Original Article

Comparing three clinical prediction rules for primarily predicting the 30-day mortality of patients with pulmonary embolism: The "Simplified Revised Geneva Score," the "Original PESI," and the "Simplified PESI"

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Abstract

Background: Patients with suspected pulmonary embolism (PE) should be evaluated for the clinical probability of PE using an applicable risk score. The Geneva prognostic score, the PE Severity Index (PESI), and its simplified version (sPESI) are well-known clinical prognostic scores for PE. The purpose of this study was to analyze these clinical scores as prognostic tools.

Materials and Methods: A historical cohort study was conducted on patients with acute PE in Al-Zahra Teaching Hospital, Isfahan, Iran, from June 2013 to August 2014. To compare survival in the 1-month follow-up and factor-analyze mortality from the survival graph, Kaplan–Meier, and log-rank logistic regression were applied.

Results: Two hundred and twenty four patients were assigned to two "low risk" and "high risk" groups using the three versions of "Simplified PESI, Original PESI, and Simplified Geneva." They were followed for a period of 1 month after admission. The overall mortality rate within 1 month from diagnosis was about 24% (95% confidence interval, 21.4–27.2). The mortality rate of low risk PE patients was about 4% in the PESI, 17% in the Geneva, and <1% in the simplified PESI scales ($P < 0.005$). The mortality rate among high risk patients was 33%, 33.5%, and 27.5%, respectively.

Conclusions: Among patients with acute PE, the simplified PESI model was able to accurately predict mortality rate for low risk patients. Among high risk patients, however, the difference between the three models in predicting prognosis was not significant.

Key Words: Mortality, pulmonary embolism, pulmonary embolism/diagnosis, pulmonary thromboembolism

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INTRODUCTION

Venous thromboembolism (VTE) is known as the third leading cause of death following coronary artery diseases and stroke.[1,2] The number of preventable deaths caused by thrombosis in Europe is an average 500,000 deaths/year.[3] It is said that 10–30%

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of patients with VTE die within a month of the incident, and most of them are related to pulmonary embolism (PE). PEs constitute one-third of all VTEs. The prognosis of PE ranges from the early discharge of patients to sudden death. Hence, awareness regarding its prognosis has become extremely important. In the recent decade, multiple studies have shown that the outpatient treatment of a hemodynamically stable group of patients is safe and that its advantages are as follows: (1) Saving hospital admission costs, (2) lower risk of acquiring hospital infections, and (3) improved quality of life and increased physical and social activity. There are many internationally valid criteria available that can determine the prognosis of patients admitted to the emergency [Table 1]: The Geneva prognostic score (GPS), the "PE Severity Index" (PESI), its simplified version, and the Wells score.[4-9]

On the whole, it may be said that if used alongside a natural D-dimer result in patients suspected to have acute PE, the abovementioned models can be used to rule out acute PE in the absence of a lung computed tomography (CT) scan and/or ventilation-perfusion scan. Hence, antithrombotic medications may be discontinued more safely.[10] We must remind here that prognostic scores have high accuracy in the short-term prediction of complications and morbidity and mortality of low risk patients with acute PE only.[11,12]

MATERIALS AND METHODS

A retrospective cohort study was conducted. At the patients' arrival, the three aforementioned scales were applied, and diagnostic and therapeutic procedures were carried out according to the conventional protocol. CT pulmonary angiography (multi-slice method, pulmonary thromboembolism protocol) was performed for the patients that participated in this project. The patients' data were collected in the checklists and after initial diagnosis was made and their treatments were started they were transferred to the pulmonary – medical ward and/or the Intensive Care Unit.

Patients and data collection

The target population consisted of all patients who had been admitted to the emergency ward of Isfahan's Al-Zahra Hospital from June 2013 to August 2014 with the primary symptoms of PE. The study population included patients who had been admitted with the following symptoms that were suggestive of PE: Dyspnea at rest, orthopnea (≥2 pillows), chest pain, pleuritic pain, cough, hemoptysis, wheeze, tachycardia, unilateral swelling with tenderness, and erythema of the lower limbs—with an apparent difference in size. Upon physical examination, they had tachypnea (Respiratory Rate ≥20/min), tachycardia (100/min), elevated P2 upon cardiac auscultation, rales or crackles in the lungs, and obvious signs of deep venous thrombosis. The aforementioned were the inclusion criteria of the study. Those who were diagnosed with the help of the multi-slice multi-detector CT angiography and clinical tests were also included in the study.

