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Validation of the 2019 European Society of Cardiology risk stratification algorithm for pulmonary embolism in normotensive elderly patients

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Abstract:

Background: The 2019 European Society of Cardiology (ESC) guidelines recommend evaluation for right ventricular dysfunction in all normotensive patients with acute pulmonary embolism (PE). We compared the predictive performance of the 2019 and 2014 ESC risk stratification algorithms and the Pulmonary Embolism Severity Index (PESI).

Methods: We performed a post-hoc analysis of normotensive patients aged ≥65 years with acute PE from a prospective cohort. The primary outcome was overall mortality; secondary outcomes were PE-related mortality and adverse outcomes (PE-related death, cardiopulmonary resuscitation, intubation, catecholamine use, recurrent venous thromboembolism) at 30 days. We assessed outcomes in intermediate-high, intermediate-low, and low risk groups according to the 2019 and 2014 ESC algorithms and the PESI. Discriminative power was compared using the area under the receiver operating curve (AUC).

Results: Among 419 patients, 14 (3.3%) died (7 from PE) and 16 (3.8%) had adverse outcomes within 30 days. The 2019 ESC algorithm classified more patients as intermediate-high risk (45%) than the 2014 ESC algorithm (24%) or PESI (37%), and only 19% as low risk (32% with 2014 ESC or PESI). Discriminatory power for overall mortality was lower with the 2019 ESC algorithm (AUC 63.6%), compared to the 2014 ESC algorithm (AUC 71.5%) or PESI (AUC 75.2%), although the difference did not reach statistical significance (p=0.063). Discrimination for PE-related mortality and adverse outcomes was similar.

Conclusions: While categorizing more patients in higher-risk groups, the 2019 ESC algorithm for PE did not improve prediction of short-term outcomes compared to the 2014 ESC algorithm or the PESI.

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Validation of the 2019 European Society of Cardiology Risk Stratification Algorithm for Pulmonary Embolism in Normotensive Elderly Patients

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ABSTRACT

Background: The 2019 European Society of Cardiology (ESC) guidelines recommend evaluation for right ventricular dysfunction in all normotensive patients with acute pulmonary embolism (PE). We compared the predictive performance of the 2019 and 2014 ESC risk stratification algorithms and the Pulmonary Embolism Severity Index (PESI).

Methods: We performed a post-hoc analysis of normotensive patients aged $\geq$65 years with acute PE from a prospective cohort. The primary outcome was overall mortality; secondary outcomes were PE-related mortality and adverse outcomes (PE-related death,

cardiopulmonary resuscitation, intubation, catecholamine use, recurrent venous thromboembolism) at 30 days. We assessed outcomes in intermediate-high, intermediate-low, and low risk groups according to the 2019 and 2014 ESC algorithms and the PESI. Discriminative power was compared using the area under the receiver operating curve (AUC).

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Keywords: Pulmonary Embolism Severity Index**,** echocardiography, right ventricular dysfunction, venous thromboembolism

INTRODUCTION

Pulmonary embolism (PE) can lead to acute hemodynamic instability and death.[1] PE patients presenting with hemodynamic instability have an average short-term mortality of 14% to 50%,[2, 3] and immediate thrombolysis must be considered in these high risk patients.[4] While up to 98% of patients with PE are hemodynamically stable during initial presentation,[5, 6] a subset will develop early complications.[7] Identifying these patients is critical to determine the optimal management approach.[4, 8]

The 2019 European Society of Cardiology (ESC) guidelines propose a risk-adjusted management algorithm for patients with acute PE based on clinical assessment (vital signs, use of a clinical prognostic model, such as the Pulmonary Embolism Severity Index [PESI] or its simplified version), evaluation of right ventricular (RV) function using transthoracic echocardiography (TTE) or computed tomography angiography (CTPA), and troponin measurement.[4, 9] The recommendation to assess RV function in all patients, even those who are clinically at low risk of complications, is new compared with the 2014 guideline version.[4, 10] Whether systematic RV assessment is efficient and can improve patient safety compared with selective assessment of RV function in higher-risk patients only is uncertain.

In the elderly population, cardiorespiratory comorbidities associated with RV dysfunction are more prevalent than in younger individuals.[11, 12] This may limit the benefit of RV function measurement for risk assessment in PE and may result in misclassification of the risk for adverse outcomes in this population.[13, 14] We therefore externally validated the prognostic performance of the 2019 ESC risk stratification algorithm in normotensive elderly PE patients from a prospective multicenter cohort and compared it to the 2014 ESC risk stratification algorithm and to risk stratification using PESI alone.

METHODS

Study design and population

This study was a post-hoc analysis of the prospective multicenter SWITCO65+ cohort study to assess outcomes in elderly patients with acute venous thromboembolism (VTE) from all 5 Swiss university and 4 large-volume non-university hospitals. Between September 2009 and March 2012, consecutive in- and outpatients aged ≥65 years with acute symptomatic PE and/or deep vein thrombosis (DVT) were enrolled. Exclusion criteria were thrombosis at a

different site than the lower extremities, catheter-related thrombosis, inability to provide informed consent (i.e., severe dementia), conditions incompatible with follow up (i.e., terminal illness), insufficient German or French speaking ability, or previous enrollment. The study methods have previously been described.[6]

For the current analysis, we only considered patients with acute symptomatic PE with hemodynamic stability (systolic blood pressure ≥90 mmHg at presentation) and available RV function assessment by TTE or CTPA within two days. We defined acute symptomatic PE as acute chest pain, new or worsening dyspnea, hemoptysis, or syncope with PE confirmed by CTPA, pulmonary angiography, or high probability ventilation-perfusion scan; or if patients had proximal DVT documented by compression ultrasonography or contrast venography with symptoms compatible with PE.[6]

This study was conducted in accordance with the Declaration of Helsinki. Approval was provided by the local Ethics Committee from each participating site. All participants or their legal representatives gave informed consent.

Baseline data collection

Trained study nurses collected information on demographics, comorbidities, vital signs at the time of presentation, laboratory results, and PE-related treatments.[6] Baseline blood samples were centrifuged, and stored at -80°C. For hs-cTnT measurement, electrochemiluminescence methods (Cobas e 601 analyzer, Hoffmann-La Roche, Rotkreuz, Switzerland) were used.[15]

Assessment of RV function

In all study participants, RV function was prospectively assessed by on-site cardiologists using TTE.[6] Assessment of RV function was based on 6 of 8 criteria recommended by the 2019 ESC PE guidelines (Supplementary Methods).[4] In patients without

TTE examination within two days, the initial CTPA images were used to assess RV function. RV dysfunction on CTPA was independently assessed by two radiologists and defined as RV/ LV diameter ratio of ≥1.0.[4, 16]

Risk categories

Patients were stratified as intermediate-high, intermediate-low, and low risk according to the 2019 and 2014 ESC guidelines (Table 1). Among the clinical risk assessment scores suggested by these guidelines, we used the PESI;[4, 10, 17] the PESI contains 11 clinical items and has been validated to predict early mortality and adverse outcomes in acute PE.[9] Patients were classified into risk categories according to the 2019 and 2014 ESC guidelines as shown in Table 1.[4, 10] A positive troponin was defined as hs-cTnT >14ng/L. Given that troponin is not consistently measured in all PE patients who have a low complication risk in clinical practice, and current risk stratification algorithms (ESC 2014, 2019) do not explicitly recommend the systematic measurement of troponin in low risk patients but rather mention it as an option, [4, 10] we did not consider troponin values in clinical low risk patients in our primary comparison. However, we performed a sensitivity analysis to determine the difference in outcomes between considering and not considering elevated troponin in low-risk patients. To allow a comparison with the 2019 and 2014 ESC risk stratification algorithms, we trichotomised PESI into a lower (PESI risk class I/II), an intermediate (class III), and a higher risk group (class IV/V) (Table 1).

