ERJ Express. Published on July 22, 2010 as doi: 10.1183/09031936.00070110

USEFULNESS OF THE SHOCK INDEX AND THE SIMPLIFIED PULMONARY EMBOLISM SEVERITY INDEX FOR IDENTIFICATION OF LOW-RISK PATIENTES WITH ACUTE PULMONARY EMBOLISM

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Short title: Shock index vs simplified PESI

Word count: 2,711

June 10, 2010

ABSTRACT

We compared the test characteristics of the Shock Index (**SI**) and the simplified Pulmonary Embolism Severity Index (**sPESI**) for predicting 30-day outcomes in a cohort of 1,206 patients with objectively confirmed pulmonary embolism (**PE**). The primary outcome of the study was all-cause mortality. The secondary outcome was non fatal symptomatic recurrent VTE or non fatal major bleeding. Overall, 119 out of 1,206 patients died (9.9%; 95% confidence interval [**CI**], 8.2% to 11.5%) during the first month of follow-up. The sPESI classified fewer patients as low risk (31% [369/1,206], 95% CI: 28% to 33%) compared to the SI (85% [1,024/1,206], 95% CI: 83% to 87%) (P < 0.001). Low-risk patients based on the sPESI had a lower 30-day mortality than those based on the SI (1.6% [95% CI, 0.3-2.9] versus 8.3% [95% CI, 6.6-10.0]), while the 30-day rate of non fatal recurrent VTE or major bleeding was similar (2.2% [95%CI, 0.7% to 3.6%] versus 3.3% [95%CI, 2.2% to 4.4%]). The net reclassification improvement with the sPESI was 13.4% (P = 0.07). The integrated discrimination improvement was estimated as 1.8% (P < 0.001). The sPESI quantified the prognosis of patients with PE better than the SI.

Abstract word count: 194

Key words: Lung, prognosis, thrombosis, pulmonary embolism.

INTRODUCTION

Recent guidelines emphasize the importance of early risk stratification of patients with acute pulmonary embolism (**PE**) (1). Risk stratification of patients with PE may identify patients at high risk of early death who may benefit from more intensive surveillance or aggressive therapy (2, 3). Alternatively, patients deemed low risk for early complications (i.e., death, recurrent VTE, and major bleeding) might be considered for partial or complete outpatient treatment of their PE (4, 5).

The Pulmonary Embolism Severity Index (**PESI**) was developed to estimate 30-day mortality in patients with acute PE. The PESI used objective clinical items to produce a risk stratification score. Some investigators have used the PESI to identify patients with a low mortality risk who may be suitable for home management (6-8). Use of the PESI may not be practical for routine application in busy hospital emergency departments because it requires computation of a score based on 11 different variables, and each variable has a different weight. Recently, Jimenez et al developed a simplified version of the PESI (i.e., simplified PESI) (9). The simplified PESI included the variables of age (> 80 years vs. other), history of cancer, history of chronic cardiopulmonary disease, heart rate ($\geq$ 110 beats/minute vs. other), systolic blood pressure (< 100 mm Hg vs. other), and oxyhemoglobin saturation (< 90% vs. other). Patients with none of the variables present are categorized as low-risk, and those with any variable present are categorized as high-risk. The study showed that the simplified PESI successfully predicts 30-day mortality after acute symptomatic PE, and reduces the complexity of the original prediction rule.

The shock index (**SI**), defined as heart rate divided by systolic blood pressure, is an independent predictor of 30-day mortality in patients with acute PE (10). In a novel management strategy, shock index was used to accelerate the triage of patients with suspected acute PE. Those with a shock index $\geq$ 1 and right ventricular (**RV**) dysfunction on echocardiogram received early reperfusion therapy to avoid lengthy imaging tests (11). Alternatively, shock index showed a

high sensitivity to identify a subgroup of patients at low risk of death in a multinational cohort (RIETE registry) of patients with acute PE (10).

Since the simplified PESI and the shock index are easily measurable and might be accurate for identifying low-risk patients with acute PE in real-world clinical situations, this study aimed to compare both prediction rules in a large sample of ambulatory patients with acute symptomatic PE. The study also assessed the ability of the prediction rules to identify low-risk patients with acute PE who might be candidates for treatment in the outpatient setting.

