Adverse Events and Mortality in Anticoagulated Patients with Different Categories of Pulmonary Embolism

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Abstract

Objective: To determine whether the pulmonary embolism (PE) categories of massive, submassive, PE with no right ventricle dysfunction (NRVD), and subsegmental only (SSO) adequately predict clinical outcome.

Methods: Patients treated for acute PE (March 1, 2013, through July 31, 2019) were followed forward prospectively to compare venous thromboembolism (VTE) recurrence, all-cause mortality, major bleeding, and clinically relevant nonmajor bleeding (CRNMB) across 4 PE categories.

Results: Of 2703 patients with VTE, 1188 (44%) had PE, of which 1021 (85.9%) completed at least 3 months of therapy or had clinical outcomes precluding further treatment (27 with massive, 217 submassive, 557 NRVD, and 220 SSO PE). One patient with massive, 8 with submassive, 23 with NRVD, and 5 with SSO PE had recurrent VTE (3.90, 5.33, 5.36, and 3.66 per 100 person-years, respectively; $P=0.84$). There were 3 deaths in massive, 27 in submassive, 140 in NRVD, and 34 in SSO PE groups (11.59, 17.37, 31.74, and 24.74 per 100 person-years, respectively; $P=0.02$); when adjusted for cancer, the relationship was no longer significant ($P=0.27$). One patient with massive, 5 with submassive, 22 with NRVD, and 5 with SSO PE had major bleeding (3.90, 3.31, 5.24, and 3.75 per 100 person-years, respectively; $P=0.66$). Similar cumulative rates for CRNMB were observed ($P=0.87$). Three-month rates of VTE recurrence, death, major bleeding, and CRNMB did not differ by PE category.

Conclusion: In the setting of anticoagulation therapy with maximal standardization and evidence-based practice, there is no evidence of a difference between PE categories and outcomes.

Trial Registration: NCT03504007

Pulmonary embolism (PE) is an acute complication of deep vein thrombosis (DVT) and is the third most common cause of cardiovascular death.1–3 Pulmonary embolism encompasses a wide range of presentations, from asymptomatic to hemodynamic instability and sudden death. Several prognostic stratification tools have been proposed comprising a mixture of clinical, laboratory, and anatomical findings. These stratification qualifiers were created based on their effect on PE clinical outcomes, particularly mortality.4,5 The American Heart Association (AHA) uses the presence or absence of sustained hypotension to differentiate PE into massive or not massive.4 Pulmonary embolism without hemodynamic instability is further differentiated into PE with right ventricle (RV) dysfunction, which is called submassive or intermediate-risk PE, and PE without RV dysfunction, called low-risk PE. In addition to the AHA-recommended PE categories, other groups have defined a distinct category of PE termed isolated subsegmental PE in which the most proximal occlusive defect is found in the
subsegmental arteries. The European Society of Cardiology uses the Pulmonary Embolism Severity Index (PESI) or the simplified PESI score, and defines normotensive patients with PE as intermediate risk if the PESI class is III or greater or if the simplified PESI score is 1 or more. Further stratification into intermediate-high risk or intermediate-low risk depends on the presence or absence of RV dysfunction.

Advances in PE diagnosis, such as the use of d-dimer measurement and particularly the introduction of multidetector row computed tomography (CT) pulmonary angiography, which facilitates detection of very small emboli, raise the concern for overdiagnosis of potentially less significant PE. Some researchers have proposed that subsegmental PE, if not associated with DVT, and particularly if in an asymptomatic patient with good cardiorespiratory reserve, does not require treatment with anticoagulation. Classical, high-risk PE is thought to encompass massive and submassive PE categories, whereas patients with subsegmental defects on radiographic imaging are thought to have a more benign course.

The aim of this study was to analyze prospectively collected data from patients with confirmed PE to compare demographic and clinical features as well as outcome measures, such as venous thromboembolism (VTE) recurrence, major bleeding, clinically relevant nonmajor bleeding (CRNMB), and mortality rates, across 4 PE categories.

MATERIALS AND METHODS

Patient Recruitment
Analysis included consecutive patients with acute PE who were treated for at least 3 months with anticoagulation drugs at the Thrombophilia Clinic, Gonda Vascular Center, Mayo Clinic Rochester, from March 1, 2013, through July 31, 2019. For some patients, the treatment course was prematurely aborted due to an aforementioned study outcome or death.