Study outcomes

The primary outcome was 30-day overall mortality, as stratification for early risk of death is recommended in the 2019 ESC guidelines.[4] Secondary outcomes were PE-related mortality and adverse outcomes (defined as PE-related death, cardiopulmonary resuscitation, intubation, catecholamine use, or recurrent VTE [PE or DVT]) at 30 days.[17] Outcomes were assessed by patient interview and hospital chart review, and complemented by proxy and

primary care physician interviews if necessary. All VTE outcomes and deaths were adjudicated by a committee of three blinded clinical experts. The committee classified the cause of all deaths as definitely due to PE (i.e., autopsy-confirmed or death occurring in relation to a severe PE event), possibly due to PE (i.e., sudden death without any other explanation), or due to another cause. Final classification was based on the full consensus of all committee members. PE-related deaths were defined as deaths definitely or possibly related to PE.[6]

Statistical analysis

We calculated the proportion of low, intermediate-low, and intermediate-high risk patients according to the 2019 ESC, 2014 ESC risk stratification models, and the PESI. Baseline characteristics were presented according to 2019 ESC risk categories. We reported events at 30 days (overall mortality, PE-related mortality, and adverse outcomes) in low, intermediate-low, and intermediate-high risk patients for the three risk stratification modalities and assessed cumulative incidence of overall mortality at 30 days using Kaplan-Meier curves. To assess the benefit of assessing RV function when using the PESI for risk stratification, outcomes were determined across different PESI risk categories stratified by RV function.

We assessed the discriminative power of the categorized ESC algorithms and the PESI to predict overall mortality, PE-related mortality, and adverse outcomes at 30 days by calculating the area under the receiver operating characteristic curves (AUC), and performed a non-parametric test of the equality of the AUCs. We calculated the net reclassification index (NRI) to assess whether the 2019 ESC risk assessment model resulted in improved risk prediction compared to the 2014 ESC model or the PESI. For assessment of the NRI, we used two risk categories, i.e., the intermediate risk (defined as intermediate-high and intermediate-low risk categories) vs. low risk category (see Supplementary Methods).

Missing values were considered normal, as done previously.[9] To exclude bias due to data not missing at random, we performed sensitivity analyses excluding patients with missing values for systolic blood pressure and troponin. All analyses were conducted using Stata 15 (Stata Corporation, College Station, Texas).

RESULTS

Overall, 696 patients with acute PE were enrolled in the SWITCO65+ cohort. After exclusion of 8 patients who did not allow the use of their data, 1 patient who withdrew, 10 hemodynamically unstable patients, and 258 patients without RV function assessment within 48 hours, our sample for this analysis comprised 419 patients. Compared to the 258 patients who were excluded from analysis because unavailable RV function assessment, analyzed patients were somewhat younger (median age 74 vs. 76 years; p=0.07), more likely to be men (56% vs. 47%; p=0.039), but their median troponin T values 15.4 ng/L (interquartile range 7.5; 30.5) vs. 13.7 ng/L (6.8; 29.9), overall 30-day mortality 2.7% vs. 3.3%, PE-specific 30-day mortality 0% vs. 2%, and adverse outcomes 3% vs. 4% were comparable (Supplementary Table 1).

Baseline characteristics stratified by 2019 ESC risk categories are presented in Table 2. Median age was 74 years, 233 (56%) were men, and 209 (50%) showed signs of RV dysfunction. Active cancer, chronic lung disease, and tachycardia were more frequent in the intermediate risk category compared to the low risk category. Assessment of RV function was done by TTE in 69%, and in the remaining patients by CTPA. RV dysfunction was slightly more prevalent in intermediate-high than in intermediate-low risk patients (64% vs. 58%).

Risk classification and clinical outcomes

Based on the 2019 ESC risk stratification algorithm, almost twice as many patients were categorized as intermediate-high risk (45%) compared to the 2014 ESC algorithm (24%)

and 8% more than using the PESI (37%) (Table 3). Only 19% were classified as low risk with the 2019 ESC algorithm compared to 32% with the 2014 ESC algorithm or the PESI.

Overall, 14/419 patients (3.3%) died within 30 days, of which half were PE-related deaths. Sixteen patients had adverse outcomes within 30 days after the index PE. Overall mortality at 30 days was highest in the intermediate-high risk category of any of the three risk stratification modalities (4.8%, 95% confidence interval [CI] 2.6-8.9% for the 2019 ESC algorithm; 6.9%, 95% CI 3.4-13.6% for the 2014 ESC algorithm; and 7.2%, 95% CI 4.1-12.4% for the PESI), followed by the intermediate-low and low risk categories (Table 4). No deaths occurred in the ESC or PESI low risk categories. In contrast to the 2014 ESC algorithm and the PESI, the cumulative incidence of mortality did not differ across risk categories based on the 2019 ESC algorithm (Figures 1a-c).

Among intermediate-high risk patients, PE-related mortality after 30 days was 2.7% for the 2019 ESC algorithm, 4.0% for the 2014 ESC algorithm, and 3.3% for the PESI. The proportion of intermediate-high risk patients who developed adverse outcomes within 30 days was 5.4% for the 2019 ESC algorithm, 6.9% for the 2014 ESC algorithm, and 4.6% for the PESI (Table 4). No adverse outcomes occurred in low risk patients according to the 2019 ESC algorithm, and only 1 in the low risk categories based on the 2014 ESC algorithm and the PESI (Table 4). Sensitivity analyses excluding patients with missing data on systolic blood pressure (n=3) or troponin (n=25) yielded similar results (not shown).

When examining 30-day outcomes across the PESI risk categories stratified by RV function, 54 of 133 patients (40%) in the PESI low risk group showed signs of RV dysfunction (Supplementary Table 2). No deaths occurred in the PESI low-risk group, irrespective of RV function. In the intermediate-low (PESI class III) and intermediate-high risk group (PESI classes IV/V), overall and PE-related mortality did not differ in patients with RV dysfunction compared to those without (Supplementary Table 2).

Discriminatory power and NRI

For overall 30-day mortality, the 2019 ESC risk stratification algorithm tended to have the lowest discriminatory power, with an AUC of 63.6% compared to 71.5% for the 2014 ESC algorithm and 75.2% for the PESI (p=0.063). The discriminatory power of all three risk assessment modalities for PE-related 30-day mortality and adverse outcomes was similar (Table 5). In a sensitivity analysis, 22 and 40 patients classified as low risk according to 2019 and 2014 ESC risk stratification models, respectively, were reclassified as low-intermediate risk due to an isolated troponin elevation. In this analysis, the discriminatory power of the three risk assessment models was not significantly different for any of the outcomes (data not shown).

When comparing the 2019 ESC to the 2014 ESC algorithm and the PESI, the overall NRI was negative for all outcomes, indicating no improvement in risk prediction with the 2019 ESC algorithm (Supplementary Table 3). Based on the 2019 ESC algorithm, no patient among those who died was correctly reclassified from the low to a higher-risk category. However, 54 patients who did not die were incorrectly upgraded from the low to the intermediate risk categories by the 2019 ESC algorithm compared to the 2014 ESC algorithm or the PESI.

DISCUSSION

In our study, the 2019 ESC risk stratification algorithm, which recommends a systematic assessment of RV function, categorized a substantially smaller proportion of patients with acute PE as low risk and almost twice as many as intermediate-high risk compared to the 2014 ESC algorithm or the PESI. We found no evidence that the new algorithm improved prediction of short-term overall mortality, PE-related mortality, or adverse outcomes in elderly patients. Thus, the systematic assessment of RV function in all

patients with acute PE, regardless of their clinical risk, may not confer a clinical benefit and could result in a higher utilization of health care resources.