METHODS

Study design

Using prospectively collected baseline data at the time of PE diagnosis and outcome data from this cohort, we retrospectively assessed the test characteristics of the shock index and the simplified PESI for predicting 30-day mortality, non fatal recurrent venous thromboembolism, and non fatal major bleeding. We then assessed the ability of the prediction rules to identify low-risk patients with acute PE who could be candidates for treatment in the outpatient setting. 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 ethics committee.

Patients, setting, and eligibility criteria

Patients were recruited from the Emergency Department of Ramón y Cajal Hospital, Madrid, Spain, between January 1, 2003, and December 31, 2009. Eligible patients were required to 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] (12), a lower limb venous compression ultrasonography positive for a proximal deep vein thrombosis in patients with inconclusive ventilation-perfusion scans (13), or previously

described criteria to detect acute pulmonary embolism on contrast-enhanced PE-protocol helical chest CT (14).

Study outcomes

The primary outcome used to validate the prediction rules was all-cause mortality 30 days after diagnosis of acute symptomatic PE. The secondary outcome was objectively confirmed non fatal symptomatic recurrent VTE, or non fatal major bleeding. We assessed mortality using patient or proxy interviews, and/or hospital chart review. One investigator (D.J.) adjudicated the cause of all deaths as (1) definite fatal PE, and (2) possible fatal PE, or (3) death from other causes. Death was judged to be definite fatal PE if it was confirmed by autopsy, or if death followed a clinically severe PE, either initially or shortly after an objectively confirmed recurrent event, in the absence of any alternative diagnosis. Possible fatal PE consisted of death in a patient who died suddenly or unexpectedly. 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 (15). 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 (14). 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. We calculated the simplified PESI score for each patient. Patients were classified as low- (0 points) or higher-risk ($\geq$1 point) (9). Patients with a shock index (heart rate divided by systolic blood pressure) of <1 were defined as low-risk whereas those with a shock index of $\geq$ 1 were considered higher-risk. We calculated the proportion of low-risk vs higher-risk patients based on each prognostic model and determined the proportion of patients with 30-day adverse outcomes (all cause mortality, or non fatal recurrent venous thromboembolism and non fatal major bleeding) among low- vs higher-risk patients. 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 test accuracy, we estimated sensitivity, specificity, and positive and negative predictive values and likelihood ratios for each model. We compared the discriminatory power of the two models by comparing the area under each receiver operating characteristic (**ROC**) curve (C statistic). We examined the proportion of patients who would be reclassified into higher- or lower-risk categories between the shock index and the simplified PESI, and calculated the values of the net reclassification improvement (**NRI**) and the integrated discrimination improvement (**IDI**) comparing both prognostic models (16). Ninety-five percent confidence intervals (**CI**) were computed form the binomial distribution by using Statistical Package for Social Sciences (version 15.0, 2006, SPSS Inc., Chicago, Illinois).

RESULTS

Of the 5,213 patients evaluated for possible acute symptomatic PE during the study period, 1,248 (24%) had objectively confirmed PE. Of these, 13 (1.0%) refused to give informed consent, and 29 (2.3%) were lost to follow-up, leading to a final study sample of 1,206 patients. Of these, 1,145 had a positive spiral computerized tomography, a high-probability ventilation-perfusion lung scan, or both, and 61 had a non-diagnostic ventilation-perfusion lung scan and a proximal deep vein thrombosis documented by compression ultrasonography. A fraction of patients (n = 995) was included in a previous study which developed the simplified PESI clinical prediction rule (9).