The following cases were excluded from the study: Patients who passed away before the PE was diagnosed, patients who did not attend the follow-ups,

Table 1: Pulmonary embolism severity index and simplified version of the Geneva score

Simplified Geneva prognostic score			
Cancer	+2	Low	≤2
Heart failure	+1	High	>2
Previous DVT	+1		
SBP <100 mmHg	+2		
PaO_2 <8 kPa (60 mmHg)	+1		
DVT shown by Doppler sonography	+1		

Variables	PESI: Original score	PESI: Simplified score	PESI original score: Risk stratified	
Age	Age, in year	1	I: Very low	≤65
Male sex	+10		II: Low	66-68
Cancer	+30	1	III: Intermediate	86-105
Heart failure	+10	1	IV: High	106-125
Chronic lung disease	+10		V: Very high	≥126
SBP <100 mmHg	+30	1		
Respiratory rate ≥30/min	+20			
Temperature <36°C	+20			
			PESI simplified score: Risk stratified	
Altered mental status	+60		Low	<0
Arterial blood oxygen saturation <90%	+20	1	High	≥1

PESI: Pulmonary embolism severity index, DVT: Deep venous thrombosis, SBP: Systolic blood pressure

those who had a definite diagnosis of PE before attending the emergency and had started receiving treatment, and patients with any chronic disease who had <1–2 months remaining life expectancy. The remaining patients were tested for D-dimer through the quantitative method (ELISA or immunohistochemistry). The diagnosis of PE was rejected for those who had a negative result.

The CT scans were read and reported by a radiologist (employed in Al-Zahra Hospital). However, where CT angiography was contraindicated (such as severe renal failure, hypersensitivity to intravenous contrast, and pregnancy) a combination of nuclear V/Q scan, Doppler sonography of lower limbs, and the D-dimer test (a negative test is valuable) were used.

Data analysis

Descriptive data were used such as number, relative percentage, and mean ± standard deviation. The "receiver operating characteristic" (ROC) method was used to determine the sensitivity and specificity of the aforementioned methods (sensitivity was plotted on the Y-axis and specificity was plotted on the X-axis).

We used Chi-square test, Fisher's exact test, and Kruskal-Wallis test to compare the sensitivity and specificity of the aforementioned methods with each other. Quantitative variables were compared with the *t*-test.

Descriptive variables were calculated with SPSS software, version 16.0 (SPSS, Chicago, Illinois, USA). Mean values and frequencies of the clinical characteristics of the subgroups were compared with *t*-test and Chi-square tests, respectively. Statistical significance was set at $P < 0.05$. To compare survival in the 1-month follow-up and factor-analyze mortality from the survival graph, Kaplan-Meier, and log-rank logistic regression were applied.

In this analysis, the area under curve (AUC) indices was used to compare the power of the models to predict morbidity and mortality in PE patients. Then, based on the best prediction and the selected cut-off point for sensitivity and specificity, the positive and negative predictive value for the PESI model was calculated at 70%. Afterward, the AUC was calculated using "Z", the closer the AUC to 1, the better its ability to estimate morbidity and mortality in PE patients.

This study did not disrupt the patients' treatment procedure in any way; the checklist was completed with the results of Doppler sonography, CT angiography, possibly nuclear scan, and D-dimer. The patients were followed up for morbidity and mortality.

The following variables were taken into consideration during data collection too: (1) Patients' demographic data—any associated diseases, (2) reasons behind and symptoms at the time of admission, (3) recurrence of VTE and hemorrhage attacks, and (4) death (date and cause).

Data were extracted from the files at the Emergency Department, patients' discharge reports, and relevant notes from consultations made at therapeutic units. Based on the checklist, the Geneva and PESI scores were calculated on the day of admission or the next day. Patients were instructed to return to follow-up clinic in case of recurrent symptoms of the respiratory tract or lower extremities. At the end of the follow-up, the patients were followed-up through the phone or in person at the Al-Zahra Hospital outpatient clinic for death or survival and any disease-related morbidity in the 1 month following diagnosis. During follow-up, if any patients were readmitted to the hospital for any cause or death, medical data were investigated. Then, deaths were judged as related, possibly related, or unrelated to PE.