Risk stratification of PE patients based on hemodynamic status and use of validated risk stratification tools is recommended to assist with clinical decision-making.[4, 10] Hemodynamically unstable patients are at high risk of early death and should be considered for reperfusion. On the other side of the clinical spectrum of PE severity, low risk patients can be considered for outpatient treatment or early discharge.[4] All other patients are considered at intermediate risk and should be hospitalized. The ESC guidelines further subdivide intermediate risk patients into intermediate-high and intermediate-low risk categories based on the higher risk of deterioration in patients with impaired RV function.[4] Monitoring is recommended for intermediate-high risk patients, with rescue reperfusion therapy in case of deterioration.[4] We found that using the 2019 ESC algorithm for risk stratification shifted 13% of patients from low to intermediate risk, as previously also demonstrated in another cohort.[18] This impacts the use of health care resources: fewer patients would qualify for outpatient treatment or early discharge, while the proportion of intermediate-high risk patients requiring more intensive monitoring (e.g., in an intermediate care unit) almost doubles if using the 2019 ESC risk stratification algorithm compared to the 2014 version.

The major new feature of the 2019 ESC model is the systematic RV function assessment, even in patients at low risk of death as assessed by clinical scores. In our study of elderly patients, additional RV function assessment did not result in improved prediction of short-term mortality or adverse outcomes in the low risk group. A previous meta-analysis including 21 studies with low risk PE patients assessed early mortality according to RV function.[17] Ten of 552 patients with RV dysfunction (1.8%) versus 4 of 1045 patients without RV dysfunction (0.4%) died, resulting in an increased risk for overall mortality in patients with RV dysfunction compared to those without.[17] Another recent meta-analysis of 1868 patients at low risk as identified by clinical scores demonstrated that RV dysfunction was

associated with PE-related but not overall mortality compared to absence of RV dysfunction.[19] However, the absolute number of PE-specific deaths was very low, affecting 6/447 patients with and 2/1421 patients without RV dysfunction.[19] The results from the two meta-analyses are partially driven by the results from a registry that reported 4 deaths among 145 low-risk patients (only 1 was PE-related).[20] This relatively elevated mortality may be due to the high proportion of patients with cancer in this registry (31%), which was substantially higher than in our cohort (17%) and most other PE studies. Given the low absolute risk of adverse outcome events in low-risk PE patients in these meta-analyses, it is debatable whether RV function assessment translates into a measurable clinical benefit.

While the results of two meta-analyses suggest a very limited added value of RV function assessment compared to the use of clinical parameters for risk stratification in PE, clinical risk assessment has been shown to be safe and efficient in clinical trials, allowing up to 31-51% of patients to be discharged early or entirely managed in the outpatient setting.[8, 21] In a randomized trial, outpatient management of low-risk PE patients based on the PESI and other clinical criteria without RV function assessment or cardiac biomarkers was safe.[8] In another randomized trial, early discharge of low-risk PE patients identified using the Hestia criteria alone was not only safe, but led to substantial cost reductions compared with standard in-hospital treatment.[22] Moreover, the presence of RV dysfunction or elevated troponin did not predict adverse outcomes in patients with PE selected for home treatment.[23, 24] The 2020 guidance by the U.K. National Institute for Health Care Excellence (NICE) has incorporated the recommendation of outpatient treatment for low-risk PE patients, as identified by a validated clinical risk stratification tool, and does not recommend systemic RV function assessment or cardiac markers in low-risk patients.[25] To date, no prospective management studies have compared clinical risk assessment alone with a strategy combining clinical and systematic RV function assessment in low-risk PE patients. Although observational studies have shown an increased risk of short-term mortality in low-risk PE patients with compared to

those without RV dysfunction,[17, 19] whether a treatment upgrade (e.g., hospitalization or increased monitoring) improves patient safety remains to be investigated.

In our analysis, the 2019 ESC risk stratification algorithm tended to have a lower discriminative power for short-term outcomes than the simpler 2014 ESC algorithm or the PESI. Irrespective of RV function, no deaths occurred in low risk categories of any of the three risk stratification modalities, indicating that additional risk stratification in low-risk patients based on a validated clinical score may be unnecessary. Moreover, the NRI suggests that the 2019 ESC algorithm does not improve outcome prediction over the 2014 version or the PESI. However, implementation of the 2019 ESC algorithm could lead to potential management delays and additional costs not only for obtaining TTE in patients without CTPA (9% in our sample) but also by substantially reducing the proportion of patients qualifying for less costly outpatient care. Recent guidelines by the American Society of Hematology recommend ventilation/perfusion scanning as preferred imaging method for suspected PE in patients with a low or intermediate pre-test probability,[26] which would increase the need for echocardiographic RV function assessment if the 2019 ESC algorithm was used. Overall, assessment of RV function could be avoided in a substantial proportion of hemodynamically stable patients with PE (32% of low risk patients in our study) with the use of the older 2014 ESC algorithm instead of the 2019 version.

Our study has also limitations. First, although the current results are based on prospectively collected data from a broad population of elderly PE patients, risk assessment using the 2019 ESC algorithm has been done post-hoc. A future prospective impact analysis would be ideal to compare the real-life impact of the 3 risk stratification systems. Second, RV function assessment using TTE or CTPA has not been performed within two days of presentation in 258 patients, who were excluded from this analysis and are a possible source of selection bias. However, outcomes were comparable in the patients excluded due to unavailability of timely RV assessment. Third, as the elderly generally carry the largest

burden of PE mortality,[27] our analyses are not necessarily generalizable to younger patients. Still, the development of specific risk stratification algorithms for the elderly and other subgroups with PE must be carefully weighed against the practicability of such an approach. Finally, the interpretation of our study results may be limited by the low number of outcomes precluding a determination of potential differences in outcomes in association with RV dysfunction. However, the sample size and event rate in our study is comparable to similar studies.[18, 28]

In conclusion, the 2019 ESC risk stratification algorithm for PE classified more patients in a higher risk category compared to the 2014 ESC algorithm and the PESI, but did not improve prediction of short-term outcomes in the elderly with PE. Our results suggest that implementation of the 2019 ESC algorithm with systematic assessment of RV function may not confer a safety benefit in older PE patients but rather result in a higher use of health care resources by decreasing the proportion of patients who are safely eligible for outpatient care.

What is known on this topic?

- Risk stratification algorithms assist in identifying patients with acute pulmonary embolism who are at risk of early death and may thus benefit from hospitalization or increased monitoring.
- The risk stratification algorithm proposed by the 2019 ESC guidelines newly requires systematic right ventricular function assessment in all normotensive patients with acute pulmonary embolism independent of clinical risk.

What does this paper add?

- In a cohort of 419 older patients with pulmonary embolism, the 2019 ESC risk stratification algorithm categorized substantially fewer patients as low risk compared to the 2014 version.
- Systematic assessment of right ventricular function in older pulmonary embolism patients regardless of clinical risk did not improve prediction of adverse outcomes.

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Conflict of interest

The authors declare that they have no conflict of interest.

Author Contributions

All authors participated in the research and preparation of the manuscript. Study concept and design: D. Aujesky. Data acquisition: D. Aujesky, Marie Méan. Data analysis and interpretation: J. Moor, C. Baumgartner, Marie Méan, N. Rodondi, D. Aujesky. Drafting the manuscript: J. Moor, C. Baumgartner, D. Aujesky. Critical revision of the manuscript: J. Moor, O. Stalder, A. Limacher, Marie Méan, C. Baumgartner, N. Rodondi, D. Aujesky. Statistical analyses: O. Stalder, A. Limacher. Study supervision: D. Aujesky, C. Baumgartner. Approval of the final manuscript: all authors.