Table 1 shows the patients' clinical symptoms, predisposing conditions, and relevant findings at presentation. The overall number of patients treated with inferior vena cava filters was small (1.8%; 22 of 1,206 patients). Three percent (38 of 1,206 patients) of patients were treated with thrombolytic therapy. We had echocardiographic data on 675 patients. Right ventricle dysfunction was present in 39.7% of patients (268 of 675 patients). Of these, 30 patients received thrombolytic therapy (11.2%; 95% CI, 7.4 to 15.0). Of the 1,206 patients in the study sample, 119 (9.9%; 95% CI, 8.2-11.5) died within thirty days of presentation. Overall, 58 patients (48.7%) died from definite or possible PE, 7 (5.9%) from bleeding, and 54 (45.4%) from other causes. Among the seven fatal bleeding events, three were intracranial, two retroperitoneal, and two gastrointestinal. Forty-two patients reached the secondary endpoint; 10 patients had an episode of objectively confirmed non fatal symptomatic recurrent VTE, 28 patients had an episode of non fatal major bleeding, and 4 patients both bled and recurred.

For 30-day all-cause mortality, survival was lower in the sPESI high-risk group compared to the sPESI low-risk group (log rank $p<0.001$; **figure 1**). For 30-day all-cause mortality, survival was lower in the SI high-risk group compared to the SI low-risk group (log rank $p<0.001$; **figure 2**). Using patients in this study cohort, the sPESI classified a significantly lower proportion of patients as low risk (31% [369/1,206], 95% CI: 28% to 33%) than the SI score (85%

[1,024/1,206], 95% CI: 83% to 87%) ($P < 0.001$). Compared to the SI low-risk patients the sPESI low-risk patients had a lower mortality (8.3% [85/1,024] vs 1.6% [6/369]) (**Table 2**). The sPESI high-risk patients had a slightly lower mortality (13.5% [113/837]) compared to the SI high-risk patients (18.7% [34/182]). The 30-day rate of non fatal recurrent VTE or major bleeding was similar for both prediction rules' low-risk strata (2.2% [95%CI, 0.7% to 3.6%] versus 3.3% [95%CI, 2.2% to 4.4%]).

The simplified PESI had a substantially higher sensitivity, a higher negative predictive value, and a lower negative likelihood ratio than the SI for predicting 30-day mortality in the study cohort (**Table 3**). The simplified PESI (C statistic 0.71; 95% CI, 0.68 to 0.73) had a better discriminatory power than the SI (C statistic 0.63; 95% CI, 0.61 to 0.66) to predict 30-day mortality ($P = 0.018$). When 30-days adverse events were considered, the negative predictive value for the simplified PESI low-risk strata was 98% compared to 97% for the SI (**Table 4**). When 30-days overall mortality was considered in the subgroup of 1,103 normotensive patients (i.e., systolic blood pressure $\geq$ 100 mm Hg) with acute PE, the negative predictive value for the simplified PESI (sPESI) low-risk strata was 98.4% compared to 92.0% for the SI. When 30-days adverse events were considered, the negative predictive value for the sPESI low-risk strata was 97.8% compared to 96.6% for the SI.

For 79 patients in this study's cohort who died, reclassification was more accurate when the simplified PESI was used, and for 0 participants, it became less accurate. Among the subjects who did not die, 5 were reclassified in a lower risk category and 581 were reclassified in a higher risk category. The net improvement in reclassification (**NRI**) was estimated at 0.13 (P = 0.07) with the simplified PESI, resulting from a net 66.4% increase in non survivors correctly identified as being at high risk but a net 53.0% increase in survivors incorrectly identified as at higher risk. The integrated discrimination improvement (**IDI**) was estimated as 0.018 (P < 0.001). Compared to the shock index, a history of cancer resulted in a net 49% increase in non survivors correctly identified as being at high risk. Age > 80 years resulted in a 36% increase; oxyhemoglobin

saturation < 90% resulted in a 34% increase, and chronic cardiopulmonary disease resulted in a 24% increase.

DISCUSSION

This study shows that the simplified PESI successfully predicts 30-day mortality after acute symptomatic PE. Compared to the shock index, the simplified PESI has better prognostic accuracy. Our findings further validate a previously developed simple prognostic score (i.e., sPESI) for patients with acute symptomatic PE.