RESULTS

In this study, 252 patients attending the Al-Zahra Hospital's Emergency Department with PE symptoms were selected, among which 224 possessed the inclusion criteria. The reasons for excluding 28 patients were: Lack of informed consent ($n = 5$), history of PE ($n = 4$), being on warfarin medication ($n = 4$), inability to follow-up ($n = 8$), pregnancy ($n = 3$), renal failure ($n = 3$), and allergy to contrast material ($n = 1$).

Based on the existent data in the files, the patients were retrospectively classified into two "low risk" and "high risk" groups on the basis of the three "Simplified PESI, Original PESI, and Geneva" models.[7-9] Based on phone-calls and/or the time sequence with which the patients had attended the clinic they were followed-up for a month after admission. The patients' primary data are presented in Table 2. Eventually, the mean morbidity and mortality rate of patients within 1 month of diagnosis and treatment were 24% (95% confidence interval [CI], 21.4–27.2). Based on our results, the morbidity and mortality rate of PE patients who were classified as low risk was 4% in the PESI score, 17% in the Geneva score, and <1% in the simplified PESI score [Table 3]. Figures 1-3 shows the patients' survival rates after 30 days by simplified Geneva, original PESI, and simplified PESI scores, respectively.

In evaluation of original PESI model to predict PE mortality by using of the ROC curve, AUC was 0.82 ($P < 0.001$ and %95 CI was between 0.75 and 0.88).

Table 2: Primary demographic and clinical data of participants (frequencies and percentages)

	Simplified geneva Low risk (*n*=134)	Simplified geneva High risk (*n*=90)	Original PESI Low risk (*n*=74)	Original PESI High risk (*n*=150)	Simplified PESI-low risk (*n*=39)	Simplified PESI-high risk (*n*=185)
Demographics (%)						
Male, *n* (%)	84 (63)	48 (54)	49 (66)	83 (55)	26 (20)	106 (80)
Age, mean years (±SD)	55 (19)	60 (17)	40 (15)	65 (14)	46 (18)	59 (18)
Risk factors for VTE						
Recent trauma	22 (16)	8 (9)	13 (17.5)	17 (11)	5 (13)	25 (13)
Recent surgery (s4 weeks)	38 (25)	22 (25)	23 (31)	37 (25)	9 (23)	51 (27)
VTE in history	4 (3)	21 (23)	4 (5)	21 (14)	1 (2.5)	24 (13)
Co morbidity (%)						
Cancer	0	39 (43)	1 (1.5)	38 (25)	1 (2.5)	38 (20.5)
Heart failure	5 (4)	18 (20)	0	23 (15)	0	23 (12.5)
COPD	30 (22)	20 (22)	6 (8)	44 (29)	4 (10.5)	46 (25)
CAD	22 (16)	17 (19)	5 (7)	34 (22)	4 (10)	35 (19)
STROKE	6 (4.5)	4 (4.5)	0	10 (7)	0	10 (4.5)
Altered mental status	11 (8)	9 (10)	0	20 (13)	2 (5)	18 (10)
Clinical presentation (%)						
Dyspnea	124 (92)	81 (90)	68 (92)	137 (91)	33 (85)	172 (93)
Chest pain	61 (45)	26 (29)	42 (57)	45 (30)	24 (61)	63 (34)
Circulatory collapse	2 (1.5)	13 (15)	2 (3.5)	15 (10)	0	15 (8)
Heart rate ≥110 b/min	45 (33)	43 (49)	25 (34)	63 (42)	0	88 (48)
SBP <100 mmHg	11 (8)	35 (39)	11 (15)	35 (23)	8 (20)	38 (20)
Arterial oxygen saturation <90%	85 (63)	73 (81)	31 (42)	127 (85)	5 (13)	153 (83)
Respiratory rate ≥30/min	26 (19)	16 (18)	10 (13)	32 (21)	4 (10)	38 (30)
Temperature <30°C	0	0	0	0	0	0
Echo-pap median (±SD)	51 (20)	50 (17)	49 (21)	51 (18)	49 (25)	51 (18)
ECG-S1.Q3.T3 pattern	29 (22)	16 (18)	14 (19)	31 (20)	7 (18)	38 (21)

PESI: Pulmonary embolism severity index, SD: Standard deviation, VTE: Venous thromboembolism, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, SBP: Systolic blood pressure, ECG: Electrocardiogram

Table 3: Statistical characteristics of the models applied in the study

Scores	Models characteristics (%)			
	Sensitivity	Specificity	Positive predictive value	Negative predictive value
PESI				
≥I	94	21	27	92
≥II	83	59	38	92
≥III	52	84	50	85
≥IV	5	95	30	76
V	2	100	100	76
Geneva score high risk	83	30	27	85

PESI: Pulmonary embolism severity index

DISCUSSION

The results of the current study suggest that both PESI prognostic models accurately identify patients with acute PE, who are at low risk for short-term adverse events, including death. Only three of the low risk patients died within the first 30 days. Our results are consistent with previously published studies validating the original and simplified PESI.[9,11,13]

On the other hand, the 3 months overall mortality in the low risk groups according to the original PESI model has been reported to be between 0% and 1.2%.[9,11] The overall mortality in the low risk group of our study was 0.7% (95% CI, 0.2–1.1). The overall mortality in our high risk group was 27.5% (95% CI, 16.2–30.2). Although this is not consistent with another large validation study,[9] a recent cohort reported an overall mortality of 9% in the risk classes IV and V in the first 3 months. This discrepancy might be explained by the exclusion of patients with terminal illness such as metastatic cancer and several other co-morbidities.

Many clinical prediction rules have been developed to assess the risk of mortality or VTE recurrence or major hemorrhage in acute PE patients.[8-10] The GPS has been claimed to be the strongest and best score for identifying patients.[12] The PESI predicts very well the risk of death and recurrent bleeding episodes of VTE in the first 3 months as well. However, this model is not routinely used as it requires arterial blood gas and sonography. In a cohort study conducted on 599 low risk patients with acute symptomatic PE, a comparison between GPS and PESI showed that those

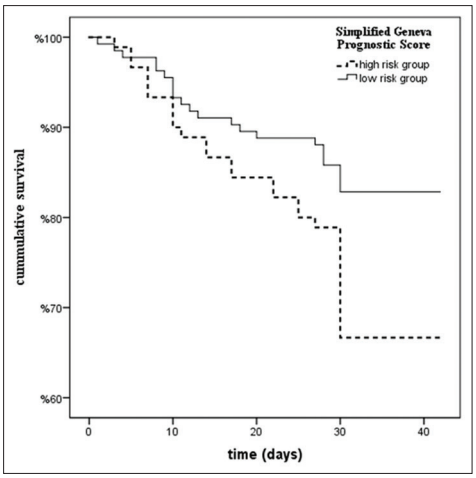

Figure 1: Survival rate on the basis of the simplified Geneva prognostic score (Kaplan–Meier graph) ($P < 0.006$)

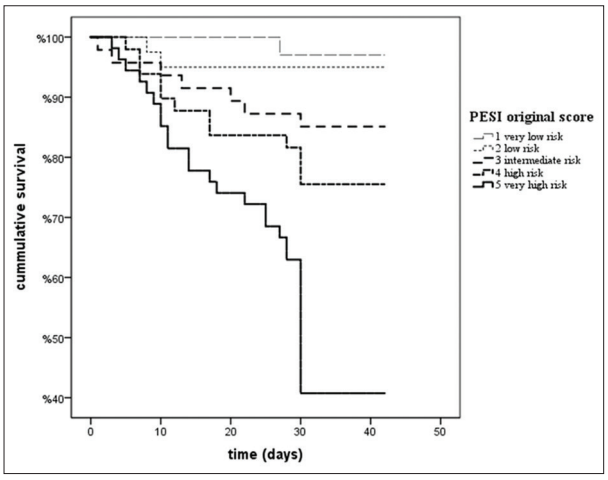

Figure 2: Patients' survival rate on the basis of the original PESI score (Kaplan–Meier graph) ($P < 0.0001$). PESI: Pulmonary Embolism Severity Index

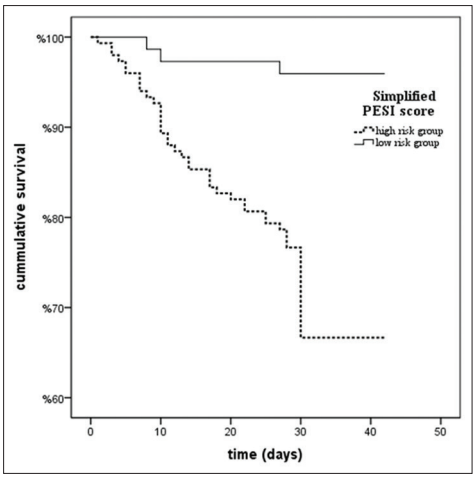

Figure 3: Patients' survival rate on the basis of the simplified PESI score (Kaplan–Meier graph) ($P < 0.0001$). PESI: Pulmonary Embolism Severity Index

predicted by PESI had lower mortality rates.[11] The PESI model classifies patients into five groups through 11 variables. Recently, the simplified PESI has been presented with a smaller scoring system with accuracy close to the original PESI.[8] The revised GPS that is a valid prognostic model is also used to diagnostically evaluate patients suspicious of PE.[6]

So far, only the simplified PESI model has yielded comparable results to those of earlier studies on the treatment of low risk outdoor patients.[11,12,14] Furthermore, diagrams exhibiting long-term examinations of PE patients indicate a change in mortality patterns after 1 month. The latter warrants the long-term assessment of clinical models in these patients.

Risk stratification of PE patients helps physicians determine the best treatment and appropriate circumstances for their initial treatment. Often, due to insufficient information about the effect and safety of outpatient treatment of PE, emergency physicians are not interested in discharging their PE patients for their outdoor management. The availability of a simple tool that can correctly predict the adverse outcomes of PE can be very valuable to physicians.[12] In its latest edition, the European Society of Cardiology offers solutions and strongly recommends that patients can be categorized on the basis of the following: Presence or absence of shock or stable hypotension, right ventricular dysfunction markers, and myocardial damage.[3] A systematic review has shown that patients with right ventricular dysfunction (upon echocardiography) and raised beta-natriuretic peptide or troponin levels have increased risk of developing the adverse effects as compared to those with normal levels of the aforementioned. Clinical models offer simpler and cheaper tools for the determination of low risk PE patients.[14-16]

In our study, the percentage of patients in different models categorized as low risk ranged from 20% to 70%. With such a range, the results of different models would be nonhomogenous; hence, drawing a specific line for low risk patients will help achieve more homogenous results.

Although the direct comparison of models is difficult when it comes to interpretation, we must admit that currently, PESI has the most integrated published data. Here too the mortality rate of patients classified as low risk by the simplified PESI was <1%.[13,15,16] Moreover, some researchers believe that re-calculating the PESI or simplified PESI after 48 h in patients admitted for acute PE could give a more accurate estimate of low risk patients and those who can be

discharged early for outpatient treatment.[17] Repeated calculations of the PESI or simplified PESI scores after 24–48 h can be considered a broad risk stratification strategy with a higher margin of safety.[13]

Our study had certain limitations, one of which was its retrospective nature. However, we did our best to avoid error when going through the emergency patients' admission files. The bias created by sample losses must also be kept in mind. Another limitation was the small number of samples, which can be explained by the shortage of time and population of patients under study. Our study needs to be supplemented by a more extensive study. Studies in tertiary hospitals that host patients with comorbidities have higher morbidity and mortality rates, which are mostly irrelevant to the risk being determined for the patients under study.

Based on the existent data, we cannot derive a definite conclusion of the optimal treatment of low risk PE patients. However, many studies have presented valuable data on the outpatient treatment of patients at home. Most of these studies are prospective cohort studies that have selected patients for treatment at home. Anyhow, the use of the simplified PESI in the current study could determine which patients to discharge earlier.

CONCLUSIONS

The simplified PESI model predicts the short-term adverse outcomes in low risk patients with PE such as death, lethal PE, recurrent VTE, and major bleeding episodes. According to earlier studies, patients categorized as high risk too were treated sufficiently as outpatients. However, further studies are required to determine the outpatient treatment of PE patients. Patients with a single episode of acute PE have different short-term and long-term prognoses. There are different ways of defining a short-term prognosis. On the other hand, there are few methods for determining long-term prognosis, which warrants further well-structured studies as well.

Clinical models based on simple clinical data routinely collected during clinical examinations are effective in determining PE patients with low risk for morbidity and mortality and other adverse outcomes. Therefore, calculating a prognostic score is beneficial when considering outpatient treatment. In any case before using any model for decision-making for PE treatment, the efficacy and safety of outpatient treatment of low risk patients should be approved by prospective studies.

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Conflicts of interest

There are no conflicts of interest.

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