The Thrombophilia Clinic’s highly organized system, which includes streamlined referrals that ensure prompt, guideline-supported patient care, has been previously described. Briefly, if a patient has positive testing for acute VTE, the radiologist reading the study contacts the Thrombophilia Center, the patient is immediately evaluated, and, when appropriate, anticoagulation therapy is initiated. Templated, continuously updated information about available Food and Drug Administration–approved anticoagulants for acute VTE is provided, using a standardized script for providers and a short summary table with medication characteristics for the patient.

In general, patients with symptomatic PE were referred for prompt hospitalization. Hospitalized patients were evaluated by vascular medicine and had a follow-up visit at the Thrombophilia Clinic arranged after discharge. For patients with asymptomatic or minimally symptomatic PE, outpatient management was offered. We used the simplified PESI score tool counting 1 point for each of the following: younger than 80 years, presence of cancer, chronic heart failure, chronic pulmonary disease, pulse rate of 110 beats/min or greater, systolic blood pressure less than 100 mm Hg, and arterial oxyhemoglobin saturation less than 90%.

For patients with cancer and, therefore, a simplified PESI score of 1, outpatient therapy was accepted after consultation with the primary Mayo Clinic hematologist/oncologist. All patients with symptoms of DVT were evaluated by ultrasonography. In addition, all patients with cancer had a lower-extremity ultrasound, and if they had a central catheter, an upper-extremity ultrasound as well.

Demographic and clinical data were gathered prospectively, and patient status was reassessed after 3 months of anticoagulation. After the initial 3 months, follow-ups were conducted when clinically indicated at 3-month intervals, or annually if there was an indication for long-term anticoagulation. Patient status was assessed in person, by mailing a written questionnaire, or via a scripted phone interview. Institutional review board approval was obtained for this prospective study.

Study Definitions and Outcome Measures
Based on AHA criteria, massive PE was defined as an acute PE with sustained hypotension (systolic blood pressure < 90 mm Hg), pulselessness, or persistent profound bradycardia (heart rate < 40 beats/min with signs or symptoms of shock). Submassive PE was
defined as an acute PE that caused biochemical or radiographic evidence of RV strain or myocardial necrosis but did not meet the criteria for massive PE. In this study, the AHA category of low-risk PE was replaced by descriptive terminology of PE with no RV dysfunction (NRVD) for those who had no imaging or laboratory indicators of RV injury. This nomenclature was used to better distinguish NRVD from subsegmental PE, which is also considered to be low risk. In previous studies, the term isolated subsegmental PE has at times been used to characterize PE of a single subsegmental location; however, in the present study, single as well as multiple subsegmental PEs were included in this category. To avoid this potentially confusing terminology in the present study, those with the largest filling defect at the subsegmental level in the category of NRVD (irrespective of 1 or multiple defects) were separated into the category of subsegmental only (SSO).

All patients with PE, irrespective of PE category, were treated with anticoagulation for a minimum of 3 months. Anticoagulation was stopped after 3 or 6 months if PE was provoked, and anticoagulation was continued long-term in those with unprovoked thromboembolic events and low bleeding risk according to current guidelines. Those with cancer had anticoagulation for a minimum of 6 months and until cancer free.

Every PE was diagnosed by contrast-enhanced CT or magnetic resonance imaging. Every DVT of the extremity was identified by ultrasonography with Doppler technique and abdominal venous thrombosis by CT venogram. All patients with massive and submassive PE underwent echocardiography. Patients with PE without RV strain on CT and normal troponin and brain natriuretic peptide levels had echocardiography ordered at the discretion of the primary medical service. The primary efficacy outcome was radiologically proven VTE recurrence as previously described. To be classified as a true recurrent event there had to be a new filling defect evident on the second study not appreciated on the original images or an interval study clearly showing thrombus resolution. Death was categorized as a result of PE, bleeding, cancer, or other established diagnoses or from unknown cause. Pulmonary embolism was considered the cause of death if there was objective documentation of the condition or if there was an unexpected sudden death in the setting of an established or highly probable PE.

The primary safety outcome was major bleeding, defined as fatal bleeding, bleeding in a critical area (intracranial, intraspinal, intraocular, retroperitoneal, pericardial), or overt bleeding causing a hemoglobin level decrease of 2 g/dL or more (to convert to g/L, multiply by 10) after the incident or warranting a transfusion of 2 U or more of packed red blood cells. The secondary safety outcome was CRNMB, defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, an unscheduled contact with a member of the health care team, or temporary cessation of treatment. All events were adjudicated independently using previous study criteria by a committee composed of 3 Thrombophilia Clinic physicians (A.I.C., D.F., W.E.W.).

