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CHANGES IN PESI SCORE PREDICT MORTALITY IN INTERMEDIATE-RISK PATIENTS WITH ACUTE PE

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ABSTRACT

Background: Although the Pulmonary Embolism Severity Index (**PESI**) accurately identifies 35% of patients with acute pulmonary embolism (**PE**) as being low-risk, some patients deemed high-risk by the PESI on admission might be treated safely in the outpatient environment.

Methods: This retrospective cohort study included a total of 304 consecutive patients with acute PE, classified at the time of hospital admission into PESI class III. The PESI was recalculated 48 hours after admission ($PESI_{48}$) and reclassified each patient into the corresponding risk category. The primary outcome of the study was all-cause mortality between day 2 and day 30 after PE diagnosis.

Results: Twenty-six patients (8.5%; 95% CI, 5.4%-11.7%) died between day 2 and day 30 after PE diagnosis. Investigators reclassified 83 patients (27.3%; 95% CI, 22.3%-32.3%) as low-risk (classes I and II) at 48 hrs. Thirty-day mortality in these patients was 1.2% (95% CI 0%-3.5%) as opposed to 11.3% (95% CI, 7.1%-15.5%) in those who remained high risk. The net improvement in reclassification was estimated at 54% ($P < 0.001$).

Conclusions: In a cohort of intermediate-risk patients with acute PE, calculation of the $PESI_{48}$ allows identification of those patients at very low risk of dying during the first month of follow-up.

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INTRODUCTION

Venous thromboembolism (**VTE**) is a common and potentially life-threatening disorder, with > 600,000 incident cases occurring annually in the United States [1]. Rapid treatment with either unfractionated heparin (**UFH**), low-molecular weight heparin (**LMWH**), or fondaparinux clearly reduces the rate of recurrent and potentially fatal events [2]. Treatment with fixed dose subcutaneous UFH, LMWH or fondaparinux does not require laboratory monitoring and facilitates outpatient therapy or early discharge from the hospital. Outpatient therapy has become the standard of care for most patients with deep vein thrombosis (**DVT**) [3, 4]. However, since patients presenting with acute pulmonary embolism (**PE**) have worse short-term outcomes and a higher risk of fatal recurrent VTE than those who present solely with acute DVT [1], physicians are reluctant to treat them outside of the hospital setting.

Risk stratification of patients with PE may allow for accurate selection of low risk patients who are appropriate candidates for outpatient treatment. Two clinical models for determining prognosis in patients with PE, the Pulmonary Embolism Severity Index (**PESI**) and the simplified PESI (**sPESI**), have been extensively externally validated [5-8]. Both models consist of objective, easily identifiable factors that can be ascertained within minutes of a patient's presentation, and they do not require laboratory or imaging assessments **(Tables 1 and 2).** Although the PESI and the sPESI accurately identify one third of low-risk patients with acute symptomatic PE, it will overestimate risk in many others, as the overall mortality in higher risk groups is only 10% [9]. These data suggest that certain subgroups of patients initially deemed high-risk by the PESI or the sPESI might also be treated safely in an outpatient environment. Moreover, for a prognostic score (i.e., PESI and sPESI) to be valid, the measure should be responsive to treatments that improve survival.

This study aimed to assess the association between repeat PESI measured 48 hours after initiation of anticoagulant therapy (**$PESI_{48}$**) and the risk of all-cause mortality in patients with an objectively confirmed episode of acute symptomatic PE, who were classified at the time of hospital admission into class III on the

basis of the PESI. In addition, we sought to examine the utility of the simplified PESI scores in these patients at admission and after 48 hours (**sPESI and sPESI$_{48}$**) as another potential way to further stratify this intermediate risk group of patients.

METHODS

Study design

For a prospective registry, we attempted to enroll all patients with a diagnosis of acute PE between January 1, 2003, and May 31, 2009. All patients provided informed consent for their participation in the prospective registry in accordance with the requirements of the ethics committee of the hospital, and this study was approved by the human subjects committee.