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Figure 1 Kaplan-Meier curves showing the cumulative incidence of 30-day overall mortality by 2019 ESC risk category. The cumulative mortality in the low, intermediate-low, and intermediate-high risk category was 0%, 3.3%, and 4.8%, respectively (p= 0.141).

Abbreviations: ESC= European Society of Cardiology.

Figure 2 Kaplan-Meier curves showing the cumulative incidence of 30-day overall mortality by 2014 ESC risk category. The cumulative mortality in the low, intermediate-low, and intermediate-high risk category was 0%, 3.8%, and 6.9%, respectively (p= 0.013).

Figure 3 Kaplan-Meier curves showing the cumulative incidence of 30-day overall mortality by PESI risk category. The cumulative mortality in the low (PESI risk classes I/II), intermediate-low (PESI risk class III), and intermediate-high risk category (PESI risk classes IV/V) was 0%, 2.2%, and 7.2%, respectively (p= 0.002).

Validation of the 2019 European Society of Cardiology risk stratification algorithm for pulmonary embolism in normotensive elderly patients

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ABSTRACT

Background: The 2019 European Society of Cardiology (ESC) guidelines recommend evaluation for right ventricular dysfunction in all normotensive patients with acute pulmonary embolism (PE). We compared the predictive performance of the 2019 and 2014 ESC risk stratification algorithms and the Pulmonary Embolism Severity Index (PESI).

Methods: We performed a post-hoc analysis of normotensive patients aged ≥65 years with acute PE from a prospective cohort. The primary outcome was overall mortality; secondary outcomes were PE-related mortality and adverse outcomes (PE-related death,

cardiopulmonary resuscitation, intubation, catecholamine use, recurrent venous thromboembolism) at 30 days. We assessed outcomes in intermediate-high, intermediate-low, and low risk groups according to the 2019 and 2014 ESC algorithms and the PESI. Discriminative power was compared using the area under the receiver operating curve (AUC).

Results: Among 419 patients, 14 (3.3%) died (7 from PE) and 16 (3.8%) had adverse outcomes within 30 days. The 2019 ESC algorithm classified more patients as intermediate-high risk (45%) than the 2014 ESC algorithm (24%) or the PESI (37%), and only 19% as low risk (32% with 2014 ESC or the PESI). Discriminatory power for overall mortality was lower with the 2019 ESC algorithm (AUC 63.6%), compared to the 2014 ESC algorithm (AUC 71.5%) or the PESI (AUC 75.2%), although the difference did not reach statistical significance (p=0.063). Discrimination for PE-related mortality and adverse outcomes was similar.

Conclusions: While categorizing more patients in higher-risk groups, the 2019 ESC algorithm for PE did not improve prediction of short-term outcomes compared to the 2014 ESC algorithm or the PESI.

Keywords: Pulmonary Embolism Severity Index**,** echocardiography, right ventricular dysfunction, venous thromboembolism

INTRODUCTION

Pulmonary embolism (PE) can lead to acute hemodynamic instability and death.[1] PE patients presenting with hemodynamic instability have an average short-term mortality of 14% to 50%,[2, 3] and immediate thrombolysis must be considered in these high risk patients.[4] While up to 98% of patients with PE are hemodynamically stable during initial presentation,[5, 6] a subset will develop early complications.[7] Identifying these patients is critical to determine the optimal management approach.[4, 8]

The 2019 European Society of Cardiology (ESC) guidelines propose a risk-adjusted management algorithm for patients with acute PE based on clinical assessment (vital signs, use of a clinical prognostic model, such as the Pulmonary Embolism Severity Index [PESI] or its simplified version), evaluation of right ventricular (RV) function using transthoracic echocardiography (TTE) or computed tomography angiography (CTPA), and troponin measurement.[4, 9] The recommendation to assess RV function in all patients, even those who are clinically at low risk of complications, is new compared with the 2014 guideline version.[4, 10] Whether systematic RV assessment is efficient and can improve patient safety compared with selective assessment of RV function in higher-risk patients only is uncertain.

In the elderly population, cardiorespiratory comorbidities associated with RV dysfunction are more prevalent than in younger individuals.[11, 12] This may limit the benefit of RV function measurement for risk assessment in PE and may result in misclassification of the risk for adverse outcomes in this population.[13, 14] We therefore externally validated the prognostic performance of the 2019 ESC risk stratification algorithm in normotensive elderly PE patients from a prospective multicenter cohort and compared it to the 2014 ESC risk stratification algorithm and to risk stratification using PESI alone.

METHODS

Study design and population

This study was a post-hoc analysis of the prospective multicenter SWITCO65+ cohort study to assess outcomes in elderly patients with acute venous thromboembolism (VTE) from all 5 Swiss university and 4 large-volume non-university hospitals. Between September 2009 and March 2012, consecutive in- and outpatients aged ≥65 years with acute symptomatic PE and/or deep vein thrombosis (DVT) were enrolled. Exclusion criteria were thrombosis at a

different site than the lower extremities, catheter-related thrombosis, inability to provide informed consent (i.e., severe dementia), conditions incompatible with follow up (i.e., terminal illness), insufficient German or French speaking ability, or previous enrollment. The study methods have previously been described.[6]

For the current analysis, we only considered patients with acute symptomatic PE with hemodynamic stability (systolic blood pressure ≥90 mmHg at presentation) and available RV function assessment by TTE or CTPA within two days. We defined acute symptomatic PE as acute chest pain, new or worsening dyspnea, hemoptysis, or syncope with PE confirmed by CTPA, pulmonary angiography, or high probability ventilation-perfusion scan; or if patients had proximal DVT documented by compression ultrasonography or contrast venography with symptoms compatible with PE.[6]

This study was conducted in accordance with the Declaration of Helsinki. Approval was provided by the local Ethics Committee from each participating site. All participants or their legal representatives gave informed consent.

Baseline data collection

Trained study nurses collected information on demographics, comorbidities, vital signs at the time of presentation, laboratory results, and PE-related treatments.[6] Baseline blood samples were centrifuged, and stored at -80°C. For hs-cTnT measurement, electrochemiluminescence methods (Cobas e 601 analyzer, Hoffmann-La Roche, Rotkreuz, Switzerland) were used.[15]

Assessment of RV function

In all study participants, RV function was prospectively assessed by on-site cardiologists using TTE.[6] Assessment of RV function was based on 6 of 8 criteria recommended by the 2019 ESC PE guidelines (Supplementary Methods).[4] In patients without

TTE examination within two days, the initial CTPA images were used to assess RV function. RV dysfunction on CTPA was independently assessed by two radiologists and defined as RV/ LV diameter ratio of ≥1.0.[4, 16]

Risk categories

Patients were stratified as intermediate-high, intermediate-low, and low risk according to the 2019 and 2014 ESC guidelines (Table 1). Among the clinical risk assessment scores suggested by these guidelines, we used the PESI;[4, 10, 17] the PESI contains 11 clinical items and has been validated to predict early mortality and adverse outcomes in acute PE.[9] Patients were classified into risk categories according to the 2019 and 2014 ESC guidelines as shown in Table 1.[4, 10] A positive troponin was defined as hs-cTnT >14ng/L. Given that troponin is not consistently measured in all PE patients who have a low complication risk in clinical practice, and current risk stratification algorithms (ESC 2014, 2019) do not explicitly recommend the systematic measurement of troponin in low risk patients but rather mention it as an option, [4, 10] we did not consider troponin values in clinical low risk patients in our primary comparison. However, we performed a sensitivity analysis to determine the difference in outcomes between considering and not considering elevated troponin in low-risk patients. To allow a comparison with the 2019 and 2014 ESC risk stratification algorithms, we trichotomised PESI into a lower (PESI risk class I/II), an intermediate (class III), and a higher risk group (class IV/V) (Table 1).