**Statistical Analysis**

Continuous numerical variables are reported as mean ± SD. Continuous variables were compared among PE categories using the analysis of variance procedure. Each pairwise comparison among the 4 groups was completed. Categorical factors were compared among groups using the \( \chi^2 \) test for independence. Follow-up end points were estimated using the Kaplan-Meier method. Summaries of these end points are provided using the person-years approach. Potential risk factors for each outcome were evaluated using proportional hazards models. The proportional hazards assumption was tested using Schoenfeld residuals. The assumption was not violated for the variables of interest in the models. The Fine and Gray method was used to evaluate outcomes using death as a competing risk for the event of interest. A \( P < .05 \) was considered statistically significant. Study data were collected and managed using REDCap (Research Electronic Data Capture), and data analysis was performed using SAS software, Version 9.4 (SAS Institute Inc).
| Variable                                           | Massive PE (n=27) | Submassive PE (n=217) | PE with NRVD (n=557) | SSO PE (n=220) | P value |
|---------------------------------------------------|------------------|-----------------------|----------------------|----------------|---------|
| Age (y), mean ± SD                                | 59.1 ± 18.0      | 63.3 ± 13.1           | 60.9 ± 14.2          | 61.4 ± 14.7    | .28     |
| Weight (kg), mean ± SD                            | 101.0 ± 20.0     | 97.1 ± 25.3           | 90.5 ± 24.8          | 87.5 ± 25.9    | <.001   |
| Female sex (No. [%])                              | 10 (37.0)        | 88 (40.6)             | 246 (44.2)           | 98 (44.5)      | .70     |
| Symptomatic (No. [%])                             | 27 (100.0)       | 191 (88.4)            | 293 (52.6)           | 104 (47.3)     | <.001   |
| Previous VTE (No. [%])                            | 4 (14.8)         | 49 (22.6)             | 98 (17.6)            | 38 (17.3)      | .37     |
| With DVT (No. [%])                                | 15 (55.6)        | 134 (61.8)            | 245 (44.0)           | 77 (35.0)      | <.001   |
| Leg, proximal DVT only                            | 6 (22.2)         | 36 (16.6)             | 58 (10.4)            | 13 (5.9)       | .001    |
| Leg, distal DVT only                              | 2 (14.3)         | 33 (28.2)             | 89 (21.2)            | 33 (18.0)      | .18     |
| Upper-extremity DVT only                          | 0                | 2 (1.7)               | 10 (2.4)             | 5 (2.7)        | .88     |
| Mesenteric only                                   | 0                | 0                     | 1 (0.2)              | 0              | .86     |
| Portal only                                       | 0                | 0                     | 2 (0.5)              | 1 (0.5)        | .88     |
| Splenic only                                      | 0                | 0                     | 1 (0.2)              | 0              | .86     |
| Ovarian only                                      | 0                | 0                     | 1 (0.2)              | 0              | .86     |
| Renal only                                        | 0                | 0                     | 1 (0.2)              | 0              | .86     |
| Cerebral only                                     | 0                | 0                     | 1 (0.2)              | 0              | .86     |
| Other DVT location only                           | 0                | 0                     | 4 (1.0)              | 1 (0.5)        | .70     |
| Provoked PE (No. [%])                             | 17 (63.0)        | 142 (65.4)            | 439 (78.8)           | 171 (77.7)     | <.001   |
| Risk factors for PE (No. [%])                     |                  |                       |                      |                |         |
| Active cancer                                     | 5 (18.5)         | 70 (32.3)             | 318 (57.1)           | 107 (48.6)     | <.001   |
| Chemotherapy (only in cancer patients)            | 1 (20.0)         | 38 (54.3)             | 212 (66.7)           | 70 (65.4)      | .04     |
| Surgery ≤30 d before PE                           | 7 (25.9)         | 29 (13.4)             | 88 (15.8)            | 26 (11.8)      | .17     |
| Immobility                                        | 6 (22.2)         | 39 (18.0)             | 70 (12.6)            | 35 (15.9)      | .5     |
| Trauma                                            | 3 (11.1)         | 12 (5.5)              | 28 (5.0)             | 9 (4.1)        | .46     |
| Thrombophilia                                     | 1 (3.7)          | 6 (2.8)               | 8 (1.4)              | 4 (1.8)        | .57     |
| Pregnancy/hormonal therapy                        | 2 (7.4)          | 7 (3.2)               | 28 (5.0)             | 12 (5.5)       | .60     |
| Other                                              | 3 (11.1)         | 25 (11.5)             | 68 (12.2)            | 36 (16.4)      | .39     |
| CrCl (mL/min/1.73 m²), mean ± SD                  | 113.1 ± 54.3     | 107.0 ± 49.6          | 103.7 ± 46.1         | 100.4 ± 47.2   | .19     |
| Distribution (No. [%])                            |                  |                       |                      |                | .28     |
| <30 mL/min/1.73 m²                                | 1 (3.7)          | 2 (0.9)               | 5 (0.9)              | 3 (1.4)        |         |
| 30 to 50 mL/min/1.73 m²                            | 5 (18.5)         | 70 (32.3)             | 175 (31.4)           | 83 (37.7)      | .77     |
| >50 mL/min/1.73 m²                                 | 21 (77.8)        | 145 (66.8)            | 377 (67.7)           | 134 (60.9)     |         |
| Platelet (x 10³/μL), mean ± SD                    | 0.20 ± 0.10      | 0.24 ± 0.11           | 0.25 ± 0.11          | 0.25 ± 0.11    | .03     |
| Distribution (No. [%])                            | 87               |                       |                      |                |         |
| <100 x 10³/μL                                     | 2 (7.4)          | 8 (3.7)               | 25 (4.5)             | 9 (4.1)        |         |
| 100-199 x 10³/μL                                  | 3 (11.1)         | 28 (12.9)             | 73 (13.1)            | 22 (10.0)      |         |
| ≥200 x 10³/μL                                     | 22 (81.5)        | 181 (83.4)            | 459 (82.4)           | 189 (85.9)     |         |
| Inferior vena cava filter (No. [%])                | 5 (18.5)         | 23 (10.6)             | 45 (8.4)             | 15 (6.8)       | .14     |
| Lytic therapy, systemic/catheter (No. [%])        | 10/2 (44.4)      | 0/11 (5.1)            | 0/8 (1.4)            | 0/2 (0.9)      | <.001   |
| First anticoagulant used (No. [%])                 | <.001            |                       |                      |                |         |
| Low-molecular-weight heparin                       | 6 (22.2)         | 82 (37.8)             | 295 (53.0)           | 115 (52.3)     |         |
| Unfractionated heparin                            | 17 (63.0)        | 84 (38.7)             | 97 (17.4)            | 39 (17.7)      |         |
| Apixaban                                          | 1 (3.7)          | 25 (11.5)             | 87 (15.6)            | 39 (17.7)      |         |
| Rivaroxaban                                       | 2 (7.4)          | 18 (8.3)              | 61 (11.0)            | 22 (10.0)      |         |