Clinical prognostic models were developed to identify low-risk patients with PE who may be candidates for outpatient care or an abbreviated hospital stay (16, 17). The most widely validated prognostic model is the Pulmonary Embolism Severity Index (**PESI**) that accurately stratifies patients into 5 risk classes (I–V) with increasing risk of short-term mortality, ranging from 1.1% in class I to 24.5% in class V (17). However, the original PESI uses 11 clinical parameters, with different assigned weights, and its scoring depends on calculations that may be difficult to apply in the clinical setting. Both the sPESI and the SI might be suitable for use in busy emergency departments, but their prognostic accuracy had not been assessed in a head-to-head comparison.

In our sample, the sPESI and the SI model showed a large discrepancy in the classification of low-risk patients. The two models demonstrated different rates of outcomes for the low-risk groups. The sPESI demonstrated a higher discriminatory power for predicting 30-day mortality than the SI. Low risk patients identified using the sPESI had a lower mortality and a higher negative predictive value for death than low-risk patients identified using the SI. Low-risk patients identified by the sPESI showed a negligible 30-days risk of death as shown by a negative predictive value of 98%. The negative predictive value of 98% for 30-days adverse events in the low-risk categories makes this score very useful for selecting patients for outpatient treatment. Because the simplified PESI was specifically developed to identify low-risk patients with PE,

the positive predictive values (11-16%) and the positive likelihood ratios (1.34-1.51) for predicting mortality were low.

The C statistic is the most commonly used method of determining model discrimination; that is, how well the model can discriminate between persons in whom the outcome of interest will develop and those who will not. In the present study, we also evaluated recently described measures of model discrimination (NRI and IDI), which appear to be more sensitive tests of improvement in model discrimination than the C statistic analyses (18). In our study, the sPESI reclassified 66% of non survivors as high risk patients. Moreover, an IDI of 0.018 suggests that the sPESI identifies low-risk patients with acute PE significantly better than the SI.

In our study, only half of the deaths were due to PE. This proportion of PE-related deaths is similar to that of the International Cooperative Pulmonary Embolism Registry (**ICOPER**) (19) and the RIETE registry (20). The variables that are used to calculate the SI (heart rate and systolic blood pressure) express the cardiopulmonary consequences of PE. We believe that the simplified PESI is more useful because it adds one domain that quantifies the age of the patients, and two domains that capture coexisting illness (cancer and chronic cardiopulmonary disease).

This study has limitations. The main limitation is the larger part of the study cohort (82%) was used to derive the sPESI. So, we actually expect that the sPESI outperforms any other prognostic model in this cohort. However, the study demonstrates nevertheless the suboptimal performance of the SI to identify low-risk patients with acute symptomatic PE. Second, although investigators prospectively collected clinical data in the study cohort, we performed a retrospective analysis, which can be subject to various biases. Third, we could not estimate the potential impact of treatments on patient outcomes, because this information was not consistently available in our sample.

In summary, the study demonstrates that the simplified PESI has better prognostic accuracy than the shock index. Our study did not directly assess the impact of the simplified PESI on the management of PE. Future studies should address if this clinical prediction rule may help identify low-risk patients, and thus possible candidates for home treatment.

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Conflict of interest statement

None reported.

Acknowledgements

This work has been supported in part by grants FIS 08/0200 and SEPAR 2008.

Table 1. Clinical symptoms and relevant findings at presentation in 1,206 consecutive patients with acute symptomatic pulmonary embolism

		30-day mortality	
Characteristic	**Patients, n (%)**	**Yes (n = 119)**	**No (n = 1,087)**
Demographic factors			
Age, years	69.3 ± 16.1	73.4 ± 15.0	68.9 ± 16.1
Age > 80 years	300 (25%)	46 (39%)	254 (23%)
Male sex	536 (44%)	53 (45%)	483 (44%)
Comorbid illness			
Cancer†	282 (23%)	54 (45%)	228 (21%)
Heart failure	82 (7%)	15 (13%)	67 (6%)
Chronic lung disease	94 (8%)	15 (13%)	79 (7%)
Clinical findings			
Pulse, beats/min	92.5 ± 19.5	98.7 ± 22.1	91.8 ± 19.0
Pulse ≥ 110 beats/min	226 (19%)	34 (29%)	192 (18%)
Systolic blood pressure, mm Hg	128.8 ± 25.7	121.3 ± 29.9	129.6 ± 25
Systolic blood pressure < 100 mm Hg	103 (8%)	22 (18%)	81 (7%)
Respiratory rate ≥ 30 breaths/min	86 (7%)	9 (8%)	77 (7%)
Temperature < 36ºC	126 (10%)	13 (11%)	113 (10%)
Altered mental status¥	17 (1%)	4 (3%)	13 (1%)
Arterial oxyhemoglobin saturation (SaO_2) < 90%	300 (25%)	44 (37%)	256 (24%)
PESI risk classes*			
I	173 (14%)	4 (3%)	169 (15%)
II	258 (21%)	12 (10%)	246 (23%)
III	332 (28%)	28 (24%)	304 (28%)
IV	262(22%)	35 (29%)	227 (21%)
V	181 (15%)	40 (34%)	141 (13%)

