Article type : Original Article - Clinical Haemostasis and Thrombosis

Prediction of short-term prognosis in elderly patients with acute pulmonary embolism: validation of the RIETE score

Running head: Validation of the RIETE score

Authors: E. Jaquet *, T. Tritschler *, O. Stalder †, A. Limacher †, M. Méan *‡, N. Rodondi *§, D. Aujesky *

Author Affiliations: *Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland; †CTU Bern, and Institute of Social and Preventive Medicine (ISPM), University of Bern, Switzerland; ‡Division of Internal Medicine, Lausanne University Hospital, Switzerland; §Institute of Primary Health Care (BIHAM), University of Bern, Switzerland

Correspondence: Tobias Tritschler, Department of General Internal Medicine, Inselspital, Bern University Hospital, 3010 Bern, Switzerland

Email: tobias.tritschler@insel.ch

Phone: +41 (0)31 632 21 11; Fax: +41 (0)31 632 88 85

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jth.14137

Trial Registration: http://clinicaltrials.gov. Identifier: NCT00973596

Key words: Elderly; Mortality; Prediction; Prognosis; Pulmonary embolism

ESSENTIALS

- The RIETE score was derived to predict 10-day adverse outcomes in acute pulmonary embolism (PE).
- We externally validated the RIETE score in a prospective cohort of patients with PE.
- The RIETE score classified fewer patients as low-risk than currently recommended scores.
- The RIETE score was not superior to other scores in predicting 10-day adverse outcomes.

SUMMARY

Introduction: The RIETE score was derived to identify patients with pulmonary embolism (PE) at low risk of overall complications.

Objective: To externally validated the RIETE score and compared its prognostic performance to the Pulmonary Embolism Severity Index (PESI), its simplified version (sPESI), and the Geneva Prognostic Score (GPS).

Methods: In a prospective multicenter cohort, we studied 687 elderly patients with acute PE. The primary outcome was 10-day overall complications (death, recurrent PE, or major bleeding), the secondary outcome was 30-day overall mortality. We compared complications and mortality in low- vs. higher-risk patients and the area under the receiver operating characteristic (ROC) curve across scores.

Results: Overall, 27 patients (3.9%) had complications within 10 days and 22 (3.2%) died within 30 days. The RIETE score classified a smaller proportion of patients as low-risk (31%) than the PESI (35%), sPESI (36%), and the GPS (90%). The proportion of low-risk patients based on the RIETE score, PESI, sPESI, and GPS who had complications was 1.9%, 1.7%, 1.6%, and 2.9%, respectively. The RIETE score had a lower area under the ROC curve (0.60) for predicting complications than the PESI (0.67), sPESI (0.65), and GPS (0.72). The area under the ROC curve for predicting mortality was similar (0.76-0.78) for all scores.

Conclusion: The RIETE score classified fewer patients as low-risk than the other scores. It accurately identified patients at low mortality risk but was not superior to other scores in predicting 10-day overall complications.

INTRODUCTION

Determination of prognosis in patients with acute pulmonary embolism (PE) is a challenging task. Several clinical scores have been developed to help physicians estimate patients' prognosis and identify potential candidates for home care (Table 1) [1-4]. The best-validated clinical prognostic score for PE is the Pulmonary Embolism Severity Index (PESI) [1]. The PESI comprises 11 easily available variables and assigns patients into five risk classes of increasing risk of 30-day mortality. Patients in risk classes I and II have a low risk of 30-day mortality (2.2%) and are candidates for less costly outpatient care [5]. A simplified 6-item version of the PESI (sPESI) is also available [2]. Patients with a point score of 0 are considered low risk and have a 30-day mortality of 1%. The Geneva Prognostic Score (GPS) consists of six clinical, laboratory, and radiologic variables [3]. Patients with a score of ≤2 points have a low risk (2.2%) of a combined adverse outcome of death, recurrent venous thromboembolism (VTE), and major bleeding within 90 days [3].

Recently, a novel prognostic score for PE, the Registro Informatizado de la Enfermedad TromboEmbolica (RIETE) score, has been developed [4]. Patients without any

of nine clinical and laboratory factors have a low risk (<1%) of a combined adverse outcome of death, recurrent PE, or major bleeding within 10 days of the index event. While the RIETE score had a higher discriminative power than the PESI and the sPESI for predicting the combined adverse outcome in the derivation study (*c* statistic 0.77 vs. 0.72 and 0.71, respectively), the RIETE score has not been externally validated to date. Furthermore, prediction models usually perform better than existing scores when validation is done using the derivation sample [6,7].