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RESULTS

Classification Data
During the study period (March 1, 2013, through July 31, 2019), there were 2703 patients with acute VTE enrolled in our standardized clinical practice, of which 1188 (44%) were diagnosed as having PE. After the exclusion of patients without research authorization (n = 97) and those who had not completed 3 months of anticoagulation for reasons other than a studied outcome event such as death (n = 70), 1021 patients were included in the study.

In this group, there were 27 patients (2.6%) with massive PE, 217 (21.3%) with submassive PE, 557 (54.6%) with PE with NRVD, and 220 (21.5%) with SSO PE. Two patients with radiographic findings of embolic thrombi limited to subsegmental territory had echocardiographic and laboratory evidence of RV strain and were, therefore, categorized as having submassive PE.

Demographic Data
Demographic and clinical characteristics of patients in the 4 categories of PE are summarized in Table 1. Patients with massive PE had higher body weight compared with the NRVD and SSO groups. By definition, all patients with massive PE were symptomatic. Patients with submassive PE were more often symptomatic compared with the NRVD and SSO PE groups. Coexisting DVT (including isolated proximal DVT) was detected more often in patients with massive and submassive PE compared with the NRVD and SSO groups. Upper-extremity DVT was found in a minority of patients with PE (0%-2.7%). Very few patients had isolated ovarian, renal, mesenteric, splenic, or portal DVT or cerebral venous sinus thrombosis (Table 1). Patients with submassive PE more often had previous VTE compared with other groups. NRVD and SSO PE were more often provoked and were more commonly associated with cancer compared with massive and submassive PE. All other provoking factors were distributed evenly among PE categories. A similar proportion of patients in each PE category had renal failure and thrombocytopenia (Table 1). More than 20% of patients with massive PE had an inferior vena cava filter placed compared with 7% of those with SSO PE (Table 1).