Abbreviations: PESI, Pulmonary Embolism Severity Index.

†Active or under treatment in the last year.

¥Defined as confusion, disorientation, or somnolence.

*The PESI score corresponds with the following risk classes: < 65 class I; 66-85 class II; 86-105 class III; 106-125 class IV; and > 125 class V. Patients in risk classes I and II are defined as low-risk.

Table 2. 30-day mortality and non fatal adverse events based on the shock index and the simplified PESI

	Study sample *Percent (95% confidence interval)*		
	Patients (N = 1,206)	**Deaths* (N = 119)**	**Non fatal adverse events* (N = 42)**
SI (11)			
Low-risk	84.9 (82.9-86.9)	8.3 (6.6-10.0)	3.3 (2.2-4.4)
High-risk	15.1 (13.1-17.1)	18.7 (13.0-24.3)	4.4 (1.4-7.4)
	Patients	**Deaths**	**Non fatal adverse events**
Simplified PESI (9)			
Low-risk	30.6 (28.0-33.2)	1.6 (0.3-2.9)	2.2 (0.7-3.6)
High-risk	69.4 (66.8-72.0)	13.5 (11.2-15.8)	4.1 (2.7-5.4)

Abbreviations: SI, shock index; PESI, Pulmonary Embolism Severity Index.

*Per risk stratum

Table 3. Simplified PESI and shock index prediction rule test characteristics for 30-day mortality

	Simplified PESI Parameter (95% CI)	SI Parameter (95% CI)
Sensitivity, %	95.0 (91.0-98.9)	28.6 (20.4-36.7)
Specificity, %	33.4 (30.6-36.2)	86.4 (84.3-88.4)
Positive predictive value, %	13.5 (11.2-15.8)	18.7 (13.0-24.3)
Negative predictive value, %	98.4 (97.1-99.7)	91.7 (90.0-93.4)
Positive likelihood ratio	1.43 (1.34-1.51)	2.10 (1.52-2.89)
Negative likelihood ratio	0.15 (0.07-0.33)	0.83 (0.74-0.93)

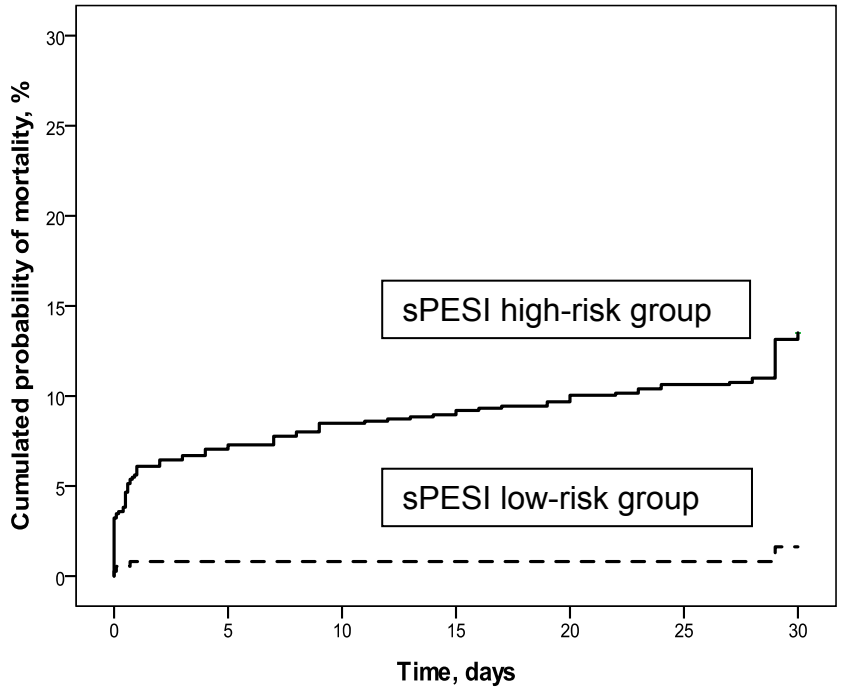
Abbreviations: PESI, Pulmonary Embolism Severity Index; SI, shock index; CI, confidence interval