Study outcomes

The primary outcome was 30-day overall mortality, as stratification for early risk of death is recommended in the 2019 ESC guidelines.[4] Secondary outcomes were PE-related mortality and adverse outcomes (defined as PE-related death, cardiopulmonary resuscitation, intubation, catecholamine use, or recurrent VTE [PE or DVT]) at 30 days.[17] Outcomes were assessed by patient interview and hospital chart review, and complemented by proxy and

primary care physician interviews if necessary. All VTE outcomes and deaths were adjudicated by a committee of three blinded clinical experts. The committee classified the cause of all deaths as definitely due to PE (i.e., autopsy-confirmed or death occurring in relation to a severe PE event), possibly due to PE (i.e., sudden death without any other explanation), or due to another cause. Final classification was based on the full consensus of all committee members. PE-related deaths were defined as deaths definitely or possibly related to PE.[6]

Statistical analysis

We calculated the proportion of low, intermediate-low, and intermediate-high risk patients according to the 2019 ESC, 2014 ESC risk stratification models, and the PESI. Baseline characteristics were presented according to 2019 ESC risk categories. We reported events at 30 days (overall mortality, PE-related mortality, and adverse outcomes) in low, intermediate-low, and intermediate-high risk patients for the three risk stratification modalities and assessed cumulative incidence of overall mortality at 30 days using Kaplan-Meier curves. To assess the benefit of assessing RV function when using the PESI for risk stratification, outcomes were determined across different PESI risk categories stratified by RV function.

We assessed the discriminative power of the categorized ESC algorithms and the PESI to predict overall mortality, PE-related mortality, and adverse outcomes at 30 days by calculating the area under the receiver operating characteristic curves (AUC), and performed a non-parametric test of the equality of the AUCs. We calculated the net reclassification index (NRI) to assess whether the 2019 ESC risk assessment model resulted in improved risk prediction compared to the 2014 ESC model or the PESI. For assessment of the NRI, we used two risk categories, i.e., the intermediate risk (defined as intermediate-high and intermediate-low risk categories) vs. low risk category (see Supplementary Methods).

Missing values were considered normal, as done previously.[9] To exclude bias due to data not missing at random, we performed sensitivity analyses excluding patients with missing values for systolic blood pressure and troponin. All analyses were conducted using Stata 15 (Stata Corporation, College Station, Texas).

RESULTS

Overall, 696 patients with acute PE were enrolled in the SWITCO65+ cohort. After exclusion of 8 patients who did not allow the use of their data, 1 patient who withdrew, 10 hemodynamically unstable patients, and 258 patients without RV function assessment within 48 hours, our sample for this analysis comprised 419 patients. Compared to the 258 patients who were excluded from analysis because unavailable RV function assessment, analyzed patients were somewhat younger (median age 74 vs. 76 years; p=0.07), more likely to be men (56% vs. 47%; p=0.039), but their median troponin T values 15.4 ng/L (interquartile range 7.5; 30.5) vs. 13.7 ng/L (6.8; 29.9), overall 30-day mortality 2.7% vs. 3.3%, PE-specific 30-day mortality 0% vs. 2%, and adverse outcomes 3% vs. 4% were comparable (Supplementary Table 1).

Baseline characteristics stratified by 2019 ESC risk categories are presented in Table 2. Median age was 74 years, 233 (56%) were men, and 209 (50%) showed signs of RV dysfunction. Active cancer, chronic lung disease, and tachycardia were more frequent in the intermediate risk category compared to the low risk category. Assessment of RV function was done by TTE in 69%, and in the remaining patients by CTPA. RV dysfunction was slightly more prevalent in intermediate-high than in intermediate-low risk patients (64% vs. 58%).

Risk classification and clinical outcomes

Based on the 2019 ESC risk stratification algorithm, almost twice as many patients were categorized as intermediate-high risk (45%) compared to the 2014 ESC algorithm (24%)

and 8% more than using the PESI (37%) (Table 3). Only 19% were classified as low risk with the 2019 ESC algorithm compared to 32% with the 2014 ESC algorithm or the PESI.

Overall, 14/419 patients (3.3%) died within 30 days, of which half were PE-related deaths. Sixteen patients had adverse outcomes within 30 days after the index PE. Overall mortality at 30 days was highest in the intermediate-high risk category of any of the three risk stratification modalities (4.8%, 95% confidence interval [CI] 2.6-8.9% for the 2019 ESC algorithm; 6.9%, 95% CI 3.4-13.6% for the 2014 ESC algorithm; and 7.2%, 95% CI 4.1-12.4% for the PESI), followed by the intermediate-low and low risk categories (Table 4). No deaths occurred in the ESC or PESI low risk categories. In contrast to the 2014 ESC algorithm and the PESI, the cumulative incidence of mortality did not differ across risk categories based on the 2019 ESC algorithm (Figures 1a-c).

Among intermediate-high risk patients, PE-related mortality after 30 days was 2.7% for the 2019 ESC algorithm, 4.0% for the 2014 ESC algorithm, and 3.3% for the PESI. The proportion of intermediate-high risk patients who developed adverse outcomes within 30 days was 5.4% for the 2019 ESC algorithm, 6.9% for the 2014 ESC algorithm, and 4.6% for the PESI (Table 4). No adverse outcomes occurred in low risk patients according to the 2019 ESC algorithm, and only 1 in the low risk categories based on the 2014 ESC algorithm and the PESI (Table 4). Sensitivity analyses excluding patients with missing data on systolic blood pressure (n=3) or troponin (n=25) yielded similar results (not shown).

When examining 30-day outcomes across the PESI risk categories stratified by RV function, 54 of 133 patients (40%) in the PESI low risk group showed signs of RV dysfunction (Supplementary Table 2). No deaths occurred in the PESI low-risk group, irrespective of RV function. In the intermediate-low (PESI class III) and intermediate-high risk group (PESI classes IV/V), overall and PE-related mortality did not differ in patients with RV dysfunction compared to those without (Supplementary Table 2).

Discriminatory power and NRI

For overall 30-day mortality, the 2019 ESC risk stratification algorithm tended to have the lowest discriminatory power, with an AUC of 63.6% compared to 71.5% for the 2014 ESC algorithm and 75.2% for the PESI (p=0.063). The discriminatory power of all three risk assessment modalities for PE-related 30-day mortality and adverse outcomes was similar (Table 5). In a sensitivity analysis, 22 and 40 patients classified as low risk according to 2019 and 2014 ESC risk stratification models, respectively, were reclassified as low-intermediate risk due to an isolated troponin elevation. In this analysis, the discriminatory power of the three risk assessment models was not significantly different for any of the outcomes (data not shown).

When comparing the 2019 ESC to the 2014 ESC algorithm and the PESI, the overall NRI was negative for all outcomes, indicating no improvement in risk prediction with the 2019 ESC algorithm (Supplementary Table 3). Based on the 2019 ESC algorithm, no patient among those who died was correctly reclassified from the low to a higher-risk category. However, 54 patients who did not die were incorrectly upgraded from the low to the intermediate risk categories by the 2019 ESC algorithm compared to the 2014 ESC algorithm or the PESI.