Enoxaparin was the first anticoagulant used in more than half of patients with NRVD and SSO PE but in a minority of those with massive and submassive PE (Table 1). In contrast, unfractionated intravenous heparin was used in two-thirds of patients with massive PE but in less than 20% of the NRVD and SSO groups. Apixaban, followed by rivaroxaban, was the most common oral anticoagulant used for initiation of therapy. Very few patients received warfarin along with parenteral anticoagulation the first day of therapy (Table 1).

In the massive PE group, systemic lytic therapy and catheter-directed thrombolysis were used in 10 and 2 patients, respectively. No patients in the other PE categories were treated with systemic thrombolysis, but 11 patients (5.2%) with submassive, 8 (1.5%) with NRVD, and 2 (0.9%) with SSO PE had catheter-based pharmacomechanical thrombolytic therapy of proximal DVT (Table 1).
Clinical Outcomes

During the study period, 1 patient with massive, 8 with submassive, 23 with NRVD, and 5 with SSO PE experienced another VTE, corresponding to recurrence rates of 3.90, 5.33, 5.36, and 3.66 per 100 person-years, respectively (\(P = .84\)) (Table 2). Kaplan-Meier curves for time to VTE recurrence by PE category are shown in the Figure, A. Three-month rates of VTE recurrence for massive (3.7%), submassive (1.4%), NRVD (2.0%), and SSO (0.9%) PE were not significantly different (\(P = .60\)).

There were 3, 27, 140, and 34 deaths in the massive, submassive, NRVD, and SSO PE groups, respectively, for mortality rates of 11.59, 17.37, 31.74, and 24.74, per 100 person-years, respectively (\(P = .02\)) (Table 2). Cumulative incidence curves for the time to death of patients in the 4 PE categories are shown in the Figure, B. When the PE with NRVD group was used as a comparator in the Cox model analysis, the SSO PE group had similar mortality, with a hazard ratio (HR) of 0.81 (95% CI, 0.55-1.18). The difference in mortality for massive PE compared with PE with NRVD was not significant (HR, 0.36; 95% CI, 0.11-1.12; \(P = .08\)). Submassive PE had significantly lower mortality compared with PE with NRVD (HR, 0.58; 95% CI, 0.38-0.84; \(P = .009\)), but after adjustment for cancer, the difference was not significant (HR, 0.79; 95% CI, 0.52-1.20; \(P = .27\)). Very low and similar 3-month mortality rates for massive, submassive, NRVD, and SSO PE (0%, 0.50%, 0.70%, and 0.90%, respectively; \(P = .92\)) were observed (Table 2). Three patients died of major bleeding, 1 patient in each of the submassive, NRVD, and SSO PE categories. There were no deaths from PE recurrence during follow-up.

### Table 2. Clinical Outcomes of Patients by Category of PE

| Outcome          | Massive PE (n=27) | Submassive PE (n=217) | PE with NRVD (n=557) | SSO PE (n=220) | \(P\) value<sup>2</sup> |
|------------------|-------------------|-----------------------|----------------------|----------------|-------------------------|
| **Efficacy**     |                   |                       |                      |                |                         |
| VTE recurrence   |                   |                       |                      |                |                         |
| Rate/100 person-years (95% CI) | 3.90 (0-11.55) | 5.33 (1.64-9.04) | 5.36 (3.17-7.55) | 3.66 (0.45-6.88) | .84                     |
| No. of events    | 1                 | 8                     | 23                   | 5              |                         |
| Total person-years | 25.63          | 149.86                | 429.21               | 136.47         |                         |
| 3-mo rate (No. [%]) | 1 (3.7)       | 3 (1.4)               | 11 (2.0)             | 2 (0.9)        | .60                     |
| Death            |                   |                       |                      |                |                         |
| Rate/100 person-years (95% CI) | 11.59 (0-24.70) | 17.37 (11.08-23.92) | 31.74 (26.48-36.99) | 24.74 (16.43-33.06) | .02                     |
| No. of events    | 3                 | 27                    | 140                  | 34             |                         |
| Total person-years | 25.89          | 155.43                | 441.14               | 137.41         |                         |
| 3-mo rate (No. [%]) | 0               | 1 (0.5)               | 4 (0.7)              | 2 (0.9)        | .92                     |
| **Safety**       |                   |                       |                      |                |                         |
| Major bleeding   |                   |                       |                      |                |                         |
| Rate/100 person-years (95% CI) | 3.90 (0-11.56) | 3.31 (0.41-6.22) | 5.24 (3.05-7.42) | 3.75 (0.46-7.03) | .69                     |
| No. of events    | 1                 | 5                     | 22                   | 5              |                         |
| Total person-years | 25.61          | 150.91                | 420.21               | 133.46         |                         |
| 3-mo rate (No. [%]) | 1 (3.7)       | 2 (0.9)               | 13 (2.3)             | 3 (1.4)        | .47                     |
| CRNMB            |                   |                       |                      |                |                         |
| Rate/100 person-years (95% CI) | 3.97 (0-11.75) | 8.87 (4.05-13.70) | 6.63 (4.18-9.09) | 7.60 (2.89-12.32) | .87                     |
| No. of events    | 1                 | 13                    | 28                   | 10             |                         |
| Total person-years | 25.20          | 146.49                | 422.26               | 131.51         |                         |
| 3-mo rate (No. [%]) | 1 (3.7)       | 10 (4.6)              | 10 (1.8)             | 6 (2.7)        | .18                     |

