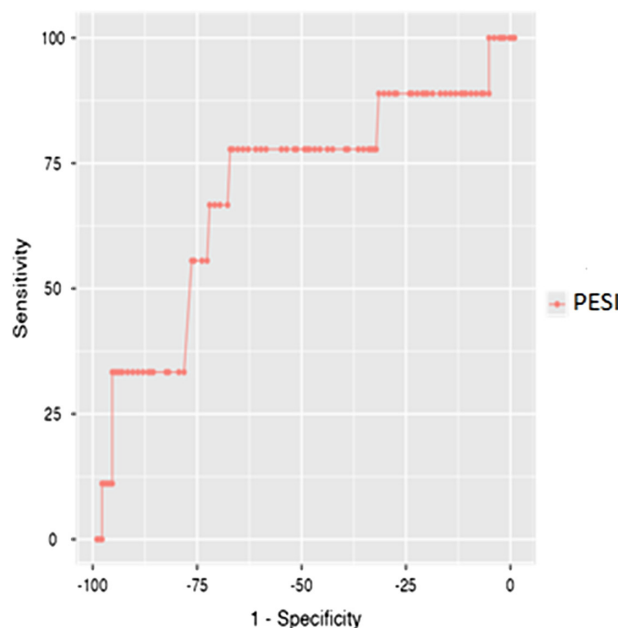


Figure 4. Receiver-operating characteristic curve of the PESI. PESI, pulmonary embolism severity index.

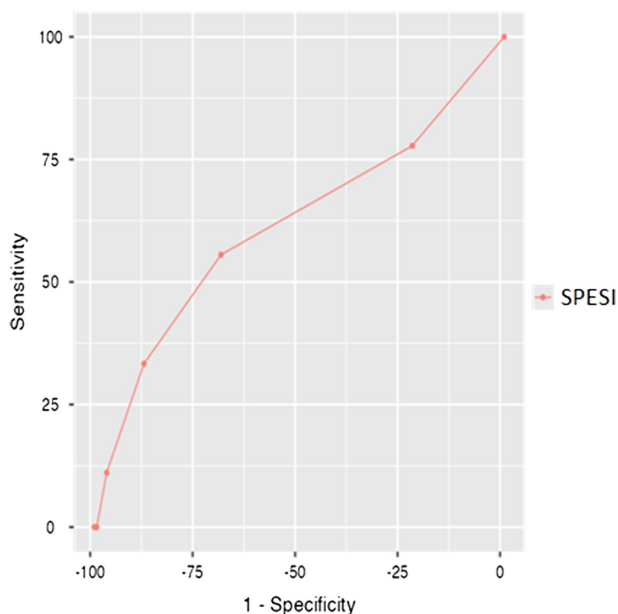


Figure 5. Receiver-operating characteristic curve of the sPESI. sPESI, simplified pulmonary embolism severity index.

highest in the t-PA group, but comparable between USAT and UFH groups. However, final MSI measures became similar among the 3 groups, and delta change in MSI was more marked in the USAT and t-PA groups as compared to those in the UFH group. These results suggest the clinical relevance of the MSI at baseline risk assessment and evaluating the benefit from reperfusion therapies. In the initial risk stratification of patients with acute PE, several scores have been proposed. The PESI and sPESI have been adopted as 2 risk stratification tools in predicting the short-term mortality in acute PE. Because of its simplicity and sensitivity, the sPESI has been commonly used in clinical practice.^{7,10,12,23} Heart rate, arterial oxygen saturation, and systolic blood pressure are parameters included in both PESI and sPESI.^{1,2,8-11}

In a study comparing the sPESI and SI in predicting the 30-day outcome in a cohort of 1206 patients with confirmed

PE, sPESI was reported to have a higher sensitivity (95%) and negative predictive value (98.4%) compared with the SI.²³ In other study evaluating the accuracy of the sPESI and SI in predicting short- and long-term mortality in symptomatic patients with PE, the sPESI was found to be superior to SI in predicting both 30-day and 3-year mortality. Moreover, for identifying LR patients, the accuracy of the sPESI was better than that of the SI.²⁴

The role of hypoxemia as a predictor of adverse events in PE patients is well established.^{10,25} The prognostic value of a novel respiratory index (RI), the ratio of O₂ Sat% in air to respiratory rate, was evaluated in the study by Vedovati et al.²⁶ and the RI was found to be an independent predictor of death either as continuous relation (odds ratio (OR) 0.48, 95% CI 0.32-0.70, *P* =.001) or as a dichotomous value of 3.8 (20.7% vs. 2.1%, OR 8.80, 95% CI 3.05-25.42, *P* =.001).²⁶

