Abstract

Aim: To investigate the diagnostic value of pulmonary embolism severity index (PESI), Simplified PESI (sPESI), Shock Index (SI), Modified SI (MSI), and Age SI (ASI) scores in predicting 30-day mortality in patients diagnosed with pulmonary thromboembolism (PTE) in the emergency department.

Materials and Methods: The retrospective study included 257 patients that presented to the emergency department and underwent contrast-enhanced computed tomography pulmonary angiogram (CTPA) due to the suspicion of PTE and were interpreted as PTE by an experienced radiologist between January 1, 2015 and September 20, 2018.The PESI, sPESI, SI, MSI, and ASI scores were calculated for each patient.

Results: On univariate logistic regression analysis, 30-day mortality was found to be significantly associated with age, mode of presentation, SBP, DBP, MAP, heart rate, respiratory rate, O_2 saturation, temperature, D-dimer, troponin I, high-sensitivity cardiac troponin (hs-cTn), lactate, and SI, MSI, ASI, PESI, and sPESI scores ($p<0.05$). PESI had the highest AUC value for the prediction of 30-day mortality among all scoring systems.

Conclusion: PESI had the highest diagnostic value in predicting 30-day mortality in the patients diagnosed with PTE in the emergency department, followed by ASI. Our findings regarding ASI may shed light on future studies evaluating critical patient groups."

Keywords: Shock index, age shock index, pulmonary thromboemboli, emergency department, mortality

INTRODUCTION

Pulmonary thromboembolism (PTE) is a serious condition resulting from the blockage of the pulmonary artery or its branches by a blood clot or substance (thrombus, air, fat, or tumor)(1). PTE does not have a specific clinical picture and has a wide spectrum of manifestations ranging from asymptomatic to obstructive shock, which affect the management of these patients in the emergency department . The mortality rate is approximately 30% in patients that cannot be diagnosed and treated appropriately, while it may be as low as2-8% in patients that are treated promptly and appropriately according to risk classification (2, 3). In 2014, the European Society of Cardiology (ESC) recommended the utilization of shock, hypotension, right ventricular dysfunction, pulmonary embolism severity index (PESI) and cardiac biomarkers in risk assessment (4). In later years, however, PESI was found to be difficult to calculate in overcrowded emergency rooms and thus a simplified PESI (sPESI) score was developed using the data obtained from a Spanish hospital (5).

The shock index (SI) has recently emerged as a popular tool in the prediction of the prognosis in patients with high-mortality conditions such as sepsis, shock, and pneumonia. SI is calculated by dividing the heart rate by systolic blood pressure (SBP) and has been shown to be a useful indicator of shock and circulation status (6).Moreover, SI has been reported to be superior to use of pulse rate or SBP alone in predicting prognosis (7, 8). However, since the diastolic blood pressure (DBP) was not taken into account in the calculation of SI,this index was considered inadequate and thus the modified shock index (MSI) was developed. In addition, ASI was developed, considering that the medical history of the elderly patients and the drugs they used affect the pulse and blood pressure values (9).

Based on the literature data above, the present study aimed to investigate the diagnostic value of PESI, sPESI, SI, MSI, and ASI scores in predicting 30-day mortality in PTE patients admitted to the emergency department.

MATERIALS AND METHODS

Study design

The retrospective study included patients that presented to the emergency department at Health Sciences University Izmir Bozyaka Training and Research Hospital. The study was approved by the local ethics committee.

Universe and sampling

The retrospective study included patients that presented to the emergency department at Health Sciences University Izmir Bozyaka Training and Research Hospital and underwent contrast-enhanced computed tomography pulmonary angiogram (CTPA) due to the suspicion of PTE and were interpreted as PTE by an experienced radiologist between January 1, 2015 and September 20, 2018.Exclusion criteria were as follows: age under 18 years, pregnancy, incomplete clinical and radiological records, unknown clinical outcomes, and a history of PTE. Additionally, seven patients whose SI, MSI and ASI scores could not be calculated were excluded from the study.