We therefore aimed to externally validate the RIETE score and to directly compare its prognostic performance to the PESI, sPESI, and GPS in a prospective multicenter cohort of elderly patients with acute PE.

METHODS

Study sample

The study was performed between September 2009 and December 2013 as part of the SWiss venous Thromboembolism COhort (SWITCO65+), a prospective multicenter cohort study that assessed long-term medical outcomes in elderly patients with acute symptomatic VTE from nine Swiss university and non-university hospitals [8]. Consecutive patients aged 65 years or older with objectively diagnosed symptomatic VTE were identified in the in- and outpatient services of all participating study sites. In this study, we considered only patients with an objectively diagnosed acute PE (n=687). The criteria used to establish the diagnosis of PE were a positive spiral computed tomography or pulmonary angiography, a high-probability ventilation-perfusion scan or a proximal deep vein thrombosis (DVT) documented by compression ultrasonography or contrast venography in patients with acute chest pain, new or worsening dyspnea, hemoptysis, or syncope [9].

Patients with catheter-related thrombosis, insufficient German or French-speaking ability, conditions incompatible with the follow-up (i.e., terminal illness or place of living too far away from the study center), the inability to provide informed consent (i.e., severe dementia) or previously enrolled in the cohort were excluded. The ethics committee at each participating center approved the study. All participants gave their informed consent. A detailed description of the study methods has been published previously [8].

Baseline data collection

For all enrolled patients, baseline demographic information (age and sex) and clinical data were prospectively collected by medical record review by trained research nurses and recorded on standard data collection forms. The comorbid conditions (active cancer, heart failure, chronic lung disease and recent major bleeding), vital parameters (mental status, heart rate, systolic blood pressure, respiratory rate, temperature and arterial oxygen saturation), laboratory findings (platelet count and creatinine clearance), and imaging results (proximal DVT by compression ultrasonography or contrast venography) that constitute the RIETE score, PESI, sPESI, and the GPS were abstracted as part of the medical record review. For all vital signs, the measurement most closely related in time to the diagnosis of PE was abstracted from patient charts.

Clinical prognostic scores

Based on patient demographics and baseline clinical data obtained by chart review, we calculated the RIETE score, PESI, sPESI, and the GPS for each patient. For the RIETE score, creatinine clearance was calculated using the Cockcroft and Gault formula [10]. We used “patients being confined to bed for >72 hours in the last 3 months” as a proxy variable for recent immobility, originally defined as nonsurgical patients who were confined to bed with bathroom privileges for >4 days in the 2

months before PE diagnosis [4]. Furthermore, we used "major bleeding occurred during last 3 months" as a proxy variable for recent major bleeding, originally defined as major bleeding <30 days before PE [4]. For the GPS, we used an oxygen saturation <90% measured by pulse oximetry as a surrogate marker for a PaO_2 <8 kPa [3]. Finally, concomitant DVT was defined as asymptomatic or symptomatic proximal DVT diagnosed by ultrasound in the GPS derivation/validation study [3,11], whereas we used objectively confirmed symptomatic proximal DVT to define DVT.

Based on commonly accepted definitions, patients with a RIETE score <1, PESI score ≤85 (risk classes I and II), sPESI score <1, and a GPS score ≤2 were considered at low risk of adverse outcomes [1-4]. All other patients were considered at higher risk of complications. Missing values were assumed to be normal, a strategy frequently used in the clinical application of clinical prognostic rules [1,12]. In a sensitivity analysis, we assumed missing variables to be abnormal.

Study outcomes

The primary outcome was overall complications within 10 days, defined as overall mortality, recurrent PE, or major bleeding. Secondary outcomes were 30-day overall mortality after the diagnosis of PE and overall complications at 90 days. Recurrent PE was defined as a new intraluminal filling defect on spiral computed tomography or pulmonary angiography, a cut-off of a vessel >2.5 mm in diameter on pulmonary angiography, a new perfusion defect involving ≥75% of a lung segment with corresponding normal ventilation (i.e., high probability lung scan) or confirmation of a new PE on autopsy [1,13].

We defined major bleeding according to the definition of the International Society of Thrombosis and Haemostasis as a fatal bleeding, a symptomatic bleeding at critical sites (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial or

intramuscular with compartment syndrome), a bleeding with a reduction of hemoglobin ≥20 g/L or a bleeding leading to the transfusion of 2 units or more of packed red blood cells [14].