Because of these limitations of SI as compared to sPESI and PESI, we have tried to modify the SI with the addition of pSat O₂%. The original SI calculated as heart rate divided by systolic blood pressure was modified by multiplication of SI with 1/pSat O₂%. Therefore, using this 3-component index, we aimed to achieve a more comprehensive bedside assessment for physiological and hemodynamic status representing the ventilation/perfusion matching both at initial evaluation and after selected reperfusion or anticoagulant therapies. The MSI was found to be significantly correlated with SI, PESI score and class, and sPESI score and class. With the multiplication of heart rate/systemic blood pressure ratio and 1/pSat O₂%, an increasing index value may represent a worsening ventilation/perfusion matching and hemodynamic deterioration in an acute setting. The MSI as compared to PESI, sPESI, and SI was found to have the highest prediction for mortality and hemodynamic deterioration during hospital stay. The AUC values of MSI, SI, PESI, and sPESI were 0.739, 0.602, 0.616, and 0.698, respectively. The cut-off value of 0.989 for MSI compared with 1.52 for SI seemed to be consistent with an increasing sensitivity by adding 1/satO₂% into the formula. However, this increased sensitivity was obtained at the expense of decreasing specificity. The sensitivity and specificity of MSI, SI, sPESI, and PESI were 73% and 54%, 36.3% and 94.7%, 55.5% and 69.1%, and 77.8% and 68%, respectively.

The monitoring of instantaneous changes in the physiological and hemodynamic status with this simple risk tool composed of heart rate, systemic blood pressure, and pulse O₂ Sat% appears to cover the cascades of obstructive burden in pulmonary circulation resulting in the ventilation/perfusion mismatching, sudden-onset RV pressure strain, and hemodynamic deterioration in acute PE.

In our single-center PE series, the current number increased to 810 patients, and USAT, rheolytic thrombectomy, systemic full-dose t-PA and low-dose, slow-infusion t-PA regimens, and UFH treatments have been utilized following the initial risk stratification. Both USAT and rheolytic thrombectomy cohorts represent the largest single-center series ever published.^{19-22,27} Moreover, a meta-analysis based on 11 USAT series published before December 2015 revealed that USAT

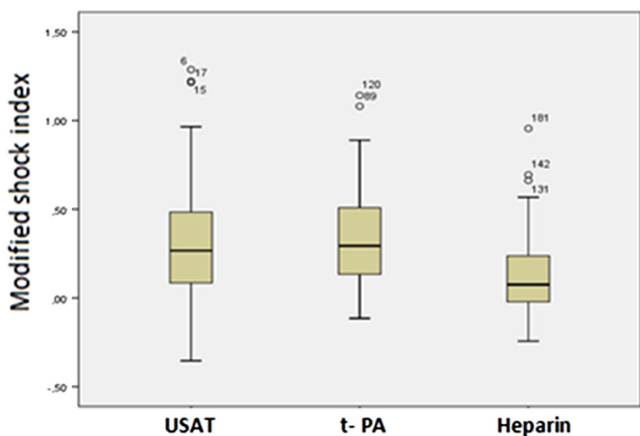


Figure 6. Comparisons of 3 groups for delta-formula change. t-PA, tissue-type plasminogen activator; USAT, ultrasound-assisted thrombolysis.

related to significant improvements in pulmonary artery mean pressures, RV/LV ratio, and CT obstruction scores. The same analysis showed that USAT compared with 3 randomized systemic thrombolysis trials was associated with a similar mortality and a lower rate of major bleeding.²⁸ Furthermore, as compared to those in systemic thrombolysis arms of 2 meta-analyses evaluating thrombolysis versus anticoagulation in acute PE, USAT provided similar mortality rates with a significantly reduced rate of major bleeding.^{29,30} In the present study, pre-treatment MSI was the highest in the t-PA group, but comparable between USAT and UFH groups. However, final MSI measures became similar among the 3 groups, as a result of the more marked delta change in the USAT and t-PA groups as compared to those in the UFH group. These results imply the clinical relevance of the MSI not only for initial risk assessment but also in monitoring the benefits of selected therapies.