DISCUSSION

In our study, the 2019 ESC risk stratification algorithm, which recommends a systematic assessment of RV function, categorized a substantially smaller proportion of patients with acute PE as low risk and almost twice as many as intermediate-high risk compared to the 2014 ESC algorithm or the PESI. We found no evidence that the new algorithm improved prediction of short-term overall mortality, PE-related mortality, or adverse outcomes in elderly patients. Thus, the systematic assessment of RV function in all

patients with acute PE, regardless of their clinical risk, may not confer a clinical benefit and could result in a higher utilization of health care resources.

Risk stratification of PE patients based on hemodynamic status and use of validated risk stratification tools is recommended to assist with clinical decision-making.[4, 10] Hemodynamically unstable patients are at high risk of early death and should be considered for reperfusion. On the other side of the clinical spectrum of PE severity, low risk patients can be considered for outpatient treatment or early discharge.[4] All other patients are considered at intermediate risk and should be hospitalized. The ESC guidelines further subdivide intermediate risk patients into intermediate-high and intermediate-low risk categories based on the higher risk of deterioration in patients with impaired RV function.[4] Monitoring is recommended for intermediate-high risk patients, with rescue reperfusion therapy in case of deterioration.[4] We found that using the 2019 ESC algorithm for risk stratification shifted 13% of patients from low to intermediate risk, as previously also demonstrated in another cohort.[18] This impacts the use of health care resources: fewer patients would qualify for outpatient treatment or early discharge, while the proportion of intermediate-high risk patients requiring more intensive monitoring (e.g., in an intermediate care unit) almost doubles if using the 2019 ESC risk stratification algorithm compared to the 2014 version.

The major new feature of the 2019 ESC model is the systematic RV function assessment, even in patients at low risk of death as assessed by clinical scores. In our study of elderly patients, additional RV function assessment did not result in improved prediction of short-term mortality or adverse outcomes in the low risk group. A previous meta-analysis including 21 studies with low risk PE patients assessed early mortality according to RV function.[17] Ten of 552 patients with RV dysfunction (1.8%) versus 4 of 1045 patients without RV dysfunction (0.4%) died, resulting in an increased risk for overall mortality in patients with RV dysfunction compared to those without.[17] Another recent meta-analysis of 1868 patients at low risk as identified by clinical scores demonstrated that RV dysfunction was

associated with PE-related but not overall mortality compared to absence of RV dysfunction.[19] However, the absolute number of PE-specific deaths was very low, affecting 6/447 patients with and 2/1421 patients without RV dysfunction.[19] The results from the two meta-analyses are partially driven by the results from a registry that reported 4 deaths among 145 low-risk patients (only 1 was PE-related).[20] This relatively elevated mortality may be due to the high proportion of patients with cancer in this registry (31%), which was substantially higher than in our cohort (17%) and most other PE studies. Given the low absolute risk of adverse outcome events in low-risk PE patients in these meta-analyses, it is debatable whether RV function assessment translates into a measurable clinical benefit.

While the results of two meta-analyses suggest a very limited added value of RV function assessment compared to the use of clinical parameters for risk stratification in PE, clinical risk assessment has been shown to be safe and efficient in clinical trials, allowing up to 31-51% of patients to be discharged early or entirely managed in the outpatient setting.[8, 21] In a randomized trial, outpatient management of low-risk PE patients based on the PESI and other clinical criteria without RV function assessment or cardiac biomarkers was safe.[8] In another randomized trial, early discharge of low-risk PE patients identified using the Hestia criteria alone was not only safe, but led to substantial cost reductions compared with standard in-hospital treatment.[22] Moreover, the presence of RV dysfunction or elevated troponin did not predict adverse outcomes in patients with PE selected for home treatment.[23, 24] The 2020 guidance by the U.K. National Institute for Health Care Excellence (NICE) has incorporated the recommendation of outpatient treatment for low-risk PE patients, as identified by a validated clinical risk stratification tool, and does not recommend systemic RV function assessment or cardiac markers in low-risk patients.[25] To date, no prospective management studies have compared clinical risk assessment alone with a strategy combining clinical and systematic RV function assessment in low-risk PE patients. Although observational studies have shown an increased risk of short-term mortality in low-risk PE patients with compared to

those without RV dysfunction,[17, 19] whether a treatment upgrade (e.g., hospitalization or increased monitoring) improves patient safety remains to be investigated.

In our analysis, the 2019 ESC risk stratification algorithm tended to have a lower discriminative power for short-term outcomes than the simpler 2014 ESC algorithm or the PESI. Irrespective of RV function, no deaths occurred in low risk categories of any of the three risk stratification modalities, indicating that additional risk stratification in low-risk patients based on a validated clinical score may be unnecessary. Moreover, the NRI suggests that the 2019 ESC algorithm does not improve outcome prediction over the 2014 version or the PESI. However, implementation of the 2019 ESC algorithm could lead to potential management delays and additional costs not only for obtaining TTE in patients without CTPA (9% in our sample) but also by substantially reducing the proportion of patients qualifying for less costly outpatient care. Recent guidelines by the American Society of Hematology recommend ventilation/perfusion scanning as preferred imaging method for suspected PE in patients with a low or intermediate pre-test probability,[26] which would increase the need for echocardiographic RV function assessment if the 2019 ESC algorithm was used. Overall, assessment of RV function could be avoided in a substantial proportion of hemodynamically stable patients with PE (32% of low risk patients in our study) with the use of the older 2014 ESC algorithm instead of the 2019 version.

Our study has also limitations. First, although the current results are based on prospectively collected data from a broad population of elderly PE patients, risk assessment using the 2019 ESC algorithm has been done post-hoc. A future prospective impact analysis would be ideal to compare the real-life impact of the 3 risk stratification systems. Second, RV function assessment using TTE or CTPA has not been performed within two days of presentation in 258 patients, who were excluded from this analysis and are a possible source of selection bias. However, outcomes were comparable in the patients excluded due to unavailability of timely RV assessment. Third, as the elderly generally carry the largest

burden of PE mortality,[27] our analyses are not necessarily generalizable to younger patients. Still, the development of specific risk stratification algorithms for the elderly and other subgroups with PE must be carefully weighed against the practicability of such an approach. Finally, the interpretation of our study results may be limited by the low number of outcomes precluding a determination of potential differences in outcomes in association with RV dysfunction. However, the sample size and event rate in our study is comparable to similar studies.[18, 28]

In conclusion, the 2019 ESC risk stratification algorithm for PE classified more patients in a higher risk category compared to the 2014 ESC algorithm and the PESI, but did not improve prediction of short-term outcomes in the elderly with PE. Our results suggest that implementation of the 2019 ESC algorithm with systematic assessment of RV function may not confer a safety benefit in older PE patients but rather result in a higher use of health care resources by decreasing the proportion of patients who are safely eligible for outpatient care.

What is known on this topic?

- Risk stratification algorithms assist in identifying patients with acute pulmonary embolism who are at risk of early death and may thus benefit from hospitalization or increased monitoring.
- The risk stratification algorithm proposed by the 2019 ESC guidelines newly requires systematic right ventricular function assessment in all normotensive patients with acute pulmonary embolism independent of clinical risk.

What does this paper add?

- In a cohort of 419 older patients with pulmonary embolism, the 2019 ESC risk stratification algorithm categorized substantially fewer patients as low risk compared to the 2014 version.
- Systematic assessment of right ventricular function in older pulmonary embolism patients regardless of clinical risk did not improve prediction of adverse outcomes.

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Conflict of interest

The authors declare that they have no conflict of interest.