We assessed outcomes using patient or proxy interviews, interview of the patient's primary care physician, and/or hospital chart review. A committee of three blinded, independent clinical experts adjudicated all outcomes and classified the cause of death. Death was judged to be a definite fatal PE if it was confirmed by autopsy or if death followed a clinically severe PE, either initially or after an objectively confirmed recurrent event. Death in a patient who died suddenly or unexpectedly was classified as possible fatal PE. Final classification was made on the basis of the full consensus of the committee.

Statistical analyses

We performed pairwise comparisons of the proportion of patients classified as low-risk by the four scores using McNemar's test and adjusted *P*-values using the Bonferroni correction. We described the proportion of 10-day and 90-day overall complications (overall mortality, recurrent PE, or major bleeding), and overall 30-day mortality in low- versus higher-risk patients for each score and in patients stratified by the RIETE score as a continuous quantitative risk scale. To determine the accuracy of each score to predict 10-day and 90-day overall complications, and 30-day overall mortality, we estimated sensitivity, specificity, positive and negative predictive values, and likelihood ratios for higher- versus low-risk patients. We assessed the discriminative power of each score to predict 10-day and 90-day overall complications, and 30-day overall mortality by calculating the area under the receiver operating characteristic (ROC) curve. We performed a non-parametric test of the equality of the areas under the four curves. We determined the goodness-of-fit of the score points for 10-day and 90-day overall complications, and 30-day mortality in a logistic regression model using the Pearson chi-square test.

All analyses were done using Stata 14 (Stata Corporation, College Station, Texas).

RESULTS

Study sample

Of the 695 identified patients with an objectively confirmed acute PE who were initially enrolled in SWITCO65+, we excluded 7 who refused the use of their data and 1 who withdrew from the study within 1 day of enrolment, leaving a final study sample of 687 patients with acute PE. The baseline characteristics are shown in Table 2.

Comparison of outcomes

Overall, 12 patients (1.8 %; 95% confidence interval [CI], 1.0-3.0%), 22 patients (3.2%; 95% CI, 2.1-4.8%), and 39 patients (5.7%; 95% CI, 4.2-7.7%) died within 10, 30, and 90 days, respectively. Seventeen patients (2.5%; 95% CI, 1.6-3.9%) suffered a major bleeding and one patient (0.2%; 95% CI, 0.0-0.8%) had a recurrent PE within 10 days. Thirty-eight patients (5.5%; 95% CI, 4.1-7.5%) suffered a major bleeding and six patients (0.9%; 95% CI, 0.4-1.9%) had a recurrent PE within 90 days. The RIETE score classified a smaller proportion of patients as low-risk (31% [215/687]) than the PESI (35% [238/687]; $P<0.001$), sPESI (36% [246/687]; $P<0.001$), and the GPS (90% [615/687]; $P<0.001$).

The 10-day overall complications among low-risk patients were 1.9% (95% CI, 0.7-4.7%) for the RIETE score, 1.7% (95% CI, 0.7-4.2%) for the PESI, 1.6% (95% CI, 0.6-4.1%) for the sPESI, and 2.9% (95% CI, 1.9-4.6%) for the GPS (Table 3). At 90 days, overall complications among low-risk patients were 3.7% (95% CI, 1.9-7.2%) for the RIETE score, 3.8% (95% CI, 2.0-7.0%) for the PESI, 3.7% (95% CI, 1.9-6.8%) for the sPESI, and 8.3% (95% CI, 6.4-10.7%) for the GPS (Table 3).

Patients classified as low-risk based on the RIETE score, PESI, and sPESI had a very low 30-day overall mortality of 0.0% (95% CI, 0.0-1.8%), 0.4% (95% CI, 0.1%-2.3%), and 0.0% (95% CI, 0.0-1.5%), respectively, whereas low-risk patients based on the GPS had a higher 30-day mortality of 2.0% (95% CI, 1.1-3.4%) (Table 3). Overall, 30-day mortality was highest in higher-risk patients based on the GPS (13.9%; 95% CI, 7.7-23.7%) and lowest in higher-risk patients based on the RIETE score (4.7%; 95% CI, 3.1-7.0%). PE-related 30-day mortality was 0.0% among low-risk patients based on the RIETE score, PESI, and sPESI, and 0.5% (95% CI, 0.2-1.4%) among low-risk patients based on the GPS.

When using the RIETE score as a continuous quantitative risk scale, complications within 10 days occurred in 1.9% (95% CI, 0.7-4.7%), 4.8% (95% CI, 2.6-8.6%), 3.2% (95% CI, 1.3-7.9%), 6.9% (95% CI, 3.0-15.3%), and 6.1% (95% CI, 2.4-14.6%) of patients with a point score of 0, 1, 2, 3, and ≥4, respectively (Table 4).