Study Limitations

The retrospective nature of analysis remains a major limitation of this study. Secondly, unfortunately, this patient population belongs to an earlier period of our institutional experience and may not represent our current PE patient's series comprising the USAT, rheolytic thrombectomy, systemic full-dose and low-dose, slow-infusion t-PA, and UFH treatment groups. Therefore, this study should be considered as a development phase for a new risk tool modified from a widely used risk index in acute PE and will be followed by an internal validation study for MSI in our PE population.

CONCLUSIONS

The MSI consisted of 3 critical physiological measures that may provide a simple and comprehensive tool for quick risk assessment at initial evaluation, monitoring the clinical benefit from selected treatments, and decision-making for escalation to other reperfusion strategies in patients with acute PE. Further studies based on the prospective design in patients with acute PE seem to be required for validation of MSI as a risk tool comparable to SI, PESI, and sPESI.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Koşuyolu Heart Training and Research Hospital (approval no: 2017.5/1-43) on 19.06.2017.

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REFERENCES

1. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;35(43):3033-3069. [\[CrossRef\]](#)
2. Konstantinides SV, Meyer G, Becattini C, et al. The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Respir J*. 2019;54(3):1901647. [\[CrossRef\]](#)
3. Barco S, Mahmoudpour SH, Planquette B, Sanchez O, Konstantinides SV, Meyer G. Prognostic value of right ventricular dysfunction or elevated cardiac biomarkers in patients with low-risk pulmonary embolism: a systematic review and meta-analysis. *Eur Heart J*. 2019;40(11):902-910. [\[CrossRef\]](#)
4. Barco S, Vicaut E, Klok FA, et al. Improved identification of thrombolysis candidates amongst intermediate-risk pulmonary embolism patients: implications for future trials. *Eur Respir J*. 2018;51(1):1701775. [\[CrossRef\]](#)
5. Bajaj A, Saleeb M, Rathor P, Sehgal V, Kabak B, Hosur S. Prognostic value of troponins in acute nonmassive pulmonary embolism: a meta-analysis. *Heart Lung*. 2015;44(4):327-334. [\[CrossRef\]](#)
6. Henzler T, Roeger S, Meyer M, et al. Pulmonary embolism: CT signs and cardiac biomarkers for predicting right ventricular dysfunction. *Eur Respir J*. 2012;39(4):919-926. [\[CrossRef\]](#)
7. Donzé J, Le Gal G, Fine MJ, et al. Prospective validation of the Pulmonary Embolism Severity Index. A clinical prognostic model for pulmonary embolism. *Thromb Haemost*. 2008;100(5):943-948. [\[CrossRef\]](#)
8. Elias A, Mallett S, Daoud-Elias M, Poggi JN, Clarke M. Prognostic models in acute pulmonary embolism: a systematic review and meta-analysis. *BMJ Open*. 2016;6(4):e010324. [\[CrossRef\]](#)
9. Kohn CG, Mearns ES, Parker MW, Hernandez AV, Coleman CI. Prognostic accuracy of clinical prediction rules for early post-pulmonary embolism all cause mortality: a bivariate meta-analysis. *Chest*. 2015;147(4):1043-1062. [\[CrossRef\]](#)
10. Jiménez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med*. 2010;170(15):1383-1389. [\[CrossRef\]](#)
11. Righini M, Roy PM, Meyer G, Verschuren F, Aujesky D, Le Gal G. The Simplified pulmonary embolism severity index (PESI): validation of a clinical prognostic model for pulmonary embolism. *J Thromb Haemost*. 2011;9(10):2115-2117. [\[CrossRef\]](#)
12. Quezada CA, Bickdeli B, Villén T, et al. Accuracy and interobserver reliability of the simplified pulmonary embolism severity index versus the Hestia criteria for patients with pulmonary embolism. *Acad Emerg Med*. 2019;26(4):394-401. [\[CrossRef\]](#). Epub 2018 Oct 10.
13. Ozsu S, Erbay M, Durmuş ZG, Ozlu T. Classification of high-risk with cardiac troponin and shock index in normotensive patients with pulmonary embolism. *J Thromb Thrombolysis*. 2017;43(2):179-183. [\[CrossRef\]](#)
14. Meinel FG, Nance JW Jr, Schoepf UJ, et al. Predictive value of computed tomography in acute pulmonary embolism: systematic review and meta-analysis. *Am J Med*. 2015;128(7):747-59.e2. [\[CrossRef\]](#)
15. Kurnicka K, Lichodziejewska B, Goliszek S, et al. Echocardiographic pattern of acute pulmonary embolism: analysis of 511 consecutive patients. *J Am Soc Echocardiogr*. 2016;29(9):907-913. [\[CrossRef\]](#)
16. Lobo JL, Holley A, Tapson V, et al. Prognostic significance of tricuspid annular displacement in normotensive patients with