Author Contributions

All authors participated in the research and preparation of the manuscript. Study concept and design: D. Aujesky. Data acquisition: D. Aujesky, Marie Méan. Data analysis and interpretation: J. Moor, C. Baumgartner, Marie Méan, N. Rodondi, D. Aujesky. Drafting the manuscript: J. Moor, C. Baumgartner, D. Aujesky. Critical revision of the manuscript: J. Moor, O. Stalder, A. Limacher, Marie Méan, C. Baumgartner, N. Rodondi, D. Aujesky. Statistical analyses: O. Stalder, A. Limacher. Study supervision: D. Aujesky, C. Baumgartner. Approval of the final manuscript: all authors.

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Figure 1 Kaplan-Meier curves showing the cumulative incidence of 30-day overall mortality by 2019 ESC risk category. The cumulative mortality in the low, intermediate-low, and intermediate-high risk category was 0%, 3.3%, and 4.8%, respectively (p= 0.141).

Abbreviations: ESC= European Society of Cardiology.

Figure 2 Kaplan-Meier curves showing the cumulative incidence of 30-day overall mortality by 2014 ESC risk category. The cumulative mortality in the low, intermediate-low, and intermediate-high risk category was 0%, 3.8%, and 6.9%, respectively (p= 0.013).

Figure 3 Kaplan-Meier curves showing the cumulative incidence of 30-day overall mortality by PESI risk category. The cumulative mortality in the low (PESI risk classes I/II), intermediate-low (PESI risk class III), and intermediate-high risk category (PESI risk classes IV/V) was 0%, 2.2%, and 7.2%, respectively (p= 0.002).

Supplementary material

Validation of the 2019 ESC risk stratification algorithm for pulmonary embolism

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Content

Supplementary methods

Assessment of RV function

RV dysfunction required presence of at least one of the following: 1) RV end-diastolic diameter >41mm, 2) right-to-left ventricle (RV/LV) diameter ratio ≥1.0, 3) septal flattening or D-shaping of the left ventricle, 4) intrahepatic vena cava inferior diameter ≥21mm and reduced/absent respiratory variability, 5) pulmonary acceleration time <60ms and pressure gradient of right ventricle/right atrium >60mmHg, or 6) tricuspid annular plane systolic excursion <16mm.[1] Two additional criteria for RV dysfunction mentioned in the 2019 ESC guidelines, presence of RV mobile thrombus and decreased peak systolic velocity of tricuspid annulus <9.5 cm/s, were unavailable for our analysis.[1]

Net reclassification index (NRI)

We calculated the NRI to assess whether the 2019 ESC risk assessment model resulted in improved risk prediction compared to the 2014 ESC model or the PESI.[3] We additionally assessed the net proportion of patients who would be reclassified into higher or lower risk category by calculating the event and non-event NRI, respectively.[3,4] The event NRI refers to the net proportion of patients who experienced an event and who are assigned a higher risk category using the 2019 ESC algorithm compared to the 2014 ESC algorithm or the PESI alone (i.e., the change in true-positive rates), and the non-event NRI refers to the net proportion of patients who did not experience an event and who are assigned a lower risk category using the 2019 ESC algorithm compared to the 2014 ESC algorithm or the PESI alone (i.e., change in false positive rates).[4] For assessment of the NRI, we used two risk categories, i.e., the intermediate risk (defined as combined intermediate-high and intermediate-low risk categories) vs. low risk category.[4]

Supplementary references

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Supplementary Table 1. Characteristics and outcomes by RV function assessment availability

Characteristic	All (n=677)	No RV function assessment (n=258)	Analyzed patients (n=419)	p-value
	n (%) or median (IQ-range)			
PESI score	94.0 (81.0; 113.0)	89.0 (79.0; 113.0)	96.0 (82.0; 113.0)	0.056
PESI cat. I/II, III or IV/V				0.039
PESI I/II	238 (35)	106 (41)	132 (32)	
PESI III	207 (31)	73 (28)	134 (32)	
PESI IV/V	232 (34)	79 (31)	153 (37)	
hs-cTnT (ng/L)	14.6 (7.5; 30.1)	13.7 (6.8; 29.9)	15.4 (7.5; 30.5)	0.387
hs-cTnT (>14 ng/L)	309 (46)	100 (39)	209 (50)	0.194
Overall 30-day mortality	21 (3)	7 (3)	14 (3)	0.820
PE-related 30-day mortality	8 (1)	1 (0)	7 (2)	0.164
30-day adverse events*	23 (3)	7 (3)	16 (4)	0.517

Abbreviations: RV= right ventricle, IQ= interquartile, PESI= Pulmonary Embolism Severity Index, hs-cTnT= high-sensitive cardiac troponin T, PE= pulmonary embolism.

*Defined as PE-related death, cardiopulmonary resuscitation, intubation, catecholamine use, or recurrent VTE at 30 days.

Supplementary Table 2. Clinical outcomes by PESI risk category and RV function

	PESI risk categories											
	Low (PESI classes I/II)				Intermediate-low (PESI class III)				Intermediate-high (PESI classes IV/V)			
30-day outcomes	**No RVD**		**RVD**		**No RVD**		**RVD**		**No RVD**		**RVD**	
	n/N	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Overall mortality	0/78	0.0	0/54	0.0	1/67	1.5	2/67	3.0	5/65	7.7	6/88	6.8
PE-related mortality	0/78	0.0	0/54	0.0	0/67	0.0	2/67	3.0	2/65	3.1	3/88	3.4
Adverse outcomes*	0/78	0.0	1/54	1.9	2/67	3.0	6/67	9.0	2/65	3.1	5/88	5.7

Abbreviations: PESI= Pulmonary Embolism Severity Index, RV= right ventricule, PE= pulmonary embolism.

*Defined as PE-related death, cardiopulmonary resuscitation, intubation, catecholamine use, or recurrent VTE at 30 days.

Supplementary Table 3. Net reclassification index across the ESC algorithms and the PESI*

30-day outcomes	Event: correctly reclassified	Event: falsely reclassified	event NRI‡	Non-event: correctly reclassified	Non-event: falsely reclassified	non-event NRI§	Overall NRI
Overall mortality							
2019 ESC vs. 2014 ESC	0	0	0.000	0	54	-0.133	-0.133
2019 ESC vs. PESI	0	0	0.000	0	54	-0.133	-0.133
2014 ESC vs. PESI	0	0	0.000	0	0	0.000	0.000
PE-related mortality							
2019 ESC vs. 2014 ESC	0	0	0.000	0	54	-0.131	-0.131
2019 ESC vs. PESI	0	0	0.000	0	54	-0.131	-0.131
2014 ESC vs. PESI	0	0	0.000	0	0	0.000	0.000
Adverse outcomes†							
2019 ESC vs. 2014 ESC	1	0	0.063	0	53	-0.132	-0.069
2019 ESC vs. PESI	1	0	0.063	0	53	-0.132	-0.069
2014 ESC vs. PESI	0	0	0.000	0	0	0.000	0.000

Abbreviations: NRI= net reclassification index, ESC= European Society of Cardiology, PESI= Pulmonary Embolism Severity Index, PE= pulmonary embolism.

*To calculate the NRI, we only considered two categories for each risk assessment modality (combined intermediate-high and intermediate-low risk categories vs. low risk category).

†Defined as PE-related death, cardiopulmonary resuscitation, intubation, catecholamine use, or recurrent VTE at 30 days.

‡The event NRI refers to the change in true-positive events and was calculated as the proportion of events that are correctly assigned to a higher risk category with the new risk stratification modality minus the proportion of events that are incorrectly assigned a lower risk category with the new modality $P(\text{up}|D=1) - P(\text{down}|D=1)$ (2).