Data collection

Based on the CTPA reports retrieved from the hospital database during the study period, patients who were interpreted as acute PTE and did not meet the exclusion criteria were included in the study.The examination records of the patients were also retrieved from the hospital database. Clinical and demographic characteristics including age, gender, history of cardiopulmonary disease and cancer, state of consciousness, vital signs on admission (SBP, DBP, cardiac pulse, respiratory rate, temperature, and peripheral oxygen saturation), blood and biochemical parameters, and blood gas values were recorded for each patient. Based on these data, the PESI, sPESI, SI, MSI, and ASI scores were calculated for each patient.

Calculation of scores

Pulmonary embolism severity index (PESI) is the best known prognostic model in patients with acute PTE andis a well-approved and highly reliable clinical prognostic model that allows clinicians to perform risk assessment at the bedside withno need for any examination (10).The PESI score is calculated based on 11 clinical parameters, including male gender (+10 points), cancer (+30 points), heart failure (+10 points), chronic lung disease (+10 points),

pulse rate ≥110 beats/min (+20 points), SBP <100 mmHg (+30 points), respiratory rate ≥30/min (+20 points), temperature <36°C (+20 points), altered mental status (+60 points), arterial oxygen saturation < 90% (+20), and patient age (in years) (11).

The classification of mortality risk based on the total PESI score is as follows:

Risk class I (<66 points)

Risk class II (66-85points)

Risk class III (86-105 points)

Risk class IV (106-125 points)

Risk class V (>125 points)

In this classification, class I and II indicate low risk and classIII, IV,and V indicate high risk of mortality (11).

Simplified PESI (sPESI) contains six of the 11 original PESI variables and is calculated by assigning a numerical value to each prognostic variable. The sPESI score is calculated based on the following criteria: age ≤80years (1 point), history of cancer (1 point), history of chronic cardiopulmonary disease (1 point), heart rate≥110 beats/min (1 point), SBP<100 mmHg (1 point), and O_2 saturation<90% (1 point)(5).Patients with none of the variables (0 points) are classified as low-risk patients. A sPESI score of ≥1 is associated with high mortality(5).

The modified shock index (MSI), which was developed by Liu et al.,includes DBP and is calculated by dividing heart rate by mean arterial pressure (MAP)(9).Unlike SI, ASI considers patient age as well (SI x age) and this index has been shown to be correlated with high mortality in patients aged over 50 years (12).

Additionally, clinical outcomes of the patients (hospital admission, discharge, treatment refusal, and intensive care unit [ICU] admission), 30-day survival, and all-cause mortality were reviewed for each patient.

Statistical analysis

Data were analyzed using SPSS for Windows version 25.0(Armonk, NY: IBM Corp.).Normal distribution of data was assessed using Shapiro-Wilk testand the homogeneity of variance was

evaluated by Levene's test. Two independent continuous variables were compared using Independent-Samples t-test with bootstrapping or Mann-Whitney U test with Monte Carlo simulation. Three or more continuous variables were compared using Kruskal-Wallis H Test with Monte Carlo simulation,followed by post-hoc Dunn's Test. Categorical variables were compared using Pearson's Chi-Square Test Exact with Monte Carlo simulation, Fisher-Freeman-Holton Testwith Monte Carlo simulation,or Fisher's Exact test with exact values, and the column proportions were compared and expressed using the corrected *p* value obtained by the Benjamini-Hochberg procedure. The mortality riskin both groups was assessed using odds ratio (OR) with 95% confidence interval(CI) and was analyzed using multivariatelogistic regression analysis with backward elimination (Wald); however, the results were not reported since no significant relationship was detected in the analysis. Relationship between the classification of the cutoff value that was calculated according to the variables of the patient groups and the real classification and the sensitivity and specificity of this relationship were assessed using the Receiver Operating Curve (ROC) analysis. The area under the ROC curve (AUC) values were classified as follows: <0.5, worthless; 0.5-0.6,bad; 0.6-0.7, fair, 0.7-0.8,good; 0.8-0.9,very good; 0.9-1.0 excellent. Continuous variables were expressed as mean ± standard deviation (SD) and median (minimum-maximum)and categorical variables were expressed as frequencies (n) and percentages (%). A *p* value of <0.05 was considered significant.