- acute symptomatic pulmonary embolism. *J Thromb Haemost.* 2014;12(7):1020-1027. [\[CrossRef\]](#)
17. Côté B, Jiménez D, Planquette B, et al. Prognostic value of right ventricular dilatation in patients with low-risk pulmonary embolism. *Eur Respir J.* 2017;50(6):1701611. [\[CrossRef\]](#)
 18. Qanadli SD, El Hajjam M, Vieillard-Baron A, et al. New CT index to quantify arterial obstruction in pulmonary embolism: comparison with angiographic index and echocardiography. *AJR Am J Roentgenol.* 2001;176(6):1415-1420. [\[CrossRef\]](#)
 19. Kaymaz C, Akbal OY, Hakgor A, et al. A five-year, single-centre experience on ultrasound-assisted, catheter-directed thrombolysis in patients with pulmonary embolism at high risk and intermediate to high risk. *EuroIntervention.* 2018;14(10):1136-1143. [\[CrossRef\]](#)
 20. Kaymaz C, Akbal OY, Keskin B, et al. An eight-year, single-center experience on ultrasound assisted thrombolysis with a moderate-dose, slow-infusion regimen in pulmonary embolism. *Curr Vasc Pharmacol.* 2022;20(4):370-378. [\[CrossRef\]](#)
 21. Kaymaz C, Öztürk S, Akbal Ö, et al. Ultrasound-assisted catheter-directed thrombolysis in high-risk and intermediate-high-risk pulmonary embolism: results from a single-center cohort. *Angiology.* 2017;68(5):433-440. [\[CrossRef\]](#). Epub 2016 Aug 1.
 22. Akbal ÖY, Keskin B, Tokgöz HC, et al. A seven-year single-center experience on AngioJet rheolytic thrombectomy in patients with pulmonary embolism at high risk and intermediate-high risk. *Anatol J Cardiol.* 2021;25(12):902-911. [\[CrossRef\]](#)
 23. Sam A, Sánchez D, Gómez V, et al. The shock index and the simplified PESI for identification of low-risk patients with acute pulmonary embolism. *Eur Respir J.* 2011;37(4):762-766. [\[CrossRef\]](#). Epub 2010 Jul 22.
 24. Kilic T, Ermis H, Gülbas G, et al. Prognostic role of the simplified pulmonary embolism severity index and shock index in pulmonary embolism. *Pol Arch Med Wewn.* 2014;124(12):678-687. [\[CrossRef\]](#). Epub 2014 Oct 10.
 25. Becattini C, Vedovati MC, Pruszczyk P, et al. Oxygen saturation or respiratory rate to improve risk stratification in hemodynamically stable patients with acute pulmonary embolism. *J Thromb Haemost.* 2018;16(12):2397-2402. [\[CrossRef\]](#)
 26. Vedovati MC, Cimini LA, Pierpaoli L, et al. Prognostic value of respiratory index in haemodynamically stable patients with acute pulmonary embolism: the Respiratory Index model study. *Eur Heart J Acute Cardiovasc Care.* 2020 June;9(4):286-292. [\[CrossRef\]](#). Epub 2020 Mar 13.
 27. Keskin B, Tokgöz HC, Akbal OY, et al. Clinical, imaging, and hemodynamic correlates and prognostic impact of syncope in acute pulmonary embolism: A single-center study. *Türk J Thorac Cardiovasc Surg.* 2022;30(3):1-9. [\[CrossRef\]](#) [in press].
 28. Kaymaz C, Akbal OY, Tanboga IH, et al. Ultrasound-assisted catheter-directed thrombolysis in high-risk and intermediate-high-risk pulmonary embolism: A meta-analysis. *Curr Vasc Pharmacol.* 2018;16(2):179-189. [\[CrossRef\]](#)
 29. Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *JAMA.* 2014;311(23):2414-2421. [\[CrossRef\]](#)
 30. Marti C, John G, Konstantinides S, et al. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. *Eur Heart J.* 2015;36(10):605-614. [\[CrossRef\]](#). Epub 2014 Jun 10.