<sup>a</sup>CRNMB = clinically relevant nonmajor bleeding; VTE = venous thromboembolism.

<sup>b</sup>\(P\) values were calculated using the Fine and Gray method or the log-rank test.
During anticoagulation, 1 patient with massive, 5 with submassive, 22 with NRVD, and 5 with SSO PE experienced major bleeding, representing rates per 100 person-years of 3.90, 3.31, 5.24, and 3.75, respectively (P = .69) (Table 2). Three-month rates of major bleeding were also similar in all 4 PE categories (3.70%, 0.90%, 2.30%, and 1.40%, respectively; P = .47). Likewise, similar rates of CRNMB per 100 person-years in all 4 categories (P = .87) and at 3 months (P = .18) were observed (Table 2). Kaplan-Meier curves for time to major bleeding and CRNMB are shown in the Figure, C and D, respectively. Composite of major bleeding and CRNMB was also not different among PE categories (P = .97).

**DISCUSSION**

The major finding of this study is that categories of PE that are considered to be low or very low risk, such as NRVD and SSO PE, have similar outcomes to categories considered to be high or intermediate risk, such as massive and submassive PE. The VTE recurrence and major bleeding rates did not differ across the 4 PE categories. Mortality was not dependent on RV function but rather was related to patients’ comorbidities, particularly underlying malignancy. We observed that patients with submassive PE had lower mortality rates compared with patients with PE with NRVD, but after adjusting for cancer, the difference was not statistically significant. The 2 opposite extremes of PE severity, massive PE...
and SSO PE, had no difference in survival compared with PE with NRVD. More patients with SSO and NRVD PE had asymptomatic PE, but more often cancer was present, compared with massive and submassive PE. In fact, cancer was present more than twice as often in SSO PE compared with submassive PE. This is likely related to more SSO PE being incidentally diagnosed in patients with cancer during imaging studies for neoplasm staging. This suggests that currently used PE categories may not adequately reflect prognosis.

Current risk stratification processes rely on the belief that acute RV dysfunction is a critical determinant of outcomes in acute PE. Indeed, previous studies reported higher risk of inhospital adverse outcomes in patients with PE with RV enlargement diagnosed by CT angiography, this includes a prospective multicenter cohort study of 457 patients. However, meta-analyses looking at the risk of RV dysfunction, as assessed by echocardiography, and short-term mortality have found overall low positive predictive values. Due to the dichotomy between burden/location-based and clinical status–based naming conventions, PE categories are not always mutually exclusive. Even patients with SSO PE by radiographic description can have a clinical presentation of submassive PE with RV strain, as was observed in the present cohort. On the other hand, more than 10% of the present patients with submassive PE were asymptomatic. The observation that SSO PE does not have a more favorable outcome compared with other PE categories is consistent with the previous study involving 748 patients with PE (SSO n=116; 16%) that showed similar rates of VTE recurrence, bleeding, and all-cause mortality between patients with subsegmental PE and nonsubsegmental categories. Also, separate analysis of EINSTEIN-PE trial data showed similar outcomes in both therapeutic groups for patients with anatomically limited PE (<25% of the vasculature of a single lobe) compared with more extensive PE, although the definition of limited PE does not select solely patients with SSO.

The present results suggest that the stratification methods recommended by the European Society of Cardiology, which implement elements of cardiorespiratory status and presence of cancer (elements of PESI score), may better reflect clinical status and clinical outcome of patients with PE. A simplified PESI score of 0 points is associated with a 1% risk of mortality within 30 days, and 1 point or more with a risk of 10.9%.

Available literature confirms that a variety of comorbidities, such as chronic heart failure, obstructive pulmonary disease, age older than 70 years, concomitant DVT, and, particularly, cancer, are important predictors of outcome in patients with PE.