Comparison of predictive accuracy and discriminative power

All four scores were less accurate in predicting overall complications than in predicting mortality, especially at 10 days (Table 5). The RIETE score, the PESI and the sPESI had all a sensitivity of 85% for predicting 10-day overall complications, whereas the GPS had a sensitivity of only 33% (Table 5). The positive predictive values for 10-day overall complications were low (<13%) and the negative predictive values were high (≥97%) for all scores (Table 5). The positive and negative likelihood ratios were generally poor except for the positive likelihood ratio of the GPS (3.49). While the areas under the ROC curve for predicting 10-day overall complications varied from 0.60 for the RIETE score to 0.72 for the GPS (Figure 1, Panel A), the areas under the ROC curve for predicting 90-day overall complications were similar for all scores (0.68-0.70) (Figure 1, Panel B).

The RIETE score and the sPESI had both a sensitivity of 100% for predicting 30-day overall mortality, whereas the PESI had a sensitivity of 96% and the GPS a sensitivity of only 46% (Table 5). As for overall complications, the positive predictive values for 30-day mortality were low (<14%) and the negative predictive values were high (≥98%) for all scores (Table 5). The RIETE score, PESI, and the sPESI showed a good negative likelihood ratio of 0.07 (95% CI, 0-1.04), 0.13 (95% CI, 0.02-0.87), and 0.06 (95% CI, 0-0.91), respectively, whereas the GPS had a poor negative likelihood ratio of 0.60 (95% CI, 0.41-0.88). The positive likelihood ratios were generally poor except for the GPS (4.88). The discriminative power for predicting 30-day overall mortality was good (area under the ROC curve 0.76-0.78) and did not significantly differ between the scores (*P*=0.87) (Figure 1, Panel C).

The goodness-of-fit was adequate for all scores. When we assumed missing variables to be abnormal in a sensitivity analysis, the area under the ROC curve for predicting 30-day overall mortality and overall complications remained similar across all scores.

DISCUSSION

In our prospective multicenter cohort of elderly patients with acute PE, the RIETE and both PESI scores accurately identified patients at low risk of 30-day overall mortality, whereas the GPS was less accurate in identifying low-risk patients. All scores were less accurate in predicting overall complications, especially at 10 days. The RIETE score classified a lower proportion of patients as low-risk than the other scores and had a somewhat lower discriminative power for 10-day complications, the outcome for which it was derived.

In contrast to the PESI and the sPESI, which were derived as mortality prediction scores, the RIETE score was developed to predict 10-day overall complications because “clinical care should be based on a broader set of medical outcomes than just mortality” [4].

It also has been argued that outcomes within 7 to 10 days may be more relevant to the hospital admission decision than outcomes within longer follow-up durations [15]. In the RIETE derivation study, the RIETE score had a statistically significantly better discriminative power for predicting 10-day overall complications than the PESI or the sPESI (area under the ROC curve 0.77 vs. 0.72 and 0.71, respectively) [4]. Even though the RIETE score was specifically derived to predict 10-day overall complications, it had a lower area under the ROC curve (0.60) for predicting complications at 10 days than the PESI (0.67), sPESI (0.65), and GPS (0.72) in our sample. Of note, in the RIETE score derivation study only patients with a PESI risk class I were considered low-risk [4], whereas in the PESI derivation and validation studies patients with risk classes I and II were considered at low risk [1,5].

Although the patients included in the RIETE derivation sample were younger than in our sample (mean age 67 years vs. median age of 75 years), they had a similar prevalence of cancer, chronic heart failure and lung disease, moderate to severe kidney impairment, and an abnormal platelet count, and a higher prevalence of tachycardia, hypotension, hypoxemia, immobility, and concurrent DVT [4]. The 10-day overall complications rate was both 3.9% in the RIETE sample and our study. Overall, our results confirm that a novel prediction model must prove its predictive performance in different patient populations and over different disease spectrums before its use can be recommended [16]. Among the clinical scores evaluated in our study, the PESI remains the only clinical prognostic model for acute PE whose effectiveness and safety has been successfully validated in a randomized-controlled trial [5]. The safety and efficacy of the sPESI and the Hestia criteria are currently evaluated in an ongoing multinational open-label randomized controlled trial (clinicaltrials.gov, identifier: NCT02811237).

As the RIETE score and the PESI both consist of 11 variables that are widely available at admission, there may not be any difference in user-friendliness between the scores. The GPS, which requires venous ultrasonography and arterial blood gas analysis, is more difficult to use.