RESULTS

The 257 patients comprised 151 (58.8%) women and 106 (41.2%) men with a mean age of 70.7±15.5 years.Hypertension was the most common comorbidity (n=91; 35.1%), followed by malignancy (n=63; 24.5%), diabetes mellitus (n=49; 19.1%), chronic obstructive pulmonary disease (COPD)/asthma (n=34; 13.2%), stroke (n=33; 12.8%), and Alzheimer's disease/dementia (n=24; 9.3%).

Table 1 presents the vital signs and the SI, MSI, ASI, PESI, and sPESI scores assessed on hospital admission.

Troponin was assessed in 209 (81.3%) patients.In 81 out of 190 patients that underwent troponin I testing, the mean troponin I value was 0.18±0.49 ng/ml, which was higher than the reference value (0.04 ng/ml).High-sensitivity cardiac troponin (hs-cTn) assay was performed in 19 (7.3%) patients, among whom 9 (47.4%) patients had a mean level of 494.0±1207.9 pg/

ml, which was higher the reference value (11.6pg/ml). The D-dimer level was assessed in 202 (78.6%) patients, who had a mean level of 4999.6±10292.63 ng/ml.

In 255 (99%) patients that underwent venous blood gas analysis, mean lactatelevel was 3.0±2.4 mmol/L, mean base deficitwas -0.4±4.8 mmol/L, and mean pH value was 7.39±0.09.

In 369 patients that underwent CTPA, 65 (16.7%) were detected with main pulmonary artery embolism and the remaining 304 (83.3%) patients were detected withsegmental/subsegmental artery embolism.

Thirty-day mortality occurred in 68 (26.5%) patients. On univariate logisticregression analysis, 30-day mortality was found to be significantly associated with age, mode of presentation, SBP, DBP, MAP, heart rate, respiratory rate, O_2 saturation, temperature, D-dimer, troponin I, hs-cTn, lactate, and SI, MSI, ASI, PESI, and sPESI scores (p<0.05)(Table 1).

On multivariate logistic regression analysis, no significant model was found for 30-day mortality. Nevertheless, ICU admission was found to be associated with SI, MSI, YSI, PESI Class V (>125 points), and sPESI ≥ 1 (high-risk) (p<0.05).

The diagnosticvalue of SI, MSI, ASI, PESI, and sPESI in PTE patients was assessed using ROC curve analysis, in which PESI had the highest AUC value (Figure 1, Table 2).

DISCUSSION

Both SI and MSI have been shown to be effective in predicting prognosis in PTE patients (13). In the present study, ASI and PESI besides MSI were found to be significant predictors of 30-day mortality.

Both PESI and sPESI have been developed based on clinical parameters for the evaluation of prognosis in patients with acute PTE(11, 14). In our study, the PESI scores indicated that 7% of the patients were at very low risk and 39.7% of them were at very high risk of adverse events. During the 30-day period, no mortality occurred in the 52 patients that were at low risk, while mortality occurred in 26.5% of the patients that were at high risk. Additionally, PESI had the highest AUC value for the prediction of 30-day mortality among all scoring systems. In a previous study that utilized PESI in the prediction of mortality in PTE patients, PESI had an AUC value of 0.92 (95%CI) and was shown to be an effective parameter in the

prediction of mortality in PTE patients(15). In a similar way to our study, Aujesky et al.reported that 47% of the patients were in the low-risk group and these patients had a mortality rate of 1.2%. The authors also noted that PESI had a sensitivity of 91% (95% CI: 81-97)and a negative predictive value (NPV) of 99% (95% CI: 97-100)in the low-risk group and suggested that PESI can safely identify low-risk patients (16).