§The non-event NRI refers to the change in false-positive events and was calculated as the proportion of non-events that are correctly assigned to a lower risk category with the new risk stratification modality minus the proportion of non-events that are incorrectly assigned a higher risk category with the new modality $P(\text{down}|D=0) - P(\text{up}|D=0)$ (2).

Table 1. Definition of ESC and PESI risk categories

	2019 ESC		2014 ESC		PESI
Risk category	**PESI class ≥III or RVD**	**Positive troponin***	**PESI class**	**RVD or positive troponin***	**PESI class ‡**
Low	Both absent		I-II	-	I-II
Intermediate-low	Either one or both present	Absent	≥III	Either one present or both absent	III
Intermediate-high	Either one or both present	Present	≥III	Both present	IV-V

Abbreviations: ESC= European Society of Cardiology, PESI= Pulmonary Embolism Severity Index, RVD= right ventricular dysfunction.

*High-sensitivity troponin of >14 ng/L.

‡ To allow direct comparison, the PESI risk classes were trichotomized as indicated. The original PESI categories were the following: class I: "very low mortality risk", class II: "low mortality risk", class III: "moderate mortality risk", class IV: "high mortality", and class V: "very high mortality risk". The PESI classes are not completely representative, because all patients classified as high-risk according to 2019 or 2014 ESC are excluded from the current study.

Table 2. Baseline characteristics by 2019 ESC risk category

Characteristic	All¿ (n = 419)	Low risk (n = 78)	Intermediate-low risk (n = 154)	Intermediate-high risk (n = 187)
	n (%) or median (interquartile range)			
Age, years	74.0 (69.0; 80.0)	72.0 (67.0; 75.0)	74.0 (69.8; 81.0)	76.0 (70.0; 82.0)
Male sex	233 (56)	33 (42)	91 (59)	109 (58)
Active cancer	70 (17)	0 (0)	33 (21)	37 (20)
Chronic heart failure	31 (7)	2 (3)	7 (5)	22 (12)
Chronic lung disease	61 (15)	1 (1)	21 (14)	39 (21)
Heart rate ≥110 beats/min.	59 (14)	0 (0)	19 (12)	40 (21)
Systolic BP 90-100 mmHg	8 (2)	0 (0)	2 (1)	6 (3)
Respiratory rate ≥30 breaths/ min.	17 (4)	0 (0)	8 (5)	9 (5)
Altered mental status†	15 (4)	0 (0)	3 (2)	12 (6)
Temperature <36°C	39 (9)	0 (0)	16 (10)	23 (12)
Diagnostic modality for PE				
CTPA	381 (91)	72 (92)	144 (94)	165 (88)
V/Q scan	25 (6)	5 (6)	6 (4)	14 (7)
Pulmonary angiography	1 (0)	0 (0)	1 (1)	0 (0)
Proximal DVT with PE	12 (3)	1 (1)	3 (2)	8 (4)

symptoms				
Positive hs-cTnT‡	209 (50)	22 (28)	0 (0)	187 (100)
Presence of RVD on TTE or CTPA	209 (50)	0 (0)	90 (58)	119 (64)

Abbreviations: ESC= European Society of Cardiology, BP= blood pressure, hs-cTnT= high-sensitive cardiac troponin T, RVD= right ventricular dysfunction, TTE= transthoracic echocardiography, CTPA= computed tomography pulmonary angiography, V/Q= ventilation-perfusion, DVT= deep vein thrombosis, PE= pulmonary embolism.

¿Data on heart rate was missing in 1%, systolic BP in 1%, respiratory rate in 23%, temperature in 3%, and hs-cTnT in 9%.

†Disorientation, lethargy, stupor, or coma.

‡Plasma concentration of >14 ng/L. As troponin was measured according to routine clinical practice in the SWITCO 65+ cohort, we only considered troponin for participants classified in the intermediate risk categories for further risk stratification as recommended.

Table 3. Risk classification according to the ESC algorithms and the PESI

	Low risk	Intermediate-low risk	Intermediate-high risk
Risk stratification modality	**n/N (%)**	**n/N (%)**	**n/N (%)**
2019 ESC	78/419 (19%)	154/419 (37%)	187/419 (45%)
2014 ESC	132/419 (32%)	186/419 (44%)	101/419 (24%)
PESI	132/419 (32%)	134/419 (32%)	153/419 (37%)

Abbreviations: ESC= European Society of Cardiology, PESI= Pulmonary Embolism Severity Index.

Table 4. Outcomes by risk categories according to the ESC algorithms and the PESI

	Low risk		Intermediate-low risk		Intermediate-high risk	
30-day outcomes	**n/N**	**% (95% CI)**	**n/N**	**% (95% CI)**	**n/N**	**% (95% CI)**
Overall mortality						
2019 ESC	0/78	0.0 (0.0-4.7)	5/154	3.3 (1.4-7.4)	9/187	4.8 (2.6-8.9)
2014 ESC	0/132	0.0 (0.0-2.8)	7/186	3.8 (1.8-7.6)	7/101	6.9 (3.4-13.6)
PESI	0/132	0.0 (0.0-2.8)	3/134	2.2 (0.8-6.4)	11/153	7.2 (4.1-12.4)
PE-related mortality						
2019 ESC	0/78	0.0 (0.0-4.7)	2/154	1.3 (0.4-4.6)	5/187	2.7 (1.2-6.1)
2014 ESC	0/132	0.0 (0.0-2.8)	3/186	1.6 (0.6-4.6)	4/101	4.0 (1.6-9.7)
PESI	0/132	0.0 (0.0-2.8)	2/134	1.5 (0.4-5.3)	5/153	3.3 (1.4-7.4)
Adverse outcomes*						
2019 ESC	0/78	0.0 (0.0-4.7)	6/154	3.9 (1.8-8.2)	10/187	5.4 (2.9-9.6)
2014 ESC	1/132	0.8 (0.1-4.2)	8/186	4.3 (2.2-8.3)	7/101	6.9 (3.4-13.6)
PESI	1/132	0.8 (0.1-4.2)	8/134	6.0 (3.1-11.3)	7/153	4.6 (2.2-9.1)

Abbreviations: ESC= European Society of Cardiology, PESI= Pulmonary Embolism Severity Index, CI= confidence interval, PE= pulmonary embolism.

§Defined as PE-related death, cardiopulmonary resuscitation, endotracheal intubation, use of intravenous catecholamines, or recurrent venous thromboembolism within 30 days.

*7 patients died due to PE, 2 had cardiopulmonary resuscitation and/or intubation, 6 received catecholamines, and 1 had recurrent VTE.

Table 5. Discriminatory power of the ESC and the PESI risk categories

30-day outcomes	AUC (95% CI)	p-value*
Overall mortality		
2019 ESC	63.6 (58.9-68.3)	0.063
2014 ESC	71.5 (67.0-75.9)	
PESI	75.2 (70.8-79.2)	
PE-related mortality		
2019 ESC	66.3 (61.6-70.9)	0.389
2014 ESC	73.7 (69.3-77.9)	
PESI	72.3 (67.8-76.5)	
Adverse outcomes†		
2019 ESC	62.9 (58.2-67.6)	0.519
2014 ESC	67.0 (62.3-71.5)	
PESI	60.9 (56.0-65.6)	

Abbreviations: PE= pulmonary embolism, AUC= area under the receiver operating curve, CI= confidence interval, ESC= European society of cardiology, PESI= Pulmonary Embolism Severity Index.

*Comparison of the 3 AUCs of the different risk stratification models.

†7 patients died due to PE, 2 had cardiopulmonary resuscitation and/or intubation, 6 received catecholamines, and 1 had recurrent VTE.