Our study has potential limitations. First, we used immobility and major bleeding within 3 months as proxy measures for recent immobility and major bleeding, which may have overestimated disease severity and decreased the prognostic performance of the RIETE score. Conversely, the fact that we included only symptomatic proximal DVT and not all proximal DVTs may have decreased disease severity as determined by the GPS. Second, for calculation of the four scores, missing variables were considered to be normal. However, the prevalence of missing values was low and when we assumed missing values to be abnormal, the results remained similar, confirming the robustness of our results. Third, because the model coefficients and intercept were not reported in the derivation study [4], we could not calibrate the model. Finally, we have not done a specific a priori power calculation for this ancillary study of SWITCO65+. Thus, our study may not have sufficient power to compare the scores' discriminative power, especially for the prediction of 10-day overall complications.

In conclusion, we externally validated the RIETE score in elderly patients with acute PE. The RIETE score had a similar discriminative power to predict 30-day mortality than both PESI scores. All scores were less accurate in identifying patients at low risk of overall complications. As the RIETE score had a somewhat lower discriminative power for 10-day complications and classified a lower proportion of patients as low-risk than the other scores, it may not offer a practical advantage over the PESI and sPESI.

ADDENDUM

E. Jaquet, T. Tritschler, O. Stalder, A. Limacher, and D. Aujesky were responsible for study concept and design. O. Stalder and A. Limacher did the statistical analyses. E. Jaquet, T. Tritschler, and D. Aujesky wrote the manuscript. A. Limacher, M. Méan, and N. Rodondi revised the manuscript. N. Rodondi and D. Aujesky collected data and obtained funding from the Swiss National Science Foundation.

ACKNOWLEDGMENT

The study was supported by a grant of the Swiss National Science Foundation (no. 33CSCO-122659/139470).

We thank all collaborators of the SWITCO65+ study.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

REFERENCES

1 Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, Roy PM, Fine MJ. Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med*. 2005; **172**: 1041-6.

2 Jimenez D, Aujesky D, Moores L, Gomez V, Lobo JL, Uresandi F, Otero R, Monreal M, Muriel A, Yusen RD, Investigators R. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med*. 2010; **170**: 1383-9.

3 Wicki J, Perrier A, Perneger TV, Bounameaux H, Junod AF. Predicting adverse outcome in patients with acute pulmonary embolism: a risk score. *Thromb Haemost*. 2000; **84**: 548-52.

4 Maestre A, Trujillo-Santos J, Riera-Mestre A, Jimenez D, Di Micco P, Bascunana J, Vela JR, Peris L, Malfante PC, Monreal M, Investigators R. Identification of Low-Risk Patients with Acute Symptomatic Pulmonary Embolism for Outpatient Therapy. *Ann Am Thorac Soc*. 2015; **12**: 1122-9.

5 Aujesky D, Roy PM, Verschuren F, Righini M, Osterwalder J, Egloff M, Renaud B, Verhamme P, Stone RA, Legall C, Sanchez O, Pugh NA, N'Gako A, Cornuz J, Hugli O, Beer HJ, Perrier A, Fine MJ, Yealy DM. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. *Lancet*. 2011; **378**: 41-8.

6 Collins GS, Moons KG. Comparing risk prediction models. *BMJ*. 2012; **344**: e3186.

7 Labarère J, Renaud B, Fine MJ. How to derive and validate clinical prediction models for use in intensive care medicine. *Intensive Care Med*. 2014; **40**: 513-27.

8 Méan M, Righini M, Jaeger K, Beer HJ, Frauchiger B, Osterwalder J, Kucher N, Lammle B, Cornuz J, Angelillo-Scherrer A, Rodondi N, Limacher A, Trelle S, Matter CM, Husmann M, Banyai M, Aschwanden M, Egloff M, Mazzolai L, Hugli O, Bounameaux H, Aujesky D. The Swiss cohort of elderly patients with venous thromboembolism (SWITCO65+): rationale and methodology. *J Thromb Thrombolysis*. 2013; **36**: 475-83.

9 Le Gal G, Righini M, Sanchez O, Roy PM, Baba-Ahmed M, Perrier A, Bounameaux H. A positive compression ultrasonography of the lower limb veins is highly predictive of pulmonary embolism on computed tomography in suspected patients. *Thromb Haemost*. 2006; **95**: 963-6.

10 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976; **16**: 31-41.

11 Nendaz MR, Bandelier P, Aujesky D, Cornuz J, Roy PM, Bounameaux H, Perrier A. Validation of a risk score identifying patients with acute pulmonary embolism, who are at low risk of clinical adverse outcome. *Thromb Haemost*. 2004; **91**: 1232-6.

12 Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997; **336**: 243-50.