Venetz et al. reported that PESI and sPESI had similar accuracyin identifying low-risk patients (10).Similarly, a systematic review that analyzed 21 studies reported that PESI and sPESI had similar accuracy in predicting mortalitywhile PESI was better in predicting earlymortality and complications (17).In our study, patients were classified as low-risk and high-risk patients based on sPESI scores and sPESI had a significant diagnostic value in identifying low-risk patientswhile it had no significant diagnostic value in identifying high-risk patients. In a similar way to the systematic review abovementioned, our study also found that PESI had a greater significant diagnostic value in predicting mortality compared to sPESI.

Previous study indicated that SI had a greater diagnostic value than that of vital signs measurements and also noted that increased SI scores were associated with mortality (18, 19). Similarly, a previous study that evaluated the reliability of SI reported that SI was superior only to pulse rate and SBP measurements (19).Additionally, numerous other studies have revealed the potential benefits of SI in predicting prognosis and mortality in patients with trauma, pneumonia, ruptured ectopic pregnancy, PTE,and acute myocardial infarction (20-27).In a similar way, we also found that SI had a significantly higher diagnostic value in predicting mortality in PTE patients in the non-surviving group compared to the surviving group.

The modified shock index (MSI) is considered an indicator of stroke volume and systemic vascular resistance (28).Singh et al.reported that patients with an MSI score of <0.7 and >1.3 had higher mortality rates (28). Liu et al. found that the MSI scorealone showed better clinical results than the measurement of blood pressure or heart rate alone in patients who were not in shock but had serious conditions such as PTE. The authors also noted that the probability of ICU admission and death was higher in patients with MSI >1.3(9). In our study, the cutoff value for MSI score was accepted as 1.7 and the MSI scores were significantly higher in the non-surviving groupthan in the surviving group.Additionally, MSI was found to be superior to SI in predicting 30-day mortality.

To our knowledge, ASI has been investigated in a limited number of studies in the literature. A previous study evaluated the diagnostic value of SI and ASI in trauma patients and reported that ASI >50 was associated with increased mortality (12). In our study, however, no significant difference was found between the surviving and non-surviving groups with regard to ASI scores.Nonetheless, it was revealed that ASI had a significantly higher diagnostic value in predicting 30-day mortality in PTE compared to SI and MSI.

Our study was limited since it was a single-center retrospective study and the vital signs of the patients were measured by different physicians. Additionally, since the troponin values of all patients could not be reached, those values may not represent the entire patient group.

CONCLUSION

The results indicated that PESI had the highest diagnostic value in predicting 30-day mortality in the patients diagnosed with PTE in the emergency department, followed by ASI. Moreover, SI and MSI were also found to have a significant value in predicting 30-day mortality in PTE patients. Accordingly, our findings regarding ASI may shed light on future studies evaluating critical patient groups.

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Table 1. Univariateanalysis of factors associated with 30-day mortality