A secondary aim of the present study was to describe the clinical presentation and demographic characteristics of the different PE groups. The average age of patients across all subtypes of PE was similar—in the early 60s—which is consistent with previous reports. In the present cohort, patients with massive and submassive PE were more often symptomatic and more often had coexisting DVT compared with those with NRVD or SSO PE, which is also consistent with previous studies. Note that 17 patients in the present cohort (1.7%) had upper-extremity DVT as the only detected source of PE. Isolated ovarian, renal, and cerebral venous thrombosis occurred in only 1 patient each. A mesenteric, splenic, or portal DVT was an isolated coexisting finding in 1 patient each, suggesting that there was a different source of pulmonary embolism because these anatomical locations cannot represent the source of embolic material to the lung.

The strengths of the present study include that it reflects real clinical practice without limitations related to exclusion criteria used in clinical trials, but in the setting of a guideline-supported structured framework. This study also represents a different quality of clinical data than “real-world” practice, such as prospective registries, retrospective analyses of case series or retrospective health care databases, or insurance claims data analyses. These have a purely observational design without any control of the quality and uniformity of the therapy and often have imprecise clinical outcome assessments. We actively prescribe and monitor anticoagulation therapy in a standardized manner so, to differentiate our model from other registries, we use the term STAGPOR (Standardized, Guideline-Directed but Patient-Oriented Prospectively Registered) clinical practice.
An organized system of follow-up, provided for every patient in our practice, allows reassessment not only of anticoagulation performance but also of RV status as recommended by current guidelines. Patients with a history of massive or submassive PE have echocardiography prescheduled for the first 3-month follow-up visit, and all patients with PE who remain symptomatic have echocardiography ordered during the follow-up visit. Patients with persistent pulmonary hypertension are referred to the Pulmonary Hypertension Clinic for consultation.

This study has several potential limitations. First, the clinical profile of the patients with massive PE is likely affected by underenrollment of early fatalities. Even in the current era of advanced diagnostic facilities, approximately 90% of patients with acute, massive PE die within 1 to 2 hours of symptom onset, and the vascular hospital consulting service might not be asked to see these critically ill patients if they died within the first hours. The relatively small sample size and low event count of the massive PE group created imbalance between PE categories, which can affect accuracy of comparison and, thus, appears as a lack of difference in outcomes between massive PE and other PE categories. In addition, more than 46% of patients with massive PE in this study had systemic lytic therapy implemented, and more than 20% had an inferior vena cava filter placed, whereas in the International Cooperative Pulmonary Embolism Registry, thrombolysis was performed in 33 of the 108 patients (30.5%) with massive PE and only 11 (10%) received an inferior vena cava filter. Second, there may also be a selection bias related to our SSO group because these patients were included in the study only if anticoagulation was initiated. It is possible that those who were treated with anticoagulation were considered to be of better clinical status, but it is also possible that the decision to not anticoagulate was based on the patient’s high bleeding risk. Nevertheless, the category of PE with minimal distal embolic material, if anticoagulated, had clinical outcomes similar to those with larger thrombotic material causing RV dysfunction up to hemodynamic collapse. Third, a selection bias may exist related to the referral of a high proportion of complex patients with multiple comorbidities, including malignancy, to tertiary referring centers. Consequently, the findings of this study may not be applicable to other patient populations with different clinical and demographic characteristics.

CONCLUSION

This large, prospective study shows that in the setting of maximal standardization of evidence-based practice, all 4 PE categories have similar clinical outcomes. Clinical outcomes were not determined by RV dysfunction but rather by comorbidities, specifically cancer, which was significantly more common in the NRVD and SSO PE categories.

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Abbreviations and Acronyms: AHA = American Heart Association; CRNMB = clinically relevant nonmajor bleeding; CT = computed tomography; DVT = deep vein thrombosis; HR = hazard ratio; NRVD = no right ventricle dysfunction; PE = pulmonary embolism; PESI = Pulmonary Embolism Severity Index; RV = right ventricle; SSO = subsegmental only; VTE = venous thromboembolism

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REFERENCES

1. Tapson VF. Acute pulmonary embolism. N Engl J Med. 2008;358(10):1037-1052.
2. Sista AK, Kuo WT, Schiebler M, Maddox DC. Stratification, imaging, and management of acute massive and submassive pulmonary embolism. Radiology. 2017;284(1):5-24.
3. Heit JA, Ashrani AA, Crusan DJ, McBane RD, Pettersen TM, Bailey KR. Reasons for the persistent incidence of venous thromboembolism. Thromb Haemost. 2017;117(2):390-400.