13 The Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. *N Engl J Med*. 1997; **337**: 657-62.

14 Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005; **3**: 692-4.

15 Jimenez D, Aujesky D, Yusen RD. Risk stratification of normotensive patients with acute symptomatic pulmonary embolism. *Br J Haematol*. 2010; **151**: 415-24.

16 Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. *Ann Intern Med*. 1999; **130**: 515-24.

LEGENDS TO FIGURES

Figure 1.

Panel A. Receiver-operating characteristic curve for 10-day overall complications

The areas under the ROC curves were 0.60 (95% CI 0.57-0.64) for the RIETE score, 0.67 (95% CI 0.64-0.71) for the PESI, 0.65 (95%CI 0.62-0.69) for the sPESI, and 0.72 (95% CI 0.68-0.75) for the GPS (*P*=0.062).

Panel B. Receiver-operating characteristic curve for 90-day overall complications

The areas under the ROC curves were 0.70 (95% CI 0.66-0.73) for the RIETE score, 0.69 (95% CI 0.66-0.73) for the PESI, 0.68 (95% CI 0.65-0.72) for the sPESI, and 0.69 (95% CI 0.66-0.73) for the GPS (*P*=0.967).

Panel C. Receiver-operating characteristic curve for 30-day overall mortality

The areas under the ROC curves were 0.76 (95% CI 0.73-0.79) for the RIETE score, 0.78 (95% CI 0.75-0.81) for the PESI, 0.78 (95%CI 0.75-0.81) for the sPESI, and 0.76 (95% CI 0.72-0.79) for the GPS (*P*=0.865).

Table 1. Clinical prognostic scores for patients with acute pulmonary embolism

RIETE score	**Points assigned**[††]	
Chronic heart failure	+1	
Cancer without metastasis[*]	+1	
Cancer with metastasis[*]	+2	
Systolic blood pressure <100 mm Hg	+1	
Oximeter oxygen saturation <90%	+1	
Heart rate ≥110 beats/min.	+1	
Creatinine clearance 30-60 ml/min.	+1	
Creatinine clearance <30 ml/min.	+3	
Recent major bleeding[†]	+2	
Recent immobility ≥4 days[‡]	+1	
Platelet count <100,000/µl or >450,000/µl	+1	
Pulmonary Embolism Severity Index	**Points assigned in original version**[‡‡]	**Points assigned in simplified version**[§§]
Age	+1 per year	+1 (age ≥80 years)
Male sex	+10	-
Cancer	+30	+1
Heart failure	+10	} +1[**]
Chronic lung disease	+10	
Heart rate ≥100 beats/min.	+20	+1
Systolic blood pressure <100 mm Hg	+30	+1
Respiratory rate ≥30 breaths/min.	+20	-
Temperature <36°C	+20	-
Altered mental status[§]	+60	-
Oximeter oxygen saturation <90%[¶]	+20	+1
Geneva Prognostic Score	**Points assigned**[¶¶]	
Cancer	+2	
Heart failure	+1	
Previous deep vein thrombosis	+1	
Systolic blood pressure <100 mm Hg	+2	
PaO_2 <8 kPa	+1	
Concomitant deep vein thrombosis	+1	

[*] Newly diagnosed cancer or cancer that is being treated with surgery, chemotherapy, radiotherapy, or hormonal or supportive therapy.

[†] During the last 30 days before PE.

[‡] Nonsurgical patients who were confined to bed with bathroom privileges for >4 days in the two months before PE diagnosis.

[§] Disorientation, lethargy, stupor, or coma.

[¶] With or without the administration of supplemental oxygen.

[**] The variables “heart failure” and “chronic lung disease” were combined into a single category of chronic cardiopulmonary disease.

[††] Overall point score is obtained by summing the points for every applicable predictor. Risk classes defined by overall point score: <1 point, low risk (10-day adverse outcome risk 0.6%); ≥1 points, higher risk (10-day adverse outcome risk 4.6%).

[‡‡] Overall point score is obtained by summing the patient’s age in years and the points for every applicable predictor. Patients with ≤85 points (risk classes I and II), low risk (30-day mortality risk 2.2%); >85 points, higher risk (30-day mortality risk 14.0%).

[§§] Overall point score is obtained by summing the points for every applicable predictor. Risk classes defined by overall point score: 0 point, low risk (30-day mortality risk 1.0%); ≥1 points, higher risk (30-day mortality risk 10.9%).

[¶¶] Overall point score is obtained by summing the points for every applicable predictor. Risk classes defined by overall point score: ≤2 points, low risk (90-day adverse outcome risk 2.2%); ≥3 points, higher risk (90-day adverse outcome risk 27.3%).