	Total (n=257)	Non-surviving (n=68)	Surviving (n=189)	*p*
Age Median (Min-Max)	70.7 (21-98)	79 (45-98)	73 (21 - 94)	**0.001** [1]
Sex n(%) **F-M**	151-106 (58.8-41.2)	43 (28.5)-25 (23.6)	108 (71.5)-81 (76.4)	0.381 2
SBP Median (Min-Max)	118.3 (63-197)	110 (63-190)	120 (80-197)	**0.013** [1]
DBP Median (Min-Max)	69.4 (40-98)	66.5 (40-90)	71 (40-98)	**0.002** [1]
Pulse Mean ± SD	108.7±22.7	114.9±24.2	106.5±21.7	**0.005** [5]
RR	22.6±5.9	23 (14-40)	20 (14 - 36)	**0.002** [1]
O_2 Saturation Median (Min-Max)	92.9 (53-100)	92 (53-100)	95 (75-100)	0.005 [1]
Fever. Median (Min-Max)	36.5 (35.7-38.2)	36.5 (35.7-38.2)	36.5 (36.0-37.1)	**0.010** [1]
MAP± SD	85.7±15.6	80.6±17.2	87.5±14.5	**0.001** [5]
D-Dimer Median (Min-Max)		3572 (752.0-117086.0)	2145 (20.2-40437.0)	**<0.001** [1]
Troponin I Median (Min-Max)		0.10 (0.0-4.30)	0.03 (0-2.33)	**<0.001** [1]
Troponin S Median (Min-Max)		89 (6.4-3841)	11.5 (0.09-1170)	**0.033** [1]
Lactate Median (Min-Max)		2.75 (1.2-18)	2.2 (0.6-11.2)	**<0.001** [1]
Base deficit Median (Min-Max)		-0.95 (-19.7 - 8.4)	0.35 (-12.9 - 17)	0.102[1]
pH Median (Min-Max)		7.39 (6.99-7.56)	7.41 (7.07-7.60)	0.128 [1]
SI Median (Min-Max)	0.96 (0.38-2.61)	1.03 (0.42-2.61)	0.88 (0.38 - 1.96)	**0.001** [1]
MSI Median (Min-Max)	1.32 (0.61-3.41)	1.44 (0.67-3.41)	1.22 (0.61 - 2.34)	**0.001** [1]
Age SI. Median (Min-Max)	67.88 (14.91-234.9)	76.78 (36.0-234.90)	60.30 (14.91 - 135.29)	
PESI (%)				**<0.001** [3]
I	18 (7)	0 (0.0)	18 (7.0)[B]	
II	34 (13.2)	0 (0.0)	34 (13.2)[B]	
III	59 (23)	11 (4.3)	48 (18.7)	
IV	44 (17.1)	10 (3.9)	34 (13.2)	
V	102 (39.7)	47 (18.3)[A]	55 (21.4)	
sPESI				**0.001** [1]
< 1%	32 (12.5)	0 (0.0)	32 (12.5) [B]	

> 95%	225 (87.5)	68 (26.5) [A]	157 (61.1)	
Clinical outcome.$_{n(\%)}$				
Hospitalization		22 (8.6)	84 (32.7)[B]	
Discharge		2 (0.8)	28 (10.9) [B]	
Treatment refusal		4 (1.6)	15 (5.8)	
ICU		40 (15.6) [A]	62 (24.1)	

[1] Mann-Whitney U test(Monte Carlo), [2] Pearson's Chi-Square Test (Exact); Post-Hoc Test: Benjamini-Hochbergcorrection, [3]Fisher-Freeman-Halton test(Monte Carlo); Post-Hoc Test: Benjamini-Hochbergcorrection, [4] Fisher's Exact test (Exact); Post-Hoc Test: Benjamini-Hochbergcorrection, [5]Independent-Samples t-test (Bootstrap), *OddsRatio (95% confidence interval), [A]Significantfor the surviving group [B]Significant compared to the non-surviving group, SD: Standard deviation, Min: Minimum, Max:Maximum

SBP: Systolic blood pressure, DBP: Diastolic blood pressure,RR: Respiratory Rate MAP: Mean arterial pressure, SI: Shock Index, MSI: Modified SI, PESI: pulmonary embolism severity index (PESI), sPESI: Simplified PESI, ICU: Intensive care unit

Table 2. AUC values of indexes in the prediction of 30-day mortality

	AUC (95% confidence interval)	***p***
SI	0.633 (0.553 - 0.718)	0.001
MSI	0.642 (0.562 - 0.725)	0.001
Age SI	0.674 (0.601 - 0.748)	<0.001
PESI	0.747 (0.690 - 0.803)	<0.001
sPESI	0.585 (0.580 - 0.711)	0.038

Roc Curve Analysis (Youden's index J - Honley&Mc Nell)

SI: Shock Index, MSI: Modified SI, PESI: pulmonary embolism severity index (PESI), sPESI: Simplified PESI, AUC: Area under the ROC curve