Table 4. Simplified PESI and shock index prediction rule test characteristics for 30-day non fatal adverse events

	Simplified PESI Parameter (95% CI)	SI Parameter (95% CI)
Sensitivity, %	80.9 (69.1-92.8)	19.0 (7.2-30.9)
Specificity, %	31.0 (28.4-33.7)	85.0 (83.0-87.1)
Positive predictive value, %	4.1 (2.7-5.4)	4.4 (1.4-7.4)
Negative predictive value, %	97.8 (96.3-99.3)	96.7 (95.6-97.8)
Positive likelihood ratio	1.17 (0.83-1.21)	1.27 (0.52-1.92)
Negative likelihood ratio	0.61 (0.56-1.78)	0.95 (0.88-1.14)

Abbreviations: PESI, Pulmonary Embolism Severity Index; SI, shock index; CI, confidence interval

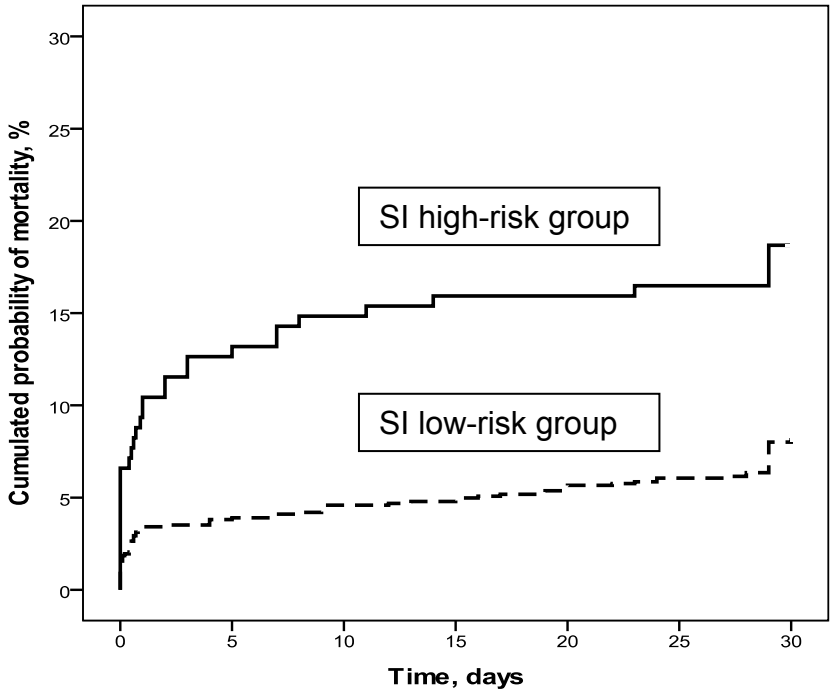
Figure 1. Kaplan-Meier 30-day all-cause mortality of positive and negative simplified PESI (sPESI) test groups



No. at Risk

sPESI high-risk group	837	778	766	762	756	748	724
sPESI low-risk group	369	366	366	366	366	366	363

Figure 2. Kaplan-Meier 30-day all-cause mortality of positive and negative shock index (SI) test groups



No. at Risk							
SI high-risk group	182	159	154	153	153	152	148
SI low-risk group	1024	985	977	975	969	962	939