Table 2. Patient baseline characteristics (N=687)

Characteristic[*]	n (%) or median (interquartile range)	Missing values n (%)
Patient age, years	75.0 (70.0; 81.0)	0 (0)
Age >80 years	185 (27)	0 (0)
Female sex	327 (48)	0 (0)
Chronic heart failure[*]	49 (7)	0 (0)
Chronic or acute heart failure[*]	81 (12)	0 (0)
Chronic lung disease[†]	104 (15)	0 (0)
Chronic heart failure and lung disease combined[*†]	161 (23)	0 (0)
Cancer without metastasis[‡]	68 (10)	0 (0)
Cancer with metastasis[‡]	49 (7)	0 (0)
Systolic blood pressure <100 mmHg	26 (4)	5 (1)
Heart rate ≥110 beats per minute	81 (12)	5 (1)
Respiratory rate ≥30 breaths per minute	29 (4)	140 (20)
Oximeter oxygen saturation <90%	103 (15)	52 (8)
Altered mental status[§]	23 (3)	0 (0)
Temperature <36°C	48 (7)	18 (3)
Creatinine clearance 30-60 ml/min.	229 (33)	13 (2)
Creatinine clearance <30 ml/min.	37 (5)	13 (2)
Major bleeding occurred during last 3 months	33 (5)	1 (0)
Recent immobility[¶]	109 (16)	3 (0)
Platelet count <100,000/µl or >450,000/µl	44 (6)	11 (2)
Previous deep vein thrombosis	113 (16)	1 (0)
Concomitant proximal deep vein thrombosis[**]	107 (16)	0 (0)

Localization of pulmonary embolism		34 (5)
Central	221 (32)	
Lobar	149 (22)	
Segmental	217 (32)	
Subsegmental	66 (10)	
Score points		
RIETE score	1 (0; 2)	67 (10)[††]
Pulmonary Embolism Severity Index	94 (81; 113)	192 (28)[††]
Simplified Pulmonary Embolism Severity Index	1 (0; 2)	53 (8)[††]
Geneva Prognostic Score	1 (0; 2)	54 (8)[††]

[*] Systolic or diastolic heart failure, left or right heart failure, forward or backward heart failure, or a known left ventricular ejection fraction of <40%.

[†] Chronic obstructive pulmonary disease, active asthma, lung fibrosis, cystic fibrosis, or bronchiectasis.

[‡] Cancer requiring surgery, chemotherapy, radiotherapy, or palliative care during the last 3 months before index PE.

[§] Disorientation, lethargy, stupor, or coma.

[¶] Patients being confined to bed for >72 hours in the last 3 months.

[**] Objectively confirmed, symptomatic proximal deep vein thrombosis.

[††] Patients with at least one missing score variable.

Table 3. Outcomes in low- vs. higher-risk patients

	Low risk		Higher risk		All patients	
Outcome	*n/N*	% (95% CI)	*n/N*	% (95% CI)	*n/N*	% (95% CI)
10-day overall complications*					27/687	3.9 (2.7-5.7)
RIETE	4/215	1.9 (0.7-4.7)	23/472	4.9 (3.3-7.2)		
PESI	4/238	1.7 (0.7-4.2)	23/449	5.1 (3.4-7.6)		
sPESI	4/246	1.6 (0.6-4.1)	23/441	5.2 (3.5-7.7)		
GPS	18/615	2.9 (1.9-4.6)	9/72	12.5 (6.7-22.1)		
30-day overall mortality					22/687	3.2 (2.1-4.8)
RIETE	0/215	0 (0-1.8)	22/472	4.7 (3.1-7.0)		
PESI	1/238	0.4 (0.1-2.3)	21/449	4.7 (3.1-7.0)		
sPESI	0/246	0 (0-1.5)	22/441	5.0 (3.3-7.4)		
GPS	12/615	2.0 (1.1-3.4)	10/72	13.9 (7.7-23.7)		
30-day PE-related mortality					8/687	1.2 (0.6-2.3)
RIETE	0/215	0 (0-1.8)	8/472	1.7 (0.9-3.3)		
PESI	0/238	0 (0-1.6)	8/449	1.8 (0.9-3.5)		
sPESI	0/246	0 (0-1.5)	8/441	1.8 (0.9-3.5)		
GPS	3/615	0.5 (0.2-1.4)	5/72	6.9 (3.0-15.3)		
90-day overall complications*					70/687	9.9 (7.9-12.4)
RIETE	8/215	3.7 (1.9-7.2)	60/472	12.7 (10.0-16.0)		
PESI	9/238	3.8 (2.0-7.0)	59/449	13.1 (10.3-16.6)		
sPESI	9/246	3.7 (1.9-6.8)	59/441	13.4 (10.5-16.9)		
GPS	51/615	8.3 (6.4-10.7)	17/72	23.6 (15.3-34.6)		

Abbreviations: CI, confidence interval; PE, pulmonary embolism.