4. Jaff MR, McNulty MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation. 2011;123(16):1788-1830.

5. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41(4):543-603.

6. Le Gal G, Righini M, Parent F, Van Strijen M, Couturaud F. Diagnosis and management of subsegmental pulmonary embolism. J Thromb Haemost. 2006;4(4):724-731.

7. den Exter PL, van Es J, Klok FA, et al. Risk profile and clinical outcome of symptomatic subsegmental acute pulmonary embolism. Blood. 2013;122(7):1144-1149.

8. Donze J, Le Gal G, Fine MJ, et al. Prospective validation of the Pulmonary Embolism Severity Index: a clinical prognostic model for pulmonary embolism. Thromb Haemost. 2008;100(5):943-948.

9. Jimenez D, Aujesky D, Moore L, et al. Simplification of the Pulmonary Embolism Severity Index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med. 2010;170(15):1383-1389.

10. Kearon C, Allderdice M, Omeida J, et al. Antithrombotic therapy for VTE disease. CHEST Guideline and Expert Panel Report. Chest. 2016;149(2):315-352.

11. Remy-Jardin M, Pistoleti M, Goodman LR, et al. Management of suspected acute pulmonary embolism in the era of CT angiography: a statement from the Fleischner Society. Radiology. 2007;245(2):315-329.

12. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. Arch Intern Med. 2011;171(9):831-837.

13. Bott-Kitslaar DM, McBane RD, Casanegra AI, et al. Apixaban and rivaroxaban in patients with acute venous thromboembolism. Mayo Clin Proc. 2019;94(7):1242-1252.

14. Wysokinski WE, Houghton DE, Casanegra AI, et al. Comparison of apixaban to rivaroxaban and enoxaparin in acute cancer-associated venous thromboembolism. Am J Hematol. 2019;94(1):1185-1192.

15. Khonra AA, Noble S, Lee AYY, et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost. 2018;16(9):1891-1894.

16. Girard P, Penaloza A, Parent F, et al. Reproducibility of clinical events adjudications in a trial of venous thromboembolism prevention. J Thromb Haemost. 2017;15(4):662-669.

17. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3(9):692-694.

18. Becattini C, Agnelli G, Vedovato MC, et al. Multidetector computed tomography for acute pulmonary embolism: diagnosis and risk stratification in a single test. Eur Heart J. 2011;32(13):1657-1663.

19. Trujillo-Santos J, den Exter PL, Gomez V, et al. Computed tomography-assessed right ventricular dysfunction and risk stratification of patients with acute nonmassive pulmonary embolism: systematic review and meta-analysis. J Thromb Haemost. 2013;11(10):1823-1832.

20. Becattini C, Agnelli G, Germino F, Vedovato MC. Computed tomography to assess risk of death in acute pulmonary embolism: a meta-analysis. Eur Respir J. 2014;43(6):1678-1690.

21. Sanchez-O, Trinquart L, Colombet L, et al. Prognostic value of right ventricular dysfunction in patients with haemodynamically stable pulmonary embolism: a systematic review. Eur Heart J. 2008;29(12):1569-1577.

22. Coutance G, Cauderlier E, Ehtisham J, Hamon M, Hamon M. The prognostic value of markers of right ventricular dysfunction in pulmonary embolism: a meta-analysis. Crit Care. 2011;15(2):R103.

23. Buller HR, Prins MH, Lensin AW, et al. EINSTEIN—PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366(14):1287-1297.

24. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet. 1999;353(9162):1386-1389.

25. Laporte S, Mismetti P, Decousus H, et al. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad Tromboembólica venosa (RIETE) Registry. Circulation. 2008;117(13):1711-1716.

26. Jimenez D, Aujesky D, Diaz G, et al. Prognostic significance of deep vein thrombosis in patients presenting with acute symptomatic pulmonary embolism. Am J Respir Crit Care Med. 2010;181(9):983-991.

27. Beyer-Westendorf J. What have we learned from real-world NOAC studies in venous thromboembolism treatment? Thromb Res. 2018:163:83-91.

28. D’Agostina C, Zorzini P, Enea L, et al. ANMCO position paper: long-term follow-up of patients with pulmonary thromboembolism. Eur Heart J Suppl. 2017;19(suppl D):D309-D332.

29. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. J Thromb Thrombolysis. 2016;41(1):3-14.

30. Kasper W, Konstantinides S, Geibel A, et al. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. J Am Coll Cardiol. 1997;30(5):165-171.