Patients, setting, and eligibility criteria

Patients were recruited from the Emergency Department of Ramón y Cajal Hospital, Madrid, Spain. Eligibility for this study required that patients have acute symptomatic PE confirmed by objective testing. A diagnosis of PE was confirmed by either a high probability ventilation-perfusion scan result [according to the criteria of the Prospective Investigation of Pulmonary Embolism Diagnosis] [10], a lower limb venous compression ultrasonography positive for a proximal deep vein thrombosis in patients with inconclusive ventilation-perfusion scans [11], or previously described criteria to detect acute pulmonary embolism on contrast-enhanced PE-protocol helical chest CT [12]. Using prospectively collected baseline data at the time of PE diagnosis, investigators retrospectively calculated the PESI. The study considered for inclusion only patients who were assigned to class III (86-105 points) according to the PESI.

Study endpoints

The primary outcome used to validate the prediction rules was all-cause mortality between day 2 and day 30 after diagnosis of acute symptomatic PE. The secondary outcome was objectively confirmed non fatal symptomatic

recurrent VTE, or non fatal major bleeding. The primary analysis compared the mortality rates in the class III patients who could be reclassified as low risk at 48 hours ($PESI_{48}$ classes I and II) compared with those who remained high risk ($PESI_{48}$ classes III-V). As a secondary analysis, we compared outcomes in those class III patients who were also high risk sPESI who were, or were not, reclassified as low risk by the $sPESI_{48}$ (see **Figure 1** for study flow).

We assessed mortality using patient or proxy interviews, and/or hospital chart review. Patients with symptoms or signs of recurrent venous thromboembolism were evaluated with objective tests. Recurrent DVT was diagnosed by the appearance of a new noncompressible vein segment, or a 4-mm or more increase in the diameter of a thrombus on venous ultrasound, or a new intraluminal filling defect or an extension of a previous filling defect on a venogram [13]. Recurrent PE was confirmed either by a new perfusion scan defect involving 75% or more of a lung segment; or by the presence of a new intraluminal filling defect or an extension of a previous filling defect on helical chest CT [12]. Trained attending radiologists blinded to patient clinical information assessed the imaging studies. Bleeding complications were classified as “major” if they were overt and were either associated with a decrease in the hemoglobin level of 2.0 g/dL or more, required a transfusion of 2 units of blood or more, or were retroperitoneal or intracranial.

Treatment

Patients were initially hospitalized and treated with therapeutic doses of parenteral anticoagulants [intravenous unfractionated heparin or weight-based doses of subcutaneous low-molecular-weight heparin (enoxaparin)] while they were converted to oral vitamin K antagonist therapy. Thrombolytic treatment was instituted in patients with confirmed PE and hemodynamic impairment as deemed appropriate by the attending physician. After the initial “overlap” treatment period, patients were continued on dose-adjusted oral vitamin K antagonist therapy [acenocoumarol; target INR of 2.5 (therapeutic range 2.0-3.0)]. The INR was usually monitored daily until the therapeutic range had been achieved, then twice or three times weekly for the first weeks, and then once a week to once a month, depending on the stability of the results. Patients that

developed contraindications to anticoagulant therapy had an inferior vena cava filter placed and the anticoagulant discontinued.

Statistical analysis

Baseline characteristics are described with mean ± SD for continuous data and counts and proportions for categorical data. Two investigators (C.Z. and V.G.) assessed each patient's characteristics 48 hours after PE diagnosis, and determined their risk classification according to the criteria for the PESI and the simplified PESI. For the PESI, risk classes I and II were assigned to the low-risk category, while risk classes III-V were assigned to the high-risk category [5]. For the simplified PESI, patients were classified as low- (0 points) or higher-risk ($\geq$1 point) [6]. In cases of disagreement between the two investigators, a third investigator (D.J.) established the final score by consensus with the other investigators. For each prognostic model's risk classes, the proportion of patients with 30-day adverse outcomes (all cause mortality, or non fatal recurrent venous thromboembolism and non fatal major bleeding) was determined. Proportions of patients in cohort risk classes and proportions of patients with adverse events among groups were compared with the chi^2 test with Yates correction or Fisher's Exact Test, and the McNemar's test. To assess the test and performance characteristics of each prediction rules low-risk versus high-risk categories, we estimated sensitivity, specificity, and positive and negative predictive values. We examined the proportion of patients who would be reclassified into higher- or lower-risk when the PESI was calculated 48 hours after admission, and calculated the values of the net reclassification improvement (**NRI**) and the integrated discrimination improvement (**IDI**) [14]. We used Statistical Package for Social Sciences (SPSS, version 15.0, 2006, SPSS Inc.) to calculate estimated odds ratios (**OR**) and 95% confidence intervals (**CI**) from the binomial distribution.

RESULTS

Of the 4,713 patients evaluated for possible acute symptomatic PE during the study period, 1,136 (24%) had objectively confirmed PE. Since 16 patients (1.4%) refused to give informed consent, and 23 (2.0%) were lost to follow-up, the evaluable population consisted of 97% (1,097 patients) of eligible patients with acute PE. Of these, the PESI classified 13.5% of patients (148/1,097) as class I, 21.3% (234/1,097) as class II, 19.4% (213/1,097) as class IV, and 17.8% (195/1,097) as class V. The PESI classified 307 patients (28.0%) as class III, of whom 3 died within the first 48 hours after diagnosis of PE, leading to a final study sample of 304 patients (**Figure 1**).

Table 3 shows the patients' clinical symptoms, predisposing conditions, and relevant findings at presentation. Of the 304 patients in the study sample, 26 (8.5%; 95% CI, 5.4%-11.7%) died between day 2 and day 30 after PE diagnosis. All patients had the primary and secondary outcomes assessed. Overall, 15 patients (57.7%) died from definite or possible PE, 1 (3.8%) from intracraneal bleeding, and 10 (38.5%) from other causes (cancer 5, infection 3, renal failure 1, seizures 1). Seven patients reached the secondary endpoint: 3 patients had an episode of objectively confirmed non fatal symptomatic recurrent VTE, and 4 patients had an episode of non fatal major bleeding. Treatment information was available for all patients that were enrolled in the study. Of the 304 patients, 272 patients (89%) received initial therapy with low-molecular-weight heparin, 30 (9.9%) received unfractionated heparin, 5 (1.6%) received an inferior vena cava filter, and 10 (3.3%) received thrombolytic therapy.

Investigators reclassified 83 of 304 patients (27.3%; 95% CI, 22.3%-32.3%) as low-risk (classes I and II) when the PESI was calculated 48 hours after diagnosis of PE (**$PESI_{48}$**). Reclassification was due to changes in heart rate in 23 patients, systolic blood pressure in 3 patients, respiratory rate in 8 patients, temperature in 23 patients, and arterial oxyhemoglobin saturation in 29 patients. The 27.3% (83/304) of patients classified as low-risk by the $PESI_{48}$ had a 30-day mortality of 1.2% (95% CI, 0%-3.5%), compared to the 11.3% (95% CI,

7.1%-15.5%) in the high-risk group. Of note, 16 patients were reclassified into classes IV (n = 7) or V (n = 9) when the PESI was calculated 48 hours after diagnosis of PE, and mortality in this group of patients was 50% (95% CI, 25.5%-74.5%). Two hundred and five patients remained Class III after 48 hours. Seventeen of these patients died. Mortality was 8.3% (95% CI, 4.5-12.1%).

Of the 304 patients who were PESI class III on admission, 250 of them were also high risk according to the sPESI. At 48 hours, 38 out of 250 patients (15.2%; 95% CI, 10.7%-19.6%) were reclassified as low-risk (**$sPESI_{48}$**). These patients had a 30-day mortality of 0%, compared to 12.3% (95% CI, 7.8%-16.7%) in the group that remained high-risk group.

The $PESI_{48}$ low-risk patients and the $sPESI_{48}$ low-risk patients had a similar mortality (0% [0/84] vs 1.2% [1/83]) during follow-up. The 30-day rate of non fatal recurrent VTE or major bleeding was similar for both prediction rules' low-risk strata (2.4% [95% CI, 0%-5.7%] versus 4.8% [95% CI, 0.2%-9.3%]).
The sensitivity, specificity and predictive values for the $PESI_{48}$ for predicting 30-day mortality and all adverse outcomes are listed in **Table 4**. Characteristics of the $sPESI_{48}$ as an additional risk stratification tool are listed in **Table 5**.

The net improvement in reclassification (**NRI**) was estimated at 54% ($P < 0.001$) with the $PESI_{48}$, resulting from a net 27% increase in non survivors correctly identified as being at high risk and a net 26% increase in survivors correctly identified as at lower risk. The integrated discrimination improvement (**IDI**) was estimated as -0.03 ($P < 0.001$). Heart rate $\geq$ 110/min resulted in a net 28% increase in survivors correctly identified as being at low risk. Systolic blood pressure < 100 mm Hg resulted in a 3.6% increase; respiratory rate $\geq$ 30/min resulted in a 9.7% increase; temperature < 36ºC resulted in a 28% increase, and arterial oxyhemoglobin saturation < 90% resulted in a 34% increase. None of the patients who were reclassified with the $sPESI_{48}$ died during follow-up. Calculation of the $sPESI_{48}$ resulted in a net 11% increase in survivors correctly identified as being at low risk. The IDI was estimated as -0.02 ($P < 0.001$).

DISCUSSION

The current analysis describes longitudinal changes of the PESI and the simplified PESI in a cohort of patients with intermediate-risk acute PE. The results suggest that the PESI and the simplified PESI change after first 48 hours of therapeutic intervention and that this change relates to subsequent mortality.

Patients with PE present with a wide spectrum of signs and symptoms, which, in the context of other co-morbidities, determines the intensity of treatment and the treatment setting. The PESI score has been shown to accurately identify patients who are low risk for short-term adverse events, such as death, recurrent VTE, fatal PE, and major bleeding [7, 8, 15]. Moreover, an international, randomized trial showed that low-risk patients (PESI classes I and II) with acute symptomatic PE can be safely treated as outpatients [16]. Although the PESI accurately identifies aproximately one third of patients with acute symptomatic PE as low-risk [17], it may overestimate the risk in many others [18] that might still benefit from early discharge.

Our data provide important insight into how short-term changes in a composite prognostic index can be used to predict mortality in a large group of treated patients with intermediate-risk PE. We noted that a decrease in PESI and sPESI after 48 hours of treatment was associated with decreased subsequent mortality during follow-up. Perhaps more importantly, patients reclassified into the high risk category had very high short term mortality. Changes in the PESI at 48 hours were mostly attributable to improved heart rate, temperature, and arterial oxyhemoglobin saturation.

Though different studies have suggested that transthoracic echocardiography and cardiac biomarkers should be combined to optimize risk stratification and to further classify intermediate-risk patients with acute symptomatic PE [19, 20], the clinical benefit of early thrombolytic treatment has not been demonstrated for this group of patients [21]. Thus, an approach might consist of the performance of serial echocardiographic testings and biomarker measurements.

However, echocardiography is not routinely performed in patients with PE, and it is an operator-dependent and time consuming modality. Our results suggest that calculation of the PESI 48 hours after diagnosis of PE is an accurate and simple method for characterizing early response to treatment; it allowed identification of an additional 8% of patients with acute PE who had very low risk of dying during the first month of follow-up. On the other hand, mortality of those patients who were reclassified into classes IV and V 48 hours after diagnosis of PE was as high as 50%. These patients should be observed in a monitored setting and future studies should assess if prognostic properties of echocardiography and cardiac biomarkers are improved in this subgroup of patients with high PESI scores despite standard anticoagulant treatment. Perhaps this is an additional group of patients that might benefit from thrombolysis.

Some limitations of our study should be noted. Since the study did not mandate treatment, we could not estimate the potential impact of treatment on patient outcomes. Second, although investigators prospectively collected clinical data in the cohort, we retrospectively calculated the clinical scores. Importantly, the sPESI was only calculated after the PESI, so a direct comparison of the two scores may not be viable. Finally, our study did not directly assess the impact of the clinical models on the management of PE. Thus, future studies will need to address the usefulness of the recalculation of clinical scores for identifying intermediate-risk patients who can be discharged early.

In conclusion, this study suggests that the PESI and the simplified PESI change after first 48 hours of therapeutic intervention and that this change relates to subsequent mortality. These data provide support that the PESI and the simplified PESI may be used to identify patients with acute PE for an abbreviated hospital stay.

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Study concept and design: Moores, Gómez, Aujesky, Yusen, Jiménez
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The corresponding author, David Jiménez, had full access to all the data in the study and had final responsibility for the decision to submit for publication.

APPENDIX

Members of the IRYCIS Pulmonary Embolism Study Group

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Table 1. The Pulmonary Embolism Severity Index (PESI)

Patient Age in years
Male patient? Yes +10
History of cancer? Yes +30
History of heart failure? Yes +10
History of chronic lung disease? Yes +10
Heart rate ≥ 110? Yes +20
Systolic blood pressure < 100 mmHg? Yes +30
Respiratory rate ≥ 30/min? Yes +20
Temperature < 36° C / 96.8° F? Yes +20
Altered mental status? Yes +60
O_2 saturation < 90% on room air? Yes +20

The PESI risk score is calculated by starting with the patient's age and adding additional points for any factors present as noted above. The patients are divided into 5 risk classes based upon the point total as follows:
Class I : <65 points
Class II: 66-85 points
Class III: 86-105 points
Class IV: 106-125 points
Class V: >126 points

Table 2. The Simplified Pulmonary Embolism Severity Index (sPESI)

Age > 80 years
History of Cancer
History of heart failure or chronic lung disease
Heart rate ≥110/min
Systolic blood pressure < 100 mmHg
O_2 saturation < 90% on room air

Patients receive a point for each item present. Patients with 0 points are low risk, patients with one or more points are high risk.

Table 3. Baseline characteristics of 304 study patients*

	Patients N (%)
Clinical characteristics,	
Age > 65 years	235 (77%)
Male gender	139 (46%)
Risk factors for VTE,	
Cancer	63 (21%)
Surgery	27 (8.9%)
Immobility for ≥ 4 days	71 (23%)
Previous VTE	36 (12%)
Comorbid diseases,	
Chronic lung disease	21 (6.9%)
Congestive heart failure	20 (6.6%)
Clinical presentation at admission,	
Syncope	43 (14%)
Chest pain	120 (39%)
Dyspnea	225 (74%)
Altered mental status	0 (0%)
Heart rate ≥ 110 bpm	46 (15%)
Arterial oxyhemoglobin saturation < 90%	64 (21%)
Respiratory rate ≥ 30/min	19 (6.2)
SBP < 100 mm Hg	5 (1.6%)
Simplified PESI risk classes	
Low-risk	54 (18%)
High-risk	250 (82%)

Abbreviations: VTE, venous thromboembolism; SBP, systolic blood pressure; PESI, Pulmonary Embolism Severity Index.

*PESI risk class III at the time of hospital admission.

Table 4. Test characteristics of $PESI_{48}$ for predicting 30 day all-cause mortality and adverse outcomes

	30-day mortality (95% CI)	Adverse outcomes (95% CI)
Sensitivity,%	96.1 (88.8-100)	71.4 (38.0-100)
Specificity,%	29.5 (24.1-34.9)	27.3 (22.2-32.3)
Positive predictive value,%	11.3 (7.1-15.5)	2.3 (0.3-4.2)
Negative predictive value,%	98.8 (96.4-100)	97.6 (94.3-100)
Positive likelihood ratio	1.4 (1.2-1.5)	1.0 (0.6-1.6)
Negative likelihood ratio	0.1 (0.02-0.9)	1.0 (0.3-3.4)

Abbreviations: PESI, Pulmonary Embolism Severity Index; CI, confidence interval.

Table 5. Test characteristics of simplified $PESI_{48}$ for predicting 30-day all-cause mortality and adverse outcomes

	30-day mortality (95% CI)	**Adverse outcomes (95% CI)**
Sensitivity,%	100 (100-100)	42.9 (6.2-79.5)
Specificity,%	30.2 (24.8-35.6)	26.9 (21.9-32.0)
Positive predictive value,%	11.8 (7.5-16.1)	1.4 (0-2.9)
Negative predictive value,%	100 (100-100)	95.2 (90.7-99.8)
Positive likelihood ratio	1.4 (1.3-1.5)	0.6 (0.2-1.4)
Negative likelihood ratio	0	2.1 (1.1-4.1)

Abbreviations: PESI, Pulmonary Embolism Severity Index; CI, confidence interval.

Figure 1. Flow- Diagram of Patient Enrollment and Outcomes