* Defined as death, major bleeding or recurrent pulmonary embolism, whichever occurred first.

Table 4. Outcomes in patients stratified by the RIETE score as a continuous risk scale

	10-day overall complications*		30-day overall mortality		90-day overall complications*	
RIETE Score	*n/N*	% (95% CI)	*n/N*	% (95% CI)	*n/N*	% (95% CI)
0 points	4/215	1.9 (0.7-4.7)	0/215	0.0 (0.0-1.8)	8/215	3.7 (1.9-7.2)
1 point	10/209	4.8 (2.6-8.6)	6/209	2.9 (1.3-6.1)	16/209	7.7 (4.8-12.1)
2 points	4/125	3.2 (1.3-7.9)	4/125	3.2 (1.3-7.9)	13/125	10.4 (6.2-17.0)
3 points	5/72	6.9 (3.0-15.3)	5/72	6.9 (3.0-15.3)	15/72	20.8 (13.1-31.6)
≥4 points	4/66	6.1 (2.4-14.6)	7/66	10.6 (5.2-20.3)	16/66	24.2 (15.5-35.8)

Abbreviations: CI, confidence interval.

* Defined as death, major bleeding or recurrent pulmonary embolism, whichever occurred first.

Table 5. Measures of performance to predict overall mortality and complications

Outcome	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Positive LHR (95% CI)	Negative LHR (95% CI)	Goodness of-fit[†]	TP	FN	FP	TN
10-day overall complications[*]											
RIETE	85 (68-94)	32 (29-36)	5 (3-7)	98 (95-99)	1.25 (1.06-1.48)	0.46 (0.19-1.15)	0.22	23	4	449	211
PESI	85 (68-94)	36 (32-39)	5 (3-8)	98 (96-99)	1.32 (1.12-1.56)	0.42 (0.17-1.04)	0.52	23	4	426	234
sPESI	85 (68-94)	37 (33-40)	5 (4-8)	98 (96-99)	1.35 (1.14-1.59)	0.40 (0.16-1.00)	0.72	23	4	418	242
GPS	33 (19-52)	91 (88-93)	13 (7-22)	97 (95-98)	3.49 (1.95-6.25)	0.74 (0.56-0.96)	0.79	9	18	63	597
30-day overall mortality											
RIETE	100 (85-100)	32 (29-36)	5 (3-7)	100 (98-100)	1.48 (1.40-1.56)	0.07 (0-1.04)[‡]	0.11	22	0	450	215
PESI	96 (78-99)	36 (32-39)	5 (3-7)	100 (98-100)	1.48 (1.33-1.65)	0.13 (0.02-0.87)	0.10	21	1	428	237
sPESI	100 (85-100)	37 (33-41)	5 (3-7)	100 (99-100)	1.59 (1.50-1.68)	0.06 (0-0.91)[‡]	0.17	22	0	419	246
GPS	46 (27-65)	91 (88-93)	14 (8-24)	98 (97-99)	4.88 (2.91-8.16)	0.60 (0.41-0.88)	0.23	10	12	62	603
90-day overall complications[*]											
RIETE	88 (79-94)	33 (30-37)	13 (10-16)	96 (93-98)	1.33 (1.20-1.47)	0.35 (0.18-0.68)	0.62	60	8	412	207
PESI	87 (77-93)	37 (33-41)	13 (10-17)	96 (93-98)	1.38 (1.23-1.54)	0.36 (0.19-0.66)	0.34	59	9	390	229
sPESI	87 (77-93)	38 (35-42)	13 (11-17)	96 (93-98)	1.41 (1.26-1.57)	0.35 (0.19-0.64)	0.21	59	9	382	237
GPS	25 (16-36)	91 (89-93)	24 (15-35)	92 (89-94)	2.81 (1.74-4.56)	0.82 (0.72-0.95)	0.04	17	51	55	564

Abbreviations: CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; LHR, likelihood ratio; TP, true positive; FN, false negative; FP, false positive; TN, true negative.

[*] Defined as death, major bleeding or recurrent pulmonary embolism, whichever occurred first.

† *P*-values from Pearson's χ^2 goodness-of-fit test. *P*-values ≥0.05 indicate an adequate goodness of fit.

‡ Computed using